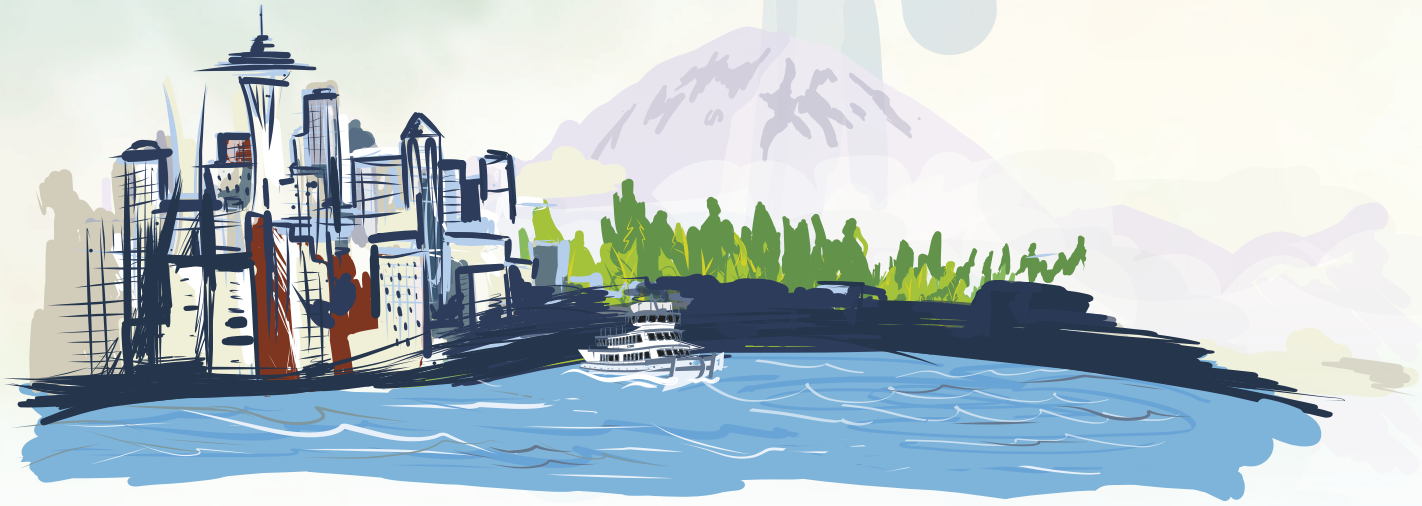
Abstract eBook

CROI 2017

Conference on Retroviruses and Opportunistic Infections



SEATTLE, WASHINGTON
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IAS–USA
International Antiviral Society–USA

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ABSTRACT PROCESS

Scientific Categories

A. Virology
B. Molecular Epidemiology and HIV/SIV Evolution
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D. Host Immune Responses to Infection, Vaccines, and Immunotherapy
E. HIV Reservoirs, Latency, and All Curative Strategies Including Therapeutic Vaccines and Gene Therapy
F. Neuropathogenesis and CNS HIV Complications
G. Clinical Pharmacology
H. Antiretroviral Therapy: Pre-Clinical and Randomized Trials
I. Antiretroviral Therapy: Efficacy and Effectiveness Studies
J. HIV Drug Resistance
K. HIV Diagnostics
L. Hepatitis Viruses and Liver Complications
M. Malignancies
N. Cardiovascular Complications of HIV Infection and Antiretroviral Therapy
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P. Tuberculosis and Other Opportunistic Infections
Q. Maternal/Fetal HIV
R. Pediatrics and Adolescents
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V. Contraceptive and Reproductive Health in Women
W. Implementation and Scale-Up of Treatment and Care
X. Population and Cost Modeling
Y. Emerging Viruses: Zika Virus

Abstract Content

Author names, institutions, abstract titles, and abstracts in the Program and Abstracts eBook are generally presented as submitted by the corresponding author.

Abstract Review Process

The PC and a panel of volunteer external reviewers reviewed approximately 2000 submitted abstracts. Each abstract was reviewed by 5 to 10 reviewers selected for each abstract category based upon their individual expertise.
PC members and external experts in the field reviewed the abstracts for the quality and originality of the work and scored them numerically. All reviewers were instructed to abstain from scoring any abstract on which they are an author or coauthor, have a financial or personal conflict of interest, or do not have the appropriate expertise to evaluate. Scores ranged from 1 (definite oral presentation) to 5 (rejected).

Scores for each abstract were averaged and the standard deviation was calculated to assess variability. If variability was high, outlier scores are identified and censored. Abstracts with high variability in scores were discussed individually during a series of conference calls. Abstracts were accepted for oral presentations, for poster presentations, or rejected. Late-breaking abstract reviews included an assessment of the late-breaking nature of the work (versus just being a late submission).

Common Reasons for Abstract Rejection

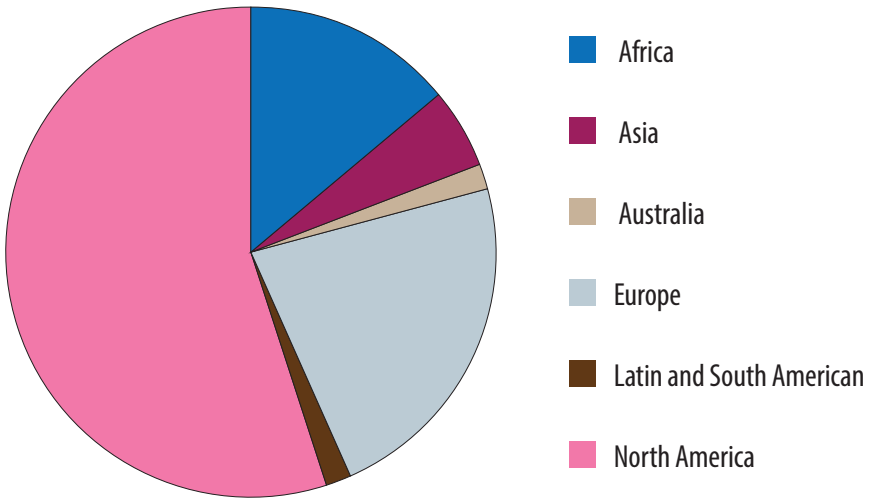
- Information is not new enough
- Methodology is inadequate or insufficient to support conclusions
- Background does not summarize the hypothesis
- Submission is poorly written
- Abstract is duplicative of other submissions
- Abstract is not appropriate for CROI
- Controls are absent or inadequate
- Statistical evaluation is inadequate or absent
- Summary of essential results is inadequate or absent
- Data are inadequate or insufficient to support conclusions
- Submission reports clinical trial and data from unplanned analysis or incomplete or ongoing studies
- Format does not follow guidelines (eg, section[s] missing, more than 1 graphic, table, or figure submitted)

Statistics for Abstracts

General abstract submitted	1751
General abstracts accepted	948
General oral abstracts	80
General poster abstracts	868
Late-breaking abstracts submitted	159
Late-breaking abstracts accepted	53
Late-breaking oral abstracts	16
Late-breaking poster abstracts	37
Total abstracts submitted	1910
Total abstract accepted	1001

All Authors on Accepted Abstracts

Region	N	Percent
Africa	265	14
Asia	99	5.2
Australia	35	1.8
Europe	432	22.5
Latin and South America	29	1.5
North America	1050	55



ORAL ABSTRACTS

1 PROGRAM COMMITTEE WORKSHOP FOR NEW INVESTIGATORS AND TRAINEES

Conveners: Serena S. Spudich, *Yale Univ, New Haven, USA and* **John W. Mellors**, *Univ of Pittsburgh, Pittsburgh, PA, USA*

Despite extraordinary advances in understanding of the pathogenesis, treatment, and prevention of HIV over the past 35 years, research has fallen short of identifying optimal strategies to provide effective antiretroviral treatment to all infected persons, prevent new infections, limit morbidity in individuals on therapy, and achieve a functional 'cure.' The annual Program Committee Workshop for New Investigators and Trainees at the Conference for Retroviruses and Opportunistic Infections (CROI) is designed to develop knowledge and discovery across a broad range of basic and clinical HIV investigation. In this half-day session, Program Committee members will succinctly encapsulate current understanding in five distinct topics, specifically identifying areas of controversy or gaps requiring new investigation and ideas. This year, **Dr Paul Bieniasz** will start the session by reviewing updated knowledge in the field of molecular virology, including advances in understanding of the viral life cycle and host restriction factors. **Dr Richard A. Koup** will report on advances in antibodies, from knowledge of existing monoclonal antibodies to progress in antibody engineering, antibody functions, and recent trials employing antibodies for HIV protection and treatment. **Dr James A. McIntyre** will cover recent advances in HIV prevention, reporting on the ongoing challenges of reaching key and vulnerable populations at high risk of infection, and describing evidence of successful implementation of new biomedical prevention strategies. **Dr Judith S. Currier** will review non-AIDS complications of HIV infection such as cardiovascular, hepatic, malignant and neurologic disease in the setting of aging, highlighting new insights into the epidemiology, pathogenesis, screening, prevention and treatment of these problems. Finally, **Dr Nicolas Chomont** will summarize state-of-the-art knowledge regarding HIV reservoirs and the potential for HIV cure, explaining how and where HIV persists during antiretroviral therapy, and describing multiple approaches to HIV eradication or remission, including early treatment strategies, latency reversal, immunotherapies, and host genetic modification. Speakers will highlight key work featured at CROI 2017, and participate in moderated question and answer sessions after each talk to stimulate thought and interactions that enhance the attendees' experience at CROI.

2 MARTIN DELANEY, PRESENTATION FROM LAB TO LICENSURE: THE IMPORTANCE OF GOOD PARTICIPATORY PRACTICE IN RESEARCH

Moderator: Mark Hubbard, *Tennessee Association of People with AIDS, Nashville, TN, USA*

Failure to effectively engage stakeholders has historically resulted in the disruption and closure of a number of large HIV prevention trials. There is a growing body of evidence that engaging stakeholders from the earliest stages of research and concept development and beyond trial site communities can strengthen efficient and ethical conduct of research. In 2007, UNAIDS and AVAC developed Good Participatory Practice (GPP) Guidelines to set global standards for stakeholder engagement throughout the research life cycle of biomedical and related HIV prevention trials. GPP establishes guiding principles and promotes the use of a range of stakeholder advisory mechanisms at all levels to help ensure meaningful, collaborative, transparent, and mutually beneficial relationships. GPP provides a flexible and dynamic roadmap for researchers, sponsors, and implementers. Panelists will provide a brief history of events prior to the development of the GPP guidelines, explain GPP and its fundamental principles as they apply to HIV prevention and cure research, and discuss how the guidelines have helped to shape stakeholder engagement in other fields of medical research. Panelists will explore the practical application of GPP to placebo-controlled clinical trials, open-label PrEP demonstration projects, and social research to guide human studies for HIV cure or long-term remission. Insights and concerns expressed by community members and other stakeholders will inform the discussion throughout. This presentation will inform new investigators and community educators about the critical importance of engaging stakeholders and inspire them to consider the use of GPP principles for all stages and types of research. **Panelists Stacey Hannah**, AVAC: *History and Principles of Good Participatory Practice Guidelines* **Deborah Baron**, Wits Reproductive Health and HIV Institute: *GPP as a Guide to Biomedical HIV Prevention Trial Design and Implementation* **David Evans**, Project Inform: *Applying GPP Principles to Cure Research.*

3 PREVENTION TRIAL DESIGN IN THE ERA OF PREP

Deborah J. Donnell, *Fred Hutchinson Cancer Rsr Center, Seattle, WA, USA*

We are at a pivotal moment in HIV prevention where daily oral PrEP has been proven effective, yet is not likely to be fully effective for all populations in need. Further advance of HIV prevention requires the development of vaccines, alternative oral regimens, longer acting or coitally dependent prevention strategies. Clinical trials in HIV prevention lack a surrogate and any efficacy study is a resource-intensive undertaking. This session presents the current designs of clinical trials advancing the pipeline of prevention agents, including the statistical issues surrounding the first active-comparator trials in HIV prevention. As we confront a potential future where highly effective prevention reduces the incidence of HIV-endpoints in prevention trials it is important to begin to consider what evidence would be sufficient to definitively establish evidence of prevention efficacy.

4 IMPLEMENTATION SCIENCE TRIALS: DO THE RULES OF RCTs APPLY?

James R. Hargreaves, *London Sch of Hygiene and Trop Med, London, United Kingdom*

Implementation science asks questions about the delivery of interventions to those who need them. Technologies such as drugs, vaccines, or surgical procedures may be the "direct mechanism" of the interventions in question. But implementation science trials answer questions about how best to implement these, about the practice of their delivery, or about the systems through which they are delivered. As such, these trials are inevitably more about human behaviour and system function than they are about the biological efficacy of the drug, vaccine or procedure. This presentation will discuss four implications of this perspective for the design of implementation science trials, illustrating key points with examples. First, such trials are usually most appropriately conducted as cluster-level trials since this is the level at which delivery packages and strategies operate. Second they should be "pragmatic", as defined in the CONSORT guidance for pragmatic trials. One implication of this is that it is important that they enrol study participants who are representative of the intended target population, rather than opportunistically recruiting selected populations as may be appropriate for individual-level efficacy trials. A further implication of "pragmatism" is that, intervention delivery should be monitored and supervised in a realistic way, not closely controlled to ensure ideal implementation as in efficacy trials. Third, integrated process evaluation, ideally guided by the UK MRC Process Evaluation framework for complex interventions, is an essential component of such trials. This framework emphasises the importance of documenting the implementation of interventions, analysing pathways of change and identifying contextual factors relevant to future policy recommendations about scale-up to other settings. Fourth and finally, owing to lack of investigator control, ethical or other reasons, it may not be feasible to undertake randomisation in some implementation science situations. While a full discussion of the range of design alternatives is beyond the scope of this presentation, I will briefly discuss a framework we have developed to map the most rigorous non-randomised impact evaluation designs against constraints to randomisation often described by practitioners in implementation settings.

5 RESPONDENT DRIVEN SAMPLING AND OTHER METHODS FOR RECRUITING HARD TO REACH POPULATIONS

Carl A. Latkin, *The Johns Hopkins Univ, Baltimore, MD, USA*

Reaching and enrolling "hidden" populations for infectious disease prevention, testing, and treatment studies and public health programs remains problematic. Adequate sampling strategies are also need to provide infectious disease modelers with accurate data. Two overlapping approaches to sampling hidden populations are respondent

driven sampling (RDS) and social network sampling. In the field of HIV and STI research, RDS has been successfully utilized to recruit substance users, commercial sex workers, and men who have sex with men. In this workshop, we review of the evidence for the use of RDS as a reliable sampling methodology, assess whether many studies meet the assumptions for RDS in order to claim a representative sample, and identify systematic biases in RDS sampling. In addition, we will review recent studies that have compared RDS to other recruitment approaches or have modified RDS methods. The presentation will also discuss how social network informed sampling may be combined with RDS to improve sampling, what types of studies may be best suited for RDS and social network sampling approaches, and what might be accomplished by an RDS approach versus more conventional sampling strategies.

6 HIGH-THROUGHPUT GENOME ENGINEERING IN PRIMARY CD4+ T CELLS

Judd F. Hultquist, *Univ of California San Francisco, San Francisco, CA, USA*

CRISPR/Cas9 gene editing strategies have revolutionized our ability to engineer the human genome for robust functional interrogation of complex biological processes. We have recently adapted this technology to primary human CD4+ T cells to generate a high-throughput platform for analyzing the role of host factors in HIV replication and pathogenesis. Unlike traditional RNA interference or complementation approaches, this technique generates permanent genetic changes to the host genome at high efficiency with only transient expression of the modifying agents. CRISPR/Cas9 ribonucleoproteins (crRNPs) are synthesized in vitro and delivered to activated primary human CD4+ T cells by electroporation. These cells are then expanded and parsed out for validation, cryopreservation, and infection. Our platform supports the arrayed generation of hundreds of specific gene manipulations in only a few hours time and is widely adaptable to an array of culturing conditions, infection protocols, and downstream applications. We first used this platform to perform proof-of-principle experiments targeting host factors with defined roles in HIV replication. As expected, CXCR4 or CCR5 knock-out primary T cells are resistant to HIV infection in a tropism-dependent manner, whereas knock-out of LEDGF or TNPO3 results in a tropism-independent reduction in infection. We next bridged this approach to other proteomic and genomic discovery platforms as a secondary screen for host factor functionality, identifying several candidate dependency and restriction factors for additional mechanistic study. Finally, we found that crRNP multiplexing allows for the editing of multiple genes simultaneously, enabling studies of functional redundancy or epistasis among multiple host and viral factors. This technology should prove useful for not only discovery-based scientific research, but may additionally accelerate target validation for pharmaceutical and cell-based therapies to cure HIV infection. We are currently adapting this technology to achieve efficient genome editing at the level of a single base pair, as well as adapting it to other primary cell types for the study of additional biological processes and disease states. Recent advances with CRISPR interference, CRISPR activation, BaseEditor technology, high-fidelity Cas9 enzymes, and Cas9 inhibitors will also be discussed.

7 IDENTIFYING AND PROFILING VIRUS-SPECIFIC T CELLS USING MASS CYTOMETRY

Evan William Newell, *Singapore Immunol Network, Singapore*

Blood and tissue samples taken as part of clinical studies and trials can provide critical information on the roles of the immune response in patient outcome. However, the cellular compositions of these samples are often highly diverse, and important information can be lost if rare cells are overlooked. For instance, antigen specific T cells are critical initiators and orchestrators of the adaptive immune response, but cells specific for any given pathogen or cancer can be exceedingly rare, especially in blood. Here, the utility of high dimensional mass cytometry analysis together with rapidly evolving computational analysis tools will be discussed. A major advantage of this approach is the ability to directly analyze relationships between antigen-specificity and each cell's phenotypic profile. This is particularly relevant for the study of T cells, whose phenotypic markers can be intuitively segregated into a number of categories such as antigen-specificity, differentiation state, functional capacity, and trafficking receptor profiles. All of these can be measured simultaneously on individual cells through the use of metal-labeled monoclonal antibodies and highly multiplexed combinatorially-coded peptide-MHC tetramers. Our ongoing analysis of T cell responses in chronic hepatitis B viral infection in human patients demonstrate the utility of this approach to identify and profile difficult to study HBV-specific T cells. Our results show that HBV-specific T cell responses are highly diverse in terms of epitopes being targeted and the phenotypes of the corresponding cells. We are investigating the potential utility of T cell phenotypes as biomarkers for patient outcomes.

8 QUANTIFYING HIV-1 mRNA STRUCTURE AND TRANSLATION EFFICIENCY IN CELLS

Silvi Rouskin, *Whitehead Inst, Cambridge, MA*

We have recently developed DMS-MaPseq, which allows for targeted RNA structure probing in vivo at single molecule and single nucleotide resolution. First, cells are treated with DMS, which rapidly modifies unpaired adenines and cytosines. Unlike other chemical reagents, DMS is a very small molecule specific to the nitrogen atoms involved in Watson-Crick base-paring, which enables probing of RNA structure in the presence of RNA binding proteins. In the DMS-MaPseq technique, we use DMS concentrations that result in multiple modifications per single molecule. We then use a newly commercialized high fidelity and processive thermostable group II reverse transcriptase (TGIRT) enzyme, which converts DMS modifications into mutations in the cDNA. The cDNA is converted to dsDNA by PCR and then sequenced on an Illumina platform with long reads. Since the mutation background is negligible, the mutations within a single sequencing read correspond to the open bases within a single RNA molecule. There are two key advantages of using this approach compared to other chemical probing approaches: 1) we can selectively probe the structure of any RNA of interest, even at very low abundance, simply by using a RNA specific RT primer 2) we can analyze multiple DMS modification sites per RNA molecule, which allows us to distinguish heterogeneous RNA structure subpopulations in vivo. We use a combination of DMS-MaPseq and ribosome profiling to quantify the HIV-1 RNA structure and translation efficiency in cells.

9 INTERACTIVE CASE-BASED WORKSHOP ON HEPATITIS C

Moderators: Susanna Naggie, *Duke Univ, Durham, NC, USA, and* **David Wyles**, *Denver Health, Denver, CO, USA*

This interactive case-based session is geared toward clinicians who are involved in HCV treatment. Speakers will present cases on: Staging and treatment of early stage HCV (**John D. Scott**, Univ of Washington, Seattle, WA, USA), effect of drug resistance on DAA treatment and re-treatment of patients with chronic HCV infection (**Alessandra Mangia**, Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy), common drug interactions with HIV/HCV coinfection treatments (**Debika Bhattacharya**, Univ of California Los Angeles, Los Angeles, CA, USA), and cirrhosis issues (**Sanjay Bhagani**, Royal Free Hosp, London, United Kingdom).

10 BERNARD FIELDS LECTURE: INSIGHTS INTO HIV PREVENTION, PATHOGENESIS, AND TREATMENT FROM NONHUMAN PRIMATE MODELS

Jeffrey D. Lifson, *Frederick National Laboratory for Cancer Research, Frederick, MD, USA*

Infection of Asian macaques with Simian Immunodeficiency Viruses (SIV) endemic in African nonhuman primates (NHP) can lead to progressive pathogenesis/immunodeficiency that recapitulates key aspects of human HIV infection and AIDS. Different NHP models, employing different naturally occurring or engineered SIVs or related chimeric viruses, used to infect different macaque species, can be used to authentically model relevant features of human HIV infection. Experimental flexibility and control, and opportunities for extensive tissue sampling afforded by NHP models provide advantages for studying virus/host interactions. NHP models have yielded key insights into AIDS virus transmission, allowing characterization of the earliest stages of infection, pathways of early viral spread, and initial host responses, and permit the preclinical safety and activity evaluation of prophylactic vaccines and other prevention approaches. When matched to conditions of clinical vaccine evaluation, results from NHP vaccine studies have been largely congruent. NHP models have also informed our understanding of the pathogenesis of AIDS virus infection, including processes such as early, extensive depletion of intestinal CD4+ T cells, mucosal disruption, microbial translocation and persisting systemic immune activation, along with inflammation related fibrotic disruption of secondary lymphoid tissues. Comparison of SIV infections in Asian macaques and African "natural host" species, where infection can result in extensive viral replication but does not typically lead to progressive disease, highlight the role of host responses in pathogenesis. NHP models have also shed light on mechanisms of viral persistence despite apparently effective viral suppression by antiretroviral drug treatment or potent immune responses, through viral sequestration in relatively immune privileged sanctuary sites such as B cell follicles in

secondary lymphoid tissues, establishment and expansion of T cell clones bearing clonally integrated proviruses, and other mechanisms, and provide the basis for experiments to evaluate the safety and in vivo activity of strategies to target residual viral reservoirs. Contributions of NHP studies to our understanding in these areas and recent developments will be reviewed, underscoring the key role that NHP models have played and will continue to play in our efforts to develop more definitive approaches for preventing, treating, and attempting to cure HIV infection.

11 N'GALY-MANN LECTURE: HIV/AIDS RESEARCH IN ZIMBABWE: PROVIDING THE EVIDENCE FOR QUALITY CARE

James G. Hakim, *University of Zimbabwe, Harare, Zimbabwe*

Following the report of the first case of AIDS in Zimbabwe in 1985 the epidemic escalated rapidly reaching an adult prevalence of 29% in the late 1990s. Given the heterosexual and generalized nature of the epidemic the social, health and economic consequences were devastating. This presentation will describe (a) some historical perspectives of AIDS and the current status of the epidemic in Zimbabwe (b) Zimbabwe's contribution to cutting edge AIDS research (c) human and research capacity building as an essential aspect of the comprehensive response to the AIDS epidemic. As the health sector and the social fabric of the country reeled under the effects of the epidemic the government took a series of steps which proved visionary given the considerable resource constraints that beset the country. An aggressive behavior change campaign, the introduction of the AIDS levy (domestic financing scheme) and the local manufacture of ARVs defying patent restrictions stand out as significant home-grown solutions complementing the global support the country was receiving. Recent data show an adult prevalence of 14.6%, incidence of 0.48% (a drop of 50% over the past 1½ decades); 900,000 people on ART and a viral suppression rate of 60.4%. Challenges remain and achievement of global targets including ending AIDS are prime aspirations for the country. In the mid-90's driven by a desire to understand the AIDS epidemic and to contribute to mitigating its effects a small band of researchers with collaborators in the US and UK embarked on high impact research in the face of meager resources and a challenging socioeconomic environment. Data emanating from these efforts have contributed significantly to local and international HIV/AIDS knowledge base and interventions. Personal relations between local and external researchers have been key ingredients in research capacity building and in escalating research in Zimbabwe. HIV prevention and therapeutics research encompassed pMTCT, microbicides, ART strategies and ART in naïve and experienced patients. Other research efforts included tuberculosis, cryptococcal disease, cervical cancer, Kaposi's sarcoma, mental health and studies among commercial sex workers. In recent years opportunities provided by PEPFAR, NIH, Wellcome Trust and others have enabled the implementation of robust training programs to improve the quality of health delivery and create the next generation of competent researchers and health provider.

12 THE EMERGING POTENTIAL FOR HIV CURE FOR INFANTS, CHILDREN, AND ADULTS

Jintanat Ananworanich, *US Military HIV Rsr Prog, USA and The Thai Red Cross AIDS Rsr Cntr, Thailand*

HIV cure is a desirable goal for children and adults living with HIV who face stigma and life-long antiretroviral therapy (ART) that requires strict adherence. In addition, treatment cost poses a significant burden to national programs and global donors that could be alleviated were a cure available. The ultimate objective is to eliminate all cells capable of producing HIV – a near unattainable goal with current therapies. The field has re-calibrated the HIV cure target to a more achievable one of HIV remission, i.e., the ability to control viral replication after ART interruption to levels below detection. The major obstacle is, however, the seeding of the HIV reservoir that occurs early during acute HIV infection and sets the stage for the establishment of latent reservoirs, particularly in long-lived CD4+ T cells and lymphoid tissues. The unique aspects of the pediatric immune system in the composition of the CD4+ T cell compartment and defense against HIV may influence HIV persistence. Early ART is an important step in the path towards an HIV cure. The pediatric population offers a unique opportunity for immediate treatment because of the known timing of HIV exposure in most newborns. Similarly, acute HIV infection studies have demonstrated the ability to identify and treat very early infection in adults. Both children and adults treated in acute HIV infection achieve significantly smaller HIV reservoirs, preserved immune functions with little viral escape to immune pressure. These qualities could enhance the effects of immune-based interventions aimed at depleting HIV-infected cells. However, despite these favorable qualities, the majority of early treated individuals do not achieve HIV remission. Therefore, additional therapies will be needed that may include latency reversing agents and passive and active immune therapies. There are exciting new developments of broadly neutralizing antibodies and therapeutic HIV vaccines that could be beneficial to HIV cure. It is highly likely that combination therapies that can generate persistent and effective immune responses to control HIV will be required for a durable HIV remission and cure. In this early discovery phase of HIV cure research that is associated with risks and uncertainties, and further complicated by the difficult concepts of remission and cure, it is also important that ethical, behavioral and social research be conducted in parallel to basic and clinical research.

13 ADVANCES IN CELLULAR THERAPY IN CANCER AND HIV

Carl H. June, *Univ of Pennsylvania, Philadelphia, PA, USA*

Chimeric antigen receptor (CAR) T cells have proven that engineered immune cells can serve as a powerful new class of cancer therapeutics. Clinical experience has helped to define the major challenges that must be met to make engineered T cells a reliable, safe, and effective platform that can be deployed against a broad range of tumors. Here I will discuss a road opened CAR T cells for cancer that leads to therapies for HIV. The emergence of synthetic biology approaches for cellular engineering is providing us with a broadly expanded set of tools for programming immune cells that can be used to contain or confer elite controller status on patients with HIV. The convergence of the field of HIV and Cancer is driven in part because both are chronic conditions of antigen overload, where chronic infections and tumors can lead to phenocopies of acquired tolerance and antigen escape.

14LB QUATERNARY CONFIGURATION OF THE FUNCTIONAL CD4-BINDING SITE IN THE HIV-1 ENV TRIMER

Qingbo Liu[1], Priyamvada Acharya[1], Michael Dolan[1], Peng Zhang[1], Aliaksandr Druz[1], William Rice[2], Bridget Carragher[2], Clinton Potter[2], Peter D. Kwong[1], Paolo Lusso[3]
[1]*NIH, Bethesda, MD, USA,* [2]*New York Structural Bio Cntr, New York, NY, USA,* [3]*NIAID, Bethesda, MD, USA*

Background: Binding of the gp120 envelope glycoprotein to the CD4 receptor is the first step in the HIV-1 infectious cycle. Although the CD4-binding site has been extensively characterized by mutagenesis and co-crystallization with soluble CD4 (sCD4), most of these studies were performed with monomeric gp120 subunits, thus hindering the evaluation of the role of quaternary elements that may be involved in the initial CD4 interaction. Moreover, the initial receptor interaction has been difficult to study because of major CD4-induced structural rearrangements.

Methods: The DS-SOSIP.664 trimer, 4-domain CD4, and PGT145 Fab were expressed in 293FS cells and purified for cryogenic electron microscopy (cryo-EM) analysis; data were acquired using the Leginon system installed on a Krios electron microscope operating at 300kV; for ELISA and SPR, wild-type (WT) and mutated SOSIP trimers and gp120 monomers were expressed in 293FS and extensively purified; WT and mutated full-length gp160 were expressed in 293T cells for flow cytometry and co-transfected with an HIV-1 backbone plasmid to produce infectious pseudoviruses; infectivity assays were performed in TZMbl cells.

Results: Cryo-EM analysis of the stabilized DS-SOSIP.664 trimer, which remains in a pre-fusion closed conformation after interaction with CD4, permitted to visualize the initial contact with CD4 at 6.8-Å resolution. We found that the initial CD4-contact site in the HIV-1 Env trimer is constituted by a quaternary surface formed by coalescence of the previously defined CD4-binding region in the outer domain of one gp120 protomer with a second CD4-binding site (CD4-BS2) that encompasses discontinuous elements from the inner domain of a neighboring gp120 protomer. Disruption of CD4-BS2 destabilized CD4-trimer interaction and abrogated HIV-1 infectivity by preventing acquisition of coreceptor-binding competence. A corresponding reduction in HIV-1 infectivity occurred upon mutation of CD4 residues that interact with CD4-BS2. Quaternary interactions were also documented for selected neutralizing antibodies to the CD4 supersite, providing evidence that the CD4-BS2 region is immunogenic in vivo.

Conclusion: These results document the critical role of quaternary interactions in the initial HIV-1 envelope-receptor contact, with implications for treatment and vaccine design.

15 EARLY CYTOPLASMIC UNCOATING IS NECESSARY FOR INFECTIVITY OF HIV-1

João I. Mamede, Gianguido C. Cianci, Meegan R. Anderson, Thomas Hope
Northwestern Univ, Chicago, IL, USA

Background: After cell fusion, HIV delivers its conical capsid into the cytoplasm. The disassembly of the capsid is termed uncoating and is critical to infection. The understanding of the kinetics, dynamics, and localization of uncoating of infectious particles has been eluded by the unavoidable presence of non-infectious particles. The timing of uncoating remains under discussion with some models proposing that uncoating happens early and other models suggest that the intact capsid docks at the nuclear pore. These different hypotheses formed from diverse assays, lack the information for the kinetics and localization of uncoating of productively infectious viral particles.
Methods: We used live-cell fluorescent imaging of intravirion fluid phase markers to determine the integrity of the HIV conical capsid core. To visualize dynamic changes in capsid integrity and composition, we utilized the HIV-iGFP construct. During viral maturation of HIV-iGFP, the GFP is liberated from Gag. A minority population of the free GFP is trapped in the capsid, while the remaining free GFP is located outside of the capsid. With this technique, the loss of the fluid phase GFP occurs in two steps: with fusion and upon the loss of capsid core integrity. Live-cell microscopy of HIV-iGFP virions with a viral complex marker such as Vpr or Integrase allows for the timing of these two steps. Through viral challenge with less than one virion per cell we are able to connect viral particle phenotype to infection.
Results: The time between fusion and capsid integrity loss, for both HIV and VSV-G mediated fusion, in tissue culture and primary cells (macrophages and T cells), is approximately 30 minutes. Also, capsid integrity loss occurs entirely in the cytoplasm and co-relates to a big loss of p24CA. With our low MOI approach, we were able to image individual particle uncoating that produces a viable infection and differentiate between different rates of uncoating. This analysis revealed that all particles associated with cellular infection showed changes in capsid integrity ~29 minutes. We were also able to halt uncoating by blocking specific steps of reverse transcription, linking uncoating to the occurrence of the first-strand transfer step.
Conclusion: Together, these observations validate the early cytoplasmic uncoating model. Our live-imaging assay has the ability to follow uncoating at the single infectious particle level providing unprecedented insights into the early steps of HIV infection.

16 ECCENTRIC VIRAL GENOMIC RNA AND INTEGRASE ARE PREMATURELY DEGRADED IN TARGET CELLS

Michaela Madison[1], Dana Q. Lawson[1], Jennifer Elliott[1], Ayse N. Ozanturk[2], Pratibha Chowdary Koneru[3], James R. Fuchs[3], Mamuka Kvaratskhelia[3], **Sebla B. Kutluay**[1]
[1]Washington Univ in St. Louis, St. Louis, MO, USA, [2]Bilkent Univ, Ankara, Turkey, [3]Ohio State Univ, Columbus, OH, USA

Background: Recent evidence indicates that inhibition of HIV-1 integrase (IN) binding to the viral RNA genome yields aberrant particles, in which the viral ribonucleoprotein complexes (vRNPs) are eccentrically localized outside the protective capsid core. These particles are non-infectious and blocked at an early reverse transcription stage in target cells. However, the basis of this reverse transcription defect is unknown, given that eccentric particles appear to retain all components necessary for reverse transcription, i.e. a dimeric viral RNA genome primed with tRNA-Lys, functional RT and normal levels of NC-RNA complexes. In addition, apart from reverse transcription products, the fates of viral core components in cells infected with eccentric particles have not been studied to date.
Methods: To determine why the eccentric virus particles, generated with class II IN mutants such as R269A/K273A or ALLINI treatments of the WT virus, fail to support reveres transcription in target cells, we have monitored the fates of eccentric particle components in infected cells. To this end, we took advantage of a previously developed elaborate approach in which we biochemically tracked multiple core components in infected cells.
Results: In this study, we show that in target cells eccentrically localized vRNPs and IN are prematurely degraded, whereas reverse transcriptase remains active and stably associated with capsid cores. Importantly, we show that in addition to viral RNAs, IN protein is also mislocalized in particles. Remarkably, the aberrantly shaped capsid cores in the eccentric particles can efficiently saturate and be degraded by a restricting TRIM5 protein, suggesting that TRIM5 recognition does not require the presence of fully formed cores.
Conclusion: We propose that IN-RNA interactions allow for packaging of both vRNPs and IN within the protective capsid cores to ensure subsequent reverse transcription and productive infection in target cells.

17 DYNAMICS OF NUCLEAR ENVELOPE ASSOCIATION AND NUCLEAR IMPORT OF HIV-1 COMPLEXES

Ryan C. Burdick, Jianbo Chen, Jaya Sastri, Wei-Shau Hu, Vinay K. Pathak
NCI, Frederick, MD, USA

Background: During productive infection, HIV-1 must enter the nucleus to integrate its DNA into host genome. However, many aspects of nuclear import process are poorly understood because they have been difficult to study using biochemical or imaging assays, and have not been visualized in living cells.
Methods: To elucidate critical HIV-1 post-entry events, we analyzed viral complexes labeled with yellow fluorescent protein-tagged APOBEC3F (A3F-YFP), a virion-incorporated host restriction factor, or Vpr-integrase-YFP fusion protein (IN-YFP) using live-cell imaging.
Results: We first examined the association between HIV-1 viral complexes and nuclear envelope (NE) by live-cell imaging, and observed that most contacts are transient (<5 sec) and very few are stable (>20 min), suggesting only a subset of viral complexes is competent to stably dock with the NE. Most HIV-1 complexes forming transient interactions with the NE may be encountering regions that did not have any nuclear pore complexes (NPCs). We found that HIV-1-NE stable association is compromised when capsid is mutated to form viral cores that are unstable (K203A) or hyperstable (E128A/R132A), or when host protein Nup358 is knocked down. These findings indicate that HIV-1 capsid and host Nup358 play critical roles in forming the stable associations. To better understand the process of nuclear import, we captured for the first time the translocation of 21 HIV-1 complexes from the cytoplasm to the nucleus and their nuclear movements. Viral complexes labeled with A3F-YFP or IN-YFP behaved similarly, suggesting that the fluorescently tagged proteins did not influence their movements. They exhibited similar long and variable residence times at the NE (1.7 ± 1.7 hours), indicating that the viral core may be undergoing extensive dissociation and/or conformational rearrangements which require an extended period of association with the NPC prior to nuclear import. After import, the viral complexes exhibited a fast phase (<9 min) as they moved away from the point of entry, followed by a slow phase for the rest of the observation time, suggesting that they quickly associate with chromatin and/or other nuclear macromolecules. The viral complexes moved away from the nuclear point of entry, but remained in the nuclear periphery.
Conclusion: The tracking of individual HIV-1 complexes provides insights into the dynamics of HIV-1 NE association, nuclear import, and movement inside the nucleus.

18 CYPA REGULATES HIV-1 ACCESS TO AN FG-GUIDED NUCLEAR ENTRY PATHWAY

Guangai Xue[1], Vineet KewalRamani[1], Shih Lin Goh[2], Hyun Jae Yu[1], Anna Gres[3], KyeongEun Lee[1], Stefan G. Sarafianos[3], Jeremy Luban[2]
[1]NCI, Frederick, MD, USA, [2]Univ of Massachusetts, Worcester, MA, USA, [3]Univ of Missouri, Columbia, MO, USA

Background: The choreography of virus infection at the cellular level involves a successive series of host factor interactions to drive the viral replication program. The role of HIV-1 capsid (CA) in the early steps of replication is includes cytoplasmic trafficking, regulation of reverse transcription, interaction with the nuclear pore complex (NPC), and chromatin access during integration. Two host factor interfaces within CA, the CPSF6 and Cyclophilin A (CypA) binding sites, are critical to these steps. The CA binding site for CPSF6 shows selective interaction with protein motifs containing an FG-dipeptide, which is abundant in one-third of nucleoporins. FG-nucleoporins (FG-Nups) maintain the nuclear diffusion barrier and provide docking sites for nuclear transport receptors (NTRs). Notably, Nup153, a makes specific contacts with the same pocket in CA via an FG-containing motif. We sought to understand the respective roles of CPSF6 or CypA binding sites in CA in regulating nuclear entry.
Methods: We performed a small interfering RNA (siRNA) screen targeting all known human nucleoporins to assess effects on Wild-type (WT) versus N74D and P90A HIV-1 infection. N74D and P90A are mutations that respectively impair either CPSF6 or CypA binding to CA. We used commercially available pools of siRNAs in the screening. Host factor specificity was confirmed by restoration of expression with siRNA-resistant isoforms of mRNA. Reverse transcription products were measured via qPCR.

Results: In addition to previously known NPC co-factors, we identify Nup35 and POM121 to aid HIV-1 infection. HIV-1 reliance on Nup35 or POM121 is linked to CA. Nup35 and POM121 are FG-Nups. Preliminary examination indicates that a C-terminal FG-motif of Nup35 is required for HIV-1 infection. Notably, HIV-1 interaction with CypA regulated dependence on the FG-Nups. Disruption of the interaction between CA and CypA either by cyclosporine A (CsA) treatment or CypA knockdown restored WT HIV-1 infectivity in Nup35 knockdown cells.
Conclusion: We hypothesize that CypA use by HIV-1 prevents access to the N74 pocket in CA until the virus docks at the NPC. We propose that the HIV-1 core, comprised of hundreds of CA molecules, directly functions as a NTR and exploits successive FG interactions to achieve nuclear entry. Thus, the development of pharmacological compounds targeting the CPSF6-binding site in CA have the potential to disrupt interactions with multiple co-factors and significantly impair HIV-1 infection.

19 COMPREHENSIVE CRISPR SCREEN IDENTIFIES NOVEL HIV RESTRICTION FACTORS

Molly Ohainle, Louisa Pendergast, Jolien Vermeire, Michael Emerman
Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA

Background: Interferon-Stimulated Genes (ISGs) inhibit HIV replication by inducing an array of antiviral effectors known as HIV restriction factors. Restriction factors, such as TRIM5, APOBEC3s, Tetherin and MxB, have previously been discovered one-by-one through classic techniques such as cDNA library screening and comparison of RNAseq data in permissive versus non-permissive cells. Here we describe a comprehensive novel CRISPR gene knockout screen to identify HIV restriction factors.
Methods: A CRISPR knockout screen was performed for wild type HIV-1 in THP-1 cells, a human monocytic cell line with strong Interferon-induced inhibition of HIV-1 replication. An available whole-genome CRISPR library was modified to allow for packaging of lentiCRISPR genomes in trans into budding HIV-1 particles after infection. Known and novel, candidate restriction factors are identified by measuring the relative enrichment of gRNAs in HIV-1 viruses released from cells (MAGeCK gRNA and gene analyses). Further, we have designed an ISG-specific gRNA CRISPR library targeting ~2000 human ISGs allowing for validation of hits from the whole-genome screen as well as identification of additional restriction factor candidate genes.
Results: Our screen identified known restriction factors, such as MxB, ZAP and ISG15. Potential previously-uncharacterized HIV restriction factors were also identified such as Nedd4-binding protein 1 (N4BP1), a nucleolar protein previously identified as an ISG that participates in PML bodies and is an inhibitor of the ubiquitin ligase ITCH.
Conclusion: We have developed a novel method to uncover HIV restriction factors. Both known and novel HIV restriction factors were identified. Our studies show that a subset of these genes can explain most of the inhibitory effects of interferon on HIV replication in THP-1 cells.

20 A RETROTRANSPOSED ESCRT-III FACTOR BLOCKS HIV-1 BUDDING WITHOUT INDUCING CYTOTOXICITY

Lara Rheinemann, Diane Downhour, Gaelle Mercenne, Alesia McKeown, John McCullough, Wes Sundquist, Nels Elde
Univ of Utah, Salt Lake City, UT, USA

Background: Most enveloped viruses, including HIV-1, exploit the endosomal sorting complexes required for transport (ESCRT) pathway to bud from cells. Owing to its essential functions in membrane fission events such as cytokinetic abscission and closure of the post-mitotic nuclear envelope, the ESCRT machinery is conserved and evolutionarily constrained. These properties pose a challenge for cells in trying to adapt to pathogens that exploit the ESCRT pathway.
Methods: Using phylogenetic analyses, we identified retrotransposed copies of numerous ESCRT factors in primate genomes including a retrogene encoding a truncated version of the ESCRT-III protein CHMP3 (retroCHMP3) in squirrel monkeys. Truncated CHMP3 proteins had previously been shown to block HIV-1 budding, apparently by dominantly inhibiting the ESCRT pathway (Zamborlini et al., 2006). We therefore hypothesized that retroCHMP3 might also inhibit the budding of HIV-1 and other enveloped viruses, and tested this hypothesis by expressing retroCHMP3 in human cells and measuring inhibition of retrovirus budding and infectivity. Evolutionary reconstruction and functional analysis of chimeric proteins showed crucial differences between retroCHMP3 and the parental CHMP3 protein.
Results: We found that both squirrel monkey retroCHMP3 and the analogously truncated endogenous CHMP3 protein potently inhibit budding of HIV-1 and other retroviruses. Importantly, however, retroCHMP3 exhibited much less cellular toxicity than the truncated parental protein. Characterization of chimeric constructs revealed that just seven amino acid changes were largely responsible for retroCHMP3 detoxification. Cytotoxicity correlated with the formation of cytoplasmic CHMP3 punctae, suggesting that the truncated parental CHMP3 protein may block both viral and cellular ESCRT pathways by sequestering essential ESCRT factors into insoluble aggregates, whereas retroCHMP3 has evolved to maintain viral inhibition without sequestering essential ESCRT factors.
Conclusion: Our studies identify retroCHMP3 proteins as broad-spectrum inhibitors of enveloped virus budding in New World monkeys. Moreover, retroCHMP3 has retained the ability to inhibit viral budding while apparently evolving to lose cellular cytotoxicity, revealing unexpected separation of cellular and viral ESCRT functions. More generally, our work illustrates how retrotransposition can create opportunities for cells to evolve new antiviral activities and counteract pathogen exploitation of essential host pathways.

21 DESIGNED PROTEINS INDUCE THE FORMATION OF NANOCAGE-CONTAINING EXTRACELLULAR VESICLES

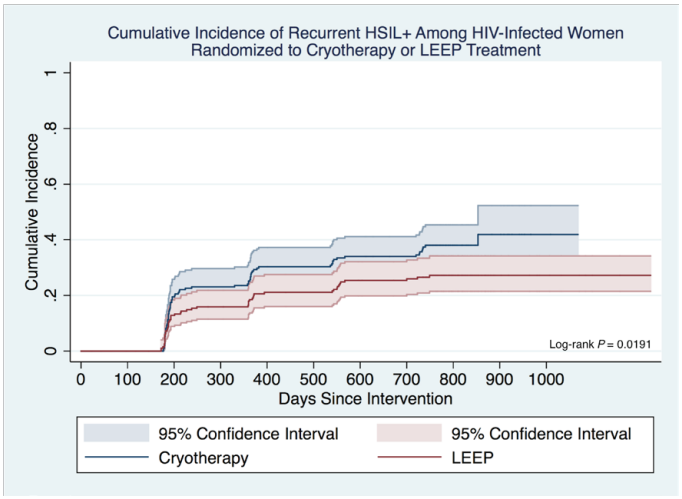
Joerg Votteler[1], Cassie Ogohara[2], Sue Yi[2], Yang Hsia[2], Una Nattermann[2], David M Belnap[1], Neil P King[2], Wes Sundquist[1]
[1]*Univ of Utah, Salt Lake City, UT, USA,* [2]*Univ of Washington, Seattle, WA, USA*

Background: The HIV-1 Gag polyprotein contains membrane binding, assembly and budding activities that are required to create extracellular virions that can transfer the viral genome from infected producer cells to new, uninfected target cells. These activities also underlie the efficacy of retroviral vectors, which have been explored extensively as potential therapeutic delivery vehicles. However, safety concerns, immunogenicity and inefficient packaging of non-nucleic acid cargoes limit their potential use. To overcome some of these limitations and to test our understanding of the fundamental principles of virion assembly and release, we have undertaken the design of new proteins that can self-assemble into enveloped protein nanocages (EPNs) and induce their own release from human cells.
Methods: We characterized: 1) cellular release of EPNs using western blot assays of cell culture supernatants, 2) membrane integrity of released EPNs using antibody and protease susceptibility, 3) EPN vesicle architectures using cryo-EM tomography, 4) nanocage structures using high resolution single particle cryo-EM reconstructions, and 5) target cell fusion and enzymatic cargo delivery by VSV-G pseudotyped EPNs using colorimetric assays of packaged β-lactamase-Vpr fusion proteins.
Results: We observed robust EPN assembly and release, which required all three design elements: membrane binding, self-assembly, and ESCRT factor recruitment. The overall strategy was very general and we have identified 16 different combinations of membrane binding, assembly and ESCRT recruiting elements that can produce EPNs. Detailed analyses of one EPN design (termed EPN-01) revealed that the protein nanocages assembled precisely as designed, and were released within membrane vesicles (110 nm average diameter), each of which contained multiple nanocages (14 nanocages/vesicle average). Pseudotyping with VSV-G allowed the EPNs to fuse with new target cells and deliver β-lactamase-Vpr cargoes.
Conclusion: We have used enveloped virus assembly principles to design new proteins that can induce the formation extracellular vesicles and transfer their contents between cells.

22 RANDOMIZED TRIAL OF LEEP VS CRYOTHERAPY TO TREAT CIN2/3 IN HIV-INFECTED WOMEN

Sharon A. Greene[1], Evans Nyongesa-Malava[1], Barbra A. Richardson[1], Grace John-Stewart[1], Hugo De Vuyst[2], Nelly Yatich[1], Catherine Kiptinness[1], Sameh Sakr[3], Nelly Mugo[4], Michael H. Chung[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Intl Agency for Rsr on Cancer, Lyon, France, [3]Coptic Hosp, Nairobi, Kenya, [4]KEMRI, Nairobi, Kenya

Background: Cervical screening and treatment using visual inspection with acetic acid (VIA) and cryotherapy (screen-and-treat) is often implemented in resource-limited settings with high HIV-1 endemicity; however, cryotherapy may be less effective than loop electrosurgical excisional procedure (LEEP) among HIV-infected women. We randomized 400 HIV-infected women to cryotherapy or LEEP and examined the recurrence of cervical disease over a 2-year follow-up.
Methods: From June 2011 to July 2014, HIV-infected women enrolled at the Coptic Hope Center for Infectious Diseases in Nairobi, Kenya underwent cervical screening with Pap smear and confirmatory biopsy. Four hundred women with cervical intraepithelial neoplasia (CIN)2/3 or carcinoma in situ (CIS) disease were randomized 1:1 to receive cryotherapy or LEEP, and were followed every 6 months with a Pap smear for 2 years. Recurrence was defined as high grade squamous intraepithelial lesions (HSIL) or greater on cytology, and outcomes were compared between arms using Chi-square tests and Cox proportional hazards regression.
Results: Sociodemographic and biological factors were balanced between arms. Median age was 37 years [interquartile range (IQR): 31-43], most women were on ART (89%) at the time of intervention, and median CD4 was 380 cells/µl (IQR: 215-524). Among women randomized to cryotherapy: 71 (35.5%) had CIN2 at baseline, 107 (53.5%) CIN3, 11 (5.5%) CIS, and 11 (5.5%) no dysplasia/CIN1. In the LEEP arm: 59 women (29.5%) had CIN2, 116 (58%) CIN3, 10 (5%) CIS, and 15 (7.5%) no dysplasia/CIN1. Median follow-up was 2.1 years in both arms and 341 (85%) women completed all 4 follow-up visits. At 12-months, more women treated with cryotherapy experienced recurrent HSIL than those who underwent LEEP (27% vs 18%; P=0.031). At 24 months, HSIL increased in both arms and remained significantly higher in the cryotherapy arm (37% vs 26%; P=0.018). Overall, the rate of recurrence of HSIL+ was 21.1 per 100 woman-years after cryotherapy and 14.0 per 100 woman-years after LEEP. Women treated with cryotherapy were 52% more likely to experience recurrence (hazard ratio (HR): 1.52, 95% confidence interval [CI]: 1.07-2.17; P=0.020) compared to LEEP.
Conclusion: Treatment with cryotherapy was associated with significantly higher risk of recurrent pre-cancerous cervical disease among HIV-infected women compared to LEEP. In high HIV-burden settings, a screen-and-treat approach coupled with HIV testing and referral for LEEP may be more effective than cryotherapy alone.



23 NATURAL HISTORY OF CERVICAL INTRAEPITHELIAL NEOPLASIA-2 AMONG HIV-INFECTED WOMEN

Christine Colie[1], L. Stewart Massad[2], Cuiwei Wang[1], **Kate Michel**[1], Gysamber D'Souza[3], Joel Palefsky[4], Howard Minkoff[5], Howard D. Strickler[6], Seble Kassaye[1]
[1]Georgetown Univ, Washington, DC, USA, [2]Washington Univ, St. Louis, MO, USA, [3]The Johns Hopkins Univ, Baltimore, MD, USA, [4]Univ of California San Francisco, San Francisco, CA, USA, [5]Maimonides Med Cntr, Brooklyn, NY, USA, [6]Albert Einstein Coll of Med, Bronx, NY, USA

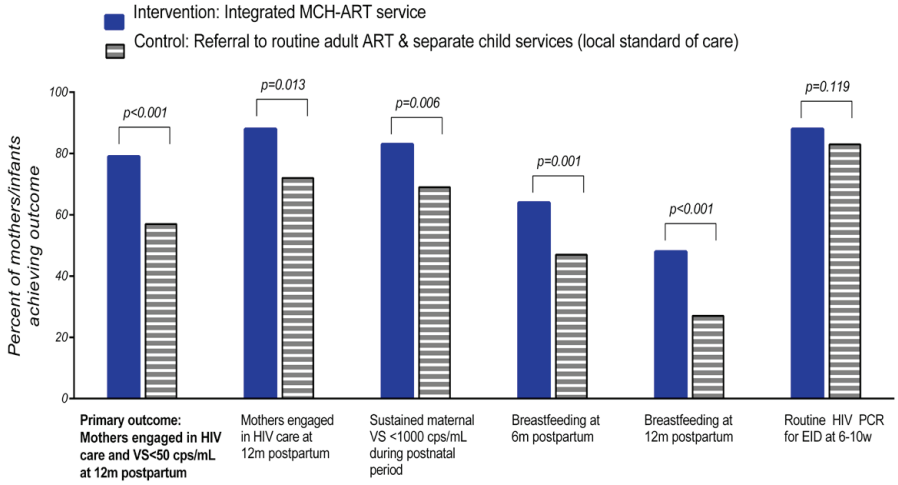
Background: Therapy for cervical intraepithelial neoplasia-2 (CIN2), a potential precursor of invasive cervical cancer, can include resection of affected tissue which can prevent progression but result in cervical incompetence and complications during pregnancy. We sought to characterize the natural history of CIN2 among HIV-positive women of childbearing age.
Methods: 126 biopsy-confirmed CIN2-diagnosed women under age 46 (109 HIV-positive and 17 HIV-negative) were included from the multi-site, observational Women's Interagency HIV Study. Kaplan-Meier curves and Cox proportional hazards models were used to assess time to CIN2 progression (CIN3+) with CD4+ T cell and HIV RNA levels analyzed as time dependent covariates (SASv9.3).
Results: CIN2-diagnosed women were primarily Black (56.4%), current smokers (51.6%), with a median age of 32 years and contributed 2,558 semi-annual visits over a median of 10 years. Among 109 HIV-positive women with CIN2, 66 (60.6%) did not receive CIN2 treatment during follow-up. CIN2 treated and untreated HIV-positive women did not differ in median follow-up time, colposcopy findings, age, CD4+ count, HIV RNA level, or combination antiretroviral therapy (cART) use. Only 21% of HIV-positive women showed CIN2 progression within the median 10-year follow-up. Three untreated women progressed to cancer. CIN2 progression rates were not significantly different in HIV-positive women treated versus untreated for CIN2 at 2 years (11.1% vs. 5.2%) or 5 years (14.8% vs. 16.2%) post-CIN2 diagnosis. Propensity weighting did not affect findings. Median time to CIN2 progression was not significantly different between treated and untreated HIV-positive women (5.8 vs. 9.0 years, p=0.14). Use of cART was associated with ~ 80% decrease in CIN2 progression (hazard ratio (aHR) 0.20; 95% CI 0.05, 0.71), adjusting for CIN2 treatment, CD4+ count, and HIV RNA levels. Similarly, each increase of 100 CD4+ T cells was associated with ~ 30% decrease in CIN2 progression (aHR=0.68; 95% CI 0.53, 0.85), adjusting for CIN2 treatment, cART use, and HIV RNA levels.
Conclusion: Progression of CIN2 is uncommon in HIV-positive women, regardless of treatment. For HIV-positive women of childbearing age who are well controlled on cART and considering pregnancy, short-term conservative management of CIN2 with close monitoring may be an alternative to immediate resection. Further studies are planned to determine the role of HPV type on cervical disease progression.

24 INTEGRATION OF POSTNATAL SERVICES IMPROVES MCH AND ART OUTCOMES: A RANDOMISED TRIAL

Landon Myer[1], Tamsin Phillips[1], Allison Zerbe[2], Kirsty Brittain[1], Stanzi M. Le Roux[1], Robert Remien[3], Claude A. Mellins[3], James A. McIntyre[4], Elaine J. Abrams[2], for the Maternal Child Health - Antiretroviral Therapy (MCH-ART) Study
[1]Univ of Cape Town, Cape Town, South Africa, [2]Columbia Univ, New York, NY, USA, [3]New York State Psychiatric Inst, New York, NY, USA, [4]Anova Hlth Inst, Johannesburg, South Africa

Background: There are global concerns about postpartum women's engagement in antiretroviral therapy (ART) services and resulting viral suppression (VS). Integration of ART into the maternal and child health (MCH) platform is routine during prenatal care but postnatal services have received little attention. We evaluated the impact of an integrated MCH-ART service on mother and infant outcomes.
Methods: From Jun 2013-Dec 2014 we enrolled consecutive HIV-infected mother-infant pairs (MIP) immediately postpartum if mothers were 18+ years of age, initiated ART in the recent pregnancy at the local MCH service and were breastfeeding (BF). MIP were randomised to either: (i) postnatal retention in the integrated MCH-ART service for the duration of BF (intervention) or (ii) immediate referral to adult ART services for mothers and separate routine 'well baby' services for infants (control; local standard of care). The primary outcome was a combined endpoint of maternal engagement in HIV care (from medical record review) and VS<50 copies/mL at 12m postpartum (measured separately from routine care).
Results: Overall, 472 women were randomised at a median of 5d postpartum (median age 28y; median pre-ART CD4 354 cells/uL; median duration of prenatal ART 18w; 76% and 94% of women with VS<50 and <1000 copies/mL at randomisation, respectively); characteristics did not differ by trial arm. 87% of MIP completed the study outcome visit at 12m postpartum with no difference in completion by arm. By design women in the intervention arm spent longer in the integrated MCH-ART service (8.7m vs 0.3m in control arm). The median duration of BF was significantly longer in intervention vs control (9.0m vs 3.1m, p<0.001). Among mothers in the control arm referred to adult ART services, 56% met the combined endpoint of engagement in care and VS<50 copies/mL compared to 77% of intervention mothers randomised to stay in the integrated MCH-ART service until the end of BF (absolute risk difference 21%; 95% CI: 12-30%; p<0.001). In secondary analyses the intervention improved sustained VS over time to <50 and <1000 copies/mL (Figure). MTCT by 12m was low (0.55%) and did not differ by arm (p=0.740); other infant outcomes were similar by arm.
Conclusion: Integrated MCH-ART services during the postnatal period lead to significant improvements in women's engagement in HIV care and viral suppression while extending breastfeeding, providing a simple, effective intervention to promote maternal and child health outcomes in the context of HIV.

Figure. Proportion of mother-infant pairs in the intervention and control arms achieving primary and secondary outcomes in the MCH-ART trial



25 ADVERSE BIRTH OUTCOMES DIFFER BY ART REGIMEN FROM CONCEPTION IN BOTSWANA

Rebecca Zash[1], Denise Jacobson[2], Modiegi Diseko[3], Gloria Mayondi[3], Mompati Mmalane[3], Chipo Petlo[4], Max Essex[2], Shahin Lockman[5], Joseph Makhema[3], Roger L. Shapiro[2]
[1]Beth Israel Deaconess Med Cntr, Boston, MA, USA, [2]Harvard Univ, Boston, USA, [3]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [4]Ministry of Hlth, Botswana, Gaborone, Botswana, [5]Brigham and Women's Hosp, Boston, MA, USA

Background: Infants exposed to 3-drug antiretroviral therapy (ART) from conception have increased risk of adverse birth outcomes, but it is not known whether risk differs by ART regimen. We evaluated adverse birth outcomes by exposure to different ART regimens from conception.
Methods: We extracted obstetric records at 8 government hospitals in Botswana. Since 2012, Botswana guidelines have recommended TDF/FTC/EFV for adults with CD4<350 and all pregnant women; those stable on other regimens were not switched. Outcomes included stillbirth (SB), preterm delivery (PTD)(<37 weeks), small for gestational age (SGA) (<10th%), neonatal death (NND)(<28 days), and a combined endpoint of any adverse outcome. For singleton births, the adjusted risk ratio (aRR) of each outcome was determined using log binomial regression to evaluate the effect of HIV and ART exposures, adjusting for maternal age, parity and education.
Results: From August 2014 to August 2016, 47180 infants were born at surveillance maternities, representing ~45% of all births in Botswana. Information was available for 47083 (99.8%): 34615 (74%) infants were HIV-unexposed, 11932 (25%) were HIV-exposed, and 479 (1%) unknown. Among HIV-exposed infants, 6178 (52%) were continuously ART-exposed from the time of conception, 4557 (38%) were ART-exposed starting in pregnancy, 1059 (9%) had no antiretroviral exposure, and 138 (1%) had unknown timing or exposure. Combined adverse birth outcomes were more common among all HIV-exposed infants than HIV-unexposed infants (34% vs. 24%, p<0.001). In adjusted models among singletons ART-exposed from conception, TDF/FTC/EFV was associated with the lowest risk for combined adverse birth outcomes (p<0.001). Compared with TDF/3TC/EFV, all other regimens were associated with higher risk of SGA; ZDV/3TC/NVP was associated with higher risk of SB, PTD and NND; and ZDV/3TC/LPV/r was associated with higher risk of PTD and NND (Table 1). Median CD4 (available for 25% exposed from conception) was 500 cells/mm3 (IQR 385, 683), and did not influence magnitude or direction of combined adverse outcomes when added to the model; nadir CD4 was not available. Time from ART start to conception, and neural tube defects by ART exposure, will be evaluated in future analyses.
Conclusion: Specific ART regimens used in pregnancy may impact adverse birth outcomes. Among infants exposed to ART from conception, TDF/FTC/EFV was associated with the fewest adverse birth outcomes.

Table 1. Adverse Birth Outcomes by HIV and ART Exposure*

		Stillbirth		Preterm Delivery		SGA		Neonatal Death		Any adverse birth outcome	
	N	N (%)	aRR (95% CI)	N (%)	aRR (95% CI)	N (%)	aRR (95% CI)	N (%)	aRR (95% CI)	N (%)	aRR (95% CI)
HIV-unexposed	34,087	709 (2.1%)	*ref*	5257 (16%)	*ref*	3585 (11%)	*ref*	410 (1.2%)	*ref*	8288 (24%)	*ref*
HIV-exposed	11,698	388 (3.3%)	1.3 (1.2,1.5)	2592 (22%)	1.5 (1.4,1.5)	1785 (16%)	1.5 (1.4,1.6)	177 (1.5%)	1.2 (1.0,1.4)	3990 (34%)	1.5 (1.4,1.5)
ART-exposed from conception (by regimen)											
TDF/FTC/EFV	2,477	59 (2.4%)	*ref*	529 (22%)	*ref*	300 (13%)	*ref*	29 (1.2%)	*ref*	766 (31%)	*ref*
TDF/FTC/NVP	761	22 (2.9%)	1.2 (0.7,1.9)	146 (19%)	0.9 (0.8,1.1)	154 (21%)	1.6 (1.4,1.9)	11 (1.3%)	1.4 (0.7,2.7)	276 (36%)	1.2 (1.1,1.3)
ZDV/3TC/NVP	1,372	82 (6.0%)	2.3 (1.6,3.2)	341 (25%)	1.2 (1.0,1.3)	321 (24%)	1.9 (1.6,2.2)	26 (1.9%)	1.8, (1.0,3.1)	576 (42%)	1.4 (1.3,1.5)
TDF/FTC/LPV/r	234	10 (4.3%)	1.8 (0.9,3.5)	55 (24%)	1.11 (0.9,1.4)	54 (25%)	1.8 (1.4,2.4)	3 (1.3%)	1.2 (0.4,4.0)	100 (43%)	1.4 (1.2,1.6)
ZDV/3TC/LPV/r	167	6 (3.6%)	1.5 (0.7,3.5)	49 (30%)	1.4 (1.1,1.8)	32 (20%)	1.5 (1.1,2.1)	5 (3.0%)	2.9 (1.1,7.5)	71 (43%)	1.4 (1.1,1.7)

*Table includes analysis from singleton births only. Total number of singletons exposed to ART from conception = 5651. Unspecified regimens (N=544) and uncommon regimens (N=96) were excluded from table. Uncommon regimens included ZDV/3TC/EFV (N=48), D4T/3TC/NVP (N=7), D4T/3TC/ALU (N=1), ABC/3TC/NVP (N=13), ABC/3TC/LPV/r (N=15), ABC/3TC/EFV (N=12)

26 EFFECT OF POINT-OF-CARE TESTING ON ANTIRETROVIRAL-THERAPY INITIATION RATES IN INFANTS

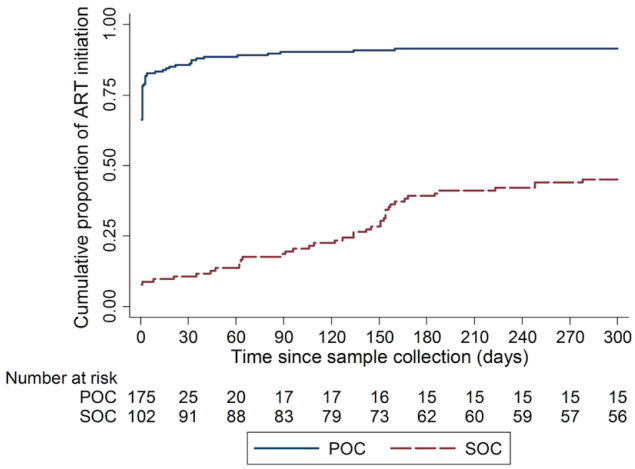
Ilesh Jani[1], Bindiya Meggi[1], Osvaldo Loquiha[2], Ocean Tobaiwa[2], Chishamiso Mudenyanga[2], Dadirayi Mutsaka[2], Nedio Mabunda[1], Adolfo Vubil[1], Lara Vojnov[2], Trevor Peter[2]
[1]Instituto Nacional de Saude, Maputo, Mozambique, [2]Clinton Hlth Access Initiative, Maputo, Mozambique

Background: Globally an estimated 35% of HIV-positive infants are on antiretroviral therapy (ART), while only approximately 50% of HIV-exposed infants under 2 months of age received early infant diagnosis (EID) results in 2015. Novel point-of-care (POC) assays may increase access to EID and positively impact clinical care. We measured the effect of POC EID on ART initiation rates in infants and retention along the cascade of care.

Methods: We conducted a prospective cluster-randomized trial at 16 primary health care clinics (PHC) in Mozambique. Eight intervention PHCs implemented the Alere q HIV-1/2 Detect POC EID test conducted by nurses using whole blood collected from infants at 4-6 weeks of age (POC arm). Eight control PHCs collected dried blood spot specimens for EID testing at standard of care (SOC arm) reference laboratories. The primary outcome was the proportion of infants initiating ART within 60 days of specimen collection. Statistical analyses used a Generalized Estimating Equations model and Kaplan-Meier curves with log-rank test.

Results: Significantly more infants in the POC arm (99.5%) received EID results within 60 days of specimen collection, compared to those in the SOC arm (11.8%; adjusted RR 9.50; p<0.001), with a median (IQR) time between sample collection and results receipt of 0 (0-0) and 122 (74-178) days, respectively. Moreover, 87.4% of infants with a positive result in the POC arm started ART within 60 days of specimen collection, compared to 12.8% of infants in the SOC arm (adjusted RR 7.12; p<0.001), with a median (IQR) time between sample collection and ART initiation of 0 (0-1) and 116 (35-154) days, respectively (Figure 1). A higher proportion of HIV-positive infants were retained at three months post-ART initiation in the POC arm compared to the SOC arm (63.1% versus 45.7%; adjusted RR 1.37; p=0.033).

Conclusion: POC EID significantly improved infant retention between testing and ART initiation and enabled earlier and increased ART initiation compared to laboratory EID testing. Decentralization of EID using POC technologies may accelerate ART initiation in challenging environments and contribute to achieving global pediatric ART targets.



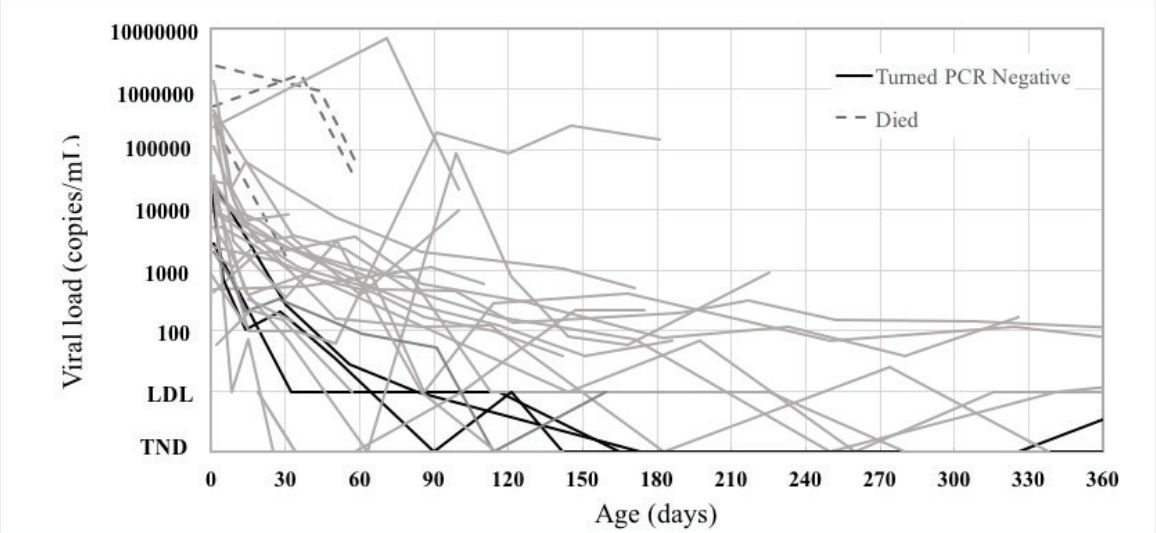
27 TREATMENT OF ACUTE HIV INFECTION IN NEONATES

Louise Kuhn[1], Karl Technau[2], Renate Strehlau[2], Stephanie Shiau[1], Faeezah Patel[2], Gayle G. Sherman[3], Caroline Tiemessen[3], Grace M. Aldrovandi[4], Ashraf Coovadia[2], Elaine J. Abrams[5]
[1]Columbia Univ, New York, NY, USA, [2]Empilweni Service and Rsr Unit, Johannesburg, South Africa, [3]Natl Inst of Communicable Diseases, Johannesburg, South Africa, [4]Univ of California Los Angeles, Los Angeles, CA, USA, [5]ICAP at Columbia Univ, New York, NY, USA

Background: Antiretroviral therapy (ART) initiated soon after primary infection is thought to influence seeding of the viral reservoir with beneficial effects for virologic control. Infants are an important group who can be identified soon after infection. Here we describe virologic dynamics following early ART in infants.

Methods: For the past 2 years, HIV PCR testing has been offered for all HIV-exposed newborns at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa. Standard HIV PCR tests are done at the national laboratory. On weekdays when staff capacity permits, point-of-care HIV PCR tests are concurrently done. All infants with reactive PCR results are actively traced for confirmatory testing and engagement in care. ART is initiated as soon as possible with nevirapine, lamivudine and zidovudine with substitution of lopinavir/ritonavir for nevirapine at 2 weeks or later. HIV RNA is measured in plasma at frequent intervals using Roche AmpliPrep/COBAS TaqMan with a lower detection limit (LDL) of 20 copies/ml and qualitative HIV diagnostic PCR tests are repeated.

Results: To date we have identified 100 HIV-infected infants as part of the birth PCR testing program (~1.5% of HIV-exposed infants tested). Of these, 68 HIV-infected infants have been enrolled into a clinical trial tracking their response to ART. Half of these infants started ART within the first 2 days of life (n=34), 25% started 3-7 days (n=17), 15% 8-15 days (n=10) and 10% 16-104 days (n=7). Three infants died in the first months of life, all of whom had started ART within the first 2 days. To examine viral response, we restricted analysis to infants who started ART 0-15 days and were alive and still in follow-up at 6 months. 11% of treated infants have persistently high HIV RNA levels, 35% have a declining trajectory that has not yet reached LDL, and 54% have declined to LDL or target not detected (TND) of the assay. Of those who achieved suppression by 6 months, 30% have changed to having a negative diagnostic HIV PCR during follow-up. Figure 1 shows the viral dynamics in the first year of life of the 34 infants who started ART 0-2 days.
Conclusion: There is variability in virologic response to early ART among HIV-infected infants identified at birth. Many clinical and social challenges affect engagement in care of this high risk group of infants. Follow-up is on-going and updated data will be provided.



28 RAPID DECLINE OF TOTAL HIV DNA IN CHILDREN STARTING ART WITHIN 8 DAYS OF BIRTH

Kirsten A. Veldsman[1], Jean Maritz[2], Shahieda Isaacs[1], Mary Grace K .Katusiime[1], Heleen la Grange[1], Anita Janse van Rensburg[1], Barbara Laughton[2], John Mellors[3], Mark Cotton[2], Gert U. van Zyl[1]
[1]Stellenbosch Univ, Parow, South Africa, [2]Stellenbosch Univ, Cape Town, South Africa, [3]Univ of Pittsburgh, Pittsburgh, PA, USA

Background: Early infant antiretroviral combination therapy (ART), initiated in the first 2 months of life, reduces HIV-1 infected and transcriptionally active cells (van Zyl, JID 2015). In the case of the Mississippi baby, very early ART, initiated shortly after birth, resulted in delayed viral rebound after therapy interruption, probably due to a very small pool of infected cells. Although there are reports from resource rich settings of undetectable or very low levels of HIV DNA in children who started ART shortly after birth, data from resource limited settings are very limited.
Methods: Eleven children diagnosed (at least 2 positive HIV nucleic acid tests) through a public health sector birth diagnosis program were initiated on ART between 0 and 8 days after birth (median 3 days). Peripheral blood mononuclear cells (PBMCs) and plasma were processed at 3 monthly visits. HIV-1 total DNA was measured with a sensitive quantitative PCR assay (Hong, JCM 2016), adapted for HIV-1 subtype C, targeting a conserved region in HIV-1 integrase (iCAD; limit of detection 3 copies/million cells). Plasma HIV-1 RNA was quantified by Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 v2.
Results: The initial ART regimen consisted of AZT/3TC/NVP, with NVP replaced by LPV/r after 2 weeks of age. Median baseline plasma HIV-1 RNA was 4.0 (range 2.4-4.7) log10 copies/ml. One child had ongoing viremia. All other children achieved plasma HIV-1 RNA <100 copies/ml after a median of 4 months, but two had subsequent single viremic episodes. Four children had no detectable HIV-1 DNA in ≥ 500,000 PBMCs assayed when first sampled at 9 days, 3.8 months, 4.9 months and 8.2 months after starting ART. Stored dried blood spots from before ART initiation were found for 3 of these children: 2 had detectable HIV-1 DNA by iCAD and one child with a low baseline plasma HIV-1 RNA load of 265 copies/mL had undetectable iCAD. In the other 6 children, excluding the child with ongoing viremia, there was progressive decline in HIV-1 DNA with 4 of 6 reaching < 10 copies per million cells within 13 months of ART initiation.
Conclusion: Early ART initiation within a few days of birth can suppress viral replication, limit the initial number of HIV infected cells and result in their subsequent decay to undetectable levels. However, this rapid decay and limited sample amount require more robust HIV-1 molecular diagnostics to detect HIV persistence on ART and to prevent misdiagnosis of HIV infection in uninfected children.

29LB LOPINAVIR/RITONAVIR 1:1 SUPER-BOOSTING OVERCOMES RIFAMPICIN INTERACTIONS IN CHILDREN

Helena Rabie[1], **Paolo Denti**[2], Janice Lee[3], Mhleli Masango[4], Ashraf Coovadia[4], Sandy Pillay[5], Afaaf Liberty[4], Helen Mcilleron[2], Mark Cotton[1], Marc Lallemant[3]
[1]Stellenbosch Univ, Cape Town, South Africa, [2]Univ of Cape Town, Cape Town, South Africa, [3]Drug for Neglected Diseases Initiative, Geneva, Switzerland, [4]Univ of the Witwatersrand, Johannesburg, South Africa, [6]Enhancing Care Foundation, Wentworth Hospital, Durban, South Africa

Background: Lopinavir/ritonavir 4:1 (LPV/r) is important in 1st-line antiretroviral therapy for infants. In high-burden settings, rifampicin based co-treatment for tuberculosis (TB) is often needed, but causes significant drug interactions. Superboosting LPV/r with ritonavir for a 1:1 ratio is considered effective, based on pharmacokinetic (PK) studies in 15 children.
Methods: In an open-label, prospective study at 5 South African sites, we studied super-boosted LPV/r (1:1) during rifampicin co-treatment and LPV/r (4:1) thereafter in children weighing 3-15 kg. PK was studied on 3 occasions in each child with blood drawn at baseline and 1, 2, 4, 6 and 10 h post-dose: PK1 and PK2 after 2 and 5 months of rifampicin co-treatment (LPV/r 1:1); PK3 2-4 weeks after stopping TB therapy (LPV/r 4:1). Population PK modelling was used to interpret the data. PK1 data was used to develop a structural PK model for LPV, which was applied to PK2 and PK3 data to estimate all PK parameters. The uncertainty of PK parameters was obtained through a nonparametric bootstrap (n=500) and used for simulating 10 000 in silico patients, assuming a 30% decrease in clearance overnight to address known diurnal variation. The percentages of model-simulated (M-PK) C0 below 1 mg/L at PK2 and PK3 were compared for non-inferiority using a 10% delta threshold.

Results: Eighty of 96 enrolled children, completed the study (Table 1: clinical data) 31% and 9% of children were <12 months at enrolment and PK 3 respectively. TB therapy was started first in 73% children. A 1-compartment PK model with 1st-order absorption and elimination, with allometric scaling to adjust for weight, best fitted the data. No age effect was identified. The percentage (95% CI) of M-PK C0 levels below target was 7.6% (0.4% to 16.2%) for superboosting during rifampicin co-treatment, versus 8.8% (0.6% to 19.8%) without rifampicin. The median value of their difference 1.1% (95%CI 6.9% to 3.2%), confirmed the non-inferiority of LPV exposure during super-boosting with rifampicin to standard LPV/r without rifampicin. Three deaths were unrelated to study treatments. One case of jaundice and elevated liver enzymes occurred, treatment was interrupted but not considered associated with the medication. No electrocardiograph abnormalities occurred. 82% of children had a VL<="" div="">
Conclusion: Super-boosting is safe and effective for TB/HIV co-treated children.

Table 1: Patient characteristics and clinical data at anrolment and each pharmacokinetic (PK) visit

	At enrolment	PK1	PK2	PK3
Number on study	96	92	82	80
Number uncluded in PK analysis		92	81	80
Median age in months (IQR)	18.2 (9.6-26.8)	19.1 (10.4-27.6)	23.3 (15.2-34.4)	25.0 (16.7-34.3)
Number younger than 12 months (%)	30 (31%)	27 (29%)	15 (18%)	7 (9%)
Female	52 (54%)			
Median weight in kg (IQR)	8.4 (6.7-10.3)	8.8 (7.1-11.1)	9.8 (8.5-12.2)	10.1 (8.9-12.3)
Clinical stage 4	60 (62%)			
CD4 count (x10^6/L) (IQR)	924 (466 - 1,738)		1,337 (1,019 - 1,956)	
Median CD4 percentage (IQR)	19.5 (11.6 – 25.7)		27.3 (20.5 – 32.6)	
Median HIV RNA viral load (log10 copies/mL) (IQR)	5.7 (4.6 - 6.3)		2.1 (<1.6 - 2.3)	
Number with VL<log 2.6	6 (6%)		67 (82%)	

30 HIV INCIDENCE, PREVALENCE, AND UNDIAGNOSED INFECTIONS IN MEN WHO HAVE SEX WITH MEN

Sonia Singh, Ruiguang Song, Anna S. Johnson, Eugene McCray, Irene Hall
CDC, Atlanta, GA, USA

Background: Gay, bisexual, and other men who have sex with men (MSM) represent approximately 2% of the United States population, yet they represent 67% of persons with HIV diagnoses in 2014. There are differences in HIV diagnoses by race/ethnicity and age, but few data are available on incidence and prevalence. We estimated HIV incidence, prevalence and percent of undiagnosed infections among MSM to better guide prevention efforts.
Methods: Data from the National HIV Surveillance System on HIV diagnoses among MSM and the first CD4 test result after diagnosis were used to estimate HIV incidence, prevalence and the percentage of undiagnosed infection by racial/ethnic and age groups for 2008-2014 using a method based on a well-characterized CD4 depletion model.
Results: Estimated annual HIV infections among Hispanic/Latino MSM increased from 6,100 in 2008 (95% confidence interval [CI]: 5,800, 6,500) to 7,200 (95% CI: 6,200, 8,300) in 2014, but decreased among black and white MSM, from 10,100 (95% CI: 9,600, 10,600) to 10,000 (95% CI: 8,800, 11,200) and 8,900 (95% CI: 8,500, 9,300) to 7,400 (95% CI: 6,600, 8,300), respectively. HIV prevalence increased for all racial/ethnic groups from 2008-2014. In 2014, the percentage of undiagnosed infections among black, Hispanic/Latino and white MSM were 20.4% (95% CI: 18.5%, 22.2%), 20.9% (95% CI: 18.6%, 23.1%) and 12.5% (95% CI: 11.0%, 14.0%), respectively. The percentage of undiagnosed infections decreased for all racial/ethnic groups from 2008-2014. Among MSM 13-24 years old, the estimated annual number of HIV infections (9,400 in 2008 to 7,700 in 2014) decreased ($p<0.05$), and prevalence decreased after 2010 (2010, 57,000; 2014, 48,000). Among MSM 25-34 years old, both the estimated annual number of HIV infections (7,100 in 2008 to 9,700 in 2014) and prevalence (84,300 in 2008 to 128,000 in 2014) increased ($p<0.05$). The percentage of undiagnosed infections decreased for MSM 13-24 years old (70.1% in 2008 to 52.0% in 2014) and 25-34 years old (32.3% in 2008 to 30.1% in 2014)($p<0.05$).
Conclusion: Decreases in HIV infections among black, white, and young (13-24 year old) MSM are encouraging, but there was an increase in HIV incidence among Hispanic/Latino MSM and MSM 25-34 years old from 2008-2014. Though there were decreases in undiagnosed HIV infections for all race/ethnic groups, expansion of HIV testing and treatment, particularly among Hispanic/Latino and MSM 13-24 and 25-34 years old, are needed to achieve the goals of the National HIV/AIDS Strategy.

31 VIRAL-LOAD DYNAMICS AMONG PERSONS WITH DIAGNOSED HIV: UNITED STATES, 2014

Nicole Crepaz[1], Tian Tang[2], Gary Marks[1], Irene Hall[1]
[1]CDC, Atlanta, GA, USA, [2]ICF Intl, Atlanta, GA, USA

Background: The most common measure of viral suppression (VS) in clinical and surveillance studies is the most recent viral load (VL) < 200 copies/mL in past 12 months. This single-value measure does not capture the VL dynamics over time. We examined durable VS, never virally suppressed, and change in VS status to offer new types of metrics that help us better understand VS patterns.
Methods: We used data from the National HIV Surveillance System reported from 33 jurisdictions among persons aged ≥ 13 years with HIV infection diagnosed by year-end 2013 and alive at year-end 2014. We calculated the percentage of HIV-diagnosed persons whose last VL was <200 copies/mL in 2014 and the percentage of HIV-diagnosed persons who had durable VS (all VLs < 200 copies/mL) in 2014. Among persons who had at least 2 VLs in 2014 (indication of being in HIV care), we calculated the percentage of persons never virally suppressed (all VLs > 200 copies/mL) and created 4 groups based on the first and last VLs in 2014: both suppressed, first unsuppressed and last suppressed (improved), first suppressed and last unsuppressed (worsen), and both unsuppressed.
Results: Of 630,965 persons with diagnosed HIV, 361,665 (57.3%) had the last VL suppressed and 316,442 (50.2%) had durable VS in 2014 (relative difference: 14.3%). Among 339,515 persons in HIV care, 28,782 (8.5%) persons never had suppressed VLs in 2014. The breakdown of change in VS status indicates that 75.4% had first and last VL suppressed, 10.5% improved, 4.2% worsened, and 9.9% had first and last unsuppressed. The percent "never suppressed" was higher among females than males (11.1% vs. 7.7%). Among race/ethnic groups, blacks/African Americans had the highest percentage of persons in HIV care never virally suppressed (see Table). This racial/ethnic disparity was observed in men who have sex with men (MSM), injection drug use (IDU) for both sexes, MSM/IDU, heterosexual contact for both sexes, and other transmission category.
Conclusion: Using single VL measures overestimated by 14.3% relative difference of HIV-diagnosed persons with durable VS. Half of HIV-diagnosed persons had durable VS in 2014. Among patients in HIV care, more showed improving than worsening VS status, yet 8.5% never had a suppressed VL within a 12-month period and racial/ethnic disparities were observed in this outcome. Targeted clinical interventions are needed to help patients achieve and maintain durable VS.

Number and percentage of never virally suppressed persons aged ≥ 13 years with HIV infection diagnosed through 2013 and alive through 2014 and had at least two VL tests in 2014, 33 U.S. areas

	All	Black/ African American	Hispanic/ Latino	White	Other Races
Transmission category					
Men who have sex with men (MSM)	6.7% (11435/170999)	11.8% (5603/47350)	5.9% (2319/39003)	3.7% (2737/73236)	6.8% (776/11410)
Injection drug use (IDU) - Male	9.8% (1959/19922)	11.4% (1048/9161)	9.2% (524/5681)	6.9% (269/3895)	10.0% (118/1185)
Injection drug use (IDU) - Female	12.5% (1663/13300)	14% (893/6394)	12.0% (351/2918)	9.9% (295/2974)	12.2% (124/1014)
MSM/IDU	10.3% (2033/19820)	13.7% (769/5623)	10.1% (421/4175)	7.7% (638/8295)	11.9% (205/1727)
Heterosexual contact – Male	9.7% (1628/16826)	11.7% (1143/9769)	7.3% (281/3842)	4.8% (101/2119)	9.4% (103/1096)
Heterosexual contact - Female	10.5% (4255/40478)	12.3% (2888/23483)	8.2% (702/8575)	6.8% (397/5855)	10.4% (268/2565)
Other	10.0% (5809/58170)	12.2% (4057/33228)	8.0% (964/12054)	4.9% (469/9596)	9.7% (319/3292)
Total	8.5% (28782/339515)	12.1% (16401/135008)	7.3% (5562/76248)	4.6% (4906/105970)	8.6% (1913/22289)

32 TIME SPENT WITH HIV VIRAL LOAD >1500 COPIES/ML AMONG PATIENTS IN HIV CARE, 2000-2014

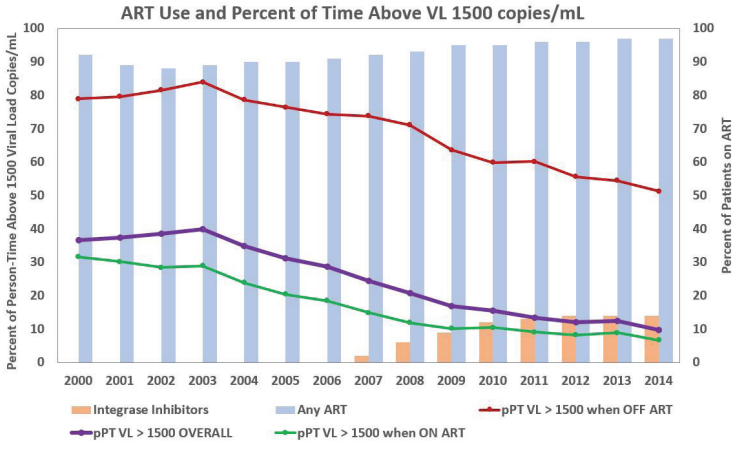
Kate Buchacz[1], Maria Mendoza[1], Carl Armon[2], Frank J. Palella[3], Charles Rose[1], Ellen Tedaldi[4], Richard Novak[5], Lytt Gardner[1], for the HIV Outpatient Study
[1]CDC, Atlanta, GA, USA, [2]Cerner Corp, Kansas City, MO, USA, [3]Northwestern Univ, Chicago, IL, USA, [4]Temple Univ, Philadelphia, PA, USA, [5]Univ of Illinois, Chicago, IL, USA

Background: Sexual HIV transmission is more likely to occur when HIV viral load (VL) exceeds 1,500 copies/mL. We assessed percentage of person-time spent with VL above 1500 copies/mL (pPT>1500) for adult patients in HIV care.

Methods: We analyzed data from medical records of the HIV Outpatient Study (HOPS) cohort participants seen at nine United States (US) HIV clinics during 2000-2014. Included patients had ≥1 HOPS clinic visit and ≥2 VLs during 2000-2014. We assessed pPT>1500 by analyzing values and time intervals between consecutive VL pairs per published methods (AIDS 2015, 29:947–954) and incorporating ART prescription data. Generalized estimating equations assuming a Poisson model and robust variance estimator were used to test for trend, and estimate the pPT>1500 and the corresponding 95% confidence intervals (CI) for patients in clinical and demographic strata.

Results: The 5,873 patients contributed 37,794 person years [py], 86% on ART, with a median 15 VLs (interquartile range: 7-27) per patient. Overall pPT>1500 was 24% (CI: 23-25), decreasing from 37% in 2000 to 10% in 2014, P for trend <0.001. More patients used ART, including integrase inhibitors, over time (Figure). During the time when ART was prescribed, pPT>1500 was 16% overall, decreasing from 32% in 2000 to 7% in 2014, P for trend <0.001. pPT>1500 was higher in patients <35 vs. ≥50 years old (31% vs. 16%), women vs. men (31% vs. 22%), black vs. white and Latino/Hispanic patients (33% vs. 20% and 24%, respectively), and in patients who started observation (baseline) with public insurance vs. private (31% vs. 21%), CD4 cell counts <500 cells/mm^3, and VLs>1500 copies/mL. In adjusted regression analyses, the significant correlates of pPT>1500 included time-updated "no ART (off ART) status" (Relative Risk [RR] 3.5, CI: 3.3-3.7), and baseline characteristics: VL>1500 (RR 2.3, CI: 2.1-2.4), age <35 years (RR 1.5, CI: 1.4-1.6) and 35-49 years (RR 1.3, CI: 1.2-1.5) vs. ≥50 years, having public insurance (RR 1.2, CI: 1.2-1.3) vs. private, and being non-Hispanic black (RR 1.2, CI: 1.1-1.3) vs. white.

Conclusion: Adult US patients in routine HIV care spent substantially less time with VLs over 1500 copies/mL from 2000 to 2014, a period characterized by the shift toward universal ART initiation and continuous improvements in ART regimens. The observed trends imply a decreasing risk of HIV transmission from persons in HIV care over the last decade and the need to focus interventions on subsets of patients more consistently viremic.

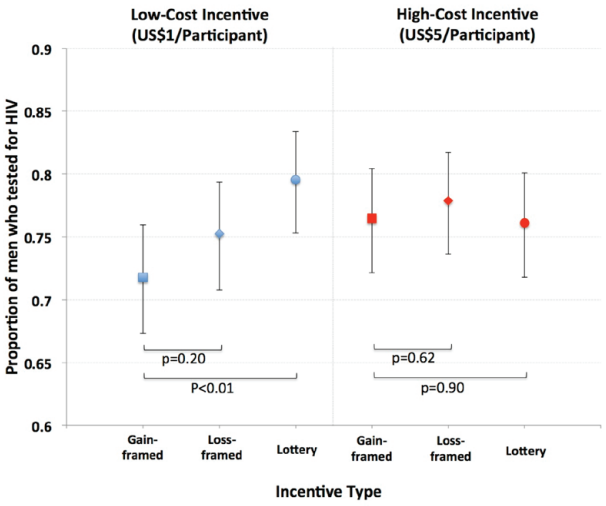


33 A RANDOMIZED TRIAL OF NOVEL STRATEGIES TO INCENTIVIZE HIV TESTING AMONG MEN IN UGANDA

Gabriel Chamie[1], Elisabeth Schaffer[2], Alex Ndyabakira[3], Devy Emperador[1], Dalsone Kwarisiima[4], Diane V. Havlir[1], James Kahn[1], Moses R. Kamya[5], Harsha Thirumurthy[2]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]Makerere Univ and Univ of California San Francisco Rsr Collab, Mbarara, Uganda, [4]Makerere Univ Joint AIDS Prog, Kampala, Uganda, [5]Makerere Univ Coll of Hlth Scis, Kampala, Uganda

Background: Despite expansion of HIV testing services in sub-Saharan Africa, men test for HIV at lower rates than women. Standard, gain-framed incentives have been shown to increase HIV testing uptake, but the comparative effectiveness of novel incentive strategies informed by behavioral economics is unknown.

Methods: From April-June 2016 we enumerated 4 rural Ugandan parishes and enrolled men aged ≥18 years. Participants were randomized to 6 groups that received incentives of varying type and amount for HIV testing at a 13-day community health campaign (CHC) in June-July 2016 (NCT02890459). Incentive types were (1) gain-framed incentives (control) in which participants were told they would receive a small prize if they came for HIV testing; (2) loss-framed incentives in which participants were told they had won a small prize, shown the prize, and told they would lose the prize if they did not come for HIV testing; or (3) lotteries in which those who came for HIV testing had a chance to instantly win large prizes. Each incentive type had a low and high amount with a program cost per participant of about US$1 and US$5, respectively. The primary outcome was HIV testing uptake at the CHC.



Results: Overall, 2,530 participants were enrolled: 1,929 (76%) tested for HIV and prevalence among those tested was 7.6%. HIV testing uptake ranged from 72% in the low-cost, gain-framed incentive group to 80% in the low-cost, lottery incentive group. Although HIV testing uptake was higher in the two lottery groups (78%; p=0.08) and the two loss-framed groups (77%; p=0.22) than in the two gain-framed groups (74%), these differences were not statistically significant. Across incentive types, there was no significant difference in testing uptake in high- vs. low-cost (76% vs. 75%; p=0.41) groups. However, among participants in the low-cost groups, testing uptake was significantly higher in the lottery than the gain-framed incentive group (80% vs. 72%; p<0.01), but not in the loss- vs. gain-framed groups (76% vs. 72%; p=0.20). Among participants in the high-cost groups, HIV testing uptake in the lottery (76%) and loss-framed (78%) groups were not significantly different than in the gain-framed incentive group (76%).

Conclusion: Low-cost, lottery-based incentives were significantly more effective in increasing HIV testing uptake among men than standard gain-framed incentives of comparable cost. Offering lottery-based rewards that have a low per-person cost is a promising way to achieve high HIV testing coverage among men.

34LB COMBINATION HIV PREVENTION AND HIV INCIDENCE IN RAKAI, UGANDA

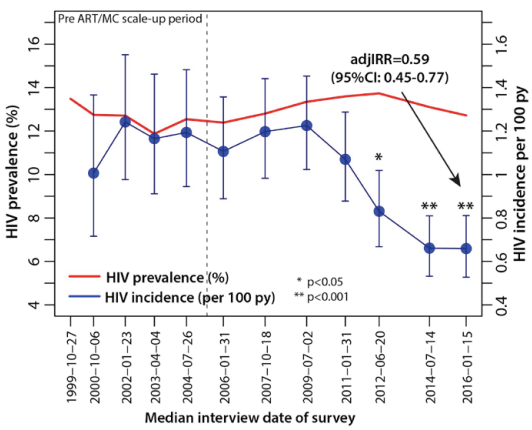
Mary K. Grabowski[1], Gertrude Nakigozi[2], Fred Nalugoda[2], Thomas Quinn[1], Godfrey Kigozi[2], Ronald H. Gray[1], David Serwadda[3], Maria Wawer[1], Steven J. Reynolds[4], Larry W. Chang[1]
[1]Johns Hopkins Univ, Baltimore, MD, USA, [2]Rakai Health Sciences Prog, Kalisizo, Uganda, [3]Makerere Univ, Kampala, Uganda, [4]NIAID, Washington, DC, USA

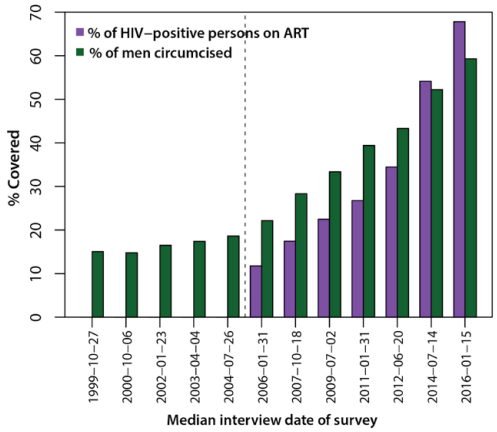
Background: To assess the impact of combination HIV prevention (CHP) on HIV incidence, we measured long-term trends in HIV incidence based on observed seroconversion data in a prospective population-based cohort in Rakai, Uganda, and evaluated their associations with antiretroviral therapy use (ART), male circumcision (MC) scale-up, population-level viral load suppression, and sexual behaviors.

Methods: Between 1999 and 2016, data were collected in 12 surveys from 30 communities in the Rakai Community Cohort Study (RCCS), an open population-based longitudinal cohort of persons aged 15-49. Poisson regression was used to assess trends in HIV incidence, self-reported ART/MC coverage, population-level HIV viral load suppression (proportion of HIV-positive population with <1000 copies/ml), and sexual behaviors. Poisson multivariate regression with generalized estimating equations and robust variance estimators was used to estimate incidence rate ratios (IRR) and 95%CI of HIV incidence at each survey interval following the availability of ART/MC compared to the period prior to ART/MC scale-up.

Results: Over the analysis period, 33,937 individuals participated in the RCCS, including 17,870 HIV-negative persons who contributed 94,427 person-years of follow-up and 931 incident HIV cases. ART was introduced in 2004 and by 2016 coverage was 69%. Increasing ART coverage was accompanied by significant changes in HIV viral load suppression rising from 42% in 2009 to 75% by 2016 among all HIV-positive persons (p<0.001). MC coverage increased from 15% in 1999 to 59% by 2016 (p<0.001). The only substantive changes in sexual behaviors occurred among persons 15-19 years reporting never having sex, which rose from 30% to 55% over the study period (p<0.001). Beginning in 2012, HIV incidence significantly declined as population-level coverage of CHP interventions were increased (Figure 1); by 2016 there was a 41% reduction in HIV incidence relative to the pre-ART/MC scale-up period from 1.17/100 py to 0.66/100 py (IRR: 0.56; 95%CI: 0.44-0.72; p<0.001; adjIRR:0.59: 95%CI: 0.45-0.77).

Conclusion: In this large prospective population-based study, HIV incidence significantly declined as ART and MC were scaled and sexual activity in young persons declined. These results provide empiric evidence that HIV control efforts utilizing combination interventions can have a substantial population-level impact





35 NAMIBIA PILOTS SENTINEL POPULATION SURVEILLANCE OF HIV INCIDENCE AND VIRAL SUPRESSION

Tuli Nakanyala[1], Andrew D. Maher[2], Nicholus Mutenda[1], Karen M. Banda[2], Anna Jonas[3], Charity Ntema[4], Ndapewa Hamunime[1], David W. Lowrance[5], Sadhna V. Patel[5], Willi McFarland[2]

[1]Ministry of Hlth and Social Services, Windhoek, Namibia, [2]Univ of California San Francisco, San Francisco, CA, USA, [3]US CDC, Windhoek, Namibia, [4]Development Aid from People to People, Windhoek, Namibia, [5]CDC, Atlanta, GA, USA

Background: Direct measures of HIV incidence and viral suppression (VS) are needed to assess population-level impact of prevention and treatment programs, particularly in an era of scaling-up efficacious interventions such as test and treat, male circumcision, and PrEP. However, gold standard longitudinal studies are scarce due to logistical complexity. We demonstrate the feasibility of using a community-based testing program to obtain sentinel, longitudinal estimates of HIV incidence and VS.

Methods: Lay health workers (LHW) of a community based organization (Total Control of the Epidemic) working in high HIV prevalence regions of Namibia are assigned fields of ~375 households to provide home-based HIV testing and case management for clients who test positive. To this program, we added risk and prevention questions, collection of dried blood spots (DBS) and targeted one-year follow-up among adults (age > 14 years) in clusters of ~70 houses within 10 fields in Namibia's Zambezi region. Fields included urban and rural areas and major cultural-linguistic groups. HIV incidence among baseline-negative adults was measured by repeat rapid testing. VS (< 1,000 copies/uL) among baseline-positive adults was measured in DBS using Abbot's m2000 Realtime system.

Results: From 12/2014-7/2015 in 1,004 households, we enrolled 2,218 adults (66.3% participation), among whom 1,339 (60.4%) were female, 815 (36.7%) age 15-24 years, 476 (21.5%) HIV positive (63.9% previously diagnosed) and 1,742 HIV negative. The effort entailed approximately two LHW per field. One year later [median (IQR) 431 (391-476) days follow-up], we performed repeat measurements among 93.2% and 88.9% of baseline-negative and positive adults, respectively. Cohort retention was significantly lower among men and baseline-positive adults. We observed 26 seroconversions in 1,970 person years (py) for a cluster-adjusted HIV incidence of 1.32 /100 py (95% CI 0.90-1.94). Cluster-adjusted VS at follow-up was 70.5% (95% CI: 61.5-79.5) among baseline-positive adults.

Conclusion: We field tested an efficient method to obtain gold standard population-level measures of HIV incidence and VS in Namibia's highest prevalence region. Differences in enrollment and retention suggest some biases to our approach. Nonetheless, the method, which utilizes existing community-based programs common to high prevalence areas of sub-Saharan Africa, can establish a system of sentinel cohorts that track changes in HIV incidence, VS and the impact of national responses to HIV.

36 SOCIAL NETWORKS AND HIV PREVALENCE IN KENYA IN THE SEARCH STUDY

Wenjing Zheng[1], Norton Sang[2], Gabriel Chamie[3], Laura B. Balzer[4], Craig Cohen[3], Tamara D. Clark[3], Edwin D. Charlebois[3], Moses R. Kamya[5], Diane V. Havlir[3], Maya L. Petersen[1]

[1]Univ of California Berkeley, Berkeley, CA, USA, [2]Kenya Med Rsr Inst, Nairobi, Kenya, [3]Univ of California San Francisco, San Francisco, CA, USA, [4]Harvard Univ, Boston, MA, USA, [5]Makerere Univ Coll of Hlth Scis, Kampala, Uganda

Background: Social network information is more accessible than sexual network information, and may capture HIV transmission risk. Social networks may also reveal the formation of peer relationships between HIV+ individuals, which are important for treatment support. To investigate the potential for social networks to capture these dynamics, we linked named social contacts to population-wide baseline HIV testing data from Kenyan communities in the intervention arm of the SEARCH HIV Test and Treat Study (NCT01864603).

Methods: During a census enumeration, 15,028 adult (age ≥15) residents of 3 communities named up to 6 friends in each of five social domains (health, money, emotional, food, and free time); 85% of residents were tested for HIV. Named contacts outside the household were matched to enumerated residents to construct community-wide social networks (Figure). Targeted maximum likelihood was used to estimate the relative risk of HIV associated with exposure to an HIV+ cross-gender or same-gender contact, adjusting for demographics, circumcision, alcohol use, contraception, mental health, work productivity, mobility and household wealth. Confidence intervals were adjusted for multiple comparisons across social domains.

Results: HIV prevalence was 16%; 12% in all men, 19.5% in all women; 1% in young (<25) men, and 9.8% in young women. Men with an HIV+ female contact in any domain were at increased risk of HIV (aRR:1.5; 95%CI:1.1,2.0). Women with an HIV+ male contact in any domain (aRR:1.4; 95%CI:1.1,1.8) or in the emotional domain (aRR:1.8; 95%CI:1.2,2.7) were at increased risk of HIV. Women's increased risk was amplified if the HIV+ male contact was >10 years older (aRR:1.6; 95%CI:1.1,2.5). Among young women, higher risk was associated with having an older HIV+ man in the free time (aRR:7.9; 95%CI:3.2,19.4), food (aRR:4.1; 95%CI:1.4,11.7), health (aRR:3.5; 95%CI:1.2,10.1), or any domain (aRR:3.4; 95%CI:1.6,7.1). Women with an HIV+ female contact in the health domain (aRR:1.6; 95%CI:1.2,2.1) were also more likely to be HIV+.

Conclusion: In this cross-sectional analysis of social network predictors of HIV risk in rural Kenya, exposure to HIV+ contacts within easily assessed social networks significantly predicted HIV risk and supported both known sexual transmission dynamics, such as those between young women and older men, and HIV+ peer relationships. These data may be useful for designing prevention and treatment support interventions for at risk populations.

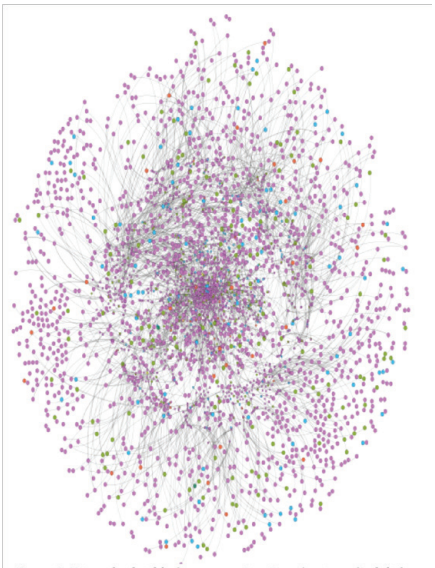


Figure 1: Network of stable (in community >6 mo/past year) adult (age >=15) residents across 3 communities in Kenya. Yellow: baseline HIV+ young (15-24) men, Red=HIV+ young women; Blue: HIV+ older adult (>=25) men; Green=HIV+ older adult women; Purple= baseline HIV-

37 HIGH RATE OF DISEASE PROGRESSION IN UNTREATED HIV-2 INFECTION

Joakim Esbjörnsson[1], Fredrik Månsson[2], Anders Kvist[3], Zacarias J. da Silva[4], Jacob Lindman[3], Angelica Palm[3], Marianne Jansson[3], Patrik Medstrand[3], Hans Norrgren[3], for the SWEGUB CORE Group

[1]Univ of Oxford, Oxford, UK, [2]Lund Univ, Malmö, Sweden, [3]Lund Univ, Lund, Sweden, [4]LNSP, Bissau, Guinea-Bissau

Background: Compared with HIV-1, HIV-2 is considered to be more benign and without severe pathogenic consequences throughout the disease course for the majority of infected individuals. However, conclusive survival data from cohorts with long follow-up and estimated time of infection is lacking.

Methods: We followed 312 participants infected with HIV-1 or HIV-2 after enrollment in a cohort from Guinea-Bissau with 23 years of follow-up, according to the time from infection to AIDS or HIV-related mortality, and measures of T-cell dynamics. Weibull distributions were fitted to the survival data to assess the hypothesis of heterogeneous disease courses among HIV-2 infected individuals.

Results: The median times to AIDS and mortality were 14.3 years (confidence interval [CI], 10.7-18.0) and 15.6 years (CI, 12.0-19.2) for HIV-2 infected participants, and 6.2 years (CI, 5.4-7.1) and 8.2 years (CI, 7.6-8.8) for HIV-1 infected individuals ($p<0.001$ for both comparisons, Log rank test). The Weibull analysis showed that HIV-2 infected individuals followed a uniform disease trajectory similar to HIV-1 infected individuals, but at a 53% lower acceleration rate. The proportion of HIV-2 infected individuals under risk at the end of follow-up was 17.5%, further supporting that the majority of HIV-2 infected individuals will progress to AIDS and HIV-related mortality if followed long enough. Linear mixed model analyses of T-cell dynamics showed both higher levels of CD4+ T-cell counts early after infection ($p<0.001$, Likelihood Ratio Test [LRT]) and slower decline rates among

HIV-2 compared with HIV-1 infected individuals (p=0.028, LRT). Finally, CD4+ T-cell levels at clinical AIDS was higher in HIV-2 compared with HIV-1 infected individuals (18.2% vs. 8.2%, p<0.001, 2-tailed Mann-Whitney U Test).
Conclusion: Our results contradicts the common assumption that the majority of HIV-2 infected individuals remain long-term-non-progressors and suggest that, similar to HIV-1 infection, HIV-2 infection will result in disease development if followed long enough. This suggests that early treatment initiation would be beneficial also for HIV-2 infected individuals.

38 DISCOVERY OF NOVEL POTENT HIV CAPSID INHIBITORS WITH LONG-ACTING POTENTIAL

Winston C. Tse, John O. Link, Andrew Mulato, Anita Niedziela-Majka, William Rowe, John R. Somoza, Armando G. Villasenor, Stephen R. Yant, Jennifer R. Zhang, Jim Zheng
Gilead Scis, Inc, Foster City, CA, USA

Background: While HIV capsid (CA) plays an essential role in multiple stages of the viral life cycle, it remains an unexplored target for antiretroviral (ARV) therapy. Here, we report the discovery of a novel class of exquisitely potent and metabolically stable HIV capsid inhibitors (CAIs) that exhibit pharmacokinetic (PK) profiles suitable for slow-release parenteral administration.
Methods: In vitro CA binding and assembly assays, together with X-ray co-crystal structures of CAIs with cross-linked CA hexamers, were used to optimize compounds for high binding affinity to CA. Medicinal chemistry approaches were employed to optimize the antiretroviral activity and drug-like properties using a cytopathic antiviral assay in conjunction with extensive metabolism and pharmacokinetic profiling. CAI resistance-associated mutations were identified by in vitro resistance selections. CAI mode-of-action was defined by inhibitor time-of-addition, virion electron microscopy and viral DNA quantification.
Results: GS-CA1, an exemplified member of a novel class of CAIs, is a highly potent inhibitor of HIV-1 replication in T cell lines (EC_{50} = 0.24 nM) and displays similar potency against multiple HIV-1 clinical isolates from all major clades in human PBMCs. Identified CAIs bind to a broadly conserved site at the interface of two adjacent monomers within a CA hexamer and accelerate CA assembly in vitro. The identified CAIs maintain full activity against HIV-1 mutants resistant to licensed ARVs and select for HIV CA variants L56I, M66I, Q67H or N74D with an attenuated in vitro replication phenotype. Mechanistic studies revealed a dual mode of action targeting both the late-stage virion maturation and post-entry CA functions. GS-CA1 shows high in vitro metabolic stability and favorable PK profiles in multiple preclinical species with low systemic drug clearances (0.08–0.33 L/hr/kg) and long half-lives (7.2–18.7 hr). Low aqueous solubility provides for an extended-release preclinical PK profile following subcutaneous administration of a solid depot formulation.
Conclusion: We have identified novel HIV-1 capsid inhibitors with uniquely potent antiviral activity and a favorable resistance profile orthogonal to existing ARVs. The high metabolic stability and low aqueous solubility of this new inhibitor class should enable the development of an extended-release parenteral formulation with the potential to be used as a novel long-acting antiretroviral treatment.

39 HUMAN CONFIRMATION OF ORAL DOSE REDUCTION POTENTIAL OF NANOPARTICLE ARV FORMULATIONS

Andrew Owen[1], Steve Rannard[1], Akil Jackson[2], Laura Dickinson[1], Marco Giardiello[1], Marco Siccardi[1], Paul Domanico[3], Melynda Watkins[3], Yao Cheng[4], Marta Boffito[5]
[1]Univ of Liverpool, Liverpool, UK, [2]Chelsea and Westminster Hosp, London, UK, [3]Clinton Hlth Access Initiative, Boston, MA, USA, [4]Med Patent Pool, Geneva, Switzerland, [5]Chelsea and Westminster NHS Fndn Trust, London, UK

Background: Emulsion-templated spray drying to form solid drug nanoparticle (SDN) formulations of efavirenz (EFV) and lopinavir (LPV) previously showed preclinical potential for dose reduction while maintaining pharmacokinetics (PK). This study sought to confirm this in healthy volunteers after single dose and at steady state.
Methods: Healthy volunteers (n=4) were consented and screened before receiving 50mg NANO-EFV OD over 21 days. A 72-hour PK profile was generated after the first dose, followed by steady-state PK profile after the final dose with 228-hour plasma decay. Single plasma concentration measurements were also made on days 7, 14, and 17. Safety (including physical examination with vital signs, ECG, urinalysis, laboratory testing) occurred at screening, day 1, 2, 14, 21 and at completion. Five volunteers were consented and screened before receiving 200mg NANO-LPV (boosted with 100mg Norvir) BID over 7 days. A 12-hour PK profile was generated after the first dose, followed by steady-state PK after the final dose with 56-hour decay. A single plasma concentration measurement was also made on day 3. Safety assessments occurred at screening, day 1 (pre morning and afternoon dose and 4 hours post afternoon dose), day 7, and at completion. PK was analysed through population-PK models, with the resulting models used to simulate (n=1000) bioequivalence with previously published clinical data.
Results: Both nanoformulations proved to be well tolerated at the studied doses, with no grade 3-4 adverse events. For NANO-EFV, simulations predicted 300mg OD would provide bioequivalence to 600mg OD Sustiva for AUC_{0-24}, C_{max}, C_{12}, but not C_{24} (see table). Importantly, bioequivalence was missed at C_{24} because concentrations were predicted to be higher than those for Sustiva. Similar simulations were made for 200mg NANO-EFV versus 400mg of the conventional formulation. For NANO-LPV, simulations predicted 200mg BID (with 100mg Norvir) would provide bioequivalence to BID Kaletra for AUC_{0-12}, C_{max}, and C_{12}.
Conclusion: These data confirm the potential for a 50% dose reduction while maintaining therapeutic exposure, using a novel approach to formation of SDNs. If confirmed in larger future studies, the approach has the potential for savings up to 243 million USD per year while also freeing up manufacturing capacity up to 930 tons per year.

	Geometric mean		Geometric Mean Ratio
EFAVIRENZ	**NANO-EFV 300 mg**	**Sustiva 600 mg**	**GMR (90% CI)***
AUC_{0-24} (mg.h/L)	51.56	58.61	0.88 (0.86-0.90)
C_{12} (mg/L)	2.03	2.51	0.81 (0.78-0.83)
C_{24} (mg/L)	1.90	1.44	1.32 (1.26-1.37)
C_{max} (mg/L)	2.99	3.36	0.89 (0.87-0.91)
LOPINAVIR	**NANO-LPV 200 mg#**	**Kaletra 400 mg**	**GMR (90% CI)***
C_{12} (mg/L)	4.16	4.02	1.04 (0.99-1.08)
AUC_{0-12} (mg.h/L)	72.35	79.07	0.92 (0.89-0.94)
C_{max} (mg/L)	10.69	9.97	1.07 (1.05-1.10)

*Nanoformulation as reference, #boosted with 100mg Norvir

40 CLINICAL PHARMACOLOGY OF THE HIV INTEGRASE STRAND TRANSFER INHIBITOR BICTEGRAVIR

Heather Zhang, **Joseph M. Custodio**, Xuelian Wei, Hui Wang, Amanda Vu, John Ling, Hal Martin, Erin Quirk, Brian P. Kearney
Gilead Sci, Foster city, CA

Background: Bictegravir (BIC) is an investigational, once-daily, unboosted HIV integrase strand transfer inhibitor (INSTI) with potent in vitro activity against most INSTI-resistant variants. BIC is currently in development as a single tablet regimen (STR) coformulated with FTC/TAF for treatment of HIV-1 infection in adults and adolescents. Clinical pharmacology assessments of the PK, ADME and DDI potential were performed.
Methods: A single- (SD) and multiple-dose (MD) randomized, double-blind, placebo-controlled (6 active; 2 placebo/cohort) of staggered dose-escalation evaluated SD BIC 5, 25, 50, 100, 300 or 600 mg; or once-daily MD 5, 25, 50, 100 or 300 mg for 14 days (fasted) in healthy volunteers. An ADME/ mass balance study included 8 healthy male subjects dosed with a SD 100 mg plus 100 µCi [14C]-labeled BIC. Blood, urine and feces samples were analyzed for total radioactivity and pooled plasma and excreta samples were radio-profiled. An open-label, six cohort (n=15/cohort), fixed sequence and cross-over study assessed the DDI liability of BIC as a victim through utilization of CYP3A4, UGT1A1, and/or P-gp inhibitors and inducers. Safety was assessed throughout each study.
Results: BIC exposure was dose proportional following SD of 25-100mg. Accumulation at steady-state was approximately 1.6x, consistent with the observed half-life of approximately 18 hours. Following a SD of [14C]-labeled BIC, the total recovery of radioactivity was 95% ± 1.5%, with 60% ± 5.5% from feces and 35% ± 5.0% from urine. Balanced glucuronidation and oxidation contributed to the major clearance pathways of BIC. The DDI study (Table 1) showed increased BIC AUC (61-74%) by CYP3A4 inhibitors voriconazole and DRV/COBI, but showed a greater increase (~4x) by potent dual inhibitors of UGT1A1 and CYP3A4, ATV and ATV+COBI. Coadministration of BIC with a potent CYP3A4/UGT1A1/P gp inducer, rifampin resulted in a 75% decrease of BIC AUC; in contrast, a lesser reduction (38%) was associated with the moderate CYP3A4/P gp inducer, rifabutin. Overall, BIC was well tolerated at all doses studied. No deaths, SAEs, or Grade 3 or 4 AEs were reported. The safety profile for BIC did not differ with increasing doses of SD or MD.
Conclusion: The favorable BIC PK profile supports once daily dosing. The DDI results of BIC are consistent with its ADME profile, in which both CYP3A4 and UGT1A1contributed to BIC elimination. BIC was safe and well tolerated in healthy volunteers.

Table 1. Effects of Concomitant Medications on BIC PK in Healthy Volunteers

BIC Coadministered Drug(s) and Dose(s)	Dose (s) of BIC	Geometric Mean Ratio % (90% CI) of BIC PK with/without Coadministered Drugs (n=15 for each cohort)		
		C_{max}	AUC	C_{tau}
ATV (400 mg) QD	BIC (75mg) SD fed	128 (123, 134)	415 (381, 451)	NA
ATV (300 mg) + COBI (150 mg) QD	BIC (75mg) SD fed	131 (123, 140)	406 (376, 438)	NA
Voriconazole (300 mg) BID	BIC (75mg) SD fasted	109 (96.1,123)	161 (141,184)	NA
DRV/COBI (800/150 mg) QD [c]	BIC (75mg) MD fed	152 (140, 164)	174 (162, 187)	211 (195, 229)
Rifabutin (300 mg) QD [c]	BIC (75mg) MD fasted	80.4 (66.9, 96.5)	62.0 (53.1, 72.5)	44.0 (37.1, 52.1)
Rifampin (600 mg) QD	BIC (75mg) SD fed	72.2 (67.1, 77.8)	24.5 (22.0, 27.3)	NA

41 RANDOMIZED TRIAL OF BICTEGRAVIR OR DOLUTEGRAVIR WITH FTC/TAF FOR INITIAL HIV THERAPY

Paul E. Sax[1], Edwin DeJesus[2], Gordon Crofoot[3], Douglas Ward[4], Paul Benson[5], Xuelian Wei[6], Kirsten L. White[6], Hal Martin[6], Andrew Cheng[6], Erin Quirk[6]
[1]Brigham and Women's Hosp, Boston, MA, USA, [2]Orlando Immunol Cntr, Orlando, FL, USA, [3]The Crofoot Rsr Cntr, Houston, TX, USA, [4]Dupont Circle Physicians Group, Washington, DC, USA, [5]Be Well Med Cntr, Berkley, MI, USA, [6]Gilead Scis, Inc, Foster City, CA, USA

Background: Because of their potency and safety, integrase strand transfer inhibitors (INSTIs) are widely recommended initial HIV-1 treatments in most major treatment guidelines. Bictegravir (BIC, GS-9883) is a novel, unboosted, once-daily INSTI that demonstrated potent activity in a 10-day monotherapy study and has in vitro activity against most INSTI-resistant viruses.
Methods: Treatment naïve, HIV-infected adults were randomized 2:1 to receive blinded treatment once daily with BIC 75 mg or dolutegravir (DTG) 50 mg; both were given with open label emtricitabine 200 mg/tenofovir alafenamide 25 mg (FTC/TAF). Treatments were administered without regard for food for 48 weeks. The primary endpoint was the proportion with HIV RNA <50 copies/mL (c/mL) at Week (W) 24 using snapshot analysis. Noninferiority was assessed through 95% confidence intervals (CI) at W24 and W48. Safety (adverse events [AEs] and laboratory results through Week 48) was a secondary endpoint.
Results: Of 98 patients enrolled, 65 were randomized to BIC+FTC/TAF and 33 to DTG+FTC/TAF. Most subjects were male, had asymptomatic HIV infection, with median HIV-1 RNA 4.4-4.5 log10; baseline characteristics were balanced between arms. Virologic success (HIV-1 RNA <50 c/mL) at W24 was 97% for the BIC arm and 94% for the DTG arm, and at W48 was 97% and 91%, respectively (Table). One subject in the DTG arm had HIV-1 RNA >50 c/mL at W48. No viral resistance was detected in the BIC+FTC/TAF arm. Mean CD4 count increases at W48 were 258 cells/µL in the BIC arm and 192 cells/µL in the DTG arm. There were no treatment-related serious adverse events and no deaths. The most commonly reported adverse events were diarrhea (12% in each arm) and nausea (8% BIC, 12% DTG). One subject in the BIC arm discontinued due to an adverse event of urticaria following the W24 visit. Median changes in estimated glomerular filtration by Cockcroft-Gault (GFRCG) at W48 were -7.0 mL/min for BIC and -11.3 mL/min for DTG, with no discontinuations due to renal adverse events.
Conclusion: Bictegravir+FTC/TAF and DTG+FTC/TAF both demonstrated high virologic response rates at W24 that were maintained at W48. No treatment-emergent resistance was detected in the BIC+FTC/TAF arm through W48. Both treatments were well tolerated, and no significant safety signal was detected in either arm. Estimated GFRCG changes were consistent with known inhibition of tubular creatinine transport by BIC and DTG. Further evaluation of BIC for the treatment of HIV infection is warranted.

	Week 24[a]		Week 48[b]	
N (%)	BIC + FTC/TAF (n=65)	DTG + FTC/TAF (n=33)	BIC + FTC/TAF (n=65)	DTG + FTC/TAF (n=33)
HIV-1 RNA < 50 copies/mL	63 (96.9)	31 (93.9)	63 (96.9)	30 (90.9)
HIV-1 RNA > 50 copies/mL	2 (3.1)	2 (6.1)	1 (1.5)	2 (6.1)
HIV-1 RNA ≥ 50 copies/mL	1 (1.5)	1 (3.0)	0	1 (3.0)
Discontinued due to lack of efficacy	0	0	0	0
Discontinued due to other reason and last HIV-1 RNA ≥ 50 copies/mL	1 (1.5)	1 (3.0)	1 (1.5)	1 (3.0)
No virologic data in window	0	0	1 (1.5)	1 (3.0)
Discontinued due to AE/death	0	0	1 (1.5)	0
Discontinued due to other reason and last HIV-1 RNA < 50 copies/mL	0	0	0	1 (3.0)
Missing data in window but on drug	0	0	0	0

a Difference in percentages (BIC+FTC/TAF vs DTG+FTC/TAF) at Week 24: 2.9% (-8.5% to 14.2%); p=0.50
b Difference in percentages (BIC+FTC/TAF vs DTG+FTC/TAF) at Week 48: 6.4% (-6.0% to 18.8%); p=0.17

42 PATHWAYS OF RESISTANCE IN SUBJECTS FAILING DOLUTEGRAVIR MONOTHERAPY

José L. Blanco[1], Celia Oldenbuettel[2], Réjean Thomas[3], Josep Mallolas[1], Eva Wolf[4], Bluma Brenner[5], Christoph D. Spinner[6], Mark A. Wainberg[5], Esteban Martinez[1], for the Redo Group
[1]Hosp Clinic Barcelona, Barcelona, Spain, [2]MVZ Karlsplatz, HIV Rsr and Clinical Care Cntr, München, Germany, [3]Clinique Médicale l'Actuel, Montreal, QC, Canada, [4]MUC Rsr, Munich, Germany, [5]McGill Univ, Montreal, QC, Canada, [6]Univ Hosp Klinikum Rechts der Isar, Munich, Germany

Background: Dolutegravir (DTG) is a second generation InSTI that has shown in both preclinical and clinical studies to have a higher barrier to resistance than first generation InSTIs (RAL and EVG).To date, no InSTI resistance-associated mutations (RAMs) have been reported in ART-naïve persons receiving DTG through 144 weeks of follow-up in clinical trials and very few cases has been reported in INSTI-naïve subjects among pretreated individuals. Our objective was to identify and characterize different pathways of resistance in subjects failing a DTG-monotherapy (DTG-M) in four large clinical cohorts

Methods: This is an international, multi-cohort, retrospective study. All subjects with no prior InSTI virological failure (InSTI-VF) failing DTG-M were included in this analysis. Virological failure (VF) was defined as two plasma viral loads (VL) above 50 cp/mL. Genotypic resistance mutations could be detected by: (i) plasma population sequencing (PS); (ii) plasma ultra-deep sequencing test (UDS); peripheral blood mononuclear cell population sequencing (PBMC-PS); and PBMC-UDS

Results: Three large clinical cohorts in Munich, Montreal and Barcelona were included in this analysis. A total of 178 ART-experienced subjects with no prior InSTI-VF changed from different ART-regimens to DTG monotherapy (DTG-M). Eleven (6.1%) had VF and 7 (3.9%) selected any InSTI-RAMs . Two of 7 were women, median (range) of previous VF 1 (0-8; 3: 0VF; 1:1VF; 3≥4). InSTI prior DTG was: 3 none, 3 RAL and 1 EGV. VL by the time of starting DTG-M was: 5= below the lower limits of detection (LLOD), 1=249 cp/mL and 1=21 cp/mL. Reasons for switch to DTG-M were: simplification (n=2), DDI (n=3), patient decision (n=3), toxicity (n=1), VF (n=1); 5 patients had at least one LLOD before VF. Median (range) time and first VL by the time of VF were 12 weeks (0-28) and 306 copies/mL (55-26180), respectively. Time to first detection of DTG-RAMs was 28 weeks (2-32). The three different pathways by the time of VF were: 148R/H in 3 patients, 155H in 2, and 118R in 2

Conclusion: Virological failure and selection of InSTI-RAMs are uncommon but they may exist in patients with no prior InSTI virological failure subjects on DTG-monotherapy. Different pathways, similar to first-generation InSTIs (RAL and EVG), 148R/H, 155H, and 118R were identified in these cases

43 PREVALENCE AND IMPACT OF PRETREATMENT DRUG RESISTANCE IN THE ANRS 12249 TASP TRIAL

Anne Derache[1], Collins C. Iwuji[2], Siva Danaviah[1], Anne-Geneviève Marcelin[3], Vincent Calvez[3], Tulio de Oliveira[4], François Dabis[5], Deenan Pillay[1], for the ANRS 12249 Treatment as Prevention Trial
[1]Africa Hlth Rsr Inst, Mtubatuba, South Africa, [2]Univ Coll London, London, UK, [3]Pitie-Salpetriere Hosp, Paris, France, [4]Univ of KwaZulu-Natal, Durban, South Africa, [5]Univ de Bordeaux, Bordeaux, France

Background: Increasing use of antiretroviral therapy (ART) in Test and Treat strategies may lead to higher levels of acquired and transmitted drug resistance (DR) and compromise ART efficacy for individual or population benefits. We assessed prevalence of pre-treatment DR (PDR) and impact on viral suppression (VS) [viral load (VL)<400 copies/mL] among ART naïve participants who initiated 1st-line ART within the ANRS 12249 cluster-randomized trial.

Methods: DR testing was done on samples from 1340 participants who were recently infected (RIn) during the trial or chronically infected (CIn) at entry (March 2012–June 2016). Pol gene Sanger sequencing was done on dried blood spots from 195 RIn participants who had not linked to HIV care. Full HIV genome sequencing using the MiSeq platform was done on plasma samples from 77 RIn and 1069 CIn participants who linked to care, of whom 838 initiated ART. Minority variants were called at a 2% level (Geneious and MiCall softwares). Cox regression was used to estimate hazard ratios (HR) for VS.

Results: Overall PDR prevalence was 8,4% (95%CI=6,7-10%) and 17,8% (95%CI=15,1-20,5%) at 20% and 2% detection levels respectively; these proportions were similar between RIn and CIn participants. Among participants with PDR, 88% had only 1 or 2 DR mutations, associated with NNRTI resistance in 73% of the cases, and 61% were detected as a majority variant (>20%). 13,5% and 8,8% were associated with NRTI and PI resistance, respectively, with 90% of them being minority variants (<20%) for both NRTI and PI. Among RIn participants with PDR, 92% were associated with a single ARV class (mostly NNRTI). Among 838 adults initiating ART, median follow-up time on ART was 16 months (m); median time to VS was 3m (IQR 2.8-3.9). Cumulative VS at 12m was 97%. After adjusting for sex, age, baseline VL and adherence, there was no evidence that PDR was associated with VS (adjusted (a)HR 0.96, 95%CI 0.75-1.23 and aHR=1.12, 95%CI 0.89-1.42, for majority and minority variants, respectively, vs no mutations). High baseline VL (>100,000 vs <10,000) was associated with a decreased rate of VS (aHR 0.75; 0.62-0.91) and good adherence (≥95% vs <95%) was associated with an increased rate of VS (aHR 1.36; 1.11-1.66).

Conclusion: The prevalence of PDR approached 10% at >20% representation among RIn and CIn participants, while deep sequencing identified double the prevalence. Longer term follow up is needed to assess the lack of virological impact of PDR.

44LB PHASE III SWORD 1&2: SWITCH TO DTG+RPV MAINTAINS VIROLOGIC SUPPRESSION THROUGH 48 WKS

Josep M. Llibre[1], Chien-Ching Hung[2], Cynthia Brinson[3], Francesco Castelli[4], Pierre-Marie Girard[5], Lesley Kahl[6], Elizabeth Blair[7], Brian Wynn[8], Kati Vandermeulen[9], Michael Aboud[7]
[1]Univ Hosp Germans Trias, Badalona, Barcelona, Spain, [2]Natl Taiwan Univ Hosp, Taipei, Taiwan, [3]Central Texas Clinical Rsr, Austin, TX, USA, [4]ASST Spedali Civili di Brescia, Brescia, Italy, [5]Saint-Antoine Hosp, Paris, France, [6]ViiV Hlthcare, Brentford, Middlesex, UK, [7]ViiV Hlthcare, Rsr Triangle Park, NC, USA, [8]ViiV Hlthcare, Collegeville, PA, USA, [9]Janssen, Beerse, Belgium

Background: The requirement for life-long antiretroviral therapy (ART) of HIV infection has highlighted interest in 2-drug regimens (2DR) to minimize cumulative drug exposure. Dolutegravir's (DTG) potency, safety and resistance barrier make it an optimal core agent for 2DR. Rilpivirine's (RPV) safety, tolerability and efficacy in switch regimens make it an ideal potential partner.

Methods: Two identical open-label, multicenter, global, phase III, non-inferiority studies evaluated the efficacy and safety of switching from a 3 or 4-drug current antiretroviral regimen (CAR) to DTG+RPV once daily in HIV-1-infected adults, with HIV-1 RNA<50c/mL (VL<50c/mL) for at least 12 months and no history of virologic failure. Participants (pts) were randomized 1:1 (stratified by baseline 3rd agent class; age.

Results: 1024 pts were randomized and exposed (DTG+RPV 513; CAR 511), across both studies. Switching to DTG+RPV was non-inferior to continuing CAR at Wk48 for VL<50c/mL in pooled analysis of both the ITTe population [95% vs. 95%; difference: -0.4% (95% CI: -3.1%, 2.3%)] and the per-protocol population [96% vs. 96%; difference: 0.7% (95% CI: -3.3%, 1.8%)]. Efficacy results for SWORD-1 (VL<50c/mL in ITTe [95% vs. 96%; difference: -0.6% (95% CI: -4.3%, 3.0%)]) and SWORD-2 (VL<50c/mL in ITTe [94% vs. 95%; difference: -0.2% (95% CI: -4.2%, 3.8%)]) were comparable. Low rates of snapshot virologic failures (VFs) at Wk48 were observed for both studies (Table 1). One pt on DTG+RPV with protocol defined VF had an NNRTI RAM (K101K/E); no pts had any INI RAMs. More adverse events (AEs) were reported and led to discontinuation in the DTG+RPV arm; no unexpected AEs were identified for either drug.
Conclusion: A switch to a novel, once daily 2DR of DTG+RPV demonstrated high efficacy and was non-inferior to the continuation of CAR in virologically suppressed HIV-1-infected adults. The safety profiles of both DTG and RPV were consistent with the respective labels. A DTG+RPV 2DR offers the potential for reduction in cumulative ART exposure, without an increased risk of virologic failure.

Table 1. Pooled SWORD-1 and SWORD-2 Efficacy and Key Safety Results for the ITTe Population

n (%)	DTG + RPV (N= 513)	CAR (N=511)
Snapshot HIV-1 RNA <50 c/mL at W48		
Virologic Success	486 (95%)	486 (95%)
Adjusted Diff (95% CI) [1]	-0.4% (-3.1%, 2.3%)	
Virologic Failure	3 (<1%)	6 (1%)
No Virologic Data	24 (5%)	19 (4%)
Disc. due to AE or Death	17 (3%)	3 (<1%)
Disc. for Other Reasons	7 (1%)	16 (3%)
Key Safety		
AEs leading to withdrawal	21 (4%)	3 (<1%)
Drug-related Grade 2-4 AEs	29 (6%)	3 (<1%)
Serious Adverse Events[2]	27 (5%)	21 (4%)

[1] Difference: (DTG + RPV) - CAR. Cochran-Mantel-Haenszel analysis adjusted for: age group and baseline third agent
[2] Drug-related SAEs DTG+RPV: 4; CAR: 1

45LB DORAVIRINE IS NON-INFERIOR TO DARUNAVIR/R IN PHASE 3 TREATMENT-NAÏVE TRIAL AT WEEK 48

Jean-Michel Molina[1], **Kathleen Squires**[2], Paul E. Sax[3], Pedro Cahn[4], Johan Lombaard[5], Edwin DeJesus[6], Xia Xu[7], Bach-Yen T. Nguyen[7], George Hanna[7], Carey Hwang[7]
[1]Hôpital St Louis, Paris, France, [2]Thomas Jefferson University, Philadelphia, PA, USA, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, [4]Fundación Huesped, Buenos Aires, Argentina, [5]Josha Research, Bloemfontein, South Africa, [6]Orlando Immunology Center, Orlando, FL, USA, [7]Merck & Co., Inc., Kenilworth, NJ, USA

Background: Doravirine (DOR) is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) with once-daily dosing and potent in vitro activity against the most common NNRTI resistant variants (K103N, Y181C, G190A). In a phase 2b study, DOR 100 mg once daily (QD) demonstrated similar efficacy to efavirenz, with favorable safety and tolerability through Week 48.
Methods: DRIVE-FORWARD is an ongoing, phase 3, multicenter, double-blind, non-inferiority trial in antiretroviral treatment-naïve adults with HIV-1 infection and pre-treatment HIV-1 RNA ≥1,000 c/mL. Participants were stratified by screening HIV-1 RNA (≤ or >100,000 c/mL) and investigator-selected NRTI backbone therapy (TDF/FTC or ABC/3TC) and randomized in a 1:1 ratio to receive DOR 100 mg QD or darunavir 800 mg with ritonavir 100 mg (DRV/r) QD, in combination with the selected NRTI, for up to 96 weeks. The primary endpoint was the proportion (%) of participants achieving HIV-1 RNA <50 c/mL at Week 48 (NC=F, FDA Snapshot approach) with predefined non-inferiority margin of 10%. A secondary objective was to evaluate the effects of DOR and DRV/r on fasting serum lipids.
Results: Of 769 participants randomized, 766 (383 in each group) received study drug and were included in the efficacy and safety analyses (mean age 35.2 years, 84% male, 73% white, 87% on TDF/FTC). DOR was non-inferior to DRV/r on the primary endpoint, with 83.8% (321/383) and 79.9% (306/383), respectively, achieving HIV-1 RNA <50 c/mL at Week 48 (difference 3.9%, 95% CI [-1.6, 9.4]). In the subgroup with baseline HIV-1 RNA >100,000 c/mL, 81.0% (64/79) on DOR and 76.4% (55/72) on DRV/r achieved HIV-1 RNA <50 c/mL at Week 48 (OF approach). Adverse event rates (overall, serious, drug-related, and leading to treatment discontinuation) were similar across treatment groups (see table). The most common drug-related AEs (>5% in one or more treatment groups) were diarrhea (5.5%, 12.8%), nausea (6.5%, 7.6%), and headache (6.0%, 2.6%) for DOR and DRV/r, respectively. Fasting LDL-C and non-HDL-C were reduced by DOR and increased by DRV/r (see table) with statistically significant treatment differences (p<0.0001).
Conclusion: At Week 48, DOR demonstrated potent efficacy and was non-inferior to DRV/r on a background of 2 NRTIs in HIV-1 treatment-naïve adults. Efficacy was similar regardless of baseline HIV-1 RNA. DOR was generally safe and well-tolerated with a superior lipid profile for fasting LDL-C and non-HDL-C compared to DRV/r.

Week 48 Efficacy and Safety Outcomes

Endpoint	DOR† (N=383)		DRV/r† (N=383)		Treatment Difference
HIV-1 RNA <50 copies/mL	**N**	**%**	**N**	**%**	**DOR – DRV/r (95% CI)**
Overall‡	383	83.8	383	79.9	3.9 (-1.6, 9.4)
BL HIV-1 RNA ≤100,000§	285	90.2	282	88.7	1.5 (-3.7, 6.8)
BL HIV-1 RNA >100,000§	79	81.0	72	76.4	3.0 (-11.2, 17.1)
BL HIV-1 RNA ≤500,000§	347	88.5	342	87.4	0.9 (-4.0, 5.9)
BL HIV-1 RNA >500,000§	17	82.4	12	50.0	30.9 (-4.1, 65.9)
NRTI = TDF/FTC§	316	88.0	312	86.5	1.3 (-3.9, 6.5)
NRTI = ABC/3TC§	48	89.6	43	83.7	5.9 (-9.1, 20.9)
BL CD4 ≤200 cells/mm3§	41	82.9	61	72.1	9.4 (-7.4, 26.2)
Adverse Event (AE) Summary	**% of Subjects**		**% of Subjects**		**DOR – DRV/r (95% CI)**
One or more AE	80.2		78.3		1.8 (-3.9, 7.6)
Drug-related AE	30.5		32.1		-1.6 (-8.1, 5.0)
Serious AE	5.0		6.0		-1.0 (-4.4, 2.3)
Discontinued due to AE	1.6		3.1		-1.6 (-4.0, 0.6)
Fasting Lipids, Change from BL	**N**	**Mean Δ**	**N**	**Mean Δ**	**DOR – DRV/r (95% CI)**
LDL cholesterol (mg/dL)	326	-4.5	318	+9.9	-14.6 (-18.2, -11.1)
Non-HDL cholesterol (mg/dL)	329	-5.3	325	+13.8	-19.3 (-23.3, -15.4)

†With TDF/FTC or ABC/3TC.
‡Non-completer=Failure (NC=F) approach, as defined by FDA Snapshot method; 95% CI for treatment difference based on stratum-adjusted Mantel-Haenszel method. Non-inferiority bound pre-specified as -10 percentage points.
§Observed Failure (OF) approach to missing data.

46 VISUALIZING PERSISTENT HIV IN CLINICAL SAMPLES

Daniel E. Kaufmann, *Univ of Montreal, Montreal, QC, Canada*

HIV cure efforts are hampered by limited characterization of the cells supporting HIV replication *in vivo* and inadequate methods for quantifying the latent viral reservoir in individuals receiving antiretroviral therapy (ART). To overcome these limitations we developed a highly specific and sensitive flow-FISH (fluorescence in situ hybridization) assay that allows for the simultaneous detection of HIV-1 transcription and translation (HIV-1 RNA+/Gag+ CD4 T cells), in conjunction with phenotypic markers in peripheral blood. The HIV RNA/Gag method is 1,000-fold more sensitive than Gag protein staining alone, with a detection limit of 0.5-1 gag-pol mRNA+/Gag protein+ infected cells per million CD4 T cells. We will present how we used this technique to quantify CD4 T cells maintaining both the ongoing infection in untreated individuals and the inducible reservoir in ART-suppressed subjects. We will illustrate the power of this technology by single-cell phenotypic analyses of translation-competent reservoirs in primary blood samples. To exemplify potential applications for HIV cure research, we will present data on latently infected cells capable of producing HIV mRNA and protein after stimulation with PMA/ionomycin and latency reversing agents (LRAs). We will show qualitative differences in the patterns of reactivation obtained by specific LRAs. We will outline some recent developments of this technology that can be applied to a broad array of research questions.

47 CHARACTERIZING HIV EXPRESSION IN VIVO

Mary F. Kearney, *NCI, NIH, Frederick, MD, USA*

HIV proviruses persist in vivo in latent and transcriptionally active forms. Little is known regarding the fraction of infected cells in blood and in tissues that are quiescent versus those that actively express HIV RNA in either ART treated or untreated individuals, although it is known that the majority of proviruses are defective for viral replication due to deletion or hypermutation. It is thought that cells expressing HIV, defective or not, are susceptible to cell killing by cytopathic effects or immune responses. It stands to reason, therefore, that long-lived latently-infected cells may accumulate over the course of HIV infection and persist after ART is initiated. Indeed, many studies have demonstrated the persistence of latently-infected cells during ART and, it is believed that such cells, when activated, are the source of viral rebound when ART is interrupted. However, it has been reported that HIV-expressing cells in lymph nodes may be protected from the cytotoxic T-cell immune response, and therefore, may persist during ART despite HIV expression and, therefore, may be the primary source of viral rebound when treatment is stopped. It was also recently discovered that HIV infected T-cells can persist in vivo through cellular proliferation, which occurs both prior to and during ART. In one case thus far, a highly expanded infected CD4+ T cell clone was shown to be the source of persistent infectious viremia during ART, demonstrating that at least some members within clones can express HIV RNA and produce virus particles. This talk will summarize emerging data from studies investigating the fraction of HIV infected cells that express HIV RNA in blood and tissues both prior to and during ART and the fraction of HIV expressing cells within cell clones, including those carrying replication-competent proviruses. Understanding the fractions of viral RNA expressing cells and levels of HIV RNA expressed by them during ART will lead to a better understanding of the HIV reservoir, the nature of latency, and the sources of rebound viremia when ART is interrupted.

48 IMMUNE-BASED INTERVENTIONS TARGETING INFLAMMATION AND VIRAL PERSISTENCE

Mirko Paiardini, *Emory Univ Sch of Med, Atlanta, GA, USA*

Antiretroviral therapy (ART) suppresses viral replication in HIV-infected individuals, but does not eliminate an extremely durable reservoir of latently infected cells that is established early after infection. Consequently, discontinuation of ART typically leads to rapid rebound of plasma viremia Understanding the phenotype and location of latently infected cells represents a critical challenge in designing a cure for HIV; furthermore, many HIV-infected individuals given ART exhibit residual inflammation, which is associated with non-AIDS-related morbidity and mortality and may contribute to virus persistence. In this context, there is a strong consensus that a cure for HIV infection will not be achieved through ART intensification alone, and that novel approaches aimed at limiting residual inflammation and targeting persistently infected cells are needed. This presentation will discuss state-of-the-art concepts and immune based strategies targeting HIV persistence developed over the past several years using the model of SIV infection in rhesus macaques (RMs). Collectively, these studies support a model in which among memory CD4+ T-cells, those expressing co-inhibitory receptors (Co-IRs) are enriched in latent HIV. Recent work identified PD-1+ follicular helper CD4+ T-cells as an important cellular compartment for viral persistence. We have described that CTLA-4+PD-1- memory CD4+ T-cells, which share phenotypic markers with regulatory T-cells and localize outside the B-cell follicle of the lymph nodes, are significantly enriched in SIV-DNA; contain robust levels of replication-competent virus; and significantly increase their contribution to the SIV reservoir with prolonged ART. Finally, we showed that Interleukin-21 administration in ART-treated, SIV-infected RMs reduces residual inflammation in blood and intestinal mucosa, which is in turn associated with diminished viral persistence during ART. These recent advancements highlight the complexity and diversity of the mechanisms and T-cell populations that can contribute to the residual reservoirs of virally infected cells. Understanding this complexity and developing a range of different interventions to target individual components of viral reservoirs represent both a formidable challenge and an exciting opportunity for the years to come.

49 THERAPEUTIC VACCINATION FOR HIV/SIV: WHAT WILL IT TAKE FOR CURE?

Louis J. Picker, *Oregon Hlth & Sci Univ, Beaverton, OR, USA*

Current understanding of the residual virus remaining in HIV-infected subjects on optimally effective antiretroviral therapy (ART) suggests that functional HIV cure will require either viral eradication or substantial viral reservoir reduction combined with potent, long-term anti-viral immunity such that any viral reactivation that occurs after ART cessation is eliminated or stringently controlled over a lifetime. Achieving this state might entail up to 4 mechanistically distinct interventions, including 1) induction of viral gene expression in the transcriptionally "quiescent", latent HIV reservoir (allowing for immune targeting of these infected cells), 2) targeted immune destruction of all cells expressing HIV gene products, 3) establishment of a long-term potently antiviral immune response for immune surveillance after ART cessation, and 4) elimination of immunologic sanctuaries, such as the B follicular barrier for infected CD4+ T follicular helper T cells, that shield virally infected cells from immune destruction. Given the unproven benefits and potential risks of such interventions, there is a great need for an animal model that can be used for concept development and both pre-clinical safety and proof-of-concept studies. Our group has invested significant effort and resources in developing appropriate, state-of-the-art nonhuman primate models for such studies. In this talk, I will review the progress made in these models to both understand the immunobiology of ART-suppressed SIV infection and post-ART viral recrudescence and to develop therapeutic vaccination strategies that counter viral persistence and post-ART viral rebound.

50 MDR-TB EPIDEMIOLOGY AND TRANSMISSION

N. Sarita Shah, *CDC, Atlanta, GA, USA*

Drug-resistant tuberculosis (TB) is a global public health crisis, with 480,000 cases occurring annually and 190,000 dying of this disease. Extensively drug-resistant (XDR) TB involves resistance to the most potent first-line and second-line drugs to treat TB and has been reported from over 100 countries. Although the End TB Strategy calls for universal access to drug-susceptibility testing (DST), less than one-third of bacteriologically-confirmed TB cases had DST done, leading to massive diagnostic gaps. Among those diagnosed with MDR-TB, inadequate access to second-line TB drugs – in part due to bottlenecks created by centralized models of MDR-TB care – result in large treatment gaps. Current treatment regimens for MDR-TB are lengthy (minimum 18-24 months), costly (10-15 times the cost of drug-susceptible TB), have numerous side effects and result in cure for less than 50% of patients. Taken together, these major shortfalls in diagnosis, treatment and outcomes create a perfect storm for perpetuating the cycle of MDR-TB transmission and epidemic spread. Although transmission of MDR-TB strains has been well-described in outbreak settings for decades, the role of transmission in widespread epidemics is less understood. Characterizing the role of transmission is critical for informing public health interventions which, until now, have focused primarily on preventing acquired resistance (though the DOTS strategy) and far less on preventing transmission (through infection control strategies). In settings that have begun to address transmission prevention, efforts

have focused on healthcare settings, with little attention to communities, where over 50% of transmission may be occurring. Known and novel interventions to halt transmission include universal access to DST, rapid initiation of effective treatment, monitoring for emergence of resistance, screening of close contacts and environmental controls (e.g., germicidal UV, improving ventilation, reducing crowding). This talk will review the global epidemiology of TB, the growing data on the role of transmission in drug-resistant TB epidemics, and potential interventions aimed at reducing transmission.

51 EMERGING TREATMENT ISSUES IN MDR-TB

Francesca Conradie, *Univ of the WItswatersrand, Johannesburg, South Africa*

The treatment of Drug Resistant TB involved the use of long regimens with poor efficacy and a high drug related adverse event rate. Internationally, a successful outcome of treatment of who are diagnosed DR TB was 50%. Many patients started on treatment are loss to the program in part due to the side effects. In addition, there is increasing evidence of that transmission of DR TB is occurring in the community. While standardised regimens are used when DR TB is diagnosed, the evidence base for is of poor quality and based largely on cohort data. However in the last few years there have been major advances. The World Health Organisation issued guideline in May 2016 that included the use of a shortened course for the treatment of MDR. This session will discuss the rationale and some of the challenges in implementing this new recommendation. In addition, there have been a number of new and repurposed drugs have been introduced into the treatment of DR TB. Some of the research into the use of these drugs will be presented as well as the outcomes of their use in National TB programs.

52 NEW DIAGNOSTIC TECHNOLOGIES FOR MDR-TB

Catharina C. Boehme, *Fndn for Innovative New Diagnostics (FIND), Geneva, Switzerland*

The diagnostic gap remains greater for TB than for any other infectious disease; more than 80% of patients with multi-drug resistance remain undiagnosed or unreported. Many years of lab strengthening efforts have shown that scaling up BSL3 capacity for culture drug susceptibility testing will not be a feasible, or sustainable solution. Remarkable progress has been made in the development and introduction of rapid molecular TB drug susceptibility tests, but limitations notably with regard to ease of use and available drug spectrum hamper the impact on case management. To address drug resistant TB, complimentary diagnostic strategies are necessary: Expanded decentralized drug susceptibility testing to inform regimen choice is required at the point of first patient contact, i.e. at low levels of the health care system, especially given the anticipated introduction of short-course regimens and decentralization of MDR treatment. Comprehensive, rapid DST for individualized therapy must be available at more centralized levels. Where are we on the R&D path to much needed new tools? The understanding of the genetics and clinical mutation relevance of TB drug resistance particularly for second-line drugs and newly developed drugs is rapidly improving. WHO and FIND hosted a meeting earlier this year that essentially concluded that genotypic testing should replace culture DST, but at this stage there is no diagnostic solution available or in development that would allow to actually do this. FIND is working with Rutgers University and Cepheid on an expanded DST cartridge for the Omni platform. Initial performance of the assay is excellent, with >95% sensitivity and >99% specificity for detection of mutations in katG, inhA, gyrA, and rrs, and >81% sensitivity for eis mutations. Other companies also join in and strive to develop expanded molecular DST. Experts agree that next generation sequencing represents the future of TB drug resistance testing, initially for surveillance, but within 5 years for individual patient management, and offers huge potential in terms of speed, comprehensiveness and ease of use. A standardized, all-in one solution would ease deployment. The successful uptake of all novel TB diagnostics will critically depend on a strengthening of the patient care cascade and innovative delivery and testing strategies.

53 THE CHALLENGES OF TREATING MDR-TB IN CHILDREN

H. Simon Schaaf, *Stellenbosch Univ, Cape Town, South Africa*

The paucibacillary nature of tuberculosis (TB) and the difficulty in obtaining samples for bacteriology in children are important barriers to diagnosis of paediatric MDR-TB. Although 25,000 children were estimated to have developed MDR-TB in 2014, only a small number are reported in the literature as appropriately treated from 1990-2014. Early and appropriate diagnosis is a major challenge in treating MDR-TB in children. The principles of MDR-TB treatment are the same for adults and children; however there are child-specific considerations. The optimal doses of second-line TB drugs, including old, repurposed and new drugs, are only now being determined through paediatric pharmacokinetic and safety studies. The lack of child-friendly formulations of these drugs makes manipulation of adult formulations necesssary, reducing medication palatability and making accurate dosing in children challenging. Extrapulmonary sites of TB, such as TB meningitis, are common in children, making drug penetration, particularly into the cerebrospinal fluid, an important consideration. Although adverse effects are common with second-line anti-TB drugs, most are mild and appear less frequent in children than adults. Some are serious and irreversible, the most important being injectable-associated permanent hearing loss, making the development of injectable-sparing regimens in children essential. Treatment success (cure/treatment completion) in children with MDR-TB is 78-91% in several studies – much better than the 54% reported in one large individual patient data analysis in adults. The generally lower bacillary load in children compared to adolescents and adults could favour MDR-TB treatment regimens with fewer drugs and shorter durations. Observational studies have shown shorter regimens, including shorter durations of injectable agents, to have good outcomes in non-severe disease. After some delay, the novel TB drugs bedaquiline and delamanid are now being evaluated in children, and are likely to be key drugs going forward. Finally, prevention is better than cure; the burden of children exposed to MDR-TB is much larger than those developing MDR-TB disease. The challenge is to determine effective regimens to prevent MDR-TB (and beyond) in high-risk child contacts of MDR-TB source cases. Several trials evaluating regimens containing fluoroquinolones or novel anti-TB drugs are underway or soon to begin, and have the opportunity to change global policy and practice.

54 VAGINAL MICROBIOME AND SUSCEPTIBILITY TO HIV

R. Scott McClelland, *Univ of Washington, Seattle, WA, USA*

Several prospective studies published over nearly two decades have explored the relationship between vaginal dysbiosis and women's risk of HIV acquisition. These studies have typically used Gram stain scoring based on bacterial morphotypes to characterize vaginal microbiota in categories including normal (scores 0-3), intermediate vaginal microbiota (scores 4-6), and bacterial vaginosis (BV; scores 7-10). Together, these data suggest that both intermediate vaginal microbiota and BV are associated with about a 1.5-fold increase in women's risk of HIV infection. Because disruption of the vaginal microbiota is highly prevalent, particularly in populations at substantial risk for HIV infection, these conditions could have a sizable impact on HIV transmission at a population level. Newer approaches that characterize the vaginal microbiota using nucleic acid amplification based techniques have illuminated much greater heterogeneity among women with vaginal dysbiosis than previously appreciated. Studies presented during the past year suggest that vaginal bacterial community characteristics and the presence of specific bacterial taxa may play a key role in mediating women's risk of HIV infection. Vaginal microbiota could impact susceptibility to HIV through multiple pathways including inflammation, the presence and concentrations of soluble innate and adaptive immune mediators, production of HIV inducing factors, and disruption of structural barriers to HIV infection including vaginal and cervical mucus and epithelium. Interventions aimed at elimination of high-risk bacterial taxa could reduce women's risk of acquiring HIV.

55 ANTIBIOTIC PROPHYLAXIS FOR STIs: PROMISES OR PERILS

Jean-Michel Molina, *Univ of Paris Diderot, Paris, France*

Background: Every day more than 1 million of STIs are acquired worldwide, and each year there are an estimated 146 million of new infections with chlamydia, 78 million of gonorrhea and 6 million of syphilis. In the US, 2015 was the second year in a row with an increase in STIs, with syphilis increasing at an alarming rate among MSM. The implementation of PrEP for HIV prevention has also highlighted the increasing prevalence and incidence of STIs in PrEP users. Current efforts to contain the spread of STIs are obviously not sufficient. In addition to counseling and behavioral interventions including condom promotion and scaling-up of more effective STIs services, new preventive

strategies have to be assessed. The success of PrEP for HIV has raised interest in biomedical interventions for STIs. Pending the development of vaccines against bacterial STIs, the potential role of antibiotic prophylaxis should be re-assessed. Early studies conducted by the military have shown the short-term efficacy and the limitations of post-exposure prophylaxis. More recently, periodic presumptive treatment in female sex workers with azithromycin alone or in combination have shown reduction in incidence of gonorrhea and chlamydia but not of syphilis or HIV. Mass treatment with azithromycin for trachoma and Yaws elimination has also shown some impact on STIs prevalence. Studies using doxycycline prophylaxis for syphilis in high risk MSM are ongoing. Such studies in selected populations should be conducted cautiously and involvement of these populations in the design, implementation and evaluation of these new interventions is crucial. Should antibiotic prophylaxis be successful at reducing STIs incidence, its short-term benefits should be balanced against the long-term efficacy of this strategy, its tolerability, cost, and more importantly the selection and dissemination of antibiotic resistance when drug resistance to gonorrhea is already a threat and only limited options are available for treatment of chlamydia infection and syphilis. Also, antibiotic prophylaxis might alter STIs presentation and lead to an increase in STIs not targeted by the prophylaxis, underscoring the need for this strategy to be included in a comprehensive prevention package with a close monitoring of all STIs. Conclusion: New strategies need to be developed to contain the spread of STIs. Antibiotic prophylaxis for bacterial STIs in high risk populations should be carefully evaluated.

56 SYPHILIS IN THE ERA OF TREATMENT AS PREVENTION AND PRE-EXPOSURE PROPHYLAXIS

Matthew R. Golden, *Univ of Washington, Seattle, WA, USA*

Rates of syphilis in most high income nations have been steadily increasing since 2000, but that increase has accelerated since 2010, rising 56-130% over the last 5 years in the US, U.K. Germany, France, and Australia. In all of these areas, syphilis predominately affects men who have sex with men (MSM), particularly HIV-infected MSM. However, some evidence suggests that the syphilis epidemic is now expanding to include HIV-negative MSM without risk factors such as methamphetamine use, and in some areas, rates are now rising among women, with an associated risk of increasing congenital syphilis. Factors contributing to the rise in syphilis include the integrated effects of widespread and effective HIV treatment, HIV pre-exposure prophylaxis (PrEP), and geosocial apps, which together facilitate condomless sex guided by diverse seroadaptive behaviors. The rise of syphilis poses challenges for clinicians as they confront increasing numbers of cases of neuro-, ocular- and otosyphilis, and dilemmas related to performing lumbar punctures and interpreting syphilis serologies in patients tested at increasing frequency. The syphilis epidemic represents a public health challenge, but it also presents opportunities. There is an urgent need to control syphilis, to mitigate the morbidity of the infection and its spread, particularly to women, while capitalizing on the diagnosis of syphilis to promote frequent testing for HIV and other sexually transmitted infections, viral suppression among HIV-infected persons, PrEP use, and condoms. This presentation will review the current epidemiology of syphilis and factors contributing to the ongoing syphilis epidemic; key clinical issues in the management of syphilis; and the public health implications of rising syphilis rates.

57 SCALE-UP OF POINT-OF-CARE TESTS FOR SEXUALLY TRANSMISSIBLE INFECTIONS

Rebecca J. Guy, *Kirby Inst, Univ of New South Wales, Sydney, Australia*

Diagnosis of sexually transmissible infections is recognized as a key to both individual treatment and public health control, but in many contexts is unavailable or inaccessible, because the diagnostic methods can only be carried out in centralized, sophisticated laboratories. Recent technological advances have generated a variety of new diagnostic options, largely based around testing by the clinician at point-of-care, or self-testing at home. However despite having technical accuracy, the scale up of these technologies in primary health care services faces uncertain pathways and multiple barriers that can impede or even prevent implementation of promising strategies. Large-scale implementation of new point-of-care technology depends on a much wider range of features than simply biological accuracy, including the clinical, social and political context into which the technology is being introduced, and has implications for clinical service delivery, training, quality assurance, data management, supply chains, funding models and the patient experience. This talk will focus on point-of-care and home-based tests that have the potential to substantially increase diagnostic coverage for sexually transmissible infections and implementation research conducted to date to assess their scalability.

58 (PREVENTING) THE COMING EPIDEMIC: HIV IN YOUTH

Shannon L. Hader, *CDC, Atlanta, GA, USA*

Youth are essential to achieving bold visions put forward by the global health community for HIV: "Fast-track: Ending the AIDS Epidemic by 2030", "Delivering on the Promise of an AIDS-free Generation", and aspiring to 'super fast-track' a lifecycle of wellness with "Start Free, Stay Free, AIDS Free" by 2020. Yet even with great gains and more tools in fighting HIV than ever before, shifting demographic patterns add complexity to interrupting HIV transmission and PREVENTING a next epidemic among youth. Successes in global health and child survival, particularly marked in sub-saharan Africa, are paying a 'demographic dividend' of the largest population in history of young people aged 12-24, expected to continue to grow through 2035. This session will examine factors critical to understanding HIV risk and response, including: shifting demographics of age and urbanization; fertility patterns and life-cycle windows of risk; HIV incidence by age and gender; contexts of multiple vulnerabilities including violence against children; targeting of age bands and timelines to HIV impact. Given promising structural, behavioral, and biomedical interventions-how do we design and deliver services that 'fit' young people for greatest public health impact? This includes reaching youth in periods of risk and reducing contexts of risk; generating demand for services; empowering youth innovation and leadership. Country profiles and possibilities vary, and it will require understanding local evidence, agility in response, and multi-sectoral leadership to achieve dynamic and effective youth-focused HIV responses.

59 ANTIVIRAL VACCINE DEVELOPMENT FROM A (AIDS) TO Z (ZIKA)

Barney S. Graham, *NIAID, VRC, NIH, Bethesda, MD, USA*

Infectious diseases pose the greatest threat to public health than any other process. Sir William Osler noted that "Humanity has but three great enemies: fever, famine, and war; of these by far the greatest, by far the most terrible, is fever." This remains true despite advances in sanitation, antimicrobials, and vaccines. Sustained by increasing global commerce and travel, disruption of ecologies from conflict or economic development, and many people living with immune deficiencies, we are faced with a continuous microbial challenge. Most emerging infectious diseases are caused by viruses and are either zoonotic or vector-borne. AIDS began as a zoonotic transmission that circulated in humans for decades before evolving to the current pandemic. The scientific effort to understand HIV pathogenesis and develop antivirals and vaccine interventions has been a key stimulus driving the evolution of modern immunology. The HIV pandemic illustrated the disruptive impact of infectious diseases on economies and social stability, clarified the importance of taking a global view towards clinical research, and directly led to the development of a substantial worldwide clinical trials infrastructure. Considering the biological and technological challenges involved, one could argue that completing the task of HIV vaccine development is the best approach to generate the tools needed to face any new emerging viral disease. The talk will review lessons learned from the response to pandemic threats over the last 3 decades, and discuss currently available technology options for designing and delivering vaccines against viral diseases that may become future global public health concerns. There are 22 virus families associated with human infection from which the next pandemic threat could arise. Within each relevant virus family a database of information with accompanying reagents, assays, and animal models could be developed for prototypic viruses based on properties of tropism, transmission routes, and other distinguishing features of pathogenesis. Candidate vaccine approaches could be designed based on virus structure, transmission dynamics, entry requirements, tropism, and replication strategy. Rapid isolation of human mAbs, structure-based antigen design, next-generation sequencing, nanoparticle technology, and chemical synthesis are key tools for rapid vaccine development, but advanced preparation will be critical for rapid vaccine deployment during future pandemics.

60 IMMUNE CORRELATES OF HIV ACQUISITION

Krystelle Nganou Makamdop[1], Slim Fourati[2], Jianfei Hu[1], Amy Ransier[1], Farida Laboune[1], Rafick-Pierre Sekaly[2], Daniel Douek[1]
[1]NIAID, Bethesda, MD, USA, [2]Case Western Reserve Univ, Cleveland, OH, USA

Background: A predictive correlate of susceptibility to HIV infection derived from the baseline inflammatory status of an individual would contribute towards understanding not only the pathogenesis of HIV transmission but also to interpret results from prophylactic vaccine studies. A retrospective study on samples from the HVTN505 trial was set out to investigate immune correlates for HIV acquisition. Because the study surveyed over 2500 at-risk volunteers for several years during which some individuals contracted HIV infection, HVTN505 provides an unequivocally perfect set of samples for a study on biomarkers predictive for HIV acquisition.

Methods: Evaluation of multiple plasma and cellular biomarkers was performed in HVTN505 participants who became HIV infected and participants who remained uninfected. All measurements were performed on several time points before infection. Soluble biomarkers measured by ELISA/luminex in plasma included 32 cytokines or chemokines of innate and adaptive cell function. Cellular responses measured in PBMC included frequencies of various innate and T cell subsets and their overall activation status as determined by flow-cytometry (FCM). All PBMC timepoints were sorted into 7 subsets covering innate (mDC, NK, monocytes) and adaptive (CD4 and CD8) cell subsets, which underwent deep sequencing for transcriptome analysis by RNA-sequencing (RNA-Seq). A multi-omics data analysis including RNA-Seq, FCM and ELISA/luminex assessments was conducted to evaluate the set of markers that best predicts HIV acquisition.

Results: By themselves, no plasma cytokines/chemokines were able to predict HIV acquisition. Analysis of the FCM data using unsupervised and supervised approaches revealed that an elevated activation status of immune cells prior to infection was associated to an increased risk of infection. RNA-Seq of sorted immune cells revealed the activation of the canonical interferon signaling pathway in particularly mDCs was the best predictor of HIV acquisition (AUC>0.701). An integrative analysis of the RNA-Seq expression and the FCM data revealed a direct positive correlation between activation of the IFN signaling pathway in mDCs and higher frequency of activated effector T-cells, which are markers of increased risk of HIV acquisition.

Conclusion: Our study reveals that higher expression of IFN signaling pathway in mDCs leading to an increase of activated effector immune cells several months before infection is identified as a new and strong correlate of HIV acquisition.

61 MARKED CHANGES IN CELLULAR BUT NOT VIRUS TRANSCRIPTOME IN CD4-LOW HIV-INFECTED CELLS

Joseph P. Casazza[1], Eli Boritz[2], David R. Ambrozak[2], Amy R. Henry[2], Farida Laboune[2], Sam Darko[2], Jianfei Hu[2], Christine Grech[2], Daniel Douek[2], Richard A. Koup[2]
[1]NIH, Bethesda, MD, USA, [2]VRC, NIAID, Bethesda, MD, USA

Background: Advances in the identification of HIV-infected CD4 T cells and next-generation sequencing now make it possible to compare the viral and cellular transcriptome at both early and late time points in infection.

Methods: Primary CD4 T cells from 5 different donors were activated with PHA-P, rested for 24 h in the presence of IL-2 and then infected with HIV_{BAL}. Seventy-two hours after infection cells were bulk sorted based on CD4 down-regulation and surface staining of gp120 by PG9 and VRC07. Viral and cellular transcriptomes were characterized by Illumina RNA-seq methodology.

Results: Results- The cellular transcriptome of HIV-infected CD4 T cells, when compared to HIV-uninfected cells, was characterized by a pattern of transcription consistent with activation of the NF-κB pathway, and increased transcription of markers of cell cycle progression. Unlike the transcription signature for NF-κB which show no clear effect of CD4 down regulation, markers of cell cycle progression clearly decreased with CD4 downregulation. Additionally, transcription of the T cell master regulatory genes TBX21, RORC, BLC6 and PRDM1 all increased with CD4 down regulation. Based on the frequency of D1 and D4A7 splices, the pattern of HIV RNA splicing did not seem to change significantly with CD4 downregulation, but total HIV reads increased with CD4 down regulation. The median frequency of HIV reads in CD4 bright Env^- cells was 0.09(range 0.05-0.18)%, 4.95(0.93-6.66)% in the CD4 bright Env^+ cells, 9.2(3.6-10.8)% in the CD4 dim Env^+ cells and 16.6(12.2-19.9)% in the CD4 null, Env^+ cells.

Conclusion: These data show a pattern of gene transcription consistent with a sequential change in cellular gene expression with progression of infection. These changes do not appear to be due to a change in the splicing pattern of HIV RNA; rather, a dramatic increase in the frequency of intracellular HIV RNA is observed which may be responsible for the changes in the cellular transcriptome observed. Our ability to use bnAbs to identify HIV-infected cells before CD4 down regulation suggest that bnAbs may have therapeutic utility in viremic and latently infected individuals.

62LB SINGLE CELL TRANSCRIPTIONAL PROFILING REVEALS A NOVEL POPULATION OF MUCOSAL TFH CELLS

Andrew R. Rahmberg[1], Premeela A. Rajakumar[1], James M. Billingsley[2], Surinder P. Gill[1], R. Paul Johnson[1]
[1]Emory Univ, Atlanta, GA, USA, [2]Yerkes Natl Primate Rsr Cntr, Decatur, GA, USA

Background: Despite extensive study, our understanding of the molecular events that determine the susceptibility of CD4+ T cells to SIV/HIV infection and the cellular events that follow lentiviral infection have been limited by our ability to track events that occur in single cells and analyze gene expression, including viral gene expression, on a single cell basis. New techniques that permit high-throughput analysis of gene expression in single cells can be used to deconvolute cell types in apparently homogenous populations of bulk cells.

Methods: We utilized acutely simian immunodeficiency virus (SIV)-infected rhesus macaques to isolate individual infected and uninfected CD4+ T cells from the intestinal mucosa, the primary site of viral replication in acute infection. Using high-throughput microfluidic quantitative real-time PCR of single cells, we measured expression of five viral transcripts used to define SIV-infected cells along with 91 cellular genes chosen for potential relevance in the viral replication cycle.

Results: Single cell analysis of over 300 single jejunal CD4+ T cells obtained 10 days after intravenous SIV infection revealed that approximately 20% of these cells were SIV-infected. Comparison of gene expression using multiple statistical methods identified PD-1 and CXCR5 as being the most significantly differentially expressed genes between infected and uninfected cells. The coexpression of PD-1 and CXCR5 on CD4+ T cells defines T follicular helper (Tfh) cells. However, Tfh have been classically associated with secondary lymphoid tissue. Flow cytometric analysis of jejunal samples from uninfected macaques identified a distinct population of PD-1+ CXCR5+ CD4+ T cells, with multiple phenotypic characteristics of classical Tfh cells, including expression of BCL-6 and IL-21. Transcriptional profiling of a panel of 70 Tfh-associated genes verified the similarity of this novel population to classical Tfh. PD-1+ CXCR5+ cells from jejunum contained an average of 3.4 SIV gag DNA copies/cell at the peak of acute infection. This level of infection over 10-times higher than that of bulk memory CD4+ T cells was observed despite low levels of cell surface expression of the SIV coreceptor CCR5.

Conclusion: This study is the first single cell gene expression analysis of primate lentivirus-infected cells, and identified a novel and highly susceptible target cell population in vivo during acute infection.

63 HIGH HIV PERMISSIVITY OF T FOLLICULAR REGULATORY CELLS IS RELATED TO Ki67 EXPRESSION

Shannon Miller[1], Brodie Miles[1], Joy Folkvord[2], Amie Meditz[3], Martin McCarter[1], Mario Santiago[1], David N. Levy[4], Samantha MaWhinney[1], **Elizabeth Connick**[2]
[1]Univ of Colorado Denver, Aurora, CO, USA, [2]Univ of Arizona, Tucson, AZ, USA, [3]Boulder Community Hosp, Boulder, CO, USA, [4]New York Univ Coll of Dentistry, New York, NY, USA

Background: HIV replication is concentrated within follicular T cells in B cell follicles (F) during asymptomatic disease. Whether T follicular regulatory cells (TFR) are more permissive than other subsets and what factors drive permissivity are not understood.

Methods: Disaggregated HIV- human tonsil cells were spinoculated with R5-tropic GFP reporter virus (NLYUV3-GFP), 3 R5-tropic transmitted/founder viruses (T/F) (CH58, CH470, CH40) or mock spinoculated at day 0 and cultured for 2 days. Some cells were cultured for 2 days alone or with imatinib, a T cell proliferation inhibitor, prior to spinoculation. GFP or p24 expression were determined by flow cytometry. Due to CD4 downregulation by HIV, we gated on CD3+CD8- cells, and defined subsets as: extrafollicular (EF; CXCR5-CD25-CD127+/-), EF Treg (CXCR5-CD25+CD127-), TFH (CXC5+CD25-CD127+/-) and TFR (CXCR5+CD25+CD127-). CCR5, HLA-DR/CD38, CD69 and Ki67 expression were determined prior to

spinoculation. Lymph node cells (LN) from HIV+ untreated subjects were sorted into EF, EF Treg, TFH and TFR, and RNA quantified by RT PCR. Data were log transformed. Mixed-effects models and repeated-measures ANOVA were used with pairwise tests if overall $p<0.05$. Geometric means and 95% CIs are reported.
Results: GFP expression differed by cell type ($p\leq0.001$) with %GFP+ cells in TFR (2.0%; 1.3, 2.8) > EF Treg (0.6%; 0.4, 0.9), TFH (0.3%; 0.2, 0.5) > EF (0.09%; 0.04, 0.18), and TFR > TFH (n=6; $p<0.01$). The same pattern was observed for p24 Ag expression in T/F infections (n=6; overall $p<0.01$). %Ki67 expression differences between cell subsets at day 0 (n=6; $p<0.001$) paralleled differences in %GFP and %p24 expression, but CCR5, CD95, and CD69 expression did not. At day 0 for each 1 log10 increase in %Ki67 expression, there was a 0.8 (0.6, 1.1) log10 increase in %GFP expression ($p<0.001$). Compared to untreated cells, imatinib reduced Ki67 expression by 34% (6, 53; p=0.02) and reduced GFP expression by 77% (61, 87; $p<0.001$), without affecting viability. In sorted HIV+ LN, TFR harbored more (1167; 207, 6577) HIV RNA copies/ng total RNA than TFH (585; 113, 3020), EF Treg (516; 163, 1641), and EF (71; 10, 507) (n=6; overall p=0.04; pairwise $p<0.05$). LN Ki67 expression was higher in TFR (20%; 13, 30) than TFH (10%; 7, 15) and higher in EF Treg (19%; 15, 24) than EF (4.7%; 2, 10) (n=6; overall p=0.01; pairwise $p<0.05$).
Conclusion: TFR are highly permissive to HIV, likely due to heightened proliferation, and harbor the highest concentrations of HIV RNA *in vivo*.

64LB VIRION INCORPORATION OF INTEGRIN α4β7: IMPLICATIONS FOR HIV-1 PATHOGENESIS

Christina Guzzo, David Ichikawa, Chung Park, Cathy Rehm, Claudia Cicala, James Arthos, Anthony S. Fauci, John Kehrl, Paolo Lusso
NIAID, Bethesda, MD, USA

Background: The intestinal mucosa is a key anatomical site for HIV-1 replication and CD4+ T-cell depletion. Accordingly, a series of in vivo studies in macaques showed that antibody-mediated blockade of the principal gut-homing integrin, α4β77, resulted in reduced SIV transmission, delayed disease progression, and effective virus control persisting for months after antibody withdrawal. We aimed at elucidating the potential mechanism(s) underlying the protective effects of anti-α4β77 antibody treatment.
Methods: HIV-1 strains were grown in human PBMC activated in the presence/absence of retinoic acid; virion-capture assays were performed using magnetic beads armed with antibodies to α44β77 or other cellular receptors, or recombinant MAdCAM-1 or ICAM-1; α44β77+ or – viral particles were produced by co-transfection of 293T cells with HIV-1 clones with or without α44 and β77; for virion-homing studies, fluorescent α44β77+ or – virus was injected into the tail vein of C57BL/6 mice, and tissues were harvested after 30 min.
Results: We found that integrin α44β77 is incorporated with remarkably high efficiency into the envelope of mature HIV-1 particles. Virion-incorporated α4β7 is functionally active as it binds the specific integrin ligand, MAdCAM-1, promoting HIV-1 capture by and infection of MAdCAM-expressing cells, which in turn mediates trans-infection of bystander susceptible cells. In vivo homing experiments in mice documented a selective and specific uptake of α4β7+, but not α4β7- HIV-1 virions by high endothelial venules in the Peyer's patches of the intestinal mucosa. The physiological relevance of α44β77 incorporation was corroborated by the observation that circulating virions from both HIV-infected patients and SIV-infected macaques invariably carry functional α44β77 in their envelope, with peak incorporation levels occurring during the early stages of infection, when the intestinal mucosa is still richly populated with α44β7-7high CD4+ T cells.
Conclusion: Our results provide new insights to interpret the protective effects of anti-α44β77 antibody treatment and may be relevant for the pathogenesis, therapy and prevention of HIV-1 infection.

65 DEFINING THE NATURE OF CD8+ T-CELL RESPONSES IN LYMPH NODES OF HIV ELITE CONTROLLER

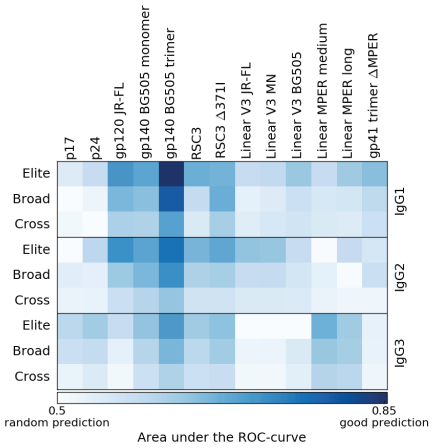
Son Nguyen[1], Marcus Buggert[1], Ali Naji[2], Perla Del Río-Estrada[3], Gustavo Reyes-Terán[3], Steven G. Deeks[4], Michael R. Betts[1]
[1]Univ of Pennsylvania, Philadelphia, PA, USA, [2]Hosp of the Univ of Pennsylvania, Philadelphia, PA, USA, [3]Rsr Cntr in Infectious Diseases, Mexico City, Mexico, [4]Univ of California San Francisco, San Francisco, CA, USA

Background: CD8+ T cells are strongly linked to viral control mechanisms in HIV elite controllers. Substantial evidence has suggested that cytolytic activity and other effector functions are the mechanism by which these cells control HIV, at least in blood. However, the vast majority of HIV replication in elite controllers likely occurs in lymphoid tissue, where CD8+ T cell immune surveillance mechanisms are undefined. Here we directly assessed the functional and phenotypic properties of tissue-based HIV-specific CD8+ T cells in the lymphoid tissues controllers.
Methods: We obtained human peripheral blood mononuclear cells (PBMC) and lymph node mononuclear cells (LNMC) from HIV-infected controllers, non-controllers and ART-treated individuals. We performed multi-parametric flow cytometry to define the phenotypic and functional profile of HIV-specific CD8+ T cells as identified by MHC-class I tetramers or responsiveness to peptide stimulation. The results were analyzed using FlowJo, GraphPad Prism, and SPICE.
Results: We here demonstrate that cytolytic memory CD8+ T cells, as defined by the expression of perforin and granzyme B, are almost absent in lymph nodes (LN) of elite controllers. While high frequencies of HIV-specific CD8+ T cells could readily be detected in LN by MHC-class I tetramers, these cells very rarely express perforin and granzyme B. Instead, HIV-specific CD8+ T cells from LN of controllers possess high levels of non-cytolytic polyfunctional responses directed against HIV peptides. Such responses were low or absent in non-controllers or those on ART. HLA-B27/57+ elite controllers demonstrate a selective and high frequencies of CD8+ T cells targeting immunodominant Gag epitopes. Finally, HIV-specific LN CD8+ T cells from EC do not display enhanced ability to enter B cell follicles as defined by the expression of the chemokine receptor CXCR5, nor are those CXCR5+ cells more cytolytic compared to non-controllers and those on ART.
Conclusion: Together these findings redefine previous concepts of CD8+ T cell mediated control of HIV disease progression. During established infection, HIV replication appears to be controlled in lymphoid tissues by non-cytolytic rather than cytolytic mechanisms. Knowledge regarding how HIV is controlled in this setting should be used to inform the identification and development of potentially curative interventions.

66 HIV-SPECIFIC BINDING ANTIBODY PROFILES ASSOCIATED WITH BROADLY NEUTRALIZING ACTIVITY

Claus Kadelka, Thomas Liechti, Hanna Ebner, Peter Rusert, Roger Kouyos, Huldrych F. Günthard, Alexandra Trkola
Univ of Zurich, Zurich, Switzerland

Background: Potent broadly neutralizing antibodies (bnAbs) are a key focus of vaccine and therapy development but they are only elicited at low frequency in natural infection. Understanding and overcoming these restrictions in bnAb induction will be decisive for HIV vaccine design. To define factors that govern bnAb induction we recently conducted the Swiss 4.5K Screen, a systematic survey of bnAb activity in 4,484 HIV-1 infected individuals (Rusert, Kouyos Nat Med 2016). This led to the identification of 239 bnAb inducers as well as the definition of several viral and disease parameters associated with bnAb development. Here, we report on an in-depth analysis of HIV-1 binding antibody data to define if and which binding antibody responses predict bnAb activity.
Methods: 4,391 plasma samples previously analyzed within the Swiss 4.5K Screen for neutralization activity were probed for binding antibodies of IgG subclasses 1, 2 and 3 against 13 HIV-1 proteins and peptides encompassing Gag (p17, p24) and Env (see Figure) using an in-house established Luminex bead assay. The area under the ROC-curve (AUC) was used to measure predictive power.
Results: Plasma samples with bnAb activity exhibited a generally higher Env binding reactivity. IgG1 binding activities to the gp140 BG505 trimer (AUC=0.85), followed by IgG2 trimer binding (AUC=0.76) and IgG2 binding to gp120 JR-FL (AUC=0.72) were particularly good predictors of HIV-1 neutralization breadth (see Figure). While

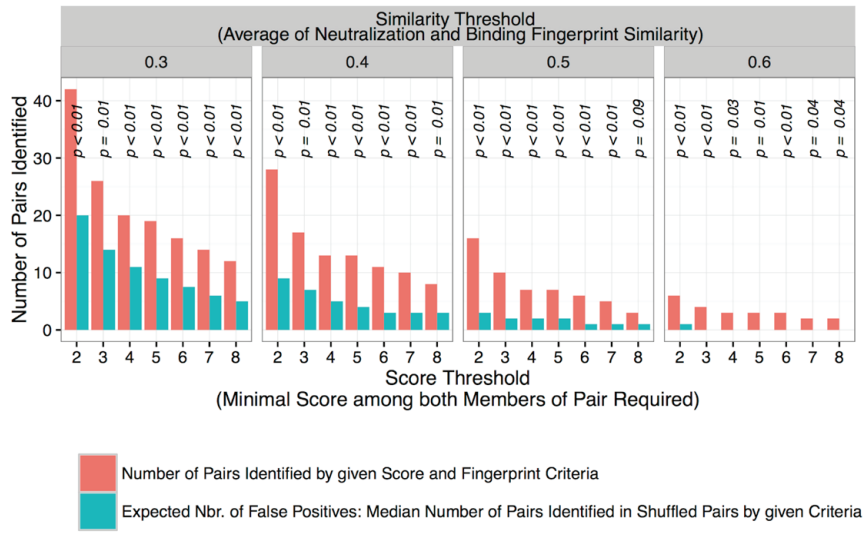


correlation of neutralization activity with trimer binding is well established we show here for the first time its efficacy of predicting neutralization breadth across HIV-1 subtypes. Based on epitope specificity (CD4bs, MPER, V1V2-loop, V3-loop) delineation analyses for 105 bnAb plasmas, we further found various binding patterns significantly associated with the presence of bnAbs directed to different antibody epitopes, highlighting that binding profiles should be included in plasma specificity delineation approaches.
Conclusion: Building on the Swiss 4.5K Screen we had the unique opportunity to assess the validity of binding antibodies as predictors of neutralization activity in several thousand patients. Our data highlight that a reliable prediction of bnAb activity by binding antibodies is possible. Whether used as first-line assay or in combination with multi-clade virus neutralization, owing to their ease in standardization binding assays will be of immense value for a controlled assessment of forthcoming vaccine efficacy trials.

67 THE IMPACT OF HIV-GENETICS ON IMPRINTING ANTIBODY RESPONSES: THE SWISS 4.5K SCREEN

Roger Kouyos, Peter Rusert, Claus Kadelka, Alex Marzel, Thomas Liechti, Merle Schanz, Hanna Ebner, Huldrych F. Günthard, Alexandra Trkola , for the Swiss HIV Cohort Study
Univ of Zurich, Zurich, Switzerland

Background: A key question on the way towards an HIV-1 vaccine is the impact of viral genetics on the neutralization response: Will a given HIV-1 envelope immunogen induce the same antibody specificities across vaccinees? Here we addressed this by studying the influence of virus genetics in potential transmission pairs identified within a recently conducted systematic screen of HIV-1 neutralization in 4,484 individuals (Swiss 4.5K Screen; Rusert, Kouyos Nat Med 2016).
Methods: Potential transmission pairs were defined based on HIV-1 pol gene phylogenies and plasma neutralization activity against a 14 multi-clade pseudovirus panel and IgG1 binding activity to 13 HIV-1 Gag and Env antigens was determined. Neutralization and binding similarity within pairs was determined by Spearman correlation and a range of shuffling tests and similarity measures.
Results: We identified 336 potential transmission pairs within the Swiss 4.5K Screen. For 7/14 pseudoviruses, we observed a significant ($p<0.05$) positive within-pair correlation of neutralization. The average Spearman correlation coefficient across all 14 viruses was weakly ($\rho=0.10$) but significantly ($p_{shuf}<0.001$) positive, even after controlling for viral subtype, infection-length and ethnicity ($p_{shuf}<0.001$). Similarly, binding to different HIV-1 antigens was significantly correlated within pairs (average $\rho_{spear}=0.18$, $p_{shuf}<0.001$). Notably, we found that two elite neutralizers (top 1% of neutralizers) formed a transmission pair and exhibited highly similar neutralization ($\rho_{spear}=0.73$) and binding ($\rho_{spear}=0.29$) fingerprints. To generalize this finding, we developed a systematic approach to identify pairs with similar neutralization and binding responses. Over a broad range of thresholds, this method identified significantly more candidate pairs than expected by chance (Figure) suggesting that the similarity of antibody responses in these transmission pairs is due to viral genetic factors.
Conclusion: Our results indicate that viral genetic factors significantly affect the breadth and specificity of the antibody responses to HIV-1. A large proportion of this effect is likely due to the env gene. Not all bnAb Envs may carry the capacity to imprint identical Ab specificity, thus utilizing Envs from bnAb inducers with proven transferability of antibody reactivities as identified here may be the ultimate immunogen candidates to base vaccine design on.



68 INTENSITY OF SUPPRESSION LINKED WITH SHIFTING COMPARTMENTALIZATION OF CNS HIV DNA

Benjamin B. Gelman[1], Joshua G. Lisinicchia[1], Lalita D. Singh[1], Vipulkumar N. Patel[1], Alexander J. Gill[2], Colleen E. Kovacsics[2], Dennis L. Kolson[2]
[1]*Univ of Texas Med Branch, Galveston, TX, USA,* [2]*Univ of Pennsylvania, Philadelphia, PA, USA*

Background: There is substantial information regarding the role of viral suppression on the latent pool of HIV DNA in blood cells, but analogous types of data pertaining to the deep body compartments such as the central nervous system (CNS) remain scarce.
Methods: In 16 HIV-infected patients already known to have relatively low viral replication rates in the brain, we mapped total and integrated gag-pol HIV DNA and RNA in brain frontal white matter, frontal neocortex and neostriatum using PCR and the two step Alu-gag assay. Patterns of brain compartmentalization were analyzed in patients with varying levels of replication control.
Results: Mean and modal averages of HIV DNA was highest in white matter versus the two gray matter sectors ($p < 0.04$, two-tailed t test), but CNS compartmentalization patterns deviated widely. 7 of 16 brains were reflective of the overall average and had highest concentrations in white matter; 6 brains had generally equivalent concentrations in white versus gray matter; 3 brains had higher concentrations in a gray matter compartment versus white matter. The white matter compartment contains the most mass, so the total sizes of the latent pools in the brain were nearly always highest in white matter. To determine whether the intensity of viral suppression could affect compartmentalization in the brain, patients were grouped according to those with intensely suppressed brain replication (log 1.52 +/- 0.42 copies of HIV RNA per gram, $n = 8$) versus less intensely suppressed (log 2.95 +/- 0.61 c/g, $n = 8$). The more intensely suppressed brain specimens contained significantly less HIV DNA in neocortex, but significantly more in white matter ($p < 0.02$), without a significant net gain or loss in total brain pool size. Precisely the same outcome was observed when the patients were grouped according to the intensity of systemic viral suppression, using spleen HIV RNA concentration as a validated postmortem surrogate for the plasma HIV replication rate (log 2.22 +/- 0.79 c/g versus 5.47 +/- 1.50 c/g).
Conclusion: Results from mapping latent HIV DNA in human brain specimens imply that more intense viral suppression, both within the CNS compartment and systemically, will produce a shift in the brain burden from gray to white matter, but will not diminish the total brain pool size substantially.

69 CNS PARENCHYMA AND CHOROID PLEXUS, NOT CSF, ARE VIRAL RESERVOIRS IN MONKEYS WITH AIDS

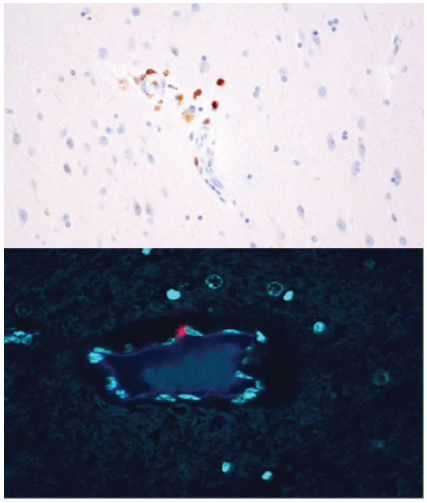
Jaclyn Mallard[1], Brittany Rife[2], Emily Papazian[1], Arianna Noggle[1], David J. Nolan[2], Marco Salemi[2], Kenneth C. Williams[1]
[1]Boston Coll, Chestnut Hill, MA, USA, [2]Univ of Florida, Gainesville, FL, USA

Background: HIV-associated neurocognitive disorders (HAND) are characterized by accumulation of monocyte/macrophages (Mo/MΦ) and virus in central nervous system (CNS). While T cells and Mo/MΦ can enter the CNS from the cerebrospinal fluid (CSF) via the choroid plexus (CP) or the blood-brain barrier at the meninges, it is thought that Mo/MΦ traffic seeds CNS reservoirs as they are the predominant cell type found in parenchymal tissues. In live humans, the CSF is the only compartment that can be sampled for CNS virus. Because T cells can traffic through the CSF, and T cells and macrophages are found in the choroid plexus that makes the CSF, we hypothesized that the CSF has a mixture virus found in CNS, plasma, Mo/MΦ, T cell derived sequences and the CP has compartmentalized virus that is found in the CNS parenchyma that is a viral reservoir.
Methods: Brain, CP, CSF, plasma, and T cells and Mo/MΦ from blood from 19 SIVmac251-infected and 2 uninfected rhesus macaques (11 CD8-depleted and 10 non-depleted) were assessed. SIV+ animals included: 4 without AIDS, 6 with AIDS and SIVE and 9 with AIDS without SIVE (SIVnoE). Double label in situ hybridization and immunohistochemistry was used to count SIV-infected T cells and Mo/MΦ in CP. Maximum Likelihood phylogenetic trees were constructed with SIV gp120 cDNA sequences that were isolated from the CSF, CP, CNS parenchyma and CD3+ T cells and CD14+ Mo/MΦ in blood. Phylogeographic analysis of SIV sequences was used to assess compartmentalization of virus to determine tissue and cellular sources of viral reservoirs.
Results: There were increased numbers of Mo/MΦ, but not T cells in CP from SIVE compared to SIVnoE animals. Mo/MΦ and T cells in the CP were SIV-RNA+. CSF viral sequences were dispersed between CNS and peripheral (plasma, bone marrow, Mo/MΦ, T cells) sequences. In SIVE animals, CP and CNS parenchymal sequences clustered together and were highly compartmentalized, indicating that these tissues are sources of CNS viral reservoirs.
Conclusion: The detection of SIV-RNA+ T cells and Mo/MΦ in CP underscores the CP as a source of CSF virus. The dispersed phylogeny of CSF viral sequences among peripheral and CNS sequences indicates that the CSF is not a viral reservoir. Mo/MΦ accumulation and compartmentalization of viral sequences in the CP and CNS suggests infected Mo/MΦ in these tissues are the source of CNS viral reservoir.

70 EARLY MACROPHAGE-INDEPENDENT INFLAMMATION AND SHIV-RNA IN CNS IN A RHESUS SHIV MODEL

Denise C. Hsu[1], Piyanate Sunyakumthorn[2], Matthew Wegner[2], Jacob D. Estes[3], Claire Deleage[3], Robert J. O'Connell[2], Victor Valcour[4], Serena Spudich[5], Nelson L. Michael[6], **Sandhya Vasan**[1]
[1]US Military HIV Rsr Prog, Bangkok, Thailand, [2]Armed Forces Rsr Inst of Med Scis, Bangkok, Thailand, [3]Frederick Natl Lab for Cancer Rsr, Leidos Biomed Rsr Inc, Frederick, MD, USA, [4]Univ of California San Francisco, San Francisco, CA, USA, [5]Yale Univ, New Haven, CT, USA, [6]US Military HIV Rsr Prog, Silver Spring, MD, USA

Background: Neurologic symptoms occur and HIV RNA is detectable in CSF during acute HIV infection. We developed a non-accelerated rhesus macaque model to characterize these earliest changes in an effort to inform reservoirs and cure trials.
Methods: Macaques were infected with a single SHIV1157ipd3N4 challenge intrarectally (9 males) or intravaginally (3 females). Biomarkers of immune activation were measured by Luminex at week (W)2 and W12 post infection in plasma and W12 in CSF. At W12 necropsy, brain sections from 6 SHIV+ and 6 uninfected control animals were stained with anti-CD3, CD4, and CD68 antibodies by immunohistochemistry (IHC). SHIV-infected cells were detected using RNAscope in situ hybridization.
Results: SHIV RNA was detectable in CSF (lower limit of detection of the assay is 10 copies/mL) at W12 in the 4 animals with the highest W12 plasma viral load, but not in those with plasma SHIV RNA <490 copies/mL. CSF MCP-1 and IP-10 were elevated versus control CSF (284 vs 126 pg/mL, p=0.030; 282 vs 117 pg/mL, p=0.004). The W12 CSF/serum albumin ratio was <5x10-3 in all animals, consistent with an intact blood brain barrier. IHC revealed no evidence of CD68+ or CD4+ cell inflammatory infiltrate in midbrain, frontal cortex, or basal ganglia. Some SHIV-infected animals had evidence of a mild CD3+ T cell infiltrate with qualitative pavementing along the vascular endothelium and clustering in the brain parenchyma (Fig 1). However, in the meninges, CD4+ T cells were increased in a subset of SHIV-infected animals vs controls, in the absence of CD68+ cells. Rare SHIV RNA positive cells were detectable in the cortex and/or meninges in 5 out of 6 SHIV-infected animals using RNAscope staining by both IHC and immunofluorescence. In the one animal where no SHIV RNA was detected, viral load was also undetectable in CSF and was low in plasma (18 copies/mL) at W12.
Conclusion: CSF SHIV RNA and IP-10 and MCP-1 elevations reflect a discrete neurovirologic process in early infection. This is accompanied by a mild CD3+, CD4- infiltrate in the brain parenchyma and CD4+ T cells in the meninges in the absence of macrophages, and rare but distinct SHIV-infected cells in the brain cortex. Thus the earliest stages of SHIV infection are characterized by a T-cell mediated process, which is distinct from the SIV model but closely mimics findings in early HIV infections in humans. The SHIV1157ipd3N4 non-accelerated challenge model can serve as a model for future interventional studies.



CD3+ cells (top, brown), SHIV-RNA+ cell (bottom, red) with nuclei staining (bottom, aqua) in the frontal cortex showing pavementing of cells along vascular endothelium (top, bottom) and CD3+ cells in the brain parenchyma (top).

71 DEEP SEQUENCING REVEALS RARE CNS COMPARTMENTALIZATION IN ACUTE HIV-1 INFECTION

Rujipas Sirijatuphat[1], James L. Fletcher[2], Eric Sanders-Buell[3], Jintanat Ananworanich[3], Nelson L. Michael[3], Victor Valcour[4], Sodsai Tovanabutra[3], Gustavo Kijak[3], Serena Spudic h[5], for the RV254/SEARCH 010 Team and MHRP Viral Sequencing Core
[1]Mahidol Univ, Bangkok, Thailand, [2]South East Asia Rsr Collab with Hawaii (SEARCH), Bangkok, Thailand, [3]US Military HIV Rsr Prog, Silver Spring, MD, USA, [4]Univ of California San Francisco, San Francisco, USA, [5]Yale Univ, New Haven, CT, USA

Background: HIV-1 compartmentalization plays an important role in viral pathogenesis and is considered a potential obstacle for HIV-1 cure. Viral compartmentalization has been detected in the CNS during early (> 4 months of infection) and chronic HIV, but the timing of the onset of CNS compartmentalization remains unknown. Using single genome amplification (SGA), we have found no significant compartmentalization in acute HIV-1 infection (AHI) in the Thai RV254/SEARCH010 cohort. Here, we employed targeted deep sequencing (TDS) with increased power to detect minor viral variants to evaluate HIV-1 compartmentalization between CSF and plasma during AHI.
Methods: Thirteen antiretroviral-naïve acutely infected RV254/SEARCH010 participants (Fiebig stages: II=3; III=6; IV=3; V=1) were selected (criteria: availability of paired plasma and CSF samples, with CSF HIV-1 RNA levels>10^4 $\log_{10}$ copies/ml). We studied the Protease (PR) and Reverse Transcriptase (RT) regions in paired CSF and plasma (median sampling interval: 1 day; range: 0-9), using the IonTorrent PGM platform, with a lower limit of detection for minor variants of 0.5%. Frequencies of single nucleotide variants and haplotypes were determined with the Nautilus pipeline.
Results: All of the participants (median: 22 days post estimated infection) were infected with HIV-1 CRF01_AE. A low-level of polymorphisms was detected in plasma and CSF (median 0.8%; range 0.5-10%). TDS analysis revealed that 5 participants were infected with multiple transmitted/founder (T/F) viruses; the remainder were infected with a single T/F virus. In one participant with multiple T/F infection (RV254_276; Fiebig II, sampling interval: 1 day) a minor T/F variant circulating in plasma at low frequencies (15-23%) was

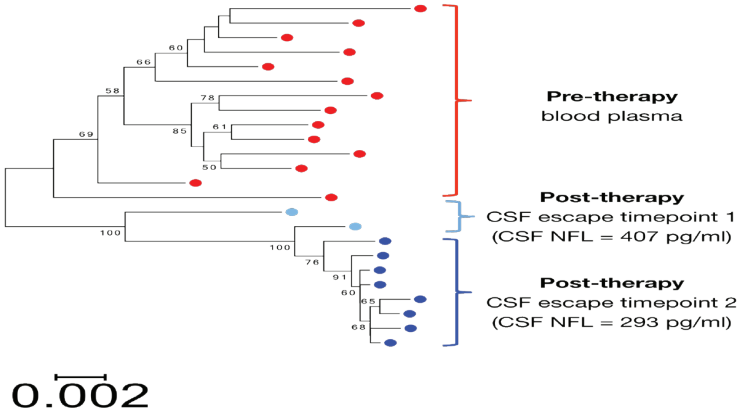
found at high frequencies in the contemporaneous CSF sample (42-50%). 12/13 participants did not show significant compartmentalization between CSF and plasma. None of the participants carried major drug-resistance mutations in either compartment.
Conclusion: This study provides evidence, for the first time, that HIV-1 compartmentalization in the CNS can occur as early as AHI, within days of exposure, though this early compartmentalization onset is uncommon. Further studies are needed to understand the forces determining initial sequestration or enrichment of T/F variants in the CNS compartment, and potential long-term implications of these findings for persistence of HIV-1 reservoirs and neurological impairment in HIV.

72 CD4/CD8 RATIO ASSOCIATES WITH NEUROPSYCHOLOGIC PERFORMANCE DURING EARLY HIV INFECTION

Leah T. Le[1], Kevin Robertson[2], Brinda Emu[1], Richard W. Price[3], Magnus Gisslén[4], Henrik Zetterberg[4], Roxane Fabre[5], Christian Pradier[5], Serena Spudich[1], Matteo Vassallo[6]
[1]Yale Univ, New Haven, CT, USA, [2]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]Univ of California San Francisco, San Fransisco, CA, USA, [4]Sahlgenska Academy at the Univ of Gothenburg, Gothenburg, Sweden, [5]Univ de Nice-Sophia Antipolis, Nice, France, [6]Cntr Hosp de Cannes, Cannes, France
Background: In chronic HIV, inversion of the CD4/CD8 ratio and its negative trajectory over time are associated with increased morbidity and mortality, systemic immune activation/immunosenescence, and risk of neurocognitive impairment, regardless of antiretroviral therapy (ART) treatment status. We examined whether the trajectory of the CD4/CD8 ratio predicted neuropsychologic performance even during primary HIV infection (PHI).
Methods: We longitudinally assessed blood and cerebrospinal fluid (CSF) markers of inflammation/immune activation and neuropsychological testing performance (NPZ4, an average of 3 motor and one processing speed test, and cognitive domains: motor, executive function, processing speed, and memory), in ART-naïve participants enrolled during PHI (<12 months after HIV infection). The majority of participants commenced ART during follow-up independent of the study. Spearman correlation and linear mixed models assessed the relationships between the trajectory of blood CD4/CD8 ratio over time and neurocognitive performance as well as blood and CSF markers of immune activation and injury.
Results: 109 PHI participants enrolled (median duration of infection 3.3 months, median plasma HIV RNA 4.63 $\log_{10}$ copies/mL, 525 total observations, and 4 median observations per participant). At baseline, median CD4/CD8 ratio and NPZ4 scores were 0.53 (IQR: 0.40, 0.86) and -0.20 (IQR: -0.56, 0.34) respectively. Mean CD4/CD8 ratio decreased with longer delayed time from infection to starting treatment ($p = 0.01$). Greater change in NPZ4 scores correlated with greater change in CD4/CD8 ratio over the course of follow-up ($p = 0.02$). Multivariate analysis adjusting for time since each visit and baseline, age, viral load, alcohol abuse and treatment status revealed that every unit increase in the CD4/CD8 ratio was associated with a 0.15 increase in NPZ4 score (95% CI: 0.002, 0.29; $p = 0.047$). Among cognitive domains, change in processing speed correlated with the trajectory of CD4/CD8 ratio over time ($p = 0.03$). The trajectory of the CD4/CD8 ratio negatively correlated with change in CSF neurofilament light chain (NFL), a marker of active neuronal injury, independently from cART ($p = 0.04$).
Conclusion: Though early ART had a beneficial effect on the CD4/CD8 ratio, this marker was associated with neuropsychological testing performance and NFL, a marker of brain injury, in PHI, independently from treatment. Its trajectory may thus predict neuropsychologic performance even during early infection.

73 ASYMPTOMATIC HIV-1 CSF ESCAPE IS UNCOMMON AND IS NOT ASSOCIATED WITH NEURONAL DAMAGE

Sarah Beth Joseph[1], Laura P. Kincer[1], Natalie M. Bowman[1], Henrik Zetterberg[2], Magnus Gisslén[2], Kevin Robertson[1], Serena Spudich[3], Joseph J. Eron[1], Richard W. Price[4], Ronald Swanstrom[1]
[1]Univ of North Carolina Chapel Hill, Chapel Hill, NC, USA, [2]Sahlgrenska Academy at the Univ of Gothenburg, Gothenburg, Sweden, [3]Yale Univ, New Haven, CT, USA, [4]Univ of California San Francisco, San Fransisco, CA, USA
Background: HIV-1 can be detected in the cerebrospinal fluid (CSF) of some subjects on antiretroviral therapy (ART). The persistence of HIV-1 in the CNS during ART is both a potential barrier to curing HIV-1 and may damage the CNS.
Methods: Single copy viral load (VL) testing was done on CSF and plasma samples from 96 neurologically asymptomatic subjects infected with HIV-1 and on stable ART. We examined the relationship between CSF VL and the presence of pleocytosis (a marker of CNS inflammation) and neurofilament light chain protein (NFL; a marker of neuronal injury) in CSF samples. Single genome amplification (SGA) and/or Illumina MiSeq deep sequencing were used to genetically characterize env genes in the CSF of 5 subjects with CSF VLs high enough for analysis. For 2 subjects, we also explored the origins of CSF escape populations by comparing viral populations in the CSF during ART to viral populations in the blood and/or CSF prior to ART (Figure 1). Finally, we examined whether env genes from subjects with CSF escape are macrophage-tropic based on their ability to enter cells expressing low levels of CD4.
Results: 17% (16) of subjects had a CSF VL above the limit of detection (LOD) of the single copy assay, and 76% (73) had a plasma VL above the LOD. Further, 6% of subjects (6 of 96) had asymptomatic CSF escape, with plasma VL ≤ 40 cp/ml and a CSF VL > 40 cp/ml, with a median CSF VL of 163 cp/ml. Overall, we did not observe a relationship between CSF VL and CSF NFL ($r = 0.06$, $p = 0.54$), nor did subjects with CSF escape have higher levels of CSF NFL in comparison to other subjects ($p = 0.1$). Further, in longitudinal analyses of two subjects with CSF escape (one persistent and one transient), we did not observe abnormal or increasing levels of CSF NFL. In contrast, CSF escape was associated with greater CSF WBC (median = 2, range = 1-134 cells/μl; $p \leq 0.01$). Finally, most CSF escape viruses were CCR5-using and adapted to entering T cells (R5 T cell-tropic); however, one persistent escape population was dominated by moderately macrophage-tropic variants.
Conclusion: These cross-sectional results suggest that in individuals without neurologic symptoms, CSF escape is uncommon, and escape viruses are typically R5 T cell-tropic and not associated with detectable neuronal injury. While our findings are limited by the paucity of CSF escape in this well-suppressed cohort and the cross-sectional design, we found no association between asymptomatic CSF escape during ART and a CSF marker of neuronal damage.



74 GENETIC VARIATION IN EIF2AK3 IS ASSOCIATED WITH NEUROCOGNITIVE IMPAIRMENT IN HIV

Scott Letendre[1], Cagla Akay-Espinoza[2], Ajay Bharti[1], Peilin Jia[3], Asha R. Kallianpur[4], Donald Franklin[1], Gerard D. Schellenberg[2], Robert K. Heaton[5], Igor Grant[5], Kelly L. Jordan-Sciutto[2]

[1]Univ of California San Diego, San Diego, CA, USA, [2]Univ of Pennsylvania, Philadelphia, PA, USA, [3]Univ of Texas Houston, Houston, TX, USA, [4]Cleveland Clinic Lerner Coll of Med, Cleveland, OH, USA, [5]Univ of California San Diego, La Jolla, CA, USA

Background: Despite its continued high prevalence, genetic vulnerability to HIV-associated neurocognitive impairment (NCI) remains less well understood than in the general population. Risk factors for NCI (e.g., HIV replication, persistent inflammation) can induce the ubiquitous unfolded protein response (UPR), which activates initiator proteins that can phosphorylate eukaryotic translation initiation factor 2α (eIF2α) and subsequently, slow global translation initiation while selectively increasing translation of transcripts such as β-site amyloid precursor protein cleaving enzyme-1. Chronic UPR activation has been implicated in Alzheimer's and Parkinson's diseases. We evaluated associations of single nucleotide polymorphisms (SNPs) in the EIF2AK3 gene with neurocognitive (NC) performance of HIV+ adults.

Methods: 1,047 participants from CHARTER's Genome-Wide Association Study (GWAS) were randomly assigned 1:1 to either a Test set or a Validation set. Using a candidate gene approach, 3 SNPs in the EIF2AK3 gene (rs6739095, rs1913671, rs11684404) were compared to the Global Deficit Score (GDS) and Global NCI using routine univariate and multivariable methods to adjust for confounding conditions.

Results: Median age was 43; 23% were women; 34% had European ancestry and 42% had African ancestry; 61% had AIDS; median CD4+ counts were 175 (nadir) and 428 (current); and 71% used antiretroviral therapy (ART) with 58% having plasma HIV RNA ≤ 50 c/mL. For rs6739095, 42% had ≥1 T allele; for rs1913671, 41% had ≥1 C allele; and for rs11684404, 39% had ≥1 C allele. Findings were similar in the Test and the Validation sets, e.g., rs11684404 was associated with GDS in a allelic dose manner (genotype-median GDS): CC-0.32, CT-0.37, TT-0.42 (p=0.032 (Test), 0.035 (Validation)). In the combined group, TT homozygotes had 46% higher risk of NCI than CC homozygotes (p=0.01). Associations of rs11684404 with either GDS or NCI persisted after multivariable adjustment (model p<0.0001). Those with non-European ancestry had stronger associations between these SNPs and GDS or NCI [e.g., 61% higher risk for rs11684404 TT than CC homozygotes (p=0.02)].

Conclusion: Variation in EIF2AK3 was associated with NC performance, with consistent effects in both test-validation and multivariable analyses, supporting the importance of UPR in HIV neuropathogenesis. EIF2AK3, and perhaps other UPR-related genes, may contribute to NCI risk in HIV+ adults.

75 CEREBRAL SMALL-VESSEL DISEASE IN HIV-INFECTED PATIENTS WELL CONTROLLED ON CART

Antoine Moulignier[1], Julien Savatovsky[1], Ophélia Godin[2], Nadia Valin[3], François-Xavier Lescure[4], Roland Tubiana[5], Ana Canestri[6], Cédric Lamirel[1], **Dominique Costagliola**[2], for the MICROBREAK ANRS Study Group

[1]Fndn Ophtalmologique Adolphe de Rothschild, Paris, France, [2]Univ Paris 06, Paris, France, [3]Saint Antoine Hosp, Paris, France, [4]Bichat Hosp, Paris, France, [5]Pitié-Salpétrière Hosp, Paris, France, [6]Tenon Hosp, Paris, France

Background: Cerebral small vessel disease (CSVD), defined by white matter hyperintensities (WMHs), silent brain infarction (SBI) or microbleeds (MBs), is a major cause of future vascular events, cognitive impairment, frailty, and poor survival. CSVD is correlated with age and cardiovascular risk factors (CVRF). Little is known on the prevalence of CSVD in persons living with HIV (PLWHIV) with controlled viral load (VL) under cART, who often present conventional and non-conventional CVRFs.

Methods: The ANRS EP51 MICROBREAK (NCT02082574) cross-sectional study, conducted in 4 Paris hospitals in France, aimed to assess the prevalence of CSVD detected by MRI in treated PLWHIV, 50 years of age or older, not HCV infected and with controlled VL for at least 12 months, in comparison with HIV negative controls (HNC), with frequency matching on age and sex. Brain 3T MRI included 3D FLAIR, DWI and T2*. All MRI were reviewed by 2 experienced neuroradiologists, blinded to HIV status, using the Fazekas scale for WMHS and Wardlaw's research criteria for SBI and MBs, with a third reader in case of discordance. We also assessed the impact of HIV on the severity of CSVD defined as WMHs Fazekas 2-3 or SBI or MBs. A logistic regression model was used to assess the impact of HIV on CSVD adjusted on traditional risk factors.

Results: Between June 2013 and May 2016, 456 PLWHIV and 154 HNC were recruited; median age was 56 and 58 years (p=0.001), 84% and 77% (p=0.030) were men, respectively. All CVRF were more frequent in PLWHIV than in HNC (hypertension 33% vs 21%, hypercholesterolemia 41% vs 19% and hypertriglyceridemia 22% vs 6%, respectively), except diabetes (8% vs 5%) and smoking (46% vs 42%). The median CD4 count in PLWHIV was 655/mm3 [IQR: 510 - 845] and 62% had been diagnosed before 1996. CSVD was detected in 51.5% of PLWHIV and 36.4% of HNC, with an adjusted odds ratio (ORa) of 2.3 (95% confidence interval: 1.5–3.6). Severe CSVD was observed in 19% of PLWHIV and 14% of HNC, with an ORa of 1.6 (0.9–2.7). As expected, older age and hypertension were also associated with the risk of CSVD. The impact of HIV was different according to age, with ORa of 5.3 (1.7–16.3), 3.7 (1.7–8.0) and 1.0 (0.5–2.2) for age of <54, 54-60 and >60 years, respectively (p=0.022).

Conclusion: Despite cART-sustained immunovirologic control, the prevalence of CSVD is twice higher in middle-aged PLWHIV. Besides age and hypertension, HIV is an independent risk factor of CSVD.

76LB A MULTICENTER DIAGNOSTIC ACCURACY STUDY OF THE XPERT ULTRA FOR TUBERCULOSIS DIAGNOSIS

Samuel G. Schumacher[1], Pamela Nabeta[1], **Catharina C. Boehme**[1], Jerrold Ellner[2], David Alland[3], Susan E. Dorman[4], Claudia M. Denkinger[1] , for the TB Clinical Diagnostics Research Consortium and FIND Trial Consortium

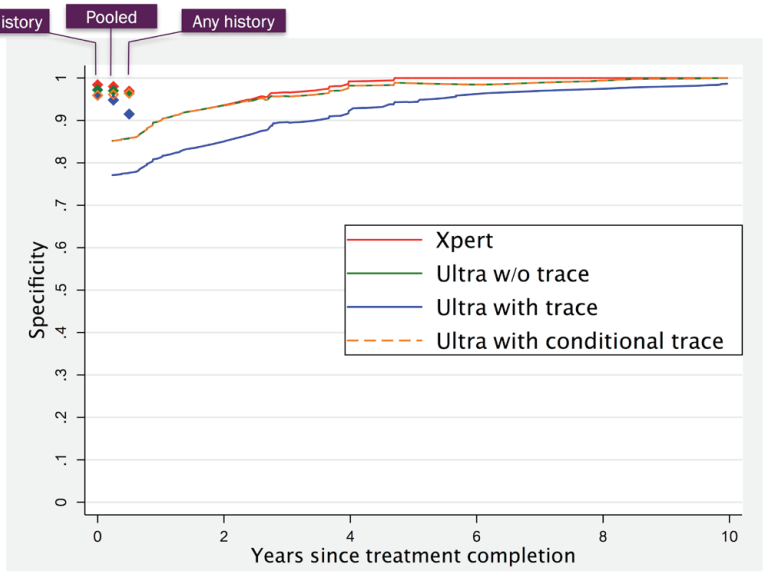
[1]FIND, Geneva, Switzerland, [2]Boston Med Cntr, Boston, MA, USA, [3]Univ of Med and Dentistry of New Jersey, Newark, NJ, USA, [4]Johns Hopkins Univ, Baltimore, MD, USA

Background: The development of the Xpert MTB/RIF (Xpert) was a major step forward for improving tuberculosis (TB) and rifampin (RIF) diagnosis globally. However, Xpert sensitivity is imperfect in smear-negative and HIV-associated TB and some limitations also remain in the determination of RIF-resistance status. The Xpert Ultra (Ultra) has been developed as the next-generation assay to overcome these limitations.

Methods: This was a prospective multicenter diagnostic accuracy study in adults with signs/symptoms of pulmonary TB. Xpert and Ultra were performed from the same specimen and accuracy determined with four cultures as the reference standard for TB detection (two MGIT tubes + two LJ slants, performed on two specimens obtained on separate days) and phenotypic drug-susceptibility testing for RIF resistance detection.

Results: 1,520 patients were enrolled in 10 sites across 8 countries. Sensitivity of the Ultra was 5% higher than that of Xpert (95%CI +2.7, +7.8) but specificity was 3.2% lower (95%CI -2.1, -4.7). Sensitivity-increases were higher among smear-negative patients (+17%, 95%CI +10, +25) and among HIV-infected patients (+12%, 95%CI +4.9, +21). Specificity-decreases were higher in patients with a history of TB (-5.4%, 95%CI -9.1, -3.1) than in patients with no history of TB (-2.4%, 95%CI -4.0, -1.3). Reclassifying 'trace calls' (the semi-quantitative category of the Ultra assay that corresponds to the lowest bacillary burden) as 'TB-negative'-either in all cases or in those with a history- mitigates some of the specificity losses (Specificity –1.0%/-1.9% if trace reclassified for all cases/cases with history) while maintaining some of the sensitivity gains over Xpert (Sensitivity +7.6%/+15%). Ultra classified more patients correctly as RIF-resistant (+1.1%, 95%CI -2.0, +4.6) and RIF-sensitive (+2.6%, 95%CI +0.2, +5.2) overall because the Xpert missed TB in patients with very paucibacillary disease entirely.

Conclusion: Ultra has higher sensitivity than Xpert in smear-negative and HIV-infected patients and improved accuracy for RIF detection. However, as a result of the increased sensitivity, Ultra also detects TB DNA in some patients with prior TB disease, possibly due to persistence of non-viable bacilli, leading to reduced specificity. Similar results can be expected for other upcoming next-generation molecular TB assays. A discussion of resulting implementation challenges and the willingness to trade off specificity for increased sensitivity in different settings is urgently needed.



Lines are running-line least squares (mean) smoothers using a bandwidth of 0.8 (Cleveland, JASA, 1979)

77 WHOLE-GENOME SEQUENCING AND SPATIAL ANALYSIS OF XDR TB TRANSMISSION IN SOUTH AFRICA

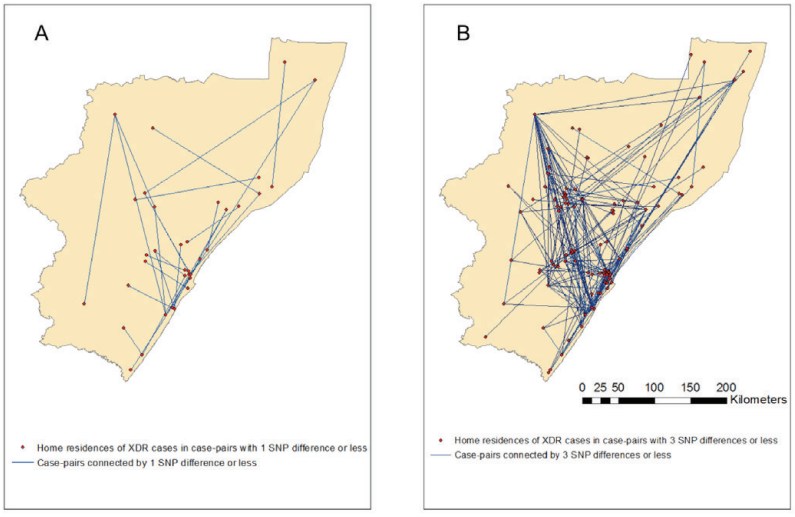
Kristin N. Nelson[1], Neel R. Gandhi[1], Sara C. Auld[1], James C. Brust[2], Barun Mathema[3], Nazir Ismail[4], Pravi Moodley[5], Angela Campbell[1], Salim Allana[1], N. Sarita Shah[6]
[1]Emory Univ, Atlanta, GA, USA, [2]Albert Einstein Coll of Med, Bronx, NY, USA, [3]Columbia Univ, New York, NY, USA, [4]NICD, Johannesburg, South Africa, [5]Univ of KwaZulu-Natal, Durban, South Africa, [6]CDC, Atlanta, GA, USA

Background: Transmission of drug-resistant tuberculosis (TB) is a major threat to TB control, especially in high HIV prevalence settings. We have previously shown that nearly 70% of extensively drug-resistant (XDR) TB cases in KwaZulu-Natal province, South Africa are due to transmission, rather than unsuccessful TB treatment. We identified epidemiologic links through close contacts or hospital admission for 30% of cases, but found no epidemiologic link for the remaining 70%. We hypothesize that genomically-linked cases live or seek healthcare near one another and may have unrecognized epidemiologic links. We compared geospatial distances between homes and health facilities for participants with ≤ 5 single nucleotide polymorphism (SNP) differences to determine geographic proximity.

Methods: We enrolled culture-confirmed XDR TB cases in KwaZulu-Natal from 2011-2014. We collected clinical and demographic characteristics, GPS coordinates of homes and XDR TB diagnosis facility, and performed whole genome sequencing (WGS) of TB isolates. We defined a SNP difference of ≤ 5 as genomic evidence of transmission between two cases ('case-pair'). We calculated spatial distances using Haversine's formula and defined geographic proximity as < 20 km. We stratified the analysis by participants' HIV status to determine the association with spatial clustering.

Results: We enrolled 296 participants with WGS results, from all 11 districts in KwaZulu-Natal. Among these, 179 (66%) participants formed 671 case-pairs with ≤ 5 SNPs. The median distance between home residences of case-pairs was 115 km (IQR 63-154) (Figure 1); the median distance between diagnosing facilities was 93 km (IQR 44-131). Only 116 (17%) case-pairs lived or were diagnosed within 20 km of each other. Median distance did not vary significantly when the SNP threshold was reduced to 3 and 1 SNP (p=0.27 for homes, p=0.56 for diagnosing facilities). There was no significant difference in geographic distances for case-pairs based on whether both were HIV-positive, HIV-negative or had discordant HIV status (p=0.87 for homes, p=0.20 for diagnosing facilities).

Conclusion: Although two-thirds of XDR TB participants from KwaZulu-Natal, South Africa were genomically-linked, only 17% lived or were diagnosed at a health facility within 20 km of their case-pair. Further research examining migratory patterns, particularly between rural and urban areas, is needed to determine their role in TB transmission and the spread of drug resistance.



78 SIX-MONTH IPT REDUCES MORTALITY INDEPENDENTLY OF ART IN AFRICAN ADULTS WITH HIGH CD4

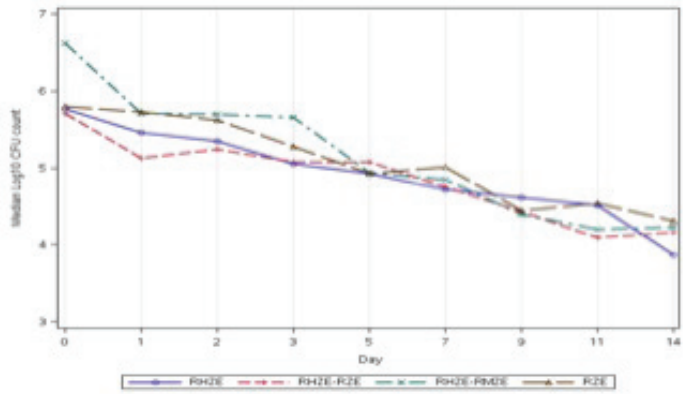
Anani D. Badje[1], Raoul Moh[2], Delphine Gabillard[1], Calixte Guehi[3], Mathieu Kabran[2], Hervé Menan[2], André Inwoley[2], Christine Danel[1], Serge Eholie[4], Xavier Anglaret[1]
[1]INSERM, Bordeaux, France, [2]Prog PAC-CI, ANRS Rsr site, Abidjan, Cote d'Ivoire, [3]INSERM, Abidjan, Cote d'Ivoire, [4]Service des Maladies Infectieuses et Tropes, Abidjan, Cote d'Ivoire

Background: Temprano was a factorial 2x2 trial that assessed the benefits of early antiretroviral therapy (ART) and 6-month isoniazid prophylaxis (IPT) among HIV-infected adults in Côte d'Ivoire. Participants were randomly assigned to four groups (deferred-ART- No-IPT, deferred-ART-plus-IPT, early-ART-No-IPT, early ART-IPT). Early ART and IPT were shown to independently reduce the risk of severe morbidity at 30 months. Here we present the efficacy of IPT in reducing mortality in the long term.
Methods: Participants who completed the trial follow up were invited to participate in a post trial phase (PTP). The PTP endpoint was death in an intention-to-treat analysis. We used Cox proportional models to compare mortality between the IPT and No-IPT strategies from inclusion in Temprano to January 2015.
Results: 2,056 patients (mean baseline CD4 count 477/mm3) were followed for 9,404 patient-years (Temprano 4,757; PTP 4,647). A total of 86 deaths were observed (Temprano 47; PTP 39), 34 in patients randomized to IPT (six-year probability 4.1%, 95% CI 2.9 to 5.7) and 52 in those randomized to No-IPT (six-year probability 6.9%, 95% CI 5.1 to 9.2). The hazard ratio of death for IPT compared to No-IPT was 0.63 (95% CI, 0.41 to 0.97) after adjusting for the ART strategy (Early vs. Deferred), and 0.61 (95% CI, 0.39 to 0.94) after adjusting for the ART strategy, baseline CD4 count and other key factors.
Conclusion: In these African HIV-infected adults with high CD4 counts, 6-month IPT led to a 39% decrease in mortality, independently of ART initiation and baseline CD4 count.

79 THE ESSENTIALITY OF INH DURING THE FIRST 14 DAYS OF TB THERAPY: THE A5307 EBA TRIAL

Andreas H. Diacon[1], Sachiko Miyahara[2], Xin Sun[2], Richard Hafner[3], **Florian von Groote-Bidlingmaier**[4], Courtney Fletcher[5], Evelyn Hogg[6], Rodney Dawson[7], Susan Swindells[5], William Bishai[8]
[1]Stellenbosch Univ, Cape Town, South Africa, [2]Harvard Univ, Boston, MA, USA, [3]NIH, Bethesda, MD, USA, [4]TASK Applied Sci, Cape Town, South Africa, [5]Univ of Nebraska Med Cntr, Omaha, NE, USA, [6]Social &Scientific Systems, Silver Spring, MD, USA, [7]Univ of Cape Town, Mowbray, South Africa, [8]The Johns Hopkins Univ, Baltimore, MD, USA

Background: Clinical and animal model studies suggest that isoniazid contributes a significant level of early bactericidal activity (EBA) during the initial 2 days of treatment, but the bactericidal rates decline significantly beginning at day 3 in patients with uncomplicated, smear-positive pulmonary tuberculosis.
Methods: We conducted a 14-day randomized phase II early bactericidal activity (EBA0-14) trial to determine how isoniazid (INH) affects EBA in combination with rifampicin, pyrazinamide, and ethambutol (RZE). Four study arms included (1) isoniazid, rifampicin, pyrazinamide, and ethambutol (RHZE) for 14 days, (2) RHZE for 2 days and omitting INH for days 3-14, (3) RHZE for 2 days and replacing INH with moxifloxacin for days 3-14, and (4) RZE for 14 days. EBA0-14 was measured by: (1) rate of M. tuberculosis decline per day in sputum by colony forming unit (CFU) count [primary endpoint], and (2) increase in time to positivity in liquid culture [secondary endpoint].
Results: Of the 69 randomized participants, 63 completed the study with 15-17 participants in each study arm. Most participants (83%) were male and HIV-negative (94%); median age was 31 and median BMI was 18.9. EBA0-14 was not different across all arms (figure 1). The mean baseline bacterial sputum load for all participants was 5.80 log10CFU (Standard Deviation [SD] 0.98) and the median daily decline in CFU count over 14 days was 0.12 log10CFU (Inter Quartile Range [IQR] 0.06 to 0.17). The mean baseline time to culture positivity in liquid medium was 109 hours (SD 29) and the median daily increase in time to positivity was 12 hours (IQR 9 to 16). EBA0-2 in the arms containing INH was not different compared to the arm without INH, and the median daily decline in CFU count over 2 days for all participants was 0.16 log10CFU (IQR -0.09 to 0.47). Exploratory sub-analysis revealed that participants with higher sputum baseline loads had higher initial EBA irrespective of treatment. Grade 3 or 4 adverse events were rare and not significantly different across arms.
Conclusion: The EBA over 14 days for all study arms was not different from each other. INH did not appear to significantly add to the 14-day EBA observed with RZE. Unlike earlier studies, significant EBA over 2 days due to INH was not observed. The absence of the expected bi-phasic INH response might be due to the relatively low baseline bacterial load in this study. Lower bacterial loads have been reported in recent EBA studies and it is likely due to early detection of TB.



80LB THE NIX-TB TRIAL OF PRETOMANID, BEDAQUILINE AND LINEZOLID TO TREAT XDR-TB

Francesca Conradie[1], Andreas H. Diacon[2], Daniel Everitt[3], Carl Mendel[3], Christo van Niekerk[4], Pauline Howell[5], Kyla Comins[6], Mel Spigelman[3]
[1]Univ of the WItswatersrand, Johannesburg, South Africa, [2]Stellenbosch Univ, Cape Town, South Africa, [3]Global Alliance for TB Drug Development, New York, NY, USA, [4]Global Alliance for TB Drug Development, Pretoria, South Africa, [5]Clinical HIV Rsr Unit, Johannesburg, South Africa, [6]TASK Applied Science, Belville, South Africa

Background: Patients with Extensively Drug Resistant (XDR) tuberculosis (TB) have had limited options for treatment and high mortality. Nix-TB is an ongoing open label study in South Africa of bedaquiline (400 mg qd for 2 weeks followed by 200 mg tiw), pretomanid (200 mg qd) and linezolid (1200 mg qd) given orally for 6 months.
Methods: Participants are required to have documented XDR-TB, or MDR TB treatment intolerance or failure (TI or Fr). The primary endpoint is bacteriologic failure, relapse or clinical failure at 6 months after treatment. Participants who are culture positive at 4 mos treatment may extend treatment for 3 mos. Clinical, laboratory and sputum liquid culture evaluations are performed at baseline and wks 1, 2, 4, 6, 8 and then every 4-6 wks through treatment. Eye examinations with slit lamp are made 3 times. Participants who complete treatment are followed for 24 mos after treatment end with repeat clinical assessments and sputum cultures.
Results: Since April 2015, 61 participants have been enrolled as of 15 December 2016 at 2 sites. 49% of the participants are HIV positive, 79% have XDR-TB and 21% have MDR TI or Fr to prior therapy. 34 have completed the 6 months of therapy with the drug regimen and 20 have been followed to the primary endpoint at 6 months after treatment. All surviving patients were culture negative by 4 mos, with 74% negative at 8 wks. 4 participants died within the first 8 wks of therapy; 3 had multi-organ TB on autopsy and 1 had a GI bleed due to erosive esophagitis. 27% had serious adverse events (AE). No surviving participants have withdrawn from the study due to any clinical AE or lab abnormalities. The expected linezolid toxicities of peripheral neuropathy (PN) and myelosuppression (MSPN) were common but manageable. 71%, of participants had at least one linezolid dose

interruption (22% of all participants due to MSPN and 28% due to PN), during the 6 mos of treatment. One had peak ALT and AST > 3 X ULN and total bili > 2X ULN, but these improved and treatment restarted without a recurrence. There were 7 cases of grade 3 or 4 transaminitis and all resolved and allowed the study regimen to be continued. There were no cases of optic neuritis. As of 15 December, 2016, there has been 1 microbiological relapse.
Conclusion: Current results of this greatly simplified and shortened all-oral regimen for drug resistant TB are encouraging in terms of both efficacy and safety.
Prior Presentation or Publication: Yes - Data was presented at the Union conference (Liverpool, England) in October 2016 on the 15 participants that completed six months of treatment and reached the primary endpoint of six months post-treatment. This abstract provides more data as now 61 patients have been enrolled, with 34 having completed the 6 months of therapy and 20 have been followed to the primary endpoint at 6 months at treatment. Given the high rate of TB/HIV, we feel it is important to bring this information to CROI.

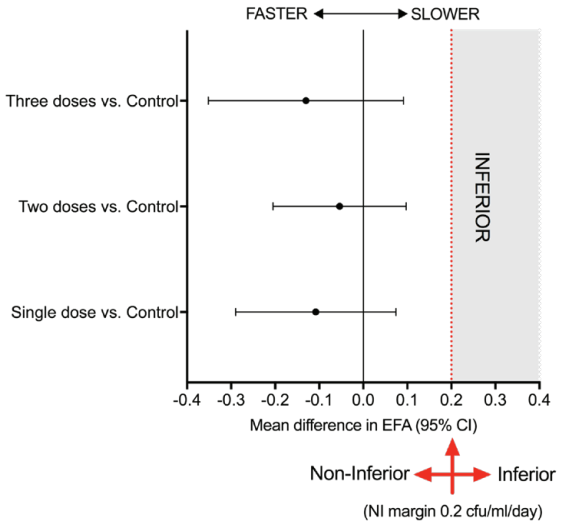
81LB RANDOMIZED CONTROLLED TRIAL OF PREDNISONE FOR PREVENTION OF PARADOXICAL TB-IRIS

Graeme Meintjes[1], Cari Stek[2], Liz Blumenthal[1], Friedrich Thienemann[1], Charlotte Schutz[1], Jozefien Buyze[2], Gary Maartens[1], Robert Wilkinson[3], Lutgarde Lynen[2] , for the PredART Trial Team
[1]Univ of Cape Town, Cape Town, South Africa, [2]Inst of Tropical Med, Antwerp, Belgium, [3]Imperial Coll, London, UK
Background: Early initiation of antiretroviral therapy (ART) in patients with TB reduces mortality in those with low CD4 counts, but increases the risk of paradoxical TB-IRIS. Prednisone reduces symptoms when used to treat TB-IRIS. We determined whether prophylactic prednisone in patients at high risk for paradoxical TB-IRIS safely reduces the incidence of TB-IRIS.
Methods: 1:1 randomized, double-blind, placebo-controlled trial of prednisone (40 mg/day for 2 weeks then 20 mg/day for 2 weeks) started with ART in ART-naïve adults at high risk of TB-IRIS (within 30 days of TB treatment initiation and CD4 count ≤100/µl) followed for 12 weeks. Exclusion criteria included rifampicin resistance, neurological TB, Kaposi's sarcoma, hepatitis BsAg+ and poor clinical response to TB treatment. Primary endpoint was development of TB-IRIS, defined using the International Network for the Study of HIV-associated IRIS (INSHI) consensus case definition, adjudicated by an independent committee. Final results are presented.
Results: 240 participants were enrolled: median age 36.8 (IQR=30-42.8), 60% men, median CD4 49/µl (IQR=24-86), and median HIV RNA 337,775 copies/ml (IQR=162,223-810,812). TB was microbiologically confirmed in 175. 18 were lost to follow-up or withdrew. TB-IRIS fulfilling INSHI criteria was diagnosed in 56 in the placebo arm (46.7%) and 39 in the prednisone arm (32.5%) (p=0.02, relative risk (RR)=0.70 (95%CI=0.51-0.96)). Open label corticosteroids to treat TB-IRIS was prescribed as necessary in 34 of the placebo arm (28.3%) and 16 (13.3%) of the prednisone arm (RR=0.47 (95%CI=0.27-0.83)). 4 deaths occurred in the placebo arm (1 attributed to TB-IRIS) and 5 in the prednisone arm (p=1.0). 27 were hospitalized (all-cause) in the placebo arm compared with 17 in the prednisone arm (p=0.10). Grade 3 adverse events occurred more frequently in the placebo arm (45.4% vs 29.4%, p=0.01), but grade 4 adverse events were similar by arm (8.4% vs 7.6%, p=0.81). Severe infections (AIDS-defining or invasive bacterial) occurred in 18 in the placebo arm and 11 in the prednisone arm (p=0.17). There was a trend towards fewer interruptions of ART or TB treatment in the prednisone arm (8.3% vs 15.8%, p=0.07).
Conclusion: In patients at high risk of paradoxical TB-IRIS, prednisone during the first 4 weeks of ART reduced the risk of TB-IRIS by 30% and further reduced the requirement for corticosteroids to treat TB-IRIS by 53%. The intervention was well-tolerated with no excess risk of infection or malignancy.

82 AMBITION-CM: HIGH-DOSE LIPOSOMAL AMPHOTERICIN FOR HIV-RELATED CRYPTOCOCCAL MENINGITIS

Joseph N. Jarvis[1], Tshepo B. Leeme[2], Awilly A. Chofle[3], Gabriella Bidwell[3], Mooketsi Molefi[4], Katlego Tsholo[2], Nametso Lekwape[2], Charles Muthoga[2], Síle Molloy[5], Thomas S. Harrison[5]
[1]CDC Botswana, Gaborone, Botswana, [2]Botswana–UPenn Partnership, Gaborone, Botswana, [3]Natl Inst of Med Rsr, Mwanza, Tanzania, [4]Univ of Botswana, Gaborone, Botswana, [5]St. George's Univ of London, London, UK
Background: Cryptococcal meningitis (CM) is associated with 10-20% of deaths in HIV-programs in Africa. Current antifungal treatments are inadequate and new treatment strategies are urgently needed. Recent data suggest it may be possible to deliver highly effective induction therapy with very few large doses of liposomal amphotericin B (L-AmB). We performed a phase-II randomized controlled non-inferiority trial examining the Early Fungicidal Activity (EFA) of three alternative short-course high-dose L-AmB schedules for the treatment of HIV-associated CM in Tanzania and Botswana.
Methods: HIV-infected patients admitted with a first episode of cryptococcal meningitis were randomised to one of four treatment regimens: (i) L-AmB 10 mg/kg day 1 (single dose); (ii) L-AmB 10 mg/kg day 1, L-AmB 5 mg/kg day 3 (two doses); (iii) L-AmB 10 mg/kg day 1, L-AmB 5 mg/kg days 3, and 7 (three doses); (iv) standard 14-day L-AmB 3mg/kg/d (control arm). All were given with high dose fluconazole 1200mg/d. The primary endpoint was early fungicidal activity (EFA) over the initial 2 weeks of therapy, derived from serial quantitative CSF cultures. Linear regression analysis was used to compare EFA by treatment group.
Results: 80 participants were enrolled – median age 38 years, 54% male, 33% on ART, median CD4=34 cells/µL, 29% abnormal mental status at baseline. Rate of fungal clearance in all three short-course high-dose arms was non-inferior to the control arm at the predefined non-inferiority margin of 0.2 logCFU/ml/day (figure). Adjusting for baseline fungal burden, CD4 count, and mental status did not alter the strength of association. One-way ANOVA analysis comparing EFA between the three short-course treatment arms found no evidence for any significant difference. Overall mortality was 29% (23/80): 29% (6/ 21) in the control arm, 22% (4/18) in the single dose arm, 15% (3/20) in the two dose arm, and 48% (10 of 21) in the three dose arm. All treatment groups were well tolerated, with only three participants experiencing DAIDS grade 4 anemia (all in the control arm), and seven DAIDS grade 4 creatinine rises, with no participants requiring treatment interruptions.

Figure. Mean difference in EFA between short course and control regimens with 95% confidence intervals. All short course arms demonstrate non-inferiority to the control arm at the pre-defined non-inferiority (NI) margin of 0.2 cfu/ml/day.



Conclusion: Single doses of 10mg/kg L-AmB were well tolerated and led to non-inferior EFA compared to 14-day courses of 3mg/kg L-AmB in HIV-associated CM. Based on these results single dose 10mg/kg L-AmB is being taken forward to a phase 3 clinical endpoint trial.

83 A RANDOMISED CONTROLLED TRIAL OF INDUCTION THERAPY OF TALAROMYCES MARNEFFEI INFECTION

Thuy Le[1], Nguyen V. Kinh[2], Nguyen Le Nhu Tung[3], Thanh Thuy Pham Thi[4], Pham T. Phuc[5], Doan T. Hanh[6], Jeremy Day[1], Guy Thwaites[1], Marcel Wolbers[1] , for the IVAP Investigators
[1]Oxford Univ Clinical Rsr Unit in Vietnam, Ho Chi Minh, Vietnam, [2]Natl Hosp for Trop Diseases, Hanoi, Vietnam, [3]Hosp for Trop Diseases, Ho Chi Minh City, Vietnam, [4]Bach Mai Hosp, Hanoi, Vietnam, [5]Viet Tiep Hosp, Hai Phong, Vietnam, [6]Uong Bi Hosp, Quang Ninh, Vietnam

Background: Talaromyces (formerly Penicillium) marneffei infection is a leading cause of HIV-related death in South and Southeast Asia. Amphotericin B deoxycholate (dAmB) is recommended for induction therapy but has significant side effects and limited availability. Itraconazole is well-tolerated, is more widely-used, and in large case series is shown to be similar to dAmB in mortality and clinical outcomes. However, these drugs have never been tested in clinical trials.
Methods: In this open-label non-inferiority trial, we randomly assigned 440 HIV-infected adults with microbiology-confirmed talaromycosis in five major referral hospitals in Vietnam to receive dAmB (219 patients) or itraconazole (221 patients) for two weeks, followed by itraconazole consolidation and maintenance therapy in all patients. The primary outcome was mortality at two weeks. The secondary outcomes were survival until week 24, time to clinical resolution, early fungicidal activities, disease relapse, immune reconstitution inflammatory syndrome (IRIS), and grade III or higher adverse events.
Results: The mortality at two weeks was 6.5% in the dAmB group and 7.4% in the itraconazole group (absolute risk difference, 0.9%; 95% confidence interval [CI], -3.9% - 5.7%; non-inferiority P<0.0001); however, mortality at 24 weeks was 11.3% and 21.0%, respectively (hazard ratio, 1.88; 95% CI, 1.15 - 3.09; P=0.012). Consistent with the higher mortality in the itraconazole group, clinical resolution and fungal clearance were slower (P=0.049 and P<0.0001), and relapse and IRIS were more common (P=0.005 and P=0.0001). Patients on dAmB experienced more infusion reactions (P<0.0001), renal failure (P=0.006), hypokalemia (P=0.0009), hypomagnesemia (P=0.021), and anaemia (P=0.012), but these were not considered life-threatening.
Conclusion: dAmB is found to be superior to itraconazole in the induction therapy of talaromycosis in measures of overall mortality, clinical response, disease complications, and fungicidal activity, and should be made available for patients in Asia.

Figure 1a. Cumulative incidence function of the absolute risk of death until 24 weeks estimated using the Kaplan-Meier method.

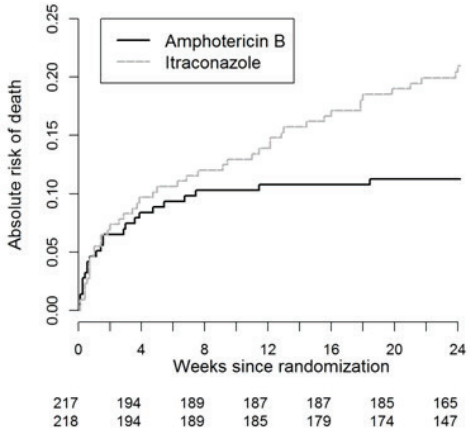
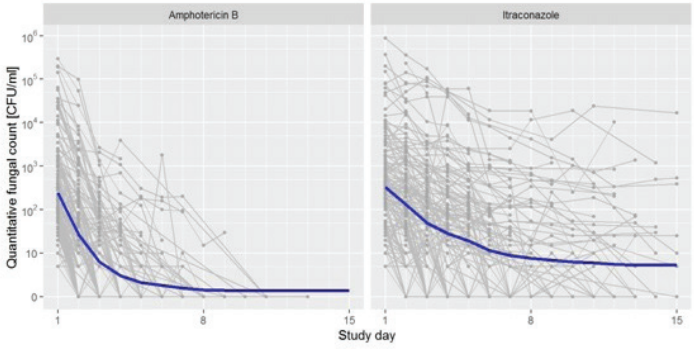


Figure 1b. Longitudinal quantitative fungal counts in blood.



84 RESISTANCE EMERGENCE IN MACAQUES ADMINISTERED CABOTEGRAVIR LA DURING ACUTE INFECTION

Jessica Radzio[1], Olivia Council[1], Mian-er Cong[1], James Mitchell[1], Shanon Ellis[1], Wei Huang[2], William Spreen[3], Walid Heneine[1], **Gerardo Garcia-Lerma**[1]
[1]CDC, Atlanta, GA, USA, [2]Monogram BioScis, San Francisco, CA, USA, [3]ViiV Hlthcare, Rsr Triangle Park, NC, USA

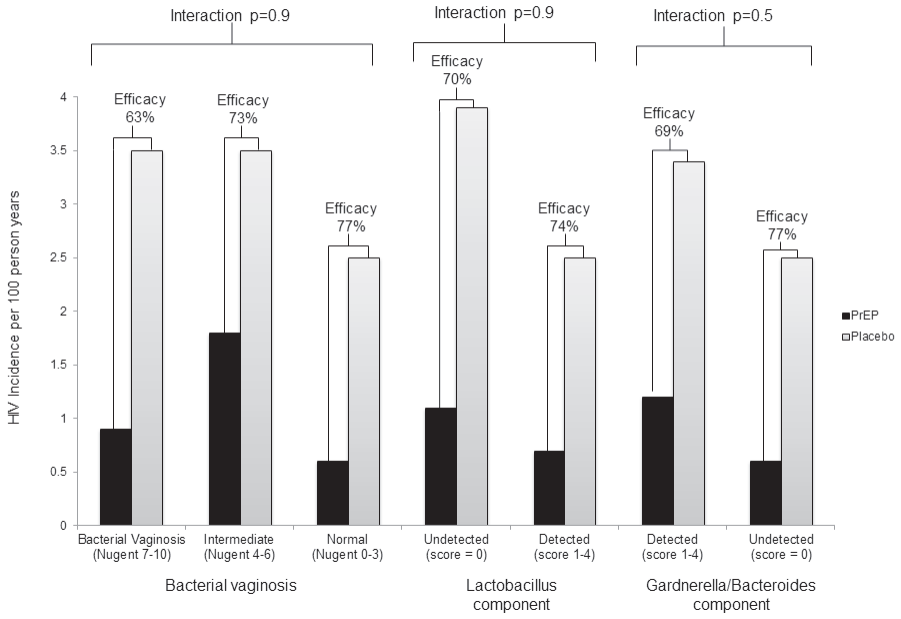
Background: Drug resistance in individuals who acquire HIV while taking pre-exposure prophylaxis (PrEP) has been rare and mostly limited to those who initiate PrEP during unrecognized acute infection. A long-acting injectable formulation of the HIV integrase inhibitor (INI) cabotegravir (CAB LA) is currently in clinical development as a PrEP agent. We used a macaque model of simian HIV (SHIV) infection to model risks of drug resistance emergence associated to CAB LA initiation during undiagnosed HIV infection.
Methods: Six rhesus macaques were infected intravenously with a pathogenic RT-SHIV containing the SIVmac239 integrase, and received 50 mg/kg of CAB LA intramuscularly prior to seroconversion. Macaques received 2 subsequent CAB LA injections 4 weeks apart to sustain plasma drug levels above 4 times the protein-adjusted IC90 (4xPA-IC90) and model humans treated with 600-800 mg every 8-12 weeks. SHIV viremia and mucosal virus shedding was monitored by RT-PCR. Integrase mutations in plasma and rectal/vaginal fluids were monitored by population sequencing. Drug concentrations were measured by LC-MS.

Results: Plasma CAB concentrations throughout weeks 1-15 were above 4xPA-IC90 and remained detectable until week 26. CAB concentrations in rectal, but not vaginal fluids, were also above 4xPA-IC90 throughout weeks 1-15. Median plasma viremia at the time of the first CAB LA injection was 7.8 log10 RNA copies/ml, fluctuated between undetectable (<50 copies) and 4.2 log10 RNA copies/ml throughout week 1-16 of treatment, and gradually increased to a plateau of ~4.0 log10 by week 19. Analysis of integrase sequences in plasma showed emergence of mutations in 3/6 macaques: one animal had G118R/A122T at weeks 8-23, one had E92G at week 20, and one had G140R at week 12, E92Q at weeks 12-19, and Q124R at weeks 22-26. The G118R/A122T and E92Q mutations were also detected in viruses from vaginal and rectal fluids. Phenotypic testing is needed to assess the level of CAB resistance conferred by these mutations.
Conclusion: CAB initiation during acute infection frequently selects for mutations that are known to be associated with resistance to other INI including G118R, E92Q, and E92G. Some of the mutations were detected as early as 8 weeks and persisted during the pharmacologic tail. The finding of G118R and E92Q in rectal and vaginal fluid highlights risks of secondary transmission of these viruses. Our results reiterate the importance of strategies to prevent CAB LA PrEP initiation during undiagnosed HIV infection.

85 DAILY ORAL PREP IS EFFECTIVE AMONG WOMEN WITH ABNORMAL VAGINAL MICROBIOTA

Renee Heffron[1], R. Scott McClelland[1], Jennifer Balkus[2], Connie L. Celum[1], Craig Cohen[3], Nelly Mugo[4], Elizabeth A. Bukusi[4], Deborah J. Donnell[2], Jared Baeten[1] , for the Partners PrEP Study Team
[1]Univ of Washington, Seattle, WA, USA, [2]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [3]Univ of California San Francisco, San Francisco, CA, USA, [4]Kenya Med Rsr Inst, Nairobi, Kenya
Background: Daily oral tenofovir-based PrEP demonstrated high efficacy in clinical trials for HIV prevention among women with high adherence. Recent data suggest that vaginal tenofovir gel may not effectively prevent HIV among women with bacterial vaginosis or other indicators of vaginal dysbiosis (e.g., non-Lactobacillus or Gardnerella¬ predominance). Those data raised concern whether daily oral tenofovir could be less effective among women with abnormal vaginal microbiota.
Methods: Using data from women in the Partners PrEP Study, a phase III placebo-controlled trial of daily oral PrEP conducted in Kenya and Uganda that had high (~80%) PrEP adherence and overall efficacy >70% in women, we assessed PrEP efficacy among subgroups of women defined by bacterial vaginosis status, measured annually. Nugent score by microscopy was used to measure bacterial vaginosis, with 0-3 indicating normal, 4-6 intermediate, and 7-10 bacterial vaginosis. We also considered the separate components of the Nugent score: detection of Gardnerella/Bacteroides and non-detection of Lactobacillus as markers of abnormal vaginal microbiota.
Results: Of 1470 women, the median age was 33 years (13% were aged <25 years), and 24% had bacterial vaginosis at enrollment. PrEP had comparable efficacy for HIV prevention among women with normal microbiota (efficacy=77%), intermediate microbiota (73%), and bacterial vaginosis (63%) (interaction p-value=0.9, Figure). Similarly, PrEP efficacy was not different among women with detected versus undetected Gardnerella/Bacteroides (69% efficacy versus 77%, interaction p=0.7) and Lactobacillus (74% versus 70%, interaction p=0.9).
Conclusion: Among African women with a high prevalence of bacterial vaginosis and high PrEP adherence, the efficacy of daily oral PrEP was not different among women with abnormal versus normal vaginal microbiota. Bacterial vaginosis and other indicators of vaginal dysbiosis do not diminish the efficacy of oral PrEP for HIV prevention.

Figure. Efficacy of daily oral PrEP for HIV prevention in women with and without vaginal dysbiosis



86LB IMPACT OF VAGINAL MICROBIOTA ON GENITAL TISSUE AND PLASMA CONCENTRATIONS OF TENOFOVIR

Sharon L. Hillier[1], Leslie A. Meyn[1], Katherine Bunge[2], Michele Austin[3], Bernard J. Moncla[1], Charlene S. Dezzutti[1], Jill Schwartz[4], Mark A. Marzinke[5], Craig Hendrix[5], Lisa C. Rohan[1]
[1]Univ of Pittsburgh, Pittsburgh, PA, USA, [2]Magee-Womens Hospital of UPMC, Pittsburgh, PA, USA, [3]Magee-Womens Rsr Inst, Pittsburgh, PA, USA, [4]CONRAD, Arlington, VA, USA, [5]Johns Hopkins Univ, Baltimore, MD, USA
Background: Secondary analyses of CAPRISA 004 showed that women with a Lactobacillus dominant vaginal microbiota had higher detection of tenofovir (TFV) in cervicovaginal lavage (CVL) fluid than women with non-Lactobacillus dominant microbiota. The objective of this secondary analysis was to evaluate the impact of vaginal microbiota on TFV concentrations in the genital tract and plasma, and tenofovir diphosphate (TFV-dp) in genital tissues following timed vaginal application.
Methods: 41 healthy HIV negative women (mean age 28, 71% white) used either TFV 1% gel (40 mg) or films (40 and 10 mg) for 6 days. After 6 self-administered doses, cervicovaginal fluid (CVF) was collected on the 7th day prior to the final dose. Women inserted the final dose in the clinic with confirmation of correct product placement. Two hours later, cervical biopsies were obtained for tissue TFV-dp. Plasma and CVL were collected for TFV quantification. Vaginal swabs for diagnosis of bacterial vaginosis (Nugent score) and quantitative PCR detection of G vaginalis (GVAG) and Atopobium vaginae (AVAG) were collected prior to product use. The relationship between vaginal microbiota and TFV concentrations was assessed using linear and quadratic regression models.

Results: After 6 days of vaginal TFV use, trough TFV concentrations were lower in the CVF (P=0.032) and plasma (P=0.05) among women having higher levels of GVAG. Two hours after the final directly observed TFV product application, higher GVAG concentrations were significantly associated with decreased TFV-dp in cervical tissues (P=0.019) and lower TFV concentrations in plasma (P=.001, Figure 1A,B). There was also a linear association between increasing concentrations of AVAG and decreased TFV-dp in cervical tissue (P=0.006) and plasma concentrations of TFV (P=0.03). Women having Lactobacillus dominant microbiota (Nugent score 0-3) had significantly higher levels of TFV in the plasma (P=0.001) and TFV-dp in cervical tissues (P=0.045). CVL concentrations of TFV two hours after product application were not associated with vaginal microbiota (P>0.08).
Conclusion: This study supports the CAPRISA findings and show that levels of TFV-dp in genital tissues and TFV in the plasma are correlated to markers of bacterial vaginosis (Nugent score, increased GVAG and AVAG). These data suggest that vaginal microbiota may impact the uptake of tenofovir when applied intravaginally. The mechanisms associated with reduced tenofovir uptake and its clinical implications require further study.

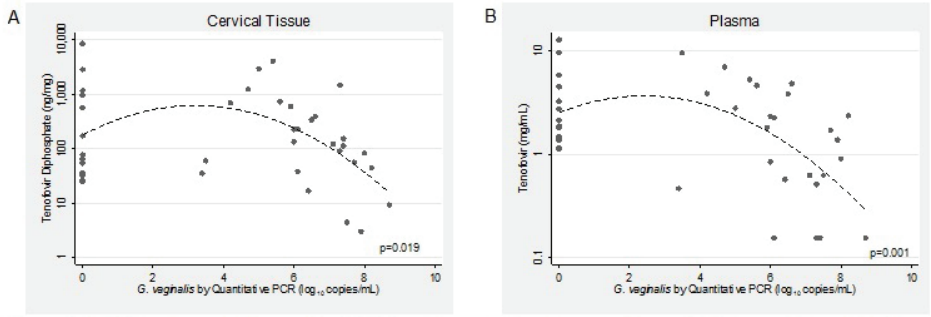


Figure 1. TFV-dp in Cervical Tissue (A) and TFV in Plasma (B) vs *Gardnerella vaginalis* Concentration in the Vagina

87 ABUNDANCE OF PENILE ANAEROBES, IL-8, AND THE RISK OF HIV ACQUISITION, RAKAI, UGANDA

Cindy M. Liu[1], Jessica Prodger[2], Aaron Tobian[2], Rupert Kaul[3], Alison Abraham[2], Godfrey Kigozi[4], Fred Nalugoda[4], David Serwadda[5], **Lance Price**[1], Ronald H. Gray[2]
[1]George Washington Univ, Washington, DC, USA, [2]Johns Hopkins Univ, Baltimore, MD, USA, [3]Univ of Toronto, Toronto, Ontario, Canada, [4]Rakai Hlth Scis Prog, Kalisizo, Uganda, [5]Makerere Univ, Kampala, Uganda

Background: The biological basis for the variability in HIV risk is not fully understood. The microbiome has been shown to affect the immune milieu of the genital mucosa, and we have shown that penile anaerobes were significantly decreased by medical male circumcision, which also reduced HIV acquisition. Thus, we hypothesize that genital microbiota may affect host susceptibility to HIV via immune activation.
Methods: We conducted a case-control study using enrollment data from a male circumcision randomized trial in Rakai, Uganda. Cases (n=68) were men who acquired HIV during the 24-month follow-up and controls (n=199) were men who remained HIV-uninfected over the study period. Cases and controls were matched by randomization assignment. Real-time PCR and sequencing of the 16S rRNA V3V6 region of DNA extracted from eluent of sub-preputial swabs were used to estimate bacterial absolute abundance as the $\log_{10}$ 16S rRNA gene copies/swab. Logistic regression was used to assess the adjusted odds ratio (adjOR) of seroconversion associated with anaerobe abundance.
Results: At enrollment, the cases had significantly higher abundance of penile anaerobes than controls, including *Prevotella*, *Dialister*, *Finegoldia*, and *Peptostreptococcus*. Higher abundance of penile anaerobes was associated with increased of HIV seroconversion (Table 1). The highest odds of HIV acquisition associated with each $\log_{10}$ increase in abundance were for *Prevotella* (adjOR=1.54, 95% CI: 1.22-1.98), *Finegoldia* (adjOR=1.50, 95% CI: 1.12-2.07), *Peptoniphilus* (adjOR=1.48, 95% CI: 1.13-1.99), and *Dialister* (adjOR=1.47, 95% CI: 1.20-1.84). Cases were more likely than the controls to have detectable levels of IL-8, MCP-1, MIG, and MIP-3α (≥ 2 cytokines, p = 0.06). Additionally, sub-preputial IL-8 levels correlated significantly with anaerobe abundance.
Conclusion: Penile anaerobes may play a role in HIV susceptibility in men comparable to bacterial vaginosis in women, suggesting the possibility that a sexually transmissible ecological imbalance increases HIV susceptibility in both sexes.

Table 1. Penile anaerobe absolute abundance at trial enrollment and odds of HIV seroconversion per 10-fold increase during 2 year study period

	Unadjusted		Adjusted*	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Gram-Negative				
Prevotella	1.27	(1.06, 1.55)	1.54	(1.22, 1.98)
Porphyromonas	1.12	(0.95, 1.34)	1.35	(1.10, 1.69)
Dialister	1.28	(1.09, 1.53)	1.47	(1.20, 1.84)
Negativicoccus	0.95	(0.85, 1.06)	0.98	(0.86, 1.11)
Mobiluncus	1.08	(0.97, 1.22)	1.27	(1.10, 1.48)
Gram-Positive				
Finegoldia	1.34	(1.04, 1.77)	1.50	(1.12, 2.07)
Peptoniphilus	1.24	(0.99, 1.58)	1.48	(1.13, 1.99)
Anaerococcus	1.20	(0.93, 1.58)	1.35	(1.00, 1.88)
Murdochiella	1.11	(0.97, 1.28)	1.21	(1.05, 1.44)
Peptostreptococcus	1.20	(1.06, 1.37)	1.21	(1.06, 1.41)

*Adjusted for age, marital status, number of extramarital sexual partners, condom use, and genital discharge symptoms

88 DAPIVIRINE RING USE DOES NOT DIMINISH THE EFFECTIVENESS OF HORMONAL CONTRACEPTION

Jennifer Balkus[1], Thesla Palanee-Phillips[2], Samantha Siva[3], Clemensia Nakabiito[4], Gonasangrie Nair[5], Samuel Kabwigu[4], Ishana Harkoo[6], Catherine Chappell[7], Lydia Soto-Torres[8], Jared Baeten[9]

[1]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [2]Wits Reproductive Hlth and HIV Inst, Johannesburg, South Africa, [3]South African Med Rsr Council, Durban, South Africa, [4]Makerere Univ-Johns Hopkins Univ Rsr Collab, Kampala, Uganda, [5]Emavundleni Rsr Cntr, Cape Town, South Africa, [6]CAPRISA, Durban, South Africa, [7]Magee-Womens Hosp of UPMC, Pittsburgh, PA, USA, [8]NIH, Bethesda, MD, USA, [9]Univ of Washington, Seattle, WA, USA

Background: Prevention of HIV-1 and unplanned pregnancy are global public health priorities for reproductive-aged women. HIV-1 treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs) has been associated with a reduced effectiveness of some hormonal contraceptives for pregnancy prevention, particularly implantable methods. A vaginal ring containing dapivirine, a novel NNRTI, has demonstrated effectiveness for HIV-1 prevention; the potential for a drug-drug interaction between vaginally-delivered dapivirine and contraceptive effectiveness has not been assessed in epidemiologic studies.

Methods: MTN-020/ASPIRE was a randomized, double-blind, placebo-controlled phase III safety and effectiveness study of the dapivirine vaginal ring for HIV-1 prevention. Sexually active women aged 18-45 years from Malawi, South Africa, Uganda, and Zimbabwe were enrolled. Use of a highly effective method of contraception was a criterion for study participation. At monthly visits, current contraceptive method was recorded on a standardized form and urine pregnancy tests were performed. If a participant became pregnant, study product was withheld for the duration of pregnancy and breastfeeding. Pregnancy incidence by arm was calculated separately for each contraceptive method and compared using an Andersen-Gill proportional hazards model stratified by site and censored at HIV-1 infection.

Results: Of 2629 women enrolled, 2536 women returned for follow-up and reported using a highly effective contraceptive method during study participation (1263 in the dapivirine arm, 1273 in the placebo arm). Overall pregnancy incidence among women reporting use of injectable depot medroxyprogesterone acetate (DMPA), injectable norethisterone enanthate (NET-EN), hormonal implants, or oral contraceptive pills (OCPs) was: 0.49, 0.58, 0.45, and 30.21 per 100 person-years, respectively. Pregnancy incidence did not differ for those assigned active dapivirine vaginal ring versus placebo ring for any of the hormonal contraceptive methods (Table).

Conclusion: Dapivirine vaginal ring use was not associated with diminished hormonal contraceptive effectiveness for pregnancy prevention. Oral contraceptive pill use was associated with high pregnancy incidence, which may be due to poor pill adherence. Injectable and implantable methods were highly effective in preventing pregnancy.

Table. Pregnancy incidence by study arm stratified by hormonal contraceptive method

Contraceptive method[1]	Study arm	# of pregnancies	# of person-yrs	Incidence[2] (95% CI)	Unadjusted HR[3] (95% CI)		Adjusted HR[4] (95% CI)	
DMPA	Dapivirine	3	692	0.43	0.78	(0.17, 3.52)	0.77	(0.17, 3.54)
	Placebo	4	744	0.54	1.00	---	1.00	---
NET-EN	Dapivirine	3	258	1.16	---	---	---	---
	Placebo	0	257	0	---	---	---	---
OCPs	Dapivirine	56	173	32.21	1.16	(0.77, 1.75)	1.29	(0.85, 1.95)
	Placebo	48	171	28.08	1.00	---	1.00	---
Implant	Dapivirine	1	458	0.22	0.34	(0.04, 3.30)	0.32	(0.03, 3.10)
	Placebo	3	434	0.69	1.00	---	1.00	---

[1]Contraceptive method considered as a time-varying factor. For missed visits, contraceptive method was imputed using last value carried forward.
[2]Incidence presented per 100 person-years
[3]Unadjusted models are stratified by site.
[4]Multivariable models are stratified by site and adjusted for the following factors: age at enrollment, marital status at enrollment, number of live births reported at enrollment, time-varying condom use at last vaginal sex act.

89 STD PARTNER SERVICES TO MONITOR AND PROMOTE PREP USE AMONG MEN WHO HAVE SEX WITH MEN

David A. Katz[1], Julia C. Dombrowski[1], Teal Bell[2], Matthew R. Golden[1]

[1]Univ of Washington, Seattle, WA, USA, [2]Washington State Dept of Hlth, Olympia, WA, USA

Background: Men who have sex with men (MSM) with bacterial STDs are at elevated risk for HIV acquisition. We used STD partner services (PS) to monitor pre-exposure prophylaxis (PrEP) use among MSM and link MSM with bacterial STDs to PrEP.

Methods: Disease Intervention Specialists (DIS) in King County, WA, attempt to provide PS to all MSM with early syphilis and to MSM with gonorrhea and chlamydia as resources allow. Public Health–Seattle & King County (PHSKC) defines MSM with any of the following as being at high risk for HIV: early syphilis, rectal gonorrhea, methamphetamine or poppers use, sex work, or an HIV-unsuppressed partner. DIS offer to refer high risk HIV-uninfected MSM to the PHSKC STD clinic to initiate PrEP and offer other MSM referrals to community medical providers. We used chi-square tests to compare PrEP use, acceptance of referrals, and initial PrEP assessment at the STD clinic by HIV risk and to assess temporal trends in current PrEP use. We evaluated trends in PrEP use among MSM with urethral gonorrhea, a largely symptomatic infection, as a measure unbiased by the high level of STD screening among MSM on PrEP.

Results: From 8/2014-6/2016, medical providers reported 3936 cases of early syphilis, gonorrhea, or chlamydial infection among HIV-uninfected MSM in King County, including 1105 of early syphilis and rectal gonorrhea (Table). Overall, 1149 (48%) of 2388 PS recipients were defined as high risk and eligible to receive PrEP at the PHSKC Clinic, of whom 956 (83%) had PrEP use assessed. Of those assessed, 407 (43%) reported already using PrEP. Among 549 not currently on PrEP, 338 (62%) were offered a referral, of whom 167 (49%) accepted. Of the 127 who accepted referral to the PHSKC Clinic, 72 (57%) attended a first PrEP assessment visit as of 9/26/16. Among PS recipients not defined as high risk, 28% were already using PrEP; among

HIV Pre-Exposure Prophylaxis (PrEP) Use and Uptake among HIV-Negative MSM with Bacterial STDs Receiving Partner Services (PS)

	Early syphilis or rectal GC	CT (any site) or urethral or pharyngeal GC		p-value
Cases	1105	2831		
Received PS (of cases)	780 (71%)	1608 (57%)		<.001
PHSKC program eligible (of PS recipients)	780 (100%)	369 (23%)		<.001
		High Risk PS recipients (N = 369)	Lower Risk PS recipients (N =1239)	
PrEP use assessed (of eligible/ineligible)	656 (84%)	300 (81%)	969 (78%)	0.005
Currently using PrEP (of assessed)	264 (40%)	143 (48%)	267 (28%)	<.001
Not currently using PrEP (of assessed)	389 (60%)	157 (52%)	702 (72%)	<.001
Offered PrEP referral (of non-users)	303 (77%)	35 (22%)	105 (15%)	<.001
Accepted PrEP referral (of non-users)	145 (48%)	22 (63%)	49 (47%)	0.216
Accepted PHSKC Clinic referral (of accepted)	115 (79%)	12 (55%)	13 (27%)	<.001
Attended PrEP assessment visit* (of Clinic referral)	66 (57%)	6 (50%)	5 (38%)	0.402

GC = gonorrhea. CT = chlamydial infection. High risk = MSM with early syphilis, rectal gonorrhea, or who report methamphetamine or poppers use, sex work, or an HIV-unsuppressed partner in the last year. *As of 9/26/2016.

non-current users offered referrals, 47% accepted. The percent of cases reporting already taking PrEP increased from 21% in 2014 to 53% in 2016 among early syphilis and rectal gonorrhea cases (p<.001), from 30% to 58% among other high risk MSM (p=.007), and 15% to 36% among lower risk MSM (p<.001). Among MSM with urethral gonorrhea, PrEP use increased from 17% to 35% (p=.03).
Conclusion: PrEP use is rapidly increasing among MSM with bacterial STDs in King County. STD PS can be used to monitor PrEP use in high risk MSM and link these men to PrEP, though additional efforts are needed to increase intervention uptake at each step of the referral process.

90 CHALLENGES OF TRANSLATING PREP INTEREST INTO UPTAKE AMONG YOUNG BLACK MSM IN ATLANTA

Charlotte-Paige M. Rolle[1], Aaron S. Siegler[1], Travis Sanchez[1], Nicole Luisi[1], Scott R. Cutro[2], Carlos del Rio[1], Patrick Sullivan[1], Eli Rosenberg[1], Colleen F. Kelley[1]
[1]Emory Univ, Atlanta, GA, USA, [2]Kaiser Permanente, Atlanta, GA, USA

Background: The highest HIV incidence rates in the US are among young, black MSM (YBMSM). We hypothesized that structural barriers (e.g. lack of health insurance) could limit PrEP uptake in this group. Here, we describe the implementation of an optional PrEP program as an addition to a standard package of HIV prevention services in a currently enrolling, HIV/STI incidence cohort of YBMSM.
Methods: The EleMENt study is an ongoing, observational cohort examining longitudinal interactions between substance use and HIV risk behavior among HIV-negative YBMSM aged 16-29 years in Atlanta, GA. Participants are offered comprehensive HIV risk reduction counseling, condoms and lubricant, and daily oral PrEP as non-incentivized standard of HIV prevention care. After viewing a brief educational video (whatisprep.org), men who express interest in PrEP are scheduled to see a study clinician to initiate PrEP. All costs associated with clinician visits and PrEP lab monitoring are covered by the study; participants use their health insurance and/or manufacturer assistance program to obtain the drug. All PrEP users receive adherence counseling/tools per CDC guidelines. Factors associated with PrEP uptake were assessed with unadjusted odds ratios.
Results: Between July 2015 and September 2016, 113 HIV-negative YBMSM enrolled; 3/113 (2.7%) were taking PrEP at study entry. After viewing the video, 17/110 (15%) men reported no interest in PrEP; 31/110 (28%) men wanted to discuss PrEP at the next study visit, and 62/110 (56%) men indicated interest in starting PrEP now. Of 62 interested men, 24 (39%) have not attended a PrEP initiation appointment despite repeated scheduling attempts. Thirty-eight men (38/110; 35%) initiated PrEP; however, 6/38 (16%) subsequently discontinued PrEP. The only evaluated factor associated with PrEP uptake was STI diagnosis in the prior year (OR 3.2 95%CI 1.27, 8.2). Of 54.5 person-years of follow-up to date, 4 HIV seroconversions have occurred in the cohort (annualized incidence rate of 7.3% [95% CI 2.3, 17.7]); 3 occurred in men who initiated PrEP but were not taking it.
Conclusion: Despite high levels of interest, uptake and adherence to PrEP appear to be suboptimal among YBMSM in this ongoing cohort even after amelioration of structural barriers that can limit PrEP use. Implementation of PrEP as standard of HIV prevention care in observational studies is feasible. However, further research will be needed to optimize uptake and adherence for YBMSM as we are observing high HIV incidence.

TABLE 1-Factors associated with PrEP initiation in a prospective observational cohort study of young black MSM, Atlanta 2015-2016

Characteristic	Initiated PrEP (n=38) n (%)	Did not initiate PrEP (n=72) n (%)	Unadjusted OR (95% CI)
Age			
<24y.o.	13 (34.2)	36 (50)	0.52 (0.23, 1.18)
≥24 y.o.	25 (65.8)	36 (50)	
Education			
High school or below	8 (21.1)	23 (31.9)	0.57 (0.22, 1.42)
At least some college	30 (78.9)	49 (68.1)	
Income			
<20,000 annually	20 (55.6)	32 (47.1)	1.4 (0.62, 3.2)
≥20,000 annually	16 (44.4)	36 (52.9)	
Insurance			
Yes	20 (52.6)	46 (63.9)	0.63 (0.28, 1.41)
No	18 (47.4)	26 (36.1)	
Has a primary care provider			
Yes	22 (57.9)	31 (43.1)	1.81 (0.81, 4.1)
No	16 (42.1)	41 (56.9)	
Sexual identity			
Homosexual	33 (86.8)	54 (75)	2.18 (0.76, 7.15)
Bisexual/Other	5 (13.2)	18 (25)	
Relationship status			
Committed relationship	8 (21.1)	21 (29.2)	0.65 (0.24, 1.63)
Not in a committed relationship	30 (78.9)	51 (70.8)	
Substance abuse in the last 6 months			
Yes	30 (78.9)	53 (73.6)	1.34 (0.53, 3.6)
No	8 (21.1)	19 (26.4)	
Any UAI in the last 6 months			
Yes	32 (84.2)	50 (69.4)	2.33 (0.87, 6.9)
No	6 (15.8)	22 (30.6)	
HIV-positive partner in the last 6 months			
Yes	6 (15.8)	3 (4.2)	4.25 (0.99, 21.96)
No	32 (84.2)	69 (95.8)	
Reported STI in the last 12 months			
Yes	14 (36.8)	11 (15.3)	**3.2 (1.27, 8.2)**
No	24 (63.2)	61 (84.7)	
HIV test in the last 12 months			
Yes	36 (94.7)	62 (86.1)	2.88 (0.66, 20.26)
No	2 (5.3)	10 (13.9)	

Note. Significant p-values (p < 0.05) have been bolded for ease of interpretation.
Abbreviations. CI, confidence interval; HIV, Human Immunodeficiency Virus; OR, Odds Ratio; PrEP, Pre-Exposure Prophylaxis; UAI, Unprotected anal intercourse; STI, Sexually Transmitted Infection

91LB ON DEMAND POST EXPOSURE PROPHYLAXIS WITH DOXYCYCLINE FOR MSM ENROLLED IN A PREP TRIAL

Jean-Michel Molina[1], Isabelle Charreau[2], Christian Chidiac[3], Gilles Pialoux[4], Eric Cua[5], Constance Delaugerre[1], Catherine Capitant[2], Daniela Rojas-Castro[6], Laurence Meyer[7] , for the ANRS IPERGAY Study Group
[1]St. Louis, Hosp, Paris, France, [2]INSERM, Villejuif, France, [3]Univ of Lyon, Lyon, France, [4]Tenon Hosp, Paris, France, [5]CHU de Nice, Nice, France, [6]AIDES, Pantin, France, [7]AP-HP, Le Kremlin-Bicetre, France

Background: A high incidence of bacterial sexually transmitted infections (STIs) has been reported in several PrEP trials and demonstration projects among MSM. We wished to assess whether on demand post-exposure prophylaxis (PEP) with doxycycline could reduce STIs incidence in this high risk group.
Methods: High risk adult MSM being followed in the open-label phase of the ANRS IPERGAY trial with on demand TDF/FTC for HIV prevention, were enrolled in a prospective randomized open-label sub-study. Participants (pts) were randomized 1:1 to take either two pills of doxycycline (100mg per pill) within 72h after condomless sexual intercourse (without exceeding 6 pills per week) or no PEP. All subjects received risk-reduction counseling and condoms, and were tested every 8 weeks for HIV and STIs with serologic assays

for HIV and syphilis and PCR assays for Chlamydia trachomatis and Neisseria gonorrhoeae in urine samples, oral and anal swabs. The primary study endpoint was the time to a first bacterial STI: gonorrhoea, chlamydia infection or syphilis. We compared the two study arms according to the intention-to-treat principle. We used time-to-event methods, including Kaplan–Meier survival curves and Cox proportional-hazards models.

Results: From July 2015 to January 2016, 232 pts were randomized, 116 in each arm. Median follow-up was 8.7 months (IQR: 7.8-9.7). Seventy-three pts acquired STIs during the study period, 28 pts in the PEP arm (24%, 37.7 events per 100 pt-years) as compared to 45 pts in the no PEP arm (38.8%, 69.7 events per 100 pt-years) for a hazard ratio (HR) of 0.53 (95% CI: 0.33-0.85, P=0.008). HR for gonorrhoea, chlamydia infection and syphilis were 0.83 (95% CI: 0.47-1.47, p=0.52), 0.30 (95% CI: 0.13-0.70, p=0.006) and 0.27 (95% CI: 0.07-0.98, p<0.05), respectively. Overall 71% of all STIs were asymptomatic. Pts in the PEP arm used a median of 7 pills/month (IQR: 3-13). Safety was good with only 8 pts (7%) discontinuing PEP because of gastro-intestinal adverse events (AEs). Gastrointestinal AEs were reported in 61 pts (53%) and 47 pts (41%) in the PEP and no PEP arms, respectively (p=0.07). There was no significant change in sexual behavior between study arms during follow-up.

Conclusion: On demand PEP with doxycycline reduced the incidence of chlamydia infection and syphilis in high risk MSM and has an acceptable safety profile. The long-term efficacy of this strategy and its impact on antibiotic resistance needs to be assessed.

92 THE FATES AND FOLDS OF HIV-1 RNA

Alice Telesnitsky, *Univ of Michigan, Ann Arbor, MI, USA*

Interconverting RNA structures composed of overlapping sequences near HIV-1 RNA's 5' end orchestrate several replication functions. For example, when folded into the packaging signal Ψ, this region of RNA dimerizes and forms a structure that is recognized by viral proteins to mediate specific encapsidation of HIV-1 genomic RNA. The same region of RNA can adopt an alternate fold that is not recognized for packaging and likely contributes to other replication functions, such as serving as mRNA. The importance of these alternate RNA structures is supported by experimental work in which mutations that stabilize the mRNA conformer decrease RNA packaging. However how HIV-1 naturally achieves the correct balance of RNA structures has remained unclear. In work comparing the folding of the packaging signal as a minimal RNA element vs in its native context, we made the surprising discovery that very subtle transcript variation-even the addition of a single nucleotide far from the sequences that fold into the packaging signal-could completely shift the equilibrium of alternate RNA structures. Our analysis suggested a model in which this tiny change could initiate a domino effect of alternating basepairs, and made us speculate that similar transcript heterogeneity could help define the balance of HIV-1 RNA structures if it existed in vivo and had gone undetected in previous analyses. Our subsequent analysis of virion and infected cell RNAs revealed that indeed, the HIV-1 RNAs in infected cells include transcripts that differ subtly from one another, and that virion and infected cell RNA populations differ significantly. Further analyses revealed that this heterogeneity results from integrated HIV-1 proviruses making use of a small cluster of transcription start sites, with the shorter of the resulting transcripts adopting the packaging-competent fold while RNAs longer by a single base or two are enriched on poly-ribosomes, and preferentially adopt the translation-competent fold. These studies represent a striking example of a previously-unrecognized form of RNA regulation, in which the folding of initial transcribed sequences can set up a cascade of RNA folding events that dictate an RNA's folded conformation, binding partners and biologic destiny.

93 STRUCTURE AND FUNCTION OF IMMATURE AND MATURE HIV CAPSIDS

Hans-Georg Kräusslich, *Heidelberg Univ, Heidelberg, Germany*

Formation of infectious HIV particles is directed by the viral Gag polyprotein and occurs at the plasma membrane of the producer cell. Gag initially assembles into an immature capsid shell structured as a truncated sphere consisting of regular hexameric subunits and irregular defects. This stable capsid structure corresponds to the production mode, while Gag proteolysis by the viral protease inside the complete virion converts the structure into the infection mode. Release of the CA domain from the polyprotein leads to disassembly of the immature shell and formation of the cone-shaped mature capsid, exhibiting a fullerene-geometry consisting of CA hexamers and pentamers. Recent cryo electron microscopy analyses have yielded unprecedented details of the structures of both the immature and the mature virion, and provided new insights into capsid function and inhibition.

94 A ROLE OF HIV-1 INTEGRASE IN ENCAPSIDATION OF THE VIRAL RNA GENOME

Mamuka Kvaratskhelia, *The Ohio State Univ, Columbus, OH, USA*

An essential role of HIV-1 integrase (IN) for integration of viral cDNA into human chromosomes is well established. However, mutagenesis studies have suggested a multifunctional role of IN in HIV-1 biology as two distinct phenotypes have been observed for IN substitutions: class I, which selectively impair integration and class II, which display additional reverse transcription and particle maturation defects. However, for the past 20 years it has remained enigmatic as to how IN could contribute to proper viral particle maturation. The interest in elucidating a potential active role of IN during virion maturation has been bolstered recently after the discovery of allosteric HIV-1 IN inhibitors (ALLINIs), which are currently in clinical trials. ALLINIs induce aberrant IN multimerization in virions and similar to class II IN substitutions yield eccentric, non-infectious virions, where ribonucleoprotein complexes are mislocalized outside of the protective capsid core. To elucidate a potential role of IN during virion maturation we used crosslinking-immunoprecipitation sequencing (CLIP-seq) and complementary in vitro biophysical approaches to test whether IN interacts with the viral RNA genome and whether these interactions contribute to correct viral particle morphogenesis. Our studies have led us to the following novel findings: i) IN binds the viral RNA genome in virions. These interactions have specificity as IN exhibits distinct preference for select viral RNA structural elements in virions and in vitro; ii) CLIP-seq results show divergent but highly reproducible binding patterns for IN and nucleocapsid (NC) on the viral RNA genome suggesting that these proteins can bind viral RNA at the same time in the virion; iii) IN R269A/K273A substitutions compromise IN binding to the viral RNA genome without significantly affecting other known functions of this viral protein and result in particles with eccentrically mislocalized ribonucleoprotein complexes; iv) Likewise, ALLINIs impair IN binding to the viral RNA genome in virions of wild type but not the escape mutant virus; v) Unlike IN-RNA interactions, NC-RNA complexes are not affected in the eccentric non-infectious virions. Collectively, these results reveal a non-catalytic biological function of IN during virion maturation, which includes its ability to bind and localize the viral RNA genome within the protective capsid core, and elucidate the mode of action of ALLINIs.

95 TRIM5ALPHA RECOGNITION OF THE HIV CAPSID

Barbie K. Ganser-Pornillos, *Univ of Virginia, Charlottesville, VA, USA*

Restriction factors and pattern recognition receptors make up intrinsic cellular defenses against viral infection. TRIM5 proteins are restriction factors and receptors that recognize the incoming capsid cores of retroviruses. Upon capsid binding, TRIM5 proteins accelerate dissociation of the viral core, inhibit reverse transcription of the viral genome, and activate ubiquitin-dependent interferon production. TRIM5 proteins contain the tripartite motif fold (RING, B-box, and coiled-coil domains) and a C-terminal domain (SPRY or CypA) that mediates direct binding to retroviral capsids. Retroviral capsids are fullerene structures composed of about 1,500 copies of the viral CA protein, which are organized on a hexagonal lattice composed of about 350 hexamers and exactly 12 pentamers. Capsid recognition is avidity-driven, requiring higher-order assembly of multiple TRIM5 protein molecules on the capsid surface. We have been using a combination of techniques, including X-ray crystallography of purified TRIM proteins and domains, biochemical reconstitution of TRIM5/capsid complexes, and cryoEM analyses of these complexes to obtain molecular insights on how the TRIM5α protein specifically recognizes the HIV-1 capsid. Our aggregate data (together with those of others) reveal that TRIM5α assembles into a two-dimensional hexagonal net that wraps around a retroviral capsid. The hexagonal TRIM net displays an array of SPRY domains to match the positions and orientations of their corresponding binding epitopes on the capsid surface. Assembly of the TRIM lattice also promotes dimerization and activation of the RING domains, leading to efficient synthesis of polyubiquitin chains. Higher-order assembly of TRIM5α therefore spatially organizes the biochemical activities of the different TRIM5α domains and directly couples capsid recognition to ubiquitin-dependent downstream processes that lead to viral inhibition and interferon signaling.

96 HEPATITIS B: PROGRESS AND PROSPECTS IN HEPATITIS B VIRUS CURE

Patrick Kennedy, *Queen Mary Univ London, London, United Kingdom*

The treatment paradigm in Hepatitis B Virus (HBV) is on the cusp of major change, with a multitude of novel agents entering various phases of clinical trials. Novel therapies designed to cure HBV should ultimately restore antiviral immunity similar to that seen in those who naturally resolve HBV infection. Achieving HBsAg loss (or functional cure) in Chronic Hepatitis B (CHB) is dependent on a functional efficient HBV-specific adaptive immune response, with potential innate immune interaction; thus global immune restoration is likely to lead to improved treatment outcomes. The current direct antiviral therapies; although able to control viral replication and limit the progression to cirrhosis; require lifelong administration owing to a lack of sustained immune control off therapy, while immune modulation with interferon is only effective in a small proportion of patients. Better utilization of current therapies through combination and/or sequential strategies has recently been investigated by us (and others) and may merit further exploration. Major challenges in the employment of novel therapeutic approaches will be better definition of which cohorts of CHB patients should be targeted and the development of strategies that preferentially suppress HBV replication, reduce or degrade the cccDNA reservoir without generating excess liver damage. HBV therapy may be more effective and even less toxic in subjects with residual HBV-specific T cells without pre-existing liver inflammation. In keeping with this, I will discuss whether young patients with chronic hepatitis B (considered immune tolerant) with normal ALT levels, harbouring more HBV-specific T cells than their adult counterparts (categorised as immune active), may be better candidates for therapy than previously thought. I will discuss strategies to utilise current therapies to harness the immune response, discuss novel agents in the pipeline along with, in whom and how best to utilize these novel therapies in order to achieve functional cure with defined treatment endpoints in CHB. In addition, I will also consider risk-stratifying patients using non-invasive tests, to determine those patients at greatest risk for the development of hepatocellular carcinoma.

97 MANAGEMENT OF CHRONIC HEPATITIS B DURING PREGNANCY

Mindie H. Nguyen, *Stanford Univ Med Cntr, Palo Alto, CA, USA*

Chronic infection with hepatitis B virus (HBV) affects more than 240 million individuals globally and can lead to serious complications, such as cirrhosis and hepatocellular carcinoma. While universal maternal screening programs and immunoprophylaxis to newborns have greatly reduced mother-to-child-transmission (MTCT), immunoprophylaxis can fail in up to 30% of infants, especially in mothers with high HBV DNA levels and positive HBeAg. As a result, there has been growing support for the initiation of antiviral therapy during late pregnancy in highly viremic women, and this has been shown in a recent randomized controlled trial to be safe and effective in preventing MTCT with antiviral therapy starting at 30-week gestation and in combination with birth-dose HBV immunoglobulin (HBIG) and vaccination followed by completion of the 3-dose vaccine series. Antiviral therapy may also be initiated to improve maternal outcomes, as immunological changes during pregnancy and post-partum can lead to acute liver failure in women. During pregnancy, cell-mediated immunity is suppressed, possibly due to an increase in adrenal corticosteroids, estrogens, and progesterone, thereby allowing the woman to tolerate the semiallogenic fetus. Post-partum, these changes are reversed. As a result, flares of alanine aminotransferase (ALT) and HBV DNA have been reported during pregnancy as well as the initial post-partum period in HBV-infected women. While most hepatic flares are during late trimester, mild and resolve spontaneously, approximately half can occur during second trimester or earlier and severe cases including liver failure have been reported both during pregnancy and postpartum. The American Association for the Study of Liver Diseases (AASLD) guidelines recommend antiviral therapy for pregnant women with HBV DNA >200,000 IU/mL, even in the absence of clinical symptoms, in order to reduce MTCT, and monitoring for ALT flares every 3 months for 6 months when antiviral therapy is discontinued. However, there is no consensus on the management of HBV in women with HBV DNA ≤200,000 IU/mL, women with active hepatic inflammation or advanced fibrosis, or who become pregnant while on therapy. In general, because significant HBV DNA and ALT flares can occur during pregnancy and early post-partum in women with CHB, HBV-infected women should be closely monitored every 4-6 weeks during pregnancy and early post-partum months three and six.

98 HEPATITIS C VIRUS: GONE BY 2030?

John W. Ward, *CDC, Atlanta, GA, USA*

Recognizing hepatitis C virus (HCV) as a major public health threat, the World Health Organization in 2016 released a strategy for global elimination by 2030 (i.e., 90% reduction in HCV transmission and 65% reduction in HCV-related mortality). The United States (US) National Academies of Sciences has deemed US elimination of HCV a feasible goal. HCV-Infected persons born during 1945-1965 are at greatest risk for HCV-related mortality. Certain strategies improve the HCV testing, care, and cure cascade and can reduce HCV-associated deaths. Provider education and adoption of clinical decision tools improve rates of HCV testing. Training and support of primary-care clinicians expand the workforce offering HCV services. Diagnosis of current HCV infection is improved by reflex testing of anti-HCV+ specimens for HCV RNA. Patient navigation services help persons begin and remain in care. At national and health-system levels, implementing policies and setting and measuring performance targets can improve quality of services. Issues with provider reimbursement for HCV treatment limit the number of persons treated through the Affordable Care Act and proposed changes might impact access to care. Creative solutions are needed for universal access to HCV treatment. Reducing US HCV transmission rate by 90% requires a targeted approach. Incidence is rising among persons who inject drugs (PWID); an increasing number of infants are born to HCV-infected mothers. Harm reduction services (e.g., clean injection equipment, drug treatment services) can prevent >70% of infections among PWID; HCV testing and treatment can enhance prevention. Access to these interventions is poor, particularly in areas with high HCV incidence. In the absence of an effective HCV vaccine, reaching elimination goals for transmission will require improved detection and investigation of transmission networks, increased availability of harm reduction services, affordable HCV therapies, and better evidence and capacity to deliver prevention services. Targeted intervention delivery to incarcerated and other vulnerable and marginalized populations is key to achieving elimination goals. With strong societal commitment and support for implementing comprehensive HCV prevention, testing, care, and treatment, HCV can be eliminated as a public health threat in the US.

99 FATTY LIVER DISEASE: A GROWING CONCERN

Rohit Loomba, *Univ of California San Diego, La Jolla, CA*

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of the chronic liver disease in the Western World. NAFLD is commonly associated with obesity and metabolic syndrome. It can be broadly sub-classified into two forms: nonalcoholic fatty liver (NAFL), the non-progressive form of NAFLD, and nonalcoholic steatohepatitis (NASH), the progressive form of NAFLD. NASH can lead to progressive fibrosis, cirrhosis and hepatocellular carcinoma. NAFLD associated with metabolic syndrome and obesity is commonly classified as primary NAFLD. NASH is typically associated with presence of steatosis in zone 3, lobular inflammation and ballooning with or without peri-sinusoidal fibrosis among individuals who consume little or no alcohol and do not have any other secondary cause of NAFLD such as hepatitis C infection, medications, lipodystrophy. Human immunodeficiency virus (HIV) infection is also been linked as a cause for secondary NAFLD due to multiple factors including increasing prevalence of metabolic syndrome in patients with HIV, use of antiretroviral therapies, presence of lipodystrophy among others. Recent data suggest that patients with HIV have higher rates of progressive form of NAFLD than non-HIV infected age, sex and Body-mass-index matched controls. There are several emerging non-invasive modalities for assessing presence of NASH and fibrosis that can now be applied to patients with HIV who may be at risk for advanced fibrosis or cirrhosis due to NAFLD. We will discuss novel data on advanced magnetic resonance imaging and elastography and it's role in disease severity assessment in NAFLD. We will also discuss novel and emerging treatment response assessment in NAFLD and it's relevance to HIV-associated NAFLD.

100 MTCT: EVOLVING EPIDEMIOLOGY AND PREGNANCY OUTCOMES

Roger L. Shapiro, *Harvard Schl of Pub Hlth, Boston, MA, USA*

Dramatic reductions in mother-to-child HIV transmission (MTCT) have accompanied the rollout of Option B+ and test-and-treat strategies throughout the world, with MTCT now below 2% in some high prevalence regions of Africa where it was over 30% early in the epidemic. However, the past decade has also brought with it a better understanding of potential risks associated with 3-drug ART use in pregnancy. Evidence points to associations between ART use (particularly from before conception) and higher risk for adverse

pregnancy outcomes, including stillbirths, preterm delivery, and low birth weight infants. Until recently there has been little data to compare individual ART exposures, but concerns have now emerged for increased risk with specific antiretroviral agents and combinations. This talk will review the current data for adverse pregnancy outcomes associated with specific ART regimens used in pregnancy. Mechanisms to explain these findings are lacking, and remain an urgent field of study. Ongoing surveillance for adverse pregnancy outcomes is warranted for women exposed to ART in pregnancy, particularly as new ART regimens become available.

101 THE ART AND SCIENCE OF INFANT DIAGNOSIS

Martina Penazzato, *WHO, Geneva, Switzerland*

Early identification of HIV infection in infants born to HIV-infected mothers is a critical intervention to accelerate treatment initiation and reduce early mortality. Despite important investments in early infant diagnosis (EID), as of December 2015, only 51% of HIV-exposed infants received a virological test by their second month of life. Rates of retention and linkage to treatment and care among those tested is low, with loss to follow-up of 30-80%. While further expansion and strengthening of existing EID programmes remains of paramount importance, promising innovative approaches have been identified and included in recommendations issued by the World Health Organization (WHO) in 2016. These include: addition of a virological test at birth to the EID algorithm, assays to be used at or close to point-of-care (POC). Birth testing enables earlier identification of infants infected in utero and allows identification of those infants who may not return for the standard 6 weeks virological test. Use of POC assays may further improve retention in the testing-to-treatment cascade by shortening results turnaround time and providing opportunities for decentralisation of EID. South Africa, which introduced birth testing in 2014, offers a model for other countries in Sub-Saharan Africa. Provision of virological testing at maternities appears to be feasible and well accepted. However, a number of challenges are being uncovered by the national scale up: increasing human resources need, importance of ensuring positive test results are confirmed, need for active tracking to ensure follow up testing and effective linkage to care when required as well as availability of the appropriate antiretrovirals in adequate formulations to treat neonates. The first point-of-care EID technologies were validated and prequalified in 2016. Field evaluations of the first commercially available POC assays have investigated their accuracy compared to laboratory EID assays and further studies are exploring their impact on the testing-to-treatment cascade. This presentation will summarize the rationale for recent global guidance on infant diagnosis, provide an overview of the emerging evidence to inform introduction of key innovations and discuss how implementation science remains critical to fully inform future policies and ensure that tailored approaches that maximize resources and outcomes are implemented.

102 THE HIV-EXPOSED AND UNINFECTED CHILD: WHAT'S TO WORRY?

Claire Thorne, *Univ College London, London, United Kingdom*

There has been a substantial increase in the proportion of pregnant and breastfeeding women receiving antiretroviral drugs worldwide, from an estimated 50% in 2010 to 77% in 2015. This reflects improved coverage of services for prevention of mother-to-child transmission and has contributed to the 51% decline in the number of new HIV infections in children aged 0-14 years since 2010. It also means that there are now over 1 million infants born every year who are exposed to both maternal HIV infection and antiretroviral drugs in utero and early life, the large majority of whom are HIV-uninfected. There is a large and growing literature focussed on the question of whether and how these exposures may impact on the health of HIV-exposed uninfected (HEU) children, with an increasing number of studies in low and middle income countries, providing important data in settings where most HEU children are born. Outcomes assessed to date have been diverse and include metabolism and mitochondrial function, neurodevelopment, immune function and infections, growth and malignancies. Although studies have provided data pointing to poorer health outcomes in HEU children, there are some conflicting results and methodological weaknesses. In this presentation, the latest literature on the health of HEU children will be synthesized, focussing on those exposed to both HIV and antiretrovirals. The challenges in assessing outcomes in HEU children and in interpreting study results will be discussed. These include the difficulties of disentangling potential effects of maternal HIV infection from antiretroviral exposure and of comparing findings from studies (often small) conducted in diverse populations with different methodologies/tools, as well as the need for studies to have appropriate HIV-unexposed controls and long-term follow-up to assess persistence of abnormalities and/or to identify potential late sequelae. In the context of Option B+, increasing numbers of infants will be exposed to antiretroviral exposure for their entire gestation, as well as during breastfeeding. This highlights the need to improve our understanding of the potential short- and long-term health outcomes associated with the changing in utero and early life exposure to antiretrovirals, in order to optimize the health of HEU children.

103 THE TREATMENT OF NEWBORNS AND INFANTS LIVING WITH HIV

Elizabeth Maleche Obimbo, *Univ of Nairobi, Nairobi, Kenya*

As HIV diagnostics improve and point of care diagnosis becomes available in wider settings it is hoped that infants with HIV-1 infection will be identified earlier and initiated on anti-retroviral therapy at a younger age. As this takes place there is need to understand which ARV drugs are available for infants, from which age, and what the persisting challenges around early ART initiation are, including paediatric drug formulation and palatability, dosing and safety. Specifically, for the newborn where evidence and ARV options have been minimal what evidence is emerging to inform therapy during the first days of life? What are our experiences on early treatment outcomes in varying settings, and how do these compare to outcomes of infants who access ART later? Given that children require lifelong treatment, there is need to better understand which ARV combinations are most durable, and what factors are impacting regimen efficacy. In the current environment where mothers living with HIV are now increasingly on combination ART during pregnancy and breastfeeding, for those infants that do become infected is there good evidence to guide the design of optimal regimens for them? The speaker shall explore and expound on emerging evidence and experiences on ART in HIV infected newborns and infants around the world.

104 ACTING OR NOT ACTING ON VIRAL LOAD

Steven J. Reynolds, *NIAID, NIH, Washington, DC, USA*

Access to routine viral load (VL) monitoring for patients on antiretroviral therapy (ART) has been limited in many resource-constrained settings until recently. Alternative monitoring approaches correlate poorly with virologic failure and can substantially delay switch to second-line therapy. The recent change in WHO monitoring guidelines to move towards routine VL monitoring as standard of care has empowered countries to scale up access to this important monitoring tool. Despite this change, the majority of individuals receiving antiretroviral therapy remain on first line treatment. Several implementation challenges have been faced by countries scaling up VL monitoring including low compliance with monitoring guidelines and frequent delays in switching patients with evidence of virologic failure to second line regimens. Delayed switching to second line therapy of patients with virologic failure could result in increased morbidity and mortality, accumulated drug resistance and increased risk of HIV transmission to partners, ultimately compromising the 90-90-90 goals set by UNAIDS. Innovative strategies will be needed in order to make viral load monitoring routine, ensure timely switching of regimens in the setting of virologic failure and ultimately maximize the benefits offered by the current scale up of this important monitoring tool.

105 MEASURING VIRAL LOAD: INNOVATIONS AND TAKING TO SCALE

Rosanna W. Peeling, *London Schl of Hygiene and Tropical Med, London, United Kingdom*

Recent technological advances have given countries a variety of options for measuring HIV Viral Load. While laboratory based nucleic acid amplification tests for quantifying viral load in plasma samples are highly accurate, these tests are costly and not widely accessible to patients outside of tertiary care settings. The use of Dried Blood Spots (DBS) has enabled country programs to increase access to VL monitoring but issues remain, such as backlogs in sample processing and the interpretation of viral load levels in patients who are plasma undetectable but DBS detectable. Innovations in VL tests that can be performed at the point-of-care (POC) have opened up possibilities of taking VL monitoring to scale within health care systems in both developed and developing countries. Continued innovations such as protocols to elute free virus from whole blood have resolved difficulties in the interpretation of plasma VL versus those measured in whole blood samples. Apart from technological innovations, there are also opportunities to introduce innovations in the

delivery of more patient-centred services and improvements in the quality of care. In the past, the introduction of POC technologies has put tremendous stresses in already fragile health care systems, amplifying by a hundred- to a thousand-fold issues of supply chain management, health care personnel shortage and quality assurance. The availability of data connectivity with these novel POC devices will allow countries to develop nationwide quality assurance and supply systems and streamline patient pathways. Lessons learnt from country uptake of other POC technologies and potential solutions have been incorporated in viral load introduction toolkits prepared by various implementing partners such as the US Centers for Disease Control and Prevention. These guidance tools need to be used with input from laboratory managers, health care providers and patient communities at every level of the health system. Leveraging innovations to take VL to scale is possible but will require closer collaboration of different stakeholders if countries were to achieve the third 90.

106 USING TECHNOLOGY TO IMPROVE ADHERENCE

Richard T. Lester, *Univ of British Columbia, Vancouver, Canada*

There already exists substantive evidence for how new and recent technologies can improve HIV treatment adherence. Yet, there remain major implementation gaps to overcome if achieving the third and final UNAIDS 90 (90% viral suppression by 2020) is to be met in a timely way at sufficient global scale. Some of the most pervasive and powerful technologies relate to the Digital Age and in particular the use of mobile phones as communication tools (mHealth) that can reach patients directly, or help their caregivers provide enhanced support. Evidence will be reviewed for what has worked, and what hasn't (focusing on randomized controlled trials and systematic reviews) and an attempt to understand why. In network meta-analyses, only SMS and enhanced counseling support improved adherence and viral suppression outcomes, and multiple modalities used in combination may be superior to single modalities alone. WelTel, a two-way communication method between patients and caregivers on a text-messaging management software platform, will be used as an illustration but other innovations will be considered. Consideration will also be given as to what adherence technology modalities are likely to: 1) reach the highest proportion of those infected with HIV; 2) be acceptable among users; and 3) be feasible to scale in health systems (in time). Digital tools are not evenly distributed and different settings and key populations may require different strategies or offer new opportunities (e.g. smartphones and internet are reaching an increasing proportion of people in LMIC and more resourced settings, but remain will a minority within the 90-90-90 timeframe). Despite available data, there has been a failure to put evidence to action thus far - we will try to learn from those lessons. Issues such a local development and ownership of digital technologies may need to be rethought in favour of programs of 'global ownership' for scale. Data for cost-effectiveness and implementation science are starting to emerge but funding mechanisms have been elusive for the massive scale required. In order to harness technologies to improve treatment adherence and impact the third 90 in less than 4 years, serious investment needs to be made in the most cost-effective and far-reaching solutions that already exist without delay, and can be improved upon as technologies continue to evolve down the line.

107 REACHING KEY AND VULNERABLE POPULATIONS TO ACHIEVE THE THIRD 90

Ruanne V. Barnabas, *Univ of Washington, Seattle, USA*

Substantial progress has been made on ART delivery, with 18 million HIV positive persons on ART (50% of people living with HIV). However, among key and vulnerable populations (men who have sex with men [MSM], sex workers, transgender people, people who inject drugs [PWID], adolescents, and children) the HIV care continuum requires strengthening, with a smaller (~5%-25%) proportion of HIV positive persons receiving ART. Reaching key populations for ART provision is critical to achieve viral suppression among 90% of persons on ART, for the clinical and transmission reduction benefits. Mathematical models estimating the impact of viral suppression among key and vulnerable populations on HIV incidence demonstrate the value of reaching key populations, particularly in concentrated epidemic settings. Effective strategies to reach key and vulnerable populations include actively involving key population members, using multicomponent interventions, and fostering open and effective client-provider communications. Simplified protocols for HIV care, including viral load testing, can strengthen services for key and vulnerable populations.

108 IF YOU CAN MAKE IT THERE: ENDING THE HIV EPIDEMIC IN NEW YORK

Demetre C. Daskalakis, *NYC DHMH, New York, NY, USA*

Science, community activism, and political will converge in the domestic epicenter of HIV/AIDS to generate a "Blueprint" to End the Epidemic (EtE) in New York City (NYC) and State. Through a process of evaluating strategies and identifying and leveraging resources, NYC continues to progress toward the achievable goal of decreasing the rate of new HIV infections to below epidemic levels. Increasing awareness of status, improving viral load suppression, magnifying the use of HIV medications for prevention, and supporting the health of often marginalized populations are the pillars of the NYC strategy to end HIV by making NYC "status neutral."

109 HTLV-1: THE OTHER HUMAN RETROVIRUS

Charles R. Bangham, *Imperial College London, London, UK*

The human leukaemia virus HTLV-1 causes disabling chronic inflammatory diseases or an aggressive, rapidly fatal malignancy in about 10% of infected people. The risk of these diseases is strongly correlated with the proviral load, which frequently exceeds 10% of peripheral blood mononuclear cells. The virus, which is non-cytolytic, drives proliferation of the infected CD4+ T cell, and the high proviral load is limited by a strong, chronically activated cytotoxic T lymphocyte (CTL) response to HTLV-1. HTLV-1 does not release cell-free virions, but propagates both within and between hosts by cell-to-cell contact, via the virological synapse. In addition to the virological synapse, the study of HTLV-1 has made many contributions to human retrovirology, including the discovery of the IL-2 receptor CD25, IL-15, selective infection of virus-specific cells, T-cell fratricide, and the dynamics and determinants of CTL quality. Until recently, it was believed that HTLV-1 was latent in vivo, and persisted chiefly by continuous oligoclonal proliferation of about 100 clones of HTLV-1-infected CD4+ T cells. However, we have shown that a typical individual carries between 10^4 and 10^5 clones, and the proviral load – the chief correlate of disease – is determined by the number of clones, not by oligoclonal proliferation. We recently made the surprising discovery that HTLV-1 alters host chromatin structure in the infected cell, by binding the chromatin architectural protein CTCF - the chief protein that regulates higher-order chromatin structure and gene expression in vertebrates. We are now testing two hypotheses that arise from this observation. First, that CTCF binding regulates HTLV-1 latency by controlling selective plus- and minus- strand transcription of the provirus, and so determines the observed single-cell heterogeneity in proviral expression, both within and between clones. Second, that the abnormal chromatin looping caused by CTCF can deregulate host gene expression and so may act as an oncogenic driver.

110 A COMBINATION INTERVENTION STRATEGY FOR HIV LINKAGE AND RETENTION IN MOZAMBIQUE

Batya Elul[1], **Matthew R. Lamb**[1], Maria Lahuerta[1], Fatima Abacassamo[2], Laurence Ahoua[3], Stephanie Kujawski[1], Maria Tomo[2], Ilesh Jani[4]
[1]Columbia Univ, New York, NY, USA, [2]Cntr for Collab in Hlth, Maputo City, Mozambique, [3]ICAP at Columbia Univ, Maputo City, Mozambique, [4]Inst Nacional de Saude, Maputo, Mozambique

Background: Identifying scalable interventions to strengthen linkage to and retention in HIV care is essential to ensuring individual and population benefits of ART.
Methods: Engage4Health, a cluster-randomized controlled trial implemented at 10 health facilities in Mozambique, evaluated the effectiveness of a combination intervention strategy (CIS) vs the standard of care (SOC) on the combined outcome of linkage to care within 1 month and retention in care at 12 months following HIV diagnosis. CIS included: (1) point-of-care CD4+ count at HIV testing sites; (2) accelerated ART initiation for eligible patients; and (3) SMS appointment reminders. A subset of CIS participants additionally received non-cash financial incentives (CIS+FI). Adults >18 years newly diagnosed with HIV and willing to receive HIV care at the diagnosing health facility were enrolled from 4/13-6/15 and followed for 12 months. Main analyses assessed outcomes at the diagnosing facility using medical record abstraction, while sensitivity analyses examined outcomes at any health facility using self-reports collected during follow-up interviews. Log-Poisson models were used to estimate the relative risk (RR) of outcomes in intent-to-treat analyses, with additional models adjusting for clustering within sites and patient characteristics using propensity score matching.

Results: Among 2004 participants (N=744 CIS, 493 CIS+FI, 767 SOC), 64% were women and the mean age was 34 years (standard deviation = 10). As shown in the table, 57% receiving CIS and 55% receiving CIS+FI achieved the primary outcome versus 35% receiving SOC (RR vs SOC: 1.63 [95%CI:1.45-1.83] for CIS; 1.56 [95%CI:1.37-1.76] for CIS+FI). Participants in the CIS (94%, RR vs SOC 1.50 [95%CI:1.42-1.49]) and CIS+FI (94%, RR 1.49 vs SOC [95%CI:1.41-1.58]) groups had higher linkage to care at 1 month versus those in the SOC (63%) group; and higher 12-month retention (CIS 59%, RR vs SOC 1.31 [95%CI:1.19-1.45], and CIS+FI 55%, RR vs SOC 1.24 [95%CI:1.11-1.38]) relative to those in SOC (45%). In sensitivity analyses considering self-reported linkage and retention at any health facility, 73% in CIS, 72% in CIS+FI, and 47% in SOC achieved the primary outcome (RR vs SOC: 1.55 [95%CI: 1.35-1.77] for CIS; 1.53 [95%CI: 1.32-1.77] for CIS+FI).
Conclusion: The CIS offers a feasible approach for enhancing outcomes across the HIV care continuum, particularly linkage to care following diagnosis. No additional benefit of non-cash financial incentives was observed.

Main Outcome analysis: Achievement of linkage to HIV care within one month and retention 12 months after HIV testing

		CIS (N = 744)		CIS+FI (N = 493)		SOC (N = 767)	
Main analysis	Achieving combined outcome[1]	425	57%	269	55%	269	35%
		RR	95% CI	RR	95% CI		
	Unadjusted	1.63	(1.45-1.83)	1.56	(1.37-1.76)	ref	
	Accounting for within-clinic correlation[2]	1.58	(1.05-2.39)	1.50	(1.02-2.26)	ref	
	Covariate-adjusted[3]	1.55	(1.07-2.25)	1.48	(1.00-2.19)	ref	
Sensitivity Analysis	Achieving combined outcome[1]	546	73%	357	72%	364	47%
	Unadjusted	1.55	(1.35-1.77)	1.53	(1.32-1.77)	ref	
	Accounting for within-clinic correlation[2]	1.50	(1.06-2.11)	1.47	(1.02-2.12)	ref	
	Covariate-adjusted[3]	1.48	(1.00-2.19)	1.47	(1.04-2.07)	ref	

1. Combined outcome is defined as successful linkage to HIV care within one month and retention 12 months after HIV testing
2. Random-intercept log-poisson relative risk regression models used to account for within-clinic correlation
3. Propensity Score analysis adjusted for: gender, region, age, education, weekly income, employment status, marital status, number of children, history of being away from home, travel time to clinic, TB status, recent hospitalization, whether this was the first HIV test, whether this wa the first positive HIV test,

111 PEER NAVIGATION ENHANCES HIV CARE RETENTION: AN RCT IN SOUTH AFRICAN PRIMARY CLINICS

Wayne T. Steward[1], Emily Agnew[1], Julia DeKadt[2], Hailey Gilmore[1], Mary-Jane Ratlhagana[2], Jessica Grignon[3], Starley B. Shade[1], John Tumbo[4], Scott Barnhart[3], Sheri A Lippman[1]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Intl Training and Educ Cntr for Hlth–South Africa, Pretoria, South Africa, [3]Univ of Washington, Seattle, WA, USA, [4]Rustenburg Sub-District Office, Rustenburg, South Africa

Background: Engagement in care is critical to meeting UNAIDS 90-90-90 goals. South Africa has improved access to antiretroviral therapy (ART) through expanded ART initiation and monitoring at primary health clinics, however nearly half of HIV-positive clients are still lost to care. To improve retention in care, we designed and implemented short message service (SMS) reminders and peer navigation (PN) to address barriers to HIV care.
Methods: The I-Care Trial (registration: NCT02417233) used a cluster randomized design to assign primary health clinics in North West Province, South Africa, to: 1) SMS check-in messages, along with appointment and healthy living reminders (6 clinics); 2) SMS reminders plus PN services (SMS+PN) to address personal barriers to care (7 clinics); and 3) standard of care (SOC; 4 clinics). From October, 2014, to April, 2015, we enrolled 752 recently HIV-diagnosed, consenting adults (292 men, 460 women) in SMS, SMS+PN, or SOC assigned clinics and followed them for up to 1 year. We extracted clinical record data and conducted intention-to-treat analyses of 12-month retention outcomes using generalized estimating equations (GEE). Retention in care was defined as: 1) an average of at least 1 clinic visit every 3 months for participants on ART, which corresponded to the minimum frequency with which ART was dispensed at the facilities; or 2) an average of at least 1 clinic visit every 6 months for pre-ART participants (those not yet eligible for ART at the time of the study). The trial is complete and results are final.
Results: Participants receiving SMS+PN services had nearly 3 times the odds of being retained in care compared to SOC participants (Table 1). SMS services alone did not significantly improve outcomes relative to SOC, although SMS demonstrated protective trends for those on ART. When analyzed by gender, men (OR=3.34, 95% CI: 1.37-8.14) and women (OR=2.64, 95% CI: 1.60-4.37) had greater odds of being retained in care when receiving SMS+PN services than when receiving SOC. There were no differences between SMS and SOC conditions for men or women in stratified analyses.
Conclusion: Peer navigation paired with SMS reminders substantially improves retention in HIV care at South African primary health clinics. The intervention offers a valuable strategy for meeting 90-90-90 campaign targets. Efforts are now needed to identify feasible strategies for wider-scale implementation in resource-constrained clinics.

Table 1. Retention in Care after 12 Months among 752 recently HIV-diagnosed adults participating in the I-Care trial, 2014-2016.

	Trial Arm	*Number of Participants*	*Number Retained in Care*	*Percent Retained in Care*	Odds Ratio	95% CI
Overall (N=752)	**SOC**	167	101	60.5	1.00	
	SMS	289	192	66.4	1.30	0.78-2.18
	SMS+PN	296	240	81.1	**2.90**	**1.67-5.06**
Pre-ART (n=124)	**SOC**	28	0	0.0		
	SMS	55	4	7.3	1.00	
	SMS+PN	41	12	29.3	**3.57**	**1.73-7.36**
ART (n=628)	**SOC**	139	101	72.7	1.00	
	SMS	234	188	80.3	1.56	0.99-2.45
	SMS+PN	255	228	89.4	**3.15**	**1.92-5.17**

112 COST-EFFECTIVENESS OF POLICY OPTIONS WHEN PRETREATMENT NNRTI DRUG RESISTANCE IS HIGH

Andrew Phillips[1], Valentina Cambiano[1], Michael Jordan[2], Fumiyo Nakagawa[1], Marco Vitoria[3], Meg Doherty[3], Paul Revill[4], Elliot Raizes[5], Silvia Bertagnolio[4] , for the Working Group on Modelling Drug Resistance in Sub-Saharan Africa
[1]Univ Coll London, London, UK, [2]Tufts Univ, Boston, MA, USA, [3]WHO, Geneva, Switzerland, [4]Univ of York, York, UK, [5]CDC, Atlanta, GA, USA

Background: The World Health Organization recommends drug resistance surveillance in people initiating antiretroviral therapy (ART). If high levels of pre-ART non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance are identified, options for ART program response must be considered. One possible option is to transition from efavirenz to dolutegravir, which is associated with a lower rate of resistance acquisition and greater tolerability.
Methods: We used an individual-based model of HIV transmission and the effect of ART which considers specific drugs and resistance mutations (HIV Synthesis Model). Multiple potential epidemics/ART programs (setting scenarios) were generated through simulation, informed by data from sub-Saharan Africa. Parameters relating to ART adherence and interruption rate, ART monitoring strategy, and switch rate to a 2nd-line regimen after 1st-line failure were varied randomly within bounds reflecting data from the region. For each setting scenario, if the pre-ART resistance in 2016 was >10% we compared outcomes of potential policy options (Table) over 2016-2036 (20 yr time horizon). Costs of all aspects of HIV testing and care included, dolutegravir cost $44, efavirenz $38, cost effectiveness threshold $500, health systems perspective, 3% discount rate.
Results: In over 2000 setting scenarios median HIV prevalence was 8% (5%-95% 5-17), 62% of HIV+ people were on ART (90% range 44-76), and 20% of ART initiators had prior drug exposure (90% range 9-34). Of ART initiators without / with prior ARV exposure the % with NNRTI resistance in majority virus was 9% (2-20) / 16% (5-34). As shown in the Table, a policy of transitioning from efavirenz to dolutegravir for all on 1st-line ART was predicted to lead to improved health outcomes and was cost effective (incremental cost effectiveness ratio (ICER) $80 per disability adjusted life year (DALY) averted). Conclusions were consistent in sensitivity analyses including a dolutegravir cost of $80/year. Updated results will be presented considering a wider range of policy options and extended sensitivity analyses.
Conclusion: A future transition from efavirenz to dolutegravir may be cost effective in low income settings in sub-Saharan Africa. The level of pre-ART NNRTI drug resistance will be just one factor to consider when estimating the potential impact of this transition. Further studies, such as stepped-wedge trials, should be conducted to understand the real-life impact of such a transition.

Outcomes of potential policy options for setting scenarios in which pre-ART NNRTI resistance in 2016 is > 10%

Policy from 2016	Outcomes over 2016-2036						
	Mean percent with viral load < 1000 cps/mL 1 year from ART initiation	Mean % of ART-naïve initiators with NNRTI resistance	Mean % of people on ART with viral load > 1000 cps/mL	Mean death rate in people on ART (/100 person years)	Increment in cost relative to no change in policy*	DALYs averted relative to no change in policy*	ICER
No change	64%	27%	29%	5.3	---	---	---
For all ART initiators: dolutegravir 1st line regimen	76%	21%	24%	4.6	$0.2m	18722	$11
For all on 1st line ART: move from efavirenz to dolutegravir	77%	11%	20%	3.9	$2.8m	51136	$80
Increase the rate of switching to 2nd-line ART	65%	25%	25%	4.5	$7.2m	18910	dominated

*Costs and DALYs are scaled up to a population of size of 10 million adults.

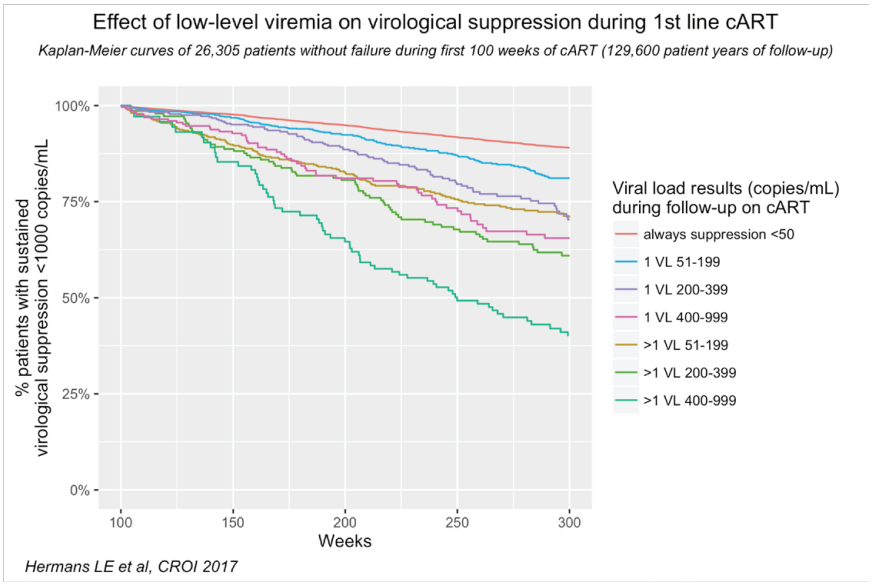
113 INCREASED RISK OF CART FAILURE AFTER LOW-LEVEL VIREMIA UNDER WHO GUIDELINES

Lucas E. Hermans[1], Michelle A. Moorhouse[2], Sergio Carmona[2], Diederick Grobbee[3], Laura Marije Hofstra[3], Douglas D. Richman[4], Hugo Tempelman[5], Willem D. Venter[2], Annemarie Wensing[3], for the Ndlovu Research Consortium
[1]Univ Med Cntr Utrecht, Utrecht, Netherlands, [2]Univ of Witwatersrand, Johannesburg, South Africa, [3]Univ Med Cntr Utrecht, Utrecht, Netherlands, [4]Univ of California San Diego, San Diego, California, USA, [5]Ndlovu Care Group, Groblersdal, South Africa

Background: Current WHO guidelines for cART in HIV-1 infected patients define failure of cART as viremia above 1000 copies/mL during therapy. Detectable viral load (VL) below 1000 copies/mL during cART (low-level viremia; LLV) has been linked to subsequent failure of cART in studies performed in high-income settings, where more stringent VL cut-off values are used. We report the prevalence of LLV and its impact on subsequent failure of cART in a large South African cohort managed according to WHO guidelines.
Methods: HIV-positive patients from 19 urban and 38 rural South African HIV treatment sites were studied. Adult patients on cART for ≥20 weeks and with ≥1 VL performed ≥20 weeks after start of cART were included. LLV was defined as viremia between 50-1000 copies/mL and stratified according to level (51-199, 200-399, and 400-999 copies/mL) and duration. Studied outcomes were failure of cART (VL ≥1000 copies/mL) and switch to second line cART. In the subset of patients with ≥100 weeks of first line cART without failure and ≥3 VLs risk of failure after LLV was estimated with survival analysis using Cox proportional hazard models corrected for sex, age and nadir CD4.
Results: 69,615 patients met inclusion criteria. Virological suppression <1000 copies/mL during cART was maintained in 80.9% of patients. LLV occurred in 23.3% of patients. A single measurement of LLV (sLLV) was more common than persistent LLV (pLLV) (78.6% vs 21.4%). LLV between 51 and 199 copies/mL (LLV51-199) was most commonly encountered (59.1%). In survival analysis (26,305 patients) LLV was associated with increased hazard of failure of cART (HR 2.8; CI-95% 2.7-2.9) and of ever switching to second line (HR 3.2; CI-95% 3.0-3.3) when compared to patients with <50 copies/mL. Risk of failure increased proportionally to level of LLV: HR 1.7 (CI-95% 1.5-1.9) for sLLV51-199, 2.7 (CI-95%

2.5-3.0) for sLLV200-399 and 3.6 (CI-95% 3.4-3.8) for sLLV400-999. Risk of failure further increased in cases of pLLV, with a HR of 3.0 (CI-95% 2.9-3.2) for pLLV50-199, 4.2 (CI-95% 4.0-4. 4) for pLLV200-399 and 7.7 (CI-95% 7.4-7.9) for pLLV400-999. Lower nadir CD4 was independently associated with LLV.

Conclusion: In this large cohort prevalence of LLV was high and patients with LLV were at increased risk of subsequent failure and switching to second line cART. These risks increased further with higher levels and longer duration of LLV. This poses concerns for the long term success of first line cART in treatment programmes in resource limited settings.



114LB REAL PROGRESS IN THE HIV EPIDEMIC: PHIA FINDINGS FROM ZIMBABWE, MALAWI, AND ZAMBIA

Jessica E. Justman[1], David Hoos[1], Graham Kalton[2], Rose Nyirenda[3], Crispin Moyo[4], Owen Mugurungi[5], Andrew Voetsch[6], Hetal Patel[6], Laura Porter[6], for the PHIA Project Teams for Malawi, Zambia, and Zimbabwe

[1]ICAP at Columbia Univ, New York, NY, USA, [2]Westat, Inc., Rockville, MD, USA, [3]Government of Malawi Ministry of Hlth, Lilongwe, Malawi, [4]Government of Zambia Ministry of Hlth, Lusaka, Zambia, [5]Ministry of Hlth and Child Welfare, Zimbabwe, Harare, Zimbabwe, [6]CDC, Atlanta, GA, USA

Background: Estimates of HIV incidence and 90/90/90 achievements have been largely based on modelling and facility-based data, respectively. The Population-based HIV Impact Assessment (PHIA) Project is the first to assess the status of the HIV epidemic in selected African countries by measuring population incidence and viral load suppression. We report the first findings from surveys in Zimbabwe, Malawi and Zambia, three contiguous countries with severe, generalized HIV epidemics.

Methods: A nationally representative, household-based sample of adults and children was recruited in each country. Consenting participants provided demographic and clinical information and blood samples for household HIV testing per national guidelines. HIV+ results were confirmed via a supplemental assay and viral load and limiting antigen enzyme immunoassay (LAg) testing were performed on all HIV+ samples. HIV incidence estimates were based on WHO criteria for recent infection (LAg < 1.5 ODn and HIV RNA > 1000 c/ml). Viral load suppression (VLS) was defined as HIV RNA <1000 c/ml. CHAID survey weights were applied and variances were estimated via jackknife series. Results for adults 60-64 y (Zimbabwe, Malawi) were excluded to produce combined estimates across the three countries.

Results: In 2015-16, a combined total of 76,442 (55,299 adults and 21,143 children) from among 34,061 selected households provided interviews and blood samples. Participation by eligible adults was higher for women than men (83.4% vs 72.3%, P<0.0001). Combined HIV prevalence estimates among adults and children were 12.4% and 1.5%, respectively. Combined HIV incidence among adults, aged 15-59 y, was 0.5% and combined mean VLS prevalence among all HIV-seropositive adults was 62.0%. Achievement of the 1st 90 target was 71.3%, the 2nd 90 was 86.8% and the 3rd 90 was 88.5% (Table).

Conclusion: Based on national population survey results, Zimbabwe, Malawi and Zambia have achieved impressive progress towards the 90-90-90 goals. HIV prevalence is stabilizing and HIV incidence is low, consistent with recent UNAIDS modeled incidence estimates (data not shown) except in Zimbabwe, which had nearly half the modeled estimate. Novel population-based data show a high prevalence of VLS, providing further evidence of effective national HIV responses. Targeted testing to identify those unaware of HIV infection (1st 90 target) and continued expansion of HIV treatment programs and other prevention interventions are needed to facilitate ultimate epidemic control.

Indicator	Zimbabwe	Malawi	Zambia	Three countries
Household participation, number (%) of selected households	11,717 (83.9)	11,385 (88.5)	10,959 (89.0)	34,061 (87.0%)
Eligible adults (15-59y) interviewed and HIV tested, number (%)				
Total adults	19,630 (81.6)	16,640 (76.3)	19,029 (77.1)	55,299 (78.4)
Adult males	8,002 (75.3)	6,924 (70.2)	8,107 (71.4)	23,033 (72.3)
Adult females	11,628 (86.8)	9,716 (81.1)	10,922 (82.0)	32,266 (83.4)
Eligible children (0-14y) HIV tested number (%)	7,041 (73.1)	6,143 (61.7)	7,959 (68.2)	21,143 (67.7)
HIV prevalence, % [95% CI]				
Total adults (15-59y)	14.6 [14.0, 15.3]	10.6 [9.9, 11.2]	12.3 [11.6, 12.9]	12.4 [12.1, 12.8]
Adult males	12.2 [11.4, 13.0]	8.1 [7.4, 8.8]	9.5 [8.8, 10.3]	9.9 [9.5, 10.3]
Adult females	16.8 [16.1, 17.6]	12.8 [11.9, 13.7]	14.9 [14.0, 15.8]	14.8 [14.3, 15.3]
HIV prevalence, % [95% CI]				
Children (0-14 y)	1.6 [1.2, 2.0]	1.6 [1.2, 2.0]	1.3 [1.0, 1.6]	1.5 [1.3, 1.7]
HIV incidence (annualized), % [95% CI]				
Total adults (15-59 y)	0.45% [0.28%, 0.63%]	0.34% [0.18%, 0.51%]	0.66% [0.45%, 0.88%]	0.50% [0.38%, 0.61%]
Adult males	0.29% [0.08%, 0.50%]	0.24% [0.03%, 0.44%]	0.33% [0.11%, 0.56%]	0.29% [0.17%, 0.42%]
Adult females	0.61% [0.34%, 0.87%]	0.45% [0.20%, 0.69%]	1.00% [0.65%, 1.36%]	0.69% [0.51%, 0.87%]
VLS prevalence, % [95% CI]				
Total HIV+ adults (15-59y)	59.9 [57.8, 62.0]	67.2 [64.6, 69.9]	59.8 [57.4, 62.2]	62.0 [60.6, 63.4]
HIV+ adult males	53.2 [49.9, 56.6]	58.3 [53.7, 62.8]	57.4 [53.4, 61.5]	56.0 [53.8, 58.3]
HIV+ adult females	64.2 [62, 66.5]	72.5 [69.5, 75.6]	61.3 [58.7, 63.8]	65.7 [64.2, 67.2]
1st 90: % HIV+ adults (15-59y), who report knowing HIV status, % [95% CI]	73.9 [72.0, 75.8]	72.4 [70.0, 74.8]	67.3 [64.8, 69.7]	71.3 [70.0, 72.6]
2nd 90: % of adults who know their HIV+ status who report ART, % [95% CI]	86.5 [85.0, 88.0]	88.5 [86.3, 90.7]	85.4 [83.4, 87.4]	86.8 [85.7, 87.8]
3rd 90: % of those who report ART with VLS, % [95% CI]	86.2 [84.5, 87.9]	90.7 [88.7, 92.7]	89.2 [87.4, 91.0]	88.5 [87.4, 89.5]

115 STRATEGIES TO ACHIEVE 90-90-90: MODELING INSIGHTS FROM ZIMBABWE

Jack Olney, Jeffrey Eaton, Ellen McRobie, Timothy B. Hallett
Imperial Coll London, London, UK

Background: To achieve the UNAIDS 90-90-90 targets by 2020, current HIV care programmes must be optimised. However, at present Zimbabwe and many other countries lack the ability to assess the prospect of achieving these goals. We used mathematical modelling to evaluate various strategies to achieve these goals, through implementing a range of interventions across the cascade over a five year period.
Methods: To explore the ability of Zimbabwe to achieve these goals, we developed a novel mathematical model encapsulating the various stages of HIV care, and capable of utilising readily available data on the cascade to identify where resources are best allocated. Using historical data from Zimbabwe on HIV incidence, disease progression, treatment guidelines and the distribution of individuals across care, the model determined the current trajectory of care. We then estimated the achievement of the 90-90-90 targets in 2020, together with any changes to new infections and AIDS-related mortality, before determining strategies to improve patient outcomes, through implementing a range of interventions, each targeting a different aspect of care. Our web-based model can be applied to almost any country and will generate country-specific cascade reports to guide policy decisions around intervention implementation and investment opportunities to achieve 90-90-90.
Results: Without intervention in the cascade, we estimated that in Zimbabwe between 2015 and 2020, an average of 14,529 individuals will initiate ART per year, 22,928 will drop out, and ART programme expenditure will cost an average of $346 million per year. However, to achieve the 90-90-90 targets, it will be necessary to initiate a further 10,990 individuals on ART and retain an additional 19,950 individuals in care annually, at a cost of an additional $25 million per year.
Conclusion: To achieve future targets countries must maximise the efficiency of current treatment programmes. With decreasing public funding and the transition of many countries to solely funding their responses to the epidemic, current budgets must be better utilised. We demonstrate that in Zimbabwe, through analysis of the cascade, investments in ART care are recommended as the most efficient means of achieving the 90-90-90 targets by 2020. However, ART programmes in different settings should focus on improving data collection practices and analysing their individual cascades to tailor their response and guide policy toward these goals.

116 HIV CASCADE OF CARE INTERVENTIONS IN KENYA: CLINICAL IMPACT AND COST-EFFECTIVENESS

Liem Binh Luong Nguyen[1], Yazdan Yazdanpanah[1], David Maman[2], Stephen Wanjala[3], Alexandra Vandenbulcke[4], Elisabeth Szumilin[4], William Hennequin[4], Robert Parker[5], Pierre Mendiharat[4], Kenneth Freedberg[5]
[1]INSERM, Paris, France, [2]Epicentre, Cape Town, South Africa, [3]MSF, Nairobi, Kenya, [4]MSF, Paris, France, [5]Massachusetts General Hosp, Boston, MA, USA

Background: In Southwest Kenya up to 24% of the adult population is HIV infected. Médecins Sans Frontières (MSF) has implemented a program to increase Voluntary Community Testing (VCT), linkage and retention to care, and ART coverage to achieve the WHO 90-90-90 targets by 2017. Our objective was to assess the clinical outcomes and cost-effectiveness of these interventions.
Methods: We developed a time-discrete, dynamic microsimulation model to project outcomes in the general population (age 15-65 y). We modeled 4 strategies in 100,000 people: VCT (to 90% coverage), VCT + linkage to care (to 90% testing and 90% linkage in those HIV+), retention interventions (to 90% ART coverage in those linked and 90% virologic suppression on ART) and all 3 interventions combined. We used MSF data, other national data, and the literature for: HIV prevalence and incidence, non-HIV and HIV risks of death, risk of opportunistic infections, treatment efficacy, cascade of care, and cost of HIV care and interventions. We also calibrated uncertain data to the observed cascade of care in 2012: 62% tested, 57% linked, 40% suppressed. Cost data for VCT, VCT+ linkage, and the 3 interventions combined included start-up costs (€37,740, €75,480, €541,210 and €616,690; respectively), monthly fixed costs (€7,930, €12,540, €20,630 and €33,090) and variable costs. Outcomes included HIV incidence, years of life saved (YLS), cost (2014 €) and discounted Incremental Cost-Effectiveness Ratios (ICERs). We performed sensitivity analyses on key model parameters.
Results: If implemented in 2014, after 15 years, VCT, VCT & linkage, retention interventions, and the 3 interventions combined increased outcomes from a base case of 69% tested, 66% linked and 31% suppressed to 73% to 94% tested; 66% to 93% linked, and 36% to 56% suppressed, depending on strategy. With current care, HIV incidence was 1.93/100 PY in 2029; the 3 interventions combined decreased incidence to 1.10/100 PY. For 100,000 individuals, the interventions combined cost € 40.2 million, led to 27,920 YLS, with an ICER of 320€/YLS compared to the base case. Baseline HIV prevalence and the interventions' fixed costs had the biggest impact on the results.
Conclusion: Interventions combining HIV testing, linkage and retention, and increased ART coverage would decrease HIV incidence by about half over 15 years. In rural Kenya, implementing these interventions together is substantially more effective and cost-effective than implementing them separately.

Interventions	Tested (%)	Linked (%)	Suppressed (%)	Incidence (per 100 PY)	Total costs (discounted)	Years of Life Saved (discounted)	ICER (€/YLS)
Base Case	69	66	31	1.93	31,344,000		-
Retention intervention	73	71	44	1.58	34,075,000	4,631	Dominated
VCT	91	82	36	1.80	37,874,000	9,626	Dominated
3 combined intervention	94	93	56	1.10	40,164,000	27,915	316
VCT + linkage	92	90	38	1.81	41,431,000	11,349	Dominated

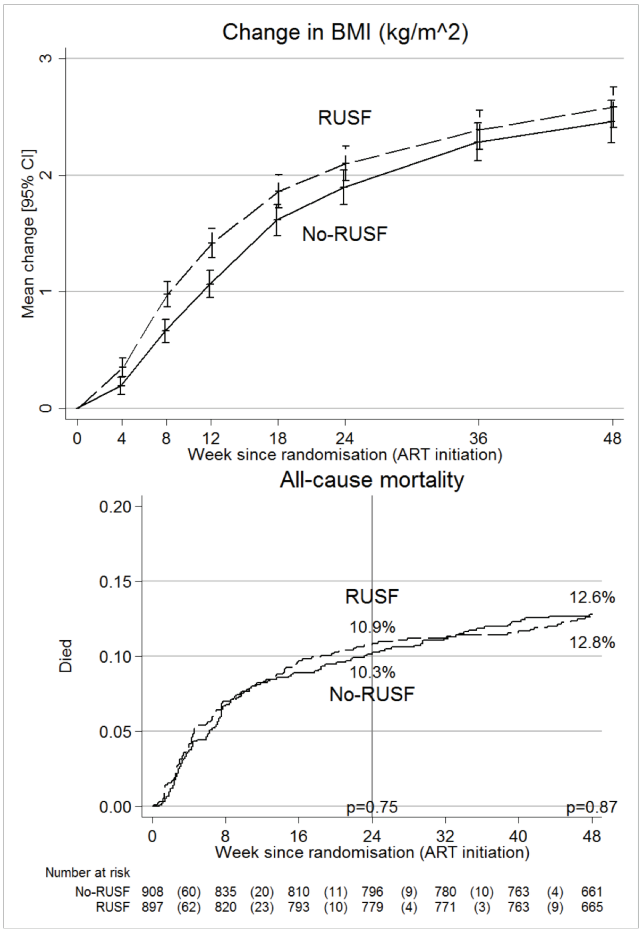
117 A RANDOMIZED TRIAL OF READY-TO-USE SUPPLEMENTARY FOOD AT ART INITIATION IN AFRICA

Jane E. Mallewa[1], Alexander J. Szubert[2], Jay Berkley[3], Sanele Nkomani[4], Abraham Siika[5], Peter Mugyenyi[5], Andrew Prendergast[6], Sarah Walker[2], Diana Gibb[2], for the REALITY Trial Team
[1]Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi, [2]Univ Coll London, London, UK, [3]KEMRI Wellcome Trust Rsr Prog, Kilifi, Kenya, [4]Univ of Zimbabwe Clinical Rsr Cntr, Harare, Zimbabwe, [5]Moi Univ, Eldoret, Kenya, [6]Queen Mary Univ of London, London, UK

Background: Early mortality after antiretroviral therapy (ART) initiation is high among HIV-infected adults and children with severe immunosuppression in sub-Saharan Africa. Baseline malnutrition is common and increases mortality, but nutritional supplementation is generally only provided at ART initiation to those with severe malnutrition. Whether universal provision for those with advanced disease would improve nutritional status and reduce early mortality is unknown.
Methods: The REALITY 2x2x2 factorial open-label randomized trial (ISRCTN43622374) enrolled ART-naïve HIV-infected adults and children ≥5 years with CD4<100 cells/mm3 from Kenya, Malawi, Uganda and Zimbabwe and ended in March 2016. This randomization compared initiating ART with/without 12 weeks of Ready-to-Use Supplementary Food (RUSF), providing 1000kcal/day with multi-vitamins/minerals. Those with severe malnutrition received Ready-to-Use Therapeutic Food (RUTF) regardless of randomization. Two other randomizations investigated 12-week raltegravir intensification or enhanced infection prophylaxis. The primary endpoint was 24-week mortality.
Results: 1805 eligible adults (n=1733; 96.0%) and older children/adolescents (n=72; 4.0%) were enrolled, median age 36 years; 53.2% male; 53.7% WHO stage 3/4, and median baseline CD4 37 cells/mm3 (IQR 16-63). For those ≥13 years, median baseline weight was 53 (IQR 47-60) kg, BMI 19.3 (17.4-21.5) kg/m2 and MUAC 24.0 (22.0-26.1) cm. Participants were randomized to RUSF (n=897) or no RUSF (n=908) with ART. 25 (2.8%) and 39 (4.3%) respectively received RUTF, following local guidelines. Follow-up was 48 weeks (3.1% loss-to-follow-up). Gains in weight, BMI (Figure) and MUAC were greater in the RUSF group (p=0.004, 0.004, 0.03). Maximum differences were at 12 weeks; +3.8 RUSF versus +2.9

kg no-RUSF, +1.4 versus +1.1 kg/m2, and +1.2 versus +1.0 cm respectively. Changes in weight with RUSF were predominantly due to gains in fat mass by bioimpedance analysis. There were no differences in grip strength between groups (p=0.36). 96 (10.9%) RUSF versus 92 (10.3%) no-RUSF died before 24 weeks (stratified hazard ratio=1.05 (95% CI 0.79-1.40) p=0.75) (to 48-weeks p=0.87), with no evidence of interaction with the two other randomizations (p>0.7). There was no difference in time to first WHO 3/4 event or death (p=0.82).

Conclusion: RUSF supplementation at ART initiation in advanced disease improved nutritional status but did not impact mortality.



118 TLR7 AGONIST GS-9620 INCREASES IMMUNE-MEDIATED CLEARANCE OF HIV-INFECTED CELLS

Alivelu Irrinki[1], Angela Tsai[1], Jasmine Kaur[1], Jay Lalezari[2], Tomas Cihlar[1], George Kukolj[1], Derek D. Sloan[3], **Jeffrey Murry**[1]
[1]Gilead Scis, Inc, Foster City, CA, USA, [2]Quest Clinical Rsr, San Francisco, CA, USA, [3]Agenovir, South San Francisco, CA, USA

Background: Reactivation of latent HIV may be necessary to efficiently clear long-lived HIV reservoirs. As reactivation alone may not induce the death of infected cells, it is important that potential reactivating agents do not impede immune mechanisms required for clearing infected cells. GS-9620 is a selective TLR7 agonist that has previously been shown to induce latent virus in vitro and in SIV-infected ART-suppressed rhesus macaques. Here, the effect of GS-9620 on the activity of immune effectors required to clear infected cells was investigated.

Methods: Peripheral blood mononuclear cells (PBMCs) isolated from ART-suppressed HIV-infected patients were treated with GS-9620 in the presence or absence of HIV peptides. To assess the role of type I interferons in the effects mediated by GS-9620, an antibody blocking IFN-α/β receptor (anti-IFNAR1) was used. HIV RNA was assessed by quantitative PCR in supernatants and flow cytometry was used to assess CD8 T cell activation. Cytolytic activity of CD8 T cells was assessed by monitoring caspase 3 activation in CD4 target cells coated with HIV peptides and co-cultured with activated CD8 T cells. Antibody-mediated killing was assessed by co-culturing GS-9620-treated PBMCs with the HIV Env-specific antibody PGT121 and autologous HIV-infected CD4 T cells.

Results: Consistent with TLR7 agonist activity, GS-9620 strongly induced IFN-α in PBMCs. GS-9620 increased IFN-γ and TNF-α production in HIV-specific proliferating CD8 T cells by 100-230% ($n = 23$; $p < 0.001$). Stimulation of intracellular cytokines correlated with increased CD8 T cell cytolytic activity. GS-9620 induced 1.5-2 fold increases in HIV RNA in cell culture supernatants compared to cells treated with vehicle control ($n = 43$; $p = 0.0002$). Blockade with anti-IFNAR1 decreased GS-9620-mediated activation of T cells as well as HIV RNA induction, suggesting these effects require signaling through type I interferons. Antibody-mediated killing of HIV-infected CD4 T cells by PGT121 was enhanced by GS-9620 treatment, demonstrating that TLR7 activation can stimulate multiple mechanisms for eliminating infected cells.

Conclusion: GS-9620 stimulated both HIV production by infected CD4 T cells and the elimination of infected cells by activation of cytolytic CD8 T cells or improved killing by an effector Ab. This indicates that GS-9620 may effectively complement orthogonal therapies designed to stimulate antiviral immunity, such as therapeutic vaccines or broadly neutralizing antibodies.

119LB VIRAL CONTROL INDUCED BY HIVCONSV VACCINES & ROMIDEPSIN IN EARLY TREATED INDIVIDUALS

Beatriz Mothe[1], José Moltó[2], Christian Manzardo[3], Josep Coll[1], Maria C. Puertas[1], Javier Martinez-Picado[1], Tomas Hanke[4], Bonaventura Clotet[1], Christian Brander[1], for the BCN02-Romi Study Group

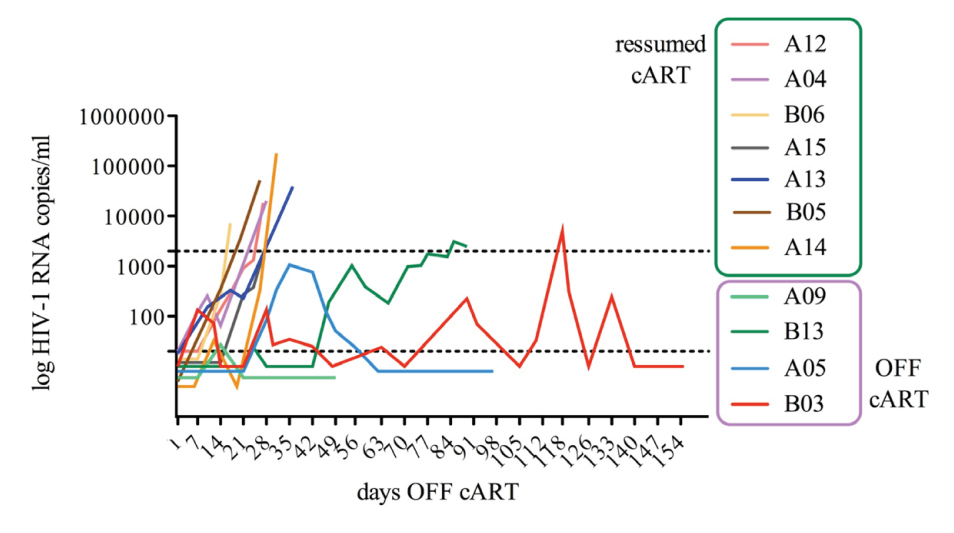
[1]IrsiCaixa AIDS Rsr Inst, Badalona, Spain, [2]Fundació Lluita Contra la Sida, Badalona, Spain, [3]Univ of Barcelona, Barcelona, Spain, [4]The Jenner Inst, Oxford, UK

Background: The combined use of therapeutic vaccination and specific drugs that can reactivate latent reservoir virus (Kick and kill strategies) hold the promise to achieve a functional cure for HIV infection. The recently completed BCN01 vaccine trial (NCT01712425) consisted in a ChAd.HIVconsv and MVA.HIVconsv prime/boost vaccination in early treated individuals (<6 months from HIV acquisition) and was able to redirect CTL responses towards highly conserved regions of HIV-1. Likewise, romidepsin (RMD) has been shown in earlier studies to induce HIV-1 transcription demonstrating that significant reversal of HIV-1 latency is possible so that a combination of these two approaches may help achieve the goal of a functional cure of HIV.

Methods: BCN02-Romi (NCT02616874) is an ongoing single-arm proof-of-concept study enrolling 15 individuals rolled-over from BCN01 trial. After 3 years under viral suppression, all participants were immunized with MVA.HIVconsv (2x10E8 pfu), followed by three weekly-doses of romidepsin (RMD, 5 mg/m2 BSA), and by a second MVA.HIVconsv vaccination. Participants underwent a monitored antiretroviral pause (MAP) and treatment was resumed if plasma viral load (pVL) increased >2,000 copies/ml.

Results: 15 participants completed all immunizations and RMD infusions, with pVL >20 copies/ml being detected during the intervention in all of them. After the first MVA. HIVconsv vaccination, HIVconsv-specific T cell responses raised to a median peak magnitude of 965 IFNg SFC/10E6 (range 400-3,340, in cryopreserved-and-thawed PBMC), which was significantly higher (p=0.0353) than peak responses during BCN01. Responses transiently decreased by 35% in magnitude after RMD in 10 individuals. However, all but two participants were able to maintain or increase HIV-consv specific responses after the 2nd vaccination relative to pre-RMD, and were therefore invited to start the MAP. To date, 11 patients have interrupted treatment: 7 had to resume cART within the first 4 wk of MAP while 4 participants remain off cART after 7, 12, 14 and 22 weeks (36% of viremic controllers)

Conclusion: Therapeutic vaccination targeting conserved regions of HIV-1 combined with HIV latency reactivation strategies may facilitate clearance of the viral reservoir in early-treated individuals. This is the first reported immune intervention demonstrating a manipulation of the CTL immunodominance pattern and a durable viremic control of HIV-1 infection in a large proportion of participants.



120 NO EVIDENCE OF ONGOING HIV REPLICATION AFTER 7 YEARS ON ART

Mary Grace K. Katusiime[1], Gert U. van Zyl[1], Ann Wiegand[2], Elias K. Halvas[3], Valerie F. Boltz[2], Barbara Laughton[1], Susan Engelbrecht[1], Mark Cotton[1], John W. Mellors[3], **Mary F. Kearney**[2]

[1]Stellenbosch Univ, Parow, South Africa, [2]NCI, Frederick, MD, USA, [3]Univ of Pittsburgh, Pittsburgh, PA, USA

Background: Although a long-term study of clinically-effective ART showed no evidence of HIV evolution in 13 of 14 adults (Kearney, 2014), a recent study (Lorenzo-Redondo, 2016) of 3 persons concluded that HIV evolution occurs on ART at a rate of 6x10^-4 to 1x10^-3 mutations/site/month due to ongoing viral replication in the lymph nodes with subsequent trafficking of newly infected T-cells to blood. We therefore looked for evidence of HIV evolution in children on long-term suppressive ART. ...

Methods: We studied children initiated on continuous ART in the CHER study (Cotton, Lancet 2013). Samples obtained near ART initiation and after 7 years of ART underwent single-genome sequencing of the p6-PR-RT region of the HIV genome. Sequences from each time point were compared for evidence of evolution by multiple, sensitive Methods: 1) calculation of average pairwise distance (APD) for sequence diversification, 2) panmixia testing for sequence divergence, and 3) construction of maximum-likelihood (ML) trees to measure root-to-tip distances for emerging new variants.

Results: 12 children were studied: 10 who started ART ≤ 1 year and had viremia suppressed on ART for 7 years and 2 "replication-controls" who had viremia for 1-3 years prior to or during ART. All children had very low viral diversity (median of 0.3%) at the time of ART initiation (Table), providing a low background on which to detect evolution. The 2 replication-controls showed obvious evidence of HIV evolution: increased viral diversity, a significant virus population shift by panmixia (Table), and longer root-to-tip distances in ML trees. In 8 of 10 children, there was no evidence of viral divergence on ART. A significant virus population shift by panmixia occurred in 1 child (PID 8) who had decreasing branch lengths on the ML tree suggesting decay of infected cells on ART. Another child (PID 9) with an HIV RNA blip to 56 copies/ml had a marginally significant shift in the virus population by panmixia from possible ongoing viral replication. The absence of viral evolution in 9 of 10 children is inconsistent with the 5-8% divergence expected from ongoing replication over 7 years predicted by Lorenzo-Redondo et al.

Conclusion: These data from early ART-treated children strongly refute the concepts that ongoing HIV replication is common on current ART regimens and that it replenishes the HIV reservoir.

PID	Gender	Age ART started (months)	Current ART regimen	Pre-ART Viremia (HIV RNA copies/mL)	% HIV diversity near start of ART	% HIV diversity after 7 years of ART	Panmixia Test (significant population shift = <0.001 due to multiple comparisons)	Change in HIV population structure on ART
Viremia Suppressed on ART								
1	Female	1.8	AZT/3TC/LPV/r	510,000	0.3	0.2	p= 0.41	No change
2	Male	1.9	ABC/3TC/LPV/r	>750,000	0.1	0.1	P=0.41	No change
3	Female	2	AZT/3TC/EFV	>750,000	0.5	0.3	p=0.16	No change
4	Female	2.2	AZT/3TC/LPV/r	>750,000	0.4	0.3	p=0.40	No change
5	Male	2.8	AZT/3TC/LPV/r	>750,000	0.3	0.1	p=0.41	No change
6	Male	5.1	AZT/3TC/LPV/r	277,000	0.3	0.3	p=0.24	No change
7	Male	6.1	AZT/3TC/LPV/r	>750,000	0.5	0.8	p=0.60	No change
8	Female	9.2	AZT/3TC/LPV/r	635,000	0.4	0.3	p<0.001	Decreased diversity
9	Female	9.3	AZT/3TC/LPV/r	>750,000	0.5	0.6	p=0.006	Possible change
10	Male	10	AZT/3TC/EFV	>750,000	0.2	0.2	p=0.04	No change
Viremia Not Fully Suppressed on ART (Positive Control for Ongoing Replication)								
11	Female	11.1	AZT/3TC/LPV/r	696,000	0.3	0.4	p<0.001	Change
12	Male	17.7	AZT/3TC/LPV/r	654,000	0.1	0.6	p<0.001	Change

121 A PROPORTION OF LATENT HIV IS MISSED BY ASSAYING ONLY RESTING CD4 T CELLS

Anthony R. Cillo, **Michele Sobolewski**, Taylor Buckley, John Bui, Joshua C. Cyktor, John W. Mellors
Univ of Pittsburgh, Pittsburgh, PA, USA

Background: An inducible HIV reservoir in resting CD4 T cells (CD3+CD4+CD25-CD69-HLA-DR-) is well characterized and is the focus of most reservoir studies and assays. However, all CD4 T cells have the potential to harbor latent HIV. We compared inducible and infectious HIV from total and resting CD4 T cells.

Methods: Total and resting CD4 T cells were isolated by negative selection from blood donors on long-term ART, stimulated with PMA/ionomycin, and virus production was measured by qPCR for HIV RNA copies. Quantitative viral outgrowth assays (QVOA, 21-day endpoint) were performed in parallel with total and resting CD4 T cells. Near-full length single genome sequencing (SGS) was performed on p24-positive viral outgrowth cultures. Cell associated HIV DNA (CA-DNA) and unspliced HIV RNA (CA-RNA) were quantified by qPCR normalized to CCR5 DNA.

Results: 11 donors on suppressive ART for a median of 9 years (range: 3-13) were studied. There was no significant difference in mean CA-DNA (727+/-578 vs. 695+/-492 copies/million cells) or CA-RNA (257+/-211 vs. 342+/-309 copies/per million cells) between total and resting CD4 cells. Virus release was infrequent from unstimulated total and resting CD4 cells. Inducible virus production from total and resting CD4 cells varied by donor (Figure), but was higher from total than resting CD4 cells (mean 2.1-fold higher; p=0.024, signed rank test). The ratio of inducible virus production from total to resting CD4 cells was positively correlated with the percent of activated (CD25+/CD69+/HLA-DR+) total CD4 cells (rho=0.74, p=0.046). Infectious virion release (IUPM) was detected in only 6 of 11 donors, but was higher from total CD4 cells in 5 of the 6 positive donors (mean 1.4-fold higher [range 1.5-16]; p=0.11, signed rank test). SGS analysis of outgrowth viruses revealed different viral clones recovered from total CD4 vs. resting CD4 cells. Inducible virus production correlated strongly with IUPM (Figure) for both total and resting CD4 cell populations (rho=0.87, p=0.0005; rho=0.68, p=0.022), suggesting that inducible virus production is a good marker of the latent infectious reservoir in both cell types.

Conclusion: Latent HIV exists in both resting and non-resting CD4 T cells. Different clonal virus populations can be recovered from the two cell types. Inducible proviruses in all CD4 T cells should be considered when evaluating strategies to reduce the size of the HIV reservoir. Focusing only on resting CD4 T cells is likely to underestimate the latent HIV reservoir.

Figure

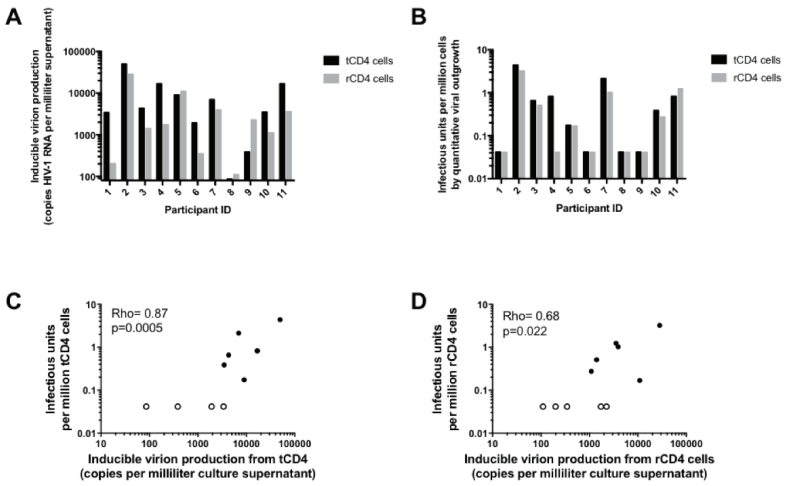
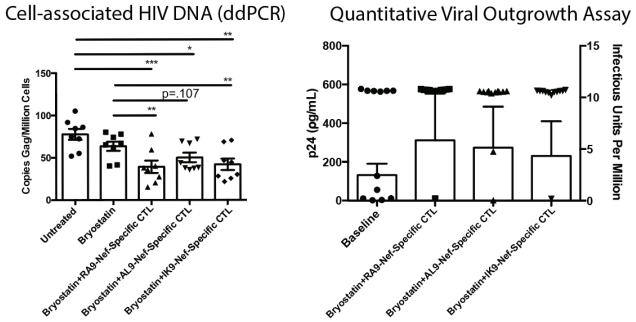


Figure. Inducible virus production and infectious viral outgrowth from total and resting CD4 T cells, and the relationship between inducible virus production and infectious virus outgrowth. **A)** Inducible virus production from total CD4 vs. resting CD4 cells. In 8 of 11 donors, total CD4 cells released more virus compared with resting CD4 from the same donor. **B)** Infectious viral outgrowth was detectable in 6 of 11 donors, and 5 of 6 donors had greater viral outgrowth from total CD4 versus resting CD4 cells. **C)** Inducible virus production per million total CD4 cells correlates with infectious units per million cells (IUPM) measured by QVOA. **D)** Inducible virus production per million resting CD4 cells correlates with infectious units per million cells (IUPM) measured by QVOA. In **A)** and **B)**, black bars are total (t)CD4 cells and gray bars are resting (r)CD4 cells. In **C)** and **D)**, open circles represent undetectable QVOA (limit of detection, 0.1 infectious units per million cells).

122 CTLs PARE DEFECTIVE HIV PROVIRUSES WITHOUT IMPACTING INFECTIOUS LATENT RESERVOIRS

Szuhan Huang[1], Allison S. Thomas[2], Sara Karandish[1], Dora Chan[1], Adam Ward[1], Ya-Chi Ho[3], Erika Benko[4], Colin Kovacs[5], R. Brad Jones[1]
[1]The George Washington Univ, Washington, DC, USA, [2]Boston Univ, Boston, MA, USA, [3]The Johns Hopkins Univ, Baltimore, MD, USA, [4]Maple Leaf Med Clinic, Toronto, Ontario, Canada, [5]Univ of Toronto, Toronto, Ontario, Canada

Background: The majority of "shock-and-kill" studies have been performed in primary-cell models of HIV latency, which are imperfect representations of natural viral reservoirs. A need remains for a rigorous investigation of whether immune effectors in combination with latency-reversing agents (LRAs) can drive reductions in replication-competent proviruses from natural reservoirs. We treated ex vivo CD4+ T-cells from HIV+ individuals on long-term ARV therapy, with LRAs and autologous HIV-specific CTL clones (targeting non-escaped epitopes), and assessed the impact on total and intact-inducible proviruses.
Methods: HIV-specific CTL clones targeting known HIV epitopes were isolated from ARV-treated subjects by limiting dilution, and killing activities were confirmed by flow cytometric assays. We developed an HIV eradication assay to test the abilities of these CTLs to reduce viral reservoirs in combination with romidepsin, vorinostat, bryostatin, ALT-803, or Pam3CSK4. Resting CD4+ T-cells from HIV+ leukapheresis samples were co-cultured with LRAs + CTLs for 5 days with ARVs, and activation/memory phenotypes were monitored. CD4+ T-cells were isolated after treatment and total/intact-inducible reservoirs were measured by cell-associated HIV DNA (ddPCR) and by quantitative viral outgrowth assay (QVOA).
Results: Combinations of bryostatin and ALT-803+Pam3CSK4 with HIV-specific CTL generally led to significant decreases in cell-associated HIV DNA, with the greatest effects observed for bryostatin (up to 50% reductions, $p < 0.01$). Critically, these decreases in HIV DNA were not associated with measurable reductions in intact-inducible virus, regardless of the CTL clone or LRA combination used (powered to detect ~50% reductions with 95% confidence). Even when combined with PMA/ionomycin, CTLs were unable to drive reductions in intact-inducible virus. CTLs degranulated (CD107a) in response to autologous activated CD4+ T-cells that had been infected with virus from positive QVOA wells, ruling out a role for immune escape in our observation.
Conclusion: Recently, it has been demonstrated that some defective proviruses can be expressed as antigens, enabling CTL recognition. Data from our ex vivo experiments are consistent with the preferential depletion of defective proviruses by CTLs, leading to reductions in HIV DNA without impacting intact proviruses. Understanding and overcoming the mechanisms limiting CTL against the intact-inducible reservoir may be key to successful CTL-based shock and kill interventions.



123 DEVELOPMENT OF A PKC AGONIST DERIVED FROM INGENOL FOR HIV LATENCY DISRUPTION IN VIVO

Jessica Brehm[1], Vincent Tai[1], David Irlbeck[1], Robert Ferris[1], Nancie Archin[2], Matt Kanke[2], Jean-Pierre Routy[3], David M. Margolis[2], Jun Tang[1], David Favre[1]
[1]GlaxoSmithKline, Durham, NC, USA, [2]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]McGill Univ Hlth Cntre, Glen Site, Montréal, QC, Canada

Background: Protein kinase C agonists (PKCa) are potent in vitro latency reversing agents (LRAs) that act synergistically with histone deacetylase inhibitors (HDACi) and bromodomain inhibitors (iBET), suggesting their potential use in HIV cure strategies. Here we confirm and extend prior testing of the PKCa Ingenol-B (IngB) in vitro. Because IngB is unstable at physiological pH conditions, a stabilized form of Ingenol (GSK445A) was developed and tested in vitro and in the non-human primate model.
Methods: The ability of IngB to reverse latency in vitro was tested in reporter cell lines and in total or resting CD4+ T cells from stably-treated HIV-infected donors. Reactivation was measured by cell-associated RNA (caRNA), tat/rev induced limiting dilution assay (TILDA) and quantitative viral outgrowth assays (QVOA). IngB, GSK445A and iBET151 as single agents, fixed-dose combination and dose-response curves were measured. Cellular responses were profiled in vitro for cytotoxicity, cell signaling and transcriptomics. The pharmacology and biomarkers of GSK445A were analyzed in blood and tissues of healthy and chronically SIV-infected rhesus macaques (RM).
Results: The effective concentrations 50 (EC50) of GSK445A and IngB were 1 and 13 nM, respectively, in HIV-Jurkat cell lines compared with ~200 nM for IngB in primary CD4+ T cells of HIV donors (caRNA), with latency reversal confirmed by TILDA and QVOA. Cell signaling and transcriptional profiling demonstrated rapid and potent activation of NFkB, Akt and MAPK pathways in CD4+ T cells. Combination activity of IngB with iBET151 showed a 5 to 10-fold increase in potency and maximal response by caRNA and was confirmed by TILDA, suggesting synergy in the reactivation of a large pool of latently infected cells. In vivo, a brief infusion of GSK445A at 5 to 20ug/kg was well tolerated in RM (n=20). Pharmacokinetics of GSK445A displayed a biphasic decline with exposure above the EC50 for 3-6 hours. Rapid increase in plasma IL-6, T cell trafficking and up-regulation of CD69 (10-60% in T cells) revealed dose-dependent responses in blood and lymphoid tissues, which returned to baseline after 6 to 48 hours.
Conclusion: In vitro, GSK445A and IngB reversed HIV latency; activity was augmented by iBET151. GSK445A was developed as a stable Ingenol derivative that was well tolerated at an effective dose in RM making GSK445A a candidate for single and combination studies to test latency reversal and clearance in vivo.

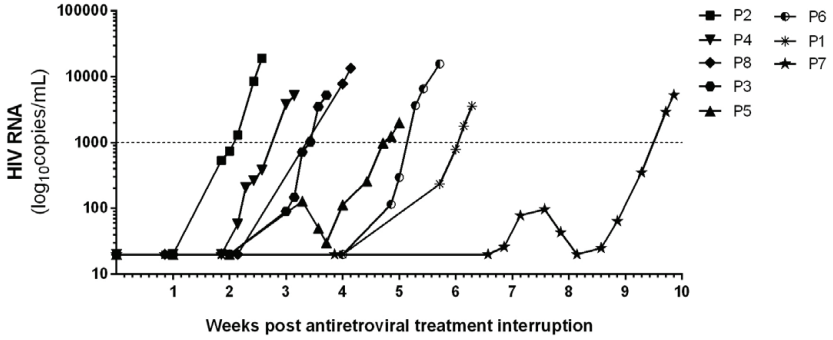
124 HIV RNA REBOUND POSTINTERRUPTION IN PERSONS SUPPRESSED IN FIEBIG I ACUTE HIV

Donn Colby[1], Nicolas Chomont[2], Eugene Kroon[1], Louise Leyre[2], Suteeraporn Pinyakorn[3], Nelson L. Michael[3], Merlin L. Robb[3], Nittaya Phanuphak[1], **Jintanat Ananworanich**[3], for the RV411 and RV254/SEARCH010 Study Groups
[1]SEARCH, The Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [2]Cntr de Rsr du Cntr Hosp de l'Univ de Montréal, Montréal, QC, Canada, [3]US Military HIV Rsr Prog, Bethesda, MD, USA

Background: Initiation of antiretroviral therapy (ART) during acute HIV infection (AHI) minimizes establishment of a latent HIV reservoir. This could, in turn, delay viral rebound following treatment interruption (TI) and potentially induce a post-treatment controller state. We investigated time to viral load (VL) rebound after ART cessation in participants who initiated ART during AHI.
Methods: Eight participants (7 male, 1 female) who initiated ART in Fiebig I (VL+, p24-, IgM-) acute infection and had VL<20 copies/ml on ART for a median of 2.8 (range 2.5-5.5) years before undergoing TI with VL monitoring every 3-7 days. VL, CD4/CD8, HIV DNA and inducible HIV RNA were examined. There was 85% power to reject the null hypothesis of 5% rate of VL < 50 copies/ml at 24 weeks post-TI if the true rate was 30% or greater.
Results: The median (range) age was 29 (22-34) years. HIV subtypes were CRF01_AE (n=6) or CRF01_AE/B (n=2). Median (range) pre-ART values included HIV RNA 4.2 (3.3-4.9) log10copies/ml, HIV DNA 66 (0-490) log10copies/106CD4, and CD4 413 (227-565) cells/mm3. Prior to TI, median (range) CD4 was 561 (425-654) cells/mm3. Total HIV DNA (LOD 5 copies/106CD4) and inducible HIV RNA (LOD 1.4 tat/rev RNA+cells/106CD4) were undetectable for all participants. All participants experienced VL rebound post-TI at a median

(range) time of 26 (13-48) days (Figure). VL at first detection was 2.1 (1.4-3.9) and the highest VL was 3.7 (3.3-4.1) log10copies/ml after 4 (1-12) days from first VL detection. CD4 change was -9 (-87 to +39) cells/mm3. There were no symptoms consistent with acute retroviral syndrome, new resistance mutations or treatment failures after ART resumption. Four of 6 participants with non-reactive 4th generation immune assay seroconverted after VL rebound. Pre-TI CD4/CD8 ratio ≤ 1 predicted time to VL rebound (p-value log-rank test 0.004). HIV reservoir markers pre-ART and pre-TI were not predictive.

Conclusion: ART initiated in Fiebig I did not result in a significantly longer time to VL detection post-TI compared to published chronic HIV cohorts infected with other HIV-1 subtypes. Despite achieving extremely small HIV reservoir size, early ART alone will infrequently induce HIV remission and additional strategies to eliminate or control latently infected cells will be required.



125 EARLY DETECTION OF HIV REBOUND BY INNATE SENSORS POST ART INTERRUPTION

Julie Mitchell[1], Eugene Kroon[2], Khunthalee Benjapornpong[2], Suteeraporn Pinyakorn[1], Praphan Phanunphak[3], Sharon R. Lewin[4], Jintanat Ananworanich[1], Mark de Souza[2], Lydie Trautmann[1], for the Search 019 Study Group

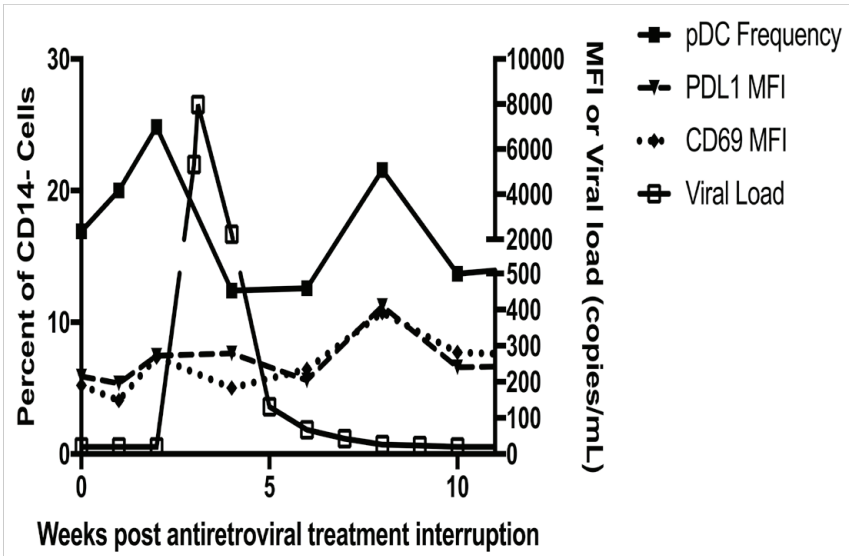
[1]Henry M. Jackson Fndn, Silver Spring, MD, USA, [2]SEARCH, The Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [3]Henry M. Jackson Fndn, Bethesda, MD, USA, [4]Doherty Inst for Infection and Immunity, Melbourne, Australia

Background: The innate immune system rapidly responds to HIV and this response could potentially be used to detect viral rebound prior to viremia following antiretroviral treatment interruption (TI). We investigated the innate subsets in participants who initiated antiretroviral therapy (ART) during acute HIV infection after TI.

Methods: Thirteen HIV infected Thais who initiated ART during Fiebig III-IV (Western blot negative/indeterminate) were studied longitudinally during TI as part of a randomized study of vorinostat/hydroxychloroquine/maraviroc plus ART given for 10 weeks (n=8) vs. ART only (n=5). During TI, dendritic cell (DC) and monocyte subsets were analyzed by flow cytometry and DCs were divided into three populations: CD1c+ myeloid DCs (MDCs), CD141+ MDCs, and CD303+ plasmacytoid DCs (pDCs). Monocyte subsets were defined by expression of CD14 and CD16. HIV RNA in plasma was measured weekly after TI.

Results: At the time of TI, all participants were on ART for ≥ 3 years, with CD4 T cells ≥ 400 cells/mm3 and HIV-1 RNA < 50 copies/ml. Viral load (VL) rebound occurred in all subjects following TI at a median (IQR) of 22 days. At TI, the frequencies of CD1c+ MDCs, CD141+ MDCs and pDCs were 27.1±8.2%, 0.38±0.36% and 10.7±4.9%, respectively. During TI, we observed a consistent increase in the percentage of pDCs at least one week before VL rebound (median increase =1.40-fold, p=0.01) while there were no consistent changes in the percentage of MDC subsets prior to VL rebound. Additionally, increased surface expression of the DC activation markers PD-L1 and CD69 occurred on pDCs prior to VL rebound (median fold increase: PD-L1=1.39, p=0.008; CD69=1.59, p=0.001). No significant difference was observed in the pDC populations between the two study arms. Analysis of monocyte subsets at TI revealed that 89.5±3.5% were classical, 3.34±1.37% were intermediate, and 1.61±1.04% were nonclassical monocytes. Nonclassical monocytes showed a 2.11-fold increase in frequency (p=0.0002) prior to VL rebound during TI.

Conclusion: These data suggest that pDCs, which sense ssRNA viruses, and inflammatory non-classical monocytes are sensing virus prior to measurable HIV RNA levels in the blood. This sensing induces their proliferation, activation and/or recirculation, suggesting that pDCs and nonclassical monocytes are innate sensors of viral replication when ART is stopped and may represent biomarkers prior to viral rebound.



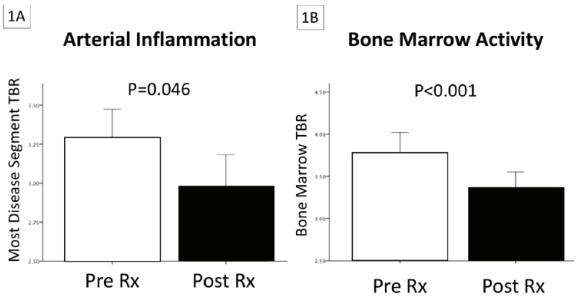
126 IL-1B INHIBITION SIGNIFICANTLY REDUCES ATHEROSCLEROTIC INFLAMMATION IN TREATED HIV

Priscilla Hsue[1], Steven G. Deeks[1], Amorina E. Ishai[2], Sophia Hur[1], Danny Li[1], Felicia Sterman[3], Jay Lalezari[4], Adam Rupert[5], Peter Ganz[1], Ahmed Tawakol[2]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Massachusetts General Hosp, Boston, MA, USA, [3]California Pacific Med Cntr, San Francisco, CA, USA, [4]Quest Clinical Rsr, San Francisco, CA, USA, [5]Natl Inst of Hlth, Frederick, MD, USA

Background: HIV infection is associated with an increased burden of atherothrombotic events, likely as a result of increased atherosclerotic inflammation. The IL-1 pathway is an upstream mediator of inflammation and inducer of innate immunity. IL-1β binds to the IL-1 receptor and is linked to both stimulating atherogenesis and HIV disease pathogenesis. The purpose of this pilot study was to evaluate the impact of IL-1β inhibition on inflammatory markers and atherosclerotic plaque inflammation using fluorodeoxyglucose positron emission tomography imaging (FDG-PET) in HIV.

Methods: Adults with treated and suppressed HIV infection and 1 cardiovascular risk factor (n= 10) were treated with a monoclonal antibody to IL-1β (canakinumab [CKB], 150mg subcutaneous injection administered once). FDG-PET imaging was performed before and 8 weeks after treatment to measure atherosclerotic inflammation in the aorta and carotids. Arterial wall FDG uptake (target) was normalized to blood pool (background), yielding a target to background ratio (TBR). The most diseased segment (MDS) was defined as the 1.5 cm segment with the highest TBR at baseline. All analyses were performed while blinded to time point.

Results: The median age was 59 (IQR 55 to 65), all were male, and 80% were on statin therapy. The median CD4 count was 748 (IQR 570 to 1142) and all had undetectable HIV RNA levels. CKB was well tolerated without a significant change in CD4 count or HIV RNA level. At 8 weeks, CKB reduced hsCRP (median [IQR]: 0.87 [0.56, 4.17] vs. 0.64 [0.24, 2.44] mg/mL, baseline vs. follow-up, p=0.02), and IL-6 (1.10 [0.69, 1.33] vs. 0.70 [0.48, 1.06] pg/ml, p=0.005). CKB attenuated arterial inflammation by 10% (mean index MD±SSD: 3.29±0.57 vs. 2.98±0.64, p=0.046, Figure 1A). This was accompanied by an 11% reduction in bone marrow metabolic activity (BM TBR: 3.78±0.72 vs. 3.37±0.55, p<0.001, Figure 1B).



Conclusion: In this first study to examine the effect of a potent anti-inflammatory strategy on atherosclerotic inflammation in HIV, we observed a substantial reduction in atherosclerotic inflammation, bone marrow metabolic activity, and inflammatory markers (hsCRP and IL-6). Larger, placebo-controlled studies are under way to further evaluate the impact of IL-1β inhibition on atherosclerotic inflammation in this population, and to assess whether this approach will translate into reductions in atherothrombotic events.

127 HYPERBILIRUBINEMIA PREVENTS CARDIOVASCULAR DISEASE FOR HIV+ AND HIV- INDIVIDUALS

Vincent C. Marconi[1], Kaku So-Armah[2], Janet Tate[3], Joseph Lim[4], Vincent Lo Re[5], Adeel A. Butt[6], Matthew B. Goetz[7], Maria Rodriguez-Barradas[8], Amy Justice[3], Matthew Freiberg[9]
[1]Emory Univ, Atlanta, GA, USA, [2]Boston Univ, Boston, MA, USA, [3]VA Connecticut Hlthcare System, West Haven, CT, USA, [4]Yale Univ, New Haven, CT, USA, [5]Univ of Pennsylvania, Philadelphia, PA, USA, [6]Weill Cornell Med Coll, New York, NY, USA, [7]VA Greater Los Angeles Hlth Care System, Los Angeles, CA, USA, [8]Baylor Coll of Med, Houston, TX, USA, [9]Vanderbilt Univ, Nashville, TN, USA

Background: Hyperbilirubinemia may protect against cardiovascular disease (CVD) by reducing oxidative stress and via its anti-atherogenic properties. Whether elevated bilirubin reduces risk of CVD events including among HIV positive (HIV+) people independently of atazanavir (ATV) use is unclear. ATV can cause unconjugated hyperbilirubinemia by competitive inhibition of the uridine diphosphate-glucuronosyl transferase (UGT) 1A1 enzyme. We assessed whether elevated bilirubin independently reduced the risk of heart failure (HF) and acute myocardial infarction (AMI) among participants in the Veterans Aging Cohort Study (VACS).

Methods: VACS participants, without CVD at baseline (first clinical visit after 4/1/2003) were included. The total bilirubin from clinical labs closest to baseline was categorized into quartiles. HF and AMI were assessed using VA, VA Fee For Service and Medicare ICD-9 codes. Participants were followed until first HF or AMI, death, last VA encounter or 12/31/2011. Cox regression was used to estimate HF/AMI risk adjusting for baseline confounders including HIV and hepatitis C, demographics, Framingham CVD risk factors, and substance abuse/dependence. Analyses restricted to HIV+ participants were further adjusted for HIV viremia and ATV use.

Results: There were 96,373 participants; mean age was 49 years, 48% were African American, and 97% were men. There were 3,844 incident HF events (median follow up 6.9 years) and 1,932 incident AMI events over (median follow up 7.4 years). Among the HIV+ participants with bilirubin >75th percentile (≥0.9 mg/dL), 9% were on ATV compared to 3%, with bilirubin <25th percentile (<0.04 mg/dL). In unadjusted models, bilirubin was inversely associated with HF and AMI risk. After adjusting for CVD risk factors, higher bilirubin was associated with a lower hazard ratio (HR) for HF and AMI (Table). When the same model included only HIV+ participants (N=30,425), results persisted for HF and similar but non-significant associations were observed for AMI. Death rates were highest in the lowest and highest bilirubin quartiles.

Conclusion: VACS participants with elevated bilirubin had lower risk of incident HF and AMI events after adjusting for known risk factors. This association persisted for HF among HIV+ people but was attenuated for AMI. Future studies, should investigate how this apparently protective effect of elevated bilirubin may be harnessed to reduce CVD risk or improve CVD risk estimation among HIV+ people.

Total bilirubin (mg/dL)	N	HF			AMI		
		Rate (95% CI)	HR (95% CI)	P	Rate (95% CI)	HR (95% CI)	P
<0.4	24229	7.95 (7.50-8.42)	**1 (ref)**	<0.01	3.81 (3.51-4.13)	**1 (ref)**	0.02
0.5-0.6	23638	7.39 (6.95-7.85)	0.88 (0.81-0.96)		3.36 (3.08-3.68)	0.85 (0.75-0.96)	
0.7-0.8	17462	6.60 (6.12-7.12)	0.79 (0.72-0.87)		3.45 (3.11-3.81)	0.89 (0.78-1.02)	
≥0.9	18523	6.41 (5.94-6.92)	0.75 (0.68-0.83)		3.07 (2.76-3.41)	0.80 (0.70-0.92)	
Missing	12521	4.89 (4.40-5.43)	0.72 (0.61-0.84)		2.01 (1.73-2.34)	0.85 (0.68-1.08)	

Models adjusted for age, race-ethnicity, systolic blood pressure, smoking, diabetes, total cholesterol, high density lipoprotein cholesterol, HIV, hepatitis C, liver fibrosis measured by FIB-4, alcohol abuse/dependence, cocaine and obesity; HF- heart failure; AMI-acute myocardial infarction; HR-Hazard Ratio; P-p-value test for overall significance of total bilirubin categories

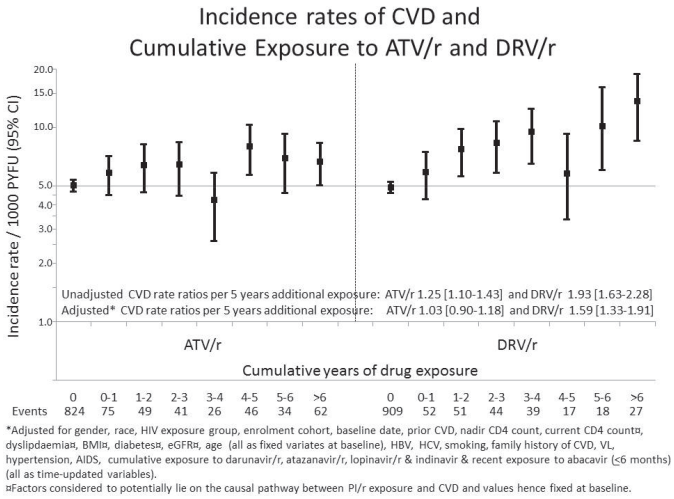
128LB ASSOCIATION BETWEEN CARDIOVASCULAR DISEASE & CONTEMPORARILY USED PROTEASE INHIBITORS

Lene Ryom[1], Jens D. Lundgren[2], Wafaa M. El-Sadr[3], Peter Reiss[4], Andrew Phillips[5], Ole Kirk[6], Rainer Weber[7], Caroline Sabin[5], Amanda Mocroft[8], for the D:A:D Study Group
[1]CHIP, Copenhagen, Denmark, [2]Univ of Copenhagen, Copenhagen, Denmark, [3]ICAP at Columbia Univ, New York, NY, USA, [4]Stichting HIV Monitoring and Academic Med Cntr Amsterdam, Amsterdam, Netherlands, [5]Univ Coll London, London, UK, [6]Rigshosp, Copenhagen, Denmark, [7]Univ of Zurich, Zurich, Switzerland, [8]Univ Coll London, London, UK

Background: While the use of older protease inhibitors (PIs) including indinavir (incidence rate ratio (IRR) 1.47/5 years) and lopinavir boosted with ritonavir (/r) (IRR 1.54/5 years) has been associated with excess risk of cardiovascular disease (CVD) it is unknown whether this also applies to contemporarily used PIs.

Methods: D:A:D study participants under follow-up (FU) after 01.01.2009 were followed to the earliest of CVD, last visit plus 6 months or 01.02.2016. CVD was defined as centrally validated myocardial infarction, stroke, sudden cardiac death or invasive cardiovascular procedures (coronary bypass, coronary angioplasty and carotid endarterectomy). Poisson regression models assessed associations between CVD and use of two contemporarily and frequently used PIs atazanavir (ATV/r) and darunavir (DRV/r).

Results: Of 35,711 included persons, 1,157 developed CVD (IR 5.3/1000 PYFU [95%CI 5.0-5.6]) during 7.0 (IQR 6.3-7.1) years median FU. The crude CVD IR increased gradually from 4.91/1000 PYFU [4.59-5.23] in those never exposed to DRV/r to 13.67/1000 PYFU [8.51-18.82] in those exposed >6 years, while the changes with ATV/r were less pronounced (from 5.03 [4.69-5.37] to 6.68/1000 PYFU [5.02-8.35]), (figure). After adjustment for factors not considered on the causal pathway between PI/r use and CVD, cumulative exposure to DRV/r, but not ATV/r, was associated with excess CVD risk (IRR 1.59 [1.33-1.91] and 1.03 [0.90-1.18]/5 years respectively). Additional adjustment for time-updated dyslipidemia, and other factors potentially on the causal pathway to CVD, did not affect the association (DRV/r 1.53 [1.28-1.84] and ATV/r 1.01 [0.88-1.16]/5 years). The associations remained consistent for; myocardial infarction and stroke separately; after adjustment for bilirubin levels (associated with ATV/r use and potentially protective of CVD); when stratifying for whether DRV/r was used as the first ever PI/r containing regimen or not (p=0.29 for interaction); whether DRV/r was used with a non-nucleoside reverse transcriptase inhibitor or not (p=0.43 for interaction); and in those at high vs. low estimated 5 year CVD risk (p=0.12 for interaction).



*Adjusted for gender, race, HIV exposure group, enrolment cohort, baseline date, prior CVD, nadir CD4 count, current CD4 count¤, dyslipdaemia¤, BMI¤, diabetes¤, eGFR¤, age (all as fixed variates at baseline), HBV, HCV, smoking, family history of CVD, VL, hypertension, AIDS, cumulative exposure to darunavir/r, atazanavir/r, lopinavir/r & indinavir & recent exposure to abacavir (≤6 months) (all as time-updated variables).
¤Factors considered to potentially lie on the causal pathway between PI/r exposure and CVD and values hence fixed at baseline.

Conclusion: In this large heterogeneous cohort of HIV-positive persons, cumulative use of DRV/r, but not ATV/r, was independently associated with a small, but gradually increasing CVD risk. Causal inference is limited by the observational nature of our data, but the findings call for further investigations into possible underlying mechanisms.

129 CARDIOVASCULAR PREVENTION POLICY IN HIV: RECOMMENDATIONS FROM A MODELING STUDY

Rosan van Zoest[1], Mikaela Smit[2], Brooke Nichols[3], Ilonca Vaartjes[4], Colette Smit[5], Marc van der Valk[6], Ferdinand Wit[5], Timothy B. Hallett[2], Peter Reiss[5], for the Netherlands ATHENA Observational HIV Cohort

[1]Amsterdam Inst for Global Hlth and Development and Academic Med Cntr, Amsterdam, Netherlands, [2]Imperial Coll London, London, UK, [3]Erasmus Univ Med Cntr, Rotterdam, Netherlands, [4]Univ Med Cntr Utrecht, Utrecht, Netherlands, [5]Stichting HIV Monitoring, Amsterdam, Netherlands, [6]Academic Med Cntr, Amsterdam, Netherlands

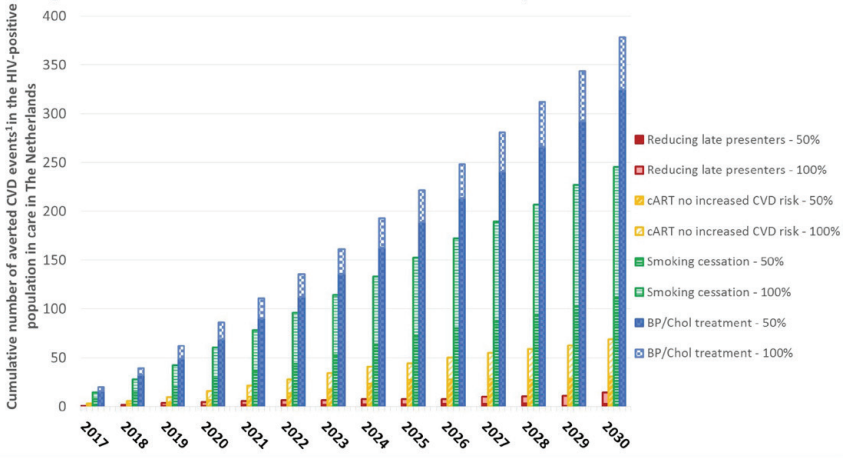
Background: Cardiovascular disease (CVD) is expected to contribute the largest non-communicable disease burden amongst HIV-positive people over the coming decades. We modeled the impact of different CVD prevention interventions in Dutch HIV-positive patients and determined which is best use of resources.

Methods: An individual-based model of CVD in ageing Dutch HIV-positive patients was constructed using 1996-2010 data from 8,791 patients on combination antiretroviral therapy (cART) from the national ATHENA cohort. The model follows patients in care, including new patients, as they age, develop (risk factors for) CVD (by incorporating the D:A:D CVD risk equation) and start CVD medication, and was validated on 2010-2015 data. Four interventions were evaluated between 2017 and 2030, assuming 100% and 50% implementation success: 1) reducing the number of late presenters (i.e. CD4 count <500 cells/mm^3); 2) use of cART with no known increased CVD risk; 3) a smoking cessation program; 4) intensified monitoring and drug treatment of hypertension and dyslipidemia. Interventions were evaluated in all patients and in moderate to high CVD risk patients only (HR, 5-year CVD risk ≥5%). Economic evaluations were performed assuming 50% implementation success, accounting for all costs related to HIV/CVD treatment.

Results: The model predicts that CVD incidence will increase by 50% between 2015 and 2030 and that intensified monitoring and treatment of hypertension and dyslipidemia will have the greatest impact on averting CVD events, followed by a smoking cessation program (Figure). Economic evaluations identified three interventions with the potential to be cost-effective: smoking cessation in HR patients, decreasing the number of late presenters in all patients, and intensified monitoring and treatment of hypertension and dyslipidemia in HR patients. The latter is most likely to be the best use of resources and could be cost-effective or even cost-saving.

Conclusion: Our study is the first to provide evidence to guide policy makers concerning which high-impact CVD prevention interventions to prioritize as part of HIV care, recommending intensified monitoring and successful treatment of hypertension and dyslipidemia in moderate to high CVD risk patients as the best use of resources by focusing on addressing the gap between current clinical care and standard guidelines. Quantifying additional public health benefits, beyond CVD, of all four interventions, is likely to provide further evidence for policy development.

Figure. Cumulative number of averted CVD events[1] for four modelled CVD prevention interventions[2]



Abbreviations: 50%, 50% implementation success; 100%, 100% implementation success; BP, blood pressure; cART, combination antiretroviral therapy; Chol, cholesterol; CVD, cardiovascular disease.
[1] CVD includes myocardial infarction, stroke, coronary artery angioplasty, coronary by-pass, carotid endarterectomy, and deaths from other coronary heart disease.
[2] Four CVD prevention interventions include: 1) reducing the number of late presenters (i.e. CD4 count <500 cells/mm3); 2) use of cART with no known increased CVD risk; 3) a smoking cessation program; 4) intensified monitoring and drug treatment of hypertension and dyslipidemia.

130 IMPACT OF SMOKING, HYPERTENSION & CHOLESTEROL ON MYOCARDIAL INFARCTION IN HIV+ ADULTS

Keri N. Althoff[1], Frank J. Palella[2], Kelly Gebo[1], Stephen J. Gange[1], Charles Rabkin[3], Jennifer E. Thorne[4], Micheal A. Horberg[5], Daniel B. Klein[6], Mari Kitahata[7], Richard D. Moore[8]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Northwestern Univ, Chicago, IL, USA, [3]NCI, Rockville, MD, USA, [4]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [5]Kaiser Hosp, San Leandro, CA, USA, [6]Univ of Washington, Seattle, WA, USA

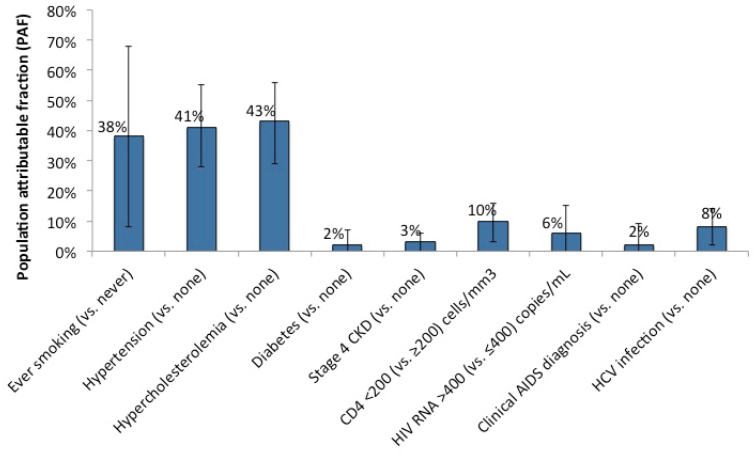
Background: HIV-infected adults have a 1.5-to-2-fold increase in risk of myocardial infarctions (MIs) compared with uninfected adults. Our objective was to estimate the population attributable fractions (PAFs) of HIV-related and traditional MI risk factors, interpreted as the proportion of MIs that could potentially be avoided if HIV-infected adults were unexposed to these risk factors.

Methods: We included adults from 7 contributing cohorts to the NA-ACCORD with validated first occurrence of a type 1 myocardial infarction, which are MIs from plaque rupture that would be most susceptible to traditional MI risk factors. Modifiable HIV-related risk factors included CD4 <200 cells/mm3, detectable plasma HIV RNA (≥400 copies/mL), and history of clinical AIDS. Modifiable traditional risk factors included tobacco smoking, treated hypertension (HTN), hypercholesterolemia (HC, defined as use of statins or a total cholesterol >240 mg/dL), type II diabetes, stage 4 chronic kidney disease (CKD), and hepatitis C virus (HCV) infection. Cox proportional hazard models with piecewise constant baseline hazard functions were used to estimate hazard ratios (adjusted for age, sex, race, and injection drug use). These hazard ratios were combined with the prevalence of the risk factor among persons with MIs to estimate adjusted PAFs for modifiable risk factors. Smoking and HCV infection were measured at study entry. All other variables were time-updated.

Results: A total of 29,515 adults contributed 131,137 person-years and 347 MIs; median follow up was 3.5 years. At baseline, participants who subsequently had an MI were older, more likely to be black, have smoked, had HTN, HC, diabetes, stage 4 CKD, a low CD4, a clinical AIDS diagnosis, and HCV infection. Adjusting for demographics, eliminating smoking, HTN, and HC would avert 38%, 41% and 43% of MIs, respectively (Figure 1); eliminating all three would avert 86% of MIs. HIV-related risk factors and HCV infection had smaller PAFs. A subgroup analyses accounting for BMI showed similar results, with the exception of a reduction in the PAF for HC.

Conclusion: Preventing smoking, hypertension, and HC each could result in a ~40% reduction in MIs among aging HIV-infected adults; further reductions in MIs can be achieved with aggressive antiretroviral management. These results underscore the need to implement traditional MI risk reduction interventions soon after prompt HIV treatment initiation in order to reduce excess MI burden among aging HIV-infected adults.

Figure 1: Population attributable fractions and 95% confidence intervals for traditional and HIV-related risk factors, and hepatitis C virus infection, NA-ACCORD (1 Jan 2000 – 31 Dec 2013)



Population attributable fractions have been adjusted for all the risk factors in the figure, as well as age, sex, race, HIV transmission risk, diabetes, and stage 4 chronic kidney disease.

131 CESSATION OF CIGARETTE SMOKING AND THE IMPACT ON CANCER INCIDENCE IN THE D:A:D STUDY

Leah Shepherd[1], Lene Ryom[2], Kathy Petoumenos[3], Camilla Ingrid Hatleberg[2], Antonella d'Arminio Monforte[4], Fabrice Bonnet[5], Peter Reiss[6], Jens D. Lundgren[2], Amanda Mocroft[1], for the D:A:D Study Group
[1]Univ Coll London, London, UK, [2]CHIP, Copenhagen, Denmark, [3]Kirby Inst, Sydney, Australia, [4]Univ of Milan, Milan, Italy, [5]CHU de Bordeaux, Bordeaux, France, [6]Stichting HIV Monitoring and Academic Med Cntr, Amsterdam, Netherlands

Background: Cancers are a major source of morbidity and mortality in the cART era. The prevalence of smoking in HIV+ people is 40–70% and the clinical benefits of smoking cessation on cancer risk have not been reported. We aimed to estimate cancer rates after smoking cessation in persons from the D:A:D study.

Methods: Persons were followed from the latest of study entry or 1/1/2004 until earliest of first cancer diagnosis, last visit plus 6 months, death, or 1/2/2015. Three outcomes were considered: all cancers combined, lung cancer, and other smoking-related excluding lung cancer (OSRC; see footnote). Smoking status was defined as current and never smokers, those who stopped during follow-up (<1,1-2,2-3,3-5,5> years since stopping) and those who stopped prior to baseline. Adjusted rate ratios (aRR) were calculated using Poisson regression.

Results: 39701 persons contributed 315327 person years of follow-up (PYFU) (median: 9 IQR: 6, 11 years per person). At baseline, 41% of people were current smokers, 17% were ex-smokers, 27% never smoked. 2230 developed cancer (IR 7.1/1000 PYFU, 95%CI: 6.8, 7.4), of which 251 were lung cancers (IR 0.8/1000 PYFU, 95%CI: 0.7, 0.9) and 516 were OSRC (IR 1.6/1000 PYFU 95%CI: 1.5, 1.8). Incidence of all cancers combined (Figure) was highest <1 year after quitting compared to those who had never smoked (aRR: 1.62 95%CI: 1.32, 1.99) and was similar to never smokers thereafter. Lung cancer incidence was over 11-fold higher <1 year after quitting (aRR: 11.72 95%CI: 4.81, 28.57) and remained >8-fold higher even after 5 years (aRR: 8.26 95%CI: 2.83, 24.09) with no evidence of decline when compared to non-smokers. OSRC incidence was almost 3-fold higher <1 year after quitting (aRR2.52 95%CI: 1.69, 3.74), but was similar to never smokers thereafter. Smoking duration was associated with the occurrence of all cancers combined (Per year longer aRR: 1.03 95%CI: 1.01,1.04), lung (aRR: 1.07 95%CI: 1.01, 1.12), but not OSRC (aRR: 1.03 95%CI: 0.99, 1.06). No significant interactions between smoking status and age, gender or CD4 were found.

Conclusion: Overall cancer incidence declined to that of non-smokers after one year quitting except for lung cancer incidence, which did not decrease even >5 years after quitting. Smoking cessation efforts should be a priority to reduce the risk of cancer, however, surveillance and screening of lung cancer should not be stopped in patients who stop smoking.

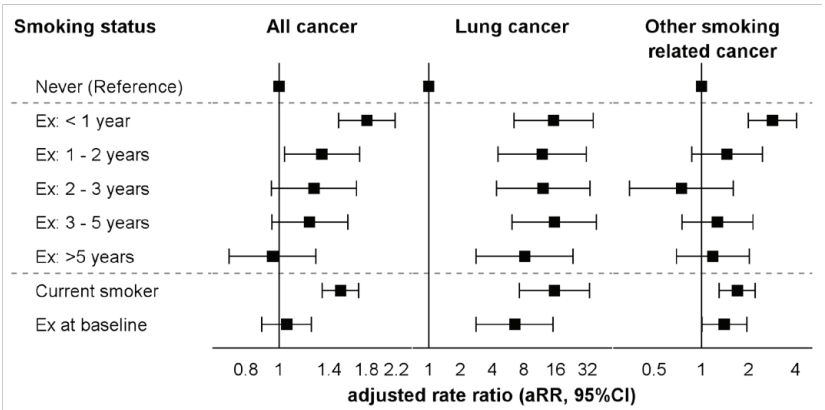


Figure: Adjusted rate ratios (aRR) for cancers, lung cancer and other smoking related cancers (OSRC, which excludes lung cancer). OSRC: head and neck, oesophagus, stomach, pancreas, liver, kidney and urinary cancers, colon and rectal, cervical, ovary and acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML). All models were adjusted for age, gender, HIV risk group, race, BMI, calendar year, current CD4 and HIV-viral load, duration of past smoking, HCV and HBV status, prior AIDS events, anaemia, hypertension, cardiovascular events, diabetes, and cART use.

132 BONE DENSITY AND TRABECULAR BONE SCORE IMPROVE FRACTURE PREDICTION IN HIV+ WOMEN

Jingyan Yang[1], Anjali Sharma[2], Josh Aschheim[3], Kathryn Anastos[2], Mardge H. Cohen[4], Elizabeth T. Golub[5], Deborah Gustafson[6], Daniel Merenstein[7], Phyllis Tien[8], Michael T. Yin[1]
[1]Columbia Univ Med Cntr, New York, NY, USA, [2]Albert Einstein Coll of Med, Bronx, NY, USA, [3]Arcadia Hlth, New York, USA, [4]John H.Stroger Jr. Hosp of Cook County, Chicago, IL, USA, [5]The Johns Hopkins Univ, Baltimore, MD, USA, [6]SUNY Downstate Med Cntr, Brooklyn, NY, USA, [7]Georgetown Univ, Washington, DC, USA, [8]Univ of California San Francisco, San Francisco, CA, USA

Background: The FRAX algorithm predicts the 10-year risk of a major osteoporotic (MO) fracture at the spine, hip or forearm combined or at just the hip using clinical risk factors (CRF) alone or with addition of dual-energy xray absorptiometry (DXA) measures: femoral neck bone mineral density T-scores (FNT) and lumbar spine trabecular bone score (TBS), a measure of gray scale homogeneity that correlates with trabecular microarchitecture. FRAX based upon CRF alone underestimates fracture risk in HIV-infected adults. Our objective was to determine whether addition of FNT and TBS improves accuracy of fracture probability assessment in HIV-infected women enrolled in the Women's Interagency HIV Study.

Methods: We included 1148 women (900 HIV-infected and 248 uninfected) with age > 40 years, complete CRF data for FRAX calculation, and 10-year observational data for incident fragility fractures. 220 (19%) of the women had baseline DXA measurements of FNT and TBS. Accuracy of the FRAX calculation was compared by the observed/estimated (O/E) ratios of fracture in 3 models: CRF only; CRF and FNT; or CRF, FNT and TBS. Accuracy is perfect if O/E=1; O/E >1 indicates underestimation.

Results: Mean age of the cohort was 47±6 years. HIV-infected women were more likely to be African American, non-smokers, and thinner than uninfected women, but less likely to report glucocorticoids or alcohol use. During the 10-year follow-up, observed fracture rates did not differ significantly in HIV-infected and uninfected women for MO (8.1% vs 5.2%, p=0.13) or hip fractures (2.7% vs 1.2%, p=0.24). FRAX using CRF was less accurate in HIV-infected than uninfected women for predicting MO (O/E=4.33 vs. 2.92, p<0.001) and hip fractures (O/E=17.96 vs 7.61, p<0.001). Among HIV-infected women, accuracy improved greatly when FNT was included in the FRAX calculation for MO (O/E=4.33 vs 3.50, p<0.001) and hip fractures (O/E=17.96 vs 2.74, p<0.001), and further improved when both FNT and TBS were included in the FRAX calculation (both p<0.05, Table). After addition of DXA measures, accuracy of FRAX no longer differed between HIV-infected and uninfected women (Table).

Conclusion: Accuracy of FRAX is improved with addition of FNT and TBS to clinical risk factors in HIV-infected women. These observational data support existing guideline recommendations for DXA screening in HIV-infected adults over age 50; and incorporation of DXA data into fracture prediction with FRAX.

Table: Comparison of accuracy of FRAX calculation in HIV-infected and uninfected women

	HIV infected (N=900)		HIV uninfected (N=248)		P-value
	O/E Ratio	95% CI	O/E Ratio	95% CI	
FRAX with CRF alone					
Major osteoporotic fracture	4.33	4.20, 4.46	2.92	2.65, 3.18	<0.001
Hip fracture	17.96	17.42, 18.50	7.61	6.84, 8.39	<0.001
	HIV infected (N=181)		HIV uninfected (N=39)		
FRAX with CRF and FNT					
Major osteoporotic fracture	3.50	3.08, 3.93	4.85	2.34, 7.37	0.281
Hip fracture	2.74	1.87, 3.60	NA*	-	-
FRAX with CRF, FNT and TBS					
Major osteoporotic fracture	2.95	2.50, 3.40	3.38	1.15, 5.62	0.699
Hip fracture	1.32	0.71, 1.93	NA*	-	-

* Insufficient hip fracture events were observed in HIV-uninfected women to calculate O/E ratio.

133 FRAILTY PROGRESSION AND RECOVERY AMONG PERSONS AGING WITH HIV AND SUBSTANCE USE

Damani A. Piggott, Karen Bandeen-Roche, Shruti H. Mehta, Todd Brown, Huanle Yang, Jeremy D. Walston, Sean X. Leng, Gregory D. Kirk
The Johns Hopkins Univ, Baltimore, MD, USA

Background: Frailty is a critical aging-related syndrome marked by diminished physiologic reserve and heightened vulnerability to stress, predictive of major adverse clinical outcomes in older adults. We have previously demonstrated that frailty burden is heightened with HIV infection and strongly associated with increased hospitalization and death among persons aging with HIV. Though frailty is considered dynamic, little data exist on the factors determining transitions between frailty states among HIV-infected or uninfected adults.

Methods: Frailty was assessed semiannually among HIV-infected and uninfected persons with a history of injection drug use in the AIDS Linked to the IntraVenous Experience (ALIVE) cohort from 2005 through 2013 based on the 5 Fried physical frailty phenotype domains – weight loss, low physical activity, exhaustion, decreased grip strength, and slow

gait speed. An inflammatory index score was constructed from serum measures of interleukin-6 (IL-6) and soluble tumor necrosis factor-α receptor-1 (sTNFR1). Markov transition models were used to assess the relationship of sociodemographics, chronic comorbid disease, HIV clinical factors and inflammation to transitions between frailty states.
Results: Among 1353 ALIVE participants with 9559 frailty transitions, 33% were HIV positive. Younger age, higher educational attainment, employment, and reduced chronic disease comorbidity were significantly associated with reduced frailty progression and greater frailty recovery. Adjusting for sociodemographics, substance use and comorbidity, HIV virologic suppression, elevated CD4 nadir (>500) and absence of a prior AIDS diagnosis were all significantly associated with reduced frailty progression and improved frailty recovery. Likelihood of frailty transition for these less advanced HIV disease states was similar to HIV seronegative status. Adjusting for sociodemographics, comorbidity, substance use and HIV disease stage, for each standard deviation decrease in inflammatory index score, there was a 22% decreased likelihood of frailty progression (aOR 0.78; 95% CI, 0.65, 0.92) and 29% increased likelihood of frailty recovery (aOR 1.29; 95% CI, 1.08, 1.53).
Conclusion: HIV virologic suppression with early ART, improved socioeconomic environment, prevention and reduction of chronic disease comorbidity, and reduced inflammation may reduce frailty progression and promote frailty recovery; these interventions could reduce hospitalization and improve survival for persons aging with HIV.

134 INCIDENCE OF HEPATITIS C AMONG HIV-INFECTED MEN WHO HAVE SEX WITH MEN, 2000–2015

Antoine Chaillon[1], Christy M. Anderson[1], Thomas C. Martin[1], Edward R. Cachay[1], David L. Wyles[2], Davey M. Smith[1], Susan J. Little[1], Richard S. Garfein[1], Natasha Martin[1]
[1]Univ of California San Diego, San Diego, CA, USA, [2]Denver Health, Denver, CO, USA

Background: International reports of a hepatitis C virus (HCV) epidemic among HIV-infected men who have sex with men (HIV+ MSM) associated with recreational drug use and with sex are causing concern. However, little is known about the HCV epidemic among MSM in San Diego. We assess HCV incidence among HIV+ MSM in San Diego in relation to injecting drug and methamphetamine use.
Methods: We performed a retrospective cohort analysis of HCV incidence among HIV+ MSM attending the largest HIV clinic in San Diego (UCSD Owen Clinic) from 2000-2015. Incident HCV infection was assessed among HIV+ MSM with a baseline negative anti-HCV test between 2000 and 2015, and defined as any new positive anti-HCV or HCV-RNA test after the start of follow-up. Group risks were defined as individuals who reported ever injecting drug use (IDU) or using methamphetamine.
Results: A total of 2,396 MSM, who were initially HCV uninfected and had at least 1 further test during a median of 5.5 years of follow-up (IQR 2.8-9.2), were included in the incidence analysis. Overall, 149 HCV seroconversions occurred over 12,560 person-years of follow-up (incidence rate = 1.19/100py, [95%CI 1.01-1.39]), which increased over time (p=0.027, Fig.1A). Individuals were tested a median 3 times (interquartile range[IQR] 2-4) with a median testing interval of 1.2 years (IQR 0.6-2.2). Incident cases were identified on average of 10.6 years (IQR: 5.7-17.5) from HIV diagnosis and 3.6 years (IQR 1.5-6.4) from the first HCV negative test. Among individuals who seroconverted for HCV, 13.4% (20/149) denied IDU and methamphetamine use. HCV incidence was significantly higher among HIV+ MSM reporting IDU compared to those not reporting IDU (2.6/100py vs 0.97/100py, p<0.001), with no evidence of an increasing trend over time (Fig.1B). HCV incidence was also significantly higher among HIV+ MSM reporting ever using meth compared to those denying meth use (1.53/100py vs 0.52/100py, p<0.001) with a significant increase of HCV incidence over time (p<.001, Fig.1C).
Conclusion: These findings suggest that HCV incidence is increasing among HIV+ MSM in San Diego. These rates are similar to London and other major European cities, and double that observed in the US Multicenter AIDS Cohort Study. This study also documented incident HCV infection among HIV+ MSM who do not inject drugs and an increased HCV incidence among individuals reporting meth use. Further work is needed to explain this trend and identify prevention strategies required to control the epidemic.

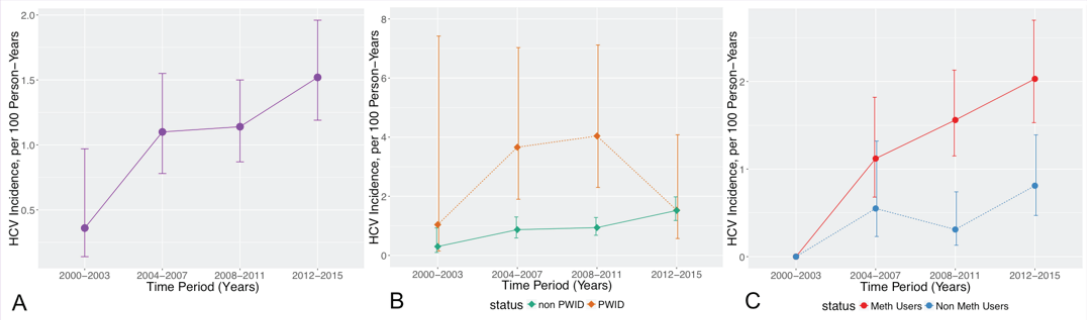


FIGURE 1. Evolution of the HCV incidence among HIV+/MSM at the Owen Clinic, San Diego between 2000-2015. HCV incidence among all HIV+/MSM (*panel A*) and stratified by history of injecting drug use (*panel B*) or methamphetamine use (*panel C*). Meth: methamphetamine; PWID: People who Inject Drug.

135 MODELING HIV-HCV EPIDEMIOLOGY IN THE DAA ERA: THE ROAD TO ERADICATION

Victor Virlogeux[1], Laurent Cotte[2], Pascal Puglièse[3], Isabelle Poizot-Martin[4], Marc-Antoine Valantin[5], Lise Cuzin[6], Jacques Reynes[7], Eric Billaud[8], Thomas Huleux[9], for the DatAIDS Study Group
[1]INSERM, Lyon, France, [2]Hospices Civils de Lyon, Lyon, France, [3]CHU de Nice, Nice, France, [4]Assistance Publique–Hôpitaux de Marseille, Marseille, France, [5]Assistance Publique–Hôpitaux de Paris, Paris, France, [6]CHU Toulouse, Toulouse, France, [7]CHU de Montpellier, Montpellier, France, [8]CHU de Nantes, Nantes, France, [9]Cntr Hosp de Tourcoing, Tourcoing, France

Background: HCV Direct-Acting Antiviral (DAA) treatment uptake has drastically increased in HIV-HCV coinfected patients in France, resulting in HCV cure in more than half of patients at the end of 2015. We used model projections to estimate the impact of DAAs on HIV-HCV epidemiology over the next decade.
Methods: The model was based on epidemiological data from the French DatAIDS cohort. Eight risk groups were considered: high-risk (HR) and low-risk (LR) MSM and males/females heterosexuals, IVDU or patients with other risk. To model HIV-HCV epidemiology we used a mathematical compartmental deterministic model calibrated using the 2012-2015 observed incidence, prevalence and treatment coverage. Figures of the undiagnosed HIV-HCV epidemic were estimated from a previously published model (Supervie AIDS 2014). The impact of scaling-up DAA on HCV prevalence was investigated across the different risk groups.
Results: On January 1st, 2016, 156,811 patients were estimated to be infected with HIV in France (under care: 131,861) of whom 7,939 (5.1%) had an active HCV infection with a detectable serum RNA (under care: 7,216 (5.5%)). Assuming a treatment coverage (TC) of 30%/year (observed rate in 2015), active HCV prevalence among patients under care dropped to 1.31% in 2021 and to 0.55% in 2026. Sub-analyses showed similar results in most risk groups, including LR MSM. Due to higher acute infection and reinfection rates, the predicted prevalence in HR MSM increased from 2.39% in 2016 to 2.46% in 2021 and 3.96% in 2026. Increasing TC in HR MSM to 50/70% per year decreased the prevalence in this group to 1.10/0.50% in 2021 and to 0.86/0.19% in 2026. With the current TC of 30%, the mean delay to reach <50 active infections per group was 10.5 years for every risk group except HR MSM. This threshold was reached at 5.5 years in HR MSM only when increasing TC to 70% in this group. At 30% TC, undiagnosed patients will account for 26.4% of patients with active HCV infection in 2021 and for 43.3% in 2026.
Conclusion: Our model suggests that DAA based treatments could nearly eradicate HIV-HCV coinfection in France within 10 years in most of the risk groups, including LR MSM. Consequently acute infections and reinfections in HR MSM and undiagnosed HIV-infected patients will account for the majority of infections in the future. Eradication in these 2 groups will require increased treatment coverage of acute infections in HR MSM and increased engagement in care for undiagnosed infections.

136 UNRESTRICTED DAA ACCESS IN THE NETHERLANDS: RAPID THERAPY UPTAKE IN HIV+HCV+ PATIENTS

Anne Boerekamps[1], Astrid Newsum[2], Colette Smit[3], Peter Reiss[4], Clemens Richter[5], Marc van der Valk[6], Joop Arends[7], Kees Brinkman[8], Bart Rijnders[1], for the Netherlands ATHENA HIV Observational Cohort and the NVHB-SHM Hepatitis Working Group

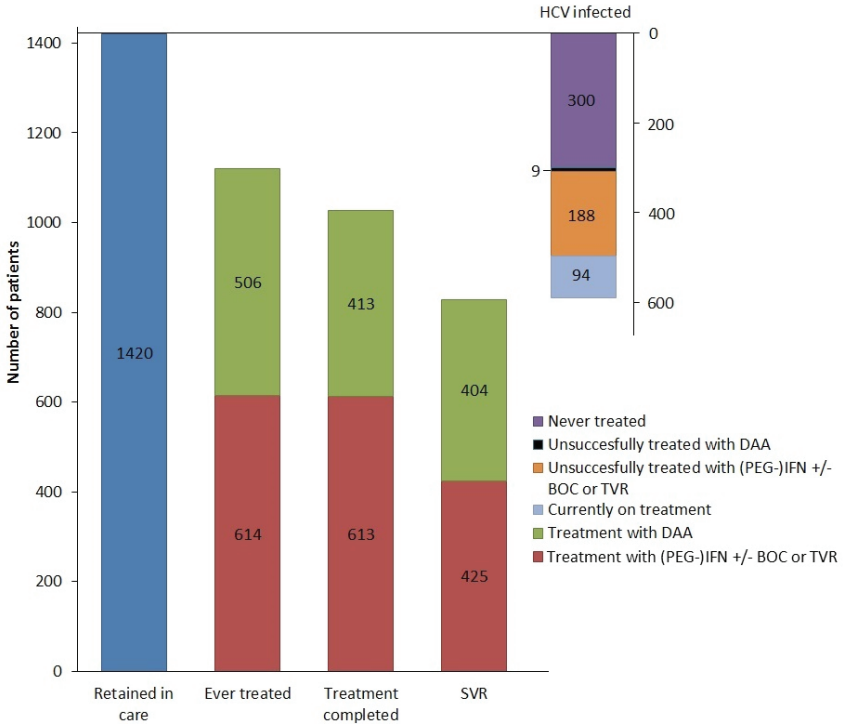
[1]Erasmus Univ Med Cntr, Rotterdam, Netherlands, [2]Pub Hlth Service of Amsterdam and Academic Med Cntr, Amsterdam, Netherlands, [3]Stichting HIV Monitoring, Amsterdam, Netherlands, [4]Stichting HIV Monitoring and Academic Med Cntr, Amsterdam, Netherlands, [5]Rijnstate Hosp, Arnhem, Netherlands, [6]Academic Med Cntr, Amsterdam, Netherlands, [7]Univ Med Cntr Utrecht, Utrecht, Netherlands, [8]OLVG, Amsterdam, Netherlands

Background: Direct acting antiviral (DAA) therapy is a short, safe and effective treatment for chronic hepatitis C virus (HCV). Its high costs led to restricted reimbursement in most countries. Since 11/2015, DAAs can be prescribed to all HIV-HCV co-infected patients in the Netherlands, regardless of the fibrosis stage. We evaluated the impact of unrestricted DAA availability on HCV treatment uptake in HIV-HCV co-infected patients.

Methods: The ATHENA cohort collects nationwide data through an opt-out system from 98% of all HIV infected patients in care since 1998, and can provide an overview of HCV treatment uptake and impact over time in this population. Data were collected up until the database lock of 05/2016, i.e. 6 months after unrestricted DAA availability. Patients were included if they ever had 1 positive HCV RNA test, were classified as having a chronic or acute HCV infection, did not spontaneously clear HCV and were still in care (at least 1 clinical visit after 06/01/2015). The presence of severe chronic liver disease (clinical, radiographic or endoscopic signs of severe liver disease, whether or not combined with a histology or FibroScan® result), treatment characteristics and sustained virological response (SVR) were analyzed. When patients were treated more than once, only the most recent treatment and its outcome was included in the analysis.

Results: Of the 22,042 HIV infected patients in the database, 1812 with HCV co-infection were included, of whom 1420 were still in care. Of the 392 patients not retained in care, 63 were lost to follow up, 269 had died and 60 had moved abroad. Of the 1420 still in care, 613 (43%) completed treatment with (PEG)-IFN +/- BOC/TVR, 413 (29%) completed treatment with DAAs, 94 (7%) had not yet completed DAA therapy and 300 (21%) remained untreated (figure). At the time of analysis, 65% (923/1420) of HCV-HIV co-infected patients had either been cured of HCV (n=829) or were completing DAA treatment (n=94). Notably, a high uptake was observed for patients without severe chronic liver disease: only 6 months after unlimited DAA availability, 33% (246/736) of those were cured with DAAs (n=192) or still on DAAs (n=54). The overall SVR after completing DAA treatment was 98% (404/413; 95%CI 96-99%).

Conclusion: Unlimited DAA availability resulted in a rapid treatment uptake among HIV-HCV co-infected patients without severe liver disease in only 6 months. Altogether, 65% of Dutch HIV-HCV co-infected patients are cured or expected to be cured in the near future.



137LB SUBSTANTIAL DECLINE IN ACUTE HCV INFECTIONS AMONG DUTCH HIV+MSM AFTER DAA ROLL OUT

Anne Boerekamps[1], Guido van den Berk[2], Fanny Lauw[3], Eliane Leyten[4], Joop Arends[5], Marjo Kasteren[6], Mark Claassen[7], Charles Boucher[1], **Bart Rijnders**[1], for the Dutch Acute HCV in HIV (DAHHS) Study Group

[1]Erasmus Univ Med Cntr, Rotterdam, Netherlands, [2]OLVG, Amsterdam, Netherlands, [3]Slotervaart MC, Amsterdam, Netherlands, [4]MC Haaglanden, The Hague, Netherlands, [5]Univ Medl Cntr Utrecht, Utrecht, Netherlands, [6]St. Elizabeth Ziekenhuis, Tilburg, Netherlands, [7]Rijnstate Hosp, Arnhem, Netherlands

Background: The incidence of acute HCV (AHCV) among Dutch HIV+MSM has been high for >10yrs. Recent modeling studies predict that prompt treatment with direct acting antivirals (DAA) may decrease this incidence substantially (CROI2016 A536) but confirmation from real-life data is awaited. In 11/2014 all oral DAA therapy became available for F3-4 fibrosis and from 09/2015 for F0-2 as well, resulting in rapid DAA uptake in Dutch HIV+MSM with chronic HCV with already 65% cured or on DAA therapy 6 months after unrestricted DAA availability (CROI 2017 Boerekamps et al). Also, in 2014 (in DAHHS1 study NCT01912495) as well as in 2016 (in ongoing DAHHS2 study NCT02600325) patients with AHCV were offered immediate therapy in DAHHS centers across the Netherlands. We hypothesized that this rapid treatment uptake will result in a lower incidence of AHCV among HIV+MSM.

Methods: AHCV was defined as HCV-RNA positivity, preceded by a negative HCV-RNA or HCV-IgG within 12 months. When stored plasma could not be retested, a normal ALT preceding the first positive HCV-RNA test together with a negative IgG any time in the past or a positive HCV-RNA and a simultaneous negative IgG was also considered diagnostic for AHCV. The incidence of AHCV was calculated by dividing the cases by the patient years of follow-up (PYFU). Data were available from 18 HIV treatment centers, geographically

spread across the Netherlands having +/-80% of Dutch HIV+MSM in care. We compared the incidence in 2014 (year preceding DAA availability) to 2016 incidence (first year after DAA availability).

Results: In 2014, 93 AHCV infections occurred in 8290 PYFU (=11.2/1000 PYFU, 95% CI 9.1-13.7). In 2016, 49 AHCV were diagnosed in 8961 PYFU (=5.5/1000 PYFU, 95% CI 4.1–7.2, p<0.001). The incidence in 2014 of 11.2/1000 showed a continuous decline to 6.9/1000 and 4.0/1000 within the first and second half of 2016. A relative increase in genotype 4 infections was observed from 19% (n=18) to 31% (n=15) (p=0.02). The absolute number of AHCV infections decreased both in patients with a first AHCV infection as well as in patients that had an AHCV reinfection (=patients previously cured of an AHCV infection), while the proportion of reinfections remained constant: 21/93 in 2014 and 12/49 in 2016 (p=0.8).

Conclusion: 1 year after unrestricted DAA availability in the Netherlands, the incidence of acute HCV in HIV+MSM decreased by 52%. For the first time, real-life data show that "HCV treatment as prevention" averts new HCV infections in HIV+MSM.

138 CORRELATION OF RENAL BIOMARKERS AND TENOFOVIR AUC IN THE ION-4 STUDY COHORT

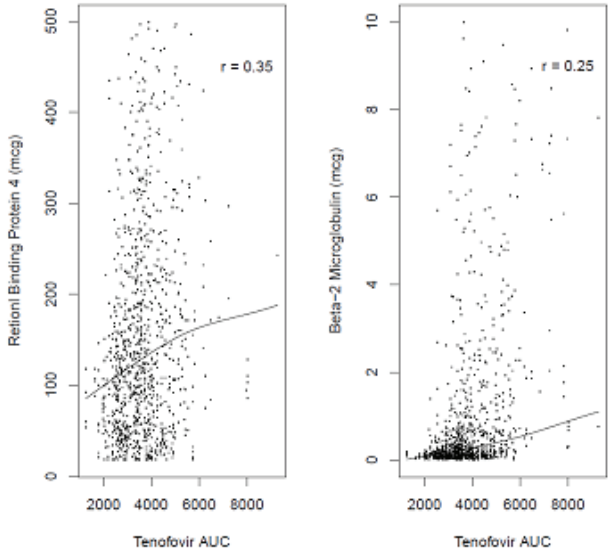
Austin W. Chan[1], Larry Park[1], Lauren F. Collins[1], Curtis Cooper[2], Michael Saag[3], Douglas Dieterich[4], Mark Sulkowski[5], Susanna Naggie[1], for the ION-4 Study Group
[1]Duke Univ, Durham, NC, USA, [2]Ottawa General Rsr Inst, Ottawa, Ontario, [3]Univ of Alabama at Birmingham, Birmingham, AL, USA, [4]Icahn Sch of Med at Mt Sinai, New York, NY, USA, [5]The Johns Hopkins Univ, Baltimore, MD, USA

Background: The ION-4 study assessed the safety and efficacy of ledipasvir/sofosubvir (LDV/SOF) for 12 weeks in patients with chronic HIV and HCV infections. Concomitant dosing of ledipasvir and tenofovir disoproxil fumarate (TDF) results in increased tenofovir (TFV) area under the curve (AUC). Retinol binding protein-4(RBP4) and β2-microglobulin(B2M) are currently the most reliable urinary biomarkers for detecting proximal tubule dysfunction. The aim of this study was to examine whether there was a correlation between urinary biomarkers RBP4 and B2M and renal toxicity and TFV AUC.

Methods: The ION-4 trial enrolled HIV/HCV patients on antiretroviral regimens with TDF containing nucleoside reverse transcriptase inhibitor (NRTI) backbones. Plasma TFV concentrations were collected on treatment at 12 and 24 hours and 4, 6, 8, 10, 12 weeks. Urine RBP4 and B2M, urine protein and serum creatinine were collected at multiple time points on and post-treatment. We assessed changes in urinary biomarkers throughout the study period and associations with clinically relevant changes in renal function [creatinine clearance decrease >25%, creatinine >0.2 mg/dL, incident proteinuria (negative/trace to ≥ 1+) and TFV AUC and other pharmacokinetic parameters.

Results: 335 patients enrolled in the ION-4 study with demographic characteristics that have been previously described. Overall 19 (5.67%) patients had creatinine clearance decrease >25%, 42 (12.5%) creatinine >0.2 mg/dL, and 114 (34.0%) had an increase in urine proteinuria from negative/trace to ≥ 1+. RBP4 increased from baseline to end of therapy in all subgroups of renal dysfunction. B2M did not demonstrate a similar change from baseline to end of therapy for any subgroup of renal dysfunction. Baseline levels of RBP4 and B2M were higher for patients with incident proteinuria (p<0.001), this was true for the other measures of renal dysfunction but was not statistically significant. Both RBP4 and B2M exhibited positive correlations with tenofovir AUC (Figure 1).

Conclusion: Drug interactions with antiretrovirals and direct acting antivirals are common in patients with HIV/HCV co-infection. Urinary biomarkers are elevated at baseline in patients who experience incident proteinuria during concomitant dosing of ledipasvir and TDF and correlate with serum TFV AUC. Urinary biomarkers, specifically RBP4, may identify patients at risk of tubular toxicity who have increased exposures to TFV.



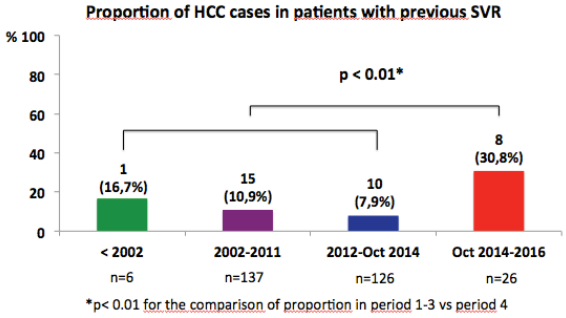
139 HEPATOCELLULAR CARCINOMA AFTER SVR WITH IFN-FREE REGIMENS IN HIV/HCV COINFECTION

Nicolás Merchante[1], Boris Revollo[2], Francisco Rodríguez-Arrondo[3], Esperanza Merino[4], Maria J. Galindo[5], Marta Montero[6], Antonio Rivero-Juárez[7], Marcial Delgado-Fernández[8], Maria J. Rios-Villegas[9], Juan A. Pineda[1]
[1]Hosp Univ de Valme, Sevilla, Spain, [2]Hosp German Trias i Pujol, Badalona, Spain, [3]Hosp Univ de Donostia, San Sebastián, Spain, [4]Hosp General Univ de Alicante, Alicante, Spain, [5]Hosp Clínico de Valencia, Valencia, Spain, [6]Hosp Univ y Politécnico La Fe, Valencia, Spain, [7]Hosp Univ Reina Sofía, Córdoba, Spain, [8]Hosp Regional Univ de Málaga, Málaga, Spain, [9]Hosp Univ Virgen Macarena, Sevilla, Spain

Background: The consecution of sustained virological response (SVR) is associated with a reduction in the risk of liver-related events, including hepatocellular carcinoma (HCC), and liver-related mortality in HIV/HCV-coinfected patients. However, HIV/HCV-coinfected patients who achieve SVR are still at risk of developing HCC. It is not known if the risk of developing HCC after SVR has been modified with the arrival of all-oral direct antiviral agents (DAA) interferon (IFN)-free regimens. Our objective was to assess the proportion of HCC cases diagnosed after SVR in HIV/HCV-coinfected patients and its evolution over time.

Methods: The GEHEP-002 multicentric cohort (ClinicalTrials.gov ID: NCT02785835) recruits HCC cases diagnosed in HIV-infected patients from 32 centers from Spain. The proportion of HCC cases after SVR and the evolution of this proportion over time were analyzed. For this purpose, we define 4 periods of time according to the changes of treatment strategies for hepatitis C in Spain: 1) Period 1 (≤ 2001): non-pegylated IFN; 2) Period 2 (2002-2011): pegylated IFN plus ribavirin; 3) Period 3 (2011-October 2014): DAA in combination with IFN and 4) Period 4 (October 2014-September 2016): DAA IFN-free regimens.

Results: 295 HCC cases diagnosed in HIV/HCV-coinfected patients have been included in the GEHEP-002 cohort. The median (Q1-Q3) age was 49 (46-52) years and 265 (90%) were male. HCV genotype distribution was: Gt 1, 114 (48%); Gt 2: 3 (1%); Gt 3, 85 (36%) and Gt 4, 35 (15%). Since 1999, when the first HCC case was recorded, 34 (11.5%) cases have occurred in patients with previous SVR. The proportion of HCC cases in patients with previous SVR was 16.7% (1 out of 6), 10.9% (15 out of 137) and 7.9% (10 out of 126) in period 1, 2 and 3, respectively (Figure 1). By contrast, this proportion increased to 30.8% (8 out of 26) in the DAA IFN-free period ($p<0.01$ for the comparison between period 1-3 vs 4) (Figure 1). Twenty-one patients with previously treated HCC received subsequent therapy with DAA IFN-free regimens. HCC recurred in 1 (4.7%) of them.
Conclusion: The proportion of HCC cases diagnosed in HIV/HCV-coinfected patients with previous SVR has significantly increased parallel to the arrival of DAA IFN-free strategies. This finding may be, at least partially, explained by the fact that DAA have allowed treating patients at advanced stages of liver disease in which the protective effect of SVR on the risk of HCC could be less marked.



140 IDENTIFICATION OF HCV INTER-SUBTYPE RECOMBINANT STRAINS WITH BREAKPOINTS IN NS5A

Suqin Cai, Alicia Newton, Wei Huang, Jeannette Whitcomb
Monogram BioScis, South San Francisco, CA, USA

Background: Hepatitis C virus (HCV) is classified into seven major genotypes (GT) and numerous subtypes. HCV GT and subtype are associated with differences in clinical outcomes, response to treatment and epidemiology. A better understanding of recombination in HCV is of practical importance and evolutionary interest.
Methods: Recombinant HCV strains were identified during routine drug resistance testing of clinical specimens. HCV RNA was isolated from plasma and NS5A amplicons were generated by RT-PCR and sequenced on a next-generation sequencing platform. Sequencing reads were analyzed using a proprietary analysis pipeline with a subtyping routine that aligns a subset of reads to a library of reference HCV strains. Samples with a large proportion of reads that aligned to two different references were evaluated as potential recombinant viruses. Consensus sequences were compared to subtype reference sequences (Bootscan, Simplot) to define recombination breakpoints. Phylogenetic analysis was performed (Clustal) to determine relatedness of independently collected HCV specimens.
Results: Ten 1a/1b recombinant viruses were identified from diverse geographic collection centers. All 10 had 5' NS5A 1a sequences and 3' NS5A 1b sequences. The recombination breakpoint for 7 of these viruses was consistently at amino acid (aa) 386 and for 2 of the viruses at aa 366 of NS5A relative to the H77 reference. All 9 of these 1a/1b recombinants had the same recombination locus in 1b at aa 348 relative to the Con1 reference. A single 1a/1b recombinant had a 1a breakpoint at aa 277 (H77) and a 1b breakpoint at aa 214 (Con1). The recombinant NS5As were longer than H77 and Con1 NS5A due to duplication of sequences at the site of recombination. Phylogenetic analysis demonstrated that the 9 1a/1b recombinant viruses with breakpoints at 366/386 in 1a and 348 in 1b were all closely related suggesting that this may represent a circulating recombinant form of HCV. We also identified one inter-genotype recombinant (1a/4), with a breakpoint in NS5A at aa 349 of H77 and at aa 339 of the GT4 ED43 reference.
Conclusion: HCV recombination is thought to be rare. However, the prevalence of recombinant forms may have been underestimated due to the use of genotyping methods, such as single-locus sequencing, that are unlikely to detect recombination. The independent identification of a similar recombinant strain from multiple samples and diverse geographic collection areas suggests that the strain exists as a circulating recombinant form.

141 SYNERGY BETWEEN COMBINATIONS OF ANTI-HCV BROADLY NEUTRALIZING MONOCLONAL ANTIBODIES

Madeleine C. Mankowski[1], Andrew I. Flyak[2], Stuart C. Ray[3], James E. Crowe[2], Justin R. Bailey[3]
[1]Johns Hopkins Univ, Severna Park, MD, USA, [2]Vanderbilt Univ, Nashville, TN, USA, [3]Johns Hopkins Univ, Baltimore, MD, USA

Background: No single broadly-neutralizing monoclonal antibody (bNAb) effectively neutralizes all strains of hepatitis C virus (HCV). Therefore, induction of antibody responses that target multiple distinct epitopes may be needed for an effective vaccine. This vaccination strategy would be most effective if bNAbs interact synergistically, and less effective if bNAbs interact antagonistically. We hypothesized that bNAbs binding to distinct epitopes would have increased neutralizing breadth and synergistic potency when used in combination. We tested 35 bNAb combinations to define effects on neutralizing breadth and potency.
Methods: Twelve bNAbs binding to distinct epitopes on HCV E2 were screened individually and in 35 2-bNAb combinations for neutralization of a panel of 11 genetically diverse HCV pseudoparticles (HCVpp). Neutralization of HCVpp by these combinations was compared to expected neutralization predicted by the Loewe additivity model, defining the interactions of the component bNAbs as either synergistic, additive, or antagonistic.
Results: BNAb combinations showed significantly greater neutralizing breadth than individual bNAbs at the same total antibody concentration, neutralizing a median of 63% of HCVpp, while individual bNAbs neutralized a median of 55% ($p<0.05$, unpaired T-test). None of the 35 bNAb combinations tested showed evidence of antagonism. Most showed additive potency, and one combination, HepC74 + HepC98, showed synergy (neutralization in excess of additive effects) at 8 of 9 antibody concentrations tested ($p<0.05$, paired T-test). Neutralization of HCV by this combination was 3-fold greater than neutralization by either bNAb individually at the same total antibody concentration.
Conclusion: By screening 35 bNAb combinations, we identified a combination that displays both increased neutralizing breadth and synergistic potency, many bNAb combinations with additive neutralization, and no combinations displaying antagonism. These results demonstrate that induction of multiple bNAbs targeting distinct epitopes could be an effective vaccine strategy for HCV. Specific induction of HepC74- and HepC98-type antibodies could be particularly effective.

142 NEUTRALIZING ANTIBODY DEVELOPMENT DURING HIV-1 INFECTION

Penelope Moore, *Univ of the Witwatersrand, Johannesburg, South Africa*

A preventative HIV vaccine is likely to require broadly neutralizing antibodies (bNAbs) able to recognize diverse circulating viruses from across the world. Such antibodies have not yet been elicited by vaccination. However some HIV-1-infected individuals naturally mount bNAb responses during chronic infection, suggesting a need for prolonged maturation towards breadth. Longitudinal studies of how bNAbs develop may provide a template for immunogen design, by defining the interplay between antibodies and HIV envelope evolution. Understanding how certain members of an antibody lineage mature towards breadth, whereas others become evolutionary dead-ends, provides insights for vaccine strategies. Similarly, studies of donors who fail to develop bNAbs despite equivalent levels of antigenic stimulation will highlight potential roadblocks. Overall, this presentation will highlight the dynamic relationship between virus and antibody in shaping breadth, with implications for HIV immunogen design.

143 IMMUNOGEN DESIGN TO INDUCE HIV NEUTRALIZING ANTIBODIES

William R. Schief, *Scripps Rsr Inst, La Jolla, CA, USA*

Abstract is available in the CROI mobile App.

144 STRUCTURAL STUDIES OF HIV NEUTRALIZING ANTIBODIES

Andrew B. Ward, *Scripps Rsr Inst, La Jolla, CA, USA*

The HIV envelope glycoprotein (Env) trimer on the surface of the virus is the sole target of broadly neutralizing antibodies. Soluble, native-like Env trimers, particularly those of the SOSIP design, have recently been developed and enabled high-resolution structural studies as well as opportunities for protein subunit vaccination with bona fide trimers. A number of labs have ongoing or completed animal immunization studies using these trimers, and there is a planned human clinical trial. The SOSIP trimers typically induce strong autologous neutralizing antibody responses and monoclonal antibodies have been isolated. Here we will describe the structures of these monoclonal neutralizing antibodies in complex with SOSIP Env trimers in an effort to describe the spectrum of responses elicited by the large antigenic surface on the Env trimer. While some responses mirror those found in natural infection, some responses appear unique to the soluble Env trimer. This catalogue of responses serves as a basis for further immunogen design and as a comparator for the upcoming human clinical trial.

145 CLINICAL STUDIES WITH BROADLY NEUTRALIZING ANTIBODIES

Michel Nussenzweig, *Rockefeller Univ, New York, NY, USA*

Clinical Studies with Broadly Neutralizing Antibodies Michel C. Nussenzweig AIDS is a preventable disease. Nevertheless, according to UNAIDS, 2.1 million of individuals were infected with HIV-1 in 2015 worldwide. An effective vaccine is highly desirable. Most vaccines in clinical use today prevent infection because they elicit antibodies that block pathogen entry. Consistent with this general rule, studies in experimental animals have shown that broadly neutralizing antibodies to HIV-1 can prevent infection, suggesting that a vaccine that elicits such antibodies would be protective. However, despite significant efforts over the last 30 years, attempts to elicit broadly HIV-1 neutralizing antibodies by vaccination failed until recent experiments in genetically engineered mice were finally successful. Nevertheless, a small fraction of HIV-1-infected individuals develop antibodies that effectively neutralize the majority of existing HIV-1 isolates. Single cell antibody cloning methods revealed that this serum neutralizing activity is due to one or a combination of monoclonal antibodies that target different non-overlapping epitopes on the HIV-1 envelope spike. When passively transferred, many of these newly discovered antibodies protect against infection in humanized mice and macaques, even when present at very low concentrations. In addition, combinations of antibodies targeting non-overlapping epitopes can control active infection in humanized mice and macaques. Finally, when they are administered together with agents that induce viral transcription to activate latently infected cells, antibodies decrease the incidence of viral rebound from the latent reservoir in HIV-1-infected humanized mice. These preclinical findings have been extended to humans in phase 1 clinical trials of 2 antibodies that target non-overlapping epitopes 3BNC117 and 10-1074. The results of those trials will be discussed.

146 HIV-1 DRUG RESISTANCE IN RESOURCE-LIMITED SETTINGS

Ravindra K. Gupta, *Univ College London, London, UK*

Introduction: The global scale up of cART has now reached 17 million treated individuals, largely in LMICs. Antiretroviral therapy (ART) is pivotal for controlling HIV-1 infection through widescale treatment as prevention (TasP) and pre-exposure prophylaxis (PreP). Pre treatment drug resistance to NNRTI is associated with a 2-3 fold higher viral failure rate in both high and low income settings, and the clinical consequences can be severe where viral load monitoring is not available. Highly potent tenofovir containing regimens are increasingly being used to treat and prevent HIV. Data from clinical trials and cohorts in high-income settings using tenofovir combined with NNRTI have reported low prevalence of tenofovir resistance at viral failure, in stark contrast to LMICs where prevalence of K65R and NNRTI resistance is much higher following viral failure of first line, thought to be due to sub-optimal monitoring. Furthermore, viruses with K65R are fit in vivo, in contrast to observations in model systems. There is also emerging evidence from LMIC that drug resistance is higher in individuals who have been pre-treated, often with thymidine analogue based regimens. The result of this emergence of HIV DR is transmission to untreated individuals that has been increasing globally since ART scale up. Conclusions: Drug resistance emerges in a high proportion of patients following virological failure across LMIC regions and has led to rising transmitted drug resistance worldwide. Effective surveillance for transmission of drug resistance is critical. Effective point-of-care viral load monitoring and point-of-care resistance tests could mitigate emergence and spread of MDR strains that threaten control efforts.

147 LONG-ACTING ANTIRETROVIRAL THERAPY: A SHOT IN THE DARK OR A PARADIGM SHIFT?

Charles W. Flexner, *The Johns Hopkins Univ, Baltimore, MD, USA*

Long-acting and extended-release (LA/ER) formulations of antiretroviral drugs have the potential to revolutionize treatment and prevention. Formulations in current development run the gamut from oral products capable of delivering effective systemic anti-HIV drug concentrations for 7-14 days after a single dose, to implants capable of providing effective treatment for as long as 6, and possibly 12 or more months. These approaches are ideal for patients having difficulty with adherence, suffering from pill fatigue, or living in areas where the stigma of taking daily HIV pills is a concern. Other important applications include use in patients who cannot or will not take daily oral medication, including infants, children, and adolescents. Recent survey research suggests widespread popularity of switching to parenteral LA/ER treatment amongst those already taking daily oral combination ART. Two injectable LA formulations -- of rilpivirine and cabotegravir -- are in Phase 3 clinical testing, and several others have entered clinical development. Other candidates for LA/ER delivery include biologics and broadly neutralizing monoclonal antibodies. New approaches to developing a broader array of possible LA/ER products include prodrug approaches to modify existing ARV's in order to make them more amenable to nanoformulation. Physiologically-based pharmacokinetic (PBPK) modeling can be used to prioritize candidate formulations for further preclinical and clinical development, based on a better understanding of the fundamental principles governing drug release from an intramuscular depot or subcutaneous implant. Class-wide problems associated with LA/ER approaches include concerns about drug resistance, missed doses, coverage of the long tail of drug concentrations when treatment is stopped or switched, and what to do about drug interactions, pregnancy, and irreversible or long-lived side effects. Although the many drawbacks of LA/ER formulations will need to be addressed during clinical development, there is little doubt that these approaches to drug delivery are going to have a meaningful impact on the treatment and prevention of HIV and other infectious diseases.

148 SIMPLE ART: MORE COMPLEX THAN THOUGHT

Jose R. Arribas, *Hosp La Paz, Madrid, Spain*

Do we need to use the same type of ART regimens in an HIV-infected patient with a viral load of 550,000 HIV RNA copies/mL and a CD4 cell count of 75 cells/µL than in a patient who has been virologically suppressed for 7 years and has a current CD4 cell count of 750 cells/µL? Can we "simplify" the ART regimen in virologically suppressed patients? These questions have been a matter of research and controversy during the last two decades. Since at the present moment HIV infection needs to be treated for the entire life of the patient there is a strong motivation to use ART regimens that are as simple, efficacious and safe as possible. Numerous clinical trials have evaluated ART simplification in virologically suppressed patients. In many occasions, the new "simple" regimens have been very different from the regimens used in antiretroviral naïve patients with active viral replication. There have been multiple attempts to use regimens with less than three antiretroviral drugs: monotherapy with boosted protease inhibitors, dual therapy completely sparing nucleoside reverse transcriptase inhibitors (NRTIs), dual therapy sparing just one NRTI and dual therapy sparing both NRTIs and boosted protease inhibitors. In many occasions, results of these trials have produced unexpectedly disappointing results. For example, it is still unclear why potent ART regimens combining a boosted protease inhibitor and an integrase inhibitor have underperformed compared to triple therapy regimens that include two NRTIs. Even if the new simple regimen includes three antiretroviral drugs

there have been unexpected failures in clinical trials when the issues of archived mutations or duration of virologically suppression have not been taken into account. Based on the results of all these clinical trials we have learnt that the success ART simplification is determined by critical pharmacological, biological and behavioural factors such as potency and the genetic barrier of the new regimen, the presence of archived mutations, duration of virological suppression and patient's pattern of adherence. With the advent of long-acting antiretrovirals and broadly neutralising antibodies, the interest in ART simplification has been renewed because we now have the types of drugs that would theoretically permit for the first time in HIV therapeutics the use of regimens that do not involve daily dosing of antiretrovirals.

149 TOWARD AN IDEAL ANTIRETROVIRAL REGIMEN FOR THE GLOBAL EPIDEMIC

Beatriz Grinsztejn, *Oswaldo Cruz Foundation - Fiocruz, Rio de Janeiro, Brazil*

Currently immediate initiation of antiretroviral therapy (ART) is recommended for all individuals with HIV infection. However, among the 37 million people estimated to live with HIV/AIDS, only 17 million are actively on treatment. Proper utilization of ART among HIV-infected and at risk individuals reduces morbidity, mortality, transmission and acquisition of HIV infection. With its ability to reduce viral reservoirs and preserve immune function, early use of ART is a key component in the care continuum. ART regimen choices are affected by factors such as economic differences between high resource and low- and middle-income countries (LIMC), drug availability, and considerations for use in special populations. Instead of "When to Start?", we are left refining our answer to the question of "What to Start?". Ideal ART regimens combine high efficacy, high tolerability, low toxicity, low pill burden, affordability and global availability. The ability to meet these criteria can be challenging in LMIC and in special populations such as pregnant women, infants, children, adolescents and those with tuberculosis or hepatitis co-infections. Transmitted drug resistance patterns among newly-infected individuals must be continuously monitored. With the scale up efforts to achieve 90-90-90 by 2020, similar considerations are needed for those transitioning to second- and third-line treatment regimens. The development of drugs for the treatment of cross-class resistance must remain a priority. Advances in drug formulations and novel compounds, such as two-drug regimens, long-acting compounds, and implantable devices for sustained drug release will further improve the clinical management of HIV prevention and treatment.

150 OVERVIEW OF THE GLOBAL BURDEN OF NONCOMMUNICABLE DISEASES IN HIV INFECTION

Pragna Patel, *CDC, Atlanta, GA, USA*

Low- and middle-income countries (LIMCs) are undergoing an 'epidemiological transition', in which the burden of non-communicable diseases (NCDs) is rising and mortality will shift from infectious diseases to NCDs. Specifically, cardiovascular disease, diabetes, renal diseases, chronic respiratory diseases, and cancer are becoming more prevalent. In some regions, particularly sub-Saharan Africa, the dual HIV and NCD epidemics will pose challenges as joint burden will have adverse effects on quality of life and will likely increase global inequities. Given the austere clinical infrastructure in many LMICs, innovative models of care delivery are needed to provide comprehensive care in resource-limited settings. This talk will review the currently available evidence and data regarding burden of HIV and NCDs and discuss risk factors and clinical issues particularly relevant to HIV-infected persons. The presentation will also highlight examples of current efforts to integrate HIV and NCD care in LMICs, and discuss priorities for future research.

151 CARDIOVASCULAR DISEASE AMONGST PEOPLE LIVING WITH HIV IN AFRICA

Aga Khan, *Univ, Nairobi, Kenya*

Cardiovascular disease (CVD), and particularly atherosclerotic and thrombotic disease, is an emerging concern amongst people living with HIV (PLWHIV) in Africa. Although AIDS defining illnesses still account for majority of admissions to hospital and in critical care areas, the proportion of Non-Communicable diseases (NCDs) is significantly rising. Similarly, in the outpatient setting, cardiovascular (CV) risk factors and evidence of early atherosclerotic diseases have been found to be significant. Since the advent of efficient antiretroviral therapies and the consequent longer patient life span, an increased risk for atherosclerotic and thrombotic diseases has been observed in PLWHIV compared with the general population. The pathophysiology of accelerated atherosclerotic process and in-situ thrombosis are complex and multifactorial. Traditional CV risk factors, often not adequately addressed in HIV treatment and care programmes, uncontrolled viral replication in the untreated and exposure to antiretroviral drugs could all promote athero-thrombotic disease. Thus, despite successful antiviral therapy, numerous studies suggest a role of chronic inflammation, together with immune activation, that could lead to vascular dysfunction and athero-thrombosis. CV risk screening and care is not routinely performed in HIV programmes in Africa. Available CV risk scores also do not include young patients (<40yrs). Moreover, the novel vascular risk factors identified in HIV-related atherosclerosis, such as chronic inflammation, immune activation, and some antiretroviral agents, are not taken into account in the available risk scores. Additionally, CVD in HIV affects both arterial and venous circulation significantly. Cardiovascular prevention in HIV-infected patients presents a new challenge and require new approaches to assess and manage CV risk in HIV and also health system changes to integrate prevention and care for communicable diseases and NCDs.

152 CAN WE LEVERAGE HIV PLATFORMS FOR PREVENTION OF CERVICAL CANCER IN LMICs IN SUB-SAHARAN AFRICA?

Doreen Ramogola-Masire, *Univ of Botswana-Univ of Pennsylvania Collaboration, Gaborone, Botswana*

The vertical platform for care delivery set up as part of the emergency response to human immunodeficiency virus (HIV) has been responsible for saving many lives in low middle income countries (LMICs). The unintended consequence of this has been the deterioration of health expenditure for general health infrastructure, especially for other disease entities such as non-communicable diseases (NCDs) including cervical cancer. As a result of the effective treatment for HIV, women live longer and therefore face an increased risk of developing cervical cancer later on in their lives. Cervical cancer is preventable in high income countries where sophisticated, well-functioning systems are in place. Although most of the LMICs in sub-Saharan Africa (sSA) have no access to these systems, most of them have benefited from the global funding for HIV care and treatment. Given new innovative cervical cancer prevention options available, this paper explores ways that LMICs countries in sub-Saharan Africa can leverage their single disease platforms set up for HIV care and treatment for prevention of cervical cancer.

153 MINIMIZING MORBIDITY: INTEGRATING CARE FOR DEPRESSION AND HIV IN LOW-RESOURCE SETTINGS

Pamela Collins, *NIMH, Bethesda, MD, USA*

Mental and substance use disorders are highly prevalent and rank among the leading causes of disability worldwide, accounting for nearly 20% of the global burden of disability in 2015. Among these, depressive disorders contribute the greatest burden and are the most prevalent, with an estimated 311 million cases globally in 2015. These are disabling disorders of youth, responsible for a greater percentage of disease burden among 15-49 year olds, thus affecting educational, employment, and relationship functioning. Notably, mental disorders frequently co-occur with HIV, both as risk factors and sequelae of HIV infection. Major depression occurs nearly twice as often among people with HIV infection and is associated with poor adherence to care, lower likelihood of virologic suppression, greater morbidity and mortality. Depression is associated with greater mortality in the initial years after antiretroviral initiation. Whereas access to outpatient mental health services for people with HIV care occurs frequently in wealthy countries, several barriers have impeded mental health care access in low-and middle-income countries (LMICs) with high HIV prevalence. The dearth of mental health human resources and limited investment in mental health in LMICs reduce access to care. As a result, most health professionals do not identify or treat disorders like depression in community care settings. The social stigma associated with psychiatric institutional care creates an additional barrier to seeking mental health care. The treatment landscape for HIV and depression has changed in recent years. Investments in HIV care and treatment have led to a chronic care infrastructure in some LMICs that can be leveraged to manage other potentially chronic, remitting conditions like depression. A growing evidence base for the use of task-shifting to deliver mental health services in LMICs is expanding options for non-specialists to treat depression. Recent trials demonstrate that lay health workers, nurses, and peers can be trained to effectively deliver evidence-based depression care in HIV and non-HIV treatment contexts. In addition, several validation studies show that commonly used assessments for depression can be meaningfully applied in varied contexts among HIV-positive patients. These developments, along with new goals for epidemic control, make the integration of HIV and depression care in LMICs necessary and feasible.

POSTER ABSTRACTS

154 PHENOTYPING AND SORTING OF INDIVIDUAL FREE INFECTIOUS HIV PARTICLES BY FLOW CYTOMETRY

Michał Bonar, John Tilton
Case Western Reserve Univ, Cleveland, OH, USA

Background: Flow cytometry has revolutionized our understanding of cell biology and immunology by revealing previously unappreciated phenotypic and functional heterogeneity of cell subsets. In contrast, our understanding of viral heterogeneity – and the role it may play in transmission, immune responses, and vaccination – is not nearly as well defined. Recent advancements in flow cytometry allow for nanoparticle analysis using a strong fluorescent signal. Here, we utilized fluorescently labeled viral particles to develop techniques to measure viral heterogeneity and perform functional analysis of viral populations purified by FACS.
Methods: We compared a standard flow cytometer and a cytometer designed for sub-micron particles for their ability to detect unlabeled or fluorescently labeled viral particles. In addition to labeling structural proteins, we adapted an MS2 RNA loop system to assess viral genome incorporation. Viral particles containing different fluorescent structural and RNA markers were sorted by FACS and analyzed for their ability to infect CD4+ T cells. Specificity of detection and purity of sorts were confirmed by confocal microscopy and standard bulk biochemical techniques.
Results: Fluorescently labeled – but not unlabeled – single viral particles could be identified and distinguished from exosomes on both cytometers. Viral genome incorporation was successfully monitored by colocalization of the fluorescently labeled structural and MS2-tagged proteins with agreement between flow cytometry and microscopy techniques. Viral particles could be sorted by genome incorporation and retained the ability to infect target cells.
Conclusion: Starting with fluorescently labeled viruses, we have developed a 'toolkit' to explore the composition and infectivity of individual live viral particles with unprecedented detail. We are currently extending this technique to unlabeled HIV using fluorescently labeled neutralizing and non-neutralizing antibodies against Env proteins. We anticipate that viral heterogeneity will reveal critical insights into viral transmission and vaccine design.

155 SINGLE VIRUS IMAGING OF HIV-1 WITH FLUORESCENTLY LABELED CA

Zeger Debyser, Irena Zurnic, Lieve Dirix, Veerle Lemmens, Veerle Lemmens, Susana Rocha, Johan Hofkens, Jelle Hendrix, **Frauke Christ**
Katholieke Univ Leuven, Leuven, Belgium

Background: HIV-1 capsid uncoating is a crucial step in HIV-1 replication. It is tightly regulated in a spatiotemporal fashion. Both accelerated and delayed uncoating hinder productive infection, and require a complex interplay between reverse transcription, uncoating and nuclear import. Although different available in vitro and in vivo uncoating assays already revealed valuable information, a consensus uncoating model is lacking. To date, uncoating is studied mostly indirectly in a heterogeneous pool of viruses during asynchronous infection, lacking the ability to discern the transient stages of uncoating. Therefore, conflicting results on the dynamics of this process have been obtained. Recently, single virus studies with imunolabelled CA suggested the presence of CA in the nucleus. Resolving the dynamics of capsid uncoating during infection awaits the development of a method to image functional virus containing labeled CA.
Methods: We fluorescently labeled CA within the molecular clone at different selected positions, and evaluated the production efficiency and single round infectivity of these labeled viruses. We generated dual labeled VSV-G pseudotyped particles containing CA-eGFP and Vpr-transincorporated IN-mCherry. Using confocal microscopy, we evaluated the potential to study HIV-1 uncoating at a single virus level. Hereto we investigated the cellular distribution of CA and IN at a single virus level in fixed HeLaP4 cells. Validation of the model was provided through the use of inhibitors blocking HIV replication at discrete steps.
Results: A specific (1:10) mixture of labeled and unlabeled CA was required to produce viral particles containing both labeled CA and IN yet maintaining infectivity in single round experiments. After entry, colocalisation of CA and IN was observed. When reaching the nuclear membrane, CA containing complexes accumulated in the perinuclear area and were depleted for IN. Using both eGFP-labeled CA and immunocytochemistry, we confirmed the presence of CA in the nucleus, although the role and nature of this nuclear CA remains unclear. Still, complexes with a high CA-eGFP content were mainly found in the cytoplasm and not in the nucleus. Most CA complexes in the nucleus did not contain IN.
Conclusion: Directly labeled CA allows single virus imaging of uncoating and provides novel insights in the cellular distribution of CA. In agreement with others we detect CA in the nucleus, but not associated with IN. Ongoing research will prove the significance of nuclear CA.

156 CHARACTERIZING CELLULAR FACTORS INVOLVED IN HIV-1 GAG TRAFFICKING TO ASSEMBLY SITES

Rachel Van Duyne, Philip R. Tedbury, Eric O. Freed
NCI, Frederick, MD, USA

Background: In the late stages of the viral replication cycle, the Gag precursor, Pr55Gag, is synthesized in the cytoplasm, cotranslationally myristylated, and recruited to the plasma membrane (PM) through binding to the phospholipid PI(4,5)P2. Though the mechanisms of virus release are well studied, the trajectory by which Gag traffics remains one of the least understood aspects of HIV-1 replication. We hypothesize that HIV-1 Gag requires a network of cooperative endosomal and secretory pathway cofactors to localize to sites of virus assembly. We previously determined that overexpression of the Golgi-localized γ-ear containing Arf-binding (GGA) proteins reduces HIV-1 particle production by impairing Gag trafficking to the membrane through disruption of Arf (ADP-ribosylation factor) protein activity. We therefore aim to characterize the role of the Arf family of vesicular trafficking proteins in the context of HIV-1 assembly and release.
Methods: We screened dominant negative (DN) mutants of the Arf family members to determine the effect that functional disruption of these proteins has HIV-1 release.
Results: Expression of Arf1DN potently inhibits not only HIV-1 release efficiency, but also processing of the viral envelope (Env) precursor gp160, and subsequently, particle infectivity. Interestingly, Arf3DN does not confer the same phenotype, despite greater than 96% sequence identity with Arf1. We demonstrate that Arf1DN inhibits virus release independent of matrix (MA), Env, and Nef as well as of mutants defective in budding, maturation, and membrane targeting. This virus release defect is not due to the mis-targeting of Gag to intracellular sites of assembly or the loss of Gag membrane binding, but rather due to the accumulation of Gag at intracellular membranes away from the PM. The retention of Gag membrane binding function, but the loss of assembly may be due to a defect in Gag oligomerization. Treatment of cells with Arf inhibitors also results in a defect in Env processing and virus release.
Conclusion: This study suggests that disruption of Arf1 function severely affects the early steps of HIV-1 Gag trafficking. The accumulation of Gag at internal membranes upon disruption of Arf1 suggests Gag may interact with other endosomal/secretory membranes and vesicles prior to association with the PM. The characterization of Arf1DN-mediated re-localization of Gag to specific membranes will assist in the elucidation of the steps in the HIV-1 Gag trafficking pathway.

157 HIV-1 RESISTANCE TO KF116 REVEALS INTEGRASE'S ROLE DURING POLYPROTEIN PROCESSING

Ashley C. Hoyte[1], Augusta V. Jamin[2], Pratibha Chowdary Koneru[1], Stephanie Rebensburg[1], Jason Anderson[1], Matthew Kobe[1], Emma N. Ivanauskas[1], James R. Fuchs[3], Alan N. Engelman[2], Mamuka Kvaratskhelia[1]
[1]The Ohio State Univ, Columbus, OH, USA, [2]Dana-Farber Cancer Inst, Boston, MA, USA, [3]The Ohio State Univ, Columbus, OH, USA

Background: The pyridine-based multimerization selective HIV-1 integrase (IN) inhibitors (MINIs) are a distinct sub-class of allosteric IN inhibitors. MINIs potently inhibit HIV-1 replication during virion maturation by inducing aberrant IN multimerization, while being ineffective during the early steps of viral replication. Here, we investigated the mechanism for evolution of a triple IN substitution (T124N/V165I/T174I) that emerges in cell culture, with a representative MINI KF116.
Methods: The mutant viruses were generated by introducing the substitutions in the IN coding sequence of HIV-1NL4-3 molecular clone using site-directed mutagenesis. Viral particles were prepared in HEK293T cells and transmission electron microscopy was utilized to visualize viral particle morphologies. In addition, viral protein processing was monitored using immunoblotting. The structure of the mutant catalytic core domain (CCD) dimer containing T124N/V165I/T174I IN substitutions was determined by X-ray crystallography. Surface plasmon resonance experiments were performed to determine K_d values for KF116 binding to wild type and mutant CCDs.
Results: We show that HIV-1NL4-3 IN(T124N/V165I/T174I) confers marked (>2000-fold) resistance to KF116. Two IN substitutions (T124N/T174I) directly weaken inhibitor binding at the dimer interface of the CCD, yet at the same time, markedly impair HIV-1 replication capacity. Unexpectedly, T124N/T174I IN substitutions inhibited proteolytic processing of HIV-1 polyproteins Gag and Gag-Pol and resulted in immature virions.
Conclusion: Strikingly, the addition of the third IN substitution (V165I) restored polyprotein processing and significant levels of replication capacity. These results reveal an unanticipated role of IN for polyprotein proteolytic processing during virion morphogenesis. The complex evolutionary pathway for the emergence of resistant viruses, which includes the need for the compensatory V165I IN substitution, highlights a relatively high genetic barrier exerted by MINI KF116. Additionally, structural studies with CCD (T124N/V165I/T174I) dimer compared to its wild type counterpart suggest a path for rationally developing second generation MINIs.

158 ROLE OF MA TRIMERIZATION IN HIV-1 ENVELOPE GLYCOPROTEIN INCORPORATION

Mariia Novikova, Philip R. Tedbury, Eric O. Freed
NCI, Frederick, MD, USA

Background: The HIV-1 envelope (Env) glycoprotein complex traffics to the plasma membrane as a heterotrimer containing three molecules each of the surface glycoprotein gp120 and the transmembrane glycoprotein gp41. The gp41 subunit contains a long cytoplasmic tail that interacts with, or is accommodated by, the matrix (MA) domain of Gag during viral assembly. It has been proposed that hexamers of MA trimers form in membrane-bound Gag, overlaying the hexameric capsid lattice. Mutations at the tips of the putative MA trimers (which face the central aperture of the hexamer) prevent the incorporation of Env into particles. The goal of this study was to elucidate the role of MA trimerization in HIV-1 Env glycoprotein incorporation.
Methods: We recently developed a glutaraldehyde cross-linking assay, using a virus with two lysine residues located near the MA trimer interface to analyze MA trimer formation in both immature and mature viral particles. This virus-based MA trimerization assay has enabled us to probe the role of MA trimer formation in Env incorporation.
Results: MA residue L74 is critical for MA trimerization and Env incorporation. This residue is located in the hydrophobic region of the MA trimer interface. Two mutant viruses, L74E and L74G, do not incorporate Env and do not replicate in T cells. MA trimers were also not detected in these viruses. We have selected compensatory mutations that rescue the Env incorporation defect imposed by these mutations. Interestingly, two identified mutations, F43I and F43L, are located in the hydrophobic core of the trimer interface close to L74. We showed that both mutations F43I and F43L, in combination with another mutation, V34I, completely rescued Env incorporation and restored virus replication and infectivity. We are currently using a variety of approaches to monitor the formation of MA trimers in the replication-competent V34I/F43I/L74E and V34I/F43I/L74G mutants.
Conclusion: We demonstrated that alterations in the structure of the MA trimer interface affect Env incorporation in assembled virions. Our findings suggest that MA trimer formation is a necessary step for Env incorporation during production of viral particles. These data may ultimately be useful for development of novel therapeutics targeting the MA trimer interface and Env incorporation.

159 PRODUCTION OF HIV-1 PROTEINS FROM "DEFECTIVE" HIV-1 PROVIRUS

Hiromi Imamichi[1], Joseph Adelsberger[2], H. Clifford Lane[1]
[1]NIAID, Bethesda, MD, USA, [2]Leidos Biomed Rsr, Inc, Frederick, MD, USA

Background: The presence of "defective" proviruses in HIV-infected patients has been well documented. As these defective proviruses are unable to encode intact viruses, they have been thought of as a silent graveyard of viral sequences. Contrary to this notion, we have recently reported that these "defective" proviruses transcribe novel protein-coding RNA species in HIV-infected patients on combination antiretroviral therapy including those with HIV-1 RNA levels <50 copies/ml. In the present study, we demonstrate the emergence of these defective proviruses during in vitro infection and their association with HIV-1 protein production in the absence of intact virions.
Methods: Single-cell clones were isolated from an H9 T-lymphoid cell line chronically infected with the MN strain of HIV-1. The H9 culture was first separated based on different cell surface characteristics of CD3 and HIV-1 Env gp120 expression by fluorescence-activated cell sorting. Positive wells by HIV-DNA PCR were further cloned by serial dilution at a cell density of 1 cell per well in 96-well plates. The identification of single-cell clones harboring "defective" proviral DNA was confirmed by combining 5'LTR-to-3'LTR single-genome amplification and direct amplicon sequencing of the genomic DNA. RNA transcription in the clones of interest was assessed by RT-PCR of near full-length unspliced HIV-1 RNA species. Cellular expression of HIV-1 proteins was analyzed by western blot and flow cytometry.
Results: Twelve HIV-1 positive individual clones were isolated. Four harbored intact proviruses and expressed Gag p55/p24, RT p66/p51, integrase and Env gp160/gp120 proteins. The remaining eight clones had lethal +1 frameshift mutations in the reverse transcriptase (RT) gene (nucleotide position 3204 of the HXB2), resulting in premature termination of RT translation at Asp 218. Consistent with the DNA and RNA data, western blots revealed the presence of Gag p55/p24 and Env gp160/gp120 proteins and a complete absence of RT p66/p51 and integrase proteins in these eight clones.
Conclusion: In the present study, we demonstrated asynchronous HIV-1 protein production from cells harboring "defective" proviruses that closely resembled the "defective" proviral species found in vivo in patients with HIV-1 infection. The proteins encoded by these "zombie" proviruses may serve as a cause of persistent immune activation during suppressive HIV treatment and may represent a significant hurdle to an HIV-1 cure.

160LB NUCLEAR PORE HETEROGENEITY AFFECTS HIV-1 INFECTION AND THE ANTIVIRAL ACTIVITY OF MX2

Melissa Kane[1], Stephanie Rebensburg[2], Matthew Takata[1], Trinity Zang[1], Masahiro Yamashita[3], Mamuka Kvaratskhelia[2], Paul Bieniasz[4]
[1]The Rockefeller Univ, New York, NY, USA,[2]The Ohio State Univ, Columbus, OH, USA, [3]Aaron Diamond AIDS Rsr Cntr, New York, NY, USA, [4]Howard Hughes Med Cntr, New York, NY, USA

Background: Mx2 (myxovirus resistance 2) is an interferon-induced inhibitor of the preintegration phases of HIV-1 infection that is localized to the nuclear pore. The HIV-1 capsid (CA) is the major viral determinant for sensitivity to Mx2 and mutations in the HIV-1 capsid protein that are known or suspected to alter the nuclear import pathways used by HIV-1 alter susceptibility to Mx2.
Methods: We explored the complex interactions between Mx2, the viral CA, and the nuclear pore complex using a systematic knock-down approach with a panel of siRNAs targeting nucleoporins and nuclear import factors.
Results: We found that cell-type, cell cycle, cyclophilin A, the viral CA, and multiple nucleoporins affect sensitivity to Mx2. Nucleoporin expression levels vary in cell lines commonly utilized in HIV-1 experimentation, and nucleoporin depletion affects HIV-1 infection in a cell-type and CA dependent manner. We observed that the subcellular localization of Mx2 is dependent upon nucleoporins, and that Mx2 is co-localized with some nucleoporins to a greater degree than others. We also pinpoint individual nucleoporins

responsible for the effect of CsA on HIV-1 infection and Mx2 sensitivity. Some, but not all of these nucleoporins also interact with the viral CA. Finally, we demonstrate that the N-terminal domain of Mx2 attached to a heterologous scaffold that does not localize to the nuclear pore complex is still able to restrict HIV-1 infection, albeit with altered requirements for nucleoporins.
Conclusion: Our data highlight the complexity of the interaction between HIV-1, the nuclear pore complex, and other cellular proteins that interact with the viral capsid, and reveal heterogeneity in nucleocytoplasmic trafficking that influences viral infection and susceptibility to an innate immune effector.

161 UBP43 (USP18) ABROGATES SAMHD1-MEDIATED RESTRICTION OF HIV-1

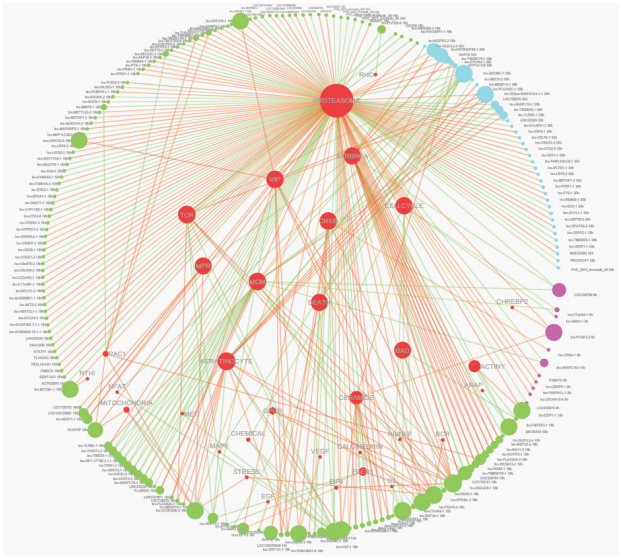
Edmund Osei-Kuffour[1], Kerstin Schott[2], Dieter Häussinger[1], Philipp A Lang[1], Karl S. Lang[3], Renate König[4], Carsten Münk[1]
[1]Heinrich Heine Univ Hosp, Düsseldorf, Germany, [2]Paul Ehrlich Institut, Fed Inst for Vaccines and BioMeds, Düsseldorf, Germany, [3]Univ Hosp, Essen, Düsseldorf, Germany, [4]Paul Ehrlich Institut, Langen, Germany

Background: The innate immune system is the first line of defense against pathogens including HIV-1. Host restriction factors are mediating the innate immune responses including the dNTPase, SAMHD1, which is efficiently antagonized by the HIV-2/SIV viral protein VPX. SAMHD1 is a protein that strongly contributes to the HIV-1 resistance of myeloid cells and of resting CD4+ T-cells. SAMHD1's dNTPase and antiviral functions in non-cycling cells are thought to be negatively regulated by phosphorylation at residue T592 by cyclin A2/CDKs. The specific phosphatase that renders SAMHD1 active and the mechanism of SAMHD1 mediated restriction in the non-cycling cells is not totally clear. Intrigued by the recent model of enforced viral replication in murine USP18 expressing macrophages (Honke et al. Nature Immunology 2011), we asked whether human USP18 ISG15 isopeptidase would be a factor influencing HIV-1 replication.
Methods: THP-1 macrophage-like cell lines were generated that stably expressed USP18 or active site mutants C64A and C64S. Undifferentiated cycling and PMA-differentiated THP-1 cells were infected by luciferase reporter viruses based on HIV-1 and HIV-2 (+/- vpx). The viral transduction was monitored by their luciferase activity in cell lysates. Immunoblots analyzed the cellular expression of USP18, SAMHD1 and phospho-SAMHD1. The interaction of SAMHD1 with USP18 was analyzed by pull-down assays and also visualized by confocal microscopy. Furthermore, the effect of USP18 on the cell cycle was analyzed by flow cytometry after fluorescent staining of the cellular DNA with propidium iodide.
Results: PMA-differentiated THP-1 cells are resistant to HIV-1 infection due to the expression of unphosphorylated SAMHD1. This restriction is ablated when USP18 is expressed. We found that the expression of USP18 in differentiated THP-1 cells increases HIV-1 infection by 16-fold and HIV-2Δvpx by 7-fold. USP18 directly bound to SAMHD1 in the cell nucleus, which induced phosphorylation of SAMHD1. Surprisingly, the presence or absence of USP18 did not influence the interaction of SAMHD1 and its kinases CDK1/2. However, USP18 interacted with S-phase Kinase Associated Protein 2 (SKP2) and retained cylin A in differentiated THP-1.USP18 cells. These activities of USP18 were independent of its ISG15 isopeptidase activity.
Conclusion: This report provides first evidence of direct involvement of USP18 in SAMHD1 restriction of lentiviruses.

162 LNCRNA DISCOVERY IN THE HIV REPLICATION CYCLE ADDS A NEW LAYER IN HIV-HOST INTERPLAY

Wim Trypsteen[1], Pejman Mohammadi[2], Clarissa Van Hecke[1], Pieter Mestdagh[1], Steve Lefever[1], Pieter De Bleser[3], Jo Vandesompele[1], Angela Ciuffi[2], Ward De Spiegelaere[1], Linos Vandekerckhove[1]
[1]Ghent Univ, Ghent, Belgium, [2]Univ of Lausanne, Lausanne, Switzerland, [3]Inflammation Rsr Cntr, Flanders Inst of BioTech, Ghent, Belgium

Background: Studying the effects of HIV infection on the host transcriptome has typically focused on protein-coding genes. However, recent advances in the field of RNA sequencing revealed that long non-coding RNAs (lncRNAs) add an extensive additional layer to the cell's molecular network and are crucial for normal cellular function. lncRNAs exert the ability to control a wide range of (post-)transcriptional processes and offer unique possibilities for pathogens like HIV to hijack the cellular machinery and reshape gene expression in their favor. Therefore, lncRNA discovery can result in new insights into the HIV-host interplay.
Methods: We performed transcriptome profiling throughout a characterized primary HIV infection in vitro to investigate lncRNA expression at the different HIV replication cycle processes (reverse transcription, integration and particle production). Subsequently, guilt-by-association, transcription factor and co-expression analysis were performed to infer biological roles for the lncRNAs identified in the HIV-host interplay.
Results: Throughout the HIV replication cycle we identified 387 lncRNAs that were differentially expressed with the majority observed at the viral integration phase. Many of these lncRNAs (173) were suggested to play a role in mechanisms at the heart of HIV-host interplay that rely on proteasomal and ubiquitination pathways (113), apoptosis inhibition (12), BRCA1/2 DNA damage responses and ATR cell cycle regulation (12). Through transcription factor binding analysis, we found that lncRNAs display a distinct transcriptional regulation profile (ao. TAF1/3/7, CHD1 and ATF3) as compared to protein coding mRNAs (ao. KLF4, SUZ12 and SOX2), suggesting that mRNAs and lncRNAs are independently modulated during HIV replication. In addition, we identified five differentially expressed lncRNA-mRNA pairs with mRNA involvement in HIV pathogenesis with possible cis regulatory lncRNAs that control nearby mRNA expression and function (ao. lnc-HES5-1 and TNFRSF14).
Conclusion: Altogether, the present study demonstrates that lncRNAs add a new dimension to the HIV-host interplay and exhibit an independent transcriptionally regulated response. These identified lncRNAs are involved in viral and antiviral response pathways and should be further investigated as they may represent possible biomarkers or targets for controlling HIV replication.



163 SPLICING IN A PANEL OF HIV-1 TRANSMITTED/FOUNDER VIRUSES

Ann Emery, Ronald Swanstrom
Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: During HIV-1 replication over 100 spliced RNA variants are generated from a single full-length viral transcript. All spliced transcripts use donor site D1 and one of nine downstream acceptors (A1-A7). About half of the spliced RNAs also undergo further splicing to remove the D4 – A7 env intron (creating the large/4 kb size class that retains the env intron and the small/1.8 kb class of viral RNAs). Additional splicing complexity comes from the use of two additional donor sites, D2 and D3, that create two small exons, one or both of which may be included in splice variants for the downstream genes. The purpose of these small exons is unknown. We examined the extent of splicing pattern variation among 8 transmitted/founder (T/F) isolates to explore the extent of natural variation in splicing patterns.
Methods: We have developed a new HIV-1 splicing assay that uses deep sequencing technology with Primer ID-tagged cDNA primers to quantify HIV-1 splicing. In this assay the presence of different spliced variants is quantified within the 4 kb and 1.8 kb size classes. Total infected cell RNA was extracted and used in cDNA reactions using primers specific for each size class, followed by PCR and paired-end deep sequencing using the MiSeq platform.
Results: Analysis of 8 subtype B T/F viruses showed that overall splicing patterns were similar in that the same splice site acceptors and donors were used, including conservation of the small exons. However there were examples of surprising ranges of variability including significant changes in the use of alternative splice sites for rev, and over-splicing to the vpr splice acceptor that was compensated by high level use of the adjacent donor D3. We also found evidence of trans-splicing among all of the T/F viruses, where a donor from one transcript splices to an upstream acceptor on another transcript.
Conclusion: The idea that splicing is tightly regulated and carefully balanced needs reexamination. The variance in the amounts of the different spliced transcripts suggests that if a virus meets a threshold level for each transcript type, it can be transmitted and continue to replicate. The overall frequency of trans-splicing was surprisingly high, with total trans-splicing occurring more often than several of the canonical spliced transcript types. Trans-splicing was much less frequent in the 4 kb class suggesting this alternative export pathway for viral mRNA experiences a subtly different splicing environment.

164 THE ROLES OF 5 CONSERVED LENTIVIRAL RNA STRUCTURES IN HIV-1 REPLICATION

Yang Liu[1], Olga A. Nikolaitchik[1], Belete A. Desimmie[1], Vinay K. Pathak[1], Kevin M. Weeks[2], Wei-Shau Hu[1]
[1]NCI, Frederick, MD, USA, [2]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: HIV-1 full-length RNA genome forms complex structures. Some of the RNA structures are known to play important roles in viral replication, which include RNA export, synthesis of GagPol polyprotein, and RNA genome packaging, whereas the functions of other RNA structures are unknown. Using chemical probing, the Weeks' group has determined the in virio RNA structures of HIV-1, SIVcpz and SIVmac. Comparison of these three RNAs revealed five conserved structures with unknown functions: three (A1 to A3) are located between regions encoding domains of polyproteins, specifically between matrix and capsid (A1), protease and reverse transcriptase (RT) (A2), and RT and integrase (A3). Two of the structures (B1 and B2) form long helical stacks in the region encoding capsid and nef, respectively. We sought to determine whether these RNA structures are important to HIV-1 replication, and if so, their potential functions.
Methods: For each RNA structure, we introduced synonymous mutations in NL4-3 to disrupt base-pairing and examined the effects of these mutations in virus production, viral infectivity, and the ability to undergo multiple rounds of viral replication in T cells. We also performed competition experiments to compare the replication fitness of these mutants with that of the wild-type NL4-3 virus.
Results: We observed that all five mutants can generate infectious viruses; furthermore, the virus production and one-round replication infectivity of the mutant viruses are not significantly different from those of wild-type NL4-3. We then performed multi-round competition assays between a mutant virus and the wild-type NL4-3 in T cells. We found that three of the mutants have replication fitness similar to that of wild-type virus, suggesting that the loss of these structures do not affect HIV-1 replication in T cells. However, mutations in the A1 or the A3 RNA structures result in loss of replication fitness. We are currently performing additional experiments to determine how these mutations contribute to the loss of replication fitness.
Conclusion: We have examined the roles of five conserved RNA structures on HIV-1 replication. Three of the structures are dispensable for HIV-1 replication. However, HIV-1 replication fitness was reduced when synonymous mutations were introduced into sequences between regions encoding matrix and capsid, and RT and integrase; these two RNA structures are likely to be important for efficient HIV-1 replication.

165 EXPONENTIAL GROWTH OF HIV DEPENDENT ON BURST SIZE BREAKTHROUGH OF THE ALLEE THRESHOLD

Jason M. Hataye[1], Joseph P. Casazza[1], David R. Ambrozak[1], Takuya Yamamoto[2], Daniel Douek[3], Alan S. Perelson[4], Richard A. Koup[3]
[1]NIH, Bethesda, MD, USA, [2]Osaka Univ, Sukta, Osaka, Japan, [3]NIAID, Bethesda, MD, USA, [4]Los Alamos Natl Lab, Los Alamos, NM, USA

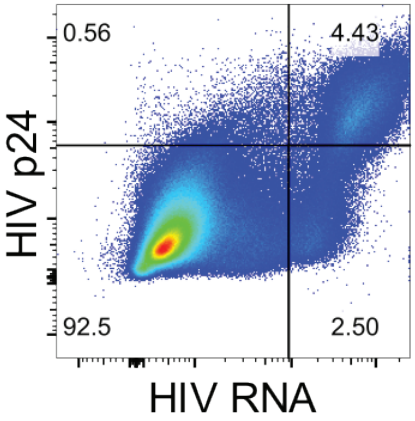
Background: Exponential growth is the mode by which a population establishes itself following arrival in a new environment. For HIV, establishment is inevitable by the time exponential growth is detected, during both acute infection following transmission, and viral rebound from the latent reservoir following interruption of suppressive antiretroviral therapy (ART). Although fundamental, the processes leading up to overt exponential growth versus extinction have eluded definition because they are simultaneously low amplitude, rare, and fleeting.
Methods: To investigate viral release and growth, resting CD4+ T cells from 8 donors on ART were stimulated with antibodies against CD3, CD2, and CD28. The cells were cultured in limiting dilution with ART to quantify initial HIV release in the absence of new infections, or with IL-2 plus exogenous cells for outgrowth. To distinguish replication-competency from establishment, supernatant positive for HIV RNA by RT-PCR on day 8 of the primary outgrowth culture was transferred to new stimulated CD4+ cells from HIV-uninfected donors. Fitting the experimental results to deterministic and stochastic models, we tested key assumptions of HIV release and early growth, and present an adapted model that not only fit existing data but was predictive of more complex experiments.
Results: Despite extensive cell division, most CD4+ T cells initially present in culture died before virus could be released, which on average began 4 days following activation. The duration of HIV release due to one latent cell ranged from less than one day up to 7 consecutive days. Such sustained detections resulted from sequentially occurring progeny releasing on average 1000 HIV RNA copies per cell for a total 3900 HIV RNA copies. Many primary culture releases consisted of virus which was confirmed intact by secondary culture, but did not result in exponential growth. Released HIV in a well was most likely to undergo exponential growth if it exceeded a critical threshold of 6000 HIV RNA copies. Establishment dependence on a low threshold is called the Allee effect and has been previously reported across diverse biological taxa including animals, plants, and non-pathogenic microorganisms.
Conclusion: This work demonstrates why integrated and intact provirus may not result in ex-vivo outgrowth, advances the theoretical foundation for rebound prediction following ART interruption, and identifies the Allee growth threshold as a population dynamically defined target for an HIV functional cure.

166 DETECTION AND CHARACTERIZATION OF CELLS EXPRESSING HIV RNA BY FLOW CYTOMETRY

Aaron Christensen-Quick[1], Amey Mukim[2], Celsa A. Spina[2], Sara Gianella[3], Davey M. Smith[3]
[1]Univ of California San Diego, San Diego, CA, USA, [2]VA San Diego Hlthcare System, San Diego, CA, USA, [3]Univ of California San Diego, La Jolla, CA, USA

Background: Our current knowledge of HIV-infected cell populations is largely derived from flow cytometry studies using antibodies to p24- the HIV capsid protein and most abundantly expressed antigen. However, p24 is an imperfect marker of infected cells that requires artificial activation for its detection, especially when analyzing rare HIV+ cells from ART-treated individuals. Much less is known about cell populations that express both p24 and HIV RNA, despite their potential importance to cure efforts.

Methods: Primary human CD4 T cells from HIV-negative blood donors were isolated by negative selection, activated with plate-bound α-CD3/CD28 and infected with HIV_{IIIB}. Infected samples and uninfected controls were analyzed by flow cytometry for their expression of immunological markers, HIV p24 and HIV RNA. Detection of HIV RNA was achieved using PrimeFlow™ probes covering the entire HIV genome. Significant differences in expression of lymphocyte markers were identified using the Wilcoxon rank test.



Results: Results: In HIV-infected CD4 T cells from five donors, we readily detected cells that expressed HIV RNA, p24, or both (see figure). Importantly, a substantial population of cells from infected samples expressed HIV RNA, but not p24 (mean=2.7% of total cells). Over a third (mean=35%) of cells that expressed HIV RNA did not co-express p24. Except for background signal, these populations were absent in uninfected controls (mean<0.25% for RNA+p24-, <0.0001% for RNA+p24+, <0.06% for HIV RNA- p24+, n=3). HIV-infected samples, but not uninfected controls, had a population of cells expressing decreased CD45RA (1.9% vs 0.005%, p<0.02), and this population of $CD45RA^{low}$ cells was enriched in both HIV RNA+p24+ cells (29.4% vs. 5.2% of total, p<0.008) and RNA+p24- cells (9.9% vs. 2.7% of total, p<0.03). Interestingly, the average percent of CD27+ cells was significantly lower in HIV RNA+ p24- cells from infected samples, but not in HIV RNA+ p24+ dual-positive cells (p<0.05 and p=.17, respectively).

Conclusion: These findings emphasize the need for a more detailed characterization of cells supporting HIV transcription. Differences between cells expressing HIV RNA and those producing p24 may have important biological consequences, especially in regard to HIV persistence.

167 INFLAMMASOME-REGULATED CYTOKINE IL-37 INHIBITS HIV-1 REPLICATION IN PRIMARY HUMAN CD4

Neel Sangal, Guido Massaccesi, Jeffrey Quinn, Andrea Cox, Matthew Winter
Johns Hopkins Univ, Baltimore, MD, USA

Background: Interleukin (IL)-37 is a recently characterized member of the IL-1 family of cytokines that regulate innate immune responses. Like other inflammasome-regulated cytokines it's maturation and release is dependent on inflammasome activity and caspase-1 activation. HIV-1 infected individuals have elevated levels of circulating inflammasome cytokines.

Methods: We assessed the effects of inflammasome-regulated cytokines on HIV-1 replication in human primary CD4+ T-cells. CD4+ T-cells were sorted from human blood and infected with HIV RF or IIIB followed by culture with cytokines in various concentrations. Viral replication was measured by p24 ELISA and viral RNA. Cytokine receptor expression was assessed by flow cytometry. Modulation of innate immune genes was determined by qRT-PCR.

Results: We find that activated T-cells express receptors for all inflammasome cytokines; however only IL-37 exerts an antiviral effect in HIV-1 infection. IL-37 induces expression of antiviral factors including IFITM proteins and APOBEC3A in CD4+ T-cells. IL-37 directly inhibits HIV-1 replication in infected primary human CD4+ T-cells by inhibiting life cycle steps prior to integration of the pro-viral genome.

Conclusion: IL-37 exerts a suppressive effect on HIV-1 by inducing expression of innate antiviral factors known to restrict HIV replication.

168 BCA2 INTERFERES WITH HIV-1 TRANSCRIPTION BY ENHANCING THE SUMOYLATION OF IKBA

Marta Colomer-Lluch
Texas Tech Univ, Lubbock, TX, USA

Background: BCA2 (breast cancer-associated gene 2) is an E3 ubiquitin ligase that serves as a co-factor in the restriction imposed by Tetherin on HIV-1. We recently demonstrated that BCA2 also has Tetherin-independent activity. Particularly, BCA2 targets HIV-1 Gag for lysosomal degradation, impairing virus assembly. Since many antiviral factors modulate the NF-κB pathway, we sought to explore if BCA2 is harnessing this innate cascade to further limit HIV-1

Methods: To study the role of BCA2 on NF-κB, gene expression and NF-κB-inducible luciferases assays were performed. Results obtained from these studies were corroborated by depleting cells from BCA2 and its co-factors using shRNAs. To examine the implication of the BCA2-mediated regulation of NF-κB in HIV-1 infectivity, replication and transcriptional assays were conducted in CD4+ cells. To identify the molecular mechanism by which BCA2 modulates this pathway, the post-translational modifications of NF-κB components were analyzed as well as their subcellular distribution

Results: Here we show that BCA2 is induced by NF-κB-activating cytokines and its up-regulation provides a negative feedback on NF-κB. Knockdown assays revealed that UBC9 is a critical BCA2 co-factor to inhibit the NF-κB pathway. UBC9 mediates the SUMOylation of IκBα, which in turn impairs the nuclear translocation of NF-κB. To explore if BCA2 participates in this process, we assessed IκBα's post-translational modifications. Remarkably, the levels of SUMOylated IκBα increase in cells overexpressing BCA2 (2-fold) whereas its phosphorylation levels diminish (10-fold). Conversely, depletion of UBC9 or BCA2 leads to a significant reduction of SUMOylated IκBα and a corresponding increase in its phosphorylation levels. In vitro SUMOylation studies revealed that BCA2 enhances IκBα SUMOylation, demonstrating for the first time that BCA2 serves as a SUMO-ligase in the regulation of the NF-κB pathway. Consistent with this, BCA2 blocks the nuclear translocation of NF-κB. Since HIV-1 needs NF-κB to enhance its replication, we studied the biological implication of the BCA2-dependent inhibition of this pathway in HIV-1 infectivity. BCA2 reduces HIV-1 transcription up to 4-fold in CD4+ cells. However, HIV-1 partially circumvents this hurdle by decreasing the steady-state levels of BCA2 via a yet unidentified mechanism

Conclusion: BCA2 poses several barriers to HIV-1 infection: not only does BCA2 prevent assembly and release of nascent virions, but also restricts HIV-1 at the transcriptional level

169 RHO FAMILY GTPASES ENHANCE HIV-1 INFECTION

Mark Lucera[1], Zach Fleissner[2], Caroline Tabler[2], Daniela Schlatzer[2], Zach Troyer[2], **John Tilton**[2]
[1]Univ of Colorado, Aurora, CO, USA, [2]Case Western Reserve Univ, Cleveland, OH, USA

Background: HIV-1 co-opts host cellular machinery to complete its replication cycle, including cytoskeletal components for intracellular trafficking, nucleoproteins for pre-integration complex (PIC) import, and the ESCRT pathway for assembly and budding. It is widely recognized that cellular post-translational modifications (PTMs) regulate protein activity within cells; however, little is known about how PTMs influence HIV replication. Previously, we reported that blocking deacetylation of tubulin using histone deacetylase (HDAC) inhibitors promoted the kinetics and efficiency of early post-entry viral events. To uncover additional PTMs that modulate entry and early post-entry stages in HIV infection, we employed a flow cytometric approach to assess a panel of small molecule inhibitors on viral fusion and LTR promoter-driven gene expression.

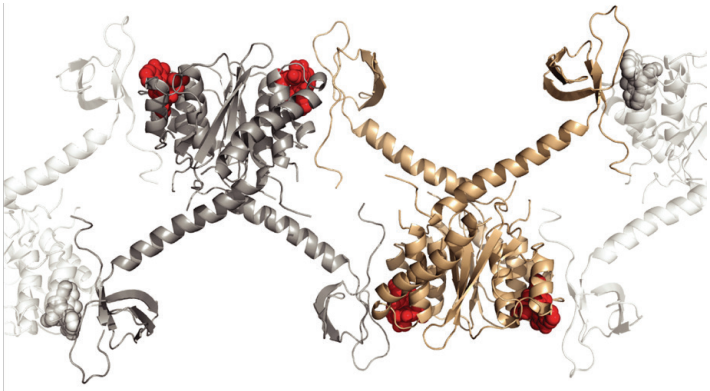
Methods: A panel of small molecule inhibitors tailored to enzymes involved in epigenetic and PTM pathways were analyzed for effects on HIV fusion and gene expression by flow cytometry. Compounds with ±0.5 log2-fold change effects on viral infection were validated in additional experiments using CD4+ T cells from 5 healthy controls. Additionally, a phosphoproteomic experiment was performed to identify signaling pathways altered by HIV binding to CD4 and CCR5.
Results: While viral fusion was not significantly affected, early post-entry viral events were modulated by drugs targeting multiple processes including histone deacetylation, methylation, and bromodomain inhibition. Most notably, we observed that inhibitors of the Rho GTPase family of cytoskeletal regulators – including RhoA, Cdc42, and Rho-associated kinase (ROCK) signaling pathways – significantly reduced viral infection. Proteins in the Rho GTPase signaling cascades were also identified using a phosphoproteomic analysis of virion-induced signaling via CD4 and CCR5, suggesting that HIV-1 initiates the manipulation of the host cytoskeletal network via interactions with CD4 and CCR5 at the cell surface to promote its replication.
Conclusion: Together, these data provide evidence that the Rho GTPase family of cytoskeletal regulators play a major role in facilitating HIV infection and suggest that the virus actively modulates the cytoskeleton by signaling through CD4 and CCR5.

170 SEMEN FACTORS ASSOCIATED WITH SEMEN VIRAL LOAD AND INFECTION-ENHANCING ACTIVITY

Christopher D. Pilcher[1], Kara Marson[1], Peter Bacchetti[1], Sheila Keating[2], Wendy Hartogensis[1], Teri Liegler[1], H. Ewa Witkowska[1], Satish K. Pillai[2], Frederick M. Hecht[1], Nadia R. Roan[3]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Blood Systems Rsr Inst, San Francisco, CA, USA, [3]Gladstone Inst of Virology, San Francisco, CA, USA
Background: We have previously reported that seminal plasma from HIV negative men can markedly enhance HIV infection of permissive cells, and that this activity is positively associated with endogenous concentrations of SEM1(86-107), a peptide derived from a protein produced by the seminal vesicles. In vitro, SEM1(86-107) polymerizes to form amyloid fibrils that enhance HIV infection, and endogenous SEM1(86-107) amyloid aggregates can be detected in semen. We hypothesized that in HIV-infected individuals, semen factors that promote HIV infection might also increase the semen HIV viral load.
Methods: We examined the relationships among semen viral load, HIV infection enhancing activity, and inflammatory cytokines in semen samples from 122 HIV-infected individuals. Samples were obtained at least 4 months post seroconversion; 149 specimens were obtained from 103 ART naïve donors, 20 donated pre-and post-ART suppression, and 20 pre-and post-interruption of ART. HIV infection of TZM-bl cells in the presence vs. absence of semen was used to quantitate viral enhancing activity. Inflammatory cytokines and chemokines were measured by Luminex in semen and blood.
Results: The degree to which semen enhanced HIV infection varied (from no enhancement to 30-fold) between HIV-infected individuals but was stable over time within individuals. Higher infectivity enhancement of semen was strongly correlated with the concentration of SEM1(86-107) in HIV-infected men ($r=0.70$, $p<0.0001$). In multivariate analyses controlling for the blood viral load, higher semen viral load was independently associated with higher semen infectivity enhancing activity ($p=0.02$) as well as with higher levels of IL8 ($p=0.01$) and IL6 ($p=0.01$). Mean IL8 levels were 245-fold higher and mean IL6 levels 25-fold higher in semen than in blood. In longitudinal experiments with patients initiating and interrupting ART, we found that changes in semen viral load with ART use did not substantially alter levels of infectivity enhancement, SEM1(86-107), or pro-inflammatory cytokines in semen.
Conclusion: The composition of semen can differ greatly between HIV-infected men. Some of the factors that vary between men, such as infection-enhancing amyloids and certain proinflammatory cytokines, may facilitate HIV transmission in two ways-by promoting local viral replication in the genital tract (increasing semen viral load), and/or by enhancing infection of mucosal target cells.

171LB STRUCTURAL BASIS FOR INHIBITOR-INDUCED AGGREGATION OF HIV INTEGRASE

Kushol Gupta[1], Vesa Turkki[1], Scott Sherrill-Mix[1], Young Hwang[1], Grant Eilers[1], Robert T. Nolte[2], Emile Velthuisen[2], Jerry Jeffrey[2], Gregory Van Duyne[1], Frederic Bushman[1]
[1]Univ of Pennsylvania, Philadelphia, PA, USA, [2]Glaxosmithkline, Rsr Triangle Park, NC, USA
Background: The allosteric integrase (IN) inhibitors (ALLINIs) target the viral-encoded IN protein and interfere with HIV replication via disruption of viral particle assembly late during HIV replication.
Methods: To investigate their inhibitory mechanism, we crystallized full-length HIV-1 IN bound to the ALLINI GSK1264, and determined the structure of the complete inhibitor interface at 4.4 Å resolution.
Results: In this structure, GSK1264 is buried between the catalytic core domain of one IN dimer and the CTD of an adjacent IN dimer. The amino-terminal domain is not resolved in the structure but does not participate in GSK1264 binding. The GSK1264 binding interface is rich in residues implicated in IN oligomerization and ALLINI sensitivity, indicating likely functional significance. The IN-IN interaction mediated by GSK1264 leads to formation of an open polymer in the crystal, a polymerization reaction that is readily reproduced in solution with purified components. To probe ALLINI function more broadly, we compared the properties of several ALLINIs in biochemical, biophysical, virological, and electron microscopic assays. Several ALLINI escape mutations encode IN substitutions at or near the inhibitor binding site, and these also resulted in decreased IN oligomerization in vitro. The results support a mechanism where ALLINIs disrupt viral particle maturation by promoting formation of the IN polymers observed in the IN-GSK1264 crystal structure. Additionally, the results support a structural model for the catalytically inactive IN tetramer discussed in several previous studies. Identification of the interface responsible for polymer formation provides data useful for improving HIV inhibitors and helps explain a wealth of previous studies of HIV IN.



172 CHARACTERIZING APOBEC3H FUNCTION AND EVOLUTION IN AFRICAN GREEN MONKEYS

Erin I. Garcia[1], Michael Emerman[2]
[1]Univ of Washington, Seattle, WA, USA, [2]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA

Background: Members of the APOBEC3 family of genes are cytidine deaminases involved in innate immune defense against retroviruses and retroelements. One member of the family, APOBEC3H (A3H), is polymorphic in humans. These polymorphisms have been demonstrated to impact not only the stability of the protein, but also affects interactions with its viral antagonist, HIV-1 Vif. We hypothesized that this mechanism of polymorphism may be evolutionarily conserved. Therefore, we characterized A3H variation within African Green Monkeys (AGM) in order to further elucidate the dynamics of the A3H-Vif interaction in this primate model.
Methods: A3H was amplified and sequenced from a panel of AGMs across all four subspecies: vervet, tantalus, sabaeus, and grivet. Phylogenetic analyses were conducted on nucleotide and protein sequences. The ability of haplotypes to restrict viral infection by SIVagm was tested in single cycle infections.
Results: We found that A3H is extraordinarily polymorphic in African Green Monkeys (AGM), which provides a unique opportunity to study the interaction of A3H haplotypes with four species specific lentiviruses. We identified a total of 35 polymorphisms in A3H of AGMs. 25 of these polymorphisms are nonsynonymous and occur across all four subspecies of AGM. Many polymorphisms are tightly linked in one region of the gene, which results in a bifurcation of the phylogenetic tree. Haplotypes that encode either a CGRELP or SRQKRQ motif within this region group together within a possible Vif-binding interface. Additionally, two species specific amino acid changes have occurred in this same region in vervet monkeys. Furthermore, a subset of haplotypes have been tested for antiviral activity in single-round infectivity assays and also demonstrate antiviral activity against SIVagm from other subspecies. The affects of this polymorphism on A3H-Vif binding interactions and virus replication and evolution are being studied.
Conclusion: Polymorphism in A3H has impacted HIV dynamics in humans, but the interaction between A3H and HIV-1 Vif is not yet fully understood. We have shown that A3H is also polymorphic in another primate model. These polymorphisms may impact A3H-Vif interactions in AGMs and would provide another forum to identify factors that are important in such interactions.

173 MAPPING THE HIV-1 VIF-CBFβ INTERACTION INTERFACE AND IDENTIFICATION OF DETERMINANTS

Belete A. Desimmie[1], Jessica Smith[1], Hiroshi Matsuo[2], Wei-Shau Hu[1], Vinay K. Pathak[1]
[1]NCI, Frederick, MD, USA, [2]Univ of Minnesota, Minneapolis, MN, USA

Background: Human APOBEC3 (A3) proteins such as A3G are host restriction factors that deaminate cytidines in DNA and potently inhibit HIV-1 replication by inducing lethal G-to-A hypermutation. However, HIV-1 encodes the accessory protein viral infectivity factor (Vif), which counteracts the antiviral activities of A3 proteins. Vif targets the A3 proteins for proteasomal degradation by recruiting components of an E3-ubiquitin ligase complex. Previous studies have demonstrated that Vif hijacks the cellular transcription co-activator core-binding subunit beta (CBFβ) to mediate A3G degradation and have identified different residues of Vif involved in Vif-CBFβ interaction. Recently a co-crystal structure of HIV-1 Vif, CBFβ, CuI5, EloB, and EloC pentameric complex was solved. However, a systematic analysis of the functional importance of the Vif-CBFβ interaction interface in cells has not been determined, and the amino acids involved in the interaction in cells have not been fully characterized.
Methods: To identify the critical Vif-CBFβ interaction determinants, we performed double-alanine scanning mutagenesis of the first 60 amino acids of Vif. We then determined the interaction efficiencies of the different Vif mutants with CBFβ by immunoprecipitation as well as the biological significance of these interactions by examining A3G degradation and viral infectivity.
Results: We found that multiple Vif residues are involved in the extensive N-terminal Vif-CBFβ interaction; particularly, ^{5}WQVMIVW^{11} region of Vif was found to be the major determinant. A minimum of three alanine substitutions were required to completely abrogate the Vif-CBFβ interaction. Furthermore, these mutants were unable to rescue HIV-1 infectivity in the presence of A3G. A reciprocal mutational analysis targeting CBFβ revealed that F68 and I55 residues are important and participate in a tripartite hydrophobic interaction to maintain a stable and functional Vif-CBFβ complex.
Conclusion: Our results provide detailed insight into the major determinants of interaction between Vif and CBFβ in cells. Together with the available structural data of the Vif-CBFβ -E3 ubiquitin ligase pentameric complex, our data provide valuable information for future structure-based rational design of a novel class of HIV-1 inhibitors targeting Vif-mediated degradation of A3 proteins.

174 THE ABILITY OF HIV-1 TO EVADE SAMHD1-MEDIATED RESTRICTION IN MACROPHAGE

Timothy Plitnik, Mark Sharkey, Mario Stevenson
Univ of Miami, Miami, FL, USA

Background: SAMHD1 has been described as an antiviral restriction factor that functions by reducing intracellular dNTP pools, thus creating hostile conditions for reverse transcription. SIV and HIV-2 encode Vpx, which promotes the degradation of SAMHD1 thereby increasing the cellular dNTP pool. Although HIV-1 lacks Vpx, it readily infects cells with SAMHD1 activity and low dNTP levels such as macrophage. Therefore, it is unclear how HIV-1 avoids antagonism by SAMHD1. We hypothesize that reverse transcriptase of HIV-1 has a lower Km for dNTPs, which allows it to overcome SAMHD1 restriction without Vpx.
Methods: Elutriated human monocytes were differentiated into macrophage with MCSF for 7 days. Cells were then infected with HIV-1 or SIV (+/- Vpx) normalized by Gag ELISA. SAMHD1 levels post-infection were quantified by FACS analysis and western blots. RNAi was used to knock-down SAMHD1 in macrophage, which were subsequently used for infection. GFP-expressing HIV-1 or SIV was used in pre-infection experiments, which were also quantified by FACS analysis. Chimeric viruses were generated using Exponential-Megapriming-PCR. Reverse transcription was quantified using qPCR for 2LTR circles normalized to genomic CCR5 copy number.
Results: We first demonstrate that HIV-1 can infect macrophage without affecting SAMHD1 levels. However, SIV reverse transcription is dependent on SAMHD1 degradation. RNAi knock-down of SAMHD1 enables SIVΔVpx infection in macrophage. Pre-infection of macrophage by HIV-1 was not sufficient to rescue a SIVΔVpx, revealing that HIV-1 is not altering the intracellular environment, and its ability to overcome SAMHD1 activity is intrinsic to the virus itself. Chimeric viruses with exchanged RTs were created and used to test the hypothesis. We found that the SIVΔVpx was not able to overcome restriction with an HIV-1 RT and that an SIV RT did not render HIV-1 susceptible to restriction.
Conclusion: HIV-1 has evolved to infect myeloid cells without Vpx, whereas SIV is highly dependent upon Vpx-mediated SAMHD1 degradation. Exchange of the RT's demonstrated that HIV-1 RT was not able to overcome SAMHD1 restriction in SIVΔVpx, nor did the SIV RT render HIV-1 susceptible to restriction. These findings indicate that kinetic differences in the RT's are not sufficient to confer the ability of HIV-1 to infect macrophage without Vpx. HIV-1 escape from SAMHD1 restriction is dependent on determinants distinct from RT.

175 MHC DOWN-MODULATION IN HIV-INFECTED CELLS OCCURS LATE IN THE VIRUS REPLICATIVE CYCLE

Rodrigo Matus Nicodemos, Daniel Douek, Richard A. Koup
Vaccine Rsr Cntr, NIAID, Bethesda, MD, USA

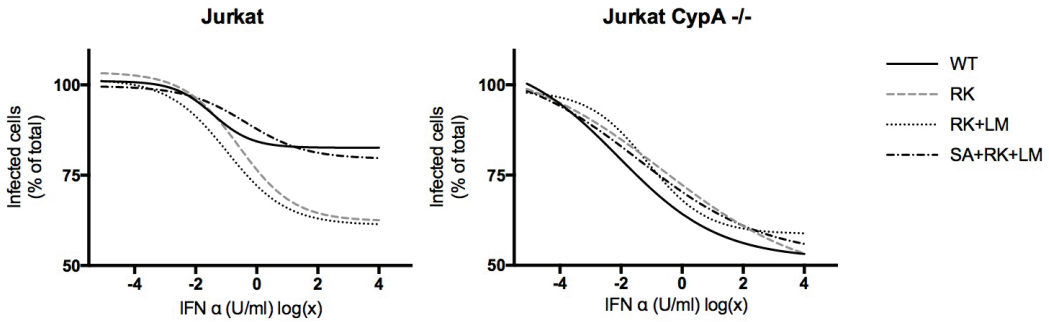
Background: In vitro studies suggest that HIV-1 Nef selectively down-modulates HLA-A and HLA-B molecules to protect the infected cells from CD8 T cell-mediated recognition and killing. However, the emergence of escape mutations in vivo clearly shows that CD8 T cells must exert selective pressure though recognition of virus epitopes presented by the MHC class I molecules. We hypothesized that virus peptide-MHCs are presented during the virus replicative cycle before Nef completely down-modulates MHC molecules. Therefore, HIV-infected cells can be recognized and eliminated by HIV-specific CD8 T cells.
Methods: To test this hypothesis we developed a FACS-based virus replicative cycle reporter system to measure the timing of MHC down-modulation. A GFP IRES Nef construct was inserted into the Nef ORF of the NL4-3 replication competent molecular clone. PHA/anti-CD28-activated primary CD4 T cells were infected for 6 hours, washed, and further incubated for 24 or 48 hours. The early stage of the virus replicative cycle was detected by the expression of GFP while the late stage was detected by intracellular staining with an anti-HIV Gag p24 antibody. We used antibodies specific to HLA-A02, A03, B07, B08, and B27 to determine the timing of the down-modulation for these molecules. As controls we

stained for the down-modulation of CD4 and T cell activation by CD69 expression. The expression levels for MHC and CD4 were compared to primary CD4 T cells that went through the experiment without virus infection.
Results: At 24 and 48 hours post-infection we detected two HIV-infected cell populations: GFP+p24- and GFP+p24+. CD4 was partially down-modulated in the GFP+p24- population and completely down-modulated in the GFP+p24+ population. The down-modulation of MHC molecules was more complex. Down-modulation of all 5 HLA molecules was only observed in the GFP+p24+ population at the 48hr time point. We also observed a significant increase in HLA expression in the GFP+p24- population at 24 hr. Finally, we also observed a significant increase in HLA expression in cells that up-regulated CD69.
Conclusion: Our results show that down-modulation of MHC molecules occurred late in the virus replicative cycle in contrast to CD4 that began earlier. These data suggest that MHCs presenting virus peptides in HIV-infected cells could be expressed for most of the virus replicative cycle. Thus, our data offer an explanation for how CD8 T cells exert selective pressure on HIV-1 in vivo even with the expression of Nef.

176 HLA-B27–RESTRICTED CTL-ESCAPE MUTATIONS INCREASE SENSITIVITY OF HIV-1 TO INTERFERON A

Philipp Schommers[1], Christopher Ford[2], Angelique Hölzemer[2], Gerd Fätkenheuer[1], Marcus Atlfeld[2]
[1]Univ of Cologne, Cologne, Germany, [2]Heinrich Pette Inst, Hamburg, Germany

Background: Type1 interferons (IFNs), including IFNα, upregulate cellular innate sensors acting as restriction factors in CD4+ T cells to suppress HIV-1 replication. HIV-1 strains can differ in their sensitivity to IFNα-mediated restriction. HLA-B27+ "Elite Controllers" have been suggested to control HIV-1 through specific cytotoxic T-cells (CTL), which exert immune selection pressure on HIV resulting in CTL-escape mutations. Our aim was to determine whether the HLA-B27-restricted CTL escape mutation R264K (RK) in p24 Gag and the compensatory mutations R264K+L268M (RK+LM) and S173A+L268M+R264K (SA+RK+LM) influence the sensitivity of HIV-1 to IFNα-induced restriction.
Methods: Site-directed mutagenesis of an HIV1 NL4-3Δenv strain expressing GFP was performed to introduce the respective p24 Gag mutations. Infection was assessed in Jurkat T-cells and Jurkat T-cells with a CypA knockout (Jurkat CypA-/-). For IFNα-sensitivity assays, HIV-1 GFP-infected Jurkats and Jurkat CypA-/- T-cells were pre-incubated with increasing doses of IFNα. Infectivity of Jurkat cells was measured using flow cytometry.
Results: Wild-type HIV-1 NL4-3 (WT) infection rates of Jurkat cells were significantly higher than those of Jurkat CypA-/- cells, suggesting dependence of WT replication on CypA. In IFNα-stimulated Jurkat cells, WT infection rates were reduced by 19%, while WT infection rates were reduced by 50% in IFNα-stimulated Jurkat CypA -/-, indicating that CypA/capsid interactions enable WT virus to evade IFNα-induced restriction factors. In contrast, HIV-1 containing the RK and RK+LM mutations showed higher infection rates of Jurkat CypA-/- cells compared to Jurkat cells, and viral replication in Jurkat cells was strongly inhibited by IFNα-exposure (RK: 41%; RK+LM: 35%). Addition of the compensatory SA mutation (SA+RK+LM) reconstituted infection rates to levels similar as WT, including increased susceptibility to IFNα-mediated inhibition in Jurkats CypA -/- cells.
Conclusion: Our data suggest that HIV containing the RK and RK+LM mutation are less dependent on CypA than WT. However, weak CypA/capsid interactions might expose these mutated strains to IFNα-induced restriction factors that compete with CypA for their binding site, thereby rendering these strains more sensitive to IFNa in Jurkats. This highlights the role of CypA/capsid interactions in protecting HIV-1 from antiviral restriction factors, and provide a mechanism by which HLA-B27-restricted CTL escape mutations in capsid can result in a loss of viral fitness.



177 CXCR4 VARIANTS ARE NEUTRALIZATION-RESISTANT COMPARED TO CCR5-USING VIRUSES IN HIV-1B

Ludy Registre[1], Yvetane Moreau[2], Sila Ataca[1], Manish Sagar[1]
[1]Boston Univ, Boston, MA, USA, [2]Boston Med Cntr, Boston, MA, USA

Background: Emergence of CXCR4 tropic variants during HIV-1 infection is associated with faster progression towards AIDS. The mechanism for emergence remains poorly understood. We hypothesized that X4-utilizing variants emerge as neutralization escape variants from selective pressure on the HIV envelope (env).
Methods: Full-length envelopes (envs) were isolated from 4 individuals from ACTG study A5095 using single genome amplification. Envs were incorporated into an NL4-3 backbone to generate replication competent recombinant viruses. Viruses were examined for co-receptor usage and neutralization sensitivity using TZM-bl cells. Neutralization was assessed by measure of area under the curve (AUC), which assesses average neutralization within the range of concentrations. Structural modeling using Rosetta Structure Predication Server was done to visualize structural differences between X4 and R5 V3 loops. Comparisons were done using a paired t test or Wilcoxon rank sum test.
Results: A median of 4.5 CCR5-using (R5) (range 1-5) and 3 co-circulating CXCR4-using (X4) envs (range 1-5) were amplified from 4 subjects. All samples were confirmed as subtype B by sequence analysis. All X4 variants (n=12) had a 2 – 3 amino acid insertion either prior to the V3 crown or towards the end of the V3 loop. Structural models of an X4 and R5 variant predicted an additional loop structure within the V3 loop of the X4 variant and not the R5 variant. In all 4 subjects, X4 envs were less neutralization sensitive to autologous contemporaneous plasma compared to the R5 envs (p=0.04). X4 and R5 envs demonstrated equivalent susceptibility to CD4 binding antibody, VRC01, suggesting the envs do not have significant differences in the CD4-binding site. Comparison of all X4 (n=12) to all R5 (n=10) envs demonstrated that X4 envs were less neutralization sensitive to anti-V3 loop directed antibody, PGT121 (p=0.03).
Conclusion: Some subtype B env X4 variants possess a unique V3 loop genotype leading to a predicted novel loop structure compared to the R5 strains. In some individuals, X4 variants are less sensitive to autologous and V3 directed antibodies, potentially suggesting that CXCR4 usage emerges as a consequence of host generated humoral immune response. Our studies imply that treatment with some broadly neutralizing antibodies, such as those directed at the V3 loop, may select for CXCR4-using strains.

178 MEASURING FITNESS OF IN VIVO ESCAPE MUTATIONS IN SIV ENV BY FITSEQ

Sergio Ita[1], Alison Hill[2], Evan Lam[2], Ismael B. Fofana[2], Welkin E. Johnson[2]
[1]Univ of California San Diego, La Jolla, CA, USA, [2]Boston Coll, Chestnut Hill, MA, USA

Background: The target of antibodies is the viral Envelope glycoprotein (Env). SIV env sequence variation arising from evasion of antibody is well known. However, the impact of antibody escape Env adaptations on viral fitness, or relative replication capacity (RRC), of SIV is poorly defined. To investigate the impact of escape mutations on inherent replicative capacity, we developed a probe-free, multiplex fitness assay based on deep-sequencing technology, which we call FITSEQ.
Methods: To measure RRC, we tested individual Env substitutions and deletions using a deep-sequencing-based viral competition assay, described here as FITseq. These changes were either reported previously or identified in a deep-sequencing longitudinal analysis of SIV env sequences isolated from macaques during early SIV infection. RRC of each mutant was measured relative to SIVmac239 in two immortalized rhesus (Rh) T-cell lines. Viral RNA isolated from supernatants was subjected to Illumina (MiSeq) sequencing and assembled to the SIVmac239 reference genome (M33262), the wild type (WT) strain. The frequency of mutant reads, relative to WT, was plotted over time and linear regression analysis was used to determine the slope of the line as a direct measure of the RRC. An F-test was used to determine whether the slope of the line was significantly different than zero for each mutant.
Results: 5 of 5 substitutions in V1 (left panel) and 2 of 4 substitutions in V4 incurred no viral fitness costs in either T-cell line (middle panel). V4 loop change P421Q incurred a minimal, but significant, reduction in RRC in Rh 221 cells ($p=0.001$) while P421S resulted in a reduced RRC in both cell lines (Rh 221: $p<0.05$, Rh 444: $p<0.05$) (middle panel). Of the two V4 loop deletion mutants tested, a four amino acid deletion (Δ423-EQHK-426; ΔV1) had no effect on RRC in either cell line (right panel). An eight amino acid deletion in V4 (Δ418-NQKPKEQH-425; ΔV2) had RRC values of -0.292 and -0.463 in the Rh 221 and 444 cell lines, respectively, with the reduction in RRC reaching significance in the Rh 444 cell line only ($p<0.05$) (right panel).
Conclusion: The observation that several variable loop changes, including antibody escape adaptations, had little to no effect on viral fitness suggests SIV Env evolves along specific sequence pathways that confer escape to antibody without hindering viral replicative fitness. Further, FITseq provides a novel high-resolution and high-throughput approach towards investigation of viral fitness.

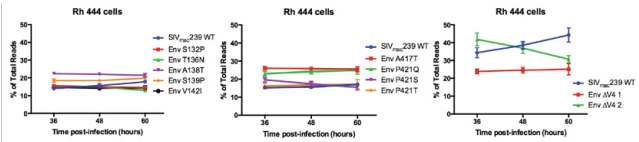


Table 1. The relative replication capacity of $SIV_{mac}239$ single point substitutions and in-frame deletions.

		Rhesus 444 cells		
Mutation	Region	RRC	R^2	p-value
S132P	V1 loop	-0.040	0.063	0.432
T136N	V1 loop	-0.083	0.269	0.084
A138T	V1 loop	-0.036	0.051	0.482
S139P	V1 loop	0.056	0.086	0.380
V142I	V1 loop	-0.011	0.005	0.830
A417T	V4 loop	-0.023	0.015	0.704
P421Q	V4 loop	0.078	0.064	0.427
P421S	V4 loop	-0.173	0.349	**0.043**
P421T	V4 loop	0.045	0.014	0.711
ΔV4 1	V4 loop	0.050	0.016	0.692
ΔV4 2	V4 loop	-0.463	0.434	**0.020**

The RRC of each mutant was calculated by linear regression analysis of mean read-frequency values. The R^2 value of each line and the p-value of a F-test is indicated. Significant p-values (< 0.05) are reported in bold.

179 SIV ESCAPE FROM A VACCINE TARGETING CLEAVAGE SITES IS ASSOCIATED WITH A FITNESS LOSS

So-Yon Lim[1], David Tang[2], David La[2], Shaun Tyler[2], Ben Liang[2], Francis Plummer[2], Ma Luo[2], James Whitney[1]
[1]Beth Israel Deaconess Med Cntr, Boston, MA, USA, [2]Natl MicroBio Lab, Winnipeg, Canada

Background: The classical approach to vaccine development against HIV has shown only limited efficacy in dealing with viral antigenic diversity. The present study was initiated to explore the efficacy of a novel HIV vaccine candidate targeting the highly conserved protease cleavage sites (PCS) in a cynomolgus macaque-SIV-challenge model. In that study, PCS specific antibody and T cell responses correlated with reduced acquisition and disease progression after SIVmac239 challenge.
Methods: We sequenced SIV populations isolated after challenge from vaccinees (n=12) immunized with a VSV vector expressing a 20-amino acid peptides overlapping each of the SIVmac239 12 PCS regions, then boosted intra-nasally with nanopackaged peptides, or from control animals that received sham inoculations (n=5). Unique mutations were identified in vaccinees and associations were analyzed between the immune driven viral mutations surrounding the PCS and alterations in viral load and CD4 count. To evaluate whether the vaccine-elicited mutations were detrimental to the virus, we produced 11 transfection-derived viral stocks harboring each PCS mutation alone or in combination. Each of these full-length mutant viral stocks was evaluated for viral p27-CA content, SIV RNA levels, replication rate and proteolytic processing of Pr55Gag.
Results: Vaccinees showed significantly higher frequencies of mutations in both PCS2 (p27/p2) and PCS12 (Nef) regions that correlated with reduced viremia post-challenge. All recombinant mutant clones containing only PCS2 preparations were impaired. Virus preparations of these mutants contained significantly reduced viral RNA levels and p27-CA content. These mutants also displayed impaired proteolyitic Gag processing. All PCS2 mutant clones were significantly impaired in their ability to replicate in CEMx174 cells. Interestingly, recombinant virus harboring only PCS12 mutations replicated at comparable rates to wild type SIV. Importantly, we observed compensation of the defects incurred by PCS2 by the addition of the PCS12 mutation. This compensating PCS12 mutation restored viral replication to PCS2 mutants, compared to those mutants harboring mutation in PCS2 region alone.
Conclusion: These results show that focused immune responses targeting the PCS region result in mutations surrounding the protease cleavage region, impair the replication ability of virus and correlate significantly with reduction in viral load, and the maintenance of CD4+ T cells in vivo.

180 MUTATIONS IN HIV-1 ENV RESCUE REPLICATION DEFECTS DESPITE POOR CELL-FREE INFECTIVITY

Rachel Van Duyne, Lillian Kuo, Ken Fujii, Eric O. Freed
NCI, Frederick, MD, USA

Background: The p6 domain of HIV-1 Gag contains a YPXnL motif, a "late" domain, which promotes the release of virions through a direct interaction with the ESCRT-associated protein Alix. We previously demonstrated a functional role for the binding between Gag p6 and Alix in HIV-1 particle production and replication by introducing mutations in the YPXnL motif. The most striking defect observed was a severe delay in virus replication. The goal of this study was to further characterize the role of Alix in HIV-1 replication by identifying compensatory mutations that correct the original replication defect.

Methods: To ascertain the nature of the replication defects, we passaged replication-defective Alix-binding site mutant viruses and selected for viral isolates containing second-site mutations with near-wild-type replication kinetics.
Results: Sequencing of the viral revertants revealed loss-of-function mutations in Vpu and novel mutations in Env. Several second-site mutations conferred full rescue of the original replication-defective Gag mutants in Jurkat T-cells; interestingly, however, these mutants were highly defective for cell-free, single-cycle infectivity. We demonstrate that the Env compensatory mutants alone replicate with wild-type or faster kinetics in Jurkat T-cells; however, they exhibit severe defects in cell-free, single-cycle infectivity. We show that the Env compensatory mutations do not affect Env expression, incorporation, or virus release efficiency. The mutations can rescue a non-budding related replication defect, suggesting that they provide a global rescue of viral fitness in the context of cell-cell transmission. This effect was cell-type dependent, as replication kinetics of the Env compensatory mutants in another T-cell line, CEM 12D7, correlate with the defects in single-cycle infectivity. Additionally, replication kinetics and infectivity of the Env mutants in PBMCs exhibit the same phenotype as in Jurkat T-cells, suggesting a physiological relevance for the mechanism of rescue observed with these Env mutants.
Conclusion: While the Env mutations under study here are defective for cell-free transmission, our data suggest that they rescue the replication-defective mutants by enhancing cell-to-cell viral transmission. Cell-to-cell HIV-1 transmission occurs more efficiently and rapidly than infection by cell-free viruses, supporting the relevance of this mode of viral dissemination. These results provide insights into the role of Env in mediating HIV-1 cell-cell transfer.

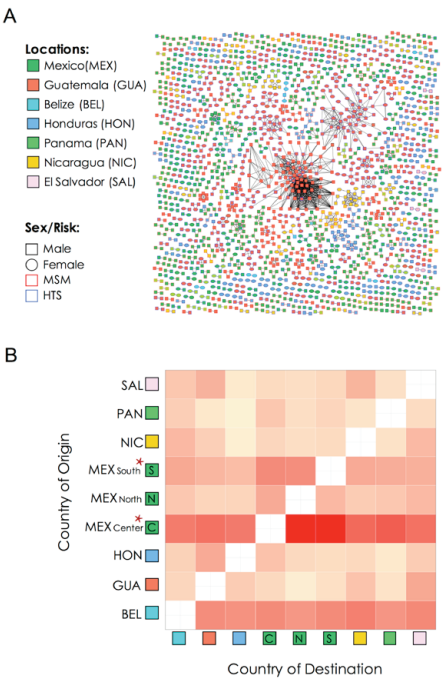
181LB RESISTANCE TO TYPE I INTERFERONS IS A MAJOR DETERMINANT OF HIV-1 TRANSMISSION FITNESS

Shilpa S. Iyer[1], Frederic Bibollet-Ruche[1], Scott Sherill-Mix[1], Gerald H. Learn[1], Lindsey J. Plenderleith[2], Andrew G. Smith[1], Ronnie M. Russell[1], Paul M. Sharp[2], Persephone Borrow[3], Beatrice H. Hahn[1]
[1]Univ of Pennsylvania, Philadelphia, PA, USA, [2]Univ of Edinburgh, Edinburgh, UK, [3]Univ of Oxford, Oxford, UK
Background: Sexual transmission of HIV-1 is an inefficient process, with only one or few variants of the donor quasispecies establishing the new infection. A critical, and as yet unresolved, question is whether the mucosal bottleneck selects for viruses with increased transmission fitness. Here, we characterized 300 limiting dilution-derived virus isolates from the plasma, and in some instances genital secretions, of eight HIV-1 donor and recipient pairs.
Methods: Plasma from chronically infected donors and acute recipients were endpoint diluted and incubated with activated CD4+T-cells both in the presence or absence of IFNα2 and IFNβ. For each virus isolate, particle Env content, infectivity, replicative capacity, IFNα2 and IFNβ IC50, residual replication at the maximal IFN dose (Vres) and particle release were determined.
Results: 300 limiting dilution-derived virus isolates were phenotypically characterized. Although there were no differences in the amount of virion-associated envelope glycoprotein, recipient isolates were on average 3-fold more infectious (P=0.0001), replicated to 1.4-fold higher titers (P=0.004), were released from infected cells 4.2-fold more efficiently (P<0.00001), and were significantly more resistant to type I interferons (IFNs) than the corresponding donor isolates. Remarkably, transmitted viruses exhibited 7.8-fold higher IFNα2 (P<0.00001) and 39-fold higher IFNβ (P<0.00001) half-maximal inhibitory concentrations (IC50) than did donor isolates, and their odds of replicating in CD4+ T cells at the highest IFNα2 and IFNβ doses were 35-fold (P<0.00001) and 250-fold (P<0.00001) greater, respectively. Interestingly, pretreatment of CD4+ T cells with IFNβ, but not IFNα2, selected donor plasma isolates that exhibited a transmitted virus-like phenotype, and such viruses were also detected in the donor genital tract. Conclusions. These data indicate that transmitted viruses are phenotypically distinct, and selected for their ability to replicate and spread efficiently in the face of a potent innate immune response.In particular, they are distinguished by increased IFN resistance, particularly to IFNβ.

182 IDENTIFICATION OF MAJOR ROUTES OF HIV TRANSMISSION THROUGHOUT MESOAMERICA

Antoine Chaillon[1], Joel O. Wertheim[1], Santiago Avila-Rios[2], Ann M. Dennis[3], Claudia García-Morales[2], Carlos Mejía-Villatoro[4], Elsa Y. Palou[5], Gustavo Reyes-Terán[6], Sanjay R. Mehta[1], for the Mesoamerican Project Group
[1]Univ of California, San Diego, San Diego, CA, USA, [2]Natl Inst of Respiratory Diseases, Mexico City, Mexico, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]Roosevelt Hosp, Guatemala City, Guatemala, [5]Hosp Escuela Univ, Tegucigalpa, Honduras, [6]Rsr Cntr in Infectious Diseases, Mexico City, Mexico
Background: Central America has some of the highest HIV infection rates in the hemisphere. The association between transportation corridors, trade, migration and HIV transmission has been well-documented in other settings. Here, using molecular epidemiologic techniques, we inferred putative clustering of HIV infected individuals sampled from across Mesoamerica, and estimated patterns of viral migration.
Methods: 6,092 HIV-1 subtype B partial pol sequences sampled from unique individuals from Mexico (40.7%), Guatemala (24.4%), Honduras (19%), Panama (8.2%), Nicaragua (5.5%), Belize (1.4%) and El Salvador (0.7%) between 2011-2016 were included. Phylogenetic and genetic network analyses were performed to infer putative relationships between HIV sequences. The demographic and geographic associations with clustering were analyzed and plotted using ArcGIS v.10.1 (ESRI, Redlands, CA). Viral migration patterns were inferred using the Slatkin-Maddison approach on 100 iterations of random subsets of equal number of sequences per location. Time to the most common recent ancestor (tMRCA) of the largest clusters were inferred with a Bayesian approach using the BEAST software package.
Results: A total of 1,959/6,092 (22.2%) of sequences demonstrated putative linkage with at least one other sequence, forming 682 transmission clusters, [range: 2-89 individuals]. Clustering individuals were significantly more likely to be younger (median age 30 vs 33 years, p<0.01) and men who have sex with men (38.7% vs 30.4%, p<0.01). Sequences from Guatemala (p<0.01) and Nicaragua (p=0.02) were significantly more likely to cluster. Of the 682 clusters, 34 (5%) included sequences from multiple countries with commonly observed linkages between Mexican and Honduran sequences (Fig.1). Eight of the 682 clusters included more than 10 individuals. These included two clusters with individuals exclusively from Guatemala, comprised of 52 and 89 individuals with a tMRCA of 1993 and 2004 respectively. Viral migration analyses showed that the Central and Southern regions of Mexico and Belize were the major source of HIV throughout the region (p<0.01). We also found evidence of significant major routes of viral migration between regions within Mexico.
Conclusion: International clusters were infrequent, suggesting moderate intermix between HIV epidemics of the different Mesoamerican countries. Nevertheless, we observed important sources of transnational HIV spread in the region, including Southern and Central Mexico, and Belize.

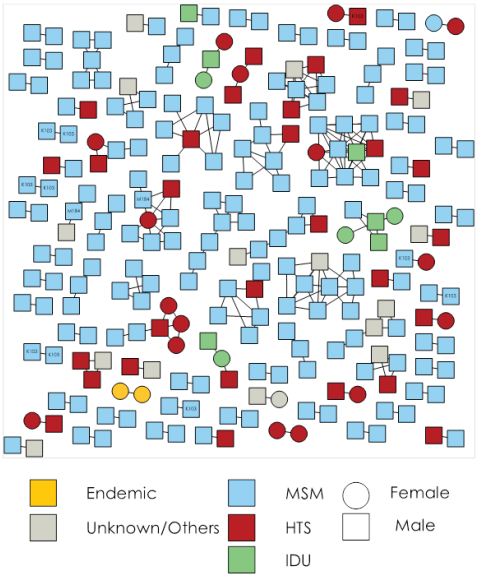
Figure. The Mesoamerican HIV Epidemics and Viral Migration between 2011-2016. A. HIV Transmission Network. All edges represent a genetic distance of ≤1.5% separating nodes. Color indicates the country of sampling; shape denotes gender (ellipse: female; square: male). **B.** Viral Migration matrix-An increase in redness represents a stronger migratory signal. Red asterisk indicates significant major sources of viral migration. Viral migration patterns were inferred using the Slatkin-Maddison approach on 100 iteration of random subsets of equal number of sequences per location.



183 REVEALING THE MOLECULAR EPIDEMIOLOGY OF THE COLOGNE, GERMANY, HIV EPIDEMIC

Melanie Stecher[1], **Martin Hoenigl**[2], Joerg Janne Vehreschild[1], Clara Lehmann[3], Gerd Fätkenheuer[3], Rolf Kaiser[1], Sanjay R. Mehta[2], Antoine Chaillon[2]
[1]Univ of Cologne, Cologne, Germany, [2]Univ of California San Diego, San Diego, CA, USA, [3]Cologne Univ Hosp, Cologne, Germany

Background: By inferring potential transmission links between risk groups, demographic sub-populations, and geography, one may better understand the drivers of spread locally, and the links between epidemics outside the region. This study focused on the HIV epidemic in Cologne, the city with the highest rate of new HIV infections in Germany.
Methods: Phylogenetic and network analyses were performed to infer putative relationships between HIV-1 partial pol sequences from unique individuals receiving care at the University Hospital of Cologne, Germany. We applied a computationally efficient network-based approach to analyze relationships between all publicly available HIV sequences found in the Los Alamos National Laboratory HIV Sequence database. We also screened all sequences from Cologne for drug resistance mutations using the Calibrated population resistance tool.
Results: The sampled population was predominantly male (80%). The most important risk factor for HIV infection (54.8% of the study population) was men reporting sex with men (MSM, 54.8%), while only 3.6% reported injection drug use as their main risk factor. 248/1,507 (16.5%) sequences linked with at least one other sequence, forming 83 transmission clusters, ranging in size from 2 to 10 sequences (Figure). Clustering individuals were significantly more likely to be younger (median age 36 vs 40, p<0.001), men (90.2% vs 78.4%, p<0.001), reporting MSM contact as main risk factor (70.6% vs 51.7%, p<.001). Drug resistance screening showed that 24.4% and 26.6% of sequences harbored at least one Nucleoside or Non-Nucleoside Reverse Transcriptase Inhibitors (NRTI/NNRTI) mutation respectively. Among clustering sequences, we found 10 sequences with K103N mutations (90% from MSM), 6 of them shared by linked sequences. By combining local data with 119,222 publicly available HIV polymerase sequences, we found a total of 78 clusters (91% subtype B) that included both sequences from Cologne and other regions in Germany (64 clusters, 82%) or predominantly European Countries.
Conclusion: In this analysis of the HIV-1 epidemic in Cologne, the city with the highest HIV incidence in Germany, we found multiple links between this epidemic and those across Germany and around the world. These results highlight the pitfalls of focusing prevention efforts and monitoring on specific risk groups or specific locales, and not taking into consideration the overall HIV epidemic.



184 STRUCTURE OF HIV-1C TRANSMISSION NETWORK IN SOUTHERN BOTSWANA, 2016

Vlad Novitsky[1], Sikhulile Moyo[2], Melissa Zahralban-Steele[1], Baitshepi Mokaleng[2], Dorcas Maruapula[2], Mary F. McLane[1], Kathleen Wirth[1], Lisa A. Mills[3], Simani Gaseitsiwe[2], Max Essex[1]
[1]Harvard Univ, Boston, MA, USA, [2]Botswana Harvard AIDs Rsr Inst Partnership, Gaborone, Botswana, [3]CDC Botswana, Gaborone, Botswana

Background: The HIV epidemic in Southern Africa is caused by multiple circulating lineages of HIV-1C. The transmission dynamics of the HIV-1C epidemic are still poorly understood.
Methods: The HIV-1C epidemic was broken down into phylogenetically distinct viral lineages using 1,793 near full-length HIV-1C genome sequences. A total of 1,349 near full-length HIV-1C genome sequences included 684 from 4 large Botswana communities-Gaborone, Mochudi, Molepolole and Lobatse - and 665 sequences from 15 small communities, primarily in the southern region. Overall, 94% of Botswana sequences (n=1,269) originated from the southern region. The circulating HIV-1C lineages were analyzed by gender and age distributions, HIV-1 RNA levels and proportion of individuals on ART.
Results: The proportion of Botswana sequences in clusters was 54% (95% CI 51.3–56.7%). Cluster analysis was limited to 189 clusters with predominantly (75%) Botswana sequences (including 5 mixed clusters) with 2 to 49 sequences per cluster. Cluster composition analysis revealed that 24% (95% CI 18–31%) of HIV-1C lineages were found only in small communities, 27% (95% CI 21–34%) only in large communities, and 49% (95% CI 41–56%) in both small and large communities. The median (IQR) number of circulating viral lineages per community was 15 (7–25) in small and 44 (40–57) in large communities (p<0.01). Within circulating HIV-1C lineages, females (median 33 y.o.; IQR 28–39 y.o.) were approximately nine years younger than males (median 42 y.o.; IQR 35–48 y.o.; p<0.0001). Recently infected individuals (n=14) were found in 12 of 189 clusters. Clusters with recent HIV infections had higher HIV-1 RNA (median (IQR) 4.4 (4.1–4.6) vs. 3.7 (2.7–4.6) log10 copies/mL; p<0.05); had lower proportions of individuals on ART (p<0.005); and tended to be younger (p<0.1). No differences between clustered (n=728) and non-clustered (n=621) Botswana individuals were found by age and gender distributions, levels of HIV-1 RNA, or proportion of individuals on ART (p-values n/s).
Conclusion: The analysis revealed the structure of HIV transmission networks in southern Botswana communities using near full-length HIV-1C genome sequences. About half of circulating viral lineages were unique for either small or large communities. Within circulating HIV-1C lineages, females were about 9 years younger than males. Clusters with recent infections had higher HIV-1 RNA loads and lower proportions of individuals on ART, and seemed to be younger.

185 PHYLOGENETICS OF A RECENT HIV OUTBREAK AMONG PEOPLE WHO INJECT DRUGS IN SCOTLAND

Manon Ragonnet-Cronin[1], Celia Jackson[2], Amanda Bradley-Stewart[2], Celia Aitken[2], Andrew McAuley[3], Norah Palmateer[3], David Goldberg[3], Catriona Milosevic[2], Andrew Leigh Brown[1]

[1]Univ of Edinburgh, Edinburgh, UK, [2]NHS Greater Glasgow and Clyde, Glasgow, UK, [3]Hlth Protection Scotland, Glasgow, UK

Background: Harm reduction interventions have dramatically reduced HIV incidence among people who inject drugs (PWID). In Glasgow, <10 infections/year have been diagnosed since the mid-90s. However in 2015 a sharp rise in HIV diagnoses was noted among PWID: all were subtype C with two identical drug resistant mutations and some displayed low avidity, suggesting the infections were linked and recently acquired. The outbreak follows reports of recent PWID outbreaks in Greece, Romania, Ireland, and the USA.

Methods: We collected pol sequences from all subtype C HIV diagnoses from Glasgow since 2010 (n=228). In parallel, we obtained sequences from the UK HIV Drug Resistance Database (UKRDB) which contains sequences from all UK patients diagnosed until 2013. We blasted the Glasgow sequences against the UKRDB and the Los Alamos National Laboratory (LANL) database and selected the ten closest matches from either database to each Glasgow sequence. A maximum likelihood phylogeny was reconstructed comprising 228 Glasgow sequences, 762 UKRDB and 1144 LANL. The outbreak cluster was identified and extracted from the tree and time-resolved in BEAST.

Results: A tight cluster of 105 sequences stood out in the ML phylogeny. All sequences originated from Glasgow and contained E138A and V179E. Mean genetic distance was <1% with multiple sets of identical sequences from different patients. Short branches in the BEAST phylogeny indicated rapid transmission (Figure 1). The outbreak subdivided into three subclusters, two of which displayed rapid and recent transmission events. The common ancestor of the outbreak dated back to 2004 and the oldest sequence represented a female PWID diagnosed in 2005. Five patients were diagnosed in 2008-2009 and all others between 2010 and 2016. We extracted node dates to estimate the timing of transmissions, demonstrating an acceleration of the transmission rate through time, culminating between 2013 and 2015 when 63 transmissions took place. All patients reported injecting drugs, and the majority were men (59/94, 63%), suggesting that infections have been transmitted primarily through injection rather than sexually. While disclosure of needle sharing was variable, the majority (88/90, 98%) were co-infected with Hepatitis C.

Conclusion: The strain is limited to Glasgow but transmission is ongoing. We are currently investigating associations between the outbreak and epidemiological parameters including homelessness.

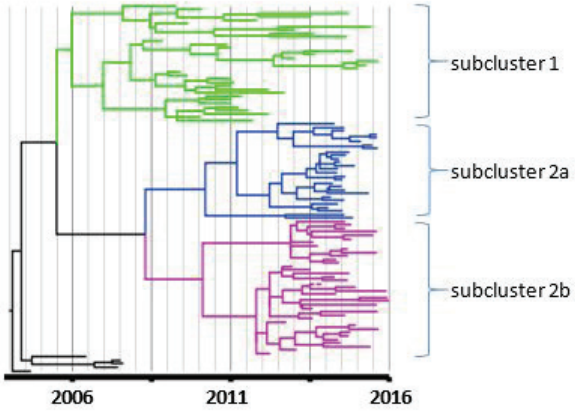


Figure 1: Time-resolved phylogeny of Glasgow outbreak among people who inject drugs.

186 NONDISCLOSED MSM LINK TOGETHER IN HIV TRANSMISSION NETWORKS

Manon Ragonnet-Cronin[1], Stéphane Hué[2], Anna Tostevin[3], Anton Pozniak[4], Tracy Fawcett[5], Alison E. Brown[6], David Dunn[3], Andrew Leigh Brown[1], for the UK HIV Drug Resistance Database

[1]Univ of Edinburgh, Edinburgh, UK, [2]London Sch of Hygiene & Tropical Med, London, UK, [3]Univ Coll London, London, UK, [4]Chelsea and Westminster NHS Fndn Trust, London, UK, [5]Leeds Teaching Hosps NHS Trust, Leeds, UK, [6]Pub Hlth England, London, UK

Background: Phylogenetic analysis has shown that some HIV positive men who self-report as heterosexual have viruses that cluster only with men who have sex with men (MSM). We characterised this group.

Methods: HIV pol sequences were obtained from the UK HIV Drug Resistance Database. To these were added the ten publicly available sequences closest to each UK sequence. Clusters were selected in maximum likelihood phylogenies for analysis in BEAST. Networks were then created by linking together nodes if sequences shared a common ancestor within the previous 5 years in time-resolved phylogenies (Figure 1). Potential nondisclosed MSM (pnMSM) were identified as self-reported heterosexual men who clustered only with men. We compared the centrality (a measure of connectedness and importance) of pnMSM and MSM and calculated assortativity (the propensity for nodes sharing attributes to link) by self-reported risk group. Finally, we evaluated whether pnMSM linked MSM and heterosexuals.

Results: In total, 49772 subtype A1, B and C pol sequences were analysed. Of these, 14405 linked within 5 years and were represented in the network, including 38452 MSM, 1743 female HET and 1341 male HET. We identified 223 network clusters comprising 955 MSM and 249 pnMSM. pnMSM represented 18.6% of linked self-reported heterosexual men, more than twice the proportion of women clustering with MSM (131/1743; 7.5%). pnMSM were more likely to be infected with subtype B than heterosexual men ($p<0.0001$) and more likely to be Black-African than both MSM and heterosexual men ($p<0.0001$). pnMSM were less likely to be diagnosed with a recent infection than MSM (12.5% vs 74.9%, $p<0.0001$) and slightly older ($p<0.05$). Betweenness centrality was lower for pnMSM than for MSM (2.37 vs 4.11, $p<0.005$), indicating that they were in peripheral positions in MSM clusters. Assortativity by risk group was higher than expected (-0.124 vs -0.196, $p<0.05$) indicating that pnMSM linked to each other. We found that self-reported male heterosexuals were much more likely than female heterosexuals to link MSM and heterosexuals (Fisher's exact test; $p<0.0005$; OR 2.24).

Conclusion: We have shown that pnMSM do not behave like MSM or male heterosexuals. This has implications both in understanding HIV epidemiology in the UK and for prevention. pnMSM appear to have fewer partners and to preferentially partner with other pnMSM. They are at higher risk for HIV than male heterosexuals and may put female partners at risk by linking the MSM and heterosexual epidemics.

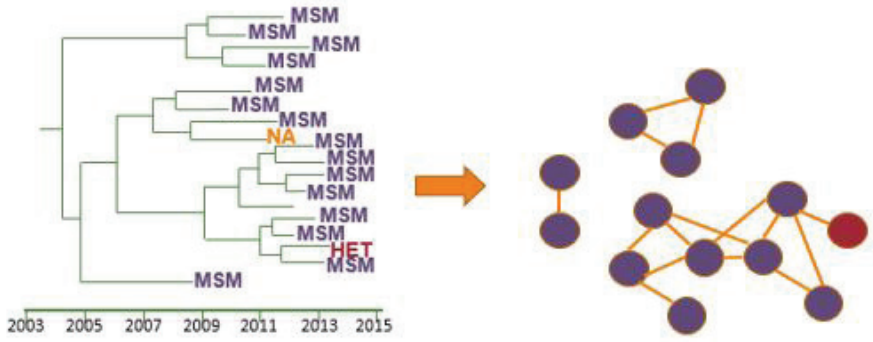


Figure 1: From time-resolved phylogeny to network.

187 ESTIMATING THE EFFECT OF COMPLETENESS OF HIV SEQUENCING DATA ON TRANSMISSION NETWORKS

Sharoda Dasgupta[1], Anne Marie France[1], Mary-Grace Brandt[2], M Cheryl B. Ocfemia[1], Tianchi Zhang[1], Nivedha Panneer[1], Angela Hernandez[1], Alexandra Oster[1]
[1]CDC, Atlanta, GA, USA, [2]Michigan Dept of Community Hlth, Detroit, MI, USA

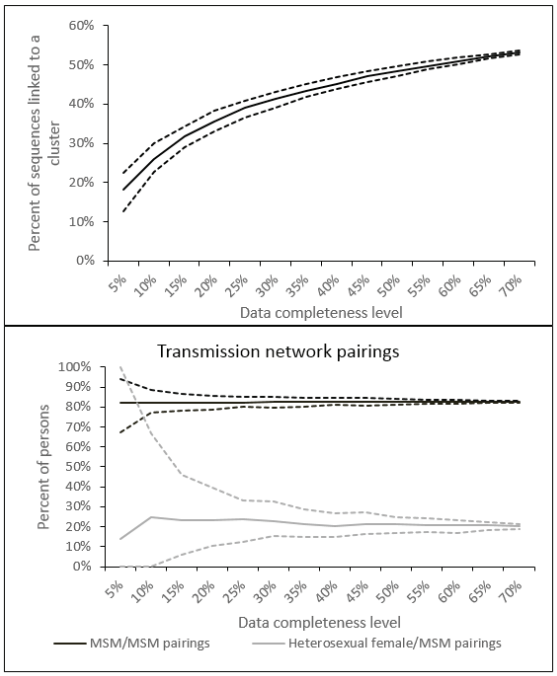
Background: Molecular HIV surveillance data can be used to understand transmission patterns. Completeness of HIV sequencing data may influence findings. We examined how completeness of reporting HIV sequences affects transmission patterns.

Methods: We analyzed National HIV Surveillance System data for the state with highest sequence completeness for diagnoses during 2008–2014 (Michigan, 73%). We took 100 random samples of the dataset with replacement at each pre-determined level of completeness, in increments of 5%, from 5%–70%. We aligned partial HIV-1 pol sequences and conducted pairwise comparisons of sequences to identify pairs with a genetic distance of ≤1.5%. We described transmission network characteristics, such as the number of clusters and links and mixing by race/ethnicity and transmission category. We estimated the median and 5% and 95% quantiles for these characteristics at each completeness level, and presented results for 70% (high) and 5% (low) completeness levels.

Results: Of 4,040 sequences reported, 2,458 were from blacks/African Americans (blacks), 210 from Hispanics/Latinos (Hispanics), 2,794 from men who have sex with men (MSM), and 619 from heterosexual women. The percent of sequences linked to ≥1 other sequence decreased from a median of 54% (53–54%) at high completeness to 18% (13–22%) at low completeness. The number of clusters decreased from a median of 400 (393–406) at high to 18 (13–23) at low completeness, and median number of links was 8267 (8041–8434) at high and 43 (24–64) at low completeness. Assortative pairing among blacks was consistent (median 86–87%) regardless of completeness, with narrower ranges of estimates with higher completeness. Among Hispanics, Hispanic/Hispanic pairings ranged from a median of 17% (15–19%) at high to 0% (0–2%) at low completeness. Pairings of MSM with other MSM remained constant (median 82–83%), with narrower ranges of estimates with higher completeness. The proportion of heterosexual women linked to MSM was 20% (19–21%) at high and 14% (0–100%) at low completeness.

Conclusion: Detection of clusters and links was sensitive to data completeness. Inferences about mixing between groups remained robust at lower completeness for larger populations, but was sensitive to change with smaller populations (Hispanics and heterosexual women). The results suggest that, with sufficient numbers of observations, inferences about transmission patterns are informative even with low coverage, though the number and size of clusters may be underestimated.

Figure. The median and quantile ranges (5%, 95%) for the percent of sequences linked to a cluster (top) and percent of pairings within and between selected transmission network groups (bottom), by level of data completeness.



188 TEMPORAL CHANGES IN HIV TRANSMISSION PATTERNS AMONG YOUNG MEN WHO HAVE SEX WITH MEN

Nivedha Panneer[1], Y. O. Whiteside[2], Anne Marie France[2], Joel O. Wertheim[3], Alexandra Oster[2]
[1]Oak Ridge Inst for Sci and Educ, Atlanta, GA, USA, [2]CDC, Atlanta, GA, USA, [3]Univ of California San Diego, San Diego, CA, USA

Background: In the United States, young men who have sex with men (YMSM), particularly black/African American (black) or Hispanic/Latino YMSM, bear a disproportionate burden of HIV infections. HIV transmission among YMSM has been found to be highly assortative by race but disassortative by age. We examined temporal trends in transmission for subgroups of YMSM (MSM aged 13-24 years).
Methods: We analyzed HIV-1 pol sequences reported to the National HIV Surveillance System for all MSM aged ≥13 years who had HIV diagnosed during 2006–2013 and were from 26 jurisdictions. We identified potential transmission pairs at a genetic distance threshold of ≤1.5% and constructed transmission networks using HIV-TRACE. For YMSM, we determined race/ethnicity and age of potential transmission partners. Assuming HIV was acquired from only one person, we assigned partners of YMSM with >1 transmission partner a weight equal to the inverse of the number of partners. We constructed two multivariable logistic regression models and calculated prevalence ratios (PRs) and 95% confidence intervals (CIs) to examine the change from 2006–2009 to 2010–2013 in the proportion of potential transmission partners 1) of the same race/ethnicity and 2) at least 5 years older, for each subgroup of YMSM, adjusting for geography and transmission category.
Results: Of 7,867 YMSM with a potential transmission partner, 67% had partners of the same race/ethnicity and 36% had partners >5 years older. Transmission among blacks remained highly assortative by race, with approximately 80% of blacks linking to other blacks. Assortativity by race/ethnicity among Hispanics/Latinos increased over time, with substantial increases seen in MSM aged 13-19 years (from 46% to 59%, PR=1.34, CI=1.10–1.64). Although a higher proportion of white YMSM had older transmission partners (48%) compared with blacks (30%) and Hispanics/Latinos (42%), the proportion of older transmission partners increased over time for all racial/ethnic groups, with the most substantial increases among blacks and Hispanics/Latinos aged 13-19 years (black: PR=1.42, CI=1.23–1.65; Hispanic/Latino: PR=1.31, CI=1.05–1.64).
Conclusion: These data provide evidence for continued transmission among networks of black YMSM and expansion of transmission among networks of Hispanic/Latino YMSM. Additionally, YMSM are increasingly linked to older partners. Prevention programs aimed at reducing incidence among YMSM may be strengthened by also ensuring that older MSM are virally suppressed.

Estimated percentages of infections from partners of the same race and older partners among MSM aged 13-24 years, 2006-2013–26 jurisdictions

	2006-2009			2010-2013			Partner of Same Race* (2010-2013 vs 2006-2009)	Older Partner*^ (2010-2013 vs 2006-2009)
	YMSM with a partner	YMSM with a partner of the same race	YMSM with an older partner^	YMSM with a partner	YMSM with a partner of the same race	YMSM with an older partner^		
Race/Ethnicity, by age	N	Row %	Row %	N	Row %	Row %	PR and 95% CI	PR and 95% CI
Total	2843	68%	32%	5024	67%	39%	--	--
Black								
13-19	576	80%	31%	684	82%	45%	1.04 (0.99, 1.09)	**1.42 (1.23, 1.65)**
20-24	1088	77%	23%	2011	77%	28%	1.02 (0.98, 1.05)	**1.24 (1.09, 1.41)**
Hispanic/Latino								
13-19	138	46%	41%	303	59%	54%	**1.34 (1.10, 1.64)**	**1.31 (1.05, 1.64)**
20-24	545	50%	36%	1185	53%	42%	**1.43 (1.01, 2.04)**	1.32 (0.92, 1.89)
White								
13-19	70	59%	53%	103	50%	64%	0.87 (0.67, 1.14)	1.17 (0.91, 1.51)
20-24	426	59%	42%	738	54%	49%	0.93 (0.84, 1.04)	**1.17 (1.03, 1.34)**

*Adjusted for U.S. census region, population of area of residence, and transmission category.
^A partner was considered an older partner if he was older by more than 5 years.

189 PHYLODYNAMIC ANALYSIS AIDS PARTNER SERVICES BY IDENTIFYING UNREPORTED TRANSMISSION

Ellsworth Campbell[1], Anupama Shankar[1], Emily Westheimer[2], Cynthia L. Gay[3], Stephanie E. Cohen[4], Jin-Fen Li[1], Jeffrey A. Johnson[1], Philip J. Peters[1], William M. Switzer[1]
[1]CDC, Atlanta, GA, USA, [2]New York City DHMH, New York, NY, USA, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]San Francisco Dept of Pub Hlth, San Francisco, CA, USA

Background: HIV transmission links can be difficult to detect via routine partner services investigations. We used phylodynamic techniques to infer transmission links between participants of a prospective study of acute HIV infection (AHI) conducted in North Carolina, New York City, and San Francisco from 2011-2013.
Methods: Participants newly diagnosed with either acute or established HIV infection were offered partner notification services and contact information was elicited for sex partners (epi links). Where HIV-1 polymerase (pol) sequences were available, transmission linkages were inferred when the genetic distance between pol sequences was <1.5%. Genetic distances (d) were calculated using a nucleotide substitution model after pairwise alignment to the HXB2 reference sequence. Drug resistance (DR) was inferred from pol sequences using SIERRA.
Results: Among the 813 newly diagnosed participants (103 with acute and 710 with established HIV infection) with a pol sequence available, 457 sex partners were reported of whom 35 (7.7%) were other participants with an available pol sequence (epi links). Among these 35 HIV epi links, 23 (65.7%) were genetically supported and 12 (34.3%) were not genetically supported. Only five epi links were between participants with acute infection and none were genetically supported. In contrast, phylodynamic inference identified 102 unreported putative transmission links including 12 links between persons with acute infection ($p<0.001$).The mean genetic distance between pol sequences from persons with acute HIV infection ($d=0.7\%$) was significantly lower ($p<0.001$) than that of inferred links between persons with established HIV infections ($d=0.9\%$), suggesting more recent transmission among the AHI group. Importantly, all putative transmission links between persons with acute infection were found among large clusters with > five members and all exhibited evidence of transmitted DR. Mean transmission cluster size was larger among those who reported having met sexual partners online (4.8, 95% CI [4.0-5.6]) than those that did not (3.4, 95% CI [2.8-3.4], $p<0.05$).
Conclusion: Phylodynamic inference of HIV transmission identified four times as many transmission links as partner services alone. Routinely applied, this technique can illuminate transmission patterns of public health importance not readily captured by conventional partner services investigations.

190 NEUTRALIZING ANTIBODIES IN HUMANS INFECTED WITH ZOONOTIC SIMIAN FOAMY VIRUSES

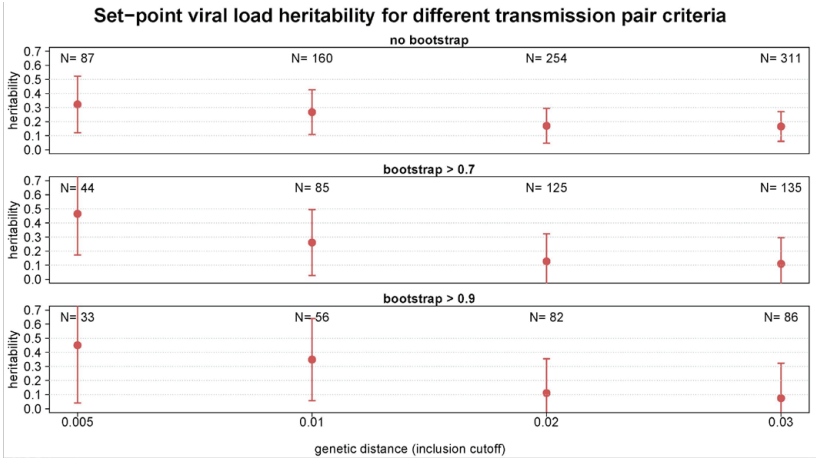
Caroline Lambert, Julie Gouzil, Léa Richard, Réjane Rua, Edouard Betsem, Antoine Gessain, **Florence Buseyne**
Inst Pasteur, Paris, France

Background: Simian foamy viruses (SFVs) are efficiently transmitted from non-human primates to humans, establishing persistent infection in the new host. Neither pathogenic effects nor human-to-human transmission have been reported, suggesting that immune control of this retrovirus is efficient. Here, we aimed at studying the humoral response. We used viral strains isolated from infected humans to study the neutralizing antibodies present in the plasma of SFV-infected people living in rural areas of South Cameroon and Gabon.

Methods: Forty-four hunters infected with a gorilla SFV were studied. Serial dilutions of their plasma were incubated with SFV strains and residual viral infectivity was quantified with an indicator cell line expressing the beta-galactosidase gene under the control of the viral LTR. Genomic DNA was extracted from the buffy coat (BC). Env fragments were amplified from BC-DNA using specific primers by nested PCR. PCR products were directly sequenced by MWG Operon (Ebersberg, Germany).
Results: Neutralizing activity of plasmas was tested against two zoonotic primary gorilla SFV strains, representative of two env genotypes circulating in Central Africa. Neutralizing activity was detected in > 90% of SFV-infected donors, and titers ranged from 1:22 to 1:14724. Two-thirds of donors recognized only the isolate from the same genotype as their own virus. One third of donors recognized the two genotypes. For half of them, env sequences from the two genotypes were amplified, demonstrating the co-infection by at least two different SFV strains. Most donors infected with a gorilla SFV neutralized chimpanzee SFV, showing the conservation of epitopes targeted by neutralizing antibodies. Patients with broader responses had higher blood viral DNA levels.
Conclusion: Gorilla SFVs transmitted to humans led to the generation of high titers of neutralizing antibodies. The high titers of neutralizing antibodies in some of them suggest that active SFV replication may occur in humans with persistent zoonotic SFV infections. This study revealed that a significant proportion of our study population was co-infected by at least two SFV strains. This result is relevant for the emergence of retroviruses in the human population.

191 ESTIMATING THE HERITABILITY OF AN HIV-1 TRAIT IN A CLINICAL SETTING

Nadine Bachmann[1], Teja Turk[1], Alex Marzel[2], Claus Kadelka[2], Thomas Klimkait[3], Vincent Aubert[4], Jürg Böni[2], Huldrych F. Günthard[2], Roger Kouyos[2]
[1]Univ Hosp Zurich, Zurich, Switzerland, [2]Univ of Zurich, Zurich, Switzerland, [3]Dept of Biomed, Basel, Switzerland, [4]Univ Hosp Lausanne, Lausanne, Switzerland
Background: Parent-offspring(PO) regression is a central tool to determine the heritability of phenotypic traits; i.e., the extent to which those traits are controlled by genetic factors. Its applicability to viral traits is unclear because the directionality of viral transmission is typically unknown and viral phylogenies are sparsely sampled. We hypothesized that PO regression is robust to these potential problems and can provide reliable estimates for the impact of viral genetics on set-point virus load. Furthermore, we test the hypothesis that heritability is not due to clustering of host-demographic factors on the viral phylogeny.
Methods: We assessed the applicability of PO regression in a realistic setting using Ornstein-Uhlenbeck simulated data on phylogenies built from 11,442 Swiss HIV Cohort Study(SHCS) partial pol sequences. The SHCS is one of the most densely sampled populations available. As approximation for parent and offspring we used transmission pairs of the phylogeny and randomly identified donor(parent) and recipient(offspring). Set-point virus load(SPVL) data was available for 3,293 patients.
Results: We found that misidentification of donor and recipient plays a minor role when measuring heritability and also showed that imperfect sampling does not influence the heritability estimated by PO regression. Our results also provided evidence that heritability is a trait of a specific population and that pairs represent non-random samples from the entire population, implying that heritability measured on pairs differs from that measured on the entire population. A mixed-effect model approach yielded the same results as PO regression but could be extended to clusters of size > 2 and allowed for the correction of confounding effects. Finally, we applied both methods to SPVL data from the SHCS and obtained heritability estimates ranging from 8% to 47% (Figure) that did not change substantially after adjusting for host-demographic factors in the mixed-effect model (±2%).
Conclusion: Our study underlines the utility of PO regression and mixed-effect models as flexible and robust tools to estimate the contribution of viral genetics to viral traits under real-life settings. Estimated heritability depends on transmission pair selection criteria - despite lower statistical power, conservative criteria should be preferred, as true heritability is reached at zero genetic distance. We find a strong effect of viral genetics on SPVL and that this effect is not confounded by host demographics.



192 NGS ANALYSIS OF HIV-1 GROUP O RT RESIDUE 181C PREVALENCE AND EVOLUTION OVER TIME

Marie Leoz[1], Myriam Vezain[2], Elodie Alessandri[1], Sophie Coutant[2], Guillemette Unal[3], Isabelle Tournier[2], Francois Simon[4], **Jean-Christophe Plantier**[1]
[1]Rouen Univ Hosp, Rouen, France, [2]Normandie Univ, Rouen, France, [3]COREVIH Haute-Normandie, Rouen, France, [4]Saint Louis Hosp, Paris, France
Background: HIV-1 group O viruses are endemic in Cameroon and found sporadically in other countries. They are subdivided into subgroups HIV-1/O-H and HIV-1/O-T. Their genetic divergence from HIV-1/M causes polymorphisms on residues associated to HIV-1/M antiretroviral resistance. In all the HIV-1, SIVcpz and SIVgor radiation, a 181Y residue is found in the Reverse Transcriptase (RT), but a Non-Nucleotide RT Inhibitors (NNRTI) resistance mutation Y181C can be naturally present in HIV-1/O, and associated to the recently emerged HIV-1/O-H subgroup. The presence of minor variants at this position, and its evolution over time was investigated.
Methods: We used Next Generation Sequencing to study the polymorphism on residue 181 and associated signature residue from the NNRTI-binding pocket in 75 NNRTI-naïve HIV-1/O patients. Evolution of residue 181 over time – with or without NNRTI – was investigated in 8 patients, as well as that of associated residues.
Results: Residue 181C was found in 40/75 NNRTI naive patients. Its association with HIV-1/O-H was confirmed ($p<0.001$). A 181C/Y mixture was found in 7 unlinked individuals. Residues at signature positions were diverse in 181Y viruses but a 28K-103K-142I-174D-178L pattern was highly conserved in 181C viruses. Evolution of residue 181 was similar to what observed in HIV-1/M for one 181Y HIV-1/O-T virus: NNRTI-associated selection of 181C, and reversion after NNRTI interruption. Three HIV-1/O-H viruses selected 181C due to NNRTIs, but conserved it several years after NNRTI interruption. Four HIV-1/O-H viruses evolved without NNRTIs (181C/Y => 181C, n=2, 181C => 181C/Y, n=2). Residues at signature positions did not evolve concomitantly when the 28K-103K-142I-174D-178L pattern was present in a first place, suggesting that this pattern was compatible with both 181C and 181Y residues.
Conclusion: Mutation 181C presence and evolution in HIV-1/O is linked to the virus genetic background. It is associated to the emergent H subgroup where it can be naturally present, or conserved after NNRTI selection, probably due to a favourable pattern on associated signature residues.

193 ANALYSIS OF NEARLY FULL-GENOME HIV-1 SEQUENCES FROM UGANDA: RESULTS FROM PANGEA_HIV

Gonzalo Yebra[1], Deogratius Ssemwanga[2], Dan Frampton[3], Brian Magambo[2], Nicholas Bbosa[2], Frederick Lyagoba[2], Rebecca N. Nsubuga[2], Pontiano Kaleebu[2], Andrew Leigh Brown[1], for the PANGEA_HIV Consortium

[1]Univ of Edinburgh, Edinburgh, UK, [2]MRC Uganda Virus Rsr Inst, Entebbe, Uganda, [3]Farr Inst of Hlth Informatics Rsr, London, UK

Background: Nearly full genome sequencing (NFGS) of HIV is increasingly available in Western countries, but its application in sub-Saharan Africa is scarce. The PANGEA_HIV project is producing HIV NFGS in African sites, including Uganda. The Ugandan epidemic features a long-term co-circulation of subtypes A1 and D, with the consequent emergence of many recombinants.

Methods: We collected 685 contemporary (2009-2014) samples from Ugandan populations (a rural cohort in Masaka, several Lake Victoria fisherfolk communities, and female sex workers from Kampala); as well as 53 historical samples taken in 1986 from AIDS patients. They were analysed using Illumina MiSeq next-generation sequencing; 609 (565 contemporary, 44 historical) yielded sequences ≥1Kb, with half of them (320, 52%) being NFGS. To identify recombinants, we adapted the SCUEAL subtyping tool for full-genome analysis. Maximum-likelihood phylogenies were built with RAxML to detect clusters using Cluster Picker. Drug-resistance mutations (DRM) and co-receptor usage were analysed using Stanford HIVdb and Geno2pheno tools, respectively.

Results: Unique recombinant forms (URF) between subtypes A1 and D accounted for 169 (29.9%) of the contemporary sequences, followed by subtypes A1 (147, 26.0%) and D (113, 20.0%). The rest belonged to other subtypes (10 C, 1 G), other URF (70, 12.4%), and recombinants showing unclassified segments (55, 9.7%), most of them due to the presence of gaps. A1/D recombinants also predominated among the historical sequences (21, 47.7%), followed by subtype A1 (10, 22.7%) and other URF (10, 22.7%). We detected 54 clusters (44 pairs, 10 triplets) among contemporary sequences, showing a clustering rate of 21.1%. Most clusters (77.8%) involved subjects from the same population only; 63.0% involved subjects from the same sampling location only. Contemporary sequences showed low DRM rates at PR+RT (3.3%) and integrase (0.5%); historical sequences showed no DRM. X4 co-receptor usage, which confers resistance to entry inhibitors, was rare (0.5%) among contemporary samples but frequent (47.4%) among historical ones, probably due to an advanced infection stage.

Conclusion: HIV recombinants dominate the Ugandan epidemics. Their prevalence analysing NFGS was higher than in earlier studies of partial sequences. We found low levels of resistance, as expected in low-income settings, and a low rate of phylogenetic clustering, with most clusters being intra-population. However, almost 40% of the clusters involved geographical mobility.

194 LTR GENETIC DIVERSITY AMONG HIV-2 ARV-NAÏVE PATIENTS IN THE ANRS CO5 HIV-2 COHORT

Quentin Le Hingrat[1], Benoit Visseaux[1], Mélanie Bertine[1], Fideline Collin[2], Florence Damond[1], Olivier Schwartz[3], Sophie Matheron[1], Diane Descamps[1], **Charlotte Charpentier**[1], for the ANRS HIV-2 CO5 Cohort

[1]Bichat Hosp, Paris, France, [2]INSERM, Bordeaux, France, [3]Inst Pasteur, Paris, France

Background: Long terminal repeat regions (LTR) include binding sites of transcription factors (TF) and are essential to HIV DNA transcription. The aim of this study was to assess associations between HIV-2 LTR genetic diversity and reservoir size.

Methods: All plasma samples of HIV-2 ARV-naïve patients included in the French ANRS HIV-2 Cohort collected with PBMC during the year 2015 were assessed. LTR sequencing was performed using Sanger technology. HIV-2 total DNA quantification was performed using a real-time PCR assay with a limit of quantification (LOQ) of 6 c/PCR. The LTR transcriptional activity was assessed using a luciferase assay on HEK293T cells transfected by LTR-luciferase plasmids.

Results: Among the 99 samples tested, LTR sequencing was successful in 65 (66%) including 27 HIV-2 group A and 38 group B, among them 8 had plasma viral load >40 c/mL. Demographic and immuno-virological characteristics were similar between group A and group B-infected patients. HIV-2 DNA was above the LOQ in 24 patients (37%) with a median of 2.04 log10c/106PBMC and was detectable below the LOQ in 39 patients (60%). The proportion of patients with a reservoir above the LOQ was significantly higher in group A than in group B (67% and 16%, respectively; $p < 0.001$). Genetic distances showed the highest variability in the U3 region of the LTR. Variability was significantly higher in group B than in group A sequences ($p<0.001$). No specific LTR mutation could be associated with the size of reservoir. However, 4 group B sequences (11%) showed a deletion in the first binding site of Sp1 TF. Interestingly, transcriptional activity of this Sp1-deleted LTR is 2-fold less than that of the group A or B references. Binding sites of the following TF: PuB2, peri-κb and NFκB were conserved among group A and group B sequences. On the contrary, the region between the PuB1 and pets TF described in group A sequences was not observed in group B sequences. Furthermore, bioinformatics analysis identified two new potential binding sites of TF: IRF in group A sequences and C/EBP in group B sequences.

Conclusion: In this first large analysis on HIV-2 LTR sequences we observed a high genetic variability in the U3 region of the LTR in which is located TF binding sites. The highest genetic variability and also the lack of some TF binding sites observed in group B sequences might be an explanation to the lowest proportion of patients with a reservoir above the LOQ observed in this group.

195 PHYLOGEOGRAPHIC STUDY OF HIV-2 GROUPS A AND B EARLY EPIDEMICS IN WESTERN AFRICA

Benoit Visseaux[1], Stéphane Hué[2], Florence Damond[3], Fideline Collin[4], Alexandre Storto[1], Genevieve Chene[4], Sophie Matheron[3], Charlotte Charpentier[3], Diane Descamps[1], for the French ANRS CO5 HIV-2 Cohort

[1]Bichat Hosp, Paris, France, [2]London Sch of Hygiene & Trop Med, London, UK, [3]Bichat–Claude Bernard Hosp, Paris, France, [4]INSERM, Bordeaux, France

Background: The early spread of HIV-2 in Western Africa has not been explored yet for group B and subtype A2 recently described using the French ANRS CO5 HIV-2 cohort datasets. In this study we performed the first phylogeographic study describing the early spreading patterns of HIV-2 subtypes A1, A2 and group B in the human population.

Methods: All publicly available HIV-2 pol sequences including both time of sampling and patient's country of birth (n=49 and 8 sequences for groups A and B, respectively) were added to 125 (group A) and 68 (group B) sequences from the ANRS cohort, sampled between 1994 and 2014. Phylogeographic reconstructions were performed under the best fitting combination of evolutionary, demographic and molecular clock models, using BEAST 1.8. The trees were assessed with maximum likelihood trees obtained using RAxML. Because of the large number of sequences sampled in France in the dataset, the patient's country of birth was used to model the geographical dispersion instead of the sampling country.

Results: The estimated time of the most common ancestors (tMRCA) of group A was 1945 [95% HPD 1935-53]. Subtype A1, mainly present in patient born Senegal, Gambia, Guinea-Bissau and Guinea, presents an early diversification in 1946 [1936-54] with two distinct epidemics in Guinea-Bissau and Senegal. Several later transmission events from Guinea-Bissau to Senegal are also observed. Subtype A2, mainly present in patients born in Ivory Coast and Mali, spreads latter than subtype A1 (1956 [1947-63]). Subtype A2 initially spreads initially in Ivory Coast and presents two introduction events in Mali in 1963 [1957-69] and 1967 [1960-74]. Group B was originally introduced in Ivory Coast in 1962 [1953-13].

Conclusion: This phylogeographic study is the first to reconstruct the early subtype A2 and group B dispersal and allows a better understanding of HIV-2 early epidemic in West Africa. These two HIV-2 clades rose at similar time but diversified latter than subtype A1. Both A2 and B clades originated in Ivory Coast, suggesting that a local historical or socio-demographic event may have triggered the dispersal of these viral strains. An early fonder effect for subtype A1 in Senegal occurred before the Guinea-Bissau independence war, suggesting that HIV-2 group A was already circulating in these countries before the war that contributed to further dispersal of HIV-2 within and outside West Africa.

196 BLIND DATING: PHYLOGENETIC DETERMINATION OF LATENT HIV SEQUENCE AGES WITHIN HOST

Bradley R. Jones[1], Joshua Horacsek[1], Jeffrey Joy[2], Zabrina Brumme[1], Art Poon[2]
[1]Simon Fraser Univ, Burnaby, British Columbia, Canada, [2]Univ of British Columbia, Vancouver, British Columbia, Canada

Background: The ability of HIV to persist within latent cellular reservoirs represents a major barrier to cure. The timing of establishment of individual viral reservoirs over the course of an infection may influence their susceptibility to elimination by immune-mediated or therapeutic approaches. However, methods to accurately estimate the age of reservoir sequences remain scarce. We propose a simple method to date suspected reservoir sequences using phylogenetically informed regression.
Methods: Our method is as follows: Taking aligned HIV sequences from a single individual sampled over multiple time points, we reconstruct a maximum-likelihood phylogeny. The location of the root in the phylogeny is determined using root-to-tip regression. Finally, the root-to-tip distances of possibly latent sequences are mapped to the optimal regression line to estimate reservoir establishment dates. To validate our method, we simulated HIV sequence evolution under a standard model and reconstructed phylogenies from these data by maximum likelihood. Latency was simulated by shortening the branch lengths of up to 50% of the tips in the tree. We employed this same approach to validate the method on HIV RNA sequences, which provided a more realistic assessment of sources of error than direct simulation.
Results: We were successfully able to extract HIV reservoir ages from simulated data. When this method was applied to HIV DNA sequences in phylogenies containing dated HIV RNA sequences, we observed that the predicted dates significantly preceded dates of sampling, which was consistent with latency.
Conclusion: Our results provide evidence that the date that a HIV lineage entered a latent state can be recovered from phylogenetic analysis of HIV RNA sequence variation from the same patient. These dates can provide important insights into the dynamics of HIV reservoirs within hosts.

197 HIV-1 SEQUENCES FROM EARLY INFECTION PREDICT THE AGE OF THE INFECTION

Morgane Rolland[1], Christopher L. Owen[1], Sodsai Tovanabutra[1], Eric Sanders-Buell[1], Lucas Maganga[2], Hannah Kibuuka[3], Sorachai Nitayaphan[4], Fredrick Sawe[5], Merlin L. Robb[1], Nelson L. Michael[1]
[1]US Military HIV Rsr Prog, Silver Spring, MD, USA, [2]MMRP, Mbeya, Tanzania, United Republic of, [3]Makerere Univ Walter Reed Proj, Kampala, Uganda, [4]AFRIMS, Bangkok, Thailand, [5]Kenya Med Reseach Inst/Walter Reed Proj, Kericho, Kenya

Background: Being able to infer the age of an HIV infection based on sequences is an invaluable tool, as biological samples often lack information on the date of transmission. Phylogenetic dating methods have been developed and tested with simulated data, but they have not been compared against real data with precise estimates of the date of infection. The RV217 cohort allows such comparisons since it enrolled more than 2,300 seronegative individuals to identify 115 acute HIV infections based on RNA tests performed twice weekly.
Methods: HIV genomes were sequenced from plasma samples following PCR amplification by endpoint-dilution. Phylogenies, divergence times, molecular rates of substitution and effective population sizes were estimated in BEASTv1.8.2 using uncorrelated lognormal relaxed-clock rates and the Bayesian Skyride tree prior for 250 million generations.
Results: For the 36 subjects in this study, the last negative HIV test occurred a median of 4 days before HIV diagnosis (range: 2-32 days), and a total of 1,190 HIV genomes were sequenced at a median (range) of 5 (1-15), 32 (27-42) and 170 (132-261) days after HIV diagnosis. Insights into the history of an HIV infection can be gained by reconstructing a molecular time-scale of its evolution. HIV in early infection did not conform to a strict molecular clock (average coefficient of variation = 0.783). HIV diversification processes varied greatly between individuals: the median substitution rate ranged between 7.26e-07 and 1.22e-04 (average = 1.55e-05). Ten of 36 individuals were infected with multiple HIV founder variants and they tended to show higher substitution rates (2.77 e-05) than subjects with single founders (1.07 e-05) ($p = 0.05$). For infections established with multiple founders, estimates for the median age of the infection were not accurate: they were significantly higher than for infections with single founders (366 vs. 204 days, $p < 0.001$), reflecting that the distinct founder variants in a given individual were sampled from a previous host in chronic infection. Among the 26 subjects with single founders, Bayesian estimates suggested that the infection started at a median of 7 days prior to the last negative HIV test (IQR= 15 day prior to 1 day after). For all but one subject, the 95% HPD encompassed the transmission window.
Conclusion: These results show that Bayesian coalescence methods allow to accurately date an HIV infection event, providing estimates that can be used when the date of HIV transmission is unknown.

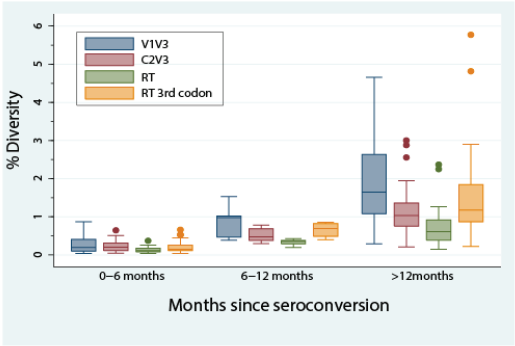
198 USING PRIMER ID DEEP SEQUENCING TO IDENTIFY RECENT HIV INFECTION IN NORTH CAROLINA

Shuntai Zhou[1], Christopher Sellers[1], Marc Potempa[1], Scott J. Zimmerman[2], Erkia Samoff[3], William C. Miller[4], Joseph J. Eron[1], Myron S. Cohen[1], Ronald Swanstrom[1], Ann M. Dennis[1]
[1]Univ of North Carolina at Chapel Hill, Chapel, NC, USA, [2]North Carolina State Lab of Pub Hlth, Raleigh, NC, USA, [3]North Carolina Div of Pub Hlth, Raleigh, NC, USA, [4]Ohio State Univ, Columbus, OH, USA

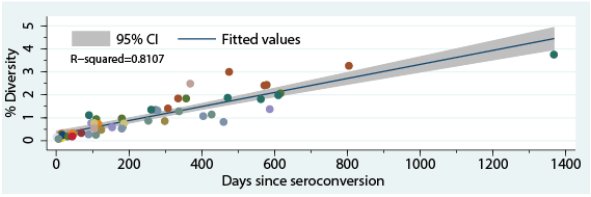
Background: Identifying recent infection is critical for monitoring HIV transmission and incidence but remains challenging. With advances in next generation sequencing (NGS) and Primer ID (PID), intra-host viral diversity biomarkers can be efficiently evaluated over multiple genomic regions and scaled to the population level. We assessed diversity over time from subjects with known infection dates (model) then applied our findings to remnant diagnostic sera from newly diagnosed, antibody positive infections reported in 2014 at the NC State Lab of Public Health (NCSLPH).
Methods: Single and longitudinal plasma specimens from ART-naïve CHAVI-001 (n=25; Feibig stage 1-4 at diagnosis) and chronically infected (n=7; sampled >1 year from diagnosis) subjects were obtained for the model. We constructed multiplexed PID libraries and sequenced RT and env V1-V3 using Illumina MiSeq. We used a PID pipeline to construct a consensus sequence (TCS) for each starting template, and calculated % pairwise diversity (π) for each region. Multi-variant or super-infection was excluded by phylogenetic analysis. We evaluated mean π over time and ROC area under the curve (AUC) to distinguish performance for different gene regions. Recent infection (<9 months since infection) was estimated for NCSLPH specimens.
Results: In the model, 68 samples were analyzed from 19/25 CHAVI (4 dual infections excluded; 2 had low RNA) and 7 chronically infected subjects. CHAVI samples ranged from 0-1367 days since seroconversion (52% were ≤6 months, 20% 6-12 months, 28% >12 months). Mean π increased significantly over time for all regions including RT, 3rd codon RT only, V1-V3, and C2/V3 only (Fig. 1A). The combined π at RT and V1-V3 (Fig. 1B) showed best discrimination for recent definitions at 9 months (AUC=0.91, 95% CI 0.85-0.97) and 12 months (AUC=0.91, CI 0.84-0.98). Among NCSLPH specimens, 70/91 had sufficient consensus at both RT and V1-V3. Subjects were representative of new HIV diagnoses in NC: 65% MSM, 61% black/AA, 66% ≤30 years. Of these, 25/70 (36%) were identified as recent infection at 9 months at combined π threshold of 0.80% (sensitivity 82%, specificity 91% in model).

Figure

1A. Boxplot of % pairwise diversity for each region over time category



1B. Combined % mean pairwise diversity for V1V3+ RT region by days since seroconversion



Conclusion: Measuring HIV-1 diversity over multiple regions using PID can be a useful tool to identify recent infection from diagnostic samples. The sequences can be used for drug resistance and phylogenetics to track transmission networks offering additional tools to direct prevention. The high capacity of NGS makes this approach feasible on a large scale.

199 CHARACTERIZATION OF RECTAL TRANSMISSION BOTTLENECK USING SIV-MACAQUE MODEL

Zhe Yuan[1], Fangrui Ma[1], Andrew J. Demers[1], Dong Wang[2], Jianqing Xu[3], Mark G. Lewis[4], Qingsheng Li[1]
[1]Univ of Nebraska–Lincoln, Lincoln, NE, USA, [2]Dow AgroScis, LLC, Indianapolis, IN, USA, [3]Fudan Univ, Shanghai, China, [4]BIOQUAL, Inc, Rockville, MD, USA

Background: Anorectal intercourse is a common route of HIV-1 transmission and a better understanding of the transmission mechanisms is critical for developing HIV-1 preventative strategies. However, it is a big challenge in human studies to unambiguously define the composition of the HIV-1 population present on mucosal surfaces of the recipient, to sample and analyze founder viruses at or near the time of transmission, or to compare the founder viruses in different recipients who have been exposed to an identical virus population to determine if founder viruses in one individual also have an advantage in other individuals. To overcome above limitations and better understand the mechanisms of HIV-1 rectal transmission, we studied the very early virological events using SIV-rhesus macaque model.

Methods: We analyzed 524 full-length env sequences from the inoculum, rectal mucosae, axillary lymph node tissues, and plasma of six rhesus macaques at 6 and 10 days post SIV rectal transmission using single genome amplification and Sanger's sequencing.

Results: We found founder virus sequences were primarily derived from rare variants in the inoculum. Despite exposure with identical viral inoculums, founder virus sequences from different animals are largely different, indicating founder viruses are animal-specific. We also identified the founder virus signature (FVS) that can distinguish dominant founder variants from minor founder variants and untransmitted variants in the inoculum. Importantly, post-transmission defective variants were mainly resulted from frameshift mutations rather than APOBEC derived mutations.

Conclusion: Founder viruses in rectal transmission are animal-specific and primarily deriving from low-abundant variants in the inoculum. Our data support a model of rectal transmission, after viruses gain entry through the anorectal mucosa, the host reduces viral diversity by converting some of the transmitted functional viruses into defective viruses mainly via frameshift mutation. Future study to elucidate the role of FVS and mechanism of frameshift mediated conversion of functional viruses into defective variants may gain new insight into the rectal transmission bottleneck, which may inform the design of new strategies to prevent HIV-1 transmission.

200 HIV-1 SUPERINFECTION AFTER RECENT INFECTION IS UNCOMMON IN SUB-SAHARAN AFRICA

Gabriel A. Wagner[1], Parris S. Jordan[1], Sergei L. Kosakovsky Pond[2], Matt A. Price[3], Eric Hunter[4], Susan Allen[4], William Kilembe[5], Douglas D. Richman[1], Antoine Chaillon[1], for the IAVI
[1]Univ of California San Diego, La Jolla, CA, USA, [2]Temple Univ, Philadelphia, PA, USA, [3]Intl AIDS Vaccine Initiative, New York, NY, USA, [4]Emory Univ, Atlanta, GA, USA, [5]Zambia–Emory HIV Rsr Proj, Atlanta, GA, USA

Background: Although recent studies have described the rate of HIV-1 superinfection among primary infection cohorts at high risk for HIV, the frequency of superinfection in heterogeneous-risk populations remains unknown. Our objective was to apply deep sequencing to longitudinally collected blood samples from recently infected individuals in sub-Saharan Africa to identify instances of superinfection and determine its rate in a mixed-risk population background.

Methods: Participants were selected from the International AIDS Vaccine Initiative (IAVI) Protocol C, a large multi-site primary infection cohort in sub-Saharan Africa, who had longitudinal follow up greater than 12 months, and remained antiretroviral (ART) naive throughout follow up (N=45). Blood plasma samples were collected, RNA was extracted, and coding regions within HIV-1 env, gag, and pol were amplified using PCR. Amplified PCR products underwent deep sequencing (454, Roche). Bioinformatics and phylogenetic analyses were applied to interrogate for evidence of superinfection. Participants were categorized as superinfected when (i) phylogenetic reconstruction demonstrated divergent viral populations in a background of epidemiologically unlinked viral sequences, and (ii) divergent clustering was confirmed in a second plasma.

Results: Forty-five participants were included from: Kigali, Rwanda (8), Masaka, Uganda (3), Kilifi, Kenya (11), Lusaka, Zambia (20), and Copperbelt, Zambia (3). A median of 3 study timepoints (IQR: 3 – 4 timepoints) were analyzed per participant, with a median follow up time of 18.4 months (IQR: 11.2 – 28.3 months) after primary infection. 24% of participants were men who have sex with men, and 76% reported heterosexual transmission as their main risk factor. Of 45 participants, 2 had confirmed superinfection, resulting in an overall proportion of 4.44% (95% CI: 1.23 – 14.83). Both cases were from Lusaka: one subtype C infected individual was superinfected with another subtype C virus between 0 and 9 months after primary infection; the other was initially infected with a unique recombinant form (URF) and became superinfected with a subtype C virus between 2 and 23 months after primary infection.

Conclusion: Two cases of HIV superinfection were observed in this study cohort, giving an overall rate of less than 5%. One superinfection case was intrasubtype-C, and the other was intersubtype URF-C. The rate was lower than previous studies, which might be associated with the risk composition of the study cohort.

201 FREQUENT INTRASUBTYPE HIV DUAL INFECTION IN TREATED CHRONICALLY INFECTED INDIVIDUALS

Gabriel A. Wagner[1], Antoine Chaillon[1], Gemma Caballero[2], Donald Franklin[1], Sergei L. Kosakovsky Pond[3], Robert K. Heaton[1], Douglas D. Richman[1], Davey M. Smith[1], for the CHARTER
[1]Univ of California San Diego, La Jolla, CA, USA, [2]VA San Diego HIthcare System, La Jolla, CA, USA, [3]Temple Univ, Philadelphia, PA, USA

Background: HIV dual infection (DI) has been increasingly described among global primary infection cohorts, and it has been associated with increased viral loads, decreased CD4+ T-cell counts, and HIV-associated neurocognitive disorder (HAND). Investigations into DI have relied mostly on extraction of viral RNA from the blood plasma of infected individuals. However, in the era of antiretroviral therapy (ART) estimates of DI have not been assessed. We hypothesized that characterizing HIV DNA populations from peripheral blood mononuclear cells (PBMC) using deep sequencing would identify instances of DI and determine its rate among chronically infected individuals on ART.

Methods: Participants of the CNS HIV AntiRetroviral Therapy Effects Research (CHARTER) cohort were selected who had > 4 years between follow-up visits and were receiving ART (N=47). Deep sequencing (454 FLX Titanium, Roche) was performed on PBMC-derived HIV DNA populations using four PCR-amplified coding regions (env C2-V3, gag p24, pol RT, and pol PR). Participants were categorized as DI when (i) phylogenetic reconstruction demonstrated divergent viral populations in a background of epidemiologically unlinked viral sequences, and (ii) divergent clustering persisted over time.

Results: Deep sequencing generated 4.9 million viral sequences from 96 PBMC samples from 47 participants, with a median number of 8,121 sequences per coding region per sample (IQR: 4049 – 14,647 sequences). Twelve out of 47 individuals had phylogenetic evidence of intrasubtype B DI present at the first study visit confirmed across longitudinal timepoints, resulting in a total proportion of DI of 25.5% (95% CI: 15.3% – 39.5%). Despite ART, 15 participants had detectable plasma viral load >500 copies/mL or >2.70 log10 copies/mL. Viremia was not associated with DI ($p = 0.73$, Fisher's exact).

Conclusion: In a US cohort of chronically infected individuals receiving ART, one quarter had intrasubtype DI before the initiation of treatment. Detectable plasma viral load was not associated with DI. Although clinically inapparent, DI is likely to be present more frequently than previously estimated and, given its association with HAND, end-organ sequelae should be further investigated.

202 FEW ACUTE HIV-1 SYMPTOMS AND HIGH SET-POINT VIRAL LOAD IN SUBTYPE-C INFECTIONS

Amin S. Hassan[1], Jonathan Hare[2], Matt A. Price[3], Per Bjorkman[4], Susan Allen[5], Jill Gilmour[2], Thumbi Ndung'u[6], Sarah Rowland-Jones[7], Eduard Sanders[8], Joakim Esbjörnsson[7]
[1]KEMRI Wellcome Trust Rsr Prog, Kilifi, Kenya, [2] Intl AIDS Vaccine Initiative Human Immunol Lab, London, UK, [3]Intl AIDS Vaccine Initiative, New York, NY, USA, [4]Lund Univ, Lund, Sweden, [5]Emory Univ, Atlanta, GA, USA, [6]KwaZulu-Natal Rsr Inst for TB and HIV, Durban, South Africa, [7]Univ of Oxford, Oxford, UK, [8]Kenya Med Rsr Inst, Kilifi, Kenya

Background: HIV-1 disease progression varies between individuals and is likely determined during acute HIV infection (AHI). Newly infected individuals mount an immune response against the infecting virus, resulting in acute retroviral syndromes (ARS) that may impact disease progression. HIV-1 subtype A has been associated with more

pronounced ARS and slower disease progression compared to subtype C or D infections. We set out to determine the impact of infecting HIV-1 subtypes on ARS and set point viral load.
Methods: We compiled and analyzed longitudinal data from five well-characterized AHI cohorts. Archived samples from 100 participants with AHI (defined as HIV-1 antibody negative and RNA or p24 antigen positive) from Europe (Sweden [n=26]) and Africa (Kenya [n=32], Rwanda [n=14], Uganda [n=13], and Zambia [n=15] were included. Participants were followed during approximately one year post estimated date of infection (EDI). HIV-1 env sequencing was done for phylogenetic subtype determination. Clinical data were assessed for ARS, defined as any of 11 reported symptoms during AHI, whilst longitudinal HIV-1 viral load data was assessed for set-point viral load.
Results: Most of the participants were male (n=83 [83.0%]). The median age at EDI was 30.3 (IQR 24.3-36.1) years. The infecting subtypes were A (n=41 [41%]), B (n=19 [19%]), C (n=17 [17%]), D (n=7 [7%]) G (n=2 [2%], F (n=2 [2%]) and different recombinant forms (n=12 [12%]). Subtype C-infected individuals were less likely to report ARS compared to those with non-C subtypes (n=8 [50.0%] vs. n=55 [78.6%], p=0.020), whilst subtype A-infected individuals were more likely to report ARS than those infected with non-A variants (n=34 [89.5%] vs. n=29 [60.4%], p=0.003). The median set-point viral load was 41,000 (IQR 16,000 – 80000) copies/ml. Subtype C-infected individuals were more likely to have higher viral set point than those infected with non-C variants (OR 5.6 [95% CI 1.6 – 19.3], p=0.003).
Conclusion: Differences in ARS and set-point viral load were inversely associated with the HIV-1 subtype C. Expression of fewer symptoms during acute subtype C-infection and the subsequently higher set-point viral load may be linked to a less robust immune response followed with poor replication control. Further work is on-going to delineate the relationship between infecting subtype and innate immune responses, and their effect on ARS and disease progression.

203 GRANULOCYTIC MYELOID-DERIVED SUPPRESSOR CELLS IN PRIMARY HIV INFECTION

Nicola Tumino, Maria Teresa Bilotta, Adriana Ammassari, Annalisa Mondi, Casetti Rita, Veronica Bordoni, Eleonora Cimini, Federico Martini, Chiara Agrati,
Sacchi Alessandra
Natl Inst for Infectious Diseases Lazzaro Spallanzani, Rome, Italy
Background: It has been demonstrated that Myeloid Derived Suppressor Cells (MDSC) are expanded in HIV-1 chronically infected individuals. The phase of HIV infection during which MDSC expansion occurs, and the mechanisms that regulate this expansion remain to be established. In this study we evaluated the frequency of MDSC in patients during primary HIV infection, and factors involved in MDSC control.
Methods: Patients with primary (PHI, n=51) and chronic (CHI, n=26) HIV infection were enrolled before and one year after therapy initiation. At baseline, median CD4 T cell count was 588 cells/mm3 (IQR 470-830) in PHI, and 499 cells/mm3 (IQR 148-644) in CHI. Median viral load was 5.31 Log RNA copies/ml (IQR 4.33-6.16) in PHI and 4.75 Log RNA copies/ml (IQR 4.44-5.34) in CHI. MDSC frequency and function were evaluated by flow cytometry. Cytokine levels were evaluated by Luminex technology. Spearman rho was calculated to evaluate correlations. Wilcoxon/Mann-Whitney test was used to compare continuous parameters.
Results: We found that, before therapy initiation, granulocytic MDSC (Gr-MDSC) frequency was higher in PHI compared to healthy donors ($p<0.0001$), but lower than CHI ($p=0.02$). Interestingly, Gr-MDSC expansion was already observed in the early phases of HIV infection (Fiebig II/III), but it was not associated to HIV viral load and CD4 T cell count. As previously demonstrated in CHI, Gr-MDSC from PHI inhibit HIV-specific T cell response, suggesting a detrimental role of Gr-MDSC. Interestingly, in PHI Gr-MDSC frequency was inversely correlated with plasmatic level of TRAIL ($r= -0.52$, $p= 0.003$), while a direct correlation was observed in CHI ($r= 0.6$, $p= 0.029$). Further, lower level of GM-CSF was observed in PHI compared with CHI ($p= 0.04$). In vitro experiments demonstrated that, differently from CHI, recombinant TRAIL induced apoptosis of Gr-MDSC from PHI, an effect that can be abrogated by GM-CSF. Antiretroviral therapy was not able to affect Gr-MDSC frequency in both PHI and CHI. However, in PHI an inverse correlation between Gr-MDSC frequency and the number of CD4 T cells was observed ($r= -0.39$, $p= 0.029$), suggesting that Gr-MDSC persistence, after treatment of acute infection, could be associated with a worst CD4 T cell recovery.
Conclusion: We found that suppressive Gr-MDSC are expanded very early during PHI, and correlate with CD4 T cell count after therapy. TRAIL and GM-CSF may play a role in regulating Gr-MDSC expansion, thus opening new perspectives for immune-based strategies.

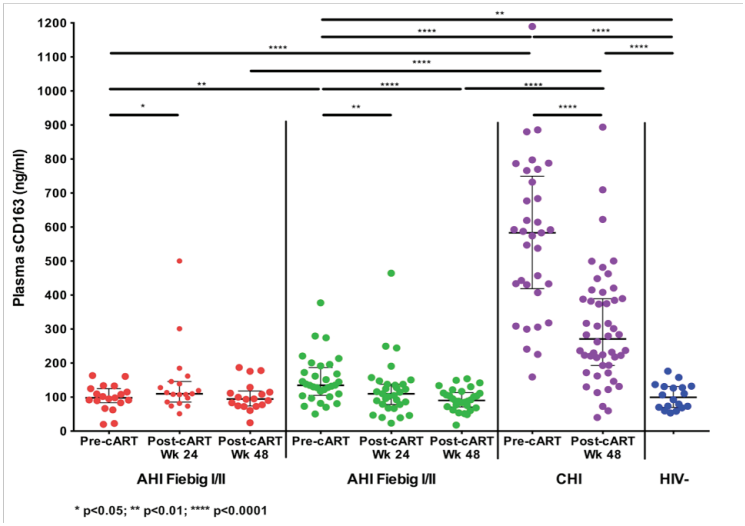
204 HIV-1 EXPLOITS THE INTERPLAY BETWEEN EPITHELIAL AND TH17 CELLS FOR DISSEMINATION

Tomas Raul Wiche Salinas[1], Annie Gosselin[1], Dragos Vlad[1], Yuwei Zhang[1], Huicheng Chen[1], Cécile Tremblay[1], Jean-Pierre Routy[2], Petronela Ancuta[1]
[1]Cntr de Rsr du Cntr Hosp de l'Univ de Montréal, [2]McGill Univ Hlth Cntr, Glen site, Montréal, Canada
Background: Epithelial cells (EC) are the first to capture HIV/SIV at portal sites of entry and transmit the virus to subjacent immune cells via transcytosis. The interplay between EC and Th17 cells is critical for the maintenance of immune homeostasis at mucosal level as well as viral dissemination. Th17 cells produce cytokines that act on EC to promote the production of CCL20/MIP-3α, an antimicrobial peptide and chemoattractant for CCR6+ Th17 cells. CCL20 was reported to limit HIV replication in T-cells by inducing APOBEC3G expression. Other studies demonstrated that CCL20 contributes to the establishment of HIV latency in CD4+ T-cells and promotes dissemination from the portal sites of entry. Herein, we investigated the impact of HIV-1 on the interplay between EC and Th17 cells and studied EC-T cell trans infection in an environment rich in CCL20.
Methods: Intestinal EC line HT-29 was stimulated with recombinant human TNF-α and/or IL-17A in the presence or absence of the wild type R5 HIV strains NL4.3BaL and transmitted founder THRO. Memory CD4+ T-cells were isolated by magnetic beads from uninfected individuals and stimulated with CD3/CD28 Abs. EC-T cell trans infection was studied in co-culture experiments between HIV-exposed EC and activated T-cells. CCL20, CXCL8/IL-8, and HIV-p24 levels were quantified in cell culture supernatants by ELISA. The expression of IL-17 receptor A and C (IL-17RA/RC) on EC and the intracellular expression of HIV-p24 in T-cells were quantified by FACS.
Results: IL-17A acted only in synergy with TNF-α to promote CCL20 but not CXCL8 production in EC. This synergy coincided with the TNF-α-mediated up-regulation of IL-17RA expression on EC. HIV exposure further increased CCL20 production by EC in response to IL-17A and TNF-α. Although CCL20 inhibited HIV replication in T-cells cultured alone, HIV trans infection of T-cells co-cultured with HIV-loaded EC occurred more robustly in the presence of high levels of CCL20 levels produced by EC in response to IL-17A and TNF-α.
Conclusion: We demonstrate that IL-17A acts in synergy with TNF-α to promote CCL20 production in intestinal EC, HIV further amplifies this synergy, and HIV transmission from EC to T-cells is proportional to the magnitude of CCL20 production by EC. Together these results reveal that HIV-1 exploits the interplay between EC and Th17 cells for its own replicative advantage and that CCL20 plays an important role in HIV dissemination from the portal sites of entry.

205 PLASMA-SOLUBLE CD163 IS SUPPRESSED UPON EARLY ART INITIATION IN ACUTE HIV INFECTION

Michelle L. D'Antoni[1], Somporn Tipsuk[2], Shelly J. Krebs[3], Thep Chalermchai[2], Duanghathai Suttichom[2], Nittaya Phanuphak[2], Victor Valcour[4], Jintanat Ananworanich[3], Lishomwa C. Ndhlovu[1], for the RV254/SEARCH 010; SEARCH013 and SEARCH011 Study Groups
[1]Univ of Hawaii, Honolulu, HI, USA, [2]SEARCH, South East Asia Rsr Collab with Hawaii, Bangkok, Thailand, [3]US Military HIV Rsr Prog, Silver Spring, MD, USA, [4]Univ of California San Francisco, San Francisco, CA, USA
Background: Plasma soluble CD163 (sCD163), a marker of myeloid cell activation, is higher in cognitively impaired than unimpaired chronically HIV infected (CHI) adults on combination antiretroviral therapy (cART). Whether early cART initiation in acute HIV-infection (AHI) impacts CD163 shedding is unknown.
Methods: We examined 51 AHI adults who were enrolled during Fiebig stage (F)I-IV and immediately initiated cART. sCD163 was measured in plasma and cerebrospinal fluid (CSF) by ELISA. For FI/II, 19/19 persons had plasma at all timepoints and for FIII, 30/32; for FI/II, 10/16 had CSF at all timepoints and for FIII, 21/22. Neuropsychological (NP) tests included Trail Making A (TM-A), Color Trails (CT1 and 2) and Grooved Pegboard (GP) to compute a summary NPZ-4. Magnetic resonance spectroscopy (MRS) assessed brain metabolites. CHI adults [N=33 pre-ART; n=48 post-ART (plasma); n=39 pre-ART; n=12 post-ART (CSF)] and 18 matched HIV- adults (CO) served as controls. Nonparametric statistics were used and a generalized estimating equation (GEE).

Results: The median age was 28, 35, and 33 years for AHI, CHI, and CO, respectively. 71% of HIV+ and 50% of HIV- were male. Plasma sCD163 (p-sCD163) levels pre-ART in FI/II (98.4ng/ml) were lower compared to FIII (150.0ng/ml, p=0.002) or CHI (565.6ng/ml, p<0.0001), but were similar to CO (101.9ng/ml). At 48 weeks (wks) post-cART, p-sCD163 decreased in FIII (93.1ng/ml; p<0.0001) to levels that did not differ from CO. However, although CHI p-sCD163, levels decreased (301.6ng/ml; p<0.0001) after cART, these levels remained elevated compared to CO (p<0.0001). CSF sCD163 (c-sCD163) pre-ART was elevated in both FIII (12.2ng/ml) and CHI (11.6ng/ml) compared to FI/II (7.6ng/ml; p=0.008 and p=0.017, respectively) or CO (7.7ng/ml; p=0.008 and p=0.014, respectively). Post-cART, c-sCD163 in FIII (24 wks; 6.4ng/ml) and CHI (48 wks; 8.5 ng/ml) decreased compared to pre-cART (p<0.001 and p=0.003, respectively) to CO levels. In FI/II pre-cART, higher p-sCD163 correlated with higher GP scores (r=0.627; p=0.044) but higher c-sCD163 post cART in FIII correlated with lower NPZ-4 (r=-0.522; p=0.020) and with lower N-acetylaspartate in basal ganglia (r=-0.500; p=0.031). In AHI, p-sCD163 associated negatively with CT 1 (p<0.0001) and positively with GP (p=0.0043). c-sCD163 associated negatively with TM-A (p<0.0001) and GP (p=0.0052).
Conclusion: Initiation of cART early in AHI (FI/II) may decrease inflammation, preventing shedding of CD163, lowering the risk of brain injury.



206 CMV REPLICATION DURING PRIMARY HIV INFECTION IS ASSOCIATED WITH T-CELL DYSFUNCTION

Jennifer M. Dan[1], Antoine Chaillon[2], Masato Nakazawa[1], Davey M. Smith[1], Milenka Vargas[2], Rachel Schrier[2], Susan J. Little[2], Sara Gianella[1]
[1]*Univ of California San Diego, La Jolla, CA, USA,* [2]*Univ of California San Diego, San Diego, CA, USA*

Background: More than half of HIV-infected men shed cytomegalovirus (CMV) DNA in their semen during primary HIV infection and subclinical CMV replication has been associated with increased T cell dysfunction and higher levels of HIV RNA transcription. The effect of persistent CMV exposure during primary HIV infection on viral specific immune responses and immune exhaustion has not been evaluated.
Methods: Paired seminal and blood samples from 53 ART-naïve early HIV-infected men from the San Diego Primary Infection Cohort (< 6 months from estimated date of infection) and 23 at-risk HIV-uninfected CMV-seropositive controls were evaluated. Levels of seminal CMV DNA and HIV RNA were measured by RT-PCR, and expression of intracellular interferon (IFN)-γ and Granzyme B production were measured by flow cytometry from peripheral blood mononuclear cells (PBMC) following overnight stimulation with whole CMV and HIV lysate. Levels of programmed death receptor-1 (PD-1) were measured on unstimulated PBMCs. Immunological and virologic markers were compared between groups (i.e. HIV-negatives, HIV-positives, CMV shedders and non shedders) using Mann-Whitney U tests.
Results: CMV DNA was detected in semen of 31 HIV-positive (58%) and 3 HIV-negative (13%) individuals (P<0.001). Overall, early HIV-infected participants presented significantly increased PD-1 expression on CD8+ (P<0.01), greater Granzyme B production by CD8+ after ex vivo stimulation with CMV (P=0.07), increased HIV-specific CD8+ immune response (IFN-γ expression) compared to HIV-uninfected, but no differences in CMV-specific immune response. Among HIV-positives, shedding of CMV DNA was associated with higher levels of seminal HIV RNA (P<0.01), increased PD-1 expression on CD4+ (p=0.03) and CD8+ T cells (p=0.08), reduced HIV-specific CD8+ immune response (P=0.02) but no differences in CMV-specific immune response. Interestingly, HIV-infected participants with no evidence of CMV shedding had similar levels of PD-1 expression on CD4+ and CD8+ compared to HIV-uninfected controls.
Conclusion: Subclinical CMV replication during early HIV-infection (but not HIV infection alone) is associated with T cell exhaustion and with impaired HIV-specific CD8+ T cell response. These findings could explain the connections between subclinical CMV replication and higher levels of seminal HIV shedding, as well as increased HIV DNA levels in blood and worse HIV disease progression. CMV might be the "smoking gun" of immune dysfunction among co-infected individuals.

207 IMPACT OF MSM-ASSOCIATED MICROBIOTA ON IMMUNE ACTIVATION AND IN VITRO HIV INFECTION

Sam Li, Abigail Armstrong, Charles P. Neff, Catherine Lozupone, Brent E. Palmer
Univ of Colorado, Aurora, CO, USA

Background: Several studies have shown that HIV infection is associated with alterations in gut microbiota composition. Recent findings from a European cohort suggest that the main alterations are associated with sexual behavior of men who have sex with men (MSM) rather than with infection itself. Given that MSM are at higher risk of becoming infected with HIV, it is of importance to understand the impact of MSM-associated microbiota on immune cells in the gut as it relates to disease and HIV transmission.
Methods: The fecal microbiota of a US cohort (n=210), including HIV-negative high-risk MSM (n=42) and low-risk heterosexual men (n=22), were analyzed using 16S rRNA gene sequencing. Feces from three representative MSM and three representative heterosexual men were used to gavage gnotobiotic mice (n≥4 mice per fecal sample), and mice were analyzed for immune activation following colonization. Bacterial cells were isolated from original fecal samples (n=8 MSM, 8 heterosexual men) using density centrifugation, and used to stimulate human peripheral blood mononuclear cells (PBMCs) and gut lamina propria cells (LPMCs). After stimulation, PBMC were analyzed for activation, and LPMCs were infected with HIV_{bal} and stained for p24 expression at 5 days post infection.
Results: Within our cohort of HIV-negative MSM in the US, the majority of subjects harbor a Prevotella-rich/Bacteroides-poor microbiome, similar to that of HIV-infected subjects and compositionally distinct from low risk HIV-negative subjects which harbor a Prevotella-poor/Bacteroides-rich microbiome. Following fecal microbial transplantation to gnotobiotic mice, T cells in the lamina propria exhibited higher CD69 expression (p=0.017), and macrophages in the mesenteric lymph node showed higher CD86 expression (p=0.006), when mice were colonized with feces from MSM. Stimulation of human PBMCs with bacteria isolated from MSM feces resulted in higher levels of HLA-DR+ CD38+

CD4+ T cells when compared with PBMCs stimulated with fecal bacteria from heterosexual men (p=0.001). Finally, stimulation of LPMCs with MSM-associated bacteria induced higher infection levels with HIV_{bal} compared with LPMCs stimulated with fecal bacteria from heterosexual men (p=0.008).
Conclusion: Our data support previous findings of gut microbiome compositional differences between MSM and heterosexual men, and suggest that microbiota of MSM may play a role in increasing their risk to HIV infection by inducing immune activation.

208 FECAL MICROBIOTA FROM HIV-INFECTED SUBJECTS INCREASES IMMUNE ACTIVATION AND INFECTION

Charles P. Neff, Sam Li, Abigail Armstrong, Catherine Lozupone, Brent E. Palmer
Univ of Colorado, Aurora, CO, USA
Background: High-throughput sequencing of 16s rRNA has shown compositional divergence of gut microbiota mediated by HIV and high risk behavior that often persist with Antiretroviral Therapy (ART). Here we further characterize the gut microbiota composition by disease status, ART and gender, and isolate fecal bacteria to evaluate the consequences of these changes in gut microbiota on immune activation and HIV infection of lamina propria T cells.
Methods: Using 16S rRNA sequencing we have examined fecal microbiota composition of 210 individuals with and without HIV infection. To explore immune-modulatory properties of these bacteria, we isolated the whole fecal bacterial community by density gradient. We then enumerated the isolated bacterial community and verified that it closely resembles the composition of the original fecal sample. We then measured the impact of the bacterial community isolated from men and women with or without HIV infection on peripheral blood and lamina propria mononuclear cells (PBMC and LPMC) by measuring T cell and myeloid cell activation and the impact of these bacterial communities on HIV infection.
Results: Within our cohort the majority of HIV+ subjects harbor a Prevotella-rich/Bacteriodes-poor fecal microbiome in contrast to low risk HIV- subjects and interestingly HIV+ women had compositional changes that were distinct from men. PBMC stimulated with fecal bacteria from HIV+ compared to HIV- subjects induced significantly higher levels of activated CD4 (p<0.0001) and CD8 (p<0.0001) T cells, macrophages (p=0.008) and dendritic cells (p=0.029). TLR2 blockade inhibited this activation (p=0.05). T cell activation was higher when cultured with fecal bacterial communities from untreated HIV+ subjects compared to those on ART (CD4 p=0.0009, CD8 p=0.009) or HIV+ females. LPMCs stimulated with fecal bacterial communities from HIV+ subjects induced higher levels of activated CD4 (p<0.0001) and CD8 (p<0.0001) T cells and increased HIV-infection of CD4+ T cells compared to normal fecal microbiota, indicating that the HIV associated gut microbiota may promote disease progression.
Conclusion: This study provides important insight regarding the consequence of the alterations in gut microbiota associated with HIV infection. These data suggest that fecal bacterial communities associated with HIV infection increase immune cell activation and infection which could potentially drive disease progression.

209 MARAVIROC INHIBITS HIV TARGET T-CELL TRAFFICKING INTO THE FEMALE GENITAL LUMEN

Alison S. Kohlmeier[1], Sean McMaster[2], Jessica Radzio[1], Mian-er Cong[1], Chuong Dinh[1], Amy Martin[1], Jacob E. Kohlmeier[2], Gerardo Garcia-Lerma[1]
[1]CDC, Atlanta, GA, USA, [2]Emory Univ, Atlanta, GA, USA
Background: Maraviroc (MVC) is an HIV entry inhibitor currently being tested in clinical studies for daily pre-exposure prophylaxis (PrEP) to prevent HIV infection. In contrast to currently approved PrEP drugs that interfere with HIV reverse transcription, MVC prevents infection by blocking the binding of HIV to CCR5 present on the surface of the target host cells, thus raising questions about potential immunological effects independent of its antiviral activity. We investigated the effect of daily oral MVC on CD4 T cell localization in the genital lumen of pigtail macaques and how these effects are influenced by the phase of the menstrual cycles.
Methods: MVC was administered orally over a course of 5 days in pigtail macaques (n=6) during the follicular or luteal phase of the menstrual cycle (estimated from weekly plasma progesterone levels). Immune characterization of CD4 T cells enriched from blood or cervicovaginal lavage was performed using flow cytometry and compared using a two-tailed t test. To investigate CCR5-mediated trafficking into the genital lumen, CD4 T cells from CCR5 knockout (KO) and wild type (wt) mice were isolated and intravenously transferred at equal ratios into RAG KO host mice. 2 weeks post transfer tissues were measured for the absolute numbers of transferred cells using flow cytometry. Statistics calculated by two-way ANOVA.
Results: Increased plasma progesterone during the luteal phase of the menstrual cycle associated with both an increased frequency of CCR5 expression and chemotaxis on circulating memory CD4 T cells, and a higher frequency of migratory memory CD4 T cells resident at the genital lumen. To determine how CCR5 signaling may influence CD4 T cell localization at the genital lumen we employed a dual adoptive transfer approach, and found that CD4 T cell steady state trafficking into the genital lumen required CCR5 signaling (p=<0.0001). MVC treatment led to reduced detection of luminal CD4 T cells during the luteal phase of the menstrual cycle (p=0.0049), while no change in CD4 T cells was detected at the follicular phase (p=0.3) or during placebo treatment (p=0.6).
Conclusion: Our results provide new insights into the mechanisms that may explain increased susceptibility to SHIV infection during the luteal phase of the menstrual cycle. Reductions in luminal CD4 T cells during the luteal phase due to MVC treatment demonstrate immunomodulatory effects of MVC that have the potential to decrease HIV infection risk.

210 INVESTIGATING THE EFFECT OF PH ON CERVICOVAGINAL MUCUS BARRIER PROPERTIES TO HIV

Julie K. Shade, Thuy Hoang, Kevin Delong, Justin Hanes, Richard Cone, Laura Ensign
The Johns Hopkins Univ, Baltimore, MD, USA
Background: Bacterial vaginosis (BV) affects ~29% of women in the US and increases risk of HIV acquisition by 60%. "Healthy" vaginal bacteria communities are dominated by Lactobacilli, lactic acid (LA) producing bacteria that acidify vaginal secretions to pH 3.0-4.0. Women with BV have polymicrobial vaginal communities with few Lactobacilli and elevated vaginal pH (>4.5). We previously found that HIV virions were adhesively trapped in human cervicovaginal mucus (CVM) from women with Lactobacilli-dominated microbiota. However, our recent unpublished work has found that HIV virions rapidly penetrate through CVM from women with BV. We hypothesized this difference in CVM barrier properties may be due to elevated vaginal pH, and may partially explain the increased risk of HIV acquisition in women with BV.
Methods: CVM was self-collected by women ages 18-45. BV was diagnosed by meeting 3/4 of Amsel's criteria and a Nugent score >7. Samples were serially alkalinized with 1M sodium hydroxide, and in some cases, re-acidified with hydrochloric acid (HCl) or LA. Internally fluorescently labeled mCherry-GAG HIV virions were added to CVM and movement of individual virions was assessed using a quantitative fluorescent microscopy technique.
Results: Similar to our prior unpublished observations, HIV was highly mobile in CVM samples from women with BV. Adhesive interactions (trapping) between HIV and CVM from women with healthy microbiota were abolished when pH was increased > 5.18 ± .13. However, trapping of HIV, as measured by the % of mobile virions, was restored when neutralized CVM was re-acidified below pH 4.90 ± .37 (n = 7). The results were similar whether using HCl or LA for re-acidification. In contrast, acidification of CVM from women with BV did not lead to trapping of HIV.
Conclusion: Increasing the pH of CVM from women with healthy vaginal microbiota led to a reduction in adhesive interactions with HIV virions, similar to what was observed in CVM from women with BV. Re-acidification of neutralized CVM from women with healthy microbiota restored adhesive interactions with HIV virions, an effect observed using both HCl and LA as the acidifying agent. However, acidification of CVM from women with BV did not lead to trapping of HIV, suggesting that elevated pH alone is not enough to explain the reduced barrier properties of BV CVM to HIV. These findings may have important implications in the design of strategies to mitigate the increased risk of HIV infection associated with BV.

211 INFLAMMATORY GUT ILCs ASSOCIATE WITH DYSBIOSIS DURING UNTREATED HIV-1 INFECTION

Stephanie Dillon[1], Daniel N. Frank[1], Gregory Austin[1], Sara Gianella[2], Moriah Castleman[1], Andrew Cogswell[3], Alan Landay[3], Edward Barker[3], Cara Wilson[1]
[1]Univ of Colorado Anschutz Med Campus, Aurora, CO, USA, [2]Univ of California San Diego, La Jolla, CA, USA, [3]Rush Univ, Chicago, IL, USA

Background: HIV-1 infection is associated with a breakdown in intestinal homeostasis and changes in the enteric microbiota including increased abundances of pathobionts (e.g. Prevotella spp.). Normally, NKp44+ innate lymphoid cells (ILCs) within the mucosa maintain gut homeostasis through production of IL-22. ILCs also display functional plasticity and can produce inflammatory cytokines (e.g., IFNγ) in response to cytokine milieu and stimulatory signals in the colon. We hypothesized that frequencies of inflammatory gut NKp44+ ILCs would be increased during HIV-1 infection and thus contribute to HIV-1 gut pathogenesis.
Methods: Following informed consent, colonic cells were collected from 22 untreated, chronic HIV-1-infected study participants (HIV+; median plasma viral load: 51,350 HIV-1 RNA/ml; median CD4 count: 425 cells/μl) and 9 HIV-1 uninfected controls (HIV-). Flow cytometry was used to determine frequencies of CD3-NKp44+CD56± ILCs and CD3+CD4 T cells expressing IL-22 or IFNγ after in vitro mitogenic stimulation and to measure myeloid dendritic cell (mDC) activation (CD40 expression) and T cell activation (CD38+HLA-DR+). Microbiome analysis was performed on colon tissue from a subset of subjects using bacterial 16S ribosomal DNA sequences. Non-parametric tests were performed.
Results: In HIV- persons, NKp44+CD56- ILCs primarily produced IL-22 (6.1%, 0-13.6%) versus IFNγ (0.6%, 0-4.0%; p=0.01). Similar percentages of NKp44+CD56+ ILCs expressed IL-22 (8.7%, 2.0-23.2%) and IFNγ (10.9%, 0.6-20.8%; p=0.91). Frequencies (#/g) of IFNγ+NKp44+CD56- and IFNγ+NKp44+CD56+ ILCs were significantly increased in HIV+ persons (P=0.002 (N=21), P=0.04 (N=22) respectively). In HIV+ persons, frequencies of IFNγ+NKp44+CD56- ILCs positively correlated with relative abundance of mucosa-associated Prevotella spp. (P. copri: R=0.68, P=0.01; P. stercorea: R=0.63, P=0.02; N=14) and frequencies of IFNγ+ CD4 T cells (R=0.53, P=0.01; N=21). IFNγ+NKp44+CD56+ ILCs positively correlated with activation of colon mDCs (R=0.56, P=0.02; N=18) and T cells (CD4: R=0.43, P=0.04; CD8: R=0.64, P=0.002; N=22).
Conclusion: Cytokine profiles of gut NKp44+ ILCs are altered during untreated, chronic HIV infection. The switch to an IFNγ-dominated ILC phenotype is associated with dysbiosis and gut mDC and T cell activation suggesting a critical interplay between gut ILCs, the microbiome and local immune responses. This inflammatory ILC functional profile likely contributes to gut mucosal inflammation and epithelial barrier breakdown.

212 GUT-MICROBIOTA–RELATED METABOLIC PATHWAYS IN ELITE CONTROLLERS AND HIV PROGRESSORS

Piotr Nowak[1], Javier Rivera[2], Jan Vesterbacka[1], Marc Noguera-Julian[2], Kajsa Noyan[1], Maria L. Calle[3], Roger Paredes[2], Anders Sönnerborg[4]
[1]Karolinska Inst, Stockholm, Sweden, [2]IrsiCaixa Inst for AIDS Rsr, Badalona, Spain, [3]Univ of Vic–Central Univ of Catalonia, Barcelona, Spain, [4]Karolinska Univ Hosp, Stockholm, Sweden

Background: Gut microbiota dysbiosis features progressive HIV infection, with subsequent microbial translocation and systemic immune activation. Still, the microbial composition in gut of elite controllers (EC) has not been extensively explored, neither the corresponding metabolic pathways.
Methods: 16 EC and 32 ART naïve progressors were recruited from a Swedish HIV cohort, and also 16 healthy controls (HC). Subjects were matched by age, gender and sexual practice. Fecal microbiota composition was determined by 16S rRNA sequencing. Plasma markers of tryptophan catabolism pathway were analyzed by HPLC. Functional content of the bacterial 16srRNA metagenome was inferred by PICRUSt software.
Results: The number of observed genera was significantly higher in EC vs progressors (median 87 vs 70; HC 78), and several α-diversity indexes were lower in patients with progressive infection (median Chao1: 95 vs 80, ACE: 93 vs 79; in HC 83 and 85, respectively). At genus level, Succinivibrio, Sutterella, Rhizobium, Delftia, Anaerofilum and Oscillospira were more abundant in EC, whereas Blautia and Anaerostipes were depleted. Plasma K/T ratio was significantly increased in progressors as compared to EC and HC. The PICRUSt analysis revealed several significant differences between groups in different metabolic pathways. Carbohydrate metabolism pathway was less represented in EC fecal microbiome. Conversely, several other metabolic pathways (fatty acid metabolism, PPAR-signalling and lipid biosynthesis proteins) were enriched in EC than in progressors. Secondary, bile acid synthesis pathway was underrepresented in EC as compared to naïve progressors and HC. Additionally, pathways related to pentose-phosphate (PPP), pentose-glucoronate interconversions, and phenylalanine-tyrosine-tryptophan biosynthesis were reduced both in EC and HC when compared to naïve progressors. Differences between EC and HC were less frequent and included pathways related to carbohydrate metabolism, biosynthesis and biodegradation of secondary metabolites, PPP and bacterial toxins.
Conclusion: EC have a richer gut microbiota than untreated HIV patients, with a unique bacterial signature at genus level. We confirm that tryptophan metabolism is altered during HIV infection, mostly in naive progressors. Functional analysis of the 16srRNA metagenome shows that EC have a distinct profile in several metabolic pathways, including metabolism of carbohydrates, lipids and tryptophan.

213 CHANGES IN THE ORAL MICROBIOME WITH ART INITIATION

Rachel Presti[1], Scott Handley[2], Lindsay Droit[2], Mahmoud Ghannoum[3], Mark Jacobson[4], Caroline H. Shiboski[4], Jennifer Webster-Cyriaque[5], Todd Brown[6], Michael T. Yin[7], Edgar T. Overton[8]
[1]Washington Univ in St. Louis, St. Louis, MO, USA, [2]Washington Univ, St. Louis, MO, USA, [3]Case Western Reserve Univ, Cleveland, OH, USA, [4]Univ of California San Francisco, San Francisco, CA, USA, [5]Univ of North Carolina at Chapel Hill, NC, USA, [6]The Johns Hopkins Univ, Baltimore, MD, USA, [7]Columbia Univ, New York, NY, USA, [8]Univ of Alabama at Birmingham, Birmingham, AL, USA

Background: Changes in human oral microbiota have been linked to diseases of aging that are common in HIV, including atherosclerosis and certain cancers. Oral pathology, including thrush, oral hairy leukoplakia and periodontal disease, is common in chronic HIV infection. HIV has been associated with shifts in the microbiome at several sites, although no studies have longitudinally assessed oral microbiome change in the setting of controlled ART initiation. Here, we characterize the oral bacterial microbiome before and after 24 weeks of ART.
Methods: Thirty-five participants co-enrolled in two ACTG studies, A5272 and A5280, were assessed. All participants were ART-naïve at baseline and received EFV/FTC/TDF in A5280. Saliva was collected as part of A5272. Paired saliva samples from both studies were evaluated for bacterial microbiome using 16S rDNA PCR followed by Illumina sequencing. Reads were analyzed using QIIME. Operational taxonomic units (OTUs) were assigned, and differences in distribution and abundance before and after ART were assessed.
Results: At entry, median age was 35 years; (89% male; 46% white, 31% African American, 20% Hispanic). Median CD4 count was 326 cells/mm3 (range: 7-804); 5 participants had CD4 counts <200 cells/mm3. Median viral load was 30,136 cp/mL; 9 participants had viral load >100,000 cp/mL. All participants suppressed on EFV/FTC/TDF to HIV VL<200, although one rebounded at week 24 after suppression. No significant change was seen between baseline and week 24 samples in either alpha or beta diversity (p>0.05 for both). Overall, the distribution of OTUs in the oral samples remained similar at weeks 0 and 24. However, participants with CD4<200 cells/mm3 had fewer Firmicutes, Actinobacteria, Bacteroidetes, and Fusobacteria, and more Proteobacteria, than those with CD4>200 cells/mm3. Importantly, these differences persisted at week 24 of ART.
Conclusion: In this prospective study of ART naïve individuals, we identified relative stability within the oral microbiome after 24 weeks of ART. However, persons with advanced HIV disease had greater representation of the phylum Proteobacteria, which has also been reported in the gut microbiome of persons with advanced HIV disease. This shift to a greater representation of pathogenic Gram-negative bacteria is a potential contributor to excess inflammation in the setting of advanced disease, and is not completely reversed by 24 weeks of effective ART.

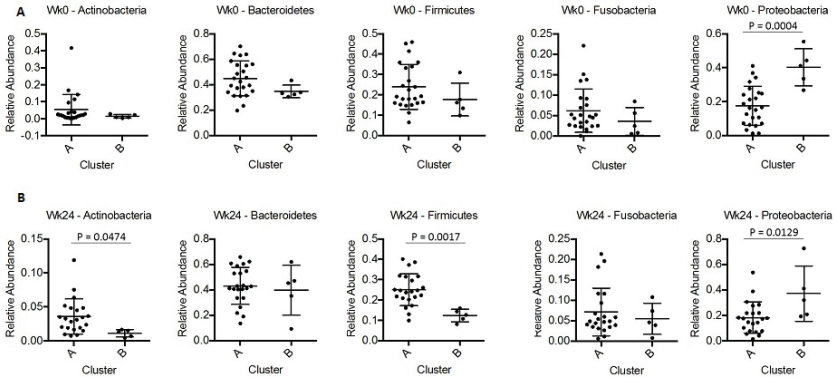


Figure 1. Relative abundance of 16S rDNA reads assigned by OTU to dominant phyla in saliva from participants with baseline CD4>200 (cluster A) versus baseline CD4<200 (cluster B). Panel A is from saliva collected participants at baseline prior to ART therapy. Panel B is from saliva collected after 24 weeks of EFV/FTC/TDF.

214 ACUTE HIV INFECTION AND HUMAN GUT MICROBIOME BEFORE AND AFTER ANTIRETROVIRAL THERAPY

Ornella Sortino[1], Nittaya Phanuphak[2], Nitiya Chomchey[3], Yasmine Belkaid[4], Jacquice Davis[4], Mariam Quinones[4], Suteeraporn Pinyakorn[5], Jintanat Ananworanich[2], Jason Brenchley[4], Irini Sereti[4]

[1]Leidos Biomed Rsr, Inc, Frederick, MD, USA, [2]SEARCH, Thai Red Cross AIDS Rsr Cntre, Bangkok, Thailand, [3]SEARCH, Bangkok, Thailand, [4]NIAID, Bethesda, MD, USA, [5]Henry M. Jackson Fndn for the Advancement of Military Med, Bethesda, MD, USA

Background: The etiology of persistent immune activation in chronic HIV infection is incompletely understood and is probably multifactorial encompassing residual HIV replication, co-infections, mucosal alterations and deficient immune restoration. The intestinal gut microbiota could act as an integral driver of pathologic inflammation that persists even during the administration of antiretroviral therapy (ART).

Methods: Anal swab samples were collected from 26 HIV- and 59 HIV+ Thai subjects with acute HIV infection (Fiebig stages I-IV) at baseline and 6 months after ART (2NRTI+Efavirenz). Total DNA was extracted from anal swabs. The V4 variable region of the 16S rRNA gene was amplified. Illumina paired-end was performed on the MiSeq platform with MiSeq Control Software. The association of inflammatory markers with any taxa was assessed using Spearman's correlation test.

Results: Changes were found in the gut bacterial communities between baseline and 6 months post-ART: an increase in Fusobacteria eg. Fusobacterium (9% vs 30%), Proteobacteria eg. Campylobacter (12% vs 16%) and Tenericutes eg. Mycoplasma (0.9% vs 4.5%). Moreover, a decrease in Bacteroidetes eg. Prevotella (58% vs 31.5%) and Firmicutes eg. Lactobacillus (20% vs 17%) was documented ($p<0.05$ for both). Comparisons between HIV+ post-ART and HIV- showed a higher proportion of Fusobacteria in HIV+ (30% vs 10%). At 6 months of ART, persons treated at Fiebig (F) stages III-IV had a higher proportion of Proteobacteria (18% vs 7%, $P<0.05$), a higher percentage of Fusobacteria (9% vs 4.5%) and a lower proportion of Bacteroidetes (37% vs 49%) compared to those treated at FI-II. At baseline, Bacteroidetes and Firmicutes proportions negatively correlated with levels of C-Reactive Protein (CRP) ($r=-0.40$, $p=0.02$) and sCD14 ($r=-0.36$, $p=0.03$) respectively. The increase in Fusobacteria after ART positively correlated with CRP ($r=0.37$, $p=0.04$) and sCD14 levels post ART ($r=0.56$, $p=0.01$) while the percentage of Firmicutes was still negatively associated with sCD14 levels post ART ($r=-0.4$ $p=0.03$).

Conclusion: Changes in the composition of the GI tract microbiome can be observed even in persons treated with ART during acute HIV infection with decreases in Bacteroides and Firmicutes. The association of specific taxa with markers of microbial translocation and systemic inflammation warrants further investigation of the potential role of microbiome alterations in HIV-associated inflammation.

Table 1. Characteristics of study participants

	HIV- subjects	HIV+ subjects
Number of subjects	26	59
Median Age (yrs)	29	28
Gender	Male	Male
Risk	MSM	MSM
Median CD4 count (cells/µl): At baseline After 6 months of ART	-	 386 600
Median HIV-1 RNA (copies/ml): At baseline After 6 months of ART	-	 334889 <50

215 TWO-YEAR CART DOES NOT RESTORE PERIPHERAL BLOOD AND INTESTINAL HIV-RELATED DYSBIOSIS

Camilla Tincati[1], Giuseppe Ancona, Esther Merlini, Antonella d'Arminio Monforte, Giulia Marchetti
Univ of Milan, Milan, Italy

Background: Microbial dysbiosis features HIV+ individuals, both naïve and cART-treated, and is linked to anatomical/structural changes in the gastrointestinal (GI) tract, leading to microbial translocation (MT) and immune activation. Given that data on microbiota modifications during long-term therapy are lacking, we investigated gut/blood microbiota during the first 2 years of suppressive cART.

Methods: We enrolled 41 HIV+, naive subjects and 14 uninfected controls. In HIV+, stool/plasma were collected at baseline (T0), after 12 (T12) and 24 months (T24) of cART. DNA extraction and 16S Metagenomic Sequencing (MiSeq Illumina®) were performed to study the relative abundance at each taxonomic level, α- and β-diversity. GI permeability (LAC/MAN test)/damage (I-FABP; E-cadherin), inflammation (faecal calprotectin) and MT (sCD14, EndocAb, LPS) were measured in HIV+ at T0 and T12 and analysed by Wilcoxon test.

Results: In our cohort 12% were female, 68% MSM, 5% HCV+; median age, CD4+ count, HIV RNA and duration of infection were respectively 42 years, 342/mmc, 5 log10cp/mL and 14 months. We did not detect major changes in plasma microbiota at T12 and T24 or differences between HIV+ and uninfected subjects in relative abundance, α- and β-diversity. With the exception of a selective increase of Negativicutes (class; T0: 6%, T12: 15%; T24: 14%), also the relative abundance of the faecal microbiota did not show significant variations during cART, with stable representation of bacterial families, genera, species. Further, compared to controls, HIV+ constantly displayed lower Ruminhococcaceae (family) and Bacteroides (genera), higher Gammaproteobacteria (class), and an overall trend to increased α-diversity measures (Figure 1A) regardless treatment status/follow-up. While PCoA plots for the study of β-diversity did not show clustering of faecal samples on the basis of the HIV serostatus and length of cART, Lefse analyses (LDS >2.0) confirmed many differences between HIV+ at all study time-points and controls (Figure 1B). At T12, HIV+ experienced a rise in IFABP (p=0.04), a reduction in calprotectin (p=0.01), with no other modifications in MT, gut structure and function.

Conclusion: HIV-related modifications of the microbiota occur within the GI tract and not in the blood and are minimally affected by long-term effective cART, despite evidence of the containment of gut inflammation. These data suggest the ability of the virus to irreversibly impact the microbiological core of chronically-infected individuals.

Figure 1

Figure 1A: Increased α-diversity in HIV+ individuals on cART

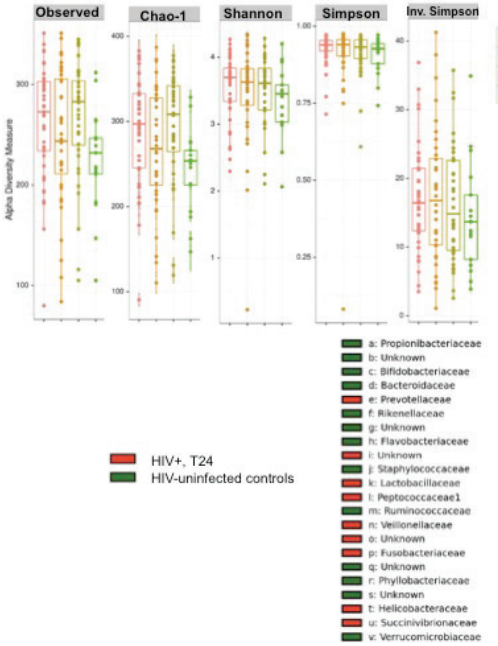
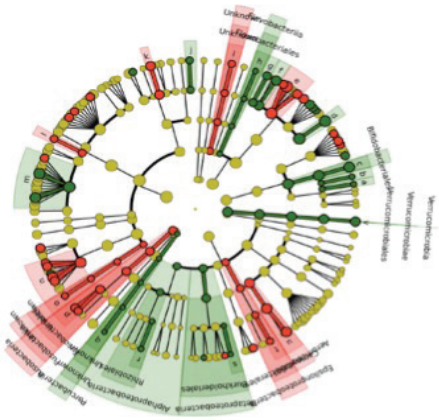


Figure 2A: LefSe Cladogram for faecal bacterial families in HIV+ individuals on stable cART (T24) and HIV-uninfected controls



216 ANTIBIOTICS DISRUPT GASTROINTESTINAL BACTERIA AND HOST IMMUNITY IN RHESUS MACAQUES

Alexander S. Zevin, Jennifer A. Manuzak, Tiffany Hensley-McBain, Ryan Cheu, Charlene Miller, Jacob Modesitt, Jeremy Smedley, Nichole Klatt
Univ of Washington, Seattle, WA, USA

Background: Antibiotics are widely used throughout the world to treat bacterial infections that occur independently or as a result of HIV infection. However, mounting evidence suggests that antibiotic therapies can disrupt the composition of the gastrointestinal (GI) microbiome. Further, HIV infection is associated with disrupted GI microbiota in individuals independent of antibiotic use. GI-resident microbiota are critical for maintaining host immune homeostasis and protecting against the expansion of pathobionts. Additionally, microbiota-derived metabolites, such as short chain fatty acids (SCFAs), are key energy sources for colonic epithelial cells. Thus, we hypothesized that antibiotic therapies would disrupt the GI microbiome and host mucosal immunity.

Methods: We administered antibiotics each to four groups of healthy female rhesus macaques and collected GI biopsies and with stool (Group 1 – enrofloxacin, Group 2 – cephalexin, Group 3 – paramomycin, Group 4 – clindamycin). We evaluated host mucosal immunity throughout the antibiotic treatment at each GI site, and tracked bacterial abundance using qPCR. Finally, we used GC-MS to evaluate the concentration of SCFAs in the stool.

Results: We found that the antibiotic treatments were linked to quantitative shifts in the bacterial abundance in the stool. Intriguingly, we found that the antibiotic treatments dramatically decreased the concentration of all measured SCFAs in the stool, some below the detection limit, including butyrate, the major energy source for colonic epithelial cells. We also demonstrated changes in mucosal immunity during the antibiotic treatment, including a significant increase in colonic and rectal mucosal neutrophils during the treatment, which returned to normal values after cessation of antibiotics. We also found increased frequencies of colonic activated IL-23-producing antigen presenting cells, activated CD4+ T-cells, and IL-17 producing CD4+ T-cells, although this did not reach statistical significance.

Conclusion: Our data demonstrate that antibiotic therapies can alter GI bacterial abundance, lead to a decrease in SCFAs, and that these changes were linked to a distinct signature of mucosal inflammation. These data demonstrate how altering the structure and function of GI bacterial communities can have a profound effect on mucosal immunity. Thus, in HIV infection, resolving bacterial dysbiosis and limiting antibiotic use may be key to maintaining mucosal health.

217 ALCOHOL CONSUMPTION INCREASES SIV FOUNDER VIRUS DIVERSITY TO ALTER DISEASE COURSE

Spencer Robichaux, Angela M. Amedee
Louisiana State Univ, New Orleans, LA, USA

Background: Alcohol abuse is a highly prevalent comorbid condition in the HIV-infected population, which increases the risk of HIV transmission and adversely affects disease progression. Using Simian Immunodeficiency Virus (SIV) infected rhesus macaques exposed to chronic binge alcohol (CBA), our studies have shown that CBA alters multiple aspects of SIV infection and disease by increasing CD4+ target cell proportions in the GALT prior to SIV, increasing susceptibility to rectal mucosal SIV challenge, increasing set point viremia, and decreasing median time to death. Our current studies sought to provide insights into virus:host interactions that affect early replication dynamics and influence disease progression in CBA animals.
Methods: We characterized the founder virus populations (FV) and replication kinetics in 14 CBA and 12 control rhesus macaques inoculated rectally with SIVmac251. FV were assessed using classic single genome amplification of SIV-gp160 and a novel next generation sequencing assay targeting V1-V2.
Results: The numbers FV genotypes transmitted to individual animals did not differ between CBA and controls, with 1-3 genotypes observed (mean of 1.67, 1.86 respectively). However, genotypic analyses of FV populations showed that CBA animals expressed a more diverse founder virus population as compared to controls ($p<0.001$). At viral set point (10 weeks p.i.), CBA-treated animals showed significantly higher levels of viral RNA in both plasma and lymph node reservoirs ($p<0.05$), while similar lymph node proviral DNA burdens were observed CBA and control animals. Further analysis at set point of intra-animal evolutionary changes in viral genotypes showed that control animals exhibited a minor increase in diversity, while CBA animals showed a significant reduction in diversity ($p<0.001$).
Conclusion: These observations suggest that CBA mitigates early host selective pressures resulting in the establishment of a more genetically diverse founder viral population. At set point, increased viral RNA levels in tissue reservoirs and higher plasma viremia in CBA animals, concomitant with a decrease in diversity of expressed viral genotypes.

218 GORILLA ENTERIC VIROME DYNAMICS IN ASSOCIATION WITH SIV INFECTION

Mirela D'arc[1], Carolina Furtado[2], Juliana D. Siqueira[2], Ahidjo Ayouba[3], Martine Peeters[3], Marcelo A. Soares[2]
[1]Univ Fed do Rio de Janeiro, Rio de Janeiro, Brazil, [2]Inst Nacional de Câncer, Rio de Janeiro, Brazil, [3]IRD, Montpellier, France

Background: The ancestors of the four groups of HIV-1 have been described in distinct communities of chimpanzee and gorilla from Cameroon. The infection of chimpanzees with SIVcpz has already been associated with progression to an AIDS-like disease. The expansion of the enteric virome associated with disease progression in an AIDS-like context has also been described in the rhesus macaques model, not observed in the non-pathogenic natural SIV infection of African green monkey. The aim of this study was to identify and compare enteric viromes of SIV-infected and uninfected gorillas, and to assess their relationship with SIVgor pathogenesis in their natural host.
Methods: We analyzed 22 fecal samples from 11 SIV-infected and 11 uninfected gorillas from Cameroon. NGS was carried out in a HiSeq 2500 Illumina platform and analyses were conducted with an in-house pipeline using the programs FastQC, Sickle-Master, BlastX - Viral Database from GenBank/NCBI, MEGAN5 and RStudio.
Results: The viral families Bromoviridae, Myoviridae, Podoviridae, Rhabdoviridae and Tymoviridae were statistically ($p<0.01$) more abundant in the uninfected group, whereas Alloherpesviridae, Herpesviridae, Reoviridae and Siphoviridae families were more abundant ($p<0.01$) in the SIV-infected group. Also, two distinct clusters were recognizable when a 1,000 cp/mL cutoff of SIVgor viral load in faeces (ranged in 655 to 31,497 cp/mL) was used to assess within-group diversity. The 6 samples with higher SIVgor viral load showed Mimiviridae, Myoviridae, Parvoviridae, Phycodnaviridae, Podoviridae, Reoviridae and Retroviridae statistically ($p\leq0.05$) more abundant families and the 5 samples with smaller viral load showed Adenoviridae, Alloherpesviridae, Inoviridae, Siphoviridae and Unclassified Phages statistically ($p<0.05$) more abundant taxa. Finally, we are able to detect adenovirus-assigned reads (virus associated with intestinal disease in rhesus monkeys with advanced AIDS) only in the SIV-infected samples that belong to the smaller viral load group with known infection status for at least 3 years.
Conclusion: The enteric virome dynamics in gorillas could be potentially associated with the SIVgor status. Virome stability studies clearly provide better markers of pathogenic infection progression than bacteriomes. Further studies are still needed to better understand the influence of SIV pathogenesis on infected gorilla populations in the wild, and to associate deeper taxa (virus genera and species) to SIV status in these animals.

219 EARLY HIV-1 DETECTION IN HUMANIZED MICE

Hang Su, Prasanta Dash, Larisa Y. Poluektova, Santhi Gorantla, Howard E. Gendelman
Univ of Nebraska, Omaha, NE, USA

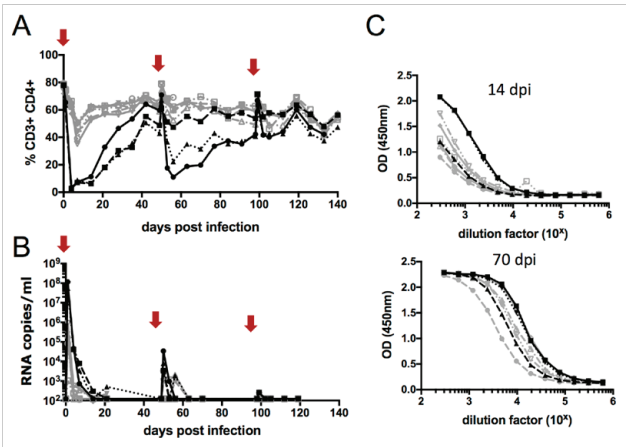
Background: HIV has limited species tropism with viral growth only observed in humans and chimpanzees. This constrains pathobiological, prevention and therapeutic studies to primates. In order to overcome restrictions for the use of small animal models, CD34+ hematopoietic stem cells(HSC) were transplanted into immune-deficient NOD.Cg- NOD. Cg-Prkdcscid Il2rgtm1Wjl/SzJ(NSG) mice. They have served as a platform for studies of HIV-virology, pathogenesis, treatment, prevention and eradication. HIV reservoirs that persist in patients even under suppressive antiretroviral therapy(ART) are major obstacles to viral "cure". As HIV reservoirs are established early in infection and can be restricted by ART, accurate timing for therapeutic intervention is essential to elicit "best" clinical outcomes. Studies of ART timing are thus essential to best understand HIV latency and provide guidance for viral eradication strategies.
Methods: Twenty humanized-NSG mice at 18weeks of age were injected intraperitoneally with HIV-1ADA at 104-tissue culture infective dose50 with 5 uninfected mice as controls. Infected animals were randomly separated into 4 groups and sacrificed at day 3, 5, 7 and 14 after infection. Blood and tissues(spleen liver lung gut kidney and brain) were harvested for immunohistochemistry(HLA-DR and HIV-1p24) and semi-nested real-time PCR tests for HIV-1 DNA and RNA.
Results: Peripheral CD4+ T cell were reduced by 20% after HIV-1 infection in all the groups. IHC-tests showed higher HIV-1p24+ cells at 14 days as compared to other time points. Plasma viral-loads(VL) were between 103 to 105 copies/ml in all 14-day infected animals. VL was detectable in 2 of 5 animals measured by COBAS-Ampliprep HIV-1 detection kit(detection limit<20copies/ml) from days 3, 5 and 7 groups. HIV-1RNA and DNA in all day-14 animals were measured by semi-nested PCR from tissues(spleen lung and gut, 106–108copies/106hCD45+cells), whereas detected(~106 copies) in 2/5 animals in days 3, 5 and 7 tissues(spleen lung liver and gut, detection limit<10copies). HIV-1 was not detected in brain samples tested. We observed a positive correlation between plasma VL and tissue HIV by semi-nested q-PCR in all infected animal groups.
Conclusion: HIV-1 can be seen in CD34+ humanized-NSG mice as early as 3 days after infection at low levels. The timing for fully HIV detection in plasma and tissues in this model is 14 days of infection, at which time any therapy can be started and tissue reservoirs in myeloid and other compartments are established.

220 AN ENGINEERED RNA VIRUS CAUSES ACUTE AIDS IN HUMAN CD4,CCR5 TRANSGENIC MICE

Rachel A. Liberatore, Emily J. Mastrocola, Elena Cassella, Jessie Willen, Fabian Schmidt, Dennis Voronin, Trinity Zang, Theodora Hatziioannou, **Paul Bieniasz**
The Rockefeller Univ, New York, NY, USA

Background: The rarity of the development of broadly neutralizing antibodies (bNAbs) combined with the lack of an inexpensive, tractable animal model has hampered the pursuit of an effective HIV-1 vaccine. In order to model interactions between HIV-1 Env and its receptors in an in vivo setting, we have generated replication competent, recombinant RNA viruses (RhIV) expressing CCR5-tropic HIV-1 envelopes from multiple clades, including transmitted founder viruses. These RhIVs are able to infect transgenic mice bearing CD4-cell restricted expression of human CD4 and CCR5. This model, by focusing entirely on Env-receptor interactions, represents a system in which strategies to block these interactions can be rapidly and rigorously tested. Additionally, these RhIVs are capable of eliciting anti-HIV-1 Env Ab responses and therefore may also be pursued as possible vaccine candidates.

Methods: The ecto- and transmembrane domains of the vesicular stomatitis virus (VSV)-G gene were replaced with those of HIV-1 Env to make RhIV. Transgenic mice were generated using a construct encoding human CD4 and CCR5 downstream of mouse CD4 transcriptional control elements. Mice deficient in type I IFN receptor signaling were made by backcrossing into IFNAR1-null mice.
Results: IFN competent (gray) or null (black) mice expressing hCD4,CCR5 were infected with RhIV.BG505 (red arrows). All animals showed significant CD4 cell depletion in as little as 4 days post infection (A), with the IFNAR1 -/- animals exhibiting an almost complete loss. Viral RNA in plasma peaked in all animals at 1 dpi (B), then rapidly declined. At 14 dpi, BG505.SOSIP-binding antibodies were readily detected by ELISA (C, upper panel). The titers of these antibodies increased significantly following a second infection (C, lower panel). The extent of CD4 depletion and level of plasma viremia were dramatically reduced following each subsequent infection (A&B, red arrows).
Conclusion: We have developed a model system in which the efficacy of HIV-1 prevention strategies that focus on blocking envelope/receptor interactions can be quickly assessed in a sensitive, in vivo setting. Additionally, the combination of RhIV with our hCD4/CCR5 mouse model enables the antibody responses to many different HIV-1 envelopes to be rapidly tested. This unique system enables us to investigate envelope immunogenicity in the context of a replication competent RNA virus, including the possibility of evolving interactions between HIV-1 envelope and anti-envelope antibodies.



221 RAPID T FOLLICULAR HELPER CELL RECONSTITUTION IN LYMPH NODES AFTER ART INITIATION

Chun-Shu Wong[1], Afroditi Boulougoura[1], Angela Kibiy[2], Jeremy Davis[3], Stefania Pittaluga[3], Maura Manion[1], Andrea Lisco[1], Virginia Sheikh[4], JoAnn Mican[1], Irini Sereti[1]
[1]NIAID, Bethesda, MD, USA, [2]Leidos Biomed Rsr, Bethesda, MD, USA, [3]NCI, Bethesda, MD, USA, [4]FDA, Silver Spring, MD, USA

Background: T follicular helper cells (Tfh), defined as CD3+CD4+PD-1+CXCR5+, are specialized T cells, residing in the B cell follicles that assist in B cell survival, proliferation, antibody class switching, and differentiation. The loss of Tfh cells, in chronically infected individuals, is associated with immune dysfunction. Tfh cells have also been implicated as a persistent reservoir of virus-infected cells in persons treated with antiretrovirals (ART) with undetectable plasma HIV RNA levels. Herein, we studied the dynamics of Tfh cells in lymph nodes (LN) before and shortly after ART initiation.
Methods: ART-naïve patients with CD4 counts <100cells/µL were enrolled in a prospective study, Inguinal LNs were collected at baseline (pre-ART) and 4-8 weeks post-ART and cells were extracted for immunophenotyping for flow cytometry. Mann-Whitney test and Wilcoxon matched pair test was used to compare groups, while Spearman's rank correction coefficient was used to test associations.
Results: 22 patients, with a median age of 36 (22-53), 6 females and 16 males, were included and underwent LN biopsies including 13 with paired (pre/post-ART) sampling. Median CD4 count at baseline was 23 cells/µL, and median HIV-RNA was 136,677 cp/mL. Median CD4 count after ART was 82 cells/µL, while median HIV-RNA was 78 c/mL (Table). In addition, median CD8 T cells counts in peripheral blood also increased post-ART from 527 to 713 cells/µL. Subsets of CD4 T cells (naïve, effector, central memory and Treg) did not differ significantly post-ART in LN. The CD8 percentage in LN decreased significantly (X vs y, P) post-ART. The percent of CD4 T cells in LN increased post-ART although the difference was only significant in paired analysis of the 13 paired sample subgroup (X vs Y, P). In contrast, the percentage of Tfh cells increased post-ART treatment in both paired and unpaired analysis (Figure). This increase of Tfh cells was not associated with baseline or post-ART HIV-RNA or CD4 count recovery.

Table. Pre and post-ART characteristics. Median values are shown with IQR in parenthesis.

	CD4 T cell counts (peripheral blood)	% CD4 (LN)	CD8 T cell counts (peripheral Blood)	% CD8 (LN)	Plasma HIV-RNA
Pre-ART	19 cells/µL (10-28)	6.43 (1.09-12.7)	513 (397-623)	71.9 (61.5-84.2)	214062 c/mL (103897-525400)
Post-ART	103 cells/µL (84-169)	15.05 (10.5-31)	713 (419-970)	37.8 (18.4-62.9)	71 c/mL (40-274)

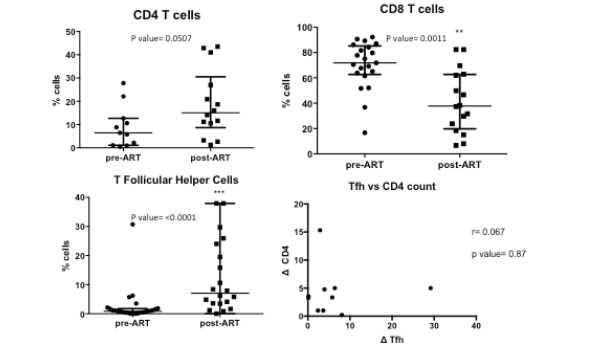


Figure. Pre and post-ART proportion of CD4, CD8 and Tfh cells. The change in Tfh post-ART did not correlate with the CD4 recovery

Conclusion: Tfh emergence in lymph nodes of advanced patients initiating ART occurs early after ART initiation and is independent of plasma viremia or CD4 restoration. The mechanisms of this accumulation are unclear and may have implications in their functionality and their role as HIV reservoirs.

222 INFLAMMASOME AND PYROPTOSIS ARE INVOLVED IN THE LACK OF IMMUNE RESPONSE DURING CART

Michela Masetti[1], Massimiliano Fabbiani[2], Mara Biasin[1], Antonio Muscatello[2], Nicola Squillace[2], Elisa Colella[2], Mario Clerici[3], Andrea Gori[2], Daria Trabattoni[1], Alessandra Bandera[2]
[1]Univ of Milan, Milan, Italy, [2]San Gerardo Hosp, Monza, Italy, [3]Univ of Milan, Segrate, Milan, Italy

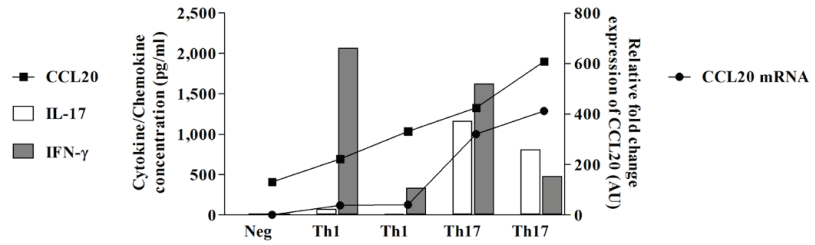
Background: Inflammasome-mediated activation of caspase-1 regulates inflammatory responses and pyroptosis. Pyroptosis was recently shown to play a major role in CD4 T lymphocyte loss and to contribute to immune activation in HIV infection1.The possible role of inflammasomes and pyroptosis in the lack of immune reconstitution seen in a percentage of ART-treated HIV patients has nevertheless not been investigated. We analyzed possible associations between inflammasome activity, caspase-1 activation, pyroptosis and immune reconstitution in HIV+ ART treated patients1Doitsh G et al., 2014

Methods: Cross-sectional, single-site study. HIV-infected patients on antiretroviral therapy for≥24 months and plasma HIV-RNA<50 cp/mL for≥12 months, matched for nadir CD4 T cell count were enrolled. Presence of opportunistic AIDS-related diseases, HBV or HCV coinfection, chronic inflammatory disorders, ongoing immunosuppressive therapy were exclusion criteria. Patients were classified as immunological responders (IR) or non responders (INR) if CD4 count was ≥500 or ≤350 cells/µL, respectively. Expression of inflammasome, caspases 1, 3, 4, and 5, pro-inflammatory cytokines and of IFI16 genes was measured in unstimulated and in AT2-HIV-1 stimulated cells of all IRs and INRs
Results: 39 patients (22 IR; 17 INR, 77% M, medians: age 47 years, time from HIV diagnosis 10 years, time with HIV-RNA<50cp/mL 57 months) were enrolled. INR patients were older (median 60vs.43 years, p<0.001) and had a higher prevalence of past AIDS-defining illnesses (76%vs.18%, p<0.001). Median CD4 count was 840 (IQR 718-1131) cells/µL in IR vs. 295 (IQR 256-343) cells/µL in INR. AT2 stimulation induced NLRP3 gene expression in both IR and INR; NLRP3 and IL-18 expression were nevertheless significantly increased in INR compared to IR (p=0.009 and p=0.004). Significant higher caspase-1 expression was seen as well in both unstimulated (p=0.02) and AT2-stimulated cells of INR (p=0.003), whereas caspase 3, 4 and 5 expression was similar in both groups. Finally, IFI16 expression as well plasma concentration of caspase-1 and IL-1β were higher in INR compared to IR patients
Conclusion: Increased inflammasome and caspase-1 activation is observed in INR patients. The upregulation of these proinflammatory mechanisms plausibly contributes to the persistent immune activation that characterize INRs. Notably, caspase-1 activation is likely to induce CD4 T cell loss via pyroptosis, contributing to the unsatisfactory CD4 recovery seen in INRs

223 INCREASED IL-18/IL-1B RATIO BLUNTS CCL20 PRODUCTION AND TH17 GUT HOMING DURING CART

Claire Loiseau[1], Mary Requena[2], Anne Laure Iscache[1], Michelle Cazabat[2], Nicolas Carrere[2], Bertrand Suc[2], Bruno Marchou[2], Jacques Izopet[2], Pierre Delobel[2]
[1]INSERM, Toulouse, France, [2]CHU Toulouse, Toulouse, France

Background: HIV-1 infection is characterized by a disruption of the intestinal immune barrier integrity. During immune reconstitution, HIV-1-infected individuals under cART do not fully reconstitute gut CD4+ T cells, especially Th17 cells, partly due to the alteration of the CCR6-CCL20 chemotactic axis. The paucity of Th17 cells in the gut mucosa contrasts with the abundance of Th1 cells in these subjects. IL-18 and IL-1β, both inflammasome-dependent mediators, govern the expansion and survival of Th1 and Th17 cells, respectively. We thus explored the role of IL-18 and IL-1β on CCL20 production by enterocytes.
Methods: IL-18 and IL-1β were quantified in blood and small intestine samples from HIV-1-infected individuals under effective cART (n=20) and uninfected controls (n=10). The direct effect of IL-18 and IL-1β on CCL20 expression was assessed ex vivo on human primary enterocytes. To explore the impact of an IL-18- or IL-1β-enriched gut microenvironment, Th1 and Th17 cells were sorted by flow cytometry on the basis of their CXCR3+CCR4-CCR6- and CXCR3-CCR4+CCR6+CD161+ phenotype respectively and ex-vivo expanded with either IL-1β/IL-23 or IL-18/IL-12. Then, cocultures between T cells and primary enterocytes were done to mimick the gut microenvironment. The transcriptome of the enterocytes and the production of cytokines/chemokines by both enterocytes and lymphocytes were evaluated by mRNA and protein multiplex assays.
Results: HIV-1-infected individuals under cART have a significant increase of IL-18 concentration compared to uninfected controls (P<0.05), leading to an increased IL-18/IL-1β ratio. Ex vivo on primary enterocytes, IL-18 induces a decrease of CCL20 expression by about 100-fold whereas a strong increase was observed after IL-1β stimulation (>100-fold). IFN-ɣ, the classical Th1-associated cytokine, also reduces CCL20 production by the enterocytes while it increases IL-18 production. In coculture experiments, CCL20 expression (mRNA and protein) decreases when epithelial cells interact with lymphocytes previously expanded in presence of IL-18. IL-18 thus contributes to reduce the production of CCL20 by the enterocytes, both directly and indirectly by promoting IFN-ɣ-producing Th1 cells.
Conclusion: An IL-18/IL-1β ratio skewing from IL-1β to IL-18 in HIV-1-infected individuals could be one of the mechanisms involved in the reduced production of CCL20 by the enterocytes, and in the imbalance between reduced Th17 and increased Th1 cells in the gut mucosa.



IL-2	-	+	+	+	+
IL-1β	-	-	+	-	+
IL-12	-	+	-	+	-
IL-18	-	+	-	+	-
IL-23	-	-	+	-	+

224 GENITAL HIV SHEDDING WHEN ANTIRETROVIRAL THERAPY (ART) SUPPRESSES PLASMA HIV RNA

Marta E. Bull[1], Caroline Mitchell[2], Corey Williams[3], Jaime Soria[4], Eduardo Ticona[5], Alberto M. La Rosa[6], Joan Dragavon[1], Robert Coombs[1], Lisa Frenkel[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Massachusetts General Hosp, Boston, MA, USA, [3]Seattle Children's Rsr Inst, Seattle, WA, USA, [4]Hosp Nacional Dos de Mayo, Lima, Peru, [5]Hosp Dos de Mayo, Lima, Peru, [6]Asociación Civil Impacta Salud y Educación, Lima, Peru

Background: HIV RNA shedding from the genital tract (GT) during antiretroviral therapy (ART) that suppresses plasma HIV RNA <30copies/mL (c/mL) (defined as discordant (DSC) shedding) has been reported in up to 50% of persons, possibly due to poor drug penetration or genital inflammation. We hypothesized DSC shedding is caused by production of HIV RNA from infected cells without full-cycles of viral replication.
Methods: HIV-infected Peruvians initiating ART were followed quarterly for 24 months to detect DSC shedding in cervicovaginal lavage (CVL) at >40c/mL, seminal plasma (SP) at >120c/mL, and rectal secretions (RS) >1,525c/mL) by real-time PCR. Subject's pre-ART specimens and DSC shedding specimens underwent single-genome-amplification (SGA) of env and pol for phylogenetic analyses.
Results: 126 ART-naïve Peruvians were enrolled; 90 completed all study visits with 82/90 (91%) having sustained ART-suppression. Subjects overall had pre-ART CD4 counts consistent with AIDS (median: 127 cells/uL, IQR: 63-213), with no differences noted in HIV RNA or PBMC DNA concentrations in those with DSC shedding compared to those with sustained genital tract suppression. DSC shedding was detected in genital secretions of 23/82 (28%) subjects at 40/726 (5%) visits. Median HIV RNA in DSC shedding specimens were: CVL 82c/mL, IQR: 53-189c/mL; SP 350c/mL IQR: 207-509c/mL; and RS 5,880c/mL, IQR: 1,758-14,484c/mL. SGA yielded HIV RNA env and pol sequences from 2/40 DSC shedding specimens (one CVL and one SP). Genital HIV RNA sequences (and DNA from the female) from these subjects clustered into a single monotypic clade in their respective

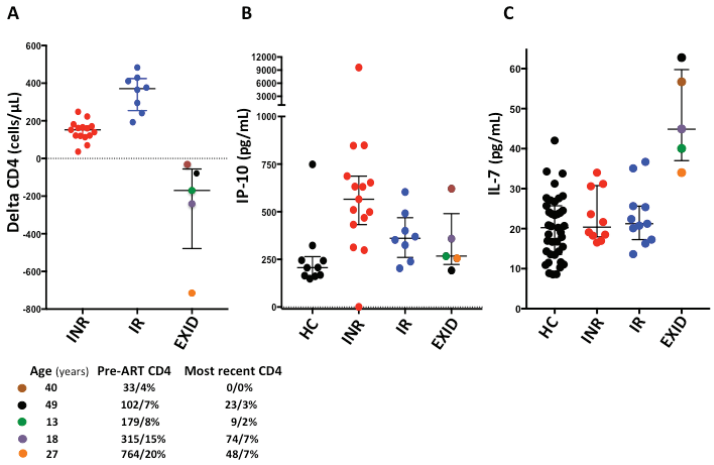
phylogenetic trees. Drug resistance mutations were not detected in DSC shedding pol specimens. Due to the unexpectedly low yield of SGA sequences, the 13 CVL that tested positive for RNA were retested by Abbott and only 2/13 (15%) specimens tested positive.
Conclusion: Intermittent DSC HIV RNA shedding from the GT when HIV replication was suppressed in plasma was detected infrequently. In cases where DSC shedding was phylogenetically characterized we found primarily monotypic RNA and DNA sequences from subjects known to have diverse HIV quasispecies prior to ART, which suggests DSC shedding may come from clones of cells that produce virions. None of our findings suggested ongoing HIV replication in the genital tract, but rather suggest that inflammatory signals may have induced cell to produced virions.

225 PREDICTORS OF IMMUNE RECOVERY AFTER ART IN VERY ADVANCED DISEASE

Pablo F. Belaunzaran-Zamudio[1], Alejandro Olmedo[1], Irini Sereti[2], Yanink Caro-Vega[1], Adam Rupert[3], Alondra López[1], Ian Sanne[4], Juan Sierra-Madero[1], Michael M. Lederman[5]
[1]Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zuirán, Mexico, Mexico, [2]NIAID, Bethesda, MD, USA, [3]Leidos Biomed Rsr, Inc, Frederick, VA, USA, [4]Univ of the Witwatersrand, Johannesburg, South Africa, [5]Case Western Reserve Univ, Cleveland, OH, USA
Background: In the CADIRIS trial ART naïve patients with CD4 <100/uL were studied to examine the effect of CCR5 antagonism on occurrence of IRIS. In this analysis we aimed to identify baseline biomarkers as predictors of immune recovery (IR).
Methods: We measured plasma levels of interferon-γ, interleukin (IL)-1b, IL-6, IL-8, IL-10, IL-12p70, IL-17, tumor necrosis factor-α (TNFα), C-Reactive Protein (CRP), serum amyloid A (SAA), P-selectin, interferon-inducible protein (IP)-10, Leukotriene B4 (LTB4), soluble (s) CD14, sCD40 ligand, sCD163, Von Willebrand Factor (vWF), fibrinogen, proteins C and S, D-Dimer, and hydroxyvitamin D before ART initiation. Immune recovery (IR) was defined as reaching CD4>200cell/uL during 48-week follow-up after ART initiation.
Results: We studied 267 Mexican and South African patients enrolled in the CADIRIS trial (133 received placebo and 134 maraviroc). One hundred and twenty-nine subjects (48%) had a CD4 measurement >200cells/uL during follow-up (48 weeks). The distribution of patients with immune recovery was not different between treatment arms (placebo 58 (44%) and maraviroc 71 (53%), p=0.1). Lower levels of CRP (OR 9.8 per mg/l, p=0.01), SAA (OR 0.99 per mg/L, p=0.04), IL-8 (OR 0.97, p=0.04), and sCD163 (OR 0.99 per ng/mL, p=0.03) were associated with increasing odds of reaching a CD4 count ≥200 cells/μL during follow-up. In multivariate analyses, including age, baseline HIV-RNA, CD4, CRP, IL-8 and IL-17 and sCD163 in a logistic model we observed significant, inverse relationships between increasing age (OR 0.96 95%CI 0.94-0.99 per increasing year, p=0.04), baseline CRP (OR 0.98 95%CI 097-0.99 for every mg/dL increase, p=0.04) and sCD163 levels (OR 0.98 95%CI 099-0.99 for every ng/mL increase, p=0.04) the likelihood of adequate immune recovery.
Conclusion: In chronically HIV-infected patients initiating ART in advanced disease, increasing age, high CRP and sCD163 levels were inversely associated with the probability of achieving adequate immune recovery during the first year after ART initiation

226 PARADOXICAL CD4 DECLINE ON ART: A NOVEL, RARE AND PERPLEXING IMMUNOLOGIC OUTCOME

Andrea Lisco[1], Itzchak Levy[2], Jason Brophy[3], Claire Deleage[4], Chun-Shu Wong[1], Adam Rupert[5], Caryn G. Morse[6], Shanna Chan[7], Jacob D. Estes[4], Irini Sereti[1]
[1]NIAID, Bethesda, MD, USA, [2]Academic Med Cntr Hosp, Tel Aviv, Israel, [3]Children's Hosp of Eastern Ontario, Ottawa, Canada, [4]Frederick Natl Lab for Cancer Rsr, Frederick, USA, [5]Leidos Biomed Rsr, Inc., Frederick, MD, USA, [6]NIH, Bethesda, MD, USA, [7]Winnipeg Regional Hlth Authority, Manitoba, Canada
Background: The goal of antiretroviral therapy (ARV) is to suppress HIV-1 replication and restore CD4 T cells. Immune activation, lymphoid tissue fibrosis and impaired homeostatic signaling have been associated with poor CD4 recovery. Here, we report on HIV-infected individuals, who had a paradoxical decline in CD4 despite ARV-mediated plasma HIV suppression. We defined such immunological outcome as extreme immune decline (EXID).
Methods: Demographic, clinical and virological characteristics were analyzed for EXID subjects (n=5), and compared to immunological responders (IR, defined as CD4 > 270 cells/μL after 2 years on ARV, n=15) and immunological non-responders (INR, defined as CD4 < 270 cells/μL after 2 years on ARV, n=8). PBMCs were immunophenotyped by flow cytometry. Plasma cytokines and anti-cytokine autoantibodies were measured by ELISA and multiplex-bead array. Continuous variables were compared by Mann–Whitney test.
Results: All EXID subjects were infected with a non-B HIV-1 subtype and 4 out of 5 (80%) were African. No subjects were on tenofovir/didanosine-based regimens and 80% of EXID subjects had received ≥3 different ARV regimens. After median ARV duration of 2 years, EXID subjects had a median CD4 decrease of 170 cells/μL, while IR and INR had a median increase of 183 cells/μL and 388 cells/μL, respectively (p=0.02, Figure 1A). The proportion of naïve CD4 cells was different between the EXID, IR and INR (4%, 15%, 33%, respectively, p<0.05). Although, the fraction of HLA-DR/CD38/CD8 T cells was different between IR and INR subjects (29% vs 19%, p=0.01), EXID had a similar proportion of these cells compared to IR or INR subjects (23%, p>0.05). No difference was noted in plasma levels of inflammatory cytokines between EXID and HIV-negative controls (HC), while TNFα, IL-8 and IP-10 were increased in INR compared to HC (p<0.03, Figure 1B). IL-7 was increased in EXID compared to HC (p<0.01), but not in IR or INR compared to HC (p>0.05, Figure1C). Anti-cytokine autoantibodies were absent in plasma of EXID subjects. Genetic screening for primary immunodeficiencies was performed in 2 EXID subjects and was unrevealing.
Conclusion: EXID can occur in absence of lymphoproliferative diseases or myelotoxic nucleoside analogues combinations and may be associated with non-B HIV subtype. EXID is a distinct entity from previously described INR, and is not linked to higher immune activation or increased level of inflammatory cytokines but is accompanied by an increase in homeostatic cytokines.



227 EFFECT OF EXOGENOUS INTERFERON ALPHA ON HIV VIRAL POPULATIONS IN VIVO

Giorgio Bozzi[1], Wei Shao[2], Robin L. Dewar[2], Vinay K. Pathak[1], Belete A. Desimmie[1], Ryan C. Burdick[1], Sara Jones[3], Claudia Balotta[4], Mary E. Wright[5], Frank Maldarelli[1]
[1]NCI, Frederick, MD, USA, [2]Leidos Biomed Rsr, Inc, Frederick, MD, USA, [3]Leidos Biomed Rsr, Inc, Bethesda, MD, USA, [4]Univ of Milan, Milan, Italy, [5]NIAID, Bethesda, MD, USA

Background: Type I interferons (IFN) reduce HIV viremia c. 0.3 log10 copies/ml in the absence of antiretroviral therapy (Tavel et al., 2010) and have been reported to delay HIV rebound after discontinuing ART (Montaner, et al., 2013). Mechanisms of viral inhibition remain poorly characterized, but may proceed by immune or direct antiviral mechanisms through IFN-stimulated genes (ISG), such as APOBEC-induced hypermutation (HM), which is induced in some cell types. The effects of IFN alone in HIV infection have not been extensively studied. We investigated the direct effect of IFN-alpha on HIV populations, analyzing stored samples from a pre-ART randomized trial of individuals undergoing therapy with interferon.

Methods: Peripheral blood lymphocytes (PBL) were obtained from a randomized study comparing the effects of therapy with IFN-alpha (1 million units sc, daily, escalating to 7.5 MIU), AZT (200 mg every 4 h), or the combination in HIV infected individuals with CD4 cells > 500 cells/µl. Samples pre/post 48 wk therapy from individuals with >1 log decrease in viremia during IFN were analyzed. HIV pro-pol single genome sequences (SGS) of c. 1200 nt were obtained from PBL-derived DNA, aligned (MEGA), and subjected to phylogenetic and population genetics analyses, including analysis to distinguish APOBEC3G (A3G) and 3F (A3F)-mediated changes (Desimmie et al., 2016). As interferon suppression of viremia was incomplete, we also investigated HIV populations in individuals in the trial treated with AZT monotherapy with comparable VL decrease.

Results: We analyzed 487 HIV DNA SGS from individuals 48 weeks before and after IFN-alpha (N=4) or AZT (N=3) monotherapy. At entry participants had relatively early HIV infection (CD4 >500 cells/µl), and a mostly low diversity, with a mean percent average pairwise difference (APD) of 0.53% [0.2-1.1]. APD increased after 48 weeks, implying replication. At baseline HM represented 0-14% of intra-patient SGS. No significant HM increase, and no significant differences in the proportion of A3G- or A3F-mediated HM were detected comparing pre/post interferon or IFN/AZT (Fisher exact N.S.). Phylogenetic and population genetic analyses revealed no evidence of population shift.

Conclusion: HIV populations were similar pre- and post-IFN, and HM did not accumulate in PBL in individuals undergoing IFN even with >1 log reduction in viremia. IFN suppressed but did not eliminate HIV variants, suggesting other ISG, such as BST-2, may contribute to reductions in viremia.

228 GENOME-WIDE METHYLATION IS ASSOCIATED WITH HIV-1 INFECTION AND DISEASE PROGRESSION

Sara Moron-Lopez[1], Judith Dalmau[1], Victor Urrea[1], Miguel Lopez[2], Maria C. Puertas[1], Beatriz Mothe[1], Christian Brander[1], Manel Esteller[2], Maria Berdasco[2], Javier Martinez-Picado[1]
[1]IrsiCaixa Inst for AIDS Rsr, Badalona, Spain, [2]Bellvitge Biomed Rsr Inst, L'Hosp de Llobregat, Spain

Background: Human genetic variation —mostly in the HLA and CCR5 regions— explains 25% of the variability in HIV-1 disease progression. However, it is also known that viral infections are able to modify cellular DNA methylation patterns. Therefore, changes in the methylation of CpGs islands could modulate HIV-1 disease progression.

Methods: We recruited 43 HIV-1 infected patients and 22 HIV-1 negative donors. A total of 84 samples were analyzed, obtained from: 22 Elite Controllers (EC group), 21 Viremic HIV-1-infected patients (Viremic group, median viral load at sample time point of 4.97 HIV-1 RNA copies/ml of plasma), 21 same Viremic patients after combination antiretroviral therapy initiation (cART group), and 22 HIV-1 negative donors (Uninfected group). Following DNA extraction from $CD4^+$ T lymphocytes, DNA was bisulfite-converted and genotyped with Illumina Infinium Human Methylation450 arrays. After normalizing the data, we compared DNA methylation patterns between the different groups (EC, Viremic-cART paired, and Uninfected).

Results: Our preliminary data highlighted 29 genes with differentially methylated promotor regions (DMR, difference in methylation >5%). The biological process enrichment analysis showed that most of these genes have a function related with either type I interferon signaling pathway, cytokine-mediated signaling pathway and regulation of viral process ($p<10^{-6}$). We selected 5 genes with several differentially methylated CGs in their promotor in Viremic and in EC. Specifically, we found that SPOCK2 was hypomethylated in Viremic compared with Uninfected individuals, cART and EC; USP18 was hypomethylated in Viremic vs. EC; MIB2 was hypomethylated in EC compared with Viremic and cART, and NSD1 and AURKC were hypermethylated in EC in comparison to Viremic and cART. These results suggest that MIB2, NSD1 and AURKC may play a role in *in vivo* HIV-1 control.

Conclusion: Our results demonstrate that cellular DNA methylation is associated with HIV-1 infection and disease progression, specifically modifying the expression of genes with an immune- or viral regulation-related function. Therefore, the epigenetic regulation of host gene expression could partially explain the variability in HIV-1 disease progression. Further knowledge of the mechanism by which host DNA methylation modulates HIV-1 progression might guide the design of future therapies to achieve the remission of HIV-1 infection.

229 MITOCHONDRIAL HAPLOGROUP AND HLA-B MAY JOINTLY INFLUENCE HIV VIRAL LOAD AND CD4 COUNT

Samuel Bailin, Mark Pilkinton, David C. Samuels, Silvana Gaudieri, Spyros Kalams, Todd Hulgan
Vanderbilt Univ, Nashville, TN, USA

Background: Genetic polymorphisms within the human leukocyte antigen (HLA) loci are important predictors of long-term HIV-1 progression. In particular, HLA-B27, B57, and B58 have been associated with lower viral load (VL) and stable CD4+ T-cell counts. More recently, studies have also shown that mitochondrial DNA (mtDNA) haplogroups are associated with CD4+ T-cell dynamics before and after initiation of antiretroviral therapy (ART). We hypothesized that HLA-B allele influence on VL and CD4+ T-cell count may differ between mtDNA haplogroups.

Methods: Individuals with HIV-1 infection, CD4+ T-cell count >350, and a range of VL off ART were recruited from the Vanderbilt Comprehensive Care Clinic. Demographic data, CD4+ T-cell count, VL, HLA class-I-allele typing, and mtDNA genotyping by Sequenom with haplogroup assignment by HaploGrep were utilized. CD4+ T-cell count and VL in individuals with HLA-B27, B57, and B58 were compared to those with other HLA-B alleles by Wilcoxon ranksum test, stratified by self-reported ancestry and mtDNA haplogroup. Frequencies of HLA-B27, B57, and B58 were compared across mtDNA haplogroup by Chi2 tests.

Results: 126 individuals had mtDNA genotyping and haplogroup assignment (median baseline age 35 years, CD4+ T-cells 563 cells/mm3, VL 2436; 28% female and 50% self-reported African-American). Mitochondrial haplogroup was not significantly associated with VL or CD4+ T-cell differences. As expected, individuals with HLA-B27, B57, or B58 alleles (HLA-B+; N=41) had higher and lower CD4+ T-cells (p=0.009) and VL (p=0.004), respectively. Higher CD4+ T-cell count was seen among HLA-B+ with European haplogroup H (N=28; p=0.03) and tended to be higher with African L2 (N=15; p=0.08), but not with other haplogroups. VL tended to be lower in HLA-B+ with non-H mtDNA haplogroups (N=24; p=0.09). Haplogroup H also tended to include a higher frequency of HLA-B27, B57, or B58 allele carriers than non-H haplogroups (p=0.06), but no differences were found within the African ancestry lineage (L1, L2, or L3) or between African and European mtDNA ancestry.

Conclusion: In this cohort of persons off ART, we observed associations between HLA-B alleles and VL and CD4+ T-cell count as previously described. Within some mtDNA haplogroups, we also observed novel differences in HLA-B frequencies, and in the influence of HLA-B alleles on VL and CD4+ T-cell count. Further studies with larger sample sizes are needed to better understand these potential genetic interactions and their implications.

230 T-CELL PHENOTYPE AND RECEPTOR DIVERSITY IN BLOOD & ADIPOSE TISSUE FROM HIV+ PERSONS

John R. Koethe[1] Arion Kennedy, Wyatt J. McDonnell, Ian Setliff, Chike O. Abana, Mark Pilkinton, Cindy Hager, Spyros Kalams, Alyssa Hasty, Simon Mallal
Vanderbilt Univ, Nashville, TN, USA

Background: A high percentage of circulating activated and memory CD4+ and CD8+ T cells is associated with increased risk of developing diabetes in HIV-infected (HIV+) and HIV-negative persons, but the physiologic basis for this finding is unclear. In adipose tissue (AT), T cells modulate local inflammation and adipocyte insulin sensitivity; therefore, we hypothesized the distribution of T cells in peripheral blood from HIV+ persons is reflective of the distribution in AT.

Methods: We recruited 10 non-diabetic HIV+ adults on long-term antiretroviral therapy with sustained virologic suppression to undergo fasting blood collection and subcutaneous abdominal AT biopsy. We measured the percentage of CD4+ and CD8+ T cells in AT and blood expressing activation (CD38, HLA-DR), exhaustion (PD-1), senescence

(CD57) and memory (CD45RO) surface markers by flow cytometry. We compared T cell surface marker expression in paired blood and AT using Wilcoxon Signed Rank tests, and the correlation using Spearman's tests. We performed T cell receptor (TCR) sequencing on sorted CD8+ cells and compared the repertoire diversity in blood versus AT using the tcR R statistics package. Proportional downsampling and bootstrapping were used to account for read count distribution differences between tissue compartments.
Results: Six subjects were female, median age was 46 years, median CD4+ count was 819 cells/µl, and median antiretroviral therapy duration was 9.6 years. AT had a higher overall percentage of CD8+ T cells compared to blood, and was also enriched for activated CD8+ T cells (p<=0.01 for all; see Table). The percentages of memory CD4+ T cells in AT and blood were correlated, as were the percentages of activated HLA-DR+ CD8+ T cells. The 10 most prevalent CD8+ TCR clones comprised a larger percentage of total clones in the AT compared to blood (25% vs. 16%, p=0.04), and the Shannon's Entropy index, a measure of overall repertoire diversity, was lower in AT compared to blood (4.39 vs. 4.46; p=0.05).
Conclusion: In this pilot study, subcutaneous AT from HIV+ patients was enriched for activated CD8+ T cells, which promote adipocyte insulin resistance, and TCR analysis showed less repertoire diversity and a disproportionate expansion of specific CD8+ T cell clones in AT compared to blood. The percentages of memory CD4+ T cells and activated CD8+ T cells were correlated between blood and AT, which may be relevant to understanding the epidemiologic association of peripheral T cell activation and diabetes risk.

Table. Surface marker expression on CD4+ and CD8+ T cells from paired blood and adipose tissue (n=10)

	Comparison of median percentage in blood vs. adipose tissue				Correlation between blood and adipose tissue	
T cell subset	Median in Blood (IQR)	Median in adipose tissue (IQR)	p-value		Spearman rho	p-value
Total CD4+ %	42.6 (35.1, 45.8)	33.1 (28.3, 38.9)	**<0.01**		0.96	**<0.001**
CD4+ PD1+% (exhaustion)	24.6 (20.2, 27.0)	24.9 (17.7, 30.5)	0.86		0.58	0.08
CD4+ CD38+% (activation)	4.0 (1.9, 6.3)	2.7 (2.0, 4.2)	0.44		0.39	0.27
CD4+ DR+% (activation)	1.0 (0.6, 1.6)	3.5 (1.5, 5.6)	**<0.01**		0.60	0.07
CD4+ CD45RO+% (memory)	51.3 (47.6, 62.7)	53.7 (47.6, 69.5)	0.96		0.84	**<0.01**
Total CD8+ %	51.7 (42.7, 59.6)	61.0 (52.8, 67.2)	**<0.01**		0.83	**<0.01**
CD8+ PD1+% (exhaustion)	20.6 (11.4, 27.7)	20.0 (13.4, 25.1)	0.89		0.84	**<0.01**
CD8+ CD38+% (activation)	0.5 (0.5, 0.6)	0.9 (0.5, 1.1)	**0.01**		0.32	0.37
CD8+ DR+% (activation)	0.9 (0.8, 1.2)	5.5 (3.2, 10.3)	**<0.01**		0.63	**<0.05**
CD8+ CD45RO+% (memory)	31.3 (18.1, 55.9)	32.6 (20.8, 54.6)	0.31		0.35	0.33

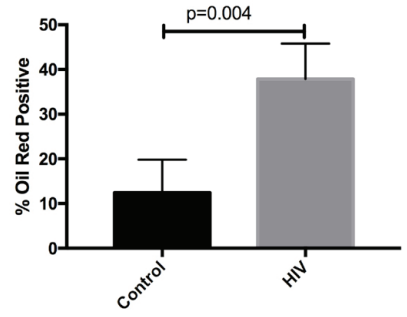
231 REDUCED APOPTOSIS CONTRIBUTES TO GASTROINTESTINAL NEUTROPHIL INFILTRATION IN HIV

Tiffany Hensley-McBain[1], Jennifer Manuzak[1], Charlene Miller[1], Alexander S Zevin[1], Eric Lee[2], Cara Wilson[2], Thomas Hope[3], Adam Burgener[4], Nichole Klatt[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Univ of Colorado Anschutz Med Campus, Aurora, CO, USA, [3]Northwestern Univ, Evanston, IL, USA, [4]Pub Hlth Agency of Canada, Winnipeg, Canada
Background: HIV infection is associated with mucosal dysfunction and inflammation, which is associated with morbidities and mortality. However, the mechanisms underlying these dysfunctions are not resolved. Imaging studies indicate increased neutrophils in the GI tract during HIV infection, potentially contributing to mucosal inflammation. In inflammatory bowel disease, neutrophils contribute to pathogenesis and GI infiltration is linked to delayed homeostatic apoptosis and longer lifespan, yet GI neutrophil apoptosis in HIV remains unexamined. Further, given the well-described shift in the GI microbiome in HIV and the fact that bacterial ligands affect neutrophil lifespan, there is potential for altered bacteria to contribute to increased GI neutrophils in HIV. Our study aimed to better assess neutrophil infiltration in the GI in HIV infection and investigate Caspase-3 dependent homeostatic apoptosis. We further sought to understand how HIV altered mucosal bacteria (HAMBs), or those increased or decreased in the GI, affect neutrophil apoptosis.
Methods: Isolated leukocytes from rectosigmoid colon biopsies taken from treated, HIV-infected (n=10) and uninfected (n=8) individuals were phenotyped by flow cytometry to examine neutrophil frequency and active Caspase-3 expression. In additional experiments, blood from infected and uninfected individuals (n=8) was stimulated for 20 hours with a panel of six HAMBs that included Gram-negative and Gram-positive bacteria and those increased or decreased in HIV prior to phenotyping.
Results: We found increased neutrophils (p=0.0219) and reduced active Caspase-3 expression in neutrophils (p<0.0001) in the GI of HIV-infected indviduals compared to uninfected controls. Further, neutrophil frequency negatively correlated with Caspase-3 expression (p=0.0207). Blood stimulations demonstrated that while dysbiotic bacteria decreased Caspase-3 expression compared to media controls, beneficial Lactobacillus increased Caspase-3 (p=0.0219).
Conclusion: These are the first data demonstrating that increased neutrophils in the GI in HIV may be a consequence of delayed homeostatic apoptosis. Our data also suggest dysbiosis that results in decreased anti-inflammatory bacteria such as Lactobacillus species and increased bacteria such as Prevotella species may alter neutrophil apoptosis and prolong GI neutrophil lifespan in HIV. These data provide a novel mechanism by which microbial dysbiosis in HIV infection may contribute to neutrophil accumulation and mucosal dysfunction.

232 HIV INDUCES LIPID ACCUMULATION IN ALVEOLAR MACROPHAGES IN VITRO

Amy K. Dickey[1], Bjorn Corleis[2], Abigail Schiff[3], Antonella Lisante[2], Benjamin Medoff[1], Josalyn Cho[1], Douglas Kwon[2]
[1]Massachusetts General Hosp, Boston, MA, USA, [2]Ragon Inst of MGH, MIT, and Harvard, Cambridge, MA, USA, [3]Harvard Univ, Boston, MA, USA
Background: In patients with HIV, infection with respiratory pathogens is an important cause of morbidity and mortality. Alveolar macrophages are the predominant immune cell in the airways in non-disease states and are thought to act as the initial defense against pulmonary pathogens. Monocytes from HIV+ individuals are known to have decreased expression of ABCA1, a gene responsible for lipid efflux, and these monocytes are more likely to become lipid-laden macrophages in arterial walls, promoting atherosclerosis. Lipid-laden macrophages are of particular interest in airway immunity because they are deficient in uptake of M. tuberculosis (Mtb) and impaired in Mtb intracellular killing, while simultaneously acting as promoter of Mtb latency. Because these studies on lipid-laden macrophages have been performed using monocyte-derived macrophages (MDMs) in vitro, it is unclear whether or not these lipid-laden macrophages are abundant in the alveolar space in patients with HIV, and, if present, what effect these cells would have on airway immunity.

Methods: MDMs and alveolar macrophages were infected with HIV in vitro, and lipid accumulation was determined both by microscopy using Oil Red staining and by flow cytometry using Bodipy staining. Lipid accumulation was also measured in macrophages isolated from bronchoalveolar lavage (BAL) fluid of patients with and without HIV using Oil Red staining. RNA sequencing was performed on the BAL fluid of patients with and without HIV.
Results: In MDMs in vitro, HIV infection resulted in lipid accumulation, as determined both by Oil Red and Bodipy staining. Similarly, alveolar macrophages infected with HIV in vitro demonstrated lipid accumulation by Oil Red staining. Surprisingly, alveolar macrophages from treated HIV+ patients demonstrated no increase in Oil Red positivity compared to HIV- controls. Furthermore, RNA sequencing data from alveolar macrophages in a separate cohort of untreated HIV+ patients demonstrated increased, not decreased, expression of ABCA1 compared to HIV- controls.
Conclusion: HIV infection induces lipid accumulation in vitro in MDMs and alveolar macrophages, but no lipid accumulation is observed in the BAL fluid of treated HIV positive patients in vivo. A possible explanation could include the differential expression of ABCA1 in the blood and alveolar space in patients with and without HIV.



HIV induces lipid accumulation in monocyte-derived macrophages on glass coverslips after 5 days of infection.

233 TIM-3 IS A MARKER OF PDC DYSFUNCTION IN HIV INFECTION

Jordan A. Schwartz[1], Kiera L. Clayton[1], Shariq Mujib[1], Hongliang Zhang[1], Nur-ur Rahman[1], Jun Liu[1], Feng Yun Yue[1], Erika Benko[2], Colin Kovacs[1], Mario Ostrowski[1]
[1]Univ of Toronto, Toronto, Canada, [2]Maple Leaf Med Clinic, Toronto, Canada

Background: The plasmacytoid dendritic cell (pDC) is a specialized type I interferon producing cell of the innate immune system; critical in the control of HIV-1 infection. Previous studies have identified pDC dysfunction in HIV-infected donors, including a decreased capacity to produce IFN-α. Recently, studies have suggested that Tim-3, a T cell marker of activation/exhaustion, has diverse effects on a wide array of leukocytes. In this study, we evaluated the role of Tim-3 in pDC dysfunction during HIV-1 infection.
Methods: Ex vivo pDCs from PBMCs of 26 HIV-infected donors were examined for Tim-3 and cytokine expression after TLR and virus stimulation. Tim-3 regulation on pDCs from HIV-uninfected donors stimulated in the presence of HIV-1, influenza, CpG, imiquimod or Sendai virus was also assessed. Tim-3 localization with signaling proteins essential for IFN-α production, TLR9, IRF7 and PI3K within pDCs was assessed using confocal microscopy.
Results: Tim-3 was upregulated on pDCs in HIV infection and was not restored to pre-infection levels by cART. Tim-3+ pDCs from HIV-infected donors displayed profound defects in IFN-α and TNF-α production. Surprisingly, in vitro stimulation of enriched pDCs from HIV-uninfected donors with exogenous HIV virions did not significantly enhance Tim-3 expression. However, Tim-3 was rapidly induced by strongly activating pDC agonists such as imiquimod and Sendai virus. Tim-3 expression positively correlated with the maximum levels of IFN-α or TNF-α induced after stimulation. Tim-3 expressing pDCs showed disrupted submembrane distribution of TLR9 and intracellular Tim-3 co-localized with PI3K and IRF7 within lysosomes.
Conclusion: Dysfunctional Tim-3 expressing pDCs are induced during HIV infection. Strongly activating stimuli were found to increase Tim-3 expression, suggesting that during HIV infection, chronic activation from opportunistic pathogens contributes to Tim-3 expression on pDCs. Tim-3 may interfere with IFN-α and TNF-α production from pDCs by displacing submembrane TLR9 and by enhancing degradation of IRF7 and PI3K.

234 IMMUNE CHECKPOINT MOLECULES IN HIV AND AGING

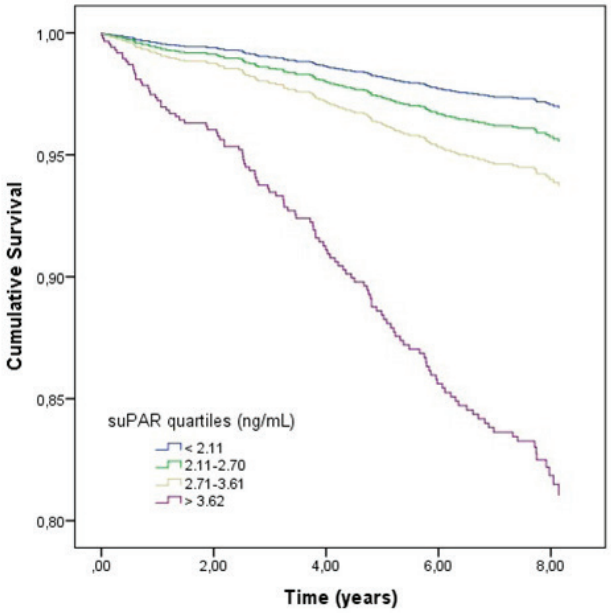
Lesley R. de Armas, Suresh Pallikkuth, Sidney Lane, Rajendra Pahwa, Varghese George, Stefano Rinaldi, Margaret Fischl, Gordon Dickinson, Allan Rodriguez, Savita Pahwa
Univ of Miami, Miami, FL, USA

Background: Immune checkpoint (IC) molecules are increasingly becoming targets for therapeutic intervention to stimulate the immune system. The objective of the current study was to examine the relationship of IC expression on T lymphocytes with biological age in anti-retroviral treated (cART), virologically suppressed HIV-infected and –uninfected (HC) participants.
Methods: Multi-parameter (15-color) flow cytometry was performed on PBMC isolated from 4 participant groups: HIV+ Young (<40yr) (Y+, n=24), HIV- Young (Y-, n=14), HIV+ Old (>60yr) (O+, n=21), and HIV- Old (O-, n=27) to evaluate IC expression (PD1, LAG3, TIM3, TIGIT, 2B4), transcription factors (EOMES, TBET), and markers of immune senescence (CD57, CD28). Total HIV DNA was measured in PBMC samples. Unpaired t test and correlation analyses were performed.
Results: First, we evaluated age-specific effects of HIV infection and found CD57+CD28- (immunosenescent) CD4 T cells to be low in Y-, but increased in Y+ as well as O- and O+ groups. Similarly, TBET expression (CD4 CD8) was lowest in the Y- group. Next, we evaluated markers of aging in HC and HIV. IC molecules LAG3 and EOMES were increased in CD4 T cells from both O groups compared to respective Y groups, while TIGIT (CD4) and TIM3 (CD4 and CD8) were lower in O- compared to Y-. Expression of PD1, TIM3, TIGIT, and 2B4 on CD4 and CD8 remained stable when comparing O+ to Y+. Interestingly, IC triple positive CD4 cells by Boolean analysis (LAG3+TIGIT+PD1+; negative for all other IC) were increased in O+ compared to Y+ ($p=0.001$) but did not correlate with HIV DNA ($p=0.45$). In fact, only 13/512 combination gates positively correlated with HIV DNA (cutoff $r>0.35$, $p<0.05$) and all 13 contained TIM3+ cells. HIV DNA did not show significant correlation with age.
Conclusion: Our results reveal complex relationships between IC expression on T lymphocytes with aging in cART-controlled HIV infection. Differences in immunosenescent cells between HIV and HC was most striking in Y and was lost in O groups, indicating its early onset and the dominant effect of age versus HIV in O groups. Increase in LAG3+ cells (+/- TIGIT, PD1) in O+ individuals is relevant as these cells harbor replication competent virus and may represent an obstacle to HIV cure in Aging persons. Association of TIM3 with HIV DNA may implicate it as a general marker of reduced immune control. Studies aimed at understanding IC expression and regulation will help guide therapeutic intervention strategies aimed at inhibiting their function.

235 SOLUBLE UPAR PREDICTS ALL-CAUSE MORTALITY FROM HIV-1 INFECTION

Ditte M Kirkegaard-Klitbo, Anne Langkilde, Niels Mejer, Ove Andersen, Jesper Eugen-Olsen, Thomas Benfield
Hvidovre Hosp, Hvidovre, Denmark

Background: Persistent inflammation and immune activation have been associated with mortality and non-AIDS comorbidity in HIV infection. The urokinase plasminogen activator receptor is involved in numerous processes including recruitment of leucocytes from the circulation to inflammatory sites. Here we investigated if inflammation measured by soluble urokinase plasminogen activator receptor (suPAR) was associated with incident non-AIDS comorbidity and all-cause mortality in HIV-1 infection.
Methods: Prospective single-center cohort study (n = 945). Plasma suPAR was quantified in HIV-1 infected individuals on antiretroviral treatment (ART) by ELISA at study entry in 2007. Associations between baseline plasma levels of suPAR and all-cause mortality and non-AIDS comorbidity were conducted by Cox regression analysis adjusted for pertinent covariates. Non-AIDS comorbidity was ascertained by registry linkage.
Results: At baseline, median age of study participants were 45 years, 73% were men, 78% were white. During a median of 7.9 years of follow up, 119 (13%) deaths occurred. Baseline median suPAR level was higher in non-survivors compared to survivors (4.03 ng/mL (IQR: 2.80-5.58) versus 2.56 ng/mL (IQR: 2.04-3.26), p < 0.001) respectively. In multivariate Cox regression analyzes, each ng/mL higher suPAR level was associated with a 42% increased risk of death (aHR (95% CI): 1.42 (1.30; 1.54), p<0.001). Highest quartile of plasma suPAR was associated with a more than 6 fold increased risk of death compared to the lowest quartile (aHR (95% CI): 6.70 (3.28; 13.70), p<0.001). Baseline median suPAR level was higher in patients with known comorbidity at baseline compared to patients without comorbidity (3.02 ng/mL (IQR: 2.33-4.11) versus 2.58 (IQR: 2.05-3.35) respectively). With baseline non-AIDS comorbidity excluded, no significant association was found between plasma levels of suPAR and diagnosis of non-AIDS comorbidity (defined as (n): cancer (70), diabetes mellitus (35), cardiovascular disease (75), chronic lung disease (57), liver disease (24) or chronic kidney disease (23)) during follow up.



Conclusion: Plasma suPAR levels were an independent marker of all-cause mortality but not incident non-AIDS comorbidity in HIV-1 infected individuals.

236 R5-TROPIC HIV RESISTANCE IN A SUBSET OF ELITE AND VIREMIC CONTROLLERS

Elena Gonzalo-GIL, Patrick Rapuano, Jimmy Auer, Zach Porterfield, Uchenna Ikediobi, Ayse Coskun, Richard Sutton
Yale Univ, New Haven, CT, USA

Background: Elite and Viremic Controllers (EC/VCs) appear to have an intrinsic ability to control HIV infection, perhaps because of host genetic determinants. Our aim is to identify EC/VCs with intrinsic resistance to HIV in vitro and to perform cell-based and genetic studies to determine if there is an associated hereditary basis.
Methods: Samples from ECs/VCs (n=154) were obtained from UCSF, Ragon, VA Medical Centers and IBIS using standard EC/VC criteria. CD4+ T cells purified from PBMCs were activated by anti-CD3/CD28 and infected with replication-defective HIV with different tropisms (R5, X4, and VSVG). Infection rate was analyzed after 3 days by flow cytometry as %YFP+ transduced cells and results were compared with healthy donors (CTRL) (n=25) and progressors on therapy (prog) (n=11). CCR5 and CCR2 surface levels and RNA expression levels were analyzed by flow and qPCR, respectively. MIP1-α and -β were analyzed by ELISA. CD4+ T cells from 2 EC family members were obtained, activated, and infected, and CCR5 and CCR2 expression levels analyzed. Statistical differences were tested by Mann-Whitney U-test or ANOVA using GraphPad Prism. P <0.05 were considered significant.
Results: For most controls and EC/VCs, there was no resistance to either VSV-G, X4-, or R5-tropic pseudotyped particle infection in activated CD4+ T cells. However, 16% of EC/VCs (24/154) showed 4-fold resistance, on average, specific to R5-tropic virus (%YFP+ EC/VCs 0.41±0.29 vs CTRL 1.35±0.51 and prog 1.54±0.48; P=0.001). CD4+ T cells from EC/VCs with R5 resistance were more susceptible to R5-tropic virus infection after overexpression of CCR5 using a lentiviral vector. Decreased CCR2 and CCR5 RNA levels (5-fold and 8-fold, respectively) in EC/VCs with R5 resistance phenotype were observed compared to CTRL and prog (P<0.0001). CCR2 and CCR5 levels (RNA and protein) were highly correlated (r=0.93; P<0.0001). Decreased levels of MIP1-α and -β in EC/VCs with R5 resistance were observed compared to CTRL (P<0.05). Resistance specific to R5 virus was observed in some EC/VC family members (3 of 7 analyzed) and also correlated with decreased CCR2 and CCR5 RNA and cell surface levels.
Conclusion: Resistance specific to R5 HIV was observed in some family members of the index EC with the same phenotype, and was associated with CCR2 and CCR5 down-regulation, suggesting a common regulatory mechanism. Further studies should help pinpoint whether the down-regulation is transcriptional or post-transcriptional in nature.

237LB MULTI-ANCESTRY GWAS IDENTIFIES NOVEL VARIANTS ASSOCIATED WITH HIV-1 VIRAL LOAD

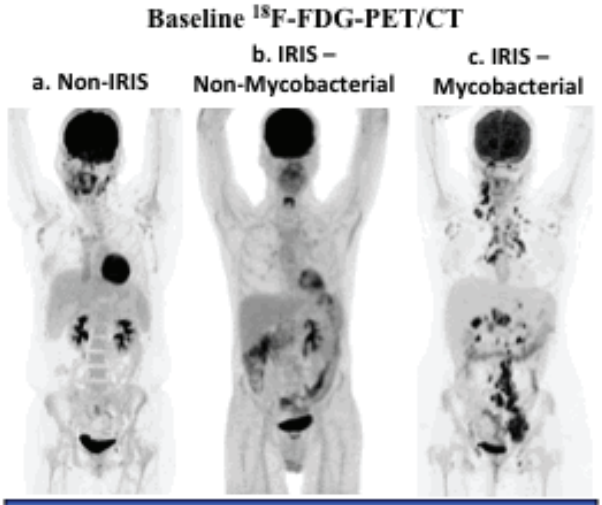
Eric O. Johnson[1], Dana B. Hancock[1], Nathan C. Gaddis[1], Christina A Markunas[1], Yuelong Guo[1], Elizabeth T. Golub[2], Mardge H. Cohen[3], Kathryn Anastos[4], Ruth Greenblatt[5], Bradley E. Aouizerat[6]
[1]RTI Intl, Rsr Triangle Park, NC, USA, [2]Johns Hopkins Univ, Baltimore, MD, USA, [3]Stroger Hosp, Chicago, IL, USA, [4]Albert Einstein Coll of Med, Bronx, NY, USA, [5]Univ of California San Francisco, San Francisco, CA, USA, [6]New York Univ, New York, NY, USA

Background: HIV viral load (VL) is a predictor of time until HIV progression, a key measure of risk and treatment response, and a critical focal point for research. Prior genome-wide association studies (GWAS) of VL set-point (VLSP) in European-descent samples found replicable variant associations in the HLA gene region. We conducted the first multi-ancestry GWAS of VLSP, followed by RNA expression quantitative trait loci (eQTL) analyses to assess putative function of nominated variants.
Methods: Discovery analyses used 20 million 1000 Genomes imputed SNPs and indels among 705 African Americans (AAs), 215 European Americans (EAs), and 110 Hispanic HIV+ participants from the Women's Interagency HIV Study. Replication was tested in the Urban Health Study: 531 AAs and 258 EAs. We assessed potential function of variants as cis-eQTLs using data from the Genotype-Tissue Expression project v6, with replication tested in GEUVADIS.
Results: One peak was identified at $p<5.0\times10^{-8}$ on chromosome 6 within the *HLA-B* gene. The 44 genome-wide significant follow-up variants constituted 14 independent tests: multiple testing p-value <0.0036. Eighteen variant associations were replicated: rs146647111 was the top replication variant (discovery $P = 4.7\times10^{-16}$; replication $P = 5.3\times10^{-5}$). Rs146647111 remained associated with VLSP after adjusting for all 8 known VL associated SNPs and two independently associated classical *HLA-B* and *HLA-A* alleles, with only a modest reduction in effect size: before adjusting $\beta = -0.53$, $P=2.4\times10^{-18}$; after adjusting $\beta = -0.51$, $P=5.0\times10^{-6}$. We tested rs146647111 (an intronic indel) as an eQTL for all genes within 1 Mb. The most significant association was with *MICB* ($P=9.9\times10^{-18}$), which replicated in the independent sample ($P=9.5\times10^{-7}$). *MICB* gene expression decreased in the presence of the minor, VLSP-protective AC allele. *MICB* encodes for a natural killer (NK) group 2 D (NKG2D) cell surface receptor ligand, which may be involved in the escape of HIV from NK cell-mediated cell death.
Conclusion: The rs146647111–VLSP association observed across multiple ancestries is novel and independent of known variants associated with VL phenotypes. The observed effect of the rs146647111-AC allele on *MICB* expression suggests a biologically plausible pathway for this association: lower expression of *MICB* reducing capacity for HIV escape from NK cell mediated cell death.

238 18F-FDG-PET/CT ABNORMALITIES ARE ASSOCIATED WITH HIGHER RISK OF IRIS IN HIV

Dima A. Hammoud[1], Georgios Z. Papadakis[1], **Afroditi Boulougoura**[2], Virginia Sheikh[3], Lori E. Dodd[4], Jing Wang[5], Angela Kibiy[6], JoAnn Mican[2], Corina Millo[1], Irini Sereti[2]
[1]NIH, Bethesda, MD, USA, [2]NIAID, Bethesda, MD, USA, [3]FDA, Silver Spring, MD, USA, [4]NIAIDs, Rockville, MD, USA, [5]Leidos Biomed Rsr, Rockville, MD, USA, [6]Leidos Biomed Rsr, Bethesda, MD, USA

Background: Immune reconstitution inflammatory syndrome (IRIS) in HIV infected patients represents a paradoxical immune response after initiation of antiretroviral therapy (ART). The pathogenesis and diagnostic criteria of IRIS remain elusive. We hypothesized that 18F-FDG-PET/CT scan could assess the acute effects of ART initiation on HIV+ patients and potentially assist in identifying those at high risk for IRIS.
Methods: 31 HIV+/ART-naïve patients with CD4 <100 cells were included in this prospective study and underwent 18F-FDG-PET/CT scans pre-ART (baseline) and 4-8 weeks after ART initiation. Regions of interest were delineated over liver, spleen, bone marrow (BM), axillary and inguinal lymph nodes (LN). SUVmean, SUVmax between baseline and post-ART among various groups were compared (Paired T-test). The lesion load was assessed as areas of non-physiologic FDG uptake (infectious/neoplastic) throughout the body with SUV > 4; Total glycolytic activity (TGA) values were obtained. Baseline TGA values and change from baseline values (between follow-up and baseline scans) were then compared between groups (Wilcoxon rank sum statistics).
Results: The median (IQR) age of the patients was 36 (32,39) and the median (IQR) hemoglobin (Hb), CD4+ T cells and HIV viral load (VL) were 10.1 (9.3, 11.5) g/dL, 25 (11, 36) cells/uL and 5.36 (4.94, 5.86) log10 copies/mL respectively. 11 patients eventually developed IRIS (6 mycobacterial IRIS-M. tuberculosis or M. avium complex). Baseline HIV VL was significantly higher in IRIS compared to non-IRIS. Mycobacterial IRIS patients had higher HIV VL and d-dimer levels, and lower Hb level than the rest of the cohort (p values 0.006, 0.038, 0.031 respectively). At baseline, lesion load TGA and volume were significantly higher in IRIS vs non-IRIS (~3X) and even more impressively in mycobacterial-IRIS vs the rest of the cohort (~10X) (table 1). Post-ART, BM and spleen SUVmean decreased in non-IRIS group by 17.8% (p=0.004) and 6.3% (p=0.013) respectively, but not significantly in the non-IRIS group. At baseline, HIV VL positively correlated with SUVmean in the spleen (r=0.48, p=0.01) and inguinal LN (r=0.49, p=0.01).
Conclusion: Higher lesion load TGA/volume at baseline could indicate increased risk of developing IRIS after ART initiation especially in mycobacterial/HIV co-infected patients. In addition, acute decrease in metabolic activity in spleen and BM in non-IRIS patients post-ART suggests an important role of these sites as tissue viral reservoirs.



Baseline Whole Body Threshold PET values			
Feature-Median (IQR)	IRIS (N=11)	Non-IRIS (N=20)	P-value
SUVmax	19.7(13.3,31.6)	12.1(8.7,19.2)	0.0272
TGA	371.4(166.9,3156)	106.4(20.1,328.8)	0.0219
TotalVolume	65.4(28.4,482)	20(4.2,58.6)	0.0335
Feature-Median (IQR)	Mycobacterial IRIS (N=6)	Others (N=25)	P-value
SUVmax	22.4(19.7,31.6)	12.4(10.2,18.8)	0.0075
TGA	1858(371.4,3821)	166.9(39.1,293.7)	0.0087
TotalVolume	284.6(65.4,536.5)	28.39(5.2,45.4)	0.0133

239 MAIT CELLS, MICROBIAL TRANSLOCATION AND THE MICROBIOME IN HIV/HCV CHRONIC INFECTIONS

Esther Merlini[1], Maddalena Cerrone[1], Bonnie van Wilgenburg[2], Leo Swadling[2], Camilla Tincati[1], Elvira S. Cannizzo[1], Antonella d'Arminio Monforte[1], Paul Klenerman[2], Giulia Marchetti[1]
[1]Univ of Milan, Milan, Italy, [2]Univ of Oxford, Oxford, UK

Background: Both HIV and HCV infections feature increased microbial translocation (MT) and gut dysbiosis that hamper immune homeostasis and disease outcome. Given their commitment to antimicrobial mucosal immunity, we investigated mucosal-associated invariant T (MAIT) cells frequency/function and association with MT/microbiome in HIV, HCV mono- and co-infection.
Methods: We enrolled 54 virally-infected (VI) patients (pts): 12 HIV on suppressive cART (scART; HIV-RNA<40cp/ml), 12 HCV naive to anti-HCV therapy; 30 HIV/HCV on scART and naive to anti-HCV; 8 age-matched healthy controls (HC). We measured: (i) circulating MAIT (CD3/CD8 CD161++TCRVa7.2+IL18R+) and CD161-TCRVa7.2+ frequency, activated (CD69), exhausted (PD1/ CD39), cytolytic phenotypes (granzymeB/perforin) and MAIT IL17/TNFa/IFNg following 5h E.Coli and PMA/ionomycin (flow cytometry); (ii) plasma/stool microbiome (16s) in 5 pts/group (MiSeq Illumina® tech). Statistical analyses as appropriate.

Results: VI pts were similar for age, HIV/HCV duration of infection and viral load, type/length of cART and fibrosis. Compared to HC, VI pts showed a trend toward lower circulating CD8+MAIT (Table1), with significant increase of CD8+CD161-Va7.2+ (HIV, p=.004; HCV, p=.023; HIV/HCV, p=.0006 versus MAIT). In VI, residual CD8+MAIT tended to have higher proportion of activated CD39+, CD69+ (in HIV alone) cells (Table1), negatively correlating with CD8+MAIT frequency (r=-0.33 p=.04; r=-0.38 p=.02, respectively). VI featured higher perforin+CD8+MAIT, yet lacked intracellular cytokine production (Table1). Similarly, CD8+CD161-Va7.2+ of VI pts, particularly HIV/HCV, displayed an activated CD69+, exhausted PD-1+ phenotype with high proportion of perforin-producing cells (Table1), positively correlating with CD8+CD161-Va7.2+ frequency (r=0.29 p=0.03). Interestingly, despite no major differences in plasma 16s rDNA and faecal/plasma microbiota among VI patients, CD69+CD8+ MAIT proportion positively correlated with 16s (r=.69 p=.019).
Conclusion: In chronically HIV/HCV pts, irrespective of mono/dual infection, we describe reduced CD8+ MAITs. Residual MAIT subset shows an activated/cytolytic phenotype, yet reduced ex vivo function, suggesting disrupted MAIT homeostasis. Excessively activated and yet functionally-impaired CD8+MAIT that positively correlate with circulating 16s, despite equivalent MT/microbiota, point to continuous MAIT engagement by microbial challenge, in turn exhausting functional competence.

Table 1. CD8+ MAIT and CD161-Va7.2+ Cell Frequency, Immunephenotype, Intracellular Cytokine Production and Plasma/Stool Microbiota Compostion in Virally-infected Patients

	HC (n=8)	HIV (n=12)	HCV (n=12)	HIV/HCV (n=30)	p
MAIT *					
CD8+CD161++Va7.2+, % (IQR)	6.47 (1.17-14.68)	0.77 (0.52-1.70)	1.22 (0.65-2.81)	0.84 (0.29-1.74)	0.084
CD8+CD161++Va7.2+IL18R+, % (IQR)	99 (98.60-99.90)	90.85 (78.65-98.05)	88.75 (61.4-95.38)	91.75 (86.7-96.25)	**0.008**
CD8+CD161++Va7.2+CD39+, % (IQR)	0.29 (0.06-0.59)	1.17 (0.34-6.41)	3.45 (0.41-25.70)	1.33 (0.34-5.76)	0.090
CD8+CD161++Va7.2+CD69+, % (IQR)	9.50 (7.23-11.70)	20.60 (9.92-22.10)	7.39 (4.84-10.08)	6.76 (4.69-17.15)	0.069
CD8+CD161++Va7.2+PD1+, % (IQR)	11.61 (0.6-35.3)	3.19 (2.53-4.94)	12.90 (0.63-40.60)	41.50 (2.45-65.40)	0.183
CD8+CD161++Va7.2+PERFORIN+, % (IQR)	0.37 (0.03-5.73)	6.22 (0.35-22.3)	9.79 (0.78-32.05)	14.6 (6.44-28.08)	**0.022**
CD8+CD161++Va7.2+GRANZYME B+, % (IQR)	0.96 (0.13-3.04)	10.9 (6.53-25.03)	23.20 (1.10-35.60)	7.86 (1.89-20.10)	0.066
CD161-Va7.2+ *					
CD8+CD161-Va7.2+, % (IQR)	3.69 (1.95-4.63)	4.23 (2.90-5.75)	3.13 (1.92-5.06)	3.37 (2.77-4.97)	0.795
CD8+CD161-Va7.2+CD39+, % (IQR)	0.86 (0.32-2.71)	1.32 (0.73-13.47)	1.49 (0.69-3.52)	2.89 (1.16-5.27)	0.365
CD8+CD161-Va7.2+CD69+, % (IQR)	1.36 (0.64-1.71)	2.72 (0.56-7.92)	1.28 (0.57-3.89)	4.46 (1.99-10.70)	**0.009**
CD8+CD161-Va7.2+PD1+, % (IQR)	7.64 (4.44-11.55)	16.72 (1.85-55.83)	8.15 (5.83-14.85)	31.20 (11.71-59.58)	**0.019**
CD8+CD161-Va7.2+PERFORIN+, % (IQR)	6.29 (2.16-34.8)	15.4 (6.62-31.9)	8.54 (3.64-16.40)	26.5 (14.20-36.35)	**0.037**
CD8+CD161-Va7.2+GRANZYME B+, % (IQR)	24.35 (7.06-34.70)	34.5 (19.7-53.7)	27.7 (9.27-50)	24.60 (4.76-36.9)	0.446
PMA IONOMYCIN stimulation *					
CD8+CD161++Va7.2+IL-17+, % (IQR)	2.42 (0.51-14.94)	0.26 (0.30-2.67)	0 (0-4.71)	0.37 (0-2.16)	0.194
CD8+CD161++Va7.2+TNFa+, % (IQR)	5.74 (3.77-9.69)	0.49 (0—1.84)	0 (0-1.20)	0 (0-0.35)	**0.002**
CD8+CD161++Va7.2+IFNg+, % (IQR)	1.78 (0.95-4.23)	1.45 (0-3.32)	0 (0-0.59)	0.35 (0-1.09)	**0.061**
E.Coli stimulation *					
CD8+CD161++Va7.2+IL-17+, % (IQR)	3.92 (0.91-5.92)	0 (0.70-2.55)	0.75 (0-4.72)	0.18 (0-0.92)	**0.029**
CD8+CD161++Va7.2+TNFa+, % (IQR)	7.14 (1.76-13.40)	2.091 (0.67-10.49)	1.92 (0-3.67)	0 (0-1.48)	**0.042**
CD8+CD161++Va7.2+IFNg+, % (IQR)	6.62 (0.71-14.90)	1.96 (0.69-2.55)	0.65 (0-2.76)	0.28 (0-2.32)	**0.046**
Plasma 16S rDNA, copies/uL	458 (235-912)	267 (107-428)	268 (259-278)	179 (82-400)	0.278
Feacal microbiota (classes)					
Actinobacteria, (%)	5.89 (2.32-14.4)	2.47 (0.50-5.43)	2.96 (0.93-8.21)	3.85 (0.71-11.6)	0.459
Bacilli, (%)	0.89 (0.21-2.85)	0.45 (0.04-3.29)	0.3 (0.13-1.09)	0.45 (0.11-0.83)	0.889
Bacteroidia, (%)	29.5 (16.7-37.5)	45.9 (8.77-48.7)	50.7 (45.8-57.4)	41.6 (18.8-56.6)	0.059
Clostridia, (%)	36.7 (31.4-47.7)	28.5 (23.5-36.6)	31.1 (19.6-40.4)	22.61 (18.7-29)	0.065
Gammaproteobacteria, (%)	2.6 (0.39-9.55)	2.6 (0.61-34.7)	0.88 (0.29-10.8)	17.8 (0.47-43.7)	0.660
Negativicutes, (%)	8.98 (1.49-19.87)	13.7 (6.64-24.5)	4.15 (3.18-5.57)	7.84 (3.72-8.84)	0.327
Plasma microbiota (classes)					
Actinobacteria, (%)	12.24 (9.83-18.9)	15.19 (5.87-22.52)	21.2 (15.7-26.8)	7.93 (5.73-36.3)	0.247
Bacilli, (%)	0.29 (0-5.22)	0.05 (0.01-6.29)	0.06 (0-9.17)	3.03 (1.42-8.31)	0.572
Alphaproteobacteria, (%)	11.84 (6.83-27.2)	24.1 (15.4-35.9)	12.6 (5.2-15.7)	4.9 (2.3-17.1)	0.125
Clostridia, (%)	0	0	0	0	
Bacteroidia, (%)	0	0	0	0	
Gammaproteobacteria, (%)	56.4 (46.6-62.1)	48.9 (16.7-59.2)	39.2 (36.6-49.4)	40.4 (24.1-61.9)	0.229
Betaproteobacteria, (%)	5.07 (0.10-12.5)	1.47 (0.6-8.07)	0.09 (0.07-24.7)	8.12 (3.26-12.2)	0.887

Note: *similar analyses were obtained in CD3+ MAIT cell subsets. All data are presented as median (Interquartile Range). Statistical analysis: Kruskal-Wallis Test with Dunn's multiple comparison test. HC healthy controls, HIV on effective cART (HIV-RNA<40cp/ml), HCV neg; HCV: chronic hepatitis C (anti-HCV Ab and HCV- RNA persistent in plasma >6 months after infection), naive to anti HCV therapy, HIV neg; HIV/HCV co-infected on effective cART, with chronic hepatitis C, naive to anti HCV therapy. Cytokine values of medium condition were subtracted from PMA/ionomycin and E.Coli stimulation. The microbiota composition is expressed as relative abundance (%)

240 IMPACT OF MUCOSAL CMV AND EBV REPLICATION ON ENTERIC MICROBIOME DURING HIV INFECTION

Antoine Chaillon[1], Sara Gianella[2], Ece A. Mutlu[3], Phillip A. Engen[3], Robin M. Voigt[3], Ali Keshavarzian[3], John Losurdo[3], Steven Lada[2], Masato Nakazawa[2], Alan Landay[3]
[1]Univ of California San Diego, San Diego, CA, USA, [2]Univ of California San Diego, La Jolla, CA, [3]Rush Univ Med Cntr, Chicago, IL, USA

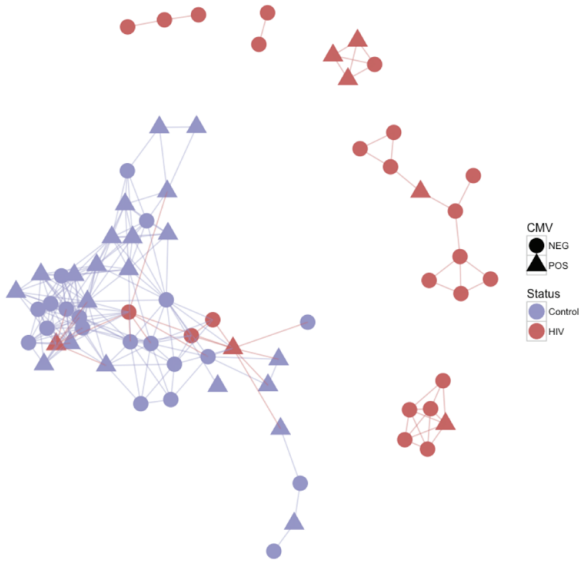
Background: HIV-infection is associated with significant alterations in the enteric microbiome. The underlying mechanisms by which HIV perturbs intestinal homeostasis remains unclear, and the impact of other viral pathogens in the gut has not been investigated.
Methods: A total of 80 mucosal biopsies from left and right colon (n=63) and terminal ileum (n=17) were collected from 18 HIV-infected and 20 uninfected healthy controls. Levels of CMV and EBV DNA were measured in each mucosal biopsy by droplet digital PCR. Microbiome analysis was performed using bacterial 16S ribosomal DNA pyrosequencing and sequences were processed with QIIME software. Bayesian hierarchical regression approach was used to model propensities to shed CMV and EBV and a negative binomial

family model was applied to estimate how CMV and EBV replication affects the microbiome composition among HIV-infected and uninfected controls in the colon and terminal ileum.

Results: Overall, CMV and EBV were detected in at least one gut sample in 61% and 79% of all participants. HIV-infected individuals were less likely to shed CMV (median Odd Ratio(OR)=0.2 [95% CI= 0.1~0.7], p=0.04) and CMV was more frequently detected in ileum than colon (OR=2.8 [CI=1.0~9.2], p=0.04). EBV shedding was more frequent among HIV-infected individuals (OR = 3.5 [CI=1.1~14.6], p=0.05) without differences by intestinal site. The relative abundance of the main phyla in the colon and ileum was assessed in relation to HIV-status and presence of CMV or EBV replication. After quality–filtering, 455,452 microbial sequences were analyzed (mean 3,733 reads/sample). While HIV-infection was associated with significantly lower beta-diversity, the number of operational taxonomic unit did not differ according to CMV or EBV detection status. Network approach based on Bray-Curtis distance confirmed clustering of samples by HIV-status but not by CMV/EBV (Fig.1). Among HIV-infected participants, higher levels of CMV were associated with greater relative abundance of Actinobacteria (b=2.1+/-0.9, p=0.02) and Beta-Proteobacteria (b=1.9+/-0.6, p=0.01) in the colon. CMV was not associated with any significant shift in the microbiome of healthy controls. There was no significant association between EBV replication and microbiome composition for either group or site.

Conclusion: These results illustrate a complex interplay between HIV and CMV replication in the gut mucosa and highlight a possible modulatory effect of CMV replication on the microbial homeostasis during HIV-infection.

Figure. Distance-based microbiome network among HIV infected and uninfected healthy control individuals by CMV replication status. Network reconstruction of the 80 mucosal samples is based on Bray Curtis distance with a threshold of 0.6. Nodes shapes denote CMV replication status (triangle for CMV DNA positive samples, circles for CMV DNA negative samples). Nodes colors denote HIV-infection status (samples from uninfected healthy controls in blue, samples from HIV infected individuals in red). No evidence of clustering was observed by CMV replication status and also by EBV replication status (not shown).



241 EFFECT OF HIV STATUS, CMV, AND EBV REPLICATION ON MUCOSAL GENE EXPRESSION IN THE GUT

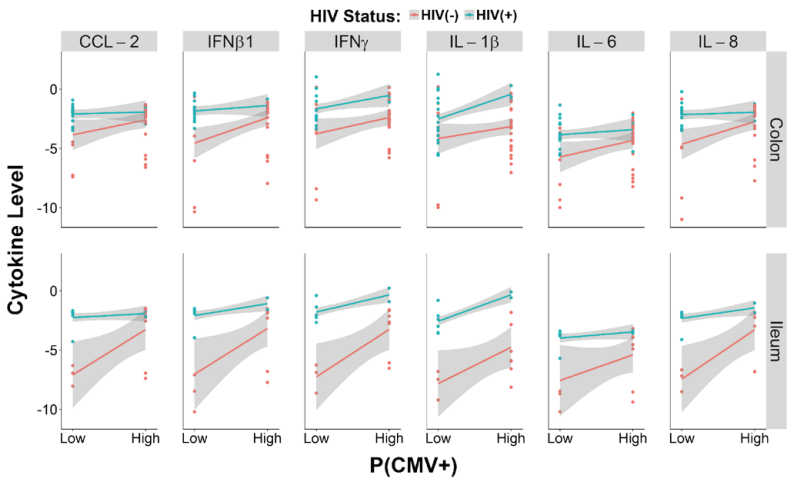
Sara Gianella[1], Antoine Chaillon[2], Ece A. Mutlu[3], Phillip A. Engen[3], Robin M. Voigt[3], Ali Keshavarzian[3], John Losurdo[3], Steven Lada[1], Masato Nakazawa[1], Alan Landay[3]
[1]Univ of California San Diego, La Jolla, CA, USA, [2]Univ of California San Diego, San Diego, CA, USA, [3]Rush Univ, Chicago, IL, USA

Background: HIV-infection is associated with pro-inflammatory changes in the intestinal mucosa, which might contribute to barrier dysfunction and dysbiosis. Cytomegalovirus (CMV) and Epstein Barr Virus (EBV) can replicate in the gut and contribute to systemic inflammation during HIV-infection. The effect of viral co-infections on intestinal mucosal gene expression has not been investigated.

Methods: Gut mucosal biopsies from left and right colon (n=57) and terminal ileum (n=36) were collected from 16 HIV-infected and 20 healthy control subjects. Levels of CMV and EBV DNA were measured in each sample by droplet digital PCR. Mucosal gene expression of 40 cytokines was measured via a QuantiGene multiplex assay and normalized by expression of housekeeping gene GAPDH. To summarize the high-dimensional dataset, factor analysis for mixed data was used to compute dimensions that together explained >60% of the total variance. A set of 3 cytokines that contributed most was identified (CCL2, IL-8, IFN-β1). Since CMV can induce IL-6, IFN-γ and IL-1β, those cytokines were selected a priori to be part of the analysis. We applied a linear mixed-effects regression model to examine how presence of CMV or EBV, HIV status, and intestinal site interacted to influence cytokine activities.

Results: CMV and EBV DNA were detected in at least one gut biopsy in 38% and 81% of HIV-infected and 77% and 77% of healthy controls, respectively. Gene expression of all 6 selected cytokines was significantly upregulated in HIV-infected subjects compared to controls (P<0.01). Additionally, we identified a significant interaction between HIV status, intestinal site, cytokine type and presence of CMV (P<0.001). Specifically among the healthy controls, the presence of detectable CMV was associated with significantly upregulated expression of all 6 cytokines in the ileum (all P<0.01) and higher expression of IL-8 and IFN-β1 in the colon (P<0.04) Figure 1. When CMV was detectable, gene expression levels in the ileum of healthy controls were similar to those of HIV-infected subjects. Presence of CMV was not associated with any difference in mucosal gene expression among HIV-infected people. There was no significant effect of EBV replication on any gut mucosal biopsy site in both groups.

Conclusion: Our data highlight a possible immune-modulatory role of CMV replication in the gut of HIV-uninfected subjects. Both HIV and CMV are associated with similar pro-inflammatory changes in the intestinal mucosa, but no additive effect was observed.



Legend: Figure shows cytokine levels for six selected cytokines (CCL-2, INFβ1, IFNγ, IL1β, IL-6 and IL-8) for HIV positive (in blue) and healthy uninfected controls (in red) divided by intestinal site (colon versus ileum). X axis shows probability of CMV shedding (low versus high), Y axis shows cytokine levels. The lines and grey areas represent model-based estimates and their 95% confidence intervals.

242 A BROAD POLYCLONAL RESPONSE IS MEDIATED BY SUPERINFECTION WITH 2 DISTINCT VIRUSES

Bingjie Wang[1], Katherine L. Williams[1], Valerie Cortez[1], James A. Williams[2], Kelly K. Lee[2], R. Scott McClelland[2], Julie Overbaugh[1]
[1]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [2]Univ of Washington, Seattle, WA, USA

Background: While broadly neutralizing antibodies (bNAbs) develop in a subset of HIV-infected individuals, the contribution of viral diversity to this process remains poorly defined. Individuals who have been infected with two or more distinct viral variants develop a broader and more potent neutralizing antibody repertoire than singly-infected individuals. Thus, superinfection provides a unique setting to examine the dynamic relationship between bNAb development and viral evolution.
Methods: We isolated and characterized neutralizing antibodies (NAb) from an individual initially infected with a subtype D variant and superinfected with a subtype A variant 11 months later. IgG-producing B cells were sorted and cultured from 2282 days post-initial infection (dpi) and HIV-specific B cells were identified using microneutralization assays. Antibody breadth was determined using a cross-clade panel of viruses. Epitope specificity of the broadest NAb was identified using negative stain electron microscopy and confirmed using viruses with mutations at the known target site. Autologous viral variants were identified using single genome PCR.
Results: Six NAbs were isolated and together recapitulated 53% of plasma breadth against a cross-clade panel of nineteen Tier 1, 2, and 3 viruses. Five of six antibodies exhibited limited neutralizing activity while one antibody, QA013.2, neutralized 42% of viruses tested in a larger panel of 31 HIV variants that includes the NIH global reference panel. This NAb is dependent upon the N332 residue in the V3 loop of gp120 and has a predicted germline gene usage pattern unique from other N332-dependent NAbs with 21% divergence in the VH gene and no indels in either the VH or VL genes. Thirty-four autologous viral variants were cloned from five timepoints following initial infection to explore the development of these antibody lineages. Two of the six NAbs originated from the same clonal lineage and preliminary data indicate that they neutralized a single clade D variant isolated from 287 dpi. In contrast, the more potent NAb QA013.2 strongly neutralized the superinfecting clade A viruses isolated at 385, 765, and 987 dpi while the remaining three NAbs neutralized one virus isolated at 385 dpi and three viruses isolated at 765 dpi.
Conclusion: These data provide strong evidence for development of a polyclonal antibody response resulting from superinfection with viruses from two different HIV clades.

243 HIGH-RESOLUTION MAPPING OF AN ENV EPITOPE BY COMPREHENSIVE ESCAPE MUTANT SELECTION

Adam Dingens, Hugh Haddox, Julie Overbaugh, Jesse Bloom
Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA

Background: A detailed understanding of broadly neutralizing antibody (bnAb) epitopes is vital to designing vaccines that target these sites of vulnerability, as well as using bnAbs as therapeutics and prophylactics. Current functional epitope mapping strategies are labor-intensive and derive from interrogation of single mutations at selected positions of Env.
Methods: We have developed a deep mutational scanning approach, which we term mutational antigenic profiling, to comprehensively map the functional epitopes of anti-Env antibodies in an unbiased fashion. This approach involves generating libraries containing viruses with nearly all amino acid mutations in Env, incubating these libraries with an antibody, and then infecting target cells. Finally, we use deep sequencing to quantify the effect of each mutation on neutralization phenotype by comparing its frequency in the selected library to a control library not treated with antibody.
Results: To validate this technique, we profiled a well-mapped bnAb, PGT151, with mutant libraries of a transmitted clade A Env, BF520. Antibody selection strongly enriched for escape mutants at a variety of sites known to be in or near the PGT151 epitope, including loss of key glycans at sites 611 and 637, sites in the fusion peptide, and sites near the gp120-gp41 interface. These precisely corresponded to epitope information known from cryo-EM and neutralization assays with panels of alanine scanning mutants. Further, we have better defined PGT151's epitope by identifying escape mutants at sites that have not been tested previously, as well as at sites where alanine scanning has been shown to not affect neutralization phenotype, but more biochemically dissimilar amino acids were enriched after selection in our experiments. Comparing amino acids that are or are not enriched suggests potential mechanisms of escape. For example, many mutations that result in loss of glycosylation at site 611 are consistently enriched, but primarily positively charged mutants are enriched in a stretch of residues in the heptad repeat 2 (HR2) that neighbors the CDRH3 of bound PGT151.
Conclusion: Mutational antigenic profiling not only identified known sites of the epitope with high accuracy, it also identified new positions that may contribute to PGT151's functional epitope. This approach has the potential to enable rapid, comprehensive, and unbiased functional epitope mapping of HIV-1 Env antibodies, as well as complete identification of pathways of viral escape.

244 INITIAL HIV DIVERSITY & NEUTRALIZING ANTIBODY DEVELOPMENT IN PEOPLE WHO INJECT DRUGS

Andrew D. Redd[1], Nicole Doria-Rose[2], Matthew Seivers[3], Stephen Schmidt[1], Oliver Laeyendecker[1], Stephen Porcella[4], Gregory D. Kirk[3], John R. Mascola[5], Shruti H. Mehta[3], Thomas C. Quinn[1]

[1]NIAID, Bethesda, MD, USA, [2]NIH, Bethesda, MD, USA, [3]The Johns Hopkins Univ, Baltimore, MD, USA, [4]NIAID, Hamilton, MT, USA, [5]Vaccine Rsr Cntr, Bethesda, MD, USA

Background: Any successful protective HIV vaccine will most likely need to generate a broad and diverse antibody response that can directly neutralize (NAb), or bind and direct virions to other cytotoxic mechanisms. An important underlying element of any vaccine construct is the ability to generate a similar immune response in a majority of vaccinees. Yet, currently it is unknown if in natural HIV infection, individuals initially infected with similar viral strains generate analogous humoral immune responses. This project examined whether initial viral genetic diversity between individuals predicted maturation pattern, strength, and breadth of the anti-HIV NAb response 3-6 years post-infection.

Methods: Recently infected HIV+ persons who inject drugs (PWID) were identified using a multi-assay algorithm from individuals who entered the AIDS Linked to the Intravenous Experience (ALIVE) study prevalently positive at enrollment (1988-89; n=23). The enrollment sample from these individuals was examined using next-generation sequencing (NGS) to examine HIV genetic diversity (HIV-SI) in two genetic regions (gp41 and pol). Viral sequences were combined to make a universal consensus sequence which was concatenated, and examined in a maximum likelihood phylogenetic tree. The NAb response in these individuals 3-6 years post-HIV diagnosis was determined using a standard panel of 21 heterologous viral isolates with multiple subtypes (A, B, and C). The NAb patterns from these individuals were analyzed for NAb fingerprint signatures that indicate the targeted epitopes.

Results: Three groups of individuals were identified who were initially infected in 1988-89 with highly similar viruses (<2% genetic distance; n=5, 5, & 6 respectively), as well as a group of non-clustered individuals (n=6; Figure 1). It was observed that the neutralization fingerprint for cluster one was significantly more correlated than the other samples (permutation test, p=0.043), and that cluster three had significantly stronger response to three viruses in the neutralization panel (p<0.05).

Conclusion: These data suggest that limited initial viral diversity between individuals can lead to similar NAb responses years later. It will be important to determine when and how these anti-HIV responses develop in these subjects, and if this phenomenon is seen in other risk groups. Although these data are preliminary, these findings are encouraging news for the prospects of developing universal vaccine strategies against HIV.

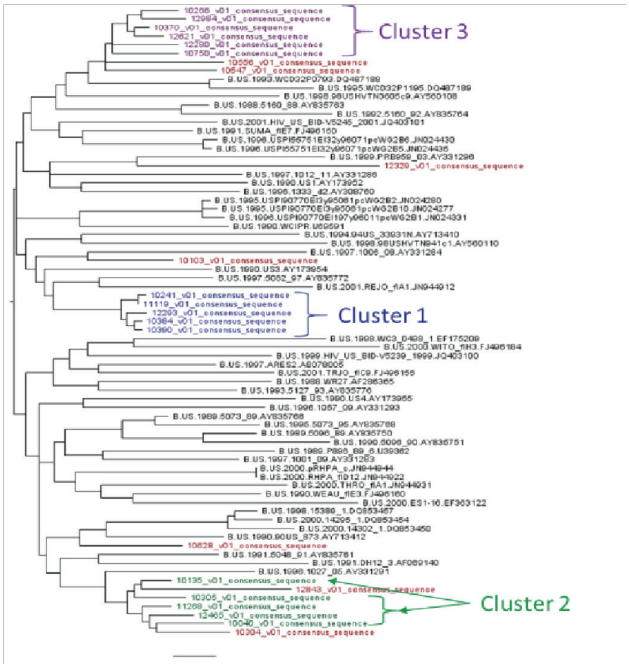


Figure 1: Maximum likelihood phylogenetic tree of concatenated consensus sequences derived from NGS sequencing of Pol and gp41. Clusters with sequences <2% genetic distance are indicated. Unclustered sequences are shown in red. Reference sequences are shown in black

245 ELITE NEUTRALIZATION AND UNIQUE EPITOPE SPECIFICITY OF A VIREMIC NONPROGRESSOR

Nandagopal Paneerselvam[1], Chinnambedu Ravichandran Swathirajan[1], Sunil S. Solomon[1], Jayantha Bhattacharya[2], Bimal K. Chakrabarti[2], Rajat Goyal[3], Aylur K. Srikrishnan[1], Kailapuri G. Murugavel[1]

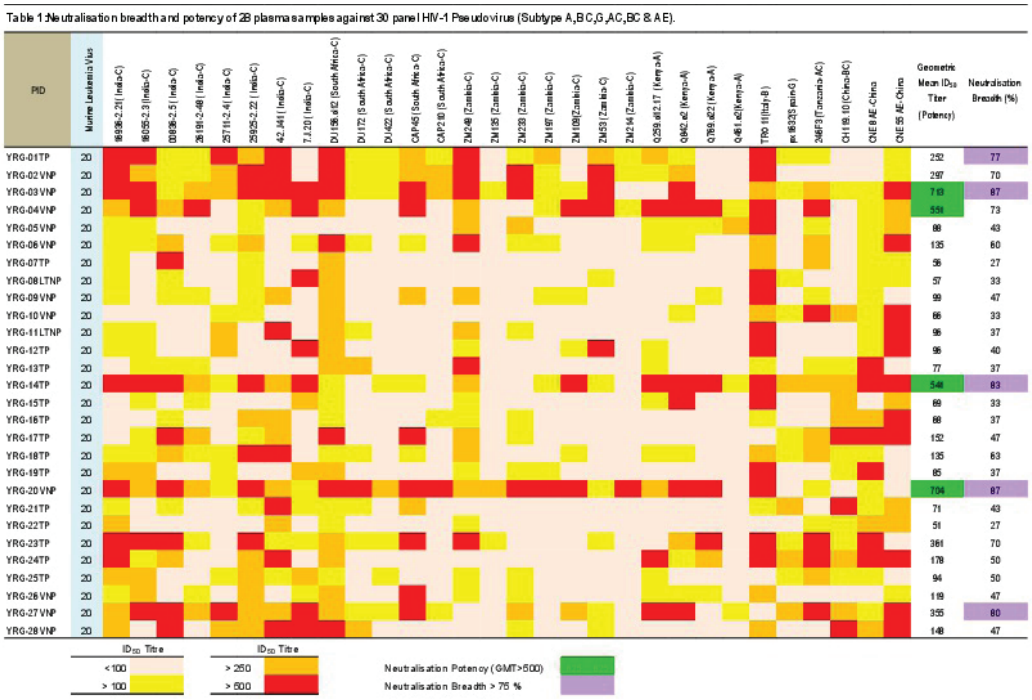
[1]YRG CARE, Chennai, India, [2]HIV Vaccine Translational Rsr Lab, Faridabad, India, [3]Intl AIDS Vaccine Initiative, New York, NY, USA

Background: In HIV infection, only 10-30% of the individuals are able to generate broadly neutralizing antibody response (bnAbs).Development of bnAb response was significantly associated with duration of infection, high viral load and low CD4 counts among typical progressors. Conversely, HIV-1 viremic non-progressors are individuals who maintain higher CD4 counts with moderate viral load without asymptomatic for > 7 yrs of infection. However, bnAb response has not been described among HIV-1 viremic non-progressors

Methods: In this study, plasma samples from a cohort of 90 ART-Naive HIV-1 infected individuals with various disease progression stages were tested against Tier-2 global virus panel (n=11) includes subtype A, B C, G, AC, BC & AE. The cohort includes viremic controllers, viremic non-progressors and typical progressors. The epitope mapping by ELISAs, neutralization of V2 (N160A &R166A) &V3 (N301A &N332A) point mutants and protein competition neutralization assay with MPER &RSC3 antigens. Samples that are able to neutralize >50% of virus with ID[50] >100 (moderate neutralization), were then tested against an extended virus panel (n=19) to find Elite neutralization. Elite neutralizers are those able to neutralize >75% of viruses tested with ID[50] >100 and geometric mean ID[50] > 500.

Results: Through screening of 90 plasma samples we observed moderate neutralization among 28 samples (Table: 1). Neutralization potency among viremic non-progressors were significantly higher than typical progressors (p=0.043). Remarkably, we were able to identify 4 elite neutralizers with geometric mean ID[50] titer between 500 and 700 and three of them were viremic non-progressors. Epitope mapping of those elite neutralizers were not specific to known targets like V2, V3, CD4bs and MPER region. Interestingly, the top most elite neutralizer has neutralized N301A mutant virus with 2.0 fold greater than the wild type. When assessed its CD4bs neutralization activity by treating with RSC3 protein, there was 1.5 fold drops in the ID[50] titer to the untreated plasma.
Conclusion: These results demonstrate that viremic non-progressors develop bnAb response and it suggests that provision of CD4 helper T cells is critical for formation of functional germinal centre. This bnAb response was associated with the presence of CD4bs Abs and it is due to viral escape in N301 glycan of V3 region which may expose occluded conserved epitope that facilitating the development of breath among elite neutralizers.

Table 1:Neutralisation breadth and potency of 28 plasma samples against 30 panel HIV-1 Pseudovirus (Subtype A,B,C,G,AC,BC & AE).



246 USING EMPIRIC SATURATION MUTAGENESIS TO IDENTIFY NOVEL ENV TRIMERS FOR VACCINES

Maria Jose Duenas Decamp[1], Li Jiang[2], Dan Bolon[1], Paul Clapham[1]
[1]Univ of Massachusetts, Worcester, MA, USA, [2]Harvard Univ, Boston, MA, USA

Background: Protective HIV-1 vaccines may need to induce antibodies that neutralize diverse HIV-1. A major target for cross-reacting neutralizing antibodies (nabs) is the CD4 binding site (CD4bs) on the envelope glycoprotein trimer (Env). There is an urgent need to identify novel Env trimers where the CD4bs is optimally displayed without exposing immunogenic sites that induce non-neutralizing antibodies or strain specific nabs. We used a novel saturation mutagenesis approach, EMPIRIC (Exceedingly Meticulous and Parallel Investigation of Randomized Individual Codons) to investigate effects of the CD4 binding loop on trimer structure and identify Env mutants with enhanced exposure of the CD4bs. This region of Env contains (1) CD4 contact sites, (2) residues that modulate trimer opening and (3) sites that influence macrophage-tropism. Here, we describe Env mutants that carry a more exposed CD4bs yet differ in the exposure of the V3 loop at the trimer apex.
Methods: Using EMPIRIC, we prepared plasmid libraries for all possible mutations covering the CD4 binding loop region (aas 361-380). Libraries were cloned into LN40 env (from an AIDS patient lymph node) incorporated in a replication competent pNL4.3 chimera. LN40/NL4.3 libraries were transfected into 293T cells and progeny virus rescued. This virus was used to infect PBMCs and the replication fitness of each mutant estimated by deep sequencing progeny virus. Env mutants that conferred wt replication or higher were investigated for their properties via Env+ pseudoviruses using Env mabs via neutralization and a trimer binding assay.
Results: Env mutants were identified that carried an exposed CD4bs and a modified trimer apex. These included mutants with substitutions at 373, 375, 377 and 380. Several substitutions at residue 380 resulted in a more exposed CD4bs and a modified trimer apex with an exposed V3 loop. In contrast, while substitutions at residue 375 also resulted in enhanced Env:CD4 interactions, the V3 loop remained occluded. The same observations were made when these substitutions were introduced into another clade B Env and a clade C Env.
Conclusion: We identified specific residues in the CD4 binding loop that expose the CD4bs, yet differ in their effects on the trimer apex and V3 loop in clade B and C Envs. Env mutants that enhance the exposure of the CD4bs yet maintain a closed trimer structure with the V3 loop occluded may be desired immunogens for inclusion in vaccines aimed at eliciting CD4bs nabs.

247 OLEANOLIC ACID DERIVATIVE OKS3-019 AS A NOVEL BIFUNCTIONAL HIV-1 ENTRY INHIBITOR

Shigeyoshi Harada[1], Kasumi Ogihara[2], Yuta Hikichi[1], Tetsuro Matano[1], Tetsuo Narumi[2], Kazuhisa Yoshimura[1]
[1]Natl Inst of Infectious Diseases, Shinjuku-ku, Tokyo, Japan, [2]Shizuoka Univ, Hamamatsu, Shizuoka, Japan

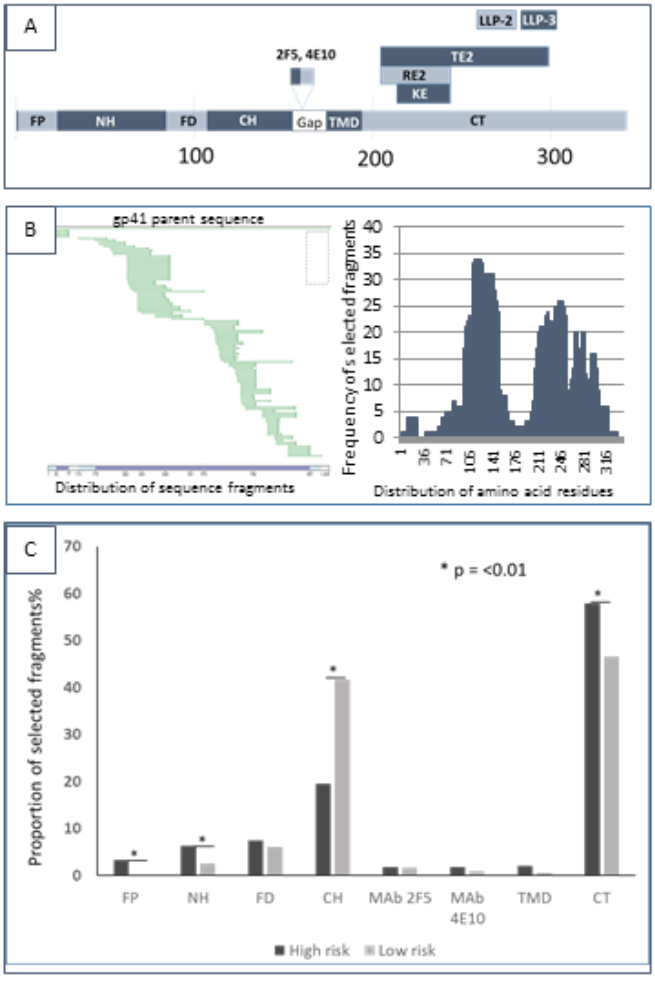
Background: CD4 mimetic small compounds, such as NBD-556, act as a bifunctional entry inhibitor of HIV-1 with respect to both neutralizing antibody activation and entry inhibition. Recently, we have also developed novel bifunctional entry inhibitors that target non-CD4-binding site of HIV-1 based on oleanolic acid derivatives. In this study, we demonstrated the antiviral potency of a selected set of oleanolic acid derivatives.
Methods: Oleanolic acids are the common starting material for the synthesis of novel bifunctional entry inhibitors. The susceptibility of the infectious HIV clones to the entry inhibitors and neutralization sensitivity to anti-HIV neutralizing antibodies (NAbs) were determined using the TZM-bl assay. We also examined synergistic effect between the oleanolic acid derivatives (OKS compounds) and seven NAbs targeting different domains in gp120 and gp41 (b12, 2F5, 4E10, 447-52D, KD-247, 2G12 and PG16) .

Results: We synthesized and tested 48 oleanolic acid derivatives and found a novel entry inhibitor OKS3-019, which could inhibit HIV-1 infection in IC_{50} values of 1.6, 1.0, 40, 26 and 28 μM for HIV-1 NL4-3, 89.6, JR-FL, YU2, and KP-5mvcR strain (primary R5 isolate), respectively. Time-of-addition experiments indicated that OKS3-019 interfered viral infection in the entry step. To investigate synergistic effect of OKS3-019 and anti-HIV-1 NAbs, we calculated Combination Indexes (CIs) using the Chow and Talalay method in combinations of the OKS3-019 and each NAb. All combinations showed synergistic effect in CI values from 0.59 to 0.81. These results demonstrate that the novel oleanolic acid derivative OKS3-019 targeting non-CD4 binding site acts as bifunctional entry inhibitors similar to CD4 mimetics.
Conclusion: In the present work, we found the novel bifunctional small molecule OKS3-019. Binding of such OKS compounds to HIV-1 envelope (Env) may affect the quaternary structure of the Env and the accessibility of NAbs to the epitopes. These findings indicate that OKS compounds might be useful in inhibiting HIV-1 infection not only by directly obstructing viral entry, but also enhancing sensitivity to neutralizing antibodies.

248 GP41 ANTIGENIC RECOGNITION AND RESPONSE IN HIV-NEGATIVE MEN WHO HAVE SEX WITH MEN

Katie McFaul, Jia Guo, Elizabeth Atkins, Xiao-Ning Xu, Peter Kelleher, for the Centre for Immunology and Vaccinology, Imperial College London
Imperial Coll London, London, UK

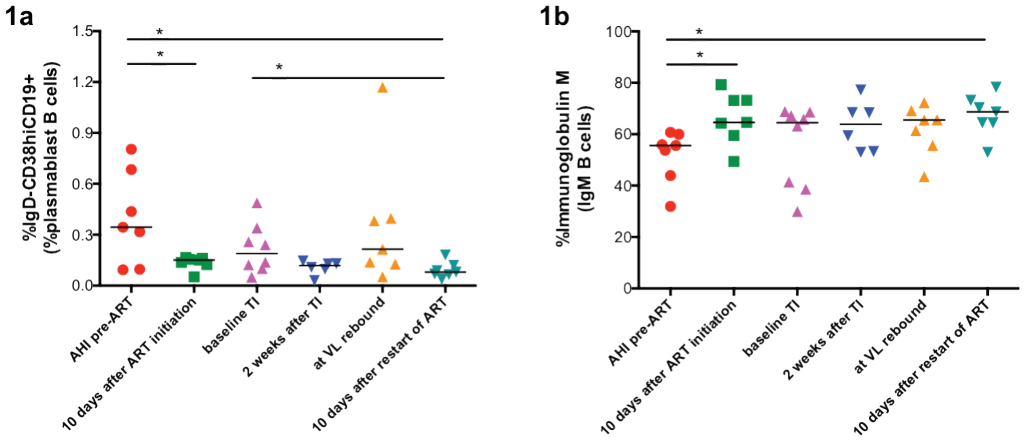
Background: Early HIV infection is characterised by polyclonal anti-HIV gp41 responses which do not control virus. This may be due to a previously educated B cell pool producing a response characteristic of a second exposure to a recognised antigen in a pre-primed host, or regular exposure to HIV antigens in individuals who remain seronegative but develop anti-HIV immune responses. Pre-existing anti-gp41 responses could divert developing mechanisms of protection in the case of future HIV acquisition. Seronegative men who have sex with men (MSM) engaging in unprotected sexual intercourse may be exposed to HIV antigens. We hypothesized seronegative MSM with either low (LR) or high risk (HR) HIV exposure history may develop varying anti-HIV responses accordingly. We sought to characterise the antigenic determinants and response to gp41 using a novel yeast surface display (YSD) mechanism.
Methods: A YSD system encompassing the gp41 gene-region (Fig 1A) was induced to display HIV gp41 epitope fragments as surface proteins. We selected serum samples from 20 HIV-negative MSM and pooled these into four groups of 5 samples (H5, H9, L6, L10). HIV risk exposure was classified according to PROUD-UK criteria. Sera from healthy controls and known HIV positive samples were used as negative and positive controls respectively. Sera were used to select reactive yeast clones by flow cytometric analysis and sorting. Reactive yeast clones were enriched and sequenced. These were aligned to the original full length gp41 sequence, and characterised according to regions identified (Fig. 1B). Amino acid residues were calculated as a proportion of total fragments identified and mapped to major gp41 epitope regions (Fig. 1C).
Results: We identified antibody responses to gp41 in both HR and LR MSM (Fig 1B and 1C). HRMSM displayed responses to all major gp41 epitopes, recognising 91.0% of gp41's 343 amino acid residues, compared to 64.1% in LR ($p<0.05$, CI 20.7- 32.9). HRMSM had greater recognition of fusion protein (FP), N-helix (NH), transmembrane (TMD) and cytoplasmic tail (CT). LRMSM had greater recognition of the C-helix (CH) ($p < 0.01$). There was no difference in recognition of monoclonal antibody (MAb) sites.
Conclusion: Serum responses to HIVgp41 epitopes vary according to exposure risk in seronegative MSM. High risk seronegative MSM have a greater breadth and magnitude of immunologic responses, which could be due to repeated viral exposure, and may influence viral dynamics in the case of future infection.



249 B-CELL RESPONSES POST-ART INTERRUPTION IN PERSONS TREATED IN FIEBIG I

Supranee Buranapraditkun[1], Donn Colby[2], Suwanna Pattamasavin[2], Suteeraporn Pinyakorn[3], Rapee Trichaviroj[4], Nelson L. Michael[5], Merlin L. Robb[3], Jintanat Ananworanich[3], Lydie Trautmann[3], for the RV411 and RV254/SEARCH010 Study Groups
[1]Henry M. Jackson Fndn for the Advancement of Military Med, Bethesda, MD, USA, [2]SEARCH, The Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [3]US Military HIV Rsr Prog, Bethesda, MD, USA, [4]Armed Forces Rsr Inst of Med Sci, Bangkok, Thailand, [5]Walter Reed Army Inst of Rsr, Silver Spring, MD, USA

Background: Humoral immunity may be important for the control of HIV replication after antiretroviral therapy (ART) interruption but B cell responses are impaired in HIV infection. We previously showed that cTfh function and the B cell compartment were preserved in Fiebig I/II very early acute HIV infection (AHI). Whether this preserved B cell compartment plays a role in controlling viral rebound following treatment interruption (TI) is unknown. We investigated the B cell response after TI in participants who initiated ART during Fiebig I AHI.
Methods: Eight HIV infected Thais who initiated ART during AHI Fiebig I (VL+, p24-, IgM-) were studied longitudinally from AHI to TI. At the time of TI, all were on ART ≥ 2 years, CD4 T cells ≥ 400 cells/mm3 and HIV-1 RNA < 50 copies/ml, all rebounded after ART cessation. B cells were characterized by flow cytometry at six time points: AHI pre-ART, 10 days after ART initiation, baseline TI, 2 weeks after TI, at viral rebound and 10 days after restart of ART.
Results: The frequencies of resting memory (RM) B cells (CD21+CD27+IgG+CD20+) were decreased during AHI but restored on ART. During TI, the frequencies of RM B cells decreased at VL rebound (p=0.01) compared to baseline but were significantly higher than in AHI, suggesting the preservation of the memory B cell compartment during TI. Frequencies of plasmablasts (IgD-CD38hiCD20+) at the viremic time points in AHI and TI were significantly higher compared to the other time points (Fig.1a), suggesting that expansion of plasmablasts was triggered by exposure to HIV Ag. In pre-ART AHI, all were IgM- by 4thGEN immunoassay and showed increased frequencies of IgM+ B cells only 10 days after ART initiation (p= 0.01) (Fig.1b). Importantly, we observed an increase of IgM+ B cells during TI between baseline and 2 weeks after TI prior to detectable viremia (p=0.06) and 4 out of 6 donors seroconverted at viral rebound suggesting that B cell responses arise earlier after TI than in AHI.
Conclusion: Treatment interruption in people treated in Fiebig I did not induce phenotypic perturbations in the mature B cell compartment observed in AHI but induced increased frequencies of plasmablasts associated with viremia. Increased frequencies of IgM+ B cells detected prior to viral rebound during TI and seropositivity at viral rebound suggest that B cell responses arise faster in TI than in AHI even though they are not sufficient to contain viral rebound.



250 DC FUNCTIONALITY DISTINGUISHES HIV-1 CONTROLLERS WITH NEUTRALIZING ANTIBODY BREADTH

Enrique Martin-Gayo[1], Zhengyu Ouyang[1], Dhohyung Kim[1], Kellie E. Kolb[2], Bruce D. Walker[1], Alex K Shalek[2], Xu G. Yu[1]
[1]Ragon Inst of MGH, MIT and Harvard, Cambridge, MA, USA, [2]MIT Inst for Med Engineering & Sci (IMES), Cambridge, MA, USA

Background: Understanding immune mechanisms driving the evolution of HIV-1 specific broadly neutralizing antibodies (bNAbs) is critical for the development of an effective vaccine against HIV-1. Typically, bNAbs develop in individuals with high-level viremia and increased immune activation, however, antibodies with high neutralizing breadth have also been detected in rare subgroups of HIV-1 controllers with low or undetectable viral loads in the absence of antiretroviral treatment. Recent data suggest that dendritic cells play an important role in development of T follicular helper cells (Tfh) and the evolution of bNAbs. Here, we studied transcriptional and functional features of primary conventional dendritic cells (cDCs) from the blood of HIV-1 controllers that develop neutralizing Ab breadth against HIV-1.
Methods: Whole genome RNAseq transcriptional data were generated from sorted circulating cDC from HIV controllers with (n=44) or without (n=9) neutralizing antibody responses. In addition, functional in vitro experiments were performed to analyze the ability of primary cDCs from the different study groups to prime allogeneic naïve CD4 T cells into CXCR5+ PD-1+ Tfh in the presence of autologous B cells after 6 days of culture.
Results: Transcriptional profiling analysis identified two different gene expression signatures in cDCs from HIV controller neutralizers, which we designate Nt1 and Nt2. While cDC signatures in Nt1 were non-distinguishable from a background cohort of non-neutralizer controllers (NC), Nt2 were defined by a distinct transcriptional cDC program characterized by a robust up-regulation of genes involved in inflammatory cytokine responses, activation of antigen presenting properties, and pathways involved in Tfh polarization. This specific gene expression profile corresponded to a higher functional ability of cDCs from Nt2 patients to prime Th1-biased PD-1+ Tfh-like cells in vitro, compared to cDCs from Nt1 (p=0.04) and NC (p=001). Moreover, Nt2 neutralizer controllers were characterized by higher residual viral loads (p=0.006) and lower frequency of protective HLA-B alleles than Nt1 (p=0.036) and NC patients (p=0.02).
Conclusion: This study suggests that at least in a subgroup of HIV-1 controller neutralizers, cDC may provide a critical role in priming and maintaining Tfh-like cells and generating HIV-1-specific antibodies with increased levels of neutralizing breadth.

251 TELMISARTAN DOES NOT IMPROVE LYMPH NODE OR FAT FIBROSIS IN TREATED HIV INFECTION

Netanya S. Utay[1], Douglas Kitch[2], Carl Fichtenbaum[3], Michael M. Lederman[4], Jacob D. Estes[5], Clara Magyar[6], Karin Klingman[7], Judith S. Currier[6], Jordan E. Lake[1], for the A5317 Team
[1]Univ of Texas, Galveston, TX, USA, [2]Harvard Univ, Boston, MA, USA, [3]Univ of Cincinnati, Cincinnati, OH, USA, [4]Case Western Reserve Univ, Cleveland, OH, USA, [5]Frederick Natl Lab for Cancer Rsr, Frederick, MD, USA, [6]Univ of California Los Angeles, Los Angeles, CA, USA, [7]DAIDS, NIAID, Bethesda, MD, USA

Background: Chronic HIV infection is characterized by persistent inflammation and immune activation that can lead to tissue injury and fibrosis. Lymph node (LN) fibrosis may limit CD4+ T-cell recovery; LN and adipose tissue (AT) fibrosis may contribute to systemic inflammation and comorbidities. Telmisartan is an angiotensin receptor blocker and

PPAR-γ agonist with anti-inflammatory and anti-fibrotic properties. We hypothesized that telmisartan would decrease LN or AT fibrosis in HIV-1 infected adults on suppressive antiretroviral therapy (ART).

Methods: In this completed, randomized-controlled trial, HIV-infected participants age ≥18 years with HIV-1 RNA <50 copies/mL on ART for ≥48 weeks received telmisartan 40mg daily for 4 weeks then 80mg daily for 44 weeks or no drug while continuing ART. Primary endpoints were changes in % collagen I deposition by immunohistochemistry (IHC) in inguinal LN and subcutaneous lower abdominal AT after 48 weeks. IHC was performed and interpreted by a blinded central reader. 36 participants would power the study to detect a 4% difference in change in collagen. Statistical testing used two-sided rank-sum and signed-rank tests (α=0.05).

Results: Of 44 randomized participants, 93% were male and 50% white non-Hispanic. Median age was 48 years, body mass index 25 kg/m^2, and CD4+ T-cell count 588 cells/mm^3. Paired AT samples were available from 34 participants and LN from 29 due to participant consent and sample quality. Baseline median (interquartile range) tissue area with collagen I deposition was 13.7% (7.5%, 21.4%) for LN and 1.9% (0.4%, 3.4%) for AT. No statistically significant between-group differences in LN or AT collagen I deposition change were observed (Table), although a larger than expected variability in LN collagen likely reduced power to see a significant LN effect. In both arms, collagen I deposition tended to decrease in LN and significantly decreased in AT over 48 weeks.

Conclusion: In HIV-1-infected adults on suppressive ART, angiotensin receptor blockade and PPAR-γ agonism with telmisartan for 48 weeks did not improve LN or AT fibrosis more than continued ART alone. Notably, continued ART decreased both LN and AT fibrosis over 48 weeks. This trial is the first longitudinal study of LN and AT fibrosis in treated HIV infection and will inform design of future studies with tissue endpoints. Analyses of tissue HIV expression and circulating and tissue-level inflammatory and fibrotic signatures are ongoing.

	Telmisartan			No Drug			Between-Group P Value
	n	48-week absolute change*	p value	n	48-week absolute change	p value	
Lymph node	17	-2.4% (-10.6%, 3.8%)	0.24	12	-6.1% (-11.7%, 5.8%)	0.23	0.97
Adipose tissue	22	-1.1% (-2.1%, -0.01%)	0.02	12	-2.2% (-3.4%, -0.02%)	0.03	0.27
*median (interquartile range)							

252 PHARMACOLOGIC INHIBITION OF IDO BLUNTS FEATURES OF SIV-RELATED CHRONIC INFLAMMATION

Richard M. Dunham[1], Kevin W. Brown[1], James M. Billingsley[2], Zhong-Min Ma[3], Gregory K. Tharp[2], Christopher J. Miller[3], Steven E. Bosinger[2], Brian A. Johns[1], David Favre[1]
[1]GlaxoSmithKline, Durham, NC, USA, [2]Yerkes Natl Primate Rsr Cntr, Atlanta, GA, USA, [3]Univ of California Davis, Davis, CA, USA

Background: The immunomodulatory and neurotoxic activities of kynurenines derived from tryptophan catabolism by indoleamine-2,3-dioxygenase (IDO1) play a role in sustaining a cycle of inflammation and immune dysfunction during HIV infection. Such a cycle may lead to increased risks of non-AIDS diseases, such as liver disease and neurocognitive impairment, despite effective cART. We hypothesized that inhibition of IDO1 may break this cycle, reversing immune dysfunction, decreasing systemic inflammation, and ultimately decreasing the incidence of non-AIDS diseases. We tested this hypothesis in a pilot study of virologically suppressed, SIV-infected rhesus macaques treated with an optimized regimen of an IDO1 inhibitor (IDOi) currently under clinical investigation (INCB024360).

Methods: Twelve rhesus macaques were infected with SIVmac251, treated with cART, and divided into two groups after virologic suppression to receive either placebo or IDOi for 8 weeks while continuing ART. Blood, lymphatic tissue, and mucosal tissues were evaluated to determine the pharmacologic, immunologic, metabolic, microbiological, and transcriptomic features of IDOi during SIV infection.

Results: SIV infection increased plasma levels of kynurenine even after ART and kynurenine was transiently suppressed after each IDOi dose. Pharmacologic inhibition of IDO1 led to increased CD4/CD8 ratio in blood and significantly decreased markers of T cell and monocyte activation in blood and lymphoid tissues. In gut mucosa, we observed a trend to increased frequency of CD4+ T cells producing IL-17, IL-22, and/or IL-21. Interestingly, we found increased plasma levels of microbial metabolites of tryptophan, such as indoleacetate, which are AHR agonists that promote intestinal barrier function through induction of IL-22 and have neuroprotective properties.

Conclusion: These results support the hypothesis that IDOi disrupts the vicious cycle of IDO1-mediated inflammation and immune dysfunction during SIV infection. This effect is associated with a shift in microbiota function characterized by increased production of anti-inflammatory postbiotic metabolites that may serve as novel biomarkers of disease and therapeutic responses. These data suggest further investigation of IDOi as a strategy to blunt or prevent non-AIDS diseases in suppressed HIV infection by targeting host and microbial metabolism in the setting of chronic inflammation.

253 HIV-SPECIFIC ANTIBODIES ENHANCE TYPE I INTERFERON PRODUCTION FROM PLASMACYTOID DCS

Rebecca Veenhuis[1], Zachary Freeman[1], Jack Korleski[1], Alessandra Tomasi[1], Austin Boesch[2], Margaret Ackerman[2], Joseph B. Margolick[1], Joel Blankson[1], Michael Chattergoon[1], Andrea Cox[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Dartmouth Coll, Hanover, NH, USA

Background: Type I interferon (IFN) production is essential in innate control of acute viral infection, but prolonged IFN production is associated with chronic immune activation in HIV. The mechanisms that maintain high-level IFN production following the acute phase are unknown. Plasmacytoid dendritic cells (pDCs) are the primary producers of type I IFN in viral infections. HIV is sensed by pDCs through endosomal Toll like receptor (TLR) 7 recognition of RNA. In this study, we further define the mechanism through which HIV activates pDC to produce IFN and demonstrate that antibodies (Abs) generated in persistent HIV infection enhance IFN production by pDCs.

Methods: Using an in vitro co-culture system of primary human pDCs and HIV cell culture isolates, we analyzed the mechanism through which HIV activates pDCs to produce IFN. We assessed whether endocytosis, HIV receptor and co-receptor engagement, fusion, uncoating, and subsequent stages of the HIV life cycle were required for IFN production. Additionally, we evaluated Toll-like receptor (TLR) utilization and downstream signaling in pDCs exposed to HIV. We next analyzed how both monoclonal HIV-specific Abs and Abs induced in natural HIV infection modulated normal pDC sensing of HIV.

Results: We found that HIV-driven activation of pDCs to produce IFN required TLR7 signaling, receptor-mediated entry, fusion, and viral uncoating, but not endocytosis or life cycle stages after uncoating. Abs directed against the HIV envelope that do not interfere with CD4 binding significantly enhanced the IFN response irrespective of capacity to neutralize CD4 T cell infection. Ab-mediated enhancement of IFN production required pDC Fc gamma receptor engagement, bypassed fusion, and initiated signaling through both TLR7 and TLR9, which was not utilized without Ab present. Polyclonal Ab isolated from 13 untreated HIV-infected subjects universally enhanced pDC production of IFN in response to HIV.

Conclusion: Identifying the cause of persistent, high-level IFN responses during chronic HIV infection is important in understanding its pathogenesis. Our data suggest that Abs produced in vivo in untreated HIV infection contributes to persistent high-level IFN responses during chronic HIV infection, representing a novel mechanism of immune activation.

254 TARGETING TYPE I INTERFERON-MEDIATED IMMUNE ACTIVATION TO CONTROL HIV INFECTION

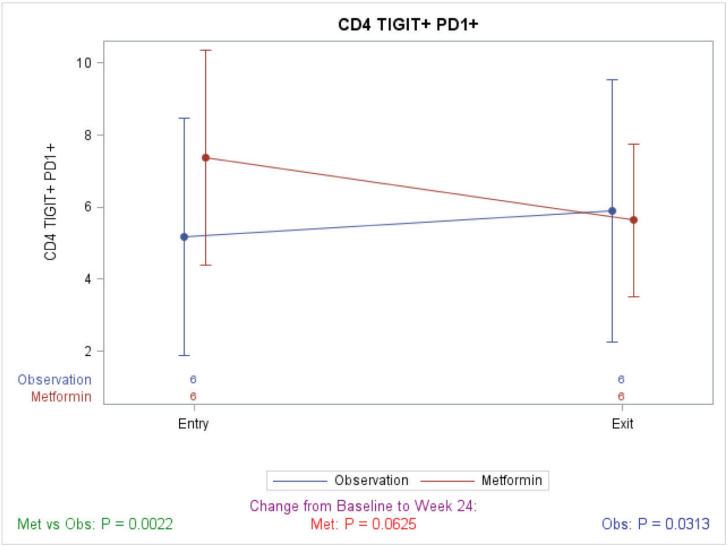
Anjie Zhen[1], Mayra A. Carrillo[1], Valerie Rezek[1], David Brooks[2], **Scott G. Kitchen**[1]
[1]Univ of California Los Angeles, Los Angeles, CA, USA, [2]Princess Margaret Cancer Cntr, Toronto, Ontario, Canada

Background: Chronic immune activation is a hallmark of HIV infection, simultaneously contributing to and combating viral replication. Persistent antigen stimulation during HIV infection leads to immune exhaustion and dysfunction, which has negative effects in the body's ability to suppress the virus. How immune dysfunction develops during chronic viral infection is largely unknown and the systematic and longitudinal characterization of immune activation and the mechanisms driving these processes are lacking. We are seeking to define the mechanisms driving immune dysfunction during HIV infection.
Methods: In this study we closely examined the development of immune dysfunction during HIV infection in vivo utilizing the NSG-BLT humanized mouse model. As chronic activation can be a driving force in immune dysfunction and type I interferons (IFN-I) are emerging as critical components underlying ongoing activation in HIV infection, we tested the effect of blocking IFN-I signaling during chronic HIV infection through therapeutic antibody blockade of the IFN-I receptor (IFNR) with and without antiretroviral therapy (ART).
Results: We found that, similar to that seen in HIV-infected individuals, chronic HIV infection of humanized mice led to significantly increased expression of immune activation molecules, including IFN-I response genes, and T cell exhaustion molecules over time. We determined that T cells from HIV-1 infected mice become functionally defective and have the impaired ability to secrete cytokines and kill infected cells. We demonstrate that blockade of IFN-I signaling during chronic HIV infection in vivo diminished HIV-driven immune activation, decreased T cell exhaustion molecule expression, restored HIV-specific CD8 T cell functions, and led to decreased viral replication. ART in combination with IFN-I blockade further decreased viral loads and reduced the latent HIV reservoir compared to ART treatment alone.
Conclusion: Our data suggest that chronic expression of IFN-I, in addition to persistent antigen stimulation, contributes to the development of dysfunctional T cells during HIV infection. We found that characteristics of immune activation and dysfunction in HIV infected humanized mice closely recapitulates that found in humans. This sets the stage for the closer examination of the mechanisms behind these defects in T cell responses to further suppress or eradicate HIV infection and the use of IFNR blockade as a therapeutic strategy to enhance antiviral immune responses.

255 METFORMIN REDUCES T-CELL EXHAUSTION IN A CLINICAL TRIAL OF HIV-INFECTED ADULTS ON ART

Glen Chew[1], Dominic Chow[1], Scott A. Souza[1], Lindsay Kohorn[1], Richard M. Watanabe[2], Ivo Sah Bandar[1], Eun-Young Park[1], Mary Margaret Byron[1], Lishomwa C. Ndhlovu[1], Cecilia Shikuma[1]
[1]Univ of Hawaii, Honolulu, HI, USA, [2]Univ of Southern California, Los Angeles, CA, USA

Background: Chronic HIV infection is associated with persistent inflammation and increased expression of negative checkpoint receptors (NCRs; eg: PD-1, TIM-3, TIGIT) on T cells that result in immune dysfunction (Chew et al 2016 PLoS Pathog) and viral persistence (Fromentin et al 2016 PLoS Pathog). Current scientific literature suggests that Metformin, an oral hypoglycemic agent used for diabetes, may have additional, previously unrecognized therapeutic effects against age-related conditions including anti-inflammatory properties. We assessed NCR in banked blood specimens from a small clinical trial of Metformin conducted in individuals with chronic HIV.
Methods: An open label, 24 week pilot study in 12 individuals on antiretroviral therapy (ART) stable for >1year with plasma HIV RNA < 50 copies/ml, median age of 58 years and majority male (11/12) randomized 1:1 to Metformin (500 mg increasing to 1000 mg at week 4) vs Observation (OBS). We assessed surface expression of T cell exhaustion receptors (PD-1,TIM-3, TIGIT) and activation (CD38+HLA-DR+) by flow cytometry on cryopreserved peripheral blood mononuclear cells collected at enrollment and study end. Statistical analyses include nonparametric Mann-Whitney Statistical T tests.
Results: Compared to OBS, Metformin led to significant 24 week decrease changes of single expressing PD-1+ CD4 T cells [Metformin -1.6 (-4.7,0.2), OBS 2.0 (0.4,3.7) p=0.026]; in dual expressing PD-1+TIGIT+ CD4 T cells [Metformin -0.9 (-2.9,-0.1), OBS 0.8 (0.2,1.2) p=0.002], and in triple expressing PD-1+TIM-3+TIGIT+ CD4 T cells [Metformin -0.9 (-1.3, -0.1), OBS (0.3 (0.07,0.6) p=0.041]. No difference in 24 week changes between the Metformin and OBS arms were observed in CD8 T cell exhaustion and CD4 or CD8 T cell activation.
Conclusion: A 24 week course of Metformin reduced CD4 T cell expression of multiple NCR among virally suppressed HIV infected adults. The data suggests the unexpected benefit of Metformin in potentially improving anti-viral T cell function or impacting the persistence of CD4 T cell viral reservoirs. Metformin may have value as an adjunctive therapy to ART in chronic HIV infection.



256 P2X PURINERGIC RECEPTORS AS THERAPEUTIC TARGETS OF HIV-1 INFECTION AND INFLAMMATION

Talia Swartz[1], Natasha Durham[2], Alexandra Soare[1], Meagan O'Brien[1], Nina Bhardwaj[1], Benjamin K. Chen[1]
[1]Icahn Sch of Med at Mt Sinai, New York, NY, USA, [2]Tufts Univ, Boston, MA, USA

Background: HIV-1 causes an incurable infection. Despite antiretroviral therapy, chronic inflammation persists which is associated with multiple co-morbidities. A clear mechanism for this inflammation has yet to be determined. Some of this inflammation is thought to be driven by enhanced mucosal translocation, resulting in elevated levels

of lipopolysaccharide (LPS), a toll-like receptor (TLR4) agonist. Purinergic receptors are inflammatory mediators that have been increasingly implicated in HIV-1 pathogenesis. These receptors signal in concert with TLR signaling. We have demonstrated that inhibition of purinergic receptors can inhibit HIV-1 fusion. Here we test whether inhibition of P2X subtypes can reduce both HIV-1 infection and pro-inflammatory cytokine production.
Methods: CD4+ T cells and peripheral mononuclear blood cells were infected with fluorescent reporter HIV-1 viruses and tested for their productive infection and proinflammatory cytokine production. Infected cells were quantified by flow cytometry and supernatants were subjected to multiplex bead capture assays to detect an array of human inflammatory cytokines. The effect of P2X selective inhibitors was tested.
Results: P2X inhibition was associated with dose-dependent inhibition of HIV-1 infection. While HIV-1 infection alone did not stimulate the production of pro-inflammatory cytokine production in peripheral mononuclear blood cells, the combination of HIV-1 infection in the presence of the toll-like receptor (TLR4) agonist lipopolysaccharide, resulted in differential cytokine stimulation that was variably blocked by purinergic inhibitors.
Conclusion: Our findings distinguish purinergic receptors as key signaling mediators of HIV-1 infection and represent important drug targets that could serve a dual role as both direct anti-retroviral agents and anti-inflammatory agents. Such a class of drugs could reduce the morbidity and mortality associated with chronic HIV-1 disease.

257 AGE AND HIV DO NOT SYNERGISTICALLY IMPACT T-CELL MATURATION OR ACTIVATION

Shelli Farhadian[1], Emilie Jalbert[2], Yanhong Deng[3], Matthew B. Goetz[4], Lesley Park[5], Amy Justice[6], Robert Dubrow[3], Brinda Emu[1], for the VACS Project Team
[1]Yale Univ, New Haven, CT, USA, [2]Univ of Colorado, Aurora, CO, USA, [3]VA Greater Los Angeles Hlth Care System, Los Angeles, CA, USA, [4]Stanford Med, Stanford, CA, USA, [5]VA Connecticut Hlthcare System, West Haven, CT, USA
Background: Chronic HIV infection is associated with clinical conditions typically associated with normal aging, suggesting that HIV may cause premature immunosenescence. This study explored whether there is a synergistic impact of age and HIV on T cell phenotypes in HIV infected and uninfected adults.
Methods: We performed a cross sectional analysis of HIV-infected (n=111) and uninfected (n=114) male adults from the Veterans Aging Cohort Study. HIV infected subjects were on antiretroviral therapy. Uninfected controls were matched by age, alcohol, and smoking history. All subjects had blood analyzed for T cell markers via flow cytometry. We evaluated the impact of HIV and age on T cell phenotypes using multivariate linear regression models, adjusted for smoking, alcohol and race.
Results: HIV infected subjects had an average duration of viral suppression of 4.9 years prior to enrollment blood draw. Their median CD4 count was 566 (IQR 378-769). The median age was 55 (IQR 55-61) in the HIV-infected and 55 (IQR 48-64) in the uninfected. HIV infection was associated with an increased proportion of activated (CD38+ and HLA-DR+) CD8+ T cells ($p<0.0001$). There was no significant impact of age on the proportion of activated CD8+ or CD4+ T cells. However, as age increased, the proportion of naïve (CD28+ CD27+ CD45RA+) CD8+ T cells decreased ($p<0.0001$), while the proportion of effector memory (CD28- CD27- CD45RA-) CD8+ T cells increased ($p=0.0004$). These age effects were found in both HIV infected and uninfected subjects, although HIV infected subjects had an overall higher proportion of effector memory CD8+ T cells at all ages ($p=0.0001$). With regards to CD4+ T cells, among both HIV-infected and uninfected subjects, older age was associated with decreased proportion of naïve CD4+ T cells ($p=0.014$). Both HIV and older age were associated with higher proportions of effector memory CD4+ T cells ($p<0.0001$ and $p=0.041$). Importantly, there were no significant interactions between HIV infection and age.
Conclusion: HIV-associated changes in T cell phenotypes (activated CD8+ T cells and effector memory CD4+ and CD8+ T cells) were not synergistically impacted by age. Likewise, age-associated changes in T cell phenotypes (naïve and effector memory CD4+ and CD8+ T cells) were not dependent on HIV status. These findings suggest that age and HIV status independently affect the immune system, but do not act synergistically to cause accelerated immunosenescence.

258 CELLULAR IMMUNE ACTIVATION IN THE ERA OF CART AND AN AGING HIV+ POPULATION

Lesley R. de Armas, Suresh Pallikkuth, Rajendra Pahwa, Stefano Rinaldi, Varghese George, Li Pan, Allan Rodriguez, Margaret Fischl, Gordon Dickinson, Savita Pahwa
Univ of Miami, Miami, FL, USA
Background: Biological aging is associated with immune activation (IA) due to systemic inflammation, and declining immunity. It is widely accepted that HIV causes persistent IA and premature immunosenescence by approx. 10 years despite cART and virologic suppression. In this study we assessed the impact of IA on Flu vaccine responses in cART-treated HIV infected individuals and healthy controls.
Methods: Peripheral blood samples were obtained from 4 participant groups: HIV+ Young (<40yr) (Y+, n=28), HIV- Young (Y-, n=42), HIV+ Old (>60yr) (O+, n=45), and HIV- Old (O-, n=42) prior to (T0) and 3 weeks after (T2) seasonal trivalent inactivated influenza vaccine (TIV) over 3 seasons (2013-16) in which pandemic 2009 H1N1 was included. Vaccine response was measured by hemagluttination titers against H1N1 at T2/T0. All HIV+ participants were on cART for >1 yr and were virologically suppressed. Multi-parameter flow cytometry was performed on T0 PBMC to evaluate IA markers (CD38, HLADR, PD1, ICOS, Ki67) on CD8 and CD4 T cells and subsets including peripheral T follicular helper (pTfh) cells, which are associated with antibody responses. Correlation analysis and Student's t test were performed to evaluate differences between groups.
Results: Vaccine response in participants exhibited the following pattern Y- > Y+ > O- = O+. CD4 counts and pTfh (CXCR5+ TCM) frequency were reduced in O- compared to Y- and independently correlated with TIV response, while HIV groups did not show these relationships to CD4 and pTfh. Evaluation of IA markers revealed that 38+DR+ co-expressing cells (CD4 and CD8) were higher in O+ compared to O- but not significantly different from Y+. CD4 and CD8 T cells expressing CD38 alone were equally reduced in O groups compared to respective Y groups. Interestingly, HLADR (CD4 and CD8) expression was elevated in O+ compared to Y+ and HC groups. To determine whether IA expression in HIV impacted TIV response, we performed correlation analysis and found negative correlation with CD4 38+DR+ and positive correlation with pTfh 38-DR- (double negative) cells and T2 H1N1 titers.
Conclusion: Our data show differential effects of Aging on IA and TIV response in HC and cART-treated, virologically suppressed HIV individuals. In HIV, TIV response negatively correlated with IA markers (38+HLADR+) but were not affected by CD4 or pTfh frequency, while the opposite was true in HC. This may reflect a poor quality of pre-vaccination pTfh despite sufficient quantity in individuals with virological suppression.

259 ADAR1, A TARGET TO BOOST HIV-1 IMMUNE RESPONSE

Maria Pujantell, Ester Ballana, Eva Riveira-Muñoz, Bonaventura Clotet, Jose A. Este
IrsiCaixa Inst for AIDS Rsr, Badalona, Spain
Background: HIV-1 infection induces innate intracellular antiviral defenses, aimed at restricting virus replication and spread. Controversial data exists regarding the capacity of HIV-1 infection to induce type I IFN and evade immune recognition in macrophages. Therefore, understanding the role and function of innate immune effectors and modulators can help to establish novel strategies for HIV-1 control.
Methods: Monocytes obtained from PBMCs were differentiated into macrophages with M-CSF and siRNA was used to inhibit target gene expression. HIV-1 infection was perfomed with VSV-pseudotyped NL4-3 GFP-expressing virus or a full-replicative R5 HIV-1 BaL strain. Proviral DNA formation, viral DNA integration and HIV transcription were quantified by qPCR. Type I IFN production, ISG induction (CXCL10, STAT1 phosphorylation) and innate immune pathway activation (DNA/RNA sensors and IRF3/7 expression and activation) were characterized by qPCR, Western Blot and ELISA. ADAR1-mediated modifications in cellular and viral RNAs were measured by direct sequencing of known ADAR1 target sites.
Results: ADAR1 knockdown (siADAR1) in primary macrophages (MDM) led to a significant increase in IFNB1 mRNA (7.5-fold, $p=0.03$) and CXCL10 gene (1000-fold, $p=0.02$) and protein expression (2.5-fold, $p=0.01$) compared to mock-transfected MDM, indicative of innate immune activation. Interestingly, siADAR1 MDM showed a significant reduction in HIV-1 infection either with a single cycle, VSV-pseudotyped NL4-3 GFP expressing virus (75% inhibition, $p<0.0001$) or a full replicative R5 HIV-1 BaL strain (80% inhibition, $p<0.0001$). Proviral DNA formation or viral DNA integration were not affected in siADAR1 MDM; however, a significant reduction in viral transcription was detected

(75% reduction, p<0.0007). Although ADAR1 deaminase activity was detected in cellular genes, direct modification of viral RNAs by ADAR1 was not observed. siADAR1 MDM also showed upregulation of MDA5 (IFIH1), the cytoplasmic sensor of ADAR1-edited RNAs. However, IFIH1 knockdown did not have a significant effect on innate immune function or HIV-1 infection. Further characterization of innate immune pathways in siADAR1 MDM showed enhanced expression of the innate immune RNA sensor RIG-I, increased STAT1-phosphorylation and IRF7 expression, comparable to that observed after LPS or poly I:C treatment in mock-transfected MDM.
Conclusion: ADAR1 knockdown in primary macrophages induces innate immune activation that confers resistance to HIV-1 infection.

260LB LIVER INFLAMMATION CORRELATES WITH SIV LEVELS AND IS ONLY PARTLY REVERSED WITH CART

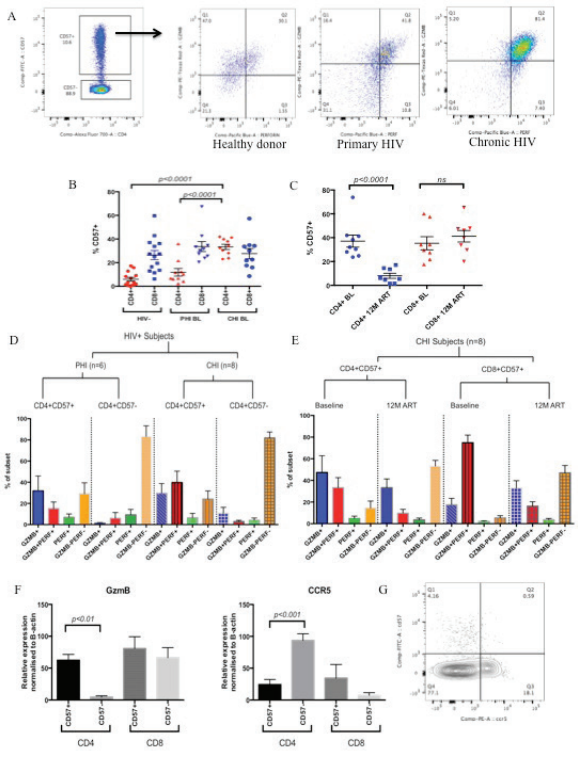
Bridget Fisher[1], Rachel Brown[1], Matthew Wood[1], Richard Green[2], Cole Fisher[1], Michael Gale[2], Guido Silvestri[3], Ann Chahroudi[3], Nichole Klatt[2], Donald Sodora[1]
[1]Cntr for Infectious Disease Rsr, Seattle, WA, USA, [2]Univ of Washington, Seattle, WA, USA, [3]Emory Univ, Atlanta, GA, USA

Background: Liver disease is a significant contributor to morbidity and mortality during HIV infection, including those receiving combination antiretroviral therapy (cART). The SIV/HIV virus may be directly influencing liver disease/inflammation through the presence of virus, or indirectly by compromising the gut mucosa, thus permitting increased levels of bacteria translocation to the liver.
Methods: Liver tissue was acquired from infant and adult rhesus macaques that were uninfected (n=7/4, infant/adult), SIV-infected (n=9/6), or SIV-infected/cART-treated (n=4/6). To evaluate liver inflammation/disease we quantified immune cell levels (microscopy using CD3 and CD68), gene expression (Agilent Microarray and qPCR), bacteria levels (16s DNA qPCR) and SIV levels (qPCR) in livers obtained at necropsy.
Results: There was a significant increase in liver macrophage levels during SIV infection (556 SIV+ vs 327 macrophages/mm2 in uninfected), which subsequently decreased following cART treatment. These macrophages likely migrated into the liver as they correlated with inflammatory (CCL3, TNFa) and pro-fibrotic (TGFb) immune mediators. Importantly, this increase in macrophage number and associated inflammation correlated with levels of SIV in the liver (p=<0.0001) and in the plasma (p=0.0014) with liver T cells identified as SIV-infected. In contrast, the levels of 16s bacterial DNA did not correlate with macrophage levels, as bacterial levels were highest in the SIV+cART treated macaques compared to uninfected (p=0.0006). Microarray analysis identified liver transcriptome changes during SIV infection, which included many immune signaling pathways, such the NF-kB, Rig-I-like receptors, and interferon signaling. Further, cART did not fully resolve immune signaling during SIV infection with a number of immune associated pathways (including NF-kB and innate/adaptive immunity) continuing to be significantly upregulated in SIV+cART macaques.
Conclusion: These data provide evidence that liver macrophage infiltration and associated inflammation during SIV infection is likely driven by SIV-infected T cells, and not by translocating bacteria. In addition, cART treatment does not fully resolve liver inflammation. These findings provide insight regarding liver disease that is occurring during SIV/HIV infection and cART, and identifies specific immune targets for reducing liver inflammation in HIV-cART individuals.

261 CD57+ CYTOTOXIC CD4+ EFFECTOR T CELLS INCREASE IN CHRONIC HIV INFECTION

Chansavath Phetsouphanh[1], Jodi Meyerowitz[1], Lyle Murray[1], Dominique Goedhals[2], Cloete Van Vuuren[2], Sarah Fidler[3], Paul Klenerman[1], John Frater[1]
[1]Univ of Oxford, Oxford, UK, [2]Univ of Free State Med Sch, Bloemfontein, South Africa, [3]Imperial Coll London, London, UK

Background: Cytotoxic CD4+ T cells play a prominent role in chronic viral infection, as evidenced by their influence in the containment of EBV and CMV replication. CD4+ CTL clones specific for HIV-1 Nef and Gag (generated from ex vivo perforin expressing CD4+ T cells) are capable of killing HIV-1 infected CD4+ T cells and macrophages. Additionally, HIV-specific cytolytic CD4+ T cell responses in acute HIV infection are predictive of disease progression. There have been minimal studies on this subset in HIV infection. Extracellular markers, specific transcription factors and mechanism of killing are yet to be determined. Whether HIV-specific CD4+ CTL function in collaboration with CD8+T cells is indicative of viral control remains to be investigated.
Methods: Cryopreserved PBMCs from participants with Primary HIV infection (PHI)(n=9; SPARTAC trial) and chronic infection (CHI) (n=9; Bloemfontein, South Africa) were analysed. All participants were not receiving antiretroviral therapy at time of sampling. Flow cytometric phenotyping was performed using BD LSRII. Cell sorting was performed on the Beckman Coulter MoFlo. RNA extraction was performed using QIAGEN RNAeasy micro kit. PCR was performed on the ROCHE Light Cycler 480.
Results: CD57 (HNK-1 or Leu2) expression on CD4s identifies cytotoxic cells (Fig. 1A). These cells are dramatically increased in CHI (~5-fold, p<0.0001). CD57 expression correlates with cytolytic granules, granzyme B and perforin expression. This is highly evident in both Primary and chronic HIV-infection (Fig. 1B&D). CD57+ CD4+ T cells decrease with 12 months of anti-retroviral therapy in CHI subjects (p<0.0001), as does Granzyme B and perforin levels (Fig. 1C&E). CD57+ CD4 CTL are CD45RO+ memory cells that lack CD28 expression. CD57+ CD4 CTL express lower CCR5 mRNA than CD57- and this correlates with protein expression (Fig 1F&G).
Conclusion: CD57 is a marker of cytotoxicity on CD4+ T cells, which allows the characterization of this subject in HIV infection. CD4 CTL increase in chronic HIV infection. CD57+CD4+ cells are highly activated expressing both granzyme B and perforin. The maintenance of these cells may be due to the low expression of HIV entry receptor CCR5. It remains to be seen whether CD57+ CD4 CTL are HIV-specific and have the potential to kill HIV-infected MHC class II presenting cells. The frequency and function of these cells in Elite controllers and Post-treatment controllers may identify possible correlates of protection.



262 TARGETING LC WITH ANTI-LANGERIN HIV FUSION MONOCLONAL AB PROMOTES TFH DIFFERENTIATION

Jérôme Kervevan[1], Aurélie Chaigneau[1], Sandy Zurawski[2], Marion Bonnet[3], Romain Marlin[4], Marie-Thérèse Nugeyre[4], Elisabeth Menu[4], Gerard Zurawski[2], Yves Levy[1], Sylvain Cardinaud[1]
[1]INSERM, Créteil, France, [2]Baylor Inst for Immunol Rsr, Dallas, TX, USA, [3]Univ of Cardiff, Cardiff, UK, [4]Inst Pasteur, Paris, France

Background: A rationale approach for vaccine design is to target HIV-1 antigen to specific receptors on dendritic cells (DCs) via fused monoclonal antibodies (mAb) with the intention to favor antigen presentation and activation of HIV-specific immune responses (Flamar A.L. et al., AIDS, 2013). In mouse and NHP models, targeting of skin LCs with anti-Langerin mAbs fused with HIV (αLC/HIV-Gag) or Flu antigen drives antigen-specific humoral responses (Yao C. et al., J Allergy Clin Immunol, 2015; Epaulard G. et al., J. Immunol.,

2014; Salabert N. et al., Eur. J. Immunol., 2015). The development of these immunization strategies in humans requires a better understanding of early immune events driven by targeted LCs. We investigated the effects of αLC/HIV-Env on the differentiation of naïve CD4+ T-cells.
Methods: Anti-human Langerin recombinant human IgG4 antibody fused with HIV-Env gp140 at the C-terminus of the H-chain were produced in CHO cells. Purified cord-blood CD34+ progenitor cells were differentiated into LCs (Caux C. et al., Blood, 1997), incubated with αLC/HIV-Env, and co-cultured eight days with autologous naïve CD4+ T-cells. T-cells differentiation was assessed by flow cytometry.
Results: We show that: i) αLC/HIV-Env candidate vaccine specifically target skin or vaginal explant LC (CD1ahi/CD207+) as demonstrated by FACS and immunohisto-staining; ii) In vitro CD34-derived LCs exhibited a phenotype similar to ex vivo isolated LCs from human skin; iii) In vitro derived LCs incubated with αLC/HIV-Env induced the differentiation of co-cultured naïve CD4+ T-cells into Tfh-like cells (CXCR5+PD-1+Bcl-6+) significantly as compared to culture conditions with control HuFc-IgG4 or aCD40 fusion antibodies; iv) In the same culture conditions, monocyte-derived DCs and BDCA1+ primary DCs did not promote this differentiation of CD4+ T cells.
Conclusion: These results revealed that LC activated through CD207 promotes the differentiation of Tfh cells. Gene expression and cytokine profiles of vaccine-targeted LC and differentiated Tfh cells are ongoing. These data support the development of novel DC targeting vaccine approaches.

263 HIV-1-INFECTION–ASSOCIATED CHANGES IN THE HUMAN CD4+ T-CELL PROTEOME

Johannes Nemeth[1], Valentina Vongrad[2], Karin Metzner[2], Victoria P. Strouvelle[2], Rainer Weber[2], Patrick Pedrioli[3], Ruedi Aebersold[3], Huldrych F. Günthard[2], Ben Collins[3]
[1]Cntr for Infectious Disease Rsr, Seattle, WA, USA, [2]Univ of Zürich, Zürich, Switzerland, [3]ETH Zürich, Zürich, Switzerland
Background: Host directed therapies against HIV-1 are supposed to be critical for long term containment of the HIV-1 pandemic but remain elusive. Since HIV-1 infects and manipulates important effectors of both the innate and adaptive immune system, identifying modulations of the host cell systems in humans during HIV-1 infection may be crucial for the development of immune based therapies.
Methods: Here, we measured the changes of the proteome in human CD4+ T cells upon HIV-1 infection, both in vitro and in vivo. To our best knowledge, this is the first attempt to measure the proteome of CD4+ T cells in HIV infected humans. In an exploratory study, a bi-phasic SWATH-MS approach was used to measure the proteome of primary CD4+ T cells infected with HIV-1 in vitro as well as CD4+ T cells from HIV-1 infected patients with paired samples on and off antiretroviral treatment.
Results: In the in vitro experiment, 1742 host cell proteins and 5 HIV-1 proteins were measured, with 121 proteins changing significantly during the time course. Changes in the proteome peaked 24 hours after infection, concomitantly with significant HIV-1 protein production. In sorted CD4+ T cells from clinical samples, 940 proteins were detected consistently, 174 of which were considered to be significantly different between viraemic patients and patients undergoing successful treatment. The proteome of in vitro infected CD4+ T cells was modulated on multiple functional levels, including TLR-4 signalling and the type 1 interferon signalling pathway. Likewise, perturbations in the type 1 interferon signalling pathway were recapitulated in CD4+ T cells from patients.
Conclusion: SWATH-MS is capable of detecting significant changes on different functional levels of the proteome human CD4+ T cells to a yet unaccomplished depth. Exploring the perturbations in the proteome associated with HIV-1 infection may help to identify new targets for immune based interventions.

264 CHARACTERIZATION OF PREEXISTING HIV-SPECIFIC CD4 T CELLS IN UNINFECTED INDIVIDUALS

Audrey Daigneault[1], Nathalie Brassard[2], Amy E. Baxter[1], Lucie Barblu[1], Colin Havenar-Daughton[3], Roxanne Charlebois[2], Jean-Pierre Routy[4], Shane Crotty[3], **Daniel E. Kaufmann**[1]
[1]Cntr de Rsr du Cntr Hosp de l'Univ de Montréal, [2]La Jolla Inst for Allergy and Immunol, La Jolla, CA, USA, [4]McGill Univ Hlth Cntr, Glen site, Montréal, Canada
Background: CD4 T cells (Thelper, TH) play a key role in antiviral immunity. The magnitude of HIV-specific TH responses generated by infection or vaccination is highly variable. Previous studies suggest that antiviral TH responses can be generated prior to pathogen exposure by cross-reactivity with other microorganisms, and may shape TH responses upon infection or immunization. However, the functionality of such pre-existing HIV-specific TH in HIV-negative subjects is unknown.
Methods: We investigated HIV-specific TH responses in HIV-uninfected donors (UD, n=18) and compared them to those of HIV-infected subjects (HI, n=53). We measured TH proliferative responses to HIV antigen (Ag) peptide pools using CFSE assays and grew HIV-specific TH cell lines (CL). We determined ex vivo responses firstly by ICS and secondly by co-upregulation of activation-induced markers (AIM) after Ag stimulation: i) CD69 and CD40L; or ii) CD25 and Ox40.
Results: We identified a high prevalence of HIV-specific proliferative TH responses in UD; 33% had a robust CFSE response to one or more HIV Ags (Gag, Env, Nef or Pol; net >1% and >2x No Ag background). Gag was less immunodominant in UD than HI: the strongest response was against Gag in 33% of UD vs. 68% of HI (p=0.013, Fisher exact test). While ICS for Th0/1 cytokines (IFNγ, IL2, TNF) and CD40L failed to identify HIV-specific TH in PBMCs directly ex vivo, the same ICS assay on Gag- and gp41-specific CL derived from UD (n=12) showed that these responses were functional and dominated by TNF and CD40L, but produced little IFNγ. In contrast to ICS, AIM assays detected HIV-specific TH from UD without pre-expansion: net HIV-specific TH frequencies (cutoff: >2x No Ag value) ranged from 0.15 to 0.79% for CD69/CD40L and 0.3 to 1.60% for CD25/Ox40. Compared to total TH, HIV-specific Ox40+CD25+ TH were enriched in central memory (median 62% vs. 36%) and T follicular helper cells (median 20% vs. 14%), and preferentially expressed CXCR3 (median 46% vs. 35%). There was a direct correlation between the magnitudes of HIV-specific TH measured by the AIM and CFSE assays (n=20; CD69/CD40L: p=0.01, r=0.55; Ox40/CD25: p=0.01, r=0.56; Spearman).
Conclusion: These results demonstrate that HIV-specific TH cells exist in a substantial proportion of UD, can target diverse HIV Ags and are detectable by functional assays including CFSE and AIM. These cross-reactive CD4 T cells could impact the development of virus-specific TH responses upon acute HIV infection and influence vaccine-induced immunity.

265LB TFH CELLS FUNCTIONAL PROFILE DRIVES ABNORMAL B CELL MATURATION IN HIV INFECTION

Giuseppe Pantaleo[1], Alessandra Noto[1], Andrew McDavid[2], Phu Van[2], Agostino Riva[3], Guy Cavet[4], Song Ding[5], Raphael Gottardo[2], Craig Fenwick[1]
[1]Univ Hosp of Lausanne, Lausanne, Switzerland, [2]FRCHC, Seattle, WA, USA, [3]Luigi Sacco Univ Hosp, Milan, Italy, Milano, Italy, [4]Atreca, Redwood City, CA, USA, [5]Eurovacc Foundation, Amsterdam, Netherlands
Background: The mechanisms underlying abnormalities in B cell maturation and antibody response in HIV-1 infection have been only partially elucidated. The large majority of the studies have been performed in blood B cells while limited information is available on B cell populations in lymph nodes and on the association between the functional profile of T follicular helper (Tfh) cells and the maturation of B cell populations in lymph nodes.
Methods: In the present study, we have investigated the phenotype and function of T follicular helper cells (Tfh) and B cells in lymph nodes of healthy and HIV-1 infected individuals using cutting-edge technologies such as mass cytometry and single cell gene expression. Lymph node biopsies were obtained from 21 HIV-1 infected viremic individuals naive to antiretroviral therapy and 18 healthy HIV negative individuals undergoing surgery for vascular pathologies or herniorrhaphy. Lymph node mononuclear cells (LNMC) were stimulated with phorbol-12-myristate-13-acetate (PMA) and ionomycin for 6 hours and stained with a unique panel of 32 markers primarily defining memory CD4 T cell and B cell populations including antibodies measuring differentiation, trafficking receptors and function.
Results: In HIV-1 infected individuals, we demonstrate a significant increase (2-3 fold) in the Tfh cells defined by the CXCR3+T-bet+ phenotype and IFN-γ production along with a significant decrease (2-3 fold) in Tfh cells expressing CCR4, CCR6 and producing IL-4. The CXCR3, T-bet and IFN-γ signatures of Tfh cells in HIV infection were strongly associated with the appearance of memory B cells expressing CXCR3 and T-bet, which accounted for 30% of memory B cells. CXCR3+ B cells had decreased expression of CXCR4 and CXCR5 and antibody production by CXCR3+ cells was different both quantitatively, e.g. higher producer cells, and qualitatively, e.g. lower levels of hyper somatic mutations, as compared to CXCR3- B cells. We then identified IFN-γ as the causative factor inducing the differentiation of the CXCR3+T-bet+ memory B cells and as a strong suppressive factor of antibody production. The identification of Th1-like Tfh cells and IFN-γ as the main mechanisms affecting B cell maturation and antibody production in HIV infection will provide novel insights into strategies to develop optimal antibody responses in HIV infection and following vaccination.

266 LYMPH NODE HIV-SPECIFIC CXCR5+ CTLs ARE ASSOCIATED WITH ENHANCED VIRAL CONTROL

Zaza Ndhlovu[1], Funsho Ogunshola[2], Omolara Baiyegunhi[2], Nikoshia Mewalal[2], Amber Moodley[2], Krista Dong[1], Thumbi Ndung'u[2], Bruce D. Walker[1]
[1]Ragon Inst of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Univ of KwaZulu Natal, Durban, South Africa

Background: HIV replication occurs in follicular CD4+ T helper cells localized within germinal centers (GC) of secondary lymphoid follicles, and exclusion of CTL within GC is thought to contribute to the maintenance of the viral reservoir. Recent studies have identified a CD8+ T cell population termed follicular CD8+ T cells that expresses the chemokine receptor CXCR5, which is associated with trafficking into GCs, which secrete its ligand CXCL13. However, the frequency, precise localization and antiviral function of HIV-specific CXCR5+ CD8+ T cells within lymph nodes have not been determined. We investigated the frequency, function and localization of HIV-specific CXCR5+ CD8+ T cells in lymph nodes (LN) and peripheral blood (PB) during treated and untreated chronic clade C HIV-1 infection.

Methods: Biopsied LN and paired PB samples from 5 chronic untreated, 2 treated in chronic phase and 2 subjects treated during hyperacute HIV infection were analyzed. MHC class I tetramers and ICS assays were used to characterize HIV-specific responses. Immunohistochemistry (IHC) staining for Gag p24 was used to identify the location of HIV infected cells. IHC was also used to locate CXCR5+ CD8+ T cells within LN.

Results: Comparative analysis of HIV-specific CD8+ T cells of the same tetramer specificity in LN and paired PB illustrated phenotypic and functional dissimilarities. Notably, in contrast to PB responses, LN cells were significantly more activated (CD38+HLA-DR+), more exhausted (PD-1 high) and secreted less cytokines upon ex vivo stimulation with mitogens (SEB). IHC revealed limited overlap between Gag p24+ CD4+ T cells and CD8+ T cells. The frequencies of CXCR5+ tetramer+ CD8+ T cells were very low in PB averaging about 0.9% (IQR 0.0:3.2), but were readily detectable in LMC samples by flowcytometry as well as in LN tissues by IHC. More importantly the frequency of CXCR5+ tetramer+ CD8+ T cells in LN inversely correlated with plasma viral load (Spearman's $r=-0.8$; $p=0.01$).

Conclusion: Taken together our results indicate that HIV-specific CD8+ T cells in LN are functionally more impaired than PB responses. Within LN, CXCR5+ tetramer+ CD8+ T cells may contribute to enhanced virus control. Therefore, efforts aimed at redirecting HIV-specific CD8+ T cells into GC though induction of CXCR5 expression may contribute to enhanced virus suppression.

267 RESIDENT MEMORY CD8+ T CELLS FORM THE FRONT-LINE DEFENSE IN HIV-INFECTED LYMPH NODES

Marcus Buggert[1], Lalit Beura[2], Son Nguyen[1], David Canaday[3], Ali Naji[4], Constantinos Petrovas[5], Gustavo Reyes-Terán[6], Steven G. Deeks[7], David Masopust[2], Michael R. Betts[1]
[1]Univ of Pennsylvania, Philadelphia, PA, USA, [2]Univ of Minnesota, Minneapolis, MN, USA, [3]Case Western Reserve Univ, Cleveland, OH, USA, [4]Hosp of the Univ of Pennsylvania, Philadelphia, PA, USA, [5]NIH, Bethesda, MD, USA, [6]Rsr Cntr in Infectious Diseases, Mexico City, Mexico, [7]Univ of California San Francisco, San Francisco, CA, USA

Background: CD8+ T cells are key players in HIV control and future cure efforts. Current knowledge of HIV-specific CD8+ T cells relies almost entirely on circulating cells, although HIV is primarily a disease of lymphoid tissue. Accumulating evidence indicates that non-circulating 'resident memory' (TRM) CD8+ T cell responses are critical for pathogen control in tissues; however, whether CD8+ TRMs are found in lymphoid tissue is uncertain. Conceptually, most lymphoid memory CD8+ T cells are thought to recirculate, but such data are based on human blood and hygienic mouse models.

Methods: Human peripheral blood and lymphoid tissues from multiple locations were collected from healthy controls and HIV-infected subjects, including ART-, ART+, and elite controllers from different sites in North and Central America. Peripheral blood and lymph nodes were also compared between laboratory mice living in ultra-hygienic specific-pathogen free (SPF) environment and "dirty" mice that had more physiologic infectious experience. Multi-parametric flow cytometry, histo-cytometry, gene expression, and tetramer analysis were used to assess the localization, phenotype, and transcriptional profile of CD8+ T cells. Data were analyzed in FlowJo, GraphPad Prism, and R Studio.

Results: We here provide evidence that a majority of memory CD8+ T cells in lymphoid tissue of healthy humans bear a TRM phenotype, with high expression of CD69 and variable levels of CD103. Furthermore, "dirty" mice exhibited substantially more of the TRM phenotype within lymph nodes than SPF mice. Lymphoid TRMs are detectable in HIV-infected lymph nodes using histo-cytometry and most CD8+ T cells with B cell follicle homing potential (CXCR5+) have a TRM phenotype. Importantly, the majority of HIV-specific CD8+ T cells in lymph nodes are TRMs and show transcriptional and phenotypic characteristics that are distinct from peripheral blood HIV-specific CD8+ T cells. Finally, we find that HLA-B57/27+ elite controllers demonstrate high magnitudes of HIV-specific TRMs in lymph nodes that selectively target immunodominant epitopes within Gag.

Conclusion: We identify that HIV-specific TRMs are the front-line defense in HIV-infected lymph nodes. TRMs do not share the same phenotypic and transcriptional characteristics with circulating HIV-specific CD8+ T cells that have classically been studied in the context of HIV pathogenesis. Elicitation of functional and high numbers of lymphoid CD8+ TRMs should be a priority for any HIV vaccine or eradication strategy.

268 HIV-1 ESCAPE FROM CD8+ CYTOTOXIC T-LYMPHOCYTES DEFINED AT CLONAL RESOLUTION

Aleksandr Gorin, Yushen Du, Ren Sun, Otto Yang
Univ of California Los Angeles, Los Angeles, CA, USA

Background: A small number of HIV-infected individuals are able to effectively suppress HIV replication without antiretroviral therapy. Certain "protective" HLA types correlate with this ability to suppress HIV replication, indicating that the CD8+ cytotoxic T-lymphocyte (CTL) response in these individuals is responsible for the efficient containment of HIV. However, the mechanism behind CTL mediated control is unclear and has been suggested to be a result of either increased ability of the CTLs to recognize escape mutants or due to the ability of protective HLA types to present conserved viral epitopes. In this project we define all possible single and double amino acid mutations that the HIV can assume to escape CTL targeting, and the effect of these mutations on relative viral fitness within two HIV-1 immunodominant epitopes: SL9 (Gag 77-85) and KF11 (Gag 162-172) presented by the non-protective HLA A*02 and the protective HLA B*5701, respectively.

Methods: Plasmid libraries encoding full length HIV with all possible single and double amino acid mutations within the SL9 and KF11 epitope were synthesized. Live virus was created from this library and passaged in HIV permissive cells in the absence or presence of epitope-specific CTLs. The passaged virus was deep sequenced to identify viable variants and variants that could escape CTL recognition.

Results: 48 variants within SL9 and 33 within KF11 maintained reasonable relative fitness. KF11 specific CTLs recognized 13-16 of these variants while SL9 specific CTLs recognized 7-24 variants. 2 KF11 and 11 SL9 variants were at least as fit as wild type. KF11 specific CTLs recognized all of these most fit variants, while SL9 specific CTLs recognized only 0-45% of the most fit variants.

Conclusion: CTLs targeting SL9 and KF11 do not differ in their ability to cross recognize escape variants. However, HIV is far less tolerant of mutations within KF11 than SL9, giving the virus fewer options for escape at this epitope. Furthermore, since KF11 specific CTLs can recognize all of the most fit KF11 variants (while SL9 specific CTLs cannot), HIV must sacrifice replicative capacity to escape CTL recognition of KF11. Our findings indicate that the beneficial effect of protective HLA types derives from the ability of these HLAs to present highly conserved regions of the virus, and from the ability of CTLs targeting these epitopes to cross recognize only the few fit variants that exist within such regions.

269 INVESTIGATING THE ROLE OF TCR STRUCTURE IN FUNCTIONAL ACTIVITY OF HIV-SPECIFIC CTLs

Nina C. Flerin[1], Tynisha Glover[1], Huabiao Chen[2], Jianhua Zheng[1], Harris Goldstein[1]
[1]Albert Einstein Coll of Med, Bronx, NY, USA, [2]Ragon Inst of Massachusetts General Hosp, Cambridge, MA, USA

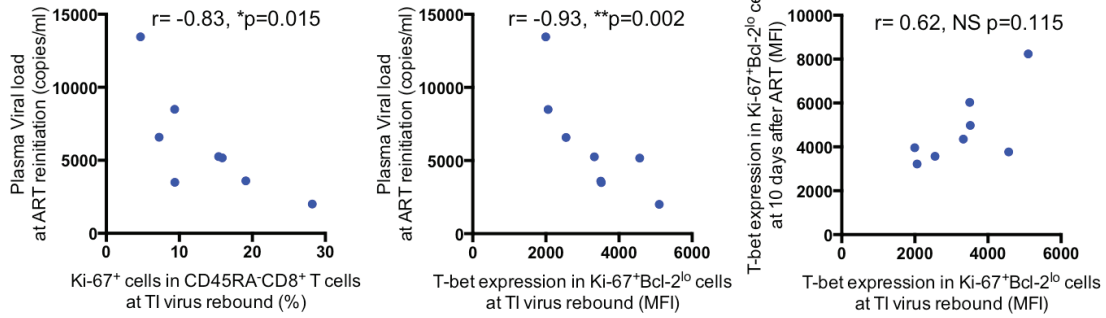
Background: Lentiviral vectors expressing effective HIV-specific TCR clonotypes can transform naïve CD8+ T cells into potent HIV-specific CTLs, a possible gene therapy approach to increase HIV-specific immunity. To optimize this approach, it is crucial to identify TCR clonotypes which confer the most potent anti-HIV activity. CTLs with superior antiviral efficacy, termed effective CTLs, are well-represented in HIV-1 controllers but are rare or absent in HIV-1 progessors. However, the contributory role of the HIV-specific CTL TCR clonotype on the potency of its antiviral activity is unclear; this compromises our ability to identify which HIV-1 specific TCR α and β chain genes most effectively convert primary CD8+ T cells into potent HIV-specific CTLs.

Methods: To directly evaluate the contribution of the TCR clonotype on the differences observed in effective or ineffective CTL clones, we cloned into TCR-expressing lentivectors the TCR α and β chain genes from one effective and two ineffective CTL clones specific for the same viral peptide, KK10, but with different TCR clonotypes, isolated from an HLA*B2705 elite controller (Chen et al., Nature Immunology 2012;13:691). We used these lentivectors to transduce Jurkat/MA cells, a T cell line engineered to measure TCR signaling using a luciferase reporter, and primary CD8+ T cells to delineate the contribution of the TCR on the functional activity of HIV-specific CTLs.
Results: Jurkat/MA cells transduced with lentiviral vectors encoding TCRs cloned from the effective or the two ineffective CTL clones expressed equivalent levels of KK10-specific TCR clonotypes and displayed comparable TCR activation by their cognate peptide, KK10. Primary CD8+ T cells transduced with lentivirus expressing the TCR from the effective CTL clone or the two ineffective CTL clones displayed equivalent levels of the KK10-specific TCR clonotypes and exhibited equivalent potent inhibition (>80%) of in vitro HIV-1 infection.
Conclusion: Taken together, these data indicated that TCR clonotypes from ineffective CTLs have the intrinsic capacity to direct primary CD8+ T cells to effectively kill HIV infected cells and support the proposition that other TCR-independent factors such as epigenetic modifications may also contribute to the effective vs. ineffective functions of some CTL clones. The effective control of HIV-1 infection in elite controllers may be due to their capacity to generate and expand these effective clonal CTL populations.

270 HIV-SPECIFIC CD8 T CELLS IN PERSONS TREATED IN FIEBIG I ACUTE INFECTION WHO STOP ART

Hiroshi Takata[1], Donn Colby[2], Eugene Kroon[2], Suteeraporn Pinyakorn[1], Nelson L. Michael[3], Merlin L. Robb[1], Jintana Intasan[2], Jintanat Ananworanich[4], Lydie Trautmann[1], for the RV411 and RV254/SEARCH010 Study Groups
[1]Walter Reed Army Inst of Rsr, Silver Spring, MD, USA, [2]SEARCH, The Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [3]Walter Reed Army Inst of Rsr, Silver Spring, MD, USA, [4]US Military HIV Rsr Prog, Silver Spring, MD, USA

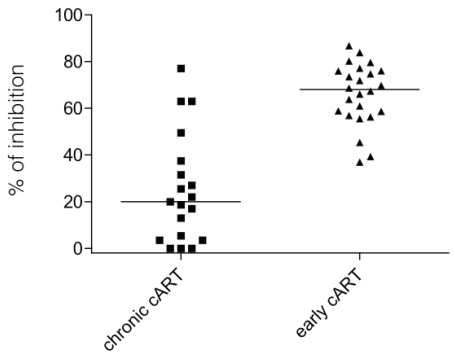
Background: Initiation of antiretroviral therapy (ART) at the earliest stage of acute HIV infection (AHI) partially preserves B cell and mucosal T cell responses. We recently showed that HIV-specific CD8+ T cells generated at Fiebig I were delayed in expanding and acquiring effector functions but were endowed with higher memory potential. Whether these preserved CD8+ T cells play a role in controlling viral rebound following treatment interruption (TI) is unknown. We investigated the HIV-specific CD8+ T cell response after TI in participants who initiated ART during AHI Fiebig I.
Methods: Eight HIV infected Thai individuals who initiated ART in during AHI Fiebig I (VL+, p24-, IgM-) were studied longitudinally in AHI and during TI. At the time of TI, all were on ART ≥ 2 years, CD4 T cells ≥ 400 cells/mm^3 and HIV-1 RNA < 50 copies/ml, all rebounded after ART cessation. We analyzed HIV-specific CD8+ T cells defined by the detection of Ki-67 and lack of Bcl-2 longitudinally during AHI and TI by flow cytometry.
Results: HIV-specific CD8+ T cells significantly increased at viral rebound compared to baseline prior to TI. Although plasma viral load was significantly lower after TI than at AHI, HIV-specific CD8+ T cell magnitude was higher in TI compared to AHI. Of note, in AHI HIV-specific CD8+ T cells frequencies increased significantly only 10 days after ART initiation. These data suggest that HIV-specific CD8+ T cells expand faster after TI than in AHI. During TI, the frequency of HIV-specific CD8+ T cells and the levels of the transcription factor T-bet (mean fluorescence intensity) were negatively correlated with plasma viremia before ART reinitiation (Fig). Moreover, T-bet expression levels in effector CD8+ T cells in AHI 10 days after ART initiation tended to be associated with T-bet expression at viral rebound in TI (Fig). These data suggest that the frequency of effector HIV-specific CD8+ T cells contributes to limiting viremia after TI and that their differentiation levels in AHI prior to ART imprints their differentiation during TI.
Conclusion: Effector CD8+ T cells expand more rapidly after TI than in AHI and contribute to virus control during TI even though they are not sufficient to contain viral rebound. Therefore, pre-TI immune boost strategies to achieve higher quantity and complete effector differentiation of HIV-specific CD8+ T cells may be required for successful viral control after TI in addition to treating early to preserve immune memory.



271 EARLY CART OF HIV-1 INFECTED SUBJECTS PRESERVES ANTIVIRAL FUNCTION OF CD8+ T CELLS

Miriam Rosas Umbert[1], Beatriz Mothe[2], Gemma Hancock[3], Hongbing Yang[3], Christian Manzardo[4], Josep Coll[1], Christian Brander[1], Lucy Dorrell[3]
[1]IrsiCaixa AIDS Rsr Inst, Badalona, Spain, [2]Hosp Germans Trias i Pujol, Badalona, Spain, [3]Univ of Oxford, Oxford, UK, [4]Univ of Barcelona, Barcelona, Spain

Background: Recent data from several clinical trials highlight the benefits of early antiretroviral treatment, including a better CD4 cell recovery, normalization of CD4/CD8 ratios, smaller HIV reservoir and limited viral diversification. Since such clinical benefits may be mediated, at least in part, by a robust and functionally intact antiviral CD8 T cell response, we assessed the HIV suppressive capacity of CD8 T cells ex vivo in replication inhibition assays in a cohort of early treated individuals. We compared these data with individuals treated at chronic stages of HIV infection.
Methods: 24 early-treated individuals (<6m from HIV-1 acquisition, median time of 84 days (Early cART) who initiated TDF/FTC/RAL 1 week after diagnosis were recruited at two HIV outpatient clinics in Barcelona. We measured CD8+ T-cell mediated viral inhibitory capacity against HIV-1 BaL and IIIB isolates at different CD8:CD4 ratios (E:T = 1:1, 1:2 and 1:10) in longitudinal cryopreserved samples obtained at 6 and ~1 year (13 -15 months) after treatment initiation. Changes in activation markers (HLA-DR, CD38, CD69, CD25) on total CD4 and CD8 were assessed by flow cytometry. Total HIV-specific T cell responses were assessed by IFNg ELISPOT. Viral inhibition data from 19 individuals who started treatment in chronic infection and had been virologically suppressed for at least one year (Chronic cART) was used for comparison.
Results: At one year after treatment initiation, CD8+ T cell viral inhibition was significantly higher in early treated individuals (median 68%) chronic cART individuals (median 20%, p=0.0001). This higher suppressive



CD8+ T cell antiviral inhibitory activity in HIV individuals that started treatment either during chronic stage (n=19) or less than 6 months after HIV-acquisition (n=24) was measured at 1:1 E:T ratio.

capacity was maintained over time, was also observed at lower E:T ratios and was confirmed with 2 clade B viruses. Suppressive activity was not associated with levels of PD-1 and HLA-DR expression on total CD4 and CD8 T cells or total HIV-specific response at any time-point assessed.
Conclusion: Early initiation of ART was associated with preservation of functional HIV-specific T cell responses. Although CD8+ T-cell mediated antiviral inhibitory activity was higher in early-treated than chronic cART individuals, levels were inferior to those reported in HIV controllers. This suggests that although early treatment was able to preserve CD8+ T cell antiviral functional capacity for at least one year, it was not able to completely prevent immune activation and T cell exhaustion.

272 WITHDRAWN

273 TRAIL-SHORT REDUCES THE CYTOTOXIC CAPACITY OF NK CELLS

Fatma Aboulnasr, Nathan Cummins, Zilin Nie, Stephen Burke, Andrew Badley
Mayo Clinic, Rochester, MN, USA
Background: TRAIL-short (TRAIL-s) is a novel splice variant of TRAIL, capable of blocking TRAIL mediated cell death. Previous studies from our lab have shown that the plasma concentration of TRAIL-s in HIV infected patients correlates with viral load and increases cell resistance to TRAIL-induced death. Natural killer (NK) cells play a key role in the antiviral response to HIV infection. While NK cells can produce TRAIL as an effector molecule to kill tumor cells, its role in antiviral defense is just emerging. In the current study we sought to determine the effect of TRAIL-s on NK function.
Methods: Jurkat cells were transfected with a control or TRAIL-short expressing plasmids, and incubated with primary NK cells from uninfected donors (N=10) at various Effector :Target ratios (1:1 to 20:1). A flow cytometric-based assay was used to determine the cytotoxic effects of the NK cells on the target Jurkat cells. The effect of TRAIL-s overexpression on NK cell activity and function was determined by staining for CD69, Perforin, CD16 and CD107a. In addition the effect of HIV IIIB- gp120, or supernatant containing HIV IIIB virus on NK expression of TRAIL and TRAIL-s was measured by surface staining.
Results: Overexpression of TRAIL-s in target cells significantly reduced the cytotoxic function of NK against these cells across a range of E:T ratios compared to the control cells (p=0.006 at an E:T ratio of 20:1).However this overexpression did not alter the expression of CD 69, CD16, Perforin or CD107a in NK cells. Interestingly pre-treatment of NK cells with culture supernatant containing HIV IIIB virus caused a large increase in surface expression of TRAIL-s, yet had no effect on TRAIL expression, whereas gp120 alone did not.
Conclusion: TRAIL-s expression significantly reduces NK mediated cytotoxicity. HIV containing supernatant alone increases the surface expression of TRAILs on NK cells. This provides new insight to the effect of TRAIL-s on NK function, and argues that blockade of TRAIL-s, may increase NK cytotoxicity against virally infected cells.

274 OF THE TB01 MOTIF KIR GENES, KIR3DS1 PLAYS ROLE IN HIV RESISTANCE & NK CELL FUNCTION

Zahra Kiani[1], Elise Jackson[1], Xin Yu Zhang[1], Irene Lisovsky[1], Benjamin Tallon[1], Julie Bruneau[2], Jean-Pierre Routy[3], Nicole Bernard[4]
[1]McGill Univ, Montreal, Quebec, [2]Univ of Montreal, Montreal, Canada, [3]McGill Univ Hlth Cntr, Glen site, Montréal, Canada, [4]Rsr Inst, McGill Univ Hlth Cntr, Montreal, Canada
Background: Some individuals, called HIV exposed seronegative (HESN), remain HIV uninfected despite repeated HIV exposures. Studying HESN improves our understanding of the mechanisms underlying resistance to HIV infection. Previous work by our group found that KIR3DS1 (3DS1) homozygotes (hmz) were more frequent among HESN than HIV+ subjects. 3DS1 is in linkage disequilibrium with other KIR genes in the telomeric KIR B region known as the TB01 motif. The TB01 motif is characterized by the presence of 3DS1 and KIR2DL5A (2DL5A) genes and the absence of a KIR2DS4 (2DS4) locus. Here, we probed the contribution of TB01 motif KIR genes to NK cell functionality.
Methods: We compared the frequency of linked 3DS1, 2DL5A and 2DS4 genes in 105 HESN and 414 HIV+ subjects. To address the contribution of 3DS1 and 2DL5 to NK cell functionality we examined the responses of 3DS1+/-/2DL5+/- NK cells from 8 subjects who were 3DS1hmz and 2DL5A+ to stimulation by the HLA-null cell line 721.221 (221). Responsiveness was measured by assessing the % of 3DS1+/-/2DL5+/- NK cells secreting IFN-γ and CCL4 and expressing CD107a.
Results: HESN. compared to HIV+ subjects, were more frequently 3DS1hmz, trended towards being more frequently 2DL5A+ and less frequently carried an expressed 2DS4 allele. Carriage of a TB01 motif and being TB01 homozygous were more frequent in HESN than HIV+ subjects (Fisher's exact tests). 221 cells stimulated a higher frequency of functional 3DS1+ than 3DS1- NK cells while expression of 2DL5A either with 3DS1 or alone did not further contribute to the frequency of HLA-null responsive cells (Friedman and Wilcoxon tests).
Conclusion: The linkage disequilibrium present among KIR genes in the TB01 KIR region confounds ascribing a role in protection from infection to one or more of these linked genes. The stochastic expression of KIR gene products on NK cells allowed us to show that 3DS1 confers functionality to NK cells populations expressing this gene product while 2DL5A does not. 3DS1 may confer functionality by interacting with HLA-F on 221 cells to transmit activating signals to 3DS1+ NK cells. The role of other TB01 KIR gene products has not been entirely eliminated but The TB01 motif lacks a 2DS4 gene and the KIR2DS3 gene in this motif encodes poorly expressed receptors. Together, these results point towards 3DS1 being a gene product important in conferring NK cell functionality associated with protection from HIV infection in HESN.

275 NO RECOVERY OF VA7.2 MAIT CELLS AFTER THERAPEUTIC IMMUNISATION PLUS IL-2/GM-CSF/RHGH

Louise Greathead, Alexander Cocker, Anna Herasimtschuk, Sundhiya Mandalia, Peter Kelleher, Nesrina Imami
Imperial Coll London, London, UK
Background: Mucosal-associated invariant T (MAIT) cells are lost in HIV-1 infection and do not recover on antiretroviral therapy (ART). Therapeutic immunisation (GTU-MultiHIV Clade B DNA vaccine) together with interleukin-2 (IL-2), granulocyte-macrophage colony-stimulating factor (GM-CSF) and recombinant human growth hormone (rhGH), has been shown to reduce immune activation and improve HIV-1-specific T-cell responses in ART-treated HIV-1 infected individuals. In this study we assessed the ability of this regimen to reconstitute MAIT cell populations.
Methods: Flow cytometry was performed on cryopreserved peripheral blood mononuclear cells taken from 12 patients at baseline, week 2 and week 48. Participants were randomised into one of three groups: 1) vaccine plus IL-2, GM-CSF and rhGH (n=3); 2) vaccine alone (n=4); or 3) IL-2, GM-CSF and rhGH alone (n=5). MAIT cells were identified as live CD3+CD45RO+ T cells co-expressing the invariant T cell receptor Vα7.2 together with the C-type lectin CD161. CD4 and CD8 memory T cell expression of CD38 was used as a marker of T-cell activation. Wilcoxon matched-pairs signed rank test and longitudinal MIXED method analysis were used to evaluate changes from baseline to week 2 and week 48. Correlations were performed using Spearman's Rho.
Results: The ratio of CD4/CD8 memory T cells rose significantly at week 2 (p=0.002) and was maintained at week 48 (p=0.005) compared to baseline in the combined group of patients. CD4 and CD8 T cell activation (CD38+) also significantly rose at week 2. There was a significant fall of CD8 T cell activation at week 48 compared to baseline (p=0.021) in the combined group. Baseline MAIT cell frequency was 1.49% (0.49-2.96) of CD3 memory T cells in the combined group. MAIT cell frequency fell to 0.85% (0.46-1.71, p=0.021) at week 2 before rising to 1.32% (0.57-2.64) at week 48 in the combined group. There was no significant change in MAIT cell frequency at week 48 in patients randomised to receive IL-2/GM-CSF and rhGH, either with (group 1) or without (group 3) vaccine. There were no correlations between baseline or week 48 MAIT cell frequencies and T-cell activation.
Conclusion: Peripheral blood MAIT cells fail to reconstitute following successful ART combined with therapeutic immunisation and IL-2, GM-CSF and rhGH administration.

276 REDUCED CD161 EXPRESSION ON MAIT CELLS IN HIV-INFECTED SUBJECTS WITH IMMUNE FAILURE

Michael L. Freeman, Michael M. Lederman
Case Western Reserve Univ, Cleveland, OH, USA
Background: Mucosa-associated invariant T (MAIT) cells are a recently identified class of innate-like T cells that are involved in the mucosal immune response. MAIT cells are characterized by expression of TCR Vα7.2 and CD161. In HIV infection there is a profound early loss of MAIT cells from the circulation that never fully recovers, even after prolonged

viral control with antiretroviral therapy (ART), but the mechanisms driving this phenomenon are unknown. Here we examined MAIT cell loss in ART-treated HIV-infected donors with or without CD4 T cell recovery.
Methods: PBMCs from fresh whole blood from HIV-negative (n=25) or ART-treated HIV-positive donors with full (Immune Success [IS]; n=18) or impaired (Immune Failure [IF]; n=13) CD4 T cell recovery were analyzed by flow cytometry for T cell markers, TCR Vα7.2, and CD161. PBMCs from healthy controls were cultured with or without TCR-mediated stimulation, and CD161 expression was assessed on Vα7.2+ T cells. Interferon-γ (IFNγ) production was assessed by intracellular cytokine staining.
Results: We find decreases in the percentage of CD3+ T cells that express CD161 (0.9% vs. 4.7%; P<0.0001) and the percentage of Vα7.2+ T cells that express CD161 (23% vs. 71%; P<0.0001) in HIV-infected individuals. We also find a significant increase in the percentage of T cells that are CD161-Vα7.2+ in IF compared to controls (3.3% vs. 1.7%; P=0.0003), accompanied by an increase in the percentage of CD161-Vα7.2+ T cells that express CD8 in IF (76% vs. 48%; P<0.0001), but not IS (P=0.2847), donors. After TCR stimulation in vitro, Vα7.2+ T cells reduced expression of CD161 by 49% (P=0.002), and CD161- Vα7.2+ cells produced less IFNγ than CD161+ Vα7.2+ cells (3.7% vs. 29.5%; P=0.016).
Conclusion: Our findings suggest that in ART-treated HIV-infected subjects who do not recover CD4 T cell numbers, the reduction in peripheral MAIT cells is due at least in part to a loss in CD161 expression, and not merely trafficking into mucosal tissues or cell death. The residual CD161-Vα7.2+ cells may be impaired in their ability to synthesize IFNγ.

277 RESIDUAL LOW-LEVEL VIREMIA ON ART NOT ASSOCIATED WITH LOWER SYSTEMIC EXPOSURE TO ARVs

Monica Gandhi[1], Andrei Stefanescu[2], Ronald Bosch[2], Rajesh T. Gandhi[3], Joshua C. Cyktor[4], Howard Horng[1], Joseph J. Eron[5], John W. Mellors[4], Deborah McMahon[4]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Harvard Univ, Boston, MA, USA, [3]Massachusettes General Hosp, Boston, MA, USA, [4]Univ of Pittsburgh, Pittsburgh, PA, USA, [5]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA
Background: The persistence of HIV has been postulated by some to be due to ongoing viral replication in reservoir sites because of inadequate antiretroviral (ARV) exposure. Few data exist on the relationship between cumulative systemic exposure to ARVs and levels of residual viremia on ART. If residual viremia were a consequence of marginal ARV exposure, then lower ARV exposure would correlate with higher levels of residual viremia.
Methods: Scalp hair and blood samples were collected as part of a longitudinal cohort study (ACTG 5321) of 112 participants with chronic HIV infection with plasma HIV RNA <50 copies/ml on ART over a prolonged duration. Small samples of hair were analyzed for ARV concentrations (as cumulative measures of exposure) using validated liquid chromatography/tandem mass spectrometry assays. Plasma samples obtained close to time of hair sampling were assayed for residual viremia (HIV RNA) by a single copy RT-PCR assay targeting integrase (LOD 0.4 cps/ml). Spearman correlations evaluated the relationship between hair ARV levels and residual viremia.
Results: Median duration of ART at study entry was 7 yrs. All participants were on TDF/FTC and a PI, INSTI or NNRTI. There was substantial (5-fold) person-to-person variability in tenofovir (TFV) levels in hair (10th-90th percentile: 0.02-0.09 ng/mg). This variability was similar to that reported for ARV-taking patterns of 4-7 doses /week in other cohorts with less well-suppressed viremia. No significant correlation was found between ARV hair concentrations and residual viremia: FTC/TFV r= 0.03 (p= 0.78); RAL r= 0.16 (p= 0.56); EFV r=-0.02 (p= 0.94); DRV r=0.11 (p= 0.73). Of note, TFV concentrations when co-administered with boosted ARVs (ATV/r, DRV/r, EVG/cobi) were 1.3-fold higher than when co-administered with unboosted ARVs (RAL, EFV, RPV) (Wilcoxon ranksum; p=0.018).
Conclusion: Hair concentrations of TFV as a cumulative measure of TFV exposure were distributed over a wide range and pharmacoenhancers (like ritonavir) increased TFV levels by 30%. Despite the variability in ARV concentrations, there was no apparent relationship between ARV exposure and the level of residual viremia. This result argues against inadequate ARV exposure allowing ongoing viral replication and resulting in residual viremia. Whether ARV exposure is associated with other markers of HIV persistence or with persistent inflammation or immune activation should be explored.

278 ANTIGP41 TITERS REFLECT RESIDUAL REPLICATION IN VIROLOGICALLY SUPPRESSED ART PATIENTS

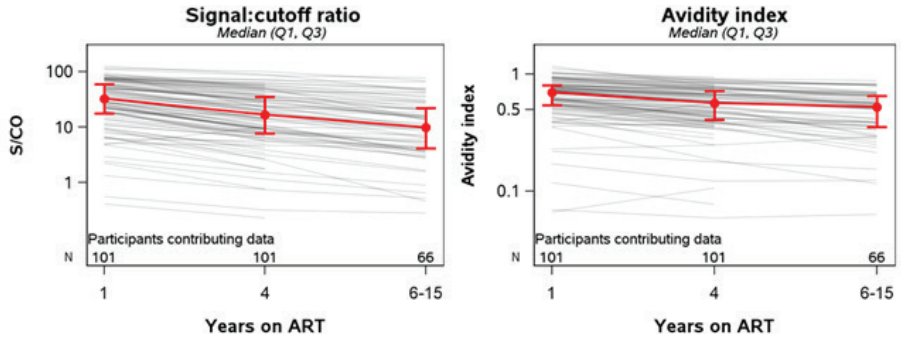
Heloise M. Delagreverie[1], Maxime Grudé[2], Sidonie Lambert[3], François Raffi[4], Catherine Leport[5], Cécile Goujard[6], Lorraine Plessis[7], Christine Katlama[8], Francis Barin[9], Constance Delaugerre[10]
[1]Hôpital Saint Louis, PARIS, France, [2]INSERM, Paris, France, [3]Institut Pierre Louis d'Epidémiologie et de Santé, Paris, France, [4]CHU Hotel-Dieu Nantes, Nantes, France, [5]Hôpital Bichat, Paris, France, [6]AP-HP, Le Kremlin-Bicêtre, France, [7]INSERM, Villejuif, France, [8]Pierre and Marie Curie Univ, Paris, France, [9]INSERM Tours, France, [10]Hôpital Saint Louis, Paris, France
Background: A major challenge to HIV cure strategies is the measurement of the total burden of persistent replication-competent HIV. Suppression of viral replication is likely to lessen antigen presentation to B cells, leading to a decrease in anti-HIV antibody production. Our aim was to determine whether anti-gp41 titer was correlated with reservoir size and could be valuable as a surrogate marker of HIV-1 reservoir in suppressed patients on antiretroviral therapy (ART).
Methods: Anti-gp41 antibody titers were assayed in an cross-sectional study of HIV-1 infected ART treated patients with plasma HIV-1 RNA viremia strictly below 50 copies/ml for 12 months, from 3 ANRS cohorts (COPANA, MONOI and APROCO). Binding to the immunodominant epitope of gp41 was measured by enzyme-linked immunoassay. Pearson correlation with age, gender, duration of HIV infection, time on ART, duration of viremia suppression, nadir and current CD4+ T-cell counts, current CD4/CD8 ratio, plasma HIV-1 RNA (ultrasensitive viral load, usVL, LOQ 1 RNA copy/ml) and blood HIV-1 DNA (LOQ 1.6 log10 DNA copies/10^6 PBMC) were tested
Results: 812 patients were included. They were mostly male (77%) with a median age of 41 yrs. Nadir CD4+ cells was 237/µl, median time since HIV diagnosis was 12 yrs and median ART duration was 9.5yrs with 4.2yrs of viral suppression. Median CD4+ T-cell count was 566/µl (CD4/CD8 ratio =0.8). Amongst the 213 patients with usVL data, 46% (n=98) tested twice consecutively below 1 copy/ml, and nadir CD4+ cells was 237/µl. Median (IQR) total HIV-DNA (n=364 patients tested) was 2.6 (2.2-3.1) log copies/10^6 PBMC. In 809 patients, the median (IQR) titer of anti-gp41 antibody was 1.5 (0.7-2.1). There was a significant inverse correlation between anti-gp41 antibody titer and time on ART, duration of viral control, current CD4+ cell count and CD4+/CD8+ ratio. Consistent usVL below 1 copy/mL was associated with a median gp41 titer of 1.1 (0.5-1.6) vs 1.4 (0.7-1.9) in patients with at least one usVL above 1 copy/ml (p=0.009). A trend towards a lower titer of anti-gp41 antibodies was observed in patients with undetectable HIV DNA: 0.7 (0.5-1.6) vs 1.3 (0.7-1.8) with detected HIV DNA, p=0.06.
Conclusion: Maximal viral suppression, leading to minimal antigen stimulation, was associated with a decrease in anti-gp41 antibodies titers. Importantly, low anti-gp41 titers were combined with a lower HIV DNA burden. Anti-gp41 titration may be an additional biomarker of effective HIV replication suppression in patients on ART.

279 ANTIBODY LEVELS CORRELATE WITH THE INFECTED CELL POPULATION IN HIV PATIENTS ON ART

Sheila Keating[1], Christina Lalama[2], Ronald Bosch[2], Deborah McMahon[3], Joshua Cyktor[3], John Mellors[3], Joseph J. Eron[4], Rajesh T. Gandhi[5], Michael P. Busch[1], for the ACTG 5321 Team
[1]Blood Systems Rsr Inst, San Francisco, CA, USA, [2]Harvard Univ, Boston, MA, USA, [3]Univ of Pittsburgh, Pittsburgh, PA, USA, [4]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [5]Massachusetts General Hosp and Ragon Inst, Boston, MA, USA
Background: Current methods to quantify the HIV reservoir in individuals on ART use large volumes of blood or tissue biopsies. In contrast, small volume, easy to perform assays to assess changes in HIV reservoir size and expression are needed. Antibody (Ab) assays can be performed with a few microliters of serum or plasma, are reproducible, and results can be obtained within hours. We assessed whether plasma Ab levels and Ab avidity to HIV are associated with the frequency of HIV-infected cells and proviral transcriptional activity in blood.
Methods: Longitudinal PBMC and plasma samples were obtained from an ART-treated cohort of individuals with virologic suppression (ACTG A5321) who had HIV RNA levels <50 cp/mL with no blips or ART interruption (≥21 consecutive days) documented from year 1 of follow-up. Virologic and immunologic testing was performed on stored PBMC and plasma samples from pre-ART (n=101), year(yr) 1 (n=101), yr4 (n=101), and yrs 6-15 (n=66) on ART. Less-sensitive VITROS (S/Co) and Avidity VITROS (AI) Ab measurements were performed on plasmas at all timepoints except pre-ART. Plasma HIV RNA, unspliced cell-associated HIV DNA and unspliced HIV RNA were measured by qPCR assays.
Results: Both HIV Ab measurements showed a statistically significant decline between yr1 and yr4 on ART with median participant-specific decline of 19%/yr for S/Co and 5.6%/yr for AI (p<0.001 for each) (Figure). No significant associations were found between yr1 HIV Ab levels and pre-ART HIV RNA, CD4 T-cell count or CD4:CD8 ratio. S/Co and AI were

positively associated with HIV DNA at yr1 (Spearman r= 0.24 and 0.27, p≤0.019) and yr4 (r= 0.31 and 0.36, p≤0.002), but not associated at pre-ART. HIV Ab measurements were not associated with cell-associated HIV RNA (CA-RNA) at pre-ART, yr1 or yr4. There was a marginal positive association between S/Co and the AI slope/yr from yr1 to yr4 with total HIV DNA at yr4 (r= 0.21 and 0.20, p≤0.05).

Conclusion: The correlations found between Ab and HIV DNA levels suggest that host immune responses may be used to estimate the frequency of HIV-infected cells in patients on suppressive ART. The finding that Ab assay results do not correlate with CA-RNA levels suggests that most CA-RNA does not result in production or presentation of viral proteins. Whether Ab measures correlate with cellular HIV antigen expression will be important to determine.



280 PERSISTENT IMMUNE ACTIVATION DESPITE ART: THE "DIE IS CAST" BEFORE ART INITIATION

Rajesh T. Gandhi[1], Deborah McMahon[2], Ronald Bosch[3], Christina Lalama[3], Bernard Macatangay[2], Joshua Cyktor[2], Ann Collier[4], Charles Rinaldo[2], Joseph J. Eron[5], John Mellors[2]
[1]Massachusetts General Hosp and Ragon Inst, Boston, MA, USA, [2]Univ of Pittsburgh, Pittsburgh, PA, USA, [3]Harvard Univ, Boston, MA, USA, [4]Univ of Washington, Seattle, WA, USA, [5]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: The relationships among pre-ART and on-ART levels of HIV, immune activation and inflammation are incompletely understood, in part because prior studies have been small or cross-sectional.

Methods: We measured HIV DNA, cell associated HIV RNA (CA-RNA), inflammatory biomarkers (IL-6, sCD14, hsCRP, sCD163), T cell activation (% CD38+/HLA-DR+) and cycling (%Ki67+) in 101 participants who initiated ART during chronic infection and had well-documented sustained suppression of plasma viremia for a median of 7 yrs (ACTG A5321). Assays were performed on samples from pre-ART and from on-ART yrs 1, 4 and yrs 6-15.

Results: Following ART initiation, HIV DNA, CA-RNA, IL-6, sCD163, T cell activation and T cell cycling declined significantly. Higher pre-ART levels of HIV DNA and CA-RNA were associated with higher on-ART levels of HIV DNA and CA-RNA at all time points (Table). Pre-ART levels of IL-6, sCD163, sCD14 and hsCRP were also significantly correlated with on-ART levels of the same biomarkers at yrs 1, 4 and 6-15 of ART, even after adjusting for pre-ART plasma HIV RNA and CD4 count. Pre-ART CD4 cell activation was directly associated with on-ART CD4 cell activation at yr 1 (r= 0.45, p<0.001) and yr 4 (r= 0.23, p=0.02), although correlations between pre-ART and on-ART T cell activation diminished over time on treatment. By contrast, pre-ART T cell cycling levels correlated with on-ART levels at all time points. Markers of inflammation and T cell activation were associated with plasma HIV RNA levels before ART was initiated (e.g. CD4 activation and plasma HIV RNA, r=0.41, p<0.001) but there were no consistent associations between these markers and HIV DNA or CA-RNA during long-term ART (e.g., CD4 activation and HIV DNA at yr 4 (n=96): r=0.10, p=0.31; at yrs 6-15 (n=62): r= −0.06, p=0.65).

Conclusion: Higher levels of inflammation and activation before ART were associated with higher levels during ART, indicating that immunologic events that occurred well before ART initiation had long-lasting effects despite sustained virologic suppression (i.e., "the die is cast" before ART initiation). We did not find evidence for HIV persistence driving or being driven by inflammation or activation during ART. These findings should stimulate studies of viral and host factors that affect immunologic, inflammatory and virologic set points prior to ART initiation and should inform the design of strategies to reduce HIV reservoirs and dampen inflammation and activation that persist despite ART.

Correlations Between Pre-ART and On-ART Measurements of HIV, Inflammation, T cell activation and cycling

Spearman (P)	1 yr	4 yrs	6-15 yrs
HIV DNA	0.81 (<0.001)	0.61 (<0.001)	0.65 (<0.001)
CA-RNA	0.50 (<0.001)	0.45 (<0.001)	0.34 (0.017)
IL-6	0.41 (<0.001)	0.41 (<0.001)	0.39 (0.001)
hs-CRP	0.33 (<0.001)	0.48 (<0.001)	0.30 (0.015)
sCD14	0.40 (<0.001)	0.47 (<0.001)	0.45 (<0.001)
sCD163	0.53 (<0.001)	0.55 (<0.001)	0.58 (<0.001)
%CD38+HLA-DR+ (CD4+ cells)	0.45 (<0.001)	0.23 (0.024)	0.18 (0.17)
%CD38+HLA-DR+ (CD8+ cells)	0.33 (<0.001)	0.11 (0.29)	0.14 (0.27)
%Ki67 on CD4+ cells	0.45 (<0.001)	0.42 (<0.001)	0.38 (0.002)
%Ki67 on CD8+ cells	0.49 (<0.001)	0.30 (0.003)	0.40 (0.001)

281 SEX-BASED DIFFERENCES IN HIV RESERVOIR ACTIVITY AND RESIDUAL IMMUNE ACTIVATION

Eileen Scully[1], Monica Gandhi[2], Rowena Johnston[3], Rob Gorelick[4], Jeffrey D. Lifson[5], Sharon R. Lewin[6], Jonathan Karn[7], Nicolas Chomont[8], Peter Bacchetti[2], Steven G. Deeks[2]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Univ of California San Francisco, San Francisco, CA, USA, [3]amfAR, New York, NY, USA, [4]Leidos Biomed Rsr, Inc, Frederick, MD, USA, [5]Frederick Natl Lab, Frederick, MD, USA, [6]Univ of Melbourne, Melbourne, Australia, [7]Case Western Reserve Univ, Cleveland, OH, USA, [8]Univ de Montréal, Montréal, QC, Canada

Background: Plasma HIV RNA levels are lower in women than men in the absence of antiretroviral therapy (ART), particularly in early infection. Less is known about sex differences in HIV during ART. We recently found that estrogen modulates HIV transcription ex vivo. Here, we sought to define sex differences in the size and activity of the HIV reservoir in a cohort of premenopausal women and matched men on ART.

Methods: Premenopausal women on ART with ≥1 year of viral suppression were prospectively enrolled (n=26) and matched with men (n=26) on age, duration of viral suppression, CD4 count/nadir and unusual clinical phenotypes. HIV persistence measurements include: integrated HIV DNA (iDNA) in CD4 T cells, residual plasma viremia by single copy assay (SCA) for HIV gag (HMMCgag), and cell associated (CA) multiply spliced (ms) and unspliced (us) HIV RNA in CD4 T cells. The frequency of CD4 T cells producing tat/rev RNA after activation was measured by TILDA in a subset of subjects. T cells were phenotyped by flow cytometry. Virologic data were analyzed by univariate and multivariate negative binomial regression and immune markers were compared with nonparametric statistics (Mann Whitney).

Results: HIV iDNA levels were comparable between men and women (p=0.47), but female sex was associated with a 76% lower level of residual viremia by SCA (p=0.011) in a multivariate model. CA msHIV RNA was also 6-fold lower in women (p=0.002) in a one-predictor model, and 4-fold lower when adjusted for nadir CD4 and controller phenotype (p=0.009). CA usRNA was ~35% lower in women by univariate and multivariate models (p>0.05). The frequency of inducible virus (TILDA: iDNA ratio) was lower in women (Mann-Whitney p=0.019), suggesting a lower inducible reservoir in women. Women demonstrated a lower proportion of HLADR/CD38+ CD4 and CD8 T cells than men (p<0.05) and lower PD-1 expression, most notably in central memory CD8 T cells (p<0.001).

Conclusion: In a well-matched cohort of ART-treated, virally suppressed women and men, multiple measures of virus activity and immune activation/exhaustion were lower in women despite comparable frequencies of CD4+ T cells harbouring HIV DNA. These data support sex differences in control of HIV latency. Biologic sex may impact the efficacy of curative interventions and manipulation of sex hormones may play a role in cure strategies.

282 SOLUBLE BIOMARKERS IN ACUTE HIV INFECTION REVEAL INSIGHT INTO HIV RESERVOIR

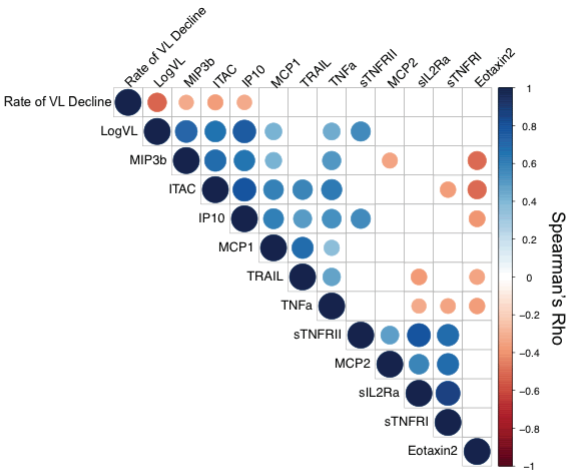
Jeffrey E Teigler[1], Bonnie Slike[1], Nicolas Chomont[2], Eugene Kroon[3], Merlin L. Robb[1], Jintanat Ananworanich[1], Nelson L. Michael[1], Hendrik Streeck[4], Shelly J. Krebs[1], for the RV254/RV217 Study Groups
[1]US Military HIV Rsr Prog, Silver Spring, MD, USA, [2]Univ de Montréal, Montreal, QC, Canada, [3]SEARCH, The Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [4]Inst for HIV Rsr, Essen, Germany

Background: Several biomarkers are induced during acute HIV infection, remain elevated during ART, and have been associated with disease progression. However, their role in HIV pathogenesis and reservoir establishment remains unclear. We explored HIV-associated biomarker signatures longitudinally and their relationship with HIV reservoir dynamics following ART initiation.

Methods: 82 biomarkers were assessed by Luminex bead technology in Thai individuals at baseline, prior to HIV infection, and during viral upslope (d1-d5), peak viral load (d9-d15), early chronic (~7m-8m) and late chronic (~2y) timepoints following infection in ART-naive (n=13) or individuals who began continuous ART during acute HIV infection (n=40) from the ongoing RV217 and RV254 trials. HIV-1 viral loads (VL) were assessed by HIV RNA in peripheral blood and cell-associated DNA.

Results: Distinct biomarker pathways were induced with differential temporal kinetics in HIV acute infection. Proinflammatory markers (e.g. MCP-1, MCP-2) significantly rose during acute infection but resolved by chronic timepoints. TNF-α- and IFN-γ-signaled pathways were induced during peak viremia and persisted in ART-naïve individuals. During acute infection, levels of MIP-3β, sTNFR-II, IP-10, I-TAC, TNF-α, MIG, sTNFR-II, MCP-1, and MCP-2 correlated positively HIV VL (p<0.01, all). In individuals given ART during acute infection, rate of HIV RNA decline in plasma was correlated with levels of MIP-3β (r = -0.318; p=0.04), I-TAC (r=-0.354; p=0.03), and IP-10 (r=-0.322; p=0.04) prior to ART initiation. Levels of cell-associated HIV DNA at week 96 post treatment initiation correlated with levels of sTNFR-II (r=0.407; p=0.04) prior to ART. HIV-associated biomarkers TNF-α, sTNFR-I, sTNFR-II, IP-10, MIG, and I-TAC remained elevated at chronic infection during treatment relative to HIV-uninfected individuals (p<0.05, all), indicating biomarkers associated with HIV VL remain elevated in the absence of detectable virus in circulation.

Conclusion: A comprehensive analysis of biomarkers induced in HIV infection reveal viral-associated factors that remain elevated despite successful ART. Levels of these markers correlate with rate of viral decline after treatment and with levels of viral reservoir two years following infection. The use of these markers to better inform treatment interruption and immune therapies remains under study.



Individuals in early acute HIV infection were immediately placed on ART and their rate of viral load decline were submitted to Spearman correlation analyses with HIV-associated biomarkers. Presence of a dot at the intersection between two variables indicates p<0.01, color of circle indicates value of Spearman's rho.

283 FAST VALIDATION TO STUDY THE BASELINE AND INDUCIBLE HIV RESERVOIR

Marilia R. Pinzone[1], Xiaohe Liu[2], Lidia Sambucetti[2], Giuseppe Nunnari[3], Una O'Doherty[1]
[1]Univ of Pennsylvania, Philadelphia, PA, USA, [2]SRI Intl, Menlo Park, USA, [3]Univ of Messina, Messina, Italy

Background: "Shock and kill" strategies require highly sensitive methods to detect HIV reactivation upon stimulation with latency reversal agents (LRAs). In this study, we validated that Fiber-optic array scanning technology (FAST) can detect reactivation of latent HIV.

Methods: Resting CD4 T cells from HIV-infected individuals or from PBMCs of uninfected donors were spinoculated with pNL4-3 virus or pLENG1-IRESGFP virus +/- an integrase inhibitor. Cells were cultured with IL-7 for 7 days and stimulated with several compounds, alone or in combination, such as prostratin (300 nM), bryostatin (1 μM), JQ1 (1 μM), or resveratrol (40 μM). After 24 hours, HIV gag or GFP expression was assessed by flow and FAST. Data are presented as mean fold increase of 3 separate experiments compared to the unstimulated control.

Results: We validated FAST ability to detect LRA reversal by comparing it to flow using an in vitro model with a high frequency of infected cells. Stimulation with LRAs was associated with an increase in the number of GFP+ or gag+ cells (GPCs). Bryostatin was the most potent compound, inducing a consistent increase in the number of GPCs detected by FAST and flow (3.5- and 4-fold, respectively). Lower fold changes were detected by FAST and flow respectively when using prostratin (1.3-3.3 fold), JQ1 (4.1-1.9 fold), or resveratrol (1.8-3.3 fold). The association of bryostatin and JQ1 was synergistic in increasing the number of GPCs by FAST (5.7-fold increase) and flow (3.8-fold increase). Side by side comparisons of diluted in vitro infected cells as well as patient samples show FAST is more sensitive than flow. All patients had detectable levels of gag+ cells at baseline and after stimulation by FAST, but not by flow. Specifically, flow failed to robustly detect cells that express HIV proteins when the frequency of infected cells is below 1 in 10,000 due to inherent technical limitations.

Conclusion: FAST detects HIV proteins expressed in resting CD4+ T cells at baseline and after stimulation providing a tool to assess HIV reactivation upon stimulation with LRAs. We find a correlation between FAST and flow at high inoculum, but flow loses sensitivity at low infection frequencies. FAST has benefits over flow cytometry, including the ability to capture events that can be missed by flow, such as syncytia of cells expressing HIV proteins. In conclusion, FAST represents a novel sensitive assay, which can help characterize the baseline and inducible reservoir of HIV-infected patients.

284 HOST TRANSCRIPTOMIC DETERMINANTS OF HIV PERSISTENCE IN VIVO

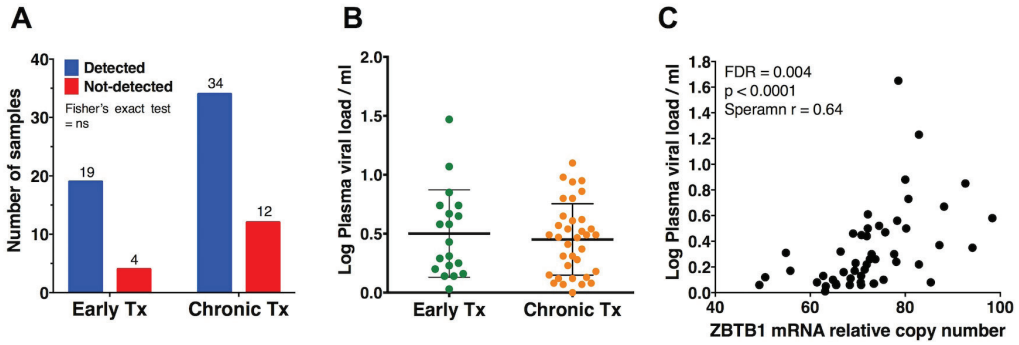
Mohamed Abdel Mohsen[1], Xutao Deng[1], Sheila Keating[1], Andrew Worlock[2], Christopher D. Pilcher[3], Michael P. Busch[1], Steven G. Deeks[3], Satish K. Pillai[1]
[1]Blood Systems Rsr Inst, San Francisco, CA, USA, [2]Hologic Corporation, Bedford, MA, USA, [3]Univ of California, San Francisco, San Francisco, CA, USA

Background: HIV eradication will likely require identification of host factors that govern HIV latency in vivo. We performed global transcriptomic profiling of CD4+ T cells from HIV-infected, ART-suppressed individuals to identify host determinants of HIV persistence.

Methods: We measured levels of cell-associated (CA) HIV RNA, and total pol and 2-LTR circle HIV DNA in CD4+ T cells from 69 HIV-infected individuals on suppressive ART for 1-2 years; 23 subjects initiated ART <6 months post-infection ("Early Tx"), and 46 subjects initiated >1 year post-infection ("Chronic Tx"). Residual plasma HIV RNA levels were measured using an ultrasensitive, real-time transcription-mediated amplification-based assay, and circulating anti-HIV-1 antibodies were characterized using a limiting antigen assay. We performed flow cytometry and RNA-seq to characterize the immunophenotype and global transcriptome of isolated CD4+ T cells, respectively. False discovery rate (FDR) was used to correct for multiple comparisons in statistical analyses.

Results: Low-level viremia was detected in 19 out of 23 Early Tx (0.5±0.37, mean log copy number ±SD) and 34 out of 46 Chronic Tx individuals (0.46±0.3); detectable frequencies and levels were similar between the two groups. Residual viremia was correlated with expression of the host transcriptional mediator ZBTB1 (Zinc finger and BTB domain containing 1) (FDR<0.005). Levels of CA HIV RNA were correlated with multiple factors belonging to the AP-1 (activator protein-1) transcription factor complex (FDR <0.05). The quantity and avidity of anti-HIV antibodies were higher in the Chronic Tx group as compared to Early Tx (p<0.0001). 71 genes were differentially expressed between the Early Tx and Chronic Tx groups (FDR <0.05), including several genes associated with mitochondrial dysfunction, oxidative phosphorylation, and the histone h3, IL12, T-cell receptor, p38 mitogen-activated protein kinase, and PI3K-Akt complex families.

Conclusion: Residual viremia was readily detectable in the majority of ART-suppressed individuals. The level of viremia was similar in those treated during early versus chronic infection, despite lower levels of immune activation and CA HIV RNA and DNA in those treated early. Several pathways were differentially expressed in the Early Tx group and may contribute to the smaller reservoir size observed in the setting of early ART. Our transcriptomic signatures reveal host factors and pathways that may be targeted to develop curative strategies for HIV infection.



285 LOW INDUCIBILITY OF THE HIV RESERVOIR IN EARLY ART-TREATED THAI CHILDREN

Marta Massanella[1], Jintanat Ananworanich[2], Louise Leyre[3], Thidarat Jupimai[4], Mark de Souza[5], Piyarat Suntarattiwong[6], Pope Kosalarksa[7], Thanyawee Puthanakit[8], Nicolas Chomont , for the HIVNAT209 and HIVNAT194 Study Groups
[1]Cntr de Rsr du Cntr Hosp de l'Univ de Montréal, Montréal, Canada, [2]Henry M. Jackson Fndn for the Advancement of Military Med, Bethesda, MD, USA, [3]HIV–NAT Rsr Collab, Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [4]SEARCH, Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [5]Queen Sirikit Natl Inst of Child Hlth, Bangkok, Thailand, [6]Khon Kaen Univ, Khon Kaen, Thailand, [7]Chulalongkorn Univ, Bangkok, Thailand

Background: Early antiretroviral therapy (ART) limits the size of the HIV reservoir in adults, however pediatric data are limited. We evaluated the impact of early ART initiation on the size of the HIV reservoir in vertically infected infants.

Methods: Vertically HIV-infected Thai children (N=58) who initiated ART within the first 6 months of life were enrolled. Blood samples were collected prior to, and following ART for at least 12 months. Total and integrated HIV DNA in PBMCs and CD4 T cells were quantified by real-time PCR. The frequency of CD4 T cells producing multiply spliced RNA after PMA/ionomycin stimulation was measured by Tat/rev Induced Limiting Dilution Assay (TILDA).
Results: Samples prior to ART were obtained from 10 infants who received prophylactic antiretrovirals (ARV) for a median of 5 IQR [4-6] weeks. Their median age was 11 IQR [8-18] weeks and their median plasma viral load was 5.3 IQR [4.6-5.9] log10 HIV RNA copies/ml. In spite of prophylactic ARV, high levels of total and integrated HIV DNA were measured in CD4 T cells from these infants (Table 1). Baseline HIV viral load strongly correlated with integrated HIV DNA in PBMCs (r=0.83, p=0.005), suggesting that the magnitude of HIV replication impacts the size of the reservoir. CD4 T cells producing tat/rev RNA were detectable in all samples (median 40 IQR [13-69]). In addition, 48 samples were obtained from fully ART-suppressed children with median ART duration of 4 IQR [1.0-5.5] years. Total and integrated HIV DNA levels remained relatively high while TILDA values were extremely low (median 0 IQR [0-2.7] Table 1). Importantly, children who initiated ART within 8 weeks of life showed reduced levels of integrated HIV DNA compared to those who started later (Table 1, p=0.03).
Conclusion: Neonatal prophylaxis ARV does not prevent the establishment of a large pool of cells harboring HIV DNA in infants. The frequency of cells with inducible HIV remained low in virally suppressed children, despite high levels of HIV DNA, suggesting that the proviral reservoir is poorly inducible. Notably, early ART (<8 weeks) dramatically restricts the pool of cells harboring integrated HIV DNA.

Table 1: HIV reservoir profiles among early antiretroviral-treated Thai children

	Age	Total HIV DNA (copies per 10^6 CD4 T cell)	Integrated HIV DNA (copies per 10^6 CD4 T cell)	TILDA (RNA+ cells per 10^6 CD4 T cell)
Prior to ART (N=10)	11 [8-18] weeks	5,168 [1,166-10,012]	356 [83-845]	40 [13-69]
After ART (N=48)	4 [2-6] years	85 [30-348]	32 [15-158]	0 [0-2.7]
Treated within 8 weeks of life (N=6)	5 [2-6] years	5 [3-76]	4 [3-15]*	0 [0-1.4]
Treated during 2-6 months of life (N=42)	4 [2-6] years	110 [35-397]	34 [15-195]	0.7 [0-2.7]

Data shown as median [IQR]; *p=0.03 (compared to children treated during 2-6 months of life)

286 CELL-ASSOCIATED HIV RNA PREDICTS POSTTREATMENT HIV CONTROL AND CD4+ T-CELL LOSS

Alexander Pasternak, Jan Prins, Ben Berkhout
Univ of Amsterdam, Amsterdam, Netherlands

Background: For the improved design of strategies towards HIV-1 functional cure, it is important to identify biomarkers that could predict the duration of post-treatment virological control and subsequent disease progression (the rate of CD4+ T-cell loss).
Methods: We studied 45 patients that received 24 or 60 weeks of temporary ART initiated at primary HIV infection (PHI) as part of a randomized trial (Primo-SHM study; PLoS Med 2012;9:e1001196). Patients were treated with a quadruple triple-class ART regimen. Cell-associated (CA) HIV nucleic acids (unspliced (US)-*gag* and multiply spliced (MS)-*tat/rev* HIV RNA and total HIV DNA) were longitudinally quantified by seminested qPCR every 12 weeks during ART and at the virological setpoint (36 weeks after discontinuation of ART).
Results: All patients experienced virological rebound (VR) (plasma viremia >50 copies/ml) within 9 months after therapy interruption. We first assessed the predictive power of the last measurements of the CA HIV biomarkers, CD4+ count, and CD4/CD8 ratio on ART before the therapy interruption, as well as of the duration of temporary ART, for the time to VR (the duration of post-treatment control). US RNA was the only significant predictor of the time to VR (HR=0.29 for patients with US RNA levels below vs. above the median, 95% CI, 0.10-0.83, p=0.021, log-rank test). Subsequently, we have assessed the predictive power of the same biomarkers and plasma viremia, measured at the virological setpoint, for the time to reach the CD4+ count of 350 cells/mm^3 in the absence of treatment. Among the virological markers, MS RNA was the strongest predictor of disease progression, whereas US RNA was not predictive. The median times to 350 cells/mm^3 in patients with MS RNA levels below and above the median were 1180 and 283 days, respectively (p=0.0002, log-rank test). In multivariate Cox regression analysis, CD4+ count (p=0.0004) and MS RNA level (p=0.011) were the only two significant predictors of disease progression.
Conclusion: Cell-associated HIV-1 US RNA was the sole predictor of the duration of post-treatment virological control after the interruption of early ART, whereas MS RNA independently predicted subsequent CD4+ T-cell loss. This suggests that reactivation of HIV and CD4+ T-cell loss after ART interruption could be driven by different mechanisms. Further exploration of the predictive potential of these biomarkers in large-scale clinical trials aimed at HIV functional cure is warranted.

287 PRE-ART TUBERCULOSIS AND TB-IRIS AFFECT THE HIV-1 RESERVOIR

Camille Lange[1], Maura Manion[2], Gregg Roby[3], Rob Gorelick[4], Virginia Sheikh[5], Joseph Adelsberger[6], Frank Maldarelli[1], Irini Sereti[2]
[1]NCI, Frederick, MD, USA, [2]NIAID, Bethesda, MD, USA, [3]NIH, Rockville, MD, USA, [4]AIDS and Cancer Virus Prog, Frederick, MD, USA, [5]FDA, Silver Spring, MD, USA, [6]Leidos Biomed Rsr, Inc, Frederick, MD, USA

Background: Tuberculosis (TB) is the most common presenting illness of people living with HIV worldwide. TB-associated immune reconstitution inflammatory syndrome (IRIS) is an aberrant inflammatory response of TB in patients starting antiretroviral therapy (ART), especially with severe CD4 lymphopenia or disseminated TB. Previous studies show TB-IRIS is driven by rapid expansion of activated TB-specific CD4+ T-cells. We hypothesized that pre-ART (baseline) TB and IRIS in HIV-1 infected patients have long-term effects on viral reservoirs.
Methods: A single copy assay was used to measure HIV viremia in baseline lymphopenic (BL) patients +/- IRIS to assess if IRIS affected HIV replication >1-2y ART (long term ART); controls had no BL, OI or IRIS. Cell-associated (CA) gag DNA and RNA levels of CD4+ T-cells were used to quantify the CD4+ reservoir, including subgroups of patients with and without TB and IRIS. We also characterized proviral populations in peripheral blood mononuclear cells with single genome sequencing (SGS) of HIV-1 p6-pol (1.1kb) at: pre-ART; 2-8

weeks of ART, during IRIS; and after long term ART. Sequences were aligned, genetic diversity determined (percent average pairwise difference; APD) and phylogenetic analysis performed. We defined clones as identical APOBEC-hypermutated sequences (HM clones) using Hypermut 2.0. Patient characteristics are in Table 1.

Results: We found no statistically significant difference in viremia after long-term ART between patient groups. IRIS patients had higher levels of CA gag DNA and lower levels of gag RNA than those without IRIS after long-term ART (Mann-Whitney; p=0.04 and p=0.045 respectively). HIV genetic diversity was substantial and comparable in patients pre- and at 2-8 weeks of ART; p>0.05. In contrast, after long term ART, diversity was higher in TB-IRIS patients compared with those without TB or IRIS (median APD [IQR] = 2.3 [1.7, 2.8] and 0.8 [0.3; 1.3] respectively; Mann-Whitney; p=0.03). We detected more HM clones in TB infected patients and an association between TB infection and the presence of HM clones (Fisher exact p=0.03).

Conclusion: Patients with TB-IRIS had a higher frequency of HIV infected cells, higher HIV genetic diversity and more HM clones after long term ART, suggesting IRIS events may permanently alter the HIV reservoir. Our data also suggest a relationship between clonal expansion and baseline TB and a shift to a more diverse proviral population after long term ART in TB-IRIS patients.

Table 1. Patient Characteristics

Assay		Plasma Viremia measured with SCA			CD4+ *CA gag* DNA & RNA		SGS (1092 sequences)		
Patient Group		Baseline Lymphopenic with OI, +/- IRIS		Controls	Baseline Lymphopenic with OI, +/- IRIS		TB Infected (n = 846)*		Controls (n = 246)*
IRIS (Yes/No)		Yes	No	No	Yes	No	Yes	No	No
Total # patients		25	84	13	11	22	3	4	5
Median Age at Enrollment (years)		33	37	36.5	34	35	45	42.5	32.5
Gender	Male	72%	77%	92%	75%	91%	100%	50%	100%
	Female	28%	23%	8%	25%	9%	0%	50%	0%
Median Baseline CD4 count (cells/ul)		12	16.5	364	26	31	28	22	240
# Patients with TB		7	4	0	10	3	3	4	0

*n is number of single genome sequences

288 CCR6+ RECTAL CD4+ T-CELLS ARE A SIGNIFICANT RESERVOIR ON ART

Jenny L. Anderson[1], Gabriela Khoury[1], Rémi Fromentin[2], Nicolas Chomont[2], Ma Somsouk[4], Wendy Hartogensis[3], Peter Bacchetti[3], Paul Cameron[1], Steven G. Deeks[3], Sharon R. Lewin[1]

[1]Univ of Melbourne, Melbourne, Australia, [2]Univ de Montréal, Montréal, Canada, [3]Univ of California San Francisco, San Francisco, CA, USA

Background: In HIV-infected individuals on antiretroviral therapy (ART), HIV integrated DNA is enriched in circulating central memory CD4+ T-cells expressing CCR6 and CXCR3. As these chemokine receptors (CKR) enable homing of CD4+ T-cells to tissue, we examined if expression of CKR and their chemokine ligands influenced HIV persistence in rectal and lymph node (LN) tissue in individuals on ART.

Methods: Blood (n=48), rectal (n=19) and inguinal LN (n=8) biopsies were collected from individuals on suppressive ART for ≥3 years. HIV integrated DNA and unspliced RNA (US-RNA) were quantified by PCR in total CD4+ T-cells sorted from each site. CKR expression was measured via flow cytometry. Chemokine protein in plasma was measured by Luminex and chemokine mRNA in tissue measured by RT-qPCR. Relationships between HIV persistence and expression of CKR or chemokines were assessed via negative binomial regression.

Results: CD4+ T-cells from rectum harboured 3.9 fold and 4.6 fold greater HIV integrated DNA and US-RNA respectively than blood (p<0.0001 for both), and 2.4 fold greater integrated DNA than LN (p=0.014). The CCL20 ligand for CCR6 was highly enriched in rectum compared to LN (12.7 fold difference). CCR6+CXCR3+ memory CD4+ T-cells were also markedly enriched in rectum compared to blood or LN (69.8%, 21.6% and 12.4% respectively, Kruskall Wallis p<0.0001). In rectum, HIV integrated DNA and US-RNA were positively associated with the frequency of CCR6+CXCR3- memory CD4+ T-cells (p=0.028 and p=0.027 respectively) but inversely associated with CCR6+CXCR3+ T-cells (p=0.025 and p=0.030 respectively). In contrast, in LN, there was no association between integrated HIV DNA and the frequency of cells expressing CCR6 or CXCR3 while there was a weak inverse association between US-RNA and the frequency of CCR6+CXCR3- T-cells (p=0.046).

Conclusion: HIV-infected individuals on ART have a high frequency of CCR6+CXCR3+ CD4+ T-cells in rectum, a positive correlation between HIV persistence and the frequency of CCR6+CXCR3- CD4+ T-cells, and high expression of CCL20 at this site. Targeting the CCR6-CCL20 axis should be considered as a novel strategy to eliminate HIV persistence.

289 BLOOD CXCR3+ CD4 T CELLS ARE ENRICHED IN INDUCIBLE REPLICATION-COMPETENT HIV

Riddhima Banga, Francesco Procopio, Matthias Cavassini, Giuseppe Pantaleo, Matthieu Perreau

Lausanne Univ Hosp, Lausanne, Switzerland

Background: We recently demonstrated that Lymph node (LN) PD-1+/T follicular helper (Tfh) cells from anti-retroviral therapy (ART) treated HIV-infected individuals were enriched in cells containing replication competent virus. However, the distribution of cells containing inducible replication competent virus has been only partially elucidated in blood memory CD4 T-cell populations including the Tfh cell counterpart circulating in blood (cTfh).

Methods: We have investigated the distribution of 1) total HIV-1-infected cells by Alu PCR and 2) cells containing replication competent HIV using virus outgrowth assay (VOA) within blood memory CD4 T-cell populations defined by chemokine receptor expression i.e CXCR3+CXCR5- (Th1), CXCR3-CXCR5+ (cTfh), CXCR3+CXCR5+ (Th1 cTfh), CCR4+CCR6- (Th2), and CCR4+CCR6+ (Th17) cells in ART treated (1.5-8 years) aviremic (<20 HIV RNA copies/ml) individuals (N=11).

Results: No significant differences in the frequency of integrated HIV DNA in the different memory CD4 T-cell populations were found (P>0.05). However, blood Th1 cells were significantly enriched in cells containing replication competent virus as compared to any other blood CD4 T-cell population (P<0.05). The mean frequency of Th1 cells containing inducible replication competent virus was about 9 cells per million as assessed by RNA-Unit Per Million. Blood Th1 cells were also the largest contributor (42%) to the total pool of blood HIV-infected cells containing replication competent virus in the cohort. Interestingly, the fraction of HIV provirus induced by VOA was higher in Th1 cells as compared to any other blood CD4 T-cell sub-populations, suggesting that Th1 cells contained either more intact or more inducible provirus. Of note, blood CD4 T-cell populations were not significantly different in terms of 1) level of activation as assessed by HLA-DR or Ki-67 expression, 2) CCR5 and CXCR4 HIV co-receptor expression and 3) SAMHD1 HIV restriction factor expression (P>0.05). However, both Th1 and cTfh cells were significantly enriched in PD-1 expressing cells as compared to Th2 and Th17 (46% and 42%, respectively) (P<0.05), but only the levels of HIV RNA of Th1 VOA culture supernatants directly correlated with the frequency of PD-1 expression on Th1 cells (P<0.05).

Conclusion: Taken together, these results indicate that blood Th1 cells represent the major blood compartment containing inducible replication competent virus in treated aviremic HIV-infected individuals.

290 SKEWED DISTRIBUTION OF HIV-2 RESERVOIR WITH LIMITED INPUT OF CENTRAL MEMORY T CELLS

Assia Samri[1], Charlotte Charpentier[2], Mélanie Bertine[2], Mariama Diallo[1], Sophie Even[1], Sophie Matheron[3], Rodolphe Thiébaut[4], Brigitte Autran[5], Francoise Brun-Vezinet[3], for the ANRS CO5 IMMUNOVIR-2 Study Group

[1]Pierre and Marie Curie Univ, Paris, France, [2]INSERM, Paris, France, [2]Bichat-Claude Bernard Hosp, Paris, France, [4]INSERM, Bordeaux, France, [5]Pitié-Salpêtrière Hosp, Paris, France

Background: HIV-2 infection is characterized by a low pathogenicity and a low virus production. We tested the hypothesis of a limited distribution of the HIV-2 reservoir among central-memory CD4 T cells (TCM), similarly to models of HIV-1 functional cure or of non pathogenic SIV infection.

Methods: 14 ARV-naïve patients with non-progressive infection included in the ANRS CO5 HIV-2 Cohort were assessed; their median CD4 cells/mm3 was 966 [IQR: 820-1216]. Subpopulations were sorted into CD3-CD4+ monocytes, CD25+CD69+HLADR+ activated, CD25-CD69-HLADR- resting CD4+ T cells and among those into naïve (TN), TCM, transitional-memory (TTM) and effector-memory (TEM) cells. Cell-associated HIV-2-DNA was isolated from sorted subsets with QIAamp DNA Mini or Micro kit® (Qiagen) according to cell numbers. HIV-2 DNA was quantified using a real-time PCR assay with a limit of detection (LOD) 95% of 3 c/PCR and a limit of quantification (LOQ) of 6 c/PCR. HIV-2 reactivation assays were performed by CD8- T cells culture with anti-CD3+CD28+IL-2+IL-7 for 30 days.

Results: Plasma viral load (pVL) was <40 c/mL in 12 patients, among them 4 had a positive ultra-sensitive pVL above 1 c/mL (IQR=1-12). Median total HIV-2 DNA in PBMC was above the LOQ in 13 patients with a median of 1.94 log10 c/106 PBMC (IQR=1.53-2.13). After sorting, HIV-2 DNA was undetectable among monocytes, and above the LOQ only in TTM from 4 patients (median=2.25 [IQR: 1.99-2.94] log10 c/106 cells) and in TCM from 1 patient (1.75 log10 c/106 cells). HIV-2 DNA levels were above the LOD in 3, 12, 9 and 10 patients in TN, TCM, TTM and TEM, respectively. When integrating subsets proportions, the median contribution of TN, TCM, TTM and TEM to the HIV-2 reservoirs was 0%, 33%, 46% and 8%, respectively. The HIV-2 DNA levels in TTM were positively correlated to those in PBMC (p=0.008; r=0.67). After CD8- T cells reactivation, HIV-2 RNA was detected in 3 of the 11 tested samples with the highest HIV-2 DNA values that were quantified in TTM (n=2) or TCM (n=1).

Conclusion: Overall, these HIV-2-infected patients had low circulating HIV-2 reservoirs that were quantifiable in only 5 of the 14 patients tested, mainly distributed in TTM and reactivable in vitro in only 3 of these 5 patients. These results confirm the hypothesis of a limited reservoir in TCM, thus supporting the concept of the relative protection of central-memory T cells as an attribute of low pathogenicity models of HIV/SIV infection.

291 ALTERED STABILITY OF HIV-INFECTED MEMORY CELLS FOLLOWING VERY EARLY ART

Louise Leyre[1], Jintanat Ananworanich[2], Claire Vandergeeten[3], Eugene Kroon[4], Nitiya Chomchey[5], Siriwat Akapirat[6], Merlin L. Robb[2], Nittaya Phanuphak[7], Nicolas Chomont[8], for the RV254/SEARCH010 and RV304 Study Groups

[1]Cntr de Rsr du Cntr Hosp de l'Univ de Montréal, Montréal, Québec, Canada[2]US Military HIV Rsr Prog, Silver Spring, MD, USA, [3]Vaccine and Gene Therapy Inst, Port St Lucie, FL, USA, [4]SEARCH, The Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [5]Armed Forces Rsr Inst of Med Scis, Bangkok, Thailand, [6]Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [7]Univ de Montréal, Montreal, QC, Canada

Background: Initiation of ART during primary HIV infection restricts the size of the HIV reservoir. However, less is known about the cell subsets in which HIV integrates and persists during the earliest phase of HIV infection.

Methods: In participants who underwent leukapheresis, integrated HIV DNA was quantified by Alu-PCR in sorted naïve (TNA), central (TCM), transitional (TTM) and effector (TEM) memory cells from infected Thai individuals who started ART within the first weeks of infection (Fiebig stages I-V based on HIV clinical assays: HIV RNA, p24, HIV antibodies). Participants who initiated ART during chronic infection were used as controls.

Results: In acutely infected individuals, there was an increase in the frequency of infected TCM, TTM and TEM when transitioning from Fiebig I, II and III stages. All 3 memory subsets were equally infected within each Fiebig group, while TNA cells were rarely infected. Integrated HIV DNA was detected in at least one memory subset in 21/22 Fiebig II-V individuals (95%) and in all subsets from chronically infected controls (n=3). In contrast, 4/7 Fiebig I individuals (57%) were devoid of HIV DNA in all subsets (limit of detection: 10 copies/10^6 cells). The frequency of infected cells in each subset was strongly correlated to plasma viral load (p<0.0001 for TCM, TTM and TEM cells). After 24-96 weeks of ART, the frequency of cells with integrated HIV DNA decreased in TCM, TTM and TEM cells from all acutely treated individuals, whereas it remained stable in individuals treated during chronic infection. With the exception of TTM cells from 1 participant, all Fiebig I individuals showed undetectable levels of HIV DNA in all subsets. Importantly, the earlier ART was initiated, the steeper was the decay in integrated HIV DNA in TCM (505, 25, 8, and 2-fold decrease (FD) in Fiebig II, III, IV-V and chronic), TTM (279, 25, 5 and 2-FD) and TEM cells (50, 35, 3 and 1-FD).

Conclusion: Memory cells harbouring integrated HIV DNA rapidly accumulated as plasma viral load increased. Whereas ART initiated in chronic infection had no impact on the amount of integrated HIV DNA in memory subsets, initiation of ART in acute infection decreased the frequency of infected TCM, TTM and TEM cells. This decrease was more pronounced in those who started very early, leading to undetectable levels of infected cells in Fiebig I individuals. These results suggest that the majority of memory cells infected during acute infection are short-lived.

292 CLONAL EXPANSION OF GENOME-INTACT HIV-1 IN FUNCTIONALLY POLARIZED T-CELL SUBSETS

Guinevere Q. Lee[1], Nina Orlova[1], Erik Serrao[2], Xiaoming Sun[1], Navin F. Chowdhury[1], Eric Rosenberg[3], Alan N. Engelman[2], Xu G. Yu[1], Mathias Lichterfeld[4]

[1]Ragon Inst of MGH, MIT and Harvard, Cambridge, MA, USA, [2]Dana-Farber Cancer Inst, Boston, MA, USA, [3]Massachusetts General Hosp, Boston, MA, USA, [4]Brigham and Women's Hosp, Boston, MA, USA

Background: HIV-1 remains an incurable disease due to long-lasting reservoirs of infected cells that are unaffected by suppressive antiretroviral therapy. However, the mechanisms that maintain long-term stability of such viral reservoirs are not well understood. Here, we used a near-full-genome deep sequencing approach to characterize HIV-1 DNA content in highly purified CD4 T cell subsets with distinct functional polarization.

Methods: Highly purified CD4 T cells secreting IFN-g (Th1), IL-4 (Th2), IL-9 (Th9), IL-17 (Th17), cytokine-negative control cells and unstimulated autologous CD4 T cells were sorted or enriched from large volumes of PBMC obtained from chronically-infected ART-suppressed HIV-infected patients. Total DNA extracted from individual cell populations was subjected to HIV-1 DNA quantification by ddPCR amplification of 5'LTR-gag (127bp) or to single-genome nested PCR with primers spanning near-full-genome HIV-1 (HXB2 coordinates 638-9632), followed by sequencing of individual products with Illumina MiSeq.

Results: Little variation was found between total HIV-1 gag DNA levels among the different polarized T cell populations in seven study subjects. In subsequent full-genome sequencing assays from six additional patients, 894 HIV-1 DNA sequences were obtained; only 7% (66/894) were genome-intact. Defective genomes had: large deletions over 1000bp 70% (623/894), APOBEC3G/3F-associated hypermutations 21% (186/894), deletions over 6bp in packaging signal 1% (9/894), and premature stop codons in gag/pol/env 0.3% (3/894). 352 HIV-1 DNA sequences were obtained from polarized CD4 T cell populations, of which 28 were sequence-intact. The proportion of genome-intact sequences relative to the pool of all viral species was highest in Th1 cells 15% (18/117), followed by cytokine-negative-Th 6% (6/99), Th9 4% (2/52), Th2 3% (1/34), Th17 2% (1/50), (Chi-square p=0.0003 for Th1 vs non-Th1 cells). In six distinct cases, groups of two to seven genome-intact viruses that shared 100% sequence identity over all 8995bp were detected from autologous polarized Th1 cells and/or unfractionated CD4 T cells, suggestive of clonal expansion of cells harboring intact provirus.

Conclusion: Th1-polarized cells seem to represent an important reservoir of cells harboring genome-intact HIV-1 sequences during antiretroviral therapy. Proliferation of such cells may contribute to maintaining and expanding the HIV-1 infected cell pool.

293 INTACT PROVIRUSES ARE UNEQUALLY DISTRIBUTED IN T CELL SUBSETS DURING ART

Bonnie Hiener[1], Bethany A. Horsburgh[1], John-Sebastian Eden[2], Kirston Barton[1], Eunok Lee[1], Steven G. Deeks[3], Jeffery Milush[3], Nicolas Chomont[4], Rémi Fromentin[4], Sarah Palmer[1]
[1]The Westmead Inst for Med Rsr, Westmead, Australia, [2]The Univ of Sydney, Sydney, Australia, [3]Univ of California San Francisco, San Francisco, CA, USA, [4]Univ de Montréal, Montreal, QC, Canada

Background: A thorough understanding of the distribution of replication-competent HIV is needed to design future eradication therapies. We studied the distribution of intact viral genomes in memory T cell subsets in the peripheral blood of individuals on long-term antiretroviral therapy. The distribution of clonal sequences was examined to determine the role of cellular proliferation as a contributor to persistence of intact HIV genomes.
Methods: To investigate the proportion of intact proviruses in T cell subsets, we developed an assay utilising Next Generation Sequencing (NGS), to amplify and sequence single near full-length (9kb; 92% of the genome) HIV-1 proviruses within CD4+ T cell subsets (naïve (TNA), central (TCM), transitional (TTM) and effector (TEM) memory) FAC sorted from peripheral blood. Between 30-40 individual proviruses were sequenced per cell subset from 5 participants treated during acute (n=2) and chronic (n=3) infection. NGS was conducted using the Illumina MiSeq platform with individual proviruses de novo assembled using a specifically designed workflow in CLC Genomics. Proviruses were characterized as defective (containing INDELs, stop codons or APOBEC3G hypermutation) or intact (full-length; lacking defects).
Results: The percentage of intact proviruses varied between participants from 6-49%, with no difference in the mean percentage of intact proviruses between participants treated during acute (27%) and chronic (20%) infection (p=0.725). Combining the data for all participants revealed that TEM contained the largest percentage of intact proviruses (8-80%; mean=40%, n=5), compared to TNA (0-22%; mean=3%, n=3), TCM (0%; mean=0%, n=3) and TTM (3-30%; mean=15%, n=4). Clonal expansions of identical proviruses were identified in 2 participants: 1 treated during acute infection, where 66% of TTM proviruses comprised a defective clonal expansion and 1 treated during chronic infection, where 60% of TEM proviruses comprised an intact clonal expansion.
Conclusion: Intact proviruses that could potentially contribute to a rebound following a treatment interruption were found unequally distributed across T cell subsets. We identified clonal expansions of intact proviruses indicating that cells that have undergone proliferation contain virus capable of rebound and actively contribute to the latent reservoir. Identification of TEM as the reservoir containing the highest proportion of intact proviruses demonstrates the importance of targeting TEM cells in future eradication strategies.

294 A SMALL FRACTION OF PROVIRUSES IN EXPANDED CLONES EXPRESS UNSPLICED HIV RNA IN VIVO

Andrew Musick[1], Jonathan Spindler[1], Brandon Keele[2], Michael J. Bale[1], Wei Shao[2], Ann Wiegand[1], John Mellors[3], John Coffin[4], Frank Maldarelli[1], Mary F. Kearney[1]
[1]NCI, Frederick, MD, USA, [2]Leidos Biomed, Inc, Frederick, MD, USA, [3]Univ of Pittsburgh, Pittsburgh, PA, USA, [4]Tufts Univ, Boston, MA, USA

Background: The vast majority of proviruses that persist on ART are defective. Of the minority that are intact (~2%), the fractions that are latent or transcriptionally active are not known. To address this question, we determined the fraction of proviruses that express HIV RNA in vivo in cell populations carrying either intact or defective proviruses.
Methods: PBMC were obtained from Patient #1 in Maldarelli, et al. (Science, 2014). This donor had multiple clones of cells that contain intact or defective proviruses. Proviral expression was determined by single-genome pro-pol sequencing (SGS) of HIV DNA and RNA from multiple aliquots of PBMC diluted to an endpoint such that each aliquot contained one to a few HIV RNA expressing cells. Intact proviruses were identified using viral outgrowth assays (VOA). The levels and fractions of cells expressing HIV RNA were determined for probable clones (identified by identical sequence matches) carrying intact and defective proviruses.
Results: A total of 77 million PBMC were analyzed, of which 10,450 contained HIV pro-pol sequences. Fourteen percent of the infected cells expressed HIV RNA. The median levels of expression in single cells was 1 RNA/cell (ranging from 1-16). We identified 412 different WT or hypermutant RNA species in infected cells. Of these, 3 were from expression of intact proviruses, 81 from obviously defective proviruses, and 328 from proviruses that were likely defective (did not grow out in VOA but did not contain stop codons in the region analyzed). The median fraction of cells in the probable clones (those with matching DNA and RNA) that carried intact proviruses (N=3) and expressed HIV RNA was 2.3% (1.2%-8.8%). For clones carrying defective proviruses (N=5), the median expressing was 3.5% (0.9%-7.0%), and for presumptive clones carrying likely defective proviruses (N=26), the median was 6.6% (1.3%-66.7%) (p =0.51 for a difference across groups).
Conclusion: The large majority (>80%) of infected cells that persist on ART are either latent or incapable of HIV RNA expression. A small fraction of proviruses within infected clones expressed unspliced HIV RNA, but this fraction was not significantly different between clones carrying intact proviruses from clones containing obviously defective proviruses, indicating that HIV RNA expression appears similarly detrimental (or non-detrimental) for infected cells regardless of whether the provirus they carry is intact.

295 PROLIFERATION OF CD4+ T CELLS CONTAINING REPLICATION-COMPETENT HIV-1

Zheng Wang, Ya-Chi Ho, Janet Siliciano, Robert Siliciano, for the Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
Johns Hopkins Univ, Baltimore, MD, USA

Background: Persistence of the human immunodeficiency virus type-1 (HIV-1) in a latent form in resting memory CD4+ T cells remains the major barrier to curing HIV-1 infection. The pool of latently infected CD4+ T cells is extremely stable and it has been shown that HIV-infected CD4+ T cells can clonally expand. However, it remains unclear what mechanism drives the expansion of HIV-infected CD4+ T cells and whether HIV-1 proviruses in these clonally expanded cells are replication competent or defective. We hypothesize that clonal expansion of HIV-1-infected CD4+ T cells is caused by physiologic stimulations including T cell activation and homeostatic proliferation and some clonally expanded CD4+ T cells can produce replication-competent virus.
Methods: Resting CD4+ T cells from aviremic patients under suppressive antiretroviral therapy were labeled with carboxyfluorescein succinimidyl ester (CFSE) and activated with CD3/CD28 costimulation or stimulated with IL-7/IL15 in the presence of enfuvirtide to prevent new rounds of infection. After 7 days of culture, CD4+ T cells were sorted based on CFSE dilution and plated at 200,000 cells per well in a viral outgrowth assay (VOA) to quantify infectious HIV-1 in both populations. Cells that have proliferated in response to IL-7/IL-15 stimulation were tested in a viral outgrowth assay with or without PHA activation to determine whether cells that proliferate with IL-7/IL-15 stimulation can produce infectious HIV-1 without activation.
Results: Our results demonstrate that HIV-infected CD4+ T cells proliferate in response to both CD3/CD28 co-stimulation and cytokine (IL-7/IL-15) stimulations. Some of the cells that have proliferated in response to CD3/CD28 costimulation produce replication-competent virus without additional PHA stimulation. However, additional viral outgrowth is observed with PHA stimulation. Cells that proliferated in response to IL-7/IL-15 treatment are able to produce infectious virus with PHA stimulation. However, no viral outgrowth is observed from this proliferated population in the VOA assay without PHA stimulation.
Conclusion: We conclude that T cell activation and homeostatic cytokines were able to induce proliferation of HIV-infected CD4+ T cells containing replication-competent viruses. The results indicate the possibility that both T cell activation and homeostatic proliferation are potential mechanisms that maintain HIV-infected CD4+ T cells containing replication-competent HIV.

296 CYTOTOXIC T LYMPHOCYTES MAY SHAPE THE HIV-1 PROVIRAL LANDSCAPE

R. Brad Jones[1], Mihaela Pertea[2], Katherine Bruner[2], Ross Pollack[2], Adam Capoferri[2], Robert Siliciano[2], **Ya-Chi Ho**[2]
[1]The George Washington Univ, Washington, DC, USA, [2]The Johns Hopkins Univ, Baltimore, MD, USA

Background: The majority of the HIV-1 proviruses are defective, making it irrelevant to use HIV-1 DNA quantitation to measure the size of the latent reservoir. However, a decrease in HIV-1 proviral DNA levels has been reported in vivo using the shock-and-kill strategy. We have previously shown that defective HIV-1 proviruses can be transcribed and translated, making them potential targets for cytotoxic T lymphocyte (CTL) elimination. We hypothesize that HIV-1 proviral landscape is dynamic, and may be shaped by CTL selection pressure.

Methods: We examined the HIV-1 proviral landscape in virally suppressed HIV-1-infected individuals. We then examined whether defective HIV-1 proviruses can be recognized by CTLs in vitro and ex vivo.
Results: In the HIV-1 proviral landscape of virally suppressed HIV-1-infected individuals, we found that the frequency of hypermutated proviruses correlates negatively with the duration of infection, while the frequency of proviruses containing large internal deletions correlates positively with the duration of infection, implying a dynamic process. To examine whether defective HIV-1 proviruses can be recognized by CTLs in vitro, we co-cultured CD4+ T cells transfected with defective HIV-1 proviruses with autologous CTL clones known to recognize specific CTL epitopes. CTL recognition of cells containing defective HIV-1 proviruses were measured by CD107a loading. Surprisingly, we found that cells containing hypermutated proviruses which have a premature stop codon or mutated start codon 5′ to an intact CTL epitope can be recognized by CTLs, while cells containing large internal deletions cannot be recognized by CTLs. To understand whether hypermutated HIV-1 proviruses may be recognized by CTLs ex vivo, we used targeted deep-sequencing to examine the frequency of APOBEC-mediated nonsense mutations in gag. We compared resting and activated CD4+ T cells treated with and without autologous prestimuated CTLs. We found that the frequency of HIV-1 RNA containing premature stop codons 5′ to the CTL recognition site decreased upon CTL co-culture, indicating that cells containing hypermutated proviruses can be eliminated by CTLs ex vivo.
Conclusion: We found that hypermutated HIV-1 proviruses may be targeted by CTLs. HIV-1 DNA measurement may in part reflect the effect of HIV-1 elimination strategies. HIV-1 proviral landscape may be shaped, at least partially, by CTL selection pressure.

297 DYNAMICS OF HIV CLONAL EXPANSION AND PERSISTENCE DURING ART

Elizabeth M Anderson[1], Shawn Hill[1], Jennifer Bell[1], Francesco R. Simonetti[2], Cathy Rehm[3], Sara Jones[4], Rob Gorelick[4], John Coffin[5], Frank Maldarelli[1]
[1]NCI, Frederick, MD, USA, [2]The Johns Hopkins Univ, Baltimore, MD, USA, [3]NIAIDs, Bethesda, MD, USA, [4]Leidos Biomed Rsr, Inc., Frederick, MD, USA, [5]Tufts Univ, Boston, MA, USA
Background: HIV persistence during antiretroviral therapy (ART) is a substantial obstacle to HIV cure. HIV infected cells can undergo clonal expansion and specific clones may be highly expanded. We previously reported one provirus integrated in the HORMAD2 gene that accounted for 20-40% of all proviruses in the patient. Although c. 98% of proviruses are defective, deleted clones may continue to express gag. Mechanisms by which clones emerge and persist over time are uncertain. To investigate the dynamics of HIV clonal expansion during ART we developed multiplexed droplet digital approaches (ddPCR) to quantify HIV proviruses, including specific integrants, prior to and following prolonged ART
Methods: HIV infected ART-naïve individuals (N=5) underwent ART and were followed for a median of 9.8 yrs (range 2.8-16.4y). Cell associated DNA (CA-DNA) was recovered from PBMCs pre-ART, during first phase viral decay, and during long term ART. CA-DNA was quantified using multiplexed ddPCR assays targeting HIV gag, the HIV LTR (RU5), as well as a host gene (CCR5). We designed a specific ddPCR primer set using oligos overlapping the host-HIV junction sequence to quantify the integrant in HORMAD2
Results: All patients had successful suppression of HIV RNA on ART to <50 c/mL plasma within 5 mos and HIV DNA/1e6 CD4+ cells decreased for both gag (avg 12.6-fold, range 8-19) and LTR (avg 8.2-fold, range 4-11). In 3 of the 5 patients the ratio of LTR to gag increased progressively between the first phase decay and long term time points (avg 6.5-fold, paired T-test $p<0.01$) demonstrating loss of full length proviruses; in 2/5 patients, LTR/gag ratios remained stable. The HORMAD2 integrant was not detectable at pre-ART, 1 mo, and 2 mos on ART (<1 cp in total of 500,000 infected cells). After 1 year on suppressive ART, however, the HORMAD2 integrant was present at a frequency of 30% of all infected cells and persisted for 6 yrs on ART
Conclusion: HIV populations change during ART with progressive gag deletion in most, but not all patients. Clonal expansion of HIV infected cells can be rapid and sustained at stable levels during prolonged ART, suggesting both antigen induced clonal expansion and homeostatic proliferation maintain HIV populations. Multiplexed quantitative assays suitable for single cell analyses can be modified to specifically quantify individual integrated proviruses. Tracking specific integrants over time sheds light on the dynamics of HIV infected cells clonal expansion and mechanisms of their persistence

298 CLONES OF HIV-INFECTED CELLS ARISE IN VIVO IN THE FIRST FEW WEEKS FOLLOWING INFECTION

David Wells[1], Jennifer M. Zerbato[2], Joann D. Kuruc[3], Joseph J. Eron[3], Mary F. Kearney[4], John Coffin[5], Frank Maldarelli[4], Xiaolin Wu[1], John W. Mellors[2], **Stephen H. Hughes**[4]
[1]Liedos Biomed Rsr, Inc, Frederick, MD, USA, [2]Univ of Pittsburgh, Pittsburgh, PA, USA, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]NCI, Frederick, MD, USA, [5]Tufts Univ, Boston, MA, USA
Background: In HIV-infected individuals on successful long-term antiretroviral therapy (ART), a significant fraction (>40%) of the infected cells are in expanded cell clones. Most of the HIV proviruses in infected cells that persist after long-term ART are defective, including most of the proviruses in clonally expanded cells. However, Simonetti et al. (Proc. Natl. Acad. Sci. USA, 2016 113: 1883-1888) showed that a large clone carried an intact provirus and released detectable levels of infectious virus into the blood. Thus, infected cell clones can make up a part of the HIV reservoir that has made it impossible to cure HIV infections with the currently available therapies. Given the importance of clonal expansion of infected cells in those on ART, we wanted to determine how soon after an individual is infected can infected clones grow large enough to be readily detectable in our integration site assay (clone size >105 cells).
Methods: Methods: We determined the HIV integration sites (using the technology described in Maldarelli et al., 2014 Science 345: 179-183) in samples of peripheral blood mononuclear cells taken at the time of HIV infection diagnosis and Fiebig staging. These individuals were placed on ART at the time of diagnosis, and the integration sites were also determined in follow-up samples, taken after 2-3.5 years of suppressive ART.
Results: Results: We have analyzed 3797 independent integration sites in samples from 7 patients: 2 from stage III, 1 from stage IV-V, and 3 from stage V. We are analyzing samples from additional stage IV and stage V patients. The integration site data (see appended table) showed that some HIV infected clones can grow large enough to be detectable as early as ~3-4 weeks after infection is detectable and that some of the early clones that arise early persist for years after ART initiation.
Conclusion: Conclusions: Clones of HIV infected cells can be detected within ~3-4 weeks following HIV infection. This finding may help explain how the HIV reservoir is established early in infection.

Table 1

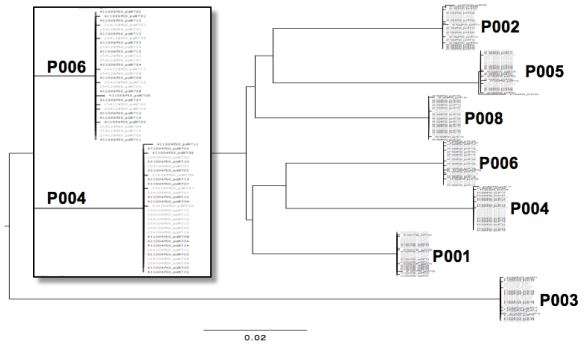
Fiebig stage of Pre-ART sample	Total integration sites Pre-ART	Clones detected Pre-ART	Total Integration sites on ART (2-3.5 years)	Clones detected on ART (2-3.5 years)
FIII	1441	0	59	3
FIII	189	0	7	1
FIV-FV	645	9	143	11*
FV	372	0	176	1
FV	427	1	65	3
FV	184	2	89	3**

*4 clones present in the pre-ART sample were also present in the on ART sample.
**The 2 clones present in the pre-ART sample were also present in the on ART sample.

299LB RESURGENCE OF HIV-1 FOUNDER VIRUSES FOLLOWING ANTIRETROVIRAL TREATMENT INTERRUPTION

Morgane Rolland[1], Eric Sanders-Buell[1], Meera Bose[1], Nittaya Phanuphak[2], Mark de Souza[3], Nelson L. Michael[1], Merlin L. Robb[1], Jintanat Ananworanich[1], Sodsai Tovanabutra[1], for the RV254/SEARCH 010 Study Groups
[1]US Military HIV Rsr Prog, Silver Spring, MD, USA, [2]Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [3]SEARCH, Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand

Background: HIV-1 infected subjects, who started antiretroviral treatment in acute infection and were treated for several years, may be able to control HIV-1 replication following treatment interruption.
Methods: Eight Thai participants (7 male, 1 female) started antiretroviral treatment days after HIV-1 diagnosis (Fiebig I) and participated in a treatment interruption study after more than 2 years of treatment (median: 1,005 days; range: 899-1994 days). HIV-1 pol sequences (1,791 nt) were obtained from plasma samples following the endpoint-dilution strategy.
Results: Following a median of 26 days (range: 13-48) after treatment interruption, HIV-1 rebounded in all participants. The highest viral load in acute infection was a median of 9,358 copies/ml (range: 3,598-20,005). After treatment interruption, HIV-1 rebounded to a median of 38,254 copies/ml (range: 11,489-137,044) before treatment was re-initiated. We compared HIV-1 pol sequences amplified at a median of 3 days (range: 1-5) after HIV-1 diagnosis to sequences obtained a median of 6 days (range: 1-15) after HIV-1 rebound. Sequences from acute HIV-1 infection (n = 15) were used to infer the founder sequence. Most sequences (71%) at HIV-1 rebound were identical to the founder sequence: a median of 11 out of 15 (range: 9-13) sequences were identical, and 91% of sequences (a median of 14 out of 15; range: 12-15) had at most 1 mutation with the founder sequence. Across all participants, mutations were found as singletons unique to a given sequence except for one G-to-A transition that was shared across 3 sequences in one participant (P002) at HIV-1 rebound. There was no evidence of drug resistance mutations, nor any evidence of selection, either positive or negative, at HIV-1 rebound. There was also no evidence of HIV-1 evolution during the 2+ years of treatment as the sequences sampled at HIV-1 rebound were not more divergent from the founder than sequences sampled during acute HIV-1 infection (Mann Whitney test: $0.241 < p < 0.999$).
Conclusion: These results indicate that rebound HIV-1 resulted from the production of viral particles from latently infected CD4+ T cells (possibly clonally expanded during treatment) rather than from a continuous low level viral replication over the treatment years. These results demonstrate that antiretroviral treatment controls HIV-1 replication but is not sufficient to eliminate a viral reservoir that was established only for the first few days of HIV-1 infection.



HIV-1 *pol* phylogenetic tree based on 210 sequences from acute infection (in gray) and from rebound (in black). The inset represents sequences from participants P006 and P004.

300 NOVEL ASSAY TO MEASURE INTEGRATED HIV DNA IN PBMC FROM ART-SUPPRESSED PERSONS

Steven Lada[1], Jake VanBelzan[2], Caroline Ignacio[1], Matthew Strain[1], Una O'Doherty[2], Douglas D. Richman[1]
[1]Univ of California San Diego, La Jolla, CA, USA, [2]Univ of Pennsylvania, Philadelphia, PA, USA

Background: Measuring integrated HIV DNA (provirus) in PBMC is important in characterizing the circulating HIV reservoir. However, these measures can be confounded by the presence of non-integrated linear and circular forms of HIV DNA. The Alu-Gag assay combined with an efficiency assumption is the current standard assay to measure integrated HIV DNA. Droplet digital PCR (ddPCR) provides an efficient, standard-independent method to measure HIV DNA, but unable to distinguish between integrated and unintegrated molecular forms. Previously, utilizing pulse-field gel electrophoresis (PFGE) we have shown a 98% clearance of circular forms of HIV DNA. Here, we applied PFGE to purify high-molecular weight DNA from linear and circular HIV DNA forms, and then assayed for integrated HIV DNA by ddPCR. In a blinded fashion, results of proviral levels were compared between Alu-Gag and PFGE+ddPCR assays.
Methods: DNA was extracted from PBMC collected from 10 ART-suppressed persons. First, using between 2-63µg of extracted DNA, samples were quantified by a standard Alu-Gag assay. Second, 1µg of DNA was used to measure HIV 2-LTR, HIV Gag, and RPP30 without any prior separation by ddPCR. Third, 5µg of DNA from each sample was loaded per well of BluePippin Gel 0.75% DF Cassettes and separated using a PFGE 15kb High-Pass protocol, and levels of HIV 2-LTR, HIV Gag, and RPP30 were then measured by ddPCR.
Results: Before PFGE separation, ddPCR detected episomal HIV 2-LTR in 6 samples and HIV Gag in all 10 samples. After processing with PFGE, HIV 2-LTR was undetectable while HIV Gag was still detected in all 10 samples. Cellular DNA recovery after PFGE, as measured by RPP30, varied between 9-42% with an average of 21% across all samples. Levels of integrated HIV DNA measured by Alu-Gag and PFGE proviral assays after unblinding were highly correlated ($R=0.7051$; $p=0.023$; Spearman's Rank-Order Correlation).
Conclusion: The PFGE+ddPCR Integrated HIV DNA assay removed episomal and linear species of HIV DNA to enable detection of provirus efficiently with as little as 5 µg (<500,000 cells) from HIV-infected persons receiving suppressive ART. These results were comparable to the standard Alu-Gag proviral assay, but the PFGE+ddPCR assay required fewer cells and was less technically difficult. Thus, the proposed PFGE+ddPCR assay provides a sensitive and precise approach to the measurement of integrated HIV DNA with sufficient throughput for translational research cure studies measuring the circulating HIV reservoir.

301 PARALLEL NEXTGEN FULL-LENGTH HIV PROVIRAL DNA SEQUENCE AND INTEGRATION SITE ANALYSIS

Mathew L. Jones, Emanuele Marchi, Jacob Hurst, Nicola Robinson, John Frater
Univ of Oxford, Oxford, UK

Background: A small population of cells harbouring an integrated copy of HIV ('the latent reservoir') persist despite effective antiretroviral therapy (ART), and is the barrier to HIV cure. The rarity of these cells and absence of a unique cell-surface marker makes study of this population difficult. Additionally, proviral sequence analysis is complicated by the excess of human genomic material in the reaction. We present a novel DNA capture assay which combined with NextGen sequencing retrieves near full-length HIV sequences and integration sites from patient samples.
Methods: Agilent's SureSelect kit was modified to enrich for HIV proviral DNA. RNA baits homologous to HIV were hybridised to 3µg CD4 T-cell DNA for 20 hours. Enrichment was achieved by selection using streptavidin-coated beads. To improve specificity, wash steps were performed at 71°C. Captured DNA was sequenced using a MiSeq and reads mapped

de novo to reconstruct the HIV genome. Integration site analysis was performed in two steps. First, reads were mapped to a HIV reference to profile the LTR. Any reads containing an LTR end motif then had the LTR sequence removed, the remaining human sequence was mapped to the hg19 genome using Novoalign to determine the integration locus.
Results: Near full-length sequence was obtained from mixes of uninfected and infected cell lines and then from 6 HIV infected patients with a range of total HIV DNA as measured by qPCR (1669 – 13186 copies per million CD4 T-cells). The depth of sequencing coverage achieved for each sample was positively correlated with HIV-DNA (p=0.013). The mean sequencing coverage for patient samples was 6x. Consistent with current literature, all primary cell integration sites mapped to intronic regions of the human genome.
Conclusion: We present the first Next Gen-based enrichment protocol which allows near full-length proviral HIV DNA sequence analysis from a broad range of HIV total DNA with integration site identification. The preliminary study of six patients supports the current understanding that a high frequency of deletions are present in the reservoir and that HIV preferentially integrates within intronic regions of highly expressed genes. A qualitative sequence-based correction of qPCR ("q^2PCR") is likely to provide a more accurate reflection of the true reservoir size. Additionally, a comprehensive map of annotated integration sites could also help identify cells most likely to constitute the reservoir.

302 HIV-1 INTEGRATION SITES ANALYSIS REVEALS DIFFERENT COMPARTMENTS OF THE HIV RESERVOIR

Eva Malatinkova[1], Wei Wang[2], Stephanie Laufs[2], Ward De Spiegelaere[1], Ning Wu[2], Saira Afzal[2], Raffaele Fronza[2], Sabine Kinloch-de Loes[3], Manfred Schmidt[2], **Linos Vandekerckhove**[1]
[1]HIV Cure Rsr Cntr, Ghent Univ, Ghent, Belgium, [2]German Cancer Rsr Cntr and Natl Cntr for Tumor Diseases, Heidelberg, Germany, [3]Royal Free Hosp, London, UK
Background: Silently persisting latent HIV-1 reservoir remains a major obstacle to an HIV-1 cure. Comparison of the viral reservoir composition by identifying the HIV-1 integration sites (IS) and clonality between blood and tissue and between different patient cohorts will lead to unreaveling the mechanisms of reservoir persistence and guide therapeutic approaches towards a functional cure.
Methods: Viral IS were identified in 15 patients of a cross-sectional study, enrolled in two clinical centers (Ghent, BE and London, UK) including three patient cohorts: early treated patients with antiretroviral therapy (ART) started during seroconversion (Early ART, n=5), patients with late ART initiation during chronic phase of HIV-1 infection (Late ART, n=5) and long-term non-progressors (LTNP, n=5). Patients within Early ART and Late ART cohorts were treated uninterrupted for a median of 10 years with undetectable viral load for at least 4 years. Viral IS were determined by linear amplification mediated PCR (LAM-PCR) both in peripheral blood mononuclear cells (PBMCs) and rectal biopsies. A semi-quantitative estimation of clonal size was done by determining the number of retrieved sequences (retrieval frequency) of individual vector-genome junctions (cell clones). The relative sequence count of all detected IS was calculated in relation to all sequences which could be mapped to a definite position in the genome.
Results: A total of 1271 IS were obtained from PBMCs or rectal biopsies from the 15 patients, these represented 1268 different integration events. Only 4 shared IS were observed between PBMCs and rectal biopsies. 44 IS (3.5%) were associated with more than 1000 sequence reads, revealing that only a small fraction of infected cells may be derived from expanded clones. Interestingly, no integrations into the BACH2 or MKL2 gene regions, which were reported to be associated with clonal expansion in previous studies, were found in the whole IS pool. No significant hotspots of virus integrations were found.
Conclusion: The HIV-1 proviral repertoire present in PBMCs and rectal biopsies revealed integrations that were not clustered in specific genomic regions without substantial signs of clonal expansion. In line with this, we did not find any integration in the previously described gene regions that were associated with clonal cell expansion. Furthermore, almost no overlap in clones was observed between the PBMCs and rectal biopsies, indicating the compartmentalized HIV-1 reservoir.

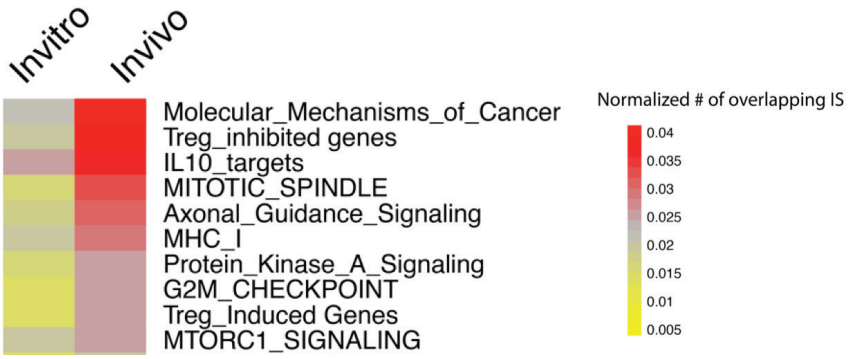
303 ENRICHMENT OF DEFECTIVE PROVIRUSES LACKING TAT-REV DURING LONG-TERM ART

Francesco R. Simonetti[1], Paolo Cattaneo[1], Alessia Lai[1], Elizabeth M. Anderson[2], Stefano Rusconi[1], Melissa Tosiano[3], John Mellors[3], Frank Maldarelli[2], Massimo Galli[4], Claudia Balotta[1]
[1]Univ of Milan, Milan, Italy, [2]NCI, Frederick, MD, USA, [3]Univ of Pittsburgh, Pittsburgh, PA, USA, [4]Luigi Sacco Univ Hosp, Milan, Italy
Background: Within a few years of ART initiation, HIV DNA in peripheral blood reaches a stable plateau and shows a proviral landscape in which 98% of genomes are not replication competent. However, the composition of these proviruses is heterogeneous, and little is known about their relative dynamics and transcription during ART. We characterized cell associated HIV DNA and RNA measuring LTR, gag and tat-rev from the blood of 75 patients.
Methods: We conducted a cross-sectional study on patients with chronic HIV infection sampled at diagnosis (N=14) and after short (N=14) or long-term ART (N=30). We also enrolled patients with acute infection sampled at diagnosis (N=8) and after early ART (N=8). Duplex assays were designed to quantify, by ddPCR, single and double positive (DP) targets on the same DNA fragment: LTR and gag, tat-rev exon-1 and -2, LTR and tat-rev exon-1. We measured plasma HIV RNA by iSCA and cell-associated RNA (us-gag, ms-tat-rev and polyA) in chronic patients on ART.
Results: Patients on ART had lower HIV DNA levels and showed higher ratios of LTR to internal regions compared to viremic patients (e.g. mean LTR/gag: 3.4 vs 1.9, p=0.0002), reflecting the loss of productively infected cells with intact HIV DNA. Copies of double positive DNA were significantly lower on ART, with DP tat-rev being the lowest (p=0.035), consistent with prior reports that a greater fraction of proviruses have deletions in these genes. In comparing patients on short and long term ART (median: 1.2 vs 11.4y), there was no significant difference in HIV DNA levels, but LTR to tat-rev ratio was significantly higher in patients with long-term treatment (4.6 vs. 2.7, p<0.0001), and correlated with years on ART (r=0.62, p<0.0001), suggesting selection of proviruses lacking tat-rev over time. In acutely treated patients, DP LTR-gag and tat-rev DNA showed a greater fold reduction (7 and 16 folds, respectively) compared to chronic patients, likely due to early ART preventing further accumulation of defective species. Of the measurements of transcriptional activity, only us-gag and polyA RNA correlated with single and double positive DNA assays, with polyA RNA and DP LTR-gag DNA showing the strongest correlation (r=0.6, p=0.0006).
Conclusion: Our data show rapid selection of deleted proviruses upon ART initiation and continued selection on long-term ART of proviruses with deletion in tat-rev sequences. The absence of genes required for proviral transcription and translation may favor the survival of infected cells.

304 HIV INTEGRATION SITE/ORIENTATION CONFER SELECTIVE ADVANTAGE FOR PERSISTENCE ON ART

Hadega Aamer[1], Malika Aid[2], Sherry McLaughlin[1], Thomas R. Sibley[3], Evan J. Silberman[3], Wenjie Deng[3], Paul Edlefsen[4], Rafick-Pierre Sekaly[5], Lisa Frenkel[3], James Mullins[3]
[1]Seattle Children's Rsr Inst, Seattle, WA, USA, [2]Harvard Univ, Boston, USA, [3]Univ of Washington, Seattle, WA, USA, [4]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [5]Case Western Reserve Univ, Cleveland, OH, USA
Background: Recent studies have shown that HIV provirus integration may play a role in infected cell persistence and proviral latency. We hypothesized that the HIV integration site (IS) and proviral orientation relative to the human gene confers a proliferative advantage to the infected cell.
Methods: We compiled published and our unpublished IS data from in vitro infections and in vivo IS data from individuals on suppressive antiretroviral therapy (ART). Provirus orientation and biological pathway associations found in cells persisting during ART compared to in vitro infected cells were evaluated by a parametric bootstrap likelihood ratio test and MsigDB using Fisher's exact test.
Results: A total of 55,365 IS were identified within genes (51,554 in vitro and 3,811 in vivo), 92% of which were in introns. Proliferation, detected by identical IS in different cells, was higher in vivo (11.5%) than in vitro (<1%). No proviral orientation bias was found in vitro, but integration in the reverse orientation with respect to the gene was detected in vivo (59%, p=0.005), across exons and introns. Pathway analysis revealed significant enrichment in pathways associated with cancer, Treg-modulation, IL10 targets, mitotic spindle, axonal guidance signaling, MHC-I, and the G2M checkpoint. These pathways were significantly more enriched in vivo than in vitro. A bias for integration in the reverse orientation was found among these pathway genes. However, examination of the cancer gene pathway, which was the most enriched pathway in vitro and in vivo, revealed a significant forward orientation bias (p<0.0001) among proviruses found in proliferating cells and a reverse bias among proviruses in non-proliferating cells.

Conclusion: Our data suggest that HIV integrated into specific genes involved with cell cycle regulation, cancer, and potentially immune signaling, may lead to enhanced proliferation and thus persistence during ART. The observed proviral orientation biases suggest that transcription of the provirus may potentially enhance or interfere with host gene expression and impact cell proliferation.



305 ROMIDEPSIN-INDUCED HIV-1 VIREMIA IS OLIGOCLONAL WITH LIMITED DELETERIOUS MUTATIONS

Anni Winckelmann[1], Kirston Barton[2], Bonnie Hiener[2], Timothy E. Schlub[3], Wei Shao[4], Thomas A. Rasmussen[1], Lars Østergaard[1], Ole S. Søgaard[1], Martin Tolstrup[1], Sarah Palmer[2]
[1]Aarhus Univ Hosp, Aarhus, Denmark, [2]Univ of Sydney, Westmead, Australia, [3]Univ of Sydney, Camperdown, New South Wales, Australia, [4]Leidos Biomed Rsr, Inc, Frederick, MD, USA

Background: The administration of the latency-reversing agent romidepsin once weekly for three consecutive weeks to individuals on suppressive antiretroviral therapy (ART) revealed quantifiable increases of cell-associated (CA) and plasma HIV-1 RNA in 5 of 6 participants, which coincided with the romidepsin infusions. However, the origin of the romidepsin-induced plasma HIV-1 RNA is unknown. To address this, we compared HIV-1 DNA and CA RNA sequences from peripheral blood CD4+ T cells to HIV-1 RNA sequences obtained from the plasma during romidepsin treatment.

Methods: CD4+ T-cells were obtained at baseline, following the second and third romidepsin infusion, and 10 weeks after the final romidepsin treatment. From three participants we obtained plasma collected 24 and 72 hours following each romidepsin infusion. Using the single-copy assay, we confirmed these plasma samples contained HIV-1 RNA from 3-70 copies/ml and no HIV-1 DNA. Single-genome sequencing of the env region was used to genetically characterize the virus from proviral DNA, the transcribed CA RNA as well as the plasma RNA pool.

Results: In all three participants with available plasma samples we identified plasma HIV-1 RNA sequences that were identical to DNA and/or CA RNA sequences from peripheral blood CD4+ T cells. Plasma HIV-1 RNA, DNA and CA RNA sequences intermingled throughout the phylogenetic trees. In two participants, we identified several expansions of identical plasma HIV-1 RNA sequences, corresponding to 62% and 100% of the total plasma RNA sequences, respectively. Proportions of defective viruses, defined as containing hypermutation or stop codons in the regions sequenced, differed significantly between HIV-1 DNA, CA RNA and plasma. Plasma HIV-1 RNA had very low amounts of defective viruses compared to CA RNA (odds ratio 20.85, $p<0.001$) and to DNA (odds ratio 7.07, $p=0.011$) during romidepsin therapy.

Conclusion: Our findings demonstrate that romidepsin induced transcription from proviruses in peripheral blood cells, which contributed to viremia in patients on suppressive ART. The intermingling of CA HIV-1 RNA with DNA sequences indicates transcription from a diverse range of proviruses. However, the oligoclonal pattern of viremia and low amounts of defective plasma HIV-1 RNA sequences indicate that the romidepsin-induced viremia arises from intact proviruses with highly similar or identical genetic backgrounds. These findings will inform future eradication strategies employing latency reversing agents.

306 MURINE MODEL TO PREDICT VIRAL REBOUND IN HIV+ ALLOTRANSPLANTED SUBJECTS

Maria Salgado[1], Mi Kwon[2], Cristina Galvez Celada[1], Monique Nijhuis[3], Cristina Vilaplana[4], Alessandra Bandera[5], Annemarie Wensing[3], Jose Luis Diez[2], Javier Martinez-Picado[1], for the IciStem Consortium
[1]IrsiCaixa AIDS Rsr Inst, Badalona, Spain, [2]Gregorio Maranon Hosp, Madrid, Spain, [3]Univ Med Cntr Utrecht, Utrecht, Netherlands, [4]Inst for Hlth Sci Rsr Germans Trias i Pujol, Badalona, Spain, [5]Univ of Milano–Bicocca, Milan, Italy

Background: Allogeneic stem cell transplantation (SCT) in HIV-infected subjects with hematological malignancies considerably reduces the viral reservoir. However, because antiretroviral treatment (cART) is maintained in these patients, it is difficult to infer the dynamics of viral rebound if cART is withdrawn. Herein, we explore the mice viral outgrowth approach (mVOA) as a potential tool to predict early viral rebound after cART discontinuation needed to evaluate the success of any eradication strategy.

Methods: Blood leukapheresis was collected from 4 subjects that had undergone SCT within the IciStem cohort, and 2 "control" HIV-infected subjects who did not receive allotransplants, all of them on cART. Purified $CD4^+$ T cells were transferred to 5 immunosupressed NSG mice per patient. Mouse health condition as well as human cell engraftment, T-cell subpopulation and T-cell activation were monitored. We quantified HIV RNA in mouse plasma, as well as total HIV-DNA on peripheral blood cells during the follow up and in spleen upon animal euthanasia. All procedures performed were reviewed and approved by the correspondent Ethical Committees and according to the national and European legislations.

Results: We transferred 10-50 million $CD4^+$ T cells per mouse. A total of five mice were used per study subject, 76% of them completing the follow up. Just one week post-infusion, we detected up to 10^4HIV RNA copies/mL in the plasma of mice to which cells from control subjects had been transferred. Total HIV DNA was also detected in peripheral blood cells between weeks 1 and 3 (10^5 copies/million cells). Conversely, after 13 weeks of follow up, no HIV RNA or DNA was detected in either plasma or peripheral blood cells of mice to which $CD4^+$ T cells from transplanted subjects had been transferred. These mice achieved a human lymphocyte engraftment over 40%, with human $CD4^+$ T cells activation levels over 50% in all cases. Finally, total HIV DNA was detected in all spleens of mice from «control» cases (10^6 copies per million cells), but not in the ones infused with cells from allotransplanted cases.

Conclusion: Mice qVOA might become a feasible tool to anticipate in vivo viral rebound dynamics after a substantial reduction of the HIV latent reservoir in eradication strategies, such as allogeneic stem cell transplantation. Compared with other assays, mVOA might reflect more physiological conditions of viral reactivation.

307 ROLE OF HIGH-MOBILITY GROUP A1 (HMGA1) GENE EXPRESSION IN REACTIVATION OF LATENT HIV

Hosiana Abewe[1], Amey Mukim[2], Savitha Deshmukh[2], Celsa A. Spina[2], Douglas D. Richman[1], Nadejda Beliakova-Bethell[2]
[1]Univ of California San Diego, La Jolla, CA, USA, [2]VA San Diego Hlthcare System, San Diego, CA, USA

Background: Histone deacetylase inhibitors (HDACi) induced HIV RNA, but did not reduce the latent HIV reservoir in clinical trials. Previously, we demonstrated that HDACi suberoylanilide hydroxamic acid (SAHA) had mixed effects on host gene and protein expression, some of which would be predicted to promote, and some inhibit HIV reactivation.

An upregulated high mobility group A1 (HMGA1) gene encodes a protein that repressed reporter transcription from HIV LTR in cell lines (Eilebrecht et al., 2013). In the present study, we investigated 1) whether the degree of HMGA1 upregulation by SAHA correlated with levels of HIV reactivation, and 2) whether knocking down HMGA1 would improve the ability of SAHA to reactivate latent HIV.
Methods: An in vitro model was used to generate latent HIV infection in resting primary CD4 T cells from 24 different blood donors. Cells were treated for 24h with 1mM SAHA or its solvent dimethyl sulfoxide (control). Expression of HIV and HMGA1 RNA was assessed by droplet digital PCR. Pearson correlation analysis between HMGA1 upregulation and HIV RNA induction was performed using 21 paired SAHA-treated and control samples. To induce HMGA1 knockdown, cells were treated for 3 days with GapmeR reagents from Exiqon, Inc. before SAHA treatment. GapmeRs contain locked nucleic acid base pairs, enter cells by gymnosis without a need for transfection, and induce stable knockdowns via target RNA degradation by RNase H. Samples from 3 blood donors were used to test whether HIV expression following SAHA treatment was greater in the samples with HMGA1 knockdown than untreated ones. Expression in SAHA-treated samples was normalized to expression in DMSO-treated samples, and a t-test was used to determine whether the difference was significant.
Results: Fold induction of HIV RNA expression upon SAHA treatment negatively correlated with the induction in HMGA1 expression (R=-0.5, p=0.02). HIV non-responders to SAHA consistently had the greatest upregulation of HMGA1 (Fig 1). GapmeRs induced, on average, 33% knockdown (p=0.03). In the presence of GapmeRs, expression of HIV following SAHA treatment was higher than in the cells incubated in parallel in the absence of GapmeRs (fold change 2.1, p=0.09).
Conclusion: To our knowledge, our data are first to demonstrate a possible role of the host factor HMGA1 in HIV reactivation from latency in primary CD4 T cells. The data suggest that inhibiting HMGA1 may improve the ability of SAHA to reactivate latent HIV.

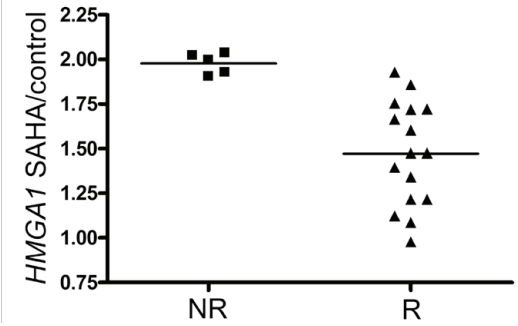


Figure 1. HIV non-responders to SAHA (fold change induction less than 1.5) consistently had the greatest upregulation of *HMGA1* RNA by SAHA. HIV responders (fold change induction greater than 1.5) had variable levels of upregulation of *HMGA1* RNA.
NR, HIV non-responders; *R*, HIV responders; Student *t*-test $p<0.01$.

308 INVESTIGATING THE MECHANISMS OF HIV-1 LATENCY BY HIGH-RESOLUTION MICROSCOPY

Luca Sardo[1], Angel Lin[1], Svetlana Khakhina[1], Lucas Beckman[1], Weam Elbezanti[1], Tara Jaison[1], Harshad D. Vishwasrao[2], Hari Shroff[2], Christopher J. Janetopoulos[1], Zachary A. Klase[1]
[1]Univ of the Scis, Philadelphia, PA, USA, [3]NIH, Bethesda, MD, USA

Background: Biochemical evidence demonstrated that the state of chromatin condensation and the recruitment of regulators of transcription on the HIV-1 LTR can control virus latency during antiretroviral therapy. However, our understanding of these mechanisms in a living cell are limited. Optical microscopy can visualize events in real-time at a single cell level, but the cell body and organelles can hamper the staining and visualization of the nucleus. In facts, high resolution microscopy techniques require fixation of the sample or expression of exogenous fluorescently tagged proteins, which are respectively limited by loss of time resolution and potential artifacts associated with over-expression. Therefore, high resolution microscopy tools to study endogenous nuclear events in real-time are in need.
Methods: Transcriptionally competent nuclei were isolated from cell line models of HIV-1 latency and immunostained without fixation for endogenous chromatin markers and chromatin modifying enzymes. Latency reversing agents (LRAs) were supplemented to isolated nuclei to induce chromatin remodeling. State of the art confocal and structural illumination multicolor live microscopy coupled with computational image analysis were used to visualize and quantify chromatin changes in real-time.
Results: The spatial organization and accumulation of novel HIV-1 LTR transcription regulators RUNX1 and STAT5 proteins was observed in response to LRAs treatment at unprecedented resolution in unfixed specimens. Microscopy observations were validated by flow cytometry and biochemical assays. In similar experiments we employed CRISPR/dCas9-SunTag to visualize the HIV-1 LTR and to study its association with chromatin markers in response to virus reactivation.
Conclusion: We have developed a high resolution, live imaging approach to investigate the in-vivo molecular mechanisms involved in HIV-1 transcriptional latency.

309 CURRENT LATENCY REVERSING AGENTS REACTIVATE A SMALL FRACTION OF LATENT PROVIRUSES

Anthony R. Cillo[1], Joshua C. Cyktor[1], **Michele Sobolewski**[1], Taylor Buckley[1], Joseph Hesselgesser[2], Tomas Cihlar[2], Romas Geleziunas[2], Jeffrey Murry[2], John W. Mellors[1]
[1]Univ of Pittsburgh, Pittsburgh, PA, USA, [2]Gilead Scis, Foster City, CA, USA

Background: Small molecule latency reversing agents (LRAs) are currently under intense investigation for their ability to reactivate latent proviruses, but the fraction of all inducible proviruses that can be reactivated by LRAs is unknown.
Methods: Resting CD4+ T (rCD4) cells were isolated by negative selection from participants on long-term ART. The frequency of infected rCD4 cells was evaluated by qPCR targeting HIV-1 pol. rCD4 cells were pulse-treated with LRAs of interest (Table) at pharmacologically achievable concentrations, and then serially diluted and cultured for 7 days. Separate serially diluted rCD4 cells were treated with medium control or anti-CD3/CD28 as negative and positive controls, respectively. Virion production (HIV-1 RNA in supernatants) was measured after 7 days by qRT-PCR (LOD 40 cps/ml). Maximum likelihood estimates were used to quantify the fraction of proviruses that were reactivated to produce virions (Cillo, et al. PNAS 2014).
Results: rCD4 cells were isolated from leukapheresis products from 8 donors on suppressive ART for an average of 9 years (range: 3-17), and pulsed with 40 nM RMD for 4 hours, 17.5 nM PAN for 30 minutes, 25 uM JQ1 for 30 minutes, or 10 nM BRY for 1 hour. Pulses with 2 LRAs were at the same concentration and duration as single LRAs. Median fold-increase in virion production over medium control was 5-fold for RMD, 1-fold for PAN, 3-fold for JQ1, 1.7-fold for BRY, 19-fold for BRY+RMD, and 22-fold for RMD+JQ1 compared with 592-fold for anti-CD3/CD28. Despite increases in virion production, only a small fraction of proviruses (between 0.012% and 0.12%) were reactivated with any LRA or combination of LRAs, compared to 3.7% of proviruses reactivated with anti-CD3/CD28 (Table). When the fraction of proviruses that were reactivated is expressed as a percent of the anti-CD3/CD28 positive control (set at 100%), only 1.4% of inducible proviruses were reactivated with RMD, 0.48% for PAN, 0.26% for JQ1, 0.31% for BRY, 3.3% for RMD+JQ1, and 1.8% for RMD+BRY.
Conclusion: Although latency reversing agents targeting HDAC, PKC, and bromodomain and extraterminal domain (Brd4) can stimulate virion production from resting CD4 cells, only a very small fraction of proviruses (<<1%) are reactivated to produce virions. Combinations of latency reversing agents increased the fraction of proviruses reactivated, but only to a few percent of that achieved with T cell activation. The "shock and kill" strategy will require latency reversing agents with much greater activity.

Table. Fraction of proviruses reactivated to produce virions *ex vivo*

Donor ID	Fractional proviral expression (% of proviruses reactivated by each LRA or LRA combination)							
	Negative control	TCR stimulation	HDAC inhibitor	HDAC inhibitor	Brd4 inhibitor	PKC agonist	HDACi + BETi	HDACi + PKC agonist
	Medium control	Anti-CD3/CD28	RMD	PAN	JQ1	BRY	RMD+JQ1	RMD+BRY
1	0.015	1.9	0.01	0.019	0.0043	ND	ND	ND
2	<0.074	9.4	0.36	0.045	0.08	ND	0.64	ND
3	0.033	3.6	0.09	<0.026	<0.043	ND	0.12	ND
4	0.043	8.2	0.062	ND	0.012	ND	0.088	ND
5	<0.024	3.4	0.043	ND	ND	0.090	ND	0.15
6	<0.068	3.8	0.083	ND	ND	<0.023	ND	0.022
7	<0.023	3.5	0.019	ND	ND	<0.017	ND	0.0094
8	<0.008	4.5	0.039	ND	ND	0.0073	ND	0.083
Median	**0.024**	**3.7**	**0.053**	**0.019**	**0.017**	**0.012**	**0.12**	**0.083**

RMD = romidepsin, PAN= panobinostat, BRY=bryostatin

310 LATENCY REVERSAL USING SPECIFIC ANTIGENS INCLUDING THOSE OF HIV-1

Thomas Vollbrecht[1], Aaron Angerstein[2], John Guatelli[2]
[1]Veterans Med Rsr Fndn, San Diego, CA, USA, [2]Univ of California San Diego, La Jolla, CA, USA

Background: Latently infected CD4-positive memory T cells are capable of producing replication competent virus and represent a barrier to cure. These cells were presumably infected while responding to specific antigen. We hypothesized that such cells would respond again to that antigen and in particular to HIV-1 antigens. By measuring latency reversal and cellular activation in cells from virally suppressed patients ex vivo using specific antigens, we aimed to show that latency is preferentially established in cells with certain antigen-specificities.

Methods: We used peptide pools of HIV-1 Gag, CMV, C. albicans, and a mixture of peptides from CMV, EBV, influenza, and tetanus toxoid (CEFT) to stimulate primary CD8-depleted PBMC from HIV-1 infected patients who were virally suppressed by cART for at least 1 year. Cells were stimulated for 3 days with each agent and then stained for expression of the early activation marker CD69. To assess latency-reversal, we measured virion-associated RNA released by the cells 3 days after activation; we also added MOLT4/R5 cells to the cultures and measured RNA after 7 days of viral outgrowth. Real-time RT-PCR of gag RNA was used as the readout.

Results: Preliminary results indicate that cellular activation was greatest in cells stimulated with beads coated with α-CD3 and α-CD28, followed by the peptide pools of CMV, CEFT, HIV-1 Gag, and C. albicans. The latency-reversal activity of the peptide pools was less than that of the antibody-coated beads, and the different antigens were not uniformly active among the different patients. In some patients the HIV-1 Gag peptide pool was the most active at latency reversal, even though it was less active at inducing CD69 expression than other antigens such as CMV.

Conclusion: Our results suggest the potential for latency to be differentially established in cells with specific antigen specificities; in some patients latency seems to be preferentially established in cells that respond to Gag peptides. By defining the specific antigens that can reactivate viral gene expression in latently infected cells, we aim to inform models of latency and in the best case derive an antigenic mixture capable of reversing latency in the majority of cells.

311 IDENTIFICATION OF LRAs ACTIVE IN DIVERSE PRIMARY T-CELL MODELS OF HIV LATENCY

Richard Barnard[1], Jenny L. Anderson[2], Daria Hazuda[1], Sharon R. Lewin[2], Laura J. Martins[3], Mauricio Montano[4], Vicente Planelles[3], Celsa A. Spina[5], for the CARE Collaboratory
[1]Merck & Co, Inc, West Point, PA, USA, [2]The Univ of Melbourne, Melbourne, Australia, [3]Univ of Utah, Salt Lake City, UT, USA, [4]Univ of California San Francisco, San Francisco, CA, USA, [5]VA San Diego Hlthcare System, San Diego, CA, USA

Background: It has been challenging to identify latency reversing agents (LRAs) broadly active across multiple primary cell latency models and patient cells ex vivo. A Jurkat CD4+ T cell model of HIV latency was used to screen the Merck library of 2.9 million compounds. Unlike prior efforts, this screen was conducted with and without a suboptimal concentration of SAHA, a histone deacetylase inhibitor (HDACi), with the goal of sensitizing the latency model to allow the discovery of novel and potentially synergistic LRAs. While 34% of compounds active in the screen acted via known mechanisms of action (HDACis or Farnesyl Transferase (FT) inhibitors) the remaining 66% acted via unknown mechanisms of action (uMOA). Based on the activity of uMOA compounds in different Jurkat T- cell models of HIV latency, 144 compounds were chosen for additional detailed analysis in primary CD4 T-cell models of HIV latency.

Methods: The 144 compounds were analyzed in seven different primary CD4 T-cell models of HIV latency using up to a six-point dose titration, in the presence of suboptimal concentration of panobinostat or vorinostat, tailored to the HDACi responsiveness of each primary cell system. Latency reversal was quantified by changes in reporter expression (eGFP or luciferase), HIV Nef or Tat gene expression, or HIV mRNA, depending model used.

Results: As expected based on previous studies of LRAs in these primary cell models (Spina, PLoS Path 2013) among the 144 selected uMOA compounds, no one tested was active in all models. However, 2 compounds displayed statistically significant activity in six of the seven cell models and 16 compounds exhibited activity in three or more systems. Of note, none of the compounds were overtly toxic at concentrations that exhibited LRA activity. Additionally, no compounds induced CD69 expression in naïve T-cells isolated from healthy volunteers, suggesting their LRA activity was not due to generalized T cell activation.

Conclusion: This novel screen was able to identify LRAs that lack generalized T cell activating properties and appear non-toxic, but display activity across multiple cell line and primary cell models of latency. The compounds appear to have mechanism(s) of action distinct from known LRAs and work in concert with HDACis, suggesting the opportunity for combination LRA therapy. Validation of these compounds in patient cells is now underway. Screening for LRAs in the presence of a sensitizing agent may be a broadly useful approach.

312 STIMULATING THE RIG-I PATHWAY TO KILL LATENT HIV-INFECTED CELLS USING ACITRETIN

Peilin Li[1], Philipp Kaiser[1], Harry Lampiris[1], Peggy Kim[2], Steven A. Yukl[1], Diane V Havlir[3], Warner C. Greene[4], Joseph K. Wong[1]
[1]San Francisco VA Med Cntr/Univ of California San Francisco, San Francisco, CA, USA, [2]San Francisco VA Med Cntr, San Francisco, CA, USA, [3]San Francisco General Hosp, Univ of California San Francisco, San Francisco, CA, USA, [4]Gladstone Inst of Virology and Immunol, San Francisco, CA, USA

Background: The persistence of latent HIV proviruses in long-lived CD4+ T cells despite ART represents a major obstacle to viral eradication. Because current candidate latency-reversing agents (LRAs) induce HIV transcription but appear to fail to clear these cellular reservoirs, new approaches for killing reactivated latent HIV reservoir cells should be

explored. Retinoic acid-inducible gene I (RIG-I) is a pathogen recognition receptor that mediates apoptosis and elimination of infected cells after recognition of viral RNA. RIG-I can recognize HIV RNA, however RIG-I signaling is disrupted by HIV infection. We hypothesize that enhancement of the RIG-I signaling pathway can promote the death of latently infected reservoir cells following activation of proviral gene expression.

Methods: CD4+Tcells from HIV+ patients on ART, CEMT4 and TZM-bl cells with latent GFP-HIV infection were treated with the retinoic acid derivative, acitretin , SAHA , and DMSO. HIV expression was assessed by qRT-PCR or GFP expression and HIV DNA copy by qPCR. Apoptosis was measured by flow cytometric measure of annexin V expression. CEMT4 cells enriched for latent viral infection were used to measure RIG-I association with mitochondrial antiviral signaling protein (MAVS) by co-immunoprecipitation and in RIG-I knockdown experiments with shRNA directed against DDX58. IFN-β and CXCL10 production were measured by ELISA. Components of RIG-I signaling were measured by immunoblotting. Statistical difference was determined using a Student's t-test.

Results: Acitretin increased HIV transcription, and increased RIG-I signaling in the presence of HIV infection, RIG-I association with MAVS ($p<0.01$) and production of IFNβ and CXCL10 ($P<0.01$). These parameters were not altered by the DMSO control. Acitretin also increased preferentially apoptosis in those cells induced to express HIV identified by GFP expression ($p<0.01$). After 7 days of treatment with acitretin, HIV DNA frequency was reduced in CD4 T cells from HIV patients on ART (compared to DMSO control $P<0.05$, $n=12$). In a CEMT4 latent infection model, knockdown of RIG-I abrogated the induction of apoptosis, the production of IFN-β and the reduction in HIV DNA by acitretin ($p<0.05$).

Conclusion: In vitro acitretin at clinically achievable concentrations is an inducer of HIV expression from cells latently-infected with HIV but effectively stimulates RIG-I signaling to induce apoptosis and elimination of HIV-infected cells. Acitretin merits further study.

313 TLR7 AGONIST GS-986 MARKEDLY ACTIVATES T & B CELLS FROM ART-SUPPRESSED DONORS

Joshua C. Cyktor[1], Anthony R. Cillo[1], John Bui[1], Joseph Hesselgesser[2], Tomas Cihlar[2], Jeffrey Murry[2], John Mellors[1]
[1]Univ of Pittsburgh, Pittsburgh, PA, USA, [2]Gilead Scis, Foster City, PA, USA

Background: TLR7 is expressed within plasmacytoid dendritic cells and B cells, and senses viral RNA to link innate and adaptive immune responses. The TLR7 agonist GS-986 (a close analog of GS-9620) induces SIV viral blips after 3-4 biweekly doses in a macaque model of ART suppression by undefined mechanisms. We investigated the immunologic and virologic effects of GS-986 ex vivo using cells from HIV-infected donors on long-term ART.

Methods: PBMC and $CD8^+$ T- or B cell-depleted PBMC were isolated from fresh blood or leukopaks and cultured for 5 days with or without 100nM GS-968. HIV-1 DNA, unspliced RNA (CA-DNA and CA-RNA), and virion release were measured by qPCR. Immune cell phenotype, cytokine production, proliferation, and antibody levels were evaluated by flow cytometry, Luminex, CFSE, and ELISA assays, respectively. After 5 days of culture, resting and total $CD4^+$ T cells were isolated and assayed for the number of cells releasing virions following maximal stimulation with PMA/ionomycin (iono).

Results: PBMC were obtained from 9 donors (5 blood; 4 leukopak) on suppressive ART (median duration: 7 years). Exposure to 100nM GS-986 for 5 days did not consistently alter CA-DNA or CA-RNA per 10^6 $CD4^+$ cells, virion release, or the number of cells releasing virions after subsequent PMA/iono stimulation. CD8- or B cell-depletion did not affect virologic responses. By contrast, GS-986 was immunologically active in all donors, doubling the proportion of CD4/CD8 double-positive T cells and having the greatest effects on CD25, CD69 and HLA-DR in this population (mean absolute increases of 11.4%, 11.9%, 18.4%, respectively). 11% of naïve B cells became activated and recall of memory plasma B cells was induced to 29%, with large increases in secreted IgM (mean 60-fold) and IgG (mean 34-fold increase), and induction of 6 rounds of proliferation by CFSE. GS-986 induced multiple cytokines, most notably IL-1β, IL-6 and IL-10 with mean increases of 6.4-, 250- and 8.2-fold, respectively.

Conclusion: Exposure of PBMC to GS-986 for 5 days markedly activated T cells and B cells, but did not consistently alter virologic measures. *Ex vivo* culture systems involving a single exposure to GS-986 induce profound immunologic responses but do not recapitulate the consistent and large effect of TLR7 agonism on viremia observed in macaques after multiple oral doses. Cumulative responses from repeated cycles of stimulation may be required to achieve such effects.

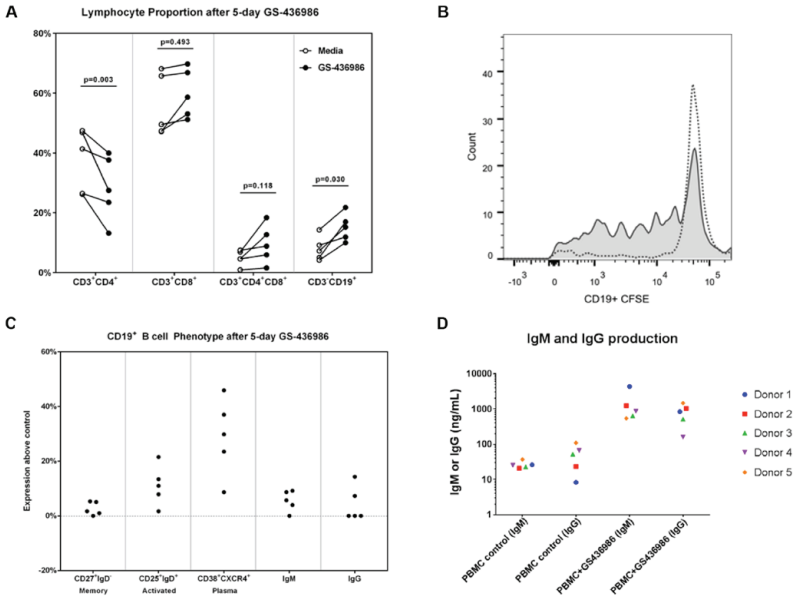


Figure 1. Preliminary experiments demonstrating the effects of GS-436986 on lymphocytes. **A)** Proportions of lymphocytes after 5-day stimulation of PMBC with media or GS-436986. **B)** CFSE staining of bulk PBMC reveals that B cells undergo >5 cell divisions (grey histogram) compared to no cell divisions in the medium control (dotted histogram). **C)** Surface staining reveals that B cell phenotypes transition from memory to plasma cell, and naïve to activated B cells following treatment with GS-436986, consistent with ligation of TLR-7 within B cells. **D)** Also consistent with transition of B cells from naïve/memory states to activated states, there was an increase in antibody (IgM and IgG) production from control to GS-436986 treated cells.

314 TLR9 AGONIST TRIGGERS POTENT INTESTINAL ANTIVIRAL RESPONSE IN HIV+ INDIVIDUALS ON ART

Astrid R. Krarup[1], Mariane H. Schleimann[1], Line K. Vibholm[1], Mohamed Abdel Mohsen[2], Anders K. Dige[1], Lars Østergaard[1], Thomas Benfield[3], Satish K. Pillai[2], Ole S. Søgaard[1], Paul W. Denton[1]
[1]Aarhus Univ Hosp, Aarhus, Denmark, [2]Blood Systems Rsr Inst, San Francisco, CA, USA, [3]Copenhagen Univ Hosp, Hvidovre, Denmark

Background: HIV persists in infected individuals despite ART. While persistent HIV becomes transcriptionally active in the presence of latency reversing agents, these agents have little effect on the size of the viral reservoir in vivo. Thus, improved killing of infected cells is essential to achieve viral eradication. Towards this goal, we tested whether a TLR9 agonist (MGN1703; lefitolimod) could enhance antiviral immunity in vivo.
Methods: Sigmoid biopsies were collected from 11 participants at baseline and 24 hours after the last dose in week 4 of a single-arm phase 1b/2a clinical trial where HIV+ adults received MGN1703 (60 mg s.c.) twice weekly for 4 weeks (NCT02443935). We quantitated IHC signal positive cell profiles (nucleus with associated signal; referred to as cells below) in fixed tissue sections for the antiviral and inflammatory response markers MxA, ISG15, IL-21, CXCL10 or MPO; data were stratified by anatomical location: lamina propria (LP) or epithelium. Remaining biopsy tissue was digested and percoll-enriched intestinal mononuclear cells were obtained for virological and immunological analyses [RNA-seq; HIV DNA/RNA levels (qPCR); CD4/CD8 T cell frequency and activation (flow)]. Plasma viremia quantitation: Cobas Taqman. Data analyses: Wilcoxon signed rank tests, mean fold change (mfc) and Ingenuity Pathway Analysis right-tailed Fisher Exact Test.
Results: RNASeq revealed 248 significantly regulated genes (FDR<0.05) and a potent antiviral response (IPA p=2*10^-14) including many IFN-a stimulated genes. Indeed, MGN1703 dosing increased the number of cells positive for MxA (LP: p=0.001, mfc=8.8; and epithelium: p=0.003, mfc=27.6), ISG15 (LP: p=0.014, mfc=5.6) and IL-21 (LP: p=0.019, mfc=0.5). In contrast, there was no change in the numbers of cells positive for CXCL10 which is IFN-g induced (LP: p=0.97). No cohort-wide changes were observed in: neutrophil infiltration (MPO LP: p=0.97); viral DNA; viral RNA; T cell subset distribution; or T cell activation. However, after stratifying according to MGN1703-induced plasma viremia status, we observed that viremic individuals had a decrease (n=3, mfc=-0.8) in integrated intestinal lymphoid tissue HIV DNA (p=0.042).
Conclusion: MGN1703 induced robust antiviral immune responses in the intestines of HIV+ individuals on ART. In addition, the observed lack of neutrophil infiltration suggests that MGN1703 does not cause destructive tissue inflammation. These data support a prominent role for MGN1703 immunotherapy in HIV eradication strategies.

315 SMALL-MOLECULE INHIBITION OF INTRINSIC STRESS PATHWAYS REDUCES HIV TRANSCRIPTION

Andrew Timmons, Robert Siliciano, Cynthia K. Bullen
The Johns Hopkins Hosp, Baltimore, MD, USA

Background: Combination antiretroviral therapy (cART) effectively reduces HIV replication to undetectable levels, but HIV persists as a stable reservoir within resting memory CD4+ T cells. Substantial effort has been applied to identifying small molecules that can perturb the stability of this reservoir. Studies in model systems have identified many latency reversing agents (LRAs), but few are efficacious in cells isolated from HIV-1 infected patients. Dose-response studies in model cells and patient cells exhibit unique patterns across multiple chemical classes of LRAs that suggest that generalized cell stress may play a role in initiating HIV transcription.
Methods: Resting T cells were isolated from HIV-1 infected individuals with suppression of viremia on cART. Cells were treated for 24 hours with the protein kinase C (PKC) agonist bryostatin and the synthetic Nrf2 agonist HBB2. Treatment was done the presence or absence of the ROS scavenger N-acetylcysteine (NAc) and the HSF-1 inhibitor KRIB11. Intracellular HIV mRNA was measured by RT-qPCR. HIV-1 RNA levels were compared to levels in T cells activated with phorbol 12-myristate 13-acetate (PMA; a PKC agonist) and ionomycin (a calcium ionophore). Cell surface markers of T cell activation were assessed by flow cytometry.
Results: Ex-vivo treatment of resting CD4+ T cells with PKC activators as well as PMA and ionomycin greatly increased levels of HIV-1 mRNAs which were significantly reduced with inclusion of the ROS scavenger NAc. Inhibition of HIV-1 transcription was observed to a much greater extent when the heat shock inhibitor KRIB11 was used instead of N-acetylcysteine with no concomitant change in surface marker expression. Gene expression analysis on cells treated with N-acetylcysteine reveals inhibition of major components of the heat shock response.
Conclusion: Inhibitors of the oxidative and heat shock stress responses substantially reduce the amount of HIV expressed in activated T cells by approximately 55 and 80%, respectively. These findings indicate that intrinsic cell stress pathways play a significant role in activating latent HIV-1 transcription in activated T cells.

316 NNRTIS DECREASE HIV-1 PRODUCTION FROM RCD4+ T CELLS FOLLOWING LATENCY REVERSAL

Jennifer M. Zerbato[1], Gilda Tachedjian[2], Nicolas Sluis-Cremer[1]
[1]Univ of Pittsburgh, Pittsburgh, PA, USA, [2]Burnet Inst, Melbourne, Australia

Background: Therapeutic strategies which target the latent HIV-1 reservoir in resting CD4+ T cells of infected-individuals are always administered in the presence of combination antiretroviral (ART) therapy. In this study, we evaluated whether the different therapeutic classes of ARV drugs impacted HIV-1 latency reversal.
Methods: Methods: Latency reversal was evaluated in a primary cell model of latency that utilizes direct infection of resting CD4+ T cells. Two hours prior to addition of anti-CD3/CD28 monoclonal antibodies, cells were treated with an entry inhibitor (AMD3100 or maraviroc), a PI (atazanavir, darunavir), NRTI (lamivudine), NNRTI (rilpivirine, efavirenz) or INSTI (raltegravir). Controls included cells that were exposed only to antibody or the ARVs. Seven days post antibody administration, cell-associated HIV-1 DNA and extracellular virion production were quantified. T cell activation and viability were assessed by flow cytometry.
Results: Results: NNRTIs were found to decrease both R5- and X4-tropic HIV-1 production (by ≥ 1-log fold-change) in resting CD4+ T cells exposed to anti-CD3/CD28 monoclonal antibodies. This decrease was not due to toxicity, or changes in T cell activation in the presence or absence of NNRTI as assessed by CD25, CD69 or HLA-DR expression. In contrast, none of the other ARVs, including PIs which target the late stages of HIV-1 replication, had a significant impact on virus production. Further analysis in a cell line model of HIV-1 latency (J89GFP cells) revealed that the NNRTIs did not interfere with HIV-1 gene transcription or translation. Instead, consistent with published studies, we propose that the NNRTIs enhance premature activation of HIV-1 PR which results in intracellular processing of Gag and Gag-Pol leading to decreased viral particle production.
Conclusion: Conclusions: NNRTIs reduce HIV-1 production from latently infected cells. Ex vivo studies that use NNRTIs to prevent virus spread or cells from donors on NNRTI containing regimens should be cautiously interpreted.

317 INDUCIBLE HIV-1 LATENT RESERVOIR INCREASES AFTER HIV+ OR HIV- SOLID ORGAN TRANSPLANT

Alyssa R. Martin[1], Andrew D. Redd[2], Gregory Laird[1], Robert Siliciano[1], Diane Brown[1], Darin Ostrander[1], Thomas Quinn[1], Dorry Segev[1], Aaron Tobian[1], Christine Durand[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]NIAID, Bethesda, MD, USA

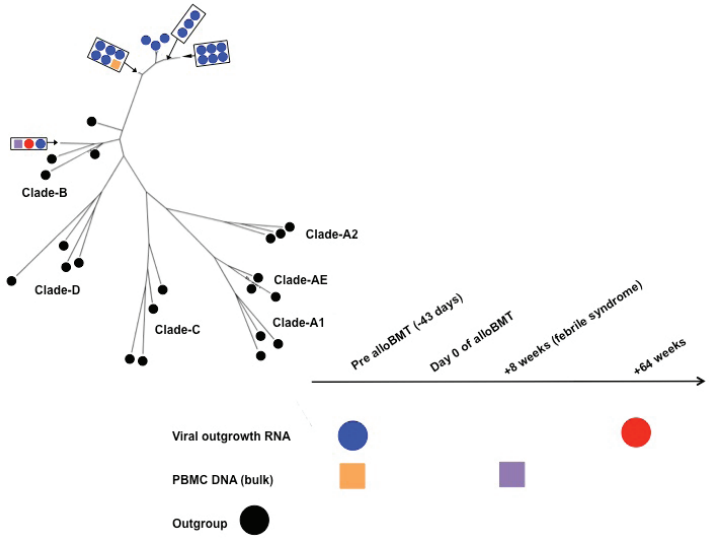
Background: The latent reservoir (LR) for HIV-1 in long-lived memory CD4+ T cells is a barrier to cure. Measuring the LR is complicated because PCR-based assays for proviral DNA cannot distinguish defective viruses making up the majority of the LR, whereas viral outgrowth assays that measure replication-competent virus have a low dynamic range and are often not feasible due to blood volume requirements. To overcome these limitations, we developed a novel quantitative viral induction assay (QVIA). In an ongoing prospective clinical trial of HIV+ individuals receiving kidney or liver transplant from HIV+ or HIV- donors (NCT02602262), we used QVIA to test the hypothesis that immunosuppressants used after solid organ transplantation may reduce the HIV-1 LR.
Methods: Immunosuppression was per transplant center standard of care and for kidney recipients included antithymocyte globulin for induction. The LR was measured before transplant and at week 13 post-transplant using QVIA, in which 4 million resting CD4+ T cells were plated at limiting dilution and treated for 18 hours with PMA and ionomycin or vehicle alone. mRNA isolation, cDNA synthesis, and qPCR specific for HIV-1 mRNA were performed. QVIA uses a cycle threshold cutoff to exclude wells with a low qPCR signal, increasing specificity for intact, induced viral RNA. Number of inducible proviruses per million cells (IPPM) was estimated by qPCR positive wells at each dilution. Pre- and post-transplant IPPMs were compared using paired student's t-test.

Results: HIV+ kidney or liver transplant recipients of both HIV+ and HIV- donors on ART were enrolled (n=17). Induced HIV-1 mRNA was detectable in all 10 samples tested. IPPMs ranged from 0.858-42.620 with a mean of 16.819. For patients with longitudinal measurements to date (n=5), all had an increase in IPPM at week 13 post-transplant compared to pre-transplant (p=0.008) with a maximum 10-fold increase in one patient.
Conclusion: We designed a novel assay to measure the inducible LR with a high dynamic range and specificity. Preliminary results demonstrated an increase in the inducible HIV-1 LR post-transplant, which could represent clonal expansion of infected cells, due to compensatory lymphocyte proliferation after immune cell depletion and/or heightened immune activation during transplant. This finding may have implications for HIV-1 cure strategies in these patients.

318 PERSISTENCE OF A MINORITY HIV VARIANT DESPITE ALLOBMT WITH COMPLETE DONOR CHIMERISM

Adam Capoferri[1], Andrew D. Redd[2], Daniel I. Rosenbloom[3], Roberto Ramirez[1], Subul Beg[1], Andrew Timmons[4], Christopher Gocke[1], Robert Siliciano[1], Richard Ambinder[1], Christine Durand[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]NIAID, Bethesda, MD, USA, [3]Columbia Univ, New York, NY, USA, [4]Johns Hopkins Hosp, Baltimore, MD, USA

Background: Continuous antiretroviral therapy (ART) with allogeneic bone marrow transplant (alloBMT) is being investigated as an HIV eradication strategy. After alloBMT, the disappearance of the HIV latent reservoir (LR) was initially observed in two reported "Boston patients"; however, with analytical ART interruption there was viral rebound from an unknown source. In a pilot clinical trial of optimized ART and alloBMT for HIV-infected patients, we present evidence of HIV persistence despite full donor chimerism.
Methods: The HIV LR was measured pre-alloBMT and every 12 weeks after with a quantitative viral outgrowth assay (qVOA), digital droplet PCR (ddPCR) with pol primers, and quantitative PCR using gag primers in peripheral blood mononuclear cells (PBMCs). The pol region from positive qVOA supernatant RNA and proviral DNA from PBMCs was sequenced (Sanger method). Sequences were aligned and phylogenetic analysis performed using a neighbor-joining tree. Chimerism from PBMCs was determined using microsatellites or short tandem repeats to distinguish donor from recipient (ABI, AmpfISTR, limit of detection 1%).
Results: The patient had chronic HIV infection on ART with relapsed Hodgkin Lymphoma and underwent a reduced-intensity haploidentical alloBMT. Week 8 post alloBMT, he had full donor chimerism in peripheral blood. By qVOA, the LR decreased from 2.76 IUPM at baseline to undetectable levels at weeks 12, 24, 36 and 52. Proviral DNA by both ddPCR and qPCR demonstrated a 1 log increase at week 8, clinically at this time the patient had CMV reactivation and suspected histoplasmosis infection. Phylogenetic analysis suggested that at baseline the patient had dual infection with two distinct viral variants. Week 8 proviral DNA was identical to a replication competent minority variant isolated in the qVOA pre-alloBMT. At week 64, the LR was detected by qVOA (0.03). The pol region of week 64 qVOA virus was identical to the pre-alloBMT minority variant and week 8 proviral DNA sequence.



Conclusion: In a patient who achieved full donor chimerism post-alloBMT, we were able to detect HIV persistence both by ddPCR and qPCR at week 8, and by viral outgrowth from resting memory CD4+ T cells at 64 weeks post-transplant. More sensitive studies of chimerism are needed to determine if this represents de novo infection of donor cells or persistence and/or clonal expansion of rare host cells.

319 TWO HUNDRED EIGHTY-EIGHT–DAY DRUG-FREE REMISSION FROM HIV REBOUND BY ALLOGENEIC PBSCT

Nathan Cummins[1], Stacey Rizza[1], Jason Baker[2], Nicolas Chomont[3], Tae-Wook Chun[4], Mathias Lichterfeld[5], Douglas D. Richman[6], Timothy Schacker[7], Joseph D. Yao[1], Andrew Badley[1]
[1]Mayo Clinic, Rochester, MN, USA, [2]Univ of Minnesota, Minneapolis, MN, USA, [3]Univ de Montréal, Montreal, QC, Canada, [4]NIH, Bethesda, MD, USA, [5]Massachusetts General Hosp, Boston, MA, USA, [6]Univ of California San Diego, La Jolla, CA, USA, [7]Univ of Minnesota, Minneapolis, MN, USA

Background: As HIV cure strategies are tested a reliable measure of cure is needed to predict drug-free remission from viral rebound. We evaluated HIV reservoir size through the post-transplant period in a patient with HIV who underwent allogeneic peripheral blood stem cell transplant (PBSCT) for acute lymphoblastic leukemia. An antiretroviral Analytic Treatment Interruption was initiated after 2 years.
Methods: PBMCs were obtained by leukapheresis for HIV reservoir size estimation. Plasma was tested with Amplicor HIV-1 DNA Test, v1.5. Total HIV DNA in CD4 T cells was measured by qPCR and digital droplet PCR separately. Integrated HIV DNA in CD4 T cell subsets was measured by Alu-nested PCR. The frequency of CD4 T cells with replication competent virus was determined by quantitative viral outgrowth assay.
Results: A 55 y.o. man with ART suppressed HIV-1 was seen at Mayo Clinic for B-cell ALL. He underwent allogeneic reduced-intensity conditioning PBSCT with an HLA- and ABO-matched sibling as donor, with tacrolimus and methotrexate for GVHD prophylaxis. Both donor and recipient were CCR5 wild-type. His course was notable for mild GVHD in colon (biopsy confirmed) and Pneumocystis jiroveci pneumonia. As of this report the ALL is in complete remission. ART was continued through the peri-transplant period, and plasma HIV-1 RNA and proviral DNA became undetectable by clinical assays. In situ hybridization for HIV in GI lymphatic tissue (colon) was negative. Table below presents results from HIV reservoir assessments. Total and integrated HIV DNA and replication competent virus in peripheral CD4 T cells decreased post-transplant to undetectable or near undetectable levels. At 784 days post PBSCT, given multiple negative tests for HIV and de-evolving western blot for antibodies to HIV, he initiated ATI of all ART. Plasma viremia was measured weekly for 8 weeks, then monthly, and remained undetectable (LLD 10 copies/ml) for 9 months post-ATI. On ATI day 288 his plasma HIV RNA level became detectable at 48 copies/ml, increased to 283 (ATI day 289), and then 1640 (ATI day 293), prompting reinitiation of ART.
Conclusion: Our case illustrates that PBSCT with ART can significantly reduce HIV reservoir size, and enable prolonged drug free remission from HIV rebound. It is unclear why in the absence of cure, HIV rebound was profoundly delayed at 288 days post ATI. Functional analyses are underway to identify immune mechanisms which may have delayed HIV rebound.

Table: Assessment of HIV Reservoir via Multiple Methods at Designated Times Following Allogenic PBSCT (Day 0) and Subsequent HIV ATI (Day +784)

HIV Reservoir Measurement	Day -11	Day +142	Day +288	Day +436	Day+888 (ATI day 104)
Amplicor HIV-1 DNA	Positive	Negative	Negative	Negative	NA
HIV-1 DNA (qPCR), copies/10^6 CD4+ T cells	722	28	NA	NA	<5
Cell-associated HIV-1 RNA (RT-PCR), copies/1.5µg of RNA from CD4+ T cells	398	515	NA	NA	17
HIV-1 DNA (ddPCR), copies/10^6 CD4+ T cells	Gag 26.99 Pol 30.29	Gag 3.01 Pol 4.22	Gag <0.36 Pol 2.31	Gag 2.74 Pol <0.34	NA
Integrated HIV DNA (Alu-nested PCR), copies/10^6 CD4+ T cells	25	2	NA	NA	NA
• Naïve	0	0			
• Central Memory	62	5			
• Transitional Memory	277	0			
• Effector Memory	16	3			
Infectious units per 10^6 CD4+ T cells (QVOA)	0.0673	<0.0121	<0.0024	<0.002	<0.002

320 PERSISTENCE OF HIV DNA IN TISSUES EARLY AFTER TRANSPLANTATION WITH CCR5Δ32 STEM CELLS

Kobus Bosman[1], Monique Nijhuis[1], Anke Bruns[1], Maria Salgado[2], Gero Hütter[3], Lodewijk Brosens[1], Javier Martinez-Picado[4], Jürgen Kuball[1], Annemarie Wensing[1], for the IciStem Consortium
[1]Univ Med Cntr Utrecht, Utrecht, Netherlands, [2]AIDS Rsr Inst IrsiCaixa, Badalona, Spain, [3]Cellex, Dresden, Germany, [4]ICREA, Barcelona, Spain

Background: Cure of HIV infection was observed following stem cell transplantation (SCT) with homozygous CCR5Δ32 donor cells in the Berlin patient. In contrast, in the Boston patients, transplanted with a regular donor, HIV rebound was observed after treatment interruption despite loss of detectable HIV DNA in PBMCs. It is unclear which reservoir fueled HIV rebound.
Methods: The impact of SCT on HIV-1 reservoir size in IciStem patients 5 and 11 was investigated. SCT was performed using HLA-matched CCR5Δ32 donors. Before SCT we performed: 1) Phenotypic and genotypic co-receptor tropism analysis 2) Quantification of the HIV reservoir in CD4 T-cell subsets subsets (Tn, Tcm, Ttm, Tem, and Tscm) and bone marrow using ddPCR 3) Single copy assay (SCA) on plasma. After graft failure, patient 11 was re-transplanted with CCR5Δ32 heterozygous donor cells. Post-SCT viral dynamics and the post-mortem viral reservoir were analyzed using ddPCR.
Results: Patients 5 and 11 harboured CCR5-tropic virus (FPR 89% and 33-49%), were treated with ART since 1999 and 1996, and were effectively suppressed for 5 and 16 years prior to SCT, respectively. Before SCT, no viral RNA was detected in routine diagnostics while SCA in plasma detected 15 c/ml (patient 5) and 2 c/ml (patient 11). In patient 5, HIV DNA was detected in PBMCs (983 c/10^6), naive T-cells (635 c/10^6) and memory T-cells (Tcm, Tm and Tem, 1537, 2832 and 3462 c/10^6). In patient 11, HIV DNA was detected in PBMCs (295 c/10^6), bone marrow (80 c/10^6), stem cell-like CD4 T-cells (490 c/10^6), naive T-cells (579 c/10^6) and memory T-cells (Tcm, Ttm and Tem, 2237, 2854, and 4687 c/10^6). SCT led to full chimerism in the PBMCs of both patients and diminished HIV DNA to undetectable levels (<1 c/10^6). Following the death of patients 5 and 11, 10-15 weeks after SCT, post-mortem analysis revealed that HIV DNA could be detected in ileum (274 and 22 c/10^6), liver (27 and 10 c/10^6), spleen (22 and 30 c/10^6) and lung (31 and 8 c/10^6), and additionally in patient 11 in bone marrow (19 c/10^6) and in CD4 cells from lymph node (40 c/10^6).
Conclusion: Within IciStem, we show that after long-term effective ART HIV DNA can readily be detected in various T-cell subsets. In the neutropenic phase post-SCT, HIV DNA could no longer be detected in PBMCs. In contrast, early after SCT, HIV DNA was still found in ileum, liver, spleen, lung, bone marrow and lymph node, indicating that tissue reservoirs may play an important role as long-standing viral reservoirs.

321 IMMUNE DYSREGULATION DICTATES SHIV REBOUND AFTER STEM-CELL TRANSPLANT IN MACAQUES

Christopher Peterson[1], Clarisse Benne[2], Patricia Polacino[3], Keith Jerome[1], Shiu-Lok Hu[4], Nichole Klatt[4], Stephen DeRosa[1], Rafick-Pierre Sekaly[2], Hans-Peter Kiem[1]
[1]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [2]Case Western Reserve Univ, Cleveland, OH, USA, [3]Washington Natl Primate Rsr Cntr, Seattle, WA, USA, [4]Univ of Washington, Seattle, WA, USA

Background: The conditioning regimen used as part of the Berlin patient's hematopoietic stem cell transplant (HSCT) likely contributed to his eradication of HIV infection. We studied the impact of conditioning (total body irradiation, TBI) in simian-human immunodeficiency virus (SHIV)-infected macaques suppressed by combination antiretroviral therapy (cART). The goal of this study was to identify the mechanism by which myeloablative conditioning impacts the latent viral reservoir.
Methods: Two cohorts of 5 pigtailed macaques were challenged with CCR5-tropic, HIV enveloped SHIV, and suppressed by three-drug cART following viral set point. In one cohort, autologous HSCT was performed following stable suppression of plasma viremia. Flow cytometry and ELISA were used to monitor changes in immune homeostasis between the two cohorts, and quantitative PCR and viral reservoir assays were used to identify virologic changes between transplanted and untransplanted control animals.
Results: The conditioning regimen resulted in a dramatic, but incomplete depletion of CD4+, CD8+ T-cells and B-cells, increased T-cell activation and exhaustion, and a significant loss of SHIV-specific antibodies in transplanted animals. The disrupted T-cell homeostasis and markers of microbial translocation positively correlated with increased viral rebound after cART interruption, which was observed in peripheral blood and in tissues. Quantitative viral outgrowth and Tat/Rev-induced limiting dilution assays showed that the size of the latent SHIV reservoir did not correlate with viral rebound.
Conclusion: These findings identify perturbations of the immune system as a mechanism for the failure of autologous transplantation to eradicate HIV, and highlight the importance of an intact immune system for viral control after cART withdrawal. Our data further demonstrate that the ability of myeloablative conditioning to decrease the size of the latent viral reservoir is limited. Our findings suggest several "next generation" HIV cure strategies that balance killing of virus-infected immune cells with retention of greater immune function. These may include immune modulators to prevent disrupted immune homeostasis, gene editing to protect transplanted cells, and/or additional gene therapy approaches to actively target latently infected cells during ongoing cART.

322 CONTROL OF PATHOGENIC SHIV INFECTION IN TRANSPLANTED MACAQUES

Christopher Peterson[1], Kevin G. Haworth[1], Bryan P. Burke[2], Patricia Polacino[3], Shiu-Lok Hu[4], Brandon Keele[5], Jeffrey S. Bartlett[2], Geoff P. Symonds[2], Hans-Peter Kiem[1]
[1]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [2]Calimmune, Inc., Pasadena, CA, USA, [3]Washington Natl Primate Rsr Cntr, Seattle, WA, USA, [4]Univ of Washington, Seattle, WA, USA, [5]NCI, Frederick, MD, USA

Background: Nearly 10 years have passed since the Berlin Patient achieved stable remission/functional cure of HIV infection, yet the relative contributions of the transplant procedure, the allogeneic "graft versus reservoir" effect, and infection-resistant donor cells, remain unclear. We have previously described a cohort of pigtailed macaques transplanted with gene-engineered hematopoietic stem and progenitor cells (HSPCs) expressing the enfuvirtide-like small peptide inhibitor of HIV/SIV fusion, mC46, which should

be resistant to infection with CCR5- and CXCR4-tropic virus. Here, we describe long-term control of plasma viremia in these animals following challenge with the HIV-enveloped simian/human immunodeficiency virus (SHIV) 89.6P.
Methods: Two animals were transplanted with autologous HSPCs that were transduced with a clinical grade lentiviral vector ("CaI-1"), which expresses the mC46 fusion inhibitor. Following infusion of gene-modified cells and extensive immune recovery, animals were challenged with SHIV 89.6P by the intravenous route. Flow cytometry and ELISA-based assays were used to monitor changes in relevant immune subsets, namely CD4+ T-cells. Quantitative PCR and sequencing of the 89.6P viral envelope were used to determine viral persistence in peripheral blood and tissues.
Results: Peripheral CD4+ T-cell counts have remained within normal range in both animals, over 2 years following infection with SHIV 89.6P. Intriguingly, plasma viral loads have incrementally decreased over the same time frame, with kinetics that are clearly distinct from previously described SHIV controllers. Anti-SHIV antibody and sequencing data suggest that viral replication persists in specific compartments, despite waning plasma viremia. We have applied tandem clonal tracking methodologies to identify persistent infected and protected clones in vivo.
Conclusion: Autologous transplantation with mC46-expressing HSPCs results in normalization of T-cell counts, prevents development of AIDS, and drives plasma viremia to nearly undetectable levels; this is especially remarkable in the context of infection with the highly pathogenic SHIV 89.6P. We find clear evidence of SHIV specific responses likely responsible for the long-term viral suppression. We are currently applying strategies that supplement mC46-dependent protection, with the goal of eradicating viral reservoirs and fully eliminating SHIV infection in these otherwise healthy animals.

323 HIV-1 DNA BLOOD RESERVOIRS ARE NOT ALTERED BY HIGH-DOSE CHEMOTHERAPY FOR LYMPHOMA

Heloise M Delagreverie[1], Antoine Chaillon[2], Laurence Gerard[1], Marie-Laure Néré[1], Romain Palich[3], Sylvain Chawki[1], Lionel Galicier[1], Eric Oksenhendler[1], Marie-Laure Chaix Baudier[1], Constance Delaugerre[1]
[1]Saint Louis Hosp, Paris, France, [2]Univ of California San Diego, San Diego, CA, USA, [3]Pitié-Salpêtrière Hosp, Paris, France
Background: High-dose chemotherapy (HDC) may have played a major role in the Berlin patient's cure from HIV by eradicating cellular reservoirs. We describe the impact of high-dose chemotherapy in HIV-related lymphoma patients treated with HDC for autologous stem cell transplantation (ASCT) on HIV-1 reservoir levels and dynamics and on the longitudinal evolution of reservoir diversity.
Methods: 6 retrospective HIV-1-related lymphoma patients with sustained viral control, treated with ASCT were included. Blood HIV-1 DNA total burden was measured by quantitative PCR targeting the viral LTR. The C2V3 viral region from 2 pre- and 2 post-ASCT longitudinal blood samples per patient (time frame 5-24 months) was amplified by nested PCR before deep-sequencing analysis. After quality filtering, haplotype reconstruction allowed the evaluation of molecular diversity (TN93) and compartmentalization between timepoints (Fst and Slatkin Maddison approaches) and the inferring of maximum likelihood (ML) phylogeny. T cell subsets were quantified by flow cytometry according to CD45RA and CCR7 expression.
Results: Mean HIV DNA quantification in PBMC over 2 years of follow-up was stable with no difference between pre- and post-ASCT periods (2.91 vs 2.65 log10 copies/10^6 cells, NS) and was measurable as early as 8 days post-ASCT. Deep sequencing of C2V3 cell-associated DNA yielded a median (IQR) depth of 4,955 (3,976-7,587) reads, further collapsed into 23 (10-31) haplotypes per sample. In 5 out of 6 (83%) participants, haplotype pools were not altered after ASCT and there was no evidence of compartmentalization of viral populations over time. Longitudinal viral diversity dropped transiently after high-dose chemotherapy/ASCT but rose back to pre-ASCT numbers (1.5-6% mean pairwise diversity estimates). Blood HIV reservoirs were thus restored to the original frequency of infected PBMC and viral haplotype variety. In addition, the median (range) fraction of memory T cells among CD4+ cells in the first 3 months post ASCT was 96.90% (89.33-98.73), suggesting early replenishment of the blood CD4+ pool from mature memory T cells after ASCT.
Conclusion: Deep sequencing of HIV-1 reservoir after ASCT for HIV-related lymphoma reveals fast viral reservoir reconstitution from memory CD4+ cells. These results point to the utmost importance of the management of infected mature memory T cells present in HIV+ autologous transplants, in the setting of present gene therapy trials in HIV-related lymphoma patients treated with ASCT.

324 THE IMPACT OF IMMUNOGLOBULIN IN PRIMARY HIV INFECTION ON THE HIV RESERVOIR

Juan Tiraboschi[1], Prabhjeet Phalora[2], Nicola Robinson[2], Emily Hopkins[2], Steve Kaye[3], Jeremy Sanderson[1], Sarah Fidler[3], Paul Klenerman[2], John Frater[2], **Julie Fox**[4]
[1]Guy´s and St Thomas´ NHS Fndn Trust, London, UK, [2]Univ of Oxford, Oxford, UK, [3]Imperial Coll London, London, UK, [4]King's Coll London, London, UK
Background: Antiretroviral therapy (ART) during primary HIV infection (PHI) restricts the HIV reservoir, but additional interventions will be necessary to induce a cure. Candidates include the passive infusion of neutralising antibodies. Intravenous immunoglobulin (IVIG) is not HIV-specific but is safe and has been reported to temporarily reduce the HIV reservoir in chronic HIV infection. We present a randomised controlled trial (RCT) to determine whether IVIG in PHI has a greater impact on the reservoir than reported for chronic infection. The aim was to investigate whether IVIG plus ART in PHI reduces the HIV reservoir and immune activation compared with ART alone.
Methods: Ten males with PHI (Fiebig II-IV) initiated ART (TNF/FTC/DRVr/RAL) at diagnosis and were randomised to ART alone or ART plus 5 days IVIG once virally suppressed (w19). Blood samples were evaluated for viral reservoir (total DNA, low copy VL, RNA transcripts), immune activation (HLA DR, CD38), immune exhaustion (PD-1, Tim-3. Lag-3) and microbial translocation (16s RNA). Flexible sigmoidoscopy was performed (n =10) at weeks 19, 24 and 48, and gut proviral DNA and cell numbers determined.
Results: From baseline to week 48, there was no difference in the decline in total DNA in the 2 groups (controls:-5045.9: cases -7513.1; p=0.49) or in plasma low copy RNA (p=0.77). However, there was a significant decrease in mean total blood HIV DNA from week 19 to 24 in the ART alone group (p=0.04) but no significant change in those receiving IVIG (-2583.7 vs 207.7 copies/million CD4 cells, respectively). In the gut, total HIV DNA declined from w19 to w48, with no significant differences between arms (10891- vs 8965 copies/million CD4 cells, respectively; p =0.67). No viral blips occurred during IVIG. Plasma levels of CRP, levels of immune activation (frequencies of CD4 and CD8 T cells expressing CD38 and HLA-DR), immune exhaustion (CD8 Tim3, Lag3, Pd-1), microbial translocation (16sRNA), and CD4:CD8 ratio were similar between arms for all comparisons.
Conclusion: Although safe, IVIG in PHI did not impact the viral reservoir, immune function or microbial translocation in peripheral blood or gut tissue at week 48. The transient halt in decline in blood HIV DNA between weeks 19 to 24 in those receiving IVIG is intriguing. The rapid recruitment and uptake of optional gut biopsies in all highlights the willingness of individuals with PHI to take part in HIV cure research.

325 RATES OF VIRAL DECAY IN HIV-1 CONTROLLERS INITIATING ANTIRETROVIRAL THERAPY

Jonathan Li[1], Heloise M. Delagreverie[2], Rachel Getz[1], Christina Lalama[3], Ronald Bosch[3], Daniel R. Kuritzkes[1], Alan Landay[4], Florencia Pereyra[1], Paul E. Sax[1], for the AIDS Clinical Trials Group A5308 Study Team
[1]Brigham and Women's Hosp, Harvard Med Sch, Boston, MA, USA, [2]Saint Louis Hosp, Paris, France, [3]Harvard Univ, Boston, MA, USA, [4]Rush Univ Med Cntr, Chicago, IL, USA
Background: Despite viremic control, many HIV controllers (HCs) have detectable viral replication and elevated systemic inflammation. Initiation of ART in HCs further decreases viral load, but the rate of viral decay has not been compared to non-controllers (NCs). Viral decay rates may provide additional insights on the composition and half-life of HIV-infected cellular reservoirs.
Methods: ACTG A5308 is a prospective, single-arm, open-label study of fixed dose RPV/FTC/TDF in treatment-naive HCs with viral loads (VLs) <500 cp/mL for ≥12 months. Plasma VLs were measured by the integrase single-copy assay (iSCA) at study entry and 0, 2, 7, 10, 14, 21, 28, 56 and 84 days after ART initiation. Soluble inflammatory markers (IL-6, IP-10, hs-CRP, sCD14, sCD163, D-Dimer) were measured by ELISA at entry and 0, 4 and 12 weeks after ART initiation. Participant-specific phase 1 viral decay rates were estimated with a censored-data linear mixed-effects model using iSCA data from day 0 to 11 of ART in those with entry iSCA ≥0.4 cp/mL. Phase 2 decay rates were estimated from day 8 to 59 of ART in those with sufficient iSCA ≥0.4 cp/mL. Exact Wilcoxon rank-sum test was performed to compare decay parameters for HCs with 41 NCs who initiated NNRTI-based regimens in previous studies.

Results: Of the 18 HCs with analyzable viral decay results, 14 (78%) had entry iSCA values ≥0.4 cp/mL and were included in estimation of phase 1 viral decay; 7 (39%) had sufficient detectable iSCA results for estimation of phase 2 viral decay. The median pre-ART VL by iSCA was 81 cp/mL for the HCs and 56,550 cp/mL for the NCs. There was a strong correlation between HIV RNA measurements by the iSCA and Abbott assays (Spearman r=0.90). Phase 1 viral decay did not differ between HCs and NCs (median 0.58 vs. 0.66 log10 cp/day, P=0.81). Phase 2 decay rates were significantly shorter in HCs compared to NCs (0.069 vs. 0.040 log10 cp/day, P=0.04), corresponding to a half-life of 10 vs. 17 days. Twelve weeks after ART initiation, 94% of HCs had iSCA VLs <0.4 cp/mL. No significant changes in soluble markers of inflammation were detected after 12 weeks of ART.
Conclusion: The viral decay results reveal the extremely low numbers of medium- and long-lived HIV-expressing cells in ART-treated HCs. Furthermore, the second phase decay rates suggest differences in the composition or turnover of the cellular populations supporting active viral replication between HCs and NCs. These findings highlight potential directions for future HIV reservoir studies.

326 PEGYLATED IFN-ALPHA-2B DECREASES LATENT HIV MEASURES IN ART-SUPPRESSED SUBJECTS

Livio Azzoni[1], Emmanouil Papasavvas[1], Nicolas Chomont[2], Qingsheng Li[3], Bonnie J. Howell[4], Douglas D. Richman[5], Pablo Tebas[6], Karam Mounzer[7], Jay Kostman[8], Luis Montaner[1]
[1]Wistar Inst, Philadelphia, PA, USA, [2]Univ de Montréal, Montreal, QC, Canada, [3]Univ of Nebraska, Lincoln, NE, USA, [4]Merck & Co, Inc, West Point, PA, USA, [5]Univ of California San Diego, La Jolla, CA, USA, [6]Univ of Pennsylvania, Philadelphia, PA, USA, [7]Philadelphia FIGHT, Philadelphia, PA, USA, [8]Philadelphia FIGHT Community Hlth Cntrs, Philadelphia, PA, USA
Background: Pegylated interferon (Peg-IFN)-α2a resulted in viral suppression and reduction in integrated proviral HIV DNA in 9 of 20 ART-suppressed subjects undergoing analytical ART interruption (ATI; NCT00594880). Here we evaluated if Peg-IFN-α2b, in the presence of HIV reactivation (ATI), would be safe, maintain viral suppression during ATI and decrease latent viral reservoir in chronic HIV infection.
Methods: 20 individuals with well controlled HIV infection (on ART, VL <50 copies/ml) received weekly 1 µg/kg Peg-IFN-α2b sc for 20 weeks, with a 4 week ATI (weeks 5-9 of IFN treatment). In addition to safety monitoring, HIV measures (see Table 1) were assessed at baseline and week 20. Final statistical analysis: we used Wilcoxon Signed rank test to test differences between time points; exact Fisher tests to compare frequency of viral suppression during ATI; Spearman tests, mixed effect models and hierarchical clustering to test relationships between HIV reservoir measurements.
Results: At completion study participants were 20% females, 70% AA. Median age was 47. 18 subjects completed treatment (2 early terminations) with 7 serious events (neutropenia). Peg-IFN-α2b suppressed plasma HIV RNA during the 4 week ATI in 52% (95% CI= 32-73%), similar to NCT00594880 and higher than historical controls (13%; 95% CI= 3-36%, p= 0.0127; NCT00051818) At week 20, we observed a significant reduction in HIV RNA-expressing GALT cells (p= 0.012) and a reduction in integrated HIV DNA in circulating CD4s (p= 0.0797). Other markers did not change significantly. However, higher baseline levels of rectal mucosa RNA, integrated DNA, TILDA, p24 and 2LTR were associated with a greater decrease after the intervention. Reservoir measurements were weakly correlated at baseline and their changes over time did not correlate to one another. Amount of HIV rebound during the 4-week ATI was not associated with a change in reservoir measures.
Conclusion: Treatment with Peg-IFN-α2b (20 weeks, 4-week ATI) 1) is safe and well tolerated, 2) maintains viral suppression during a 4-week ATI in half of the subjects and 3) is associated with significant decrease of rectal mucosa HIV RNA and a decrease trend in integrated HIV DNA (PBMC) Randomized studies incorporating an ART-only arm, repeated sampling and multiple latent reservoir assessments, such as our ongoing NCT02227277, should allow to conclusively interpret the reduction in HIV reservoir measures observed in subjects with high baselines and confirm our pilot study observations.

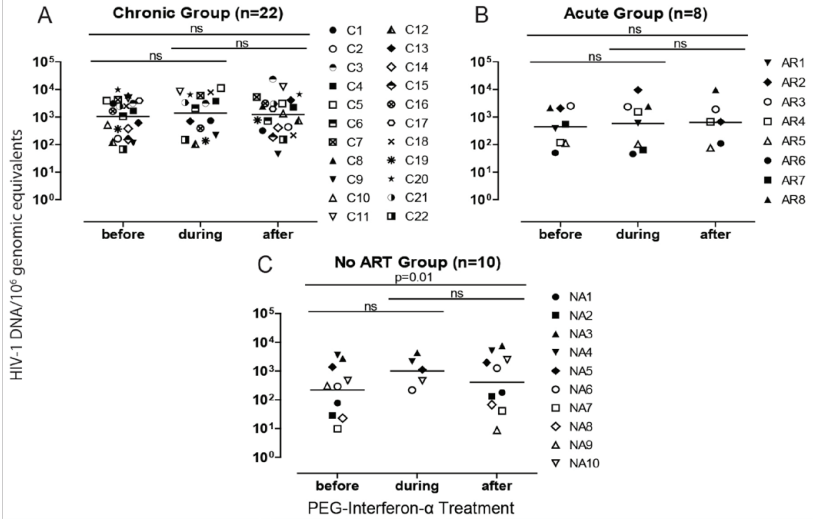
Target	*Source*	*Method*	*Baseline (median; IQR)*	*20 weeks (Median; IQR)*	*p*
Integrated proviral DNA	Whole blood-derived PBMC	Alu-Gag PCR	109.5 (58.5; 286)	98 (62; 377)	0.0797
In vitro latency reactivation	Aphaeresis-derived PBMC	Tat/rev Induced Limiting Dilution Assay (TILDA)	8.00 (4; 27.5)	6.00 (4; 22.5)	n.s.
		HIV p24 SIMOA/Quanterix	55.5 (7.5; 124.3)	14.4 (5.0; 60.2)	n.s.
Pre-integration complexes	Colorectal mucosa biopsies-derived cells	2-LTR ddPCR	1.4 (1.4; 61)	1.4 (1.4; 1.4)	n.s.
Total HIV DNA		HIV Pol ddPCR	959 (39; 2776)	994 (326; 1946)	n.s.
Total HIV RNA	Fixed colorectal mucosa biopsy slides	*In situ* hybridization (90% genome)	2.4 (0.7; 12.4)	0.8 (0.7; 3.2)	0.012

327 EFFECTS OF PEG-IFNA ON THE HIV-1 DNA LEVELS IN HIV-1/HCV COINFECTED INDIVIDUALS

Victoria P. Strouvelle, Valentina Vongrad, Dominique L. Braun, Yik Lim Kok, Roger Kouyos, Karin Metzner, Huldrych F. Günthard, for the Swiss HIV Cohort Study
Univ of Zürich, Zürich, Switzerland
Background: Studies exploring effects of PEG-IFNα (pIFNα) on total HIV-1 DNA levels in HIV-suppressed patients have varied; therefore in a retrospective longitudinal study we assessed the effects of pIFNα on HIV-1 DNA levels in PBMC from Swiss HIV Cohort Study patients.
Methods: Patients inclusion criteria were: 1. HIV-1/HCV co-infected, 2. on ART, 3. virally suppressed (< 50 HIV-1 RNA copies/ml of plasma) for ≥6 months, and 4. treated with pIFNα for ≥24 weeks. Samples were collected before, during, and post pIFN treatment (all follow-up time points available). Patients were categorised into three groups: Chronic HIV infection (n=22), Acute HIV infection (n=8), and a control group of no ART during pIFNα treatment (n=10). Patients with >1 pIFNα treatment were also included in the chronic group (n=4). HIV-1 DNA from HIV-1/HCV co-infected patients was quantified by an in-house qPCR assay measuring the U3-R region of the HIV-1 LTR. Clinical data were assessed for the effects of IFNα on the HIV-1 viral load (VL), lymphocyte and CD4 cell populations. Wilcoxon matched-pairs signed rank test was applied to all data sets to investigate significance.
Results: A total of 247 samples were quantified for HIV-1 DNA with a mean number of time points (range) of 6.6 (2-12) in chronic, 5.6 (2-10) in acute and 5.7 (3-9) in the no ART groups. Maximum follow-up time was 112 months post-pIFNα. Patients were all Caucasian, mainly male (90%) with a mean age of 42 yrs. (27-55) and infected with HIV-1 subtype B (92.5%). pIFNα treatment caused general and CD4-lymphopenia in all patients as previously described. All ART treated patients maintained an undetectable VL. In non-ART-treated patients, pIFNα treatment decreased the HIV viral load by 0.89 log on average. Pre-IFNα HIV-1 DNA levels were on average 0.66 log higher in the chronic vs. the acute group. Total HIV-1 DNA levels remained stable before, during, and after pIFNα treatment with no clear trend found to suggest an effect of pIFNα on HIV-1 DNA levels in PBMCs (Figure 1). Repeated IFNα administration did not have an additional effect on HIV-1 DNA levels in the four patients studied.

Conclusion: In contrast to other studies, our large longitudinal study in a well characterized patient group did not reveal any effect of pIFNα on the latent reservoir as measured by a HIV-1 DNA qPCR assay in PBMCs. Notably, repeated pIFNα treatment did not affect HIV-1 DNA levels. Cumulatively, no discernible effect of pIFNa on HIV-1 DNA in HIV-1/HCV co-infected individuals was detected.

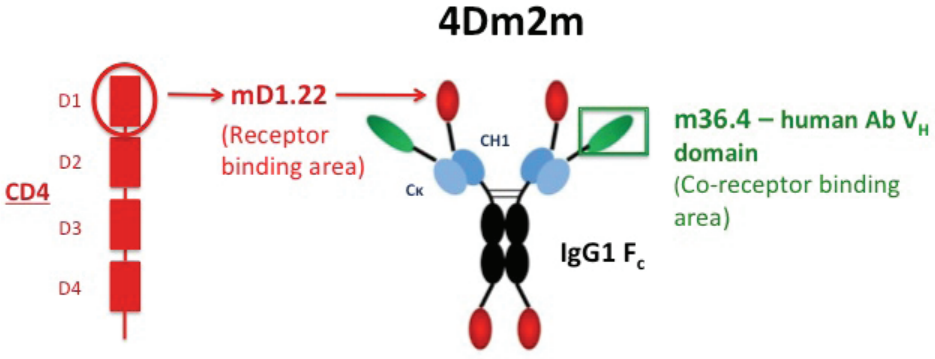
Figure 1: Mean HIV-1 DNA levels in HIV-1/HCV coinfected individuals before, during, and after PEG-IFNα



328 IN VIVO CONTROL OF HIV INFECTION BY AN ENGINEERED BI-SPECIFIC ANTI-HIV FUSION PROTEIN

Ariola Bardhi[1], Weizao Chen[2], Yanping Wang[2], Jennifer Jones[3], John C. Kappes[3], Christina Ochsenbauer[3], Dimiter S. Dimitrov[2], Harris Goldstein[1]
[1]Albert Einstein Coll of Med, Bronx, NY, USA, [2]NIH, Frederick, MD, USA, [3]Univ of Alabama at Birmingham, Birmingham, AL, USA

Background: No single natural broadly neutralizing antibody (bNAb) neutralizes all clinical isolates, enabling the recurrence of viremia by immune escape mutants thereby limiting the therapeutic efficacy of passive bNAb treatment. In addition, the avidity and potency of natural bNAb are reduced by their monospecific recognition of Env, limiting their capacity to bivalently bind to the widely dispersed Env molecules in the HIV membrane. We circumvented these limitations by engineering a multivalent bi-specific anti-HIV fusion protein, LSEVh-LS, which utilizes a human IgG1 Fc scaffold linking 4 gp120-specific CD4 domains (mD1.22) and 2 human antibody VH domains (m36.4) specific for the highly conserved, CD4-inducible HIV-1 co-receptor binding region (Figure). We also enhanced LSEVh-LS antibody dependent cellular cytotoxicity (ADCC) activity by increasing its FcγR IIIa binding affinity by rendering its Fc domain fucose-free.
Methods: LSEVh-LS neutralizing breadth was determined by in vitro infection inhibition assays using human PBMC and HIV isolates resistant to other bNAb, VRC01 and 3BNC117. LSEVh-LS in vivo neutralizing and ADCC activity was examined by infecting humanized mice constructed by intrasplenically injecting activated human PBMC into NOD-SCID-IL2rγ-/- mice (hu-spl-PBMC-NSG mice) with VRC01-sensitive and resistant isolates expressing a luciferase reporter gene.
Results: LSEVh-LS equivalently neutralized in vitro infection by 3 VRC01-sensitive, 3 VRC01-resistant and 1 VRC01/3BNC117-resistant HIV strains at lower concentrations than VRC01. Thus, LSEVh-LS has more potent and broader inhibitory activity than VRC01. These results were extended by in vivo studies in hu-spl-PBMC-NSG mice demonstrating potent in vivo reduction (>90%) of infection by an HIV expressing a VRC01-resistant Env. We investigated in vivo ADCC activity by measuring the elimination of HIV infected cells in hu-spl-PBMC-NSG mice. One day after LSEVh-LS treatment of hu-spl-PBMC-NSG mice with established in vivo infection, infection was reduced 90%, compared to a ~40% reduction of HIV infection by VRC01 treatment. LSEVh-LS treatment did not reduce HIV-infection in NSG mice intrasplenically injected with NK cell-depleted PBMC, indicating that its in vivo ADCC activity was NK cell-mediated.
Conclusion: LSEVh-LS, an engineered bi-specific multivalent antibody with more potent and broader neutralizing and ADCC activity than natural bNAb, may represent a more effective therapeutic strategy.



Modified from Chen et al., J. Virol., 2014

329 PGT121 ANTIBODY ENGINEERING: ENHANCED INFECTED CELL KILLING AND DRUG-LIKE PROPERTIES

Mini Balakrishnan, **Nathan D. Thomsen**, Craig S. Pace, Xue Zhang, Magdeleine Hung, Mark R. Nagel, Brian A. Carr, Y. E. Hu, Helen Yu, John A. Corbin
Gilead Scis, Inc, Foster City, CA, USA

Background: A therapeutic agent that mediates the selective destruction of cells harboring latent HIV may sustainably suppress viremia in the absence of antiretroviral therapy and offers the potential for a sterilizing cure. Anti-HIV-1 envelope (Env) antibodies from elite neutralizers can neutralize a high percentage of viral strains across clades. Some of these broadly neutralizing antibodies (bNAbs) can recognize Env expressed on the surface of infected cells and mediate killing via effector function.
Methods: A set of patient-derived bNAbs targeting different Env epitopes were tested for natural killer (NK) cell mediated killing of HIV-infected CD4+ T cells to identify a bNAb for further optimization. Enhancement of effector function was achieved through glycoengineering of the fragment crystallizable (Fc). Fragment antigen-binding (Fab) variants were generated via genetic engineering and screened using a panel of biochemical and functional assays for improvements in drug-like properties.
Results: PGT121 was selected as the lead bNAb for engineering on the basis of killing activity and previously demonstrated efficacy in SHIV infected monkeys (Barouch et al. Nature 2013). Fc glycoengineering increased binding affinity to Fc gamma receptor 3A ~10-fold and similarly enhanced NK cell-mediated antibody dependent cellular cytotoxicity of HIV-infected CD4+ T cells (mean EC50 = 0.82 µg/mL, mean Emax = 40%) compared to PGT121 (mean EC50 = 3.8 µg/mL, mean Emax = 10%). Genetic engineering eliminated several liabilities within the variable region of PGT121 Fab. Removal of T-cell epitopes reduced ex vivo T-cell activation rate from 32% to 12% of donors, indicating a reduction in the potential for clinical immunogenicity. Removal of three glycosylation motifs improved manufacturability by eliminating the need to monitor and control Fab glycosylation. Fab engineering did not impair Env recognition as assessed by neutralization activity (median IC50 = 0.0106 µg/ml, 67% breadth) compared to PGT121 (IC50 = 0.0163 µg/ml, 66% breadth) against a panel of 142 clade B clinical isolates.
Conclusion: Engineering of PGT121 enhanced its ability to kill HIV-infected cells and yielded a Fab variant with superior drug-like properties, while maintaining the breath of HIV Env recognition. Further validation is required to determine if this approach will be generally applicable to optimizing bNAbs for the selective elimination of cells harboring latent HIV reservoir.

330LB VRC01 INFUSION HAS NO EFFECT ON HIV-1 PERSISTANCE IN ART-SUPPRESSED CHRONIC INFECTION

Sharon Riddler[1], Christine Durand[2], Lu Zheng[3], Justin Ritz[3], Richard A. Koup[4], Julie Ledgerwood[4], Bernard Macatangay[1], Joshua C. Cyktor[1], John W. Mellors[1], for the ACTG A5342 Protocol Team
[1]Univ of Pittsburgh, Pittsburgh, PA, USA, [2]Johns Hopkins Univ, Baltimore, MD, USA, [3]Harvard Univ, Boston, MA, USA, [4]NIAID, Bethesda, MD, USA

Background: ART blocks infection of new cells but has no impact on cells already infected with latent or active proviruses. Broadly neutralizing monoclonal antibodies (bnMAb) may promote clearance of viremia and virus-expressing cells through antibody-dependent mechanisms. We evaluated whether the CD4-binding site bnMAb VRC01 affects HIV persistence in chronically-infected individuals on ART.
Methods: A5342 was a phase 1, randomized, double-blind, placebo-controlled, parallel arm study. Participants with ART-suppressed viremia (<40 copies/ml) were randomized to Arm A: 2 infusions of VRC01 (40 mg/kg) at entry and week 3 and 2 infusions of placebo (saline) at weeks 6 and 9; or Arm B: 2 infusions of placebo at entry and week 3 and 2 infusions of VRC01 at weeks 6 and 9. Primary outcomes were safety and change in cell-associated HIV RNA/DNA ratio (CAR/CAD) from baseline (BL) to week 6. Plasma viremia (single copy HIV RNA assay [SCA]) and PMA/ionomycin-stimulated virus production (HIV RNA copies/ml) from CD4+T-cells were also assessed. Changes from pre- to post-VRC01 (Arm A: entry to week 6; Arm B: week 6 to week 12) time points across both arms were evaluated.
Results: 40 participants were randomized; 20 per arm. Median age was 52 y; median CD4+ T-cell count was 696 /mm3. No treatment-related adverse events ≥grade 3 were reported during study follow up. No significant difference between VRC01 and placebo was observed for change in CAR/CAD ratio from BL to week 6 (median fold change: 1.12 vs. 0.83, p=0.16, 95% CI (0.75, 2.42)), or from pre-to post-VRC01 time points with both arms combined (1.24, 95% CI (0.83, 1.69), p=0.29; Table). At entry, 22/40 (55%) participants had SCA ≥1 copy/ml. At week 6, there was no difference in the proportion with SCA ≥1 copy/ml between the arms (42% vs. 37%, p=1.0). There were also no significant differences between arms from BL to week 6, or from pre- to post-VRC01 time points with both arms combined in PMA/ionomycin stimulated virus production (all p>0.05).
Conclusion: In individuals with chronic ART-suppressed HIV infection, VRC01 infusions were safe and well tolerated but did not affect plasma viremia, cellular HIV RNA/DNA levels, or stimulated virus production from CD4+T-cells. Potential mechanisms being evaluated to explain the lack of response include viral resistance to VRC01, poor penetration of VRC01 to sites of virus expression, or inherent inability of VRC01 to clear virus particles or virus-expressing cells.

Virologic Parameter Median (Q1, Q3)	Arm A	Arm B	p-value*	Arms A and B Combined		Change from Pre- to Post-VRC01	p-value**
	Change from baseline to Week 6			Pre-VRC01 values	Post-VRC01 values		
Cell-associated HIV RNA/DNA ratio^	1.12 (0.92, 2.15)	0.83 (0.57, 2.37)	0.16	0.04 (0.02 0.08)	0.05 (0.02, 0.08)	1.24 (0.61, 2.15)	0.29
Cell-associated HIV RNA (log_{10} copies/10^6 CD4 cells)	0.08 (-0.23, 0.32)	-0.08 (-0.26, 0.29)	0.39	1.55 (0.99, 1.99)	1.48 (0.99, 2.10)	0.09 (-0.23, 0.32)	0.64
Cell-associated HIV DNA (log_{10} copies/10^6 CD4 cells)	-0.06 (-0.13, 0.06)	-0.01 (-0.08, 0.13)	0.30	2.93 (2.43, 3.15)	2.92 (2.51, 3.11)	-0.05 (-0.12, 0.06)	0.19
Stimulated Virus Production from total CD4+T-cells (log_{10} copies/ml)	-0.13 (-0.51, 0.92)	0.12 (-0.52, 0.30)	0.91	2.99 (2.06, 3.37)	2.66 (2.28, 3.41)	-0.10 (-0.51, 0.44)	0.85
	Week 6		p-value***				p-value****
Plasma HIV RNA ≥1 copy/ml by single copy assay (%)	8/19 (42%)	7/19 (37%)	1.0	16/38 (42%)	14/38 (37%)		0.59

^Changes in RNA/DNA ratios are shown as fold change calculated by dividing the RNA/DNA ratio at the later time point by the earlier time point;
* Wilcoxon Rank Sum test ** Wilcoxon Signed Rank test *** Fisher's exact test **** McNemar's test

331 ENHANCEMENT OF THE CD4 CHIMERIC ANTIGEN RECEPTOR AGAINST HIV INFECTION

Anjie Zhen, **Mayra A. Carrillo**, Valerie Rezek, Scott G. Kitchen
Univ of California Los Angeles, Los Angeles, CA, USA

Background: Cell-based gene therapy has quickly become the new frontier for treatment of HIV infection. Clinical trials have shown CD4 chimeric antigen receptor (CD4CAR) modified T cells to be moderately effective against HIV and safe when introduced through adoptive T cell transfer. This CAR expresses CD4 attached to an intracellular CD3 zeta-domain. When bound to the HIV envelope glycoprotein 120 (gp120), CD4 CAR expressing CD8 cells elicit an immune response against infected cells. Despite its success in vitro, T cells modified with the CD4 CAR showed limited efficacy against HIV infection in clinical trials. Studies suggest that CD4 CAR modified CD8 cells may have lost their efficiency due to their susceptibility to HIV infection via CD4 expression, excessive ex vivo activation and cell processing, and immune exhaustion/premorbidity. Thus, we aim to overcome

these limitations to improve CD4CAR T cell therapy. We hypothesize that preventing exhaustion and infection in CAR expressing T cells will enhance antiviral response and efficacy against HIV infection in vivo.
Methods: To address these problems and attempt to improve CAR-driven T cell responses and prevent cellular infection, we constructed a truncated CD4 CAR molecule that contains solely the D1 and D2 domains of the CD4 molecule. In addition, we incorporated a PD-1 specific shRNA into the vector to knock down check-point inhibitor PD-1 expression on CAR modified cells to attempt to enhance their function. Humanized mice were constructed and infected with HIV and received autologous T cell transplants of modified CD4 and CD8 cells with either a control non-specific shRNA containing D1D2CD4CAR lentiviral vector or a PD1shRNA containing D1D2CD4CAR lentiviral vector.
Results: We found that the D1D2CD4CAR maintains the HIV Env binding site but does not allow HIV infection when introduced into CD8 T cells. The PD-1 shRNA effectively knocked down PD-1 expression on modified T cells both in vitro and in vivo. Further, we found that the PD-1shRNA containing D1D2CD4CAR cells have improved function and proliferation. Mice that received PD1shRNA D1D2CD4CAR cells showed improved viral control as compared to mice that received control CAR modified T cells.
Conclusion: Specific knockdown of PD-1 expression on CAR modified T cells can enhance anti-HIV efficacy and highlights the potential of targeting immune check point inhibitors to enhance T cell gene therapy.

332 HEMATOPOIETIC STEM-CELL–BASED CHIMERIC ANTIGEN RECEPTOR THERAPY FOR HIV INFECTION

Anjie Zhen[1], Christopher Peterson[2], Mayra A. Carrillo[1], Valerie Rezek[1], Masakazu Kamata[1], Jerome Zack[1], Hans-Peter Kiem[2], Scott G. Kitchen[1]
[1]Univ of California Los Angeles, Los Angeles, CA, USA, [2]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA
Background: HIV-1 specific cytotoxic T lymphocytes are key immune response to HIV and are crucial for the elimination of HIV infected cells. Previous studies showed that a chimeric antigen receptor containing the CD4 molecule linked to the signaling domain of the T cell receptor ζ chain (CD4CAR) can be used to redirect peripheral T cells to target HIV infected cells. CD4 CAR modified T cells can kill HIV infected cells in vitro, but showed limited efficacy in clinical trials. Hematopoietic Stem Cells (HSCs) based gene therapy has several advantages over T cell adoptive therapy as it provides long-term engraftment; and, modified stem cells undergo normal T cell differentiation and selection. Our previous studies using humanized mice demonstrated that HSCs modified with a protective CD4 CAR resulted in successful differentiation of CD4CAR expressing T cells and significant suppression of HIV replication, suggesting feasibility of redirecting immunity with a HSCs based approach.
Methods: We tested the safety and feasibility of engineering T cell immunity via HSCs in a non-human primate (NHP) model of SHIV infection. We utilized CD4 CAR vectors that also carry an anti-HIV protective gene (C46) that would inhibit infection. 2 pigtailed macaques (Macaca nemestrina) were transplanted with C46CD4CAR modified autologous HSCs and 2 were transplanted with control vector C46CD4CARdeltaZeta that lacks the signaling Zeta chain. After hematopoietic recovery, the animals were challenged with SHIV and monitored for viral load and CAR cell detection for over a year.
Results: We determined that engraftment of pigtailed macaques with C46CD4CAR-modified HSCs is safe and the animals have normal transplant recovery. We observed long-term engraftment and stable production of C46CD4CAR expressing cells without any significant toxicities and found that C46CD4CAR modified HSCs could differentiate into multiple hematopoietic lineages, including T cells, NK cells, granulocytes, and B cells. Following challenge of the animals with SHIV, we observed significant expansion of C46CD4CAR expressing cells after infection and found that C46CD4CAR expressing cells were capable of killing infected cells.
Conclusion: This demonstrates the safety and feasibility of a HSCs based therapy utilizing an HIV-specific chimeric antigen receptor for chronic HIV infection in NHPs. These results set the stage for future investigational development in an attempt to eradicate HIV infection and provide more effective immune surveillance of HIV.

333 LENTIVIRAL DENDRITIC CELL VACCINE RAISES PROTECTIVE CTLS AND TARGETS LATENT HIV

Thomas D. Norton[1], Anjie Zhen[2], Takuya Tada[1], Scott G. Kitchen[2], Nathaniel R. Landau[1]
[1]New York Univ, New York, NY, USA, [2]Univ of California Los Angeles, Los Angeles, CA, USA
Background: Dendritic cells (DCs) orchestrate immune responses to viral pathogens and have been used in vaccine strategies against several diseases. To further develop this approach we have established lentiviral vectors (LVs) that package the lentiviral accessory protein Vpx. Vpx increases DC transduction by two-logs allowing for long-term antigen expression, a significant improvement over peptide-pulsing. To test this approach, we generated vectors that expressed the lymphocytic choriomeningitis virus (LCMV) GP33 epitope or the major HLA-A2-restricted HIV Gag epitope SL9. The vectors co-expressed CD40L, increasing their ability to stimulate antigen-specific T cells. Cytokines released by transduced DCs reactivated latent HIV-1 provirus in latency models, supporting their use as a two-pronged approach for activating and targeting the latent reservoir in HIV+ patients. We have now tested the lentiviral DC vaccine strategy in HIV-infected humanized mouse and LCMV mouse models.
Methods: Bone marrow, liver, thymus humanized mice expressing transduced SL9-specific T cell receptor (TCR) CD8 T cells were injected with CD40L-SL9 expressing LV-transduced antigen presenting cells and then challenged with HIV-1. Expansion of SL9 TCR+ cells was quantified by flow cytometry and peripheral viral loads were quantified by RT-PCR. Wild-type mice were injected with CD40L-GP33 LV-transduced bone marrow-derived from SAMHD1-/- mice and challenged with LCMV. CD8 T cells expressing GP33-specific TCRs cells were quantified by flow cytometry and viral loads were quantified by plaque assay. Survival was monitored following lethal challenge with LCMV.
Results: In mice injected with transduced DCs, the number of SL9 TCR+ and GP33 TCR+ CD8 T cells expanded 30-fold and 10-fold, respectively. Mice injected with SL9 expressing LV-transduced DCs and then infected with HIV-1 dramatically suppressed virus loads 2-6 weeks post-infection. Mice injected with GP33 expressing LV-transduced DCs were protected against LCMV challenge. No infectious virus was detected in 4/5 immunized mice and the survival rate was close to 100%, while in mice injected with control LV-transduced DCs, virus loads reached > 2 X 10E6 PFU/mL and resulted in death.
Conclusion: This DC vaccine approach induces antigen-specific CTLs that protect against LCMV and HIV infection. This is a promising approach to restore CTLs and reduce the latent reservoir in chronically infected individuals.

334 SELF-ACTIVATING VECTORS THAT EXPRESS VIF-RESISTANT APOBEC3G FOR HIV-1 GENE THERAPY

Krista Delviks-Frankenberry[1], Daniel Ackerman[1], Nina Timberlake[2], Maria Hamscher[1], Olga A Nikolaitchik[1], Wei-Shau Hu[1], Bruce E. Torbett[2], Vinay K. Pathak[1]
[1]NCI, Frederick, MD, USA, [2]The Scripps Rsr Inst, La Jolla, CA, USA
Background: Strategies to suppress HIV-1 replication in the absence of antiviral therapy are needed to achieve a functional cure. APOBEC3G (A3G) and APOBEC3F (A3F) are host restriction factors that inhibit HIV-1 replication by inducing lethal hypermutation and inhibiting reverse transcription and integration. However, HIV-1 encodes the protein Vif, which induces A3G/A3F degradation, allowing viral replication to proceed. Here we developed novel self-activating lentiviral vectors to express Vif-resistant A3G/A3F mutants that inhibit HIV-1 replication and evaluated their potential to control HIV-1 replication in T cell lines.
Methods: Standard lentiviral vectors cannot be used for delivery of A3G/A3F because their expression in the virus producing cells inactivates the therapeutic virus. We designed novel self-activating lentiviral vectors that maintain an inactive Vif-resistant A3G(D128K) in virus producing cells using directly repeated nucleotide sequences. Upon infection, direct repeats are removed during reverse transcription to express functional A3G(D128K) in the target cells. HIV-1 replication kinetics were evaluated in infected T cell lines expressing A3G(D128K) and tested for the emergence of resistant virus.
Results: Self-activating vectors allowed for successful virus production and delivery of A3G(D128K) to target cells; direct repeat deletion was >99% efficient. CD4+ T cell lines CEM and PM1 expressing A3G(D128K) successfully restricted NL4-3 infection. Subtype C and intersubtype recombinant subtype AE also failed to replicate in A3G(D128K) expressing cells; however, SIV and HIV-2 whose Vif can neutralize A3G(D128K) were able to replicate. No A3G(D128K)-resistant NL4-3 virus emerged in CEM/A3G(D128K) cells in culture after passaging for 3.5 months. Analysis of proviral DNA showed typical G-to-A hypermutation patterns in the A3G context, consistent with inhibition by A3G(D128K) expression. Infectious titers of $>10^8$/ml allowed for efficient delivery of A3G(D128K) to CD34+ hematopoietic stem cells without cytotoxicity.

Conclusion: We have developed novel lentiviral vectors that express Vif-resistant A3G(D128K), which potently inhibited HIV-1 replication in cell culture. Our results suggest that it may be very difficult for HIV-1 to develop resistance to A3G(D128K) while retaining activity against endogenous wild-type A3 proteins. A3G(D128K) gene therapy could provide a novel strategy for treatment and functional cure of HIV-1 infection

335 ENGINEERING HIV-RESISTANT ANTI-HIV CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS

Malika Hale[1], Taylor Mesojednik[1], Guillermo Romano Ibarra[1], Jaya Sahni[1], Bryan Sands[1], Karen Sommer[1], Andrew M. Scharenberg[2], David J. Rawlings[2], Thor Wagner[2]
[1]Seattle Children's Rsr Inst, Seattle, WA, USA, [2]Univ of Washington, Seattle, WA, USA

Background: Advances in both gene editing and chimeric antigen receptor (CAR) technology have created new therapeutic possibilities for a variety of diseases. Broadly neutralizing monoclonal antibodies (bNAb) with specificity for different epitopes on the HIV envelope provide an opportunity to create multiple different CARs that target HIV-expressing cells. In combination with genetic disruption of CCR5 it may be possible to engineer long-lived immunity targeting the HIV reservoir.
Methods: CAR were designed to target four well-defined neutralization epitopes on HIV Env: the V1/V2 epitope associated with the N160 glycan, the CD4 binding site epitope, the high-mannose-patch on V3 associated with the N332 glycan, and the membrane-proximal external region on gp41; based on bNAbs PGT145, VRC07-523, PGT128, and 10E8, respectively. Single chain variable fragments (scFv) were synthesized and cloned into a 4-1BB containing CAR construct. Primary human T cells were engineered to express the anti-HIV CARs, and tested for cell activation (cell surface expression of CD137) and specific killing of HIV-infected cells (ACH-2) in the presence of ART. CCR5-disrupted CAR T cells were generated with a CCR5-specific megaTAL nuclease to induce non-homologous end-joining recombination (NHEJ) in CCR5 or via homology-directed recombination (HDR), in which the CAR construct with flanking regions homologous to CCR5 was inserted into the CCR5 locus. CCR5-disrupted CAR T cells were tested in viral culture with a R5 virus (JR-CSF) compared to CAR T cells without CCR5 disruption.
Results: Primary T cells expressing the CAR constructs were activated in the presence of HIV-infected cells, but not in the presence of HIV-uninfected cells, and specifically killed HIV-infected cells versus uninfected cells. Results with cells from three donors were statistically significant compared to cells that expressed an anti-CD19 CAR. All anti-HIV CAR T cells suppressed viral replication in culture, but after several days of viral culture CCR5-disrupted CAR T cells statistically improved viral suppression compared to CAR T cells without CCR5-disruption.
Conclusion: This work demonstrates that HIV immunotherapy utilizing potent bNAb-based scFv fused to second-generation CAR signaling domains, in combination with CCR5-disruption, is feasible and effective in vitro. This strategy has the potential to induce long-term killing of HIV-infected cells in HIV-infected individuals, which might help in the effort to cure HIV.

336 VIRAL OUTCOMES AFTER ANALYTIC TREATMENT INTERRUPTIONS TO EVALUATE A FUNCTIONAL CURE

Lorna Leal[1], Constanza Lucero[1], Montserrat Plana[1], Nuria Climent[1], Esteban Martinez[1], Pedro Castro[1], Beatriz Mothe[2], Juan Carlos López-Bernaldo[3], Jose M. Gatell[1], Felipe Garcia[1]
[1]IDIBAPS, Barcelona, Spain, [2]IrsiCaixa Inst for AIDS Rsr, Badalona, Spain, [3]Hosp Gregorio Marañón, Madrid, Spain

Background: Allowing participants to interrupt their antiretroviral treatment is still crucial to assess the efficacy of any investigational cure strategy in controlling HIV replication, but different virologic outcome vary in different analytic treatment interruptions (ATI) trials hindering the comparison between studies. Monitored Antiretroviral Pause (MAP) and restarting antiretroviral treatment (ART) at the moment of viral rebound have been proposed as safer strategies to evaluate the efficacy of interventions aimed to reduce the HIV reservoir.
Methods: Here we compiled retrospective data from 9 ATI studies in chronic HIV-positive cART-suppressed individuals (n=355) and compared virologic outcomes used. The following outcomes were compared: time to viral rebound, viral load (VL) set point (defined as the mean VL between weeks 8 and 12, if the difference was < 0.5 log10) and VL at a predefined time following ATI (w1, w2, w3, w4, w5, w6, w8, w10, w12, w24 and w48) (in both cases absolute value and Δ with pre-ART), time to reach set point, time to reach a certain threshold, peak, time to peak and area under the curve (AUC). We also performed a sensitivity analysis in which those who discontinued the ATI before week 12 were assigned a set point VL equal to their last known VL.
Results: Time to viral rebound was strongly and inversely correlated with VL set-point (absolute and Δ, and in sensitive analysis), VL at all time points after ATI, VL peak and AUC ($p<0.0001$ for all comparisons). Only 3.5% of individuals in whom VL rebounded after ATI presented a sustained VL drop to <1,000 copies/ml thereafter (3 cases to undetectable level, all with peak viremia <10,000 copies/ml). VL remained undetectable at set-point, w24 and w48 after ATI in a 3.3%, 1.9% and 0% of subjects. A significant correlation was observed between pre-ART VL and ATI VL set point, w24, w48 and peak viremia ($p<0.0001$). ATI VL remained significantly lower than pre-ART VL in all time-points [mean (SD) Δ set-point was -0.36 (0.88), $p<0.001$], except at peak viremia. 10% and 25% of patients had a Δ set-point > 1log and > 0.5 log, respectively.
Conclusion: No individual presenting a viremia above 10,000 copies/ml during ATI was able to control VL thereafter. Time to VL rebound correlates with most of virologic outcomes used in previous ATI studies, supporting its use as a valid virologic outcome in shorter, monitored antiretroviral pause for HIV cure studies.

337 A BISPECIFIC APPROACH FOR TARGETING IMRS IN HIV-1 LATENCY

Debbie S. Ruelas[1], Yanyan Zheng[1], Fahimeh Raoufi[1], Laurence Fayadat-Dilman[1], Yuan Li[2], Julie Strizki[2], Richard Barnard[2], Mohammad Tabrizifard[1], Daniel Gorman[1]
[1]Merck & Co, Palo Alto, CA, USA, [2]Merck & Co, Inc, West Point, PA, USA

Background: In cART suppressed individuals, antigen exposure, microbial translocation and increasing immune activation lead to persistent T cell dysfunction. A select group of immune modulatory receptors (IMRs) are upregulated on the surface of exhausted CD8s, and on CD4 T cells that harbor latent HIV. Blockade of IMR pathways has been shown to reverse immune cell dysfunction and lower the threshold for reactivation of latently infected cells in vitro. We hypothesize that simultaneous engagement of multiple IMR targets, via bispecific antibodies, will enhance anti-HIV efficacy compared to single or combination antibodies.
Methods: We examined the fate, and binding orientation of bispecific antibodies that target certain IMRs (PD-1, Lag3, and TIGIT) known to play a role in HIV infection. Cells that separately express specific IMRs were generated and used to measure the ability of bispecific antibodies to simultaneously bind two separate cells (trans-binding orientation). Conversely, we used an Amnis-based approach to measure the ability of bispecific antibodies to simultaneously bind two separate epitopes on the same cell (cis-binding orientation). Furthermore, we examined whether bispecific antibodies are capable of lowering the reactivation threshold of latently infected CD4s in a primary model of latency. Finally, we characterized IMR expression of HIV-specific CD8 T cells from infected individuals to examine whether bispecific antibodies are capable of reversing dysfunction.
Results: We found that bispecific antibodies are capable of binding in both cis- and trans-orientation. Bivalent and one-armed antibodies completely lacked the ability to bind two separate molecules on distinct cells whereas bispecific molecules were capable of binding in a trans-orientation with a frequency of 25% in some cases. We observed that exogenous PD-L1 is capable of blocking reactivation in a primary CD4 T cell model of latency. And, found that the IMR, Lag-3, is increased on the CD8 T cells of HIV-infected individuals compared to uninfected donors.
Conclusion: Binding orientation influences an antibody's functional potential. Our data demonstrates that bispecific anti-IMR antibodies are capable of both cis- and trans-binding. Cis-binding may enable efficient internalization of an antibody-receptor complex, thus increasing therapeutic action. These studies may inform the future design of bispecific antibodies and provide rationale for an IMR-targeting bispecific antibody approach to treat HIV infection.

338LB TLR7 AGONIST TREATMENT OF SIV+ MONKEYS ON ART CAN LEAD TO COMPLETE VIRAL REMISSION

So-Yon Lim[1], Christa Osuna[1], Joseph Hesselgesser[2], Alison Hill[3], Michael D. Miller[2], Tomas Cihlar[2], Romas Geleziunas[2], William Lee[2], **James Whitney**[1]
[1]Beth Israel Deaconess Med Cntr, Boston, MA, USA, [2]Gilead Scis, Inc, Foster City, PA, USA, [3]Boston College, Chestnut Hill, MA, USA

Background: The persistence of an HIV-1 reservoir in patients on antiretroviral therapy (ART) represents the major obstacle to HIV remission. We have previously reported that oral TLR7 agonists (GS-9620 and GS-986) can induce transient viremia in SIV-infected, ART-treated rhesus monkeys (RMs). After ART release of nine TLR7 agonist-treated RMs, complete remission was noted in two RMs, and two other RMs have exhibited significant control of recrudescent viremia.
Methods: After repeated GS-9620 or GS-986 adminsitration and ART stop, we have conducted a long-term follow up of two "remission" RMs. We also monitored 2 RMs that had rebound viremia after ART stop, as controls. We assessed multiple endpoints including: viral outgrowth (VOA) and viral co-culture (VCC) using lymph node mononuclear cells (LNMC) and PBMC. We assessed SIV-specific T cell responses at multiple time points. We also conducted in vivo CD8+ T cell depletion in remission and viremic control RMs. Finally, we adoptively transferred PBMC and LNMC cells into SIV naïve RMs, from remission RMs prior to TLR7 agonist treatment. In parallel, we also transferred PBMC and LNMC, into SIV naïve RMs, isolated from remisson RMs after GS-9620 or GS-986 treatment and ART stop.
Results: To date, both TLR7 agonist-treated RMs have remained aviremic for more than 1 year after ART cessation. Longitudinal assesment of VOA or VCC in the two remission RMs was uniformly negative, whereas viremic RMs scored consistently postive. Longitudal SIV-specific immune monitoring revealed sustained responses in viremic RMs, but no detectable SIV-specific T cell responses in remission RMs. In vivo CD8+ T cell depletion did not induce rebound viremia in remission RMs, but viremic control RMs exhibited significant increases in SIV RNA levels that later waned as CD8+ T cells recovered. Finally, the adoptive transfer of PBMC and LNMC samples (prior to TLR7 agonist treamtent) induced a persistent SIV infection into naïve RMs. Adoptive transfer of PBMC and LMNC cells from remission RMs did not induce SIV infection in naïve recipients.
Conclusion: Administration of GS-9620 or GS-986 to SIV+ ART-suppressed RM is safe, induces transient viremia and impacts SIV DNA levels. GS-986 or GS-9620 treatment can delay viral rebound or induce durable long-term remisison after ART cessation in some RMs. These novel findings highlight a possible mechanism of SIV remission after ART cessation and underscore the need for continued investigation of GS-9620 in HIV-1 infected patients on ART.

339 HEIGHTENED SYSTEMIC AND CNS IMMUNE ACTIVATION IN ACUTE HIV INFECTION WITH SYPHILIS

Phillip Chan[1], Donn Colby[1], Eugene Kroon[1], Victor Valcour[2], Napapon Sailasuta[3], Joanna Hellmuth[4], Shelly J. Krebs[5], Jintanat Ananworanich[5], Serena Spudich[6], for the RV254/SEARCH 010 Study Group
[1]SEARCH, The Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [2]Univ of California San Francisco, San Francisco, USA, [3]Univ of Hawaii, Honolulu, HI, USA, [5]US Military HIV Rsr Prog, Silver Spring, MD, USA, [6]Yale Univ, New Haven, CT, USA

Background: HIV and Treponema pallidum infection are known to alter each other's course, and both impact the central nervous system (CNS). During chronic HIV, syphilis associates with reduced CD4 count, elevated HIV viral load (VL) and impaired cognition. In a cohort with a high prevalence of syphilis, we examined systemic and CNS immune activation and neurologic performance with respect to syphilis status during acute HIV infection (AHI).
Methods: In a retrospective, cross-sectional analysis of pre-ART baseline data in the RV254/SEARCH010 Thai AHI cohort, we defined syphilis status based on serology and history: TPHA- (never syphilis), TPHA+ (any syphilis), TPHA+/VDRL+ (recent syphilis), and TPHA+/VDRL+ untreated or post-syphilis treatment ≤ 3 months (strictly active syphilis). Data included Fiebig stage, presence of acute retroviral syndrome (ARS), blood CD4 and CD8 count and VL, summarized performance on four neuropsychological tests (NPZ-4), and, in a subset, cerebral metabolite ratios on 1.5 T magnetic resonance spectroscopy and cerebrospinal fluid (CSF) VL and immune activation markers including CSF IP-10, MCP-1, neopterin, IL-6 and IFN-g. Comparisons were performed with the Chi-square and Mann-Whitney U tests.
Results: Of 377 AHI participants enrolled between May 2009 and June 2016, 69 were TPHA+ (any syphilis), 47 of these were VDRL+ (recent/active syphilis). The prevalence of VDRL+ rose from 0/10 (0%) in 2009 to 9/41 (22%) in 2016. Among VDRL+ participants, 46 had NPZ-4, 13 underwent MRS and 11 had CSF sampling. Participant characteristics were similar across groups (Table 1), except blood CD8 count which was higher in the strictly active syphilis (n=37) vs. never syphilis group (TPHA-), p=0.028. NPZ-4 performance was lower in those who ever had syphilis (all TPHA+) vs. the TPHA- group (p=0.029). Most of the CSF immune markers level were similar across groups except IFN-g statistically increased in the VDRL+ group vs. the TPHA- group (p=0.040).
Conclusion: Active syphilis associates with elevated systemic and CNS immune activation (higher blood CD8 counts and CSF IFN-g) in AHI. Additionally, during AHI, those who have ever had syphilis (all TPHA+) have lower cognitive performance than those who have not. These findings suggest that interactions between HIV and syphilis start early in HIV, and that syphilis should be evaluated as a possible contributing factor to immune activation and neurocognitive impairment that persists even after HIV treatment.

	TPHA- (n=308)	TPHA+ (n=69)	TPHA+ VDRL+ (n=47)	Strictly active syphilis * (n=37)	TPHA+ vs TPHA- p value	TPHA & VDRL+ vs TPHA- p value	Strictly active syphilis vs TPHA- p value
Fiebig stage I or II (%)	39.9	36.2	40.4	43.2	0.569	0.949	0.698
ARS (%)	68.2	68.1	63.8	62.2	0.992	0.553	0.460
CD4, Mean (SD)	401 (182)	431 (231)	455 (249)	458 (266)	0.553	0.328	0.482
CD8, Mean (SD)	709 (623)	887 (757)	930 (785)	993 (815)	0.094	0.065	0.028
CD4/CD8, Mean (SD)	0.82 (0.51)	0.72 (0.48)	0.74 (0.51)	0.67 (0.44)	0.113	0.237	0.092
Plasma VL Log_{10} copies/ml Mean (SD)	5.84 (1.09)	5.70 (1.13)	5.67 (1.12)	5.60 (1.00)	0.349	0.312	0.153
CSF VL Log_{10} copies/ml$^{\$}$, Mean (SD)	3.42 (1.19)	3.23 (1.33)	3.27 (1.50)	3.58 (1.44)	0.524	0.627	0.732
NPZ-4 composite$^{\#}$, Mean (SD)	-0.03 (0.87)	-0.28 (0.99)	-0.25 (1.02)	-0.14 (0.67)	0.029	0.104	0.150
Raised CSF IFN-g$^{\&}$ (%)	0	14.3	22.2	16.7	0.081	0.040	0.150

$ n = 89, 22% VL below detection
# n = 344
& n = 48, Fisher's Exact Test
*Strictly active:
Positive VDRL/RPR plus;
Untreated before or post-treatment = 3 months

340 CNS INFLAMMATION STILL PRESENT AFTER >10 YEARS OF EFFECTIVE ANTIRETROVIRAL THERAPY

Gustaf O. Hammarlund[1], Arvid Edén[1], Åsa Mellgren[2], Dietmar Fuchs[3], Henrik Zetterberg[1], Lars Hagberg[1], Staffan Nilsson[4], Aylin Yilmaz[1], Magnus Gisslén[1]
[1]Univ of Gothenburg, Gothenburg, Sweden, [2]South Älvsborgs Hosp, Borås, Sweden, [3]Innsbruck Med Univ, Innsbruck, Austria, [4]Chalmers Univ of Tech, Gothenburg, Sweden

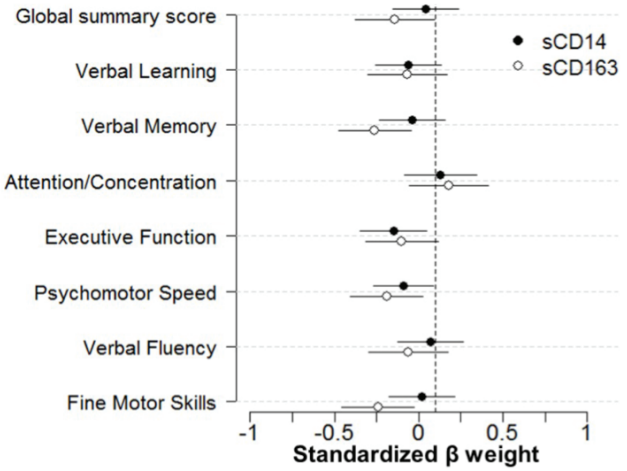
Background: Despite long-term viral suppression by antiretroviral therapy (ART), low-grade intrathecal immune activation can be found in a substantial proportion of people living with HIV (PLHIV). However, the clinical significance of ongoing immune activation during virally suppressive ART remains unclear. The aim of this study was to examine residual intrathecal immune activation in relation to signs of neuronal injury and neurocognitive impairment in PLHIV virally suppressed on ART for more than 10 years.
Methods: Neurologically asymptomatic PLHIV on ART ≥ 10 years with plasma HIV-RNA levels < 50 copies/mL for ≥ 9.5 years were retrospectively included. HIV-RNA, neopterin (a well characterized marker of microglial/macrophage activation) and neurofilament light protein (NFL), a sensitive marker of neuronal injury, were analyzed in paired plasma and cerebrospinal fluid (CSF) samples in 22 patients. Pre-treatment samples were available in 15 subjects. Cognitive function in five domains was assessed by CogState (a computerized cognitive testing system validated in PLHIV) at follow-up. The CogStateBrief Battery consists of four tests: detection (DET) measuring psychomotor function and attention, identification (ID) assessing speed of information processing and attention, one card learning (OCL) which is a learning test and one back (OB) test which assess working memory.
Results: CSF neopterin decreased significantly from in median (IQR) 18.6 (10.9-28.8) to 5.95 (4.6-7.9) nmol/L after treatment initiation ($p < 0.001$). Twelve of twenty-two (55 %) participants still had CSF neopterin above the upper normal reference limit (5.8 nmol/L) despite > 10 years of ART. CSF NFL, that normally increase with ageing, also decreased during the treatment period from in median (IQR) 1030, (541-1220), to 480 (290-750) ng/L ($p < 0.05$). No significant correlations were found between CSF neopterin and CSF NFL or neurocognitive performance. No difference was seen in CSF NFL or neurocognitive performance in subjects with normal compared to increased CSF neopterin.
Conclusion: ART significantly decreases intrathecal immune activation, but, despite effective treatment for > 10 years, 55% of PLHIV continue to show signs of macrophage/microglia activation in the central nervous system. Importantly, no associations was found between elevated neopterin and neurocognitive performance or signs of neuronal injury.

341 MONOCYTE ACTIVATION IS ASSOCIATED WITH COGNITION IN SUPPRESSED HIV-INFECTED WOMEN

Brandon M. Imp[1], Leah H. Rubin[2], Phyllis Tien[3], Michael Plankey[4], Elizabeth T. Golub[5], Audrey French[6], Victor Valcour[3], for the Women's Interagency HIV Study (WIHS)
[1]Rutgers Robert Wood Johnson Med Sch, Piscataway, NJ, USA, [2]Univ of Illinois at Chicago, Chicago, IL, USA, [3]Univ of California San Francisco, San Francsico, CA, USA, [4]Georgetown Univ, Washington, DC, [5]The Johns Hopkins Univ, Baltimore, MD, USA, [6]Rush Univ, Chicago, IL, USA

Background: Cognitive impairment in HIV-infected individuals persists despite viral suppression. Monocyte-related immune activation is a likely underlying mechanism. We measured immune activation and cognition in a cohort of HIV-infected and -uninfected women from the Women's Interagency HIV Study (WIHS).
Methods: Blood levels of inflammatory markers (soluble CD163 (sCD163), soluble CD14 (sCD14), CRP, and IL-6) and a gut microbial translocation marker (intestinal fatty acid binding protein (I-FABP)) were measured in 253 women (73% HIV-infected). All women completed a one-hour cognitive battery. Neuropsychological testing z-scores were created from internal HIV-negative controls to develop seven composite indices (verbal learning, verbal memory, attention/concentration, executive functioning, psychomotor speed, verbal fluency, and fine motor skills). Markers were compared to concurrent (+/- one semiannual visit) neuropsychological testing performance using multivariable linear regression models adjusted for enrollment site, HIV and HCV status, antidepressants, depressive symptoms, hypertension, income, and number of previous cognitive test exposures.
Results: Participants averaged 47 years old, completed 12.9 years of education, and were mostly Black, non-Hispanic (67%). 74% were HIV-infected, where 54% had a CD4 count of >500 cells/mm3 and 50% had an undetectable viral load. Higher sCD163 levels were associated with worse overall performance and worse verbal learning, verbal memory, executive function, psychomotor speed, and fine motor skills (p's<0.05). Higher sCD14 levels were associated with worse verbal learning, verbal memory, executive function, and psychomotor speed (p's<0.05). For women with viral suppression, sCD163 remained associated with worse overall performance, verbal memory, psychomotor speed, and fine motor skills (p's<0.05). sCD14 remained associated with worse executive function (p<0.05). CRP, IL-6, and I-FABP were not associated with worse cognitive performance.
Conclusion: Monocyte activation markers were associated with worse cognitive performance, and these associations persisted among HIV-infected women with viral suppression. Persistent inflammatory mechanisms related to monocytes correlate to cognitive outcomes.

Figure: Associations between plasma sCD163 and cognitive performance in virally suppressed HIV-infected women.



Note. Circles denote standardized β weight and the line denotes the 95% confidence interval around the β weight. Lines not crossing 0 are significant.

342 SYSTEMIC INFLAMMATORY AND IMMUNE BIOMARKERS IN NEUROCOGNITIVE CHANGE WITH INITIAL ART

Kevin Robertson[1], Sachiko Miyahara[2], Alan Landay[3], Todd Brown[4], Carl Fichtenbaum[5], Joseph J. Eron[6], Athe Tsibris[7], Babafemi Taiwo[8], for the ACTG 5303 Team
[1]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Harvard Univ, Boston, MA, USA, [3]Rush Univ, Chicago, IL, USA, [4]The Johns Hopkins Univ, Baltimore, MD, USA, [5]Univ of Cincinnati, Cincinnati, OH, USA, [6]Massachusetts General Hosp, Cambridge, MA, USA, [7]Northwestern Univ, Chicago, IL, USA

Background: HIV associated neurocognitive impairment remains problematic despite suppressive antiretroviral therapy (ART). Understanding the mechanisms and biomarkers of this impairment is necessary for targeted intervention and clinical trials design. We investigated the association between neurocognition and systemic immune, inflammatory and coagulation biomarkers in ACTG A5303.
Methods: ACTG A5303 enrolled ART naïve participants with CCR5 tropic HIV-1 and viral load (VL) >1000 copies/mL in the US, who were randomized to maraviroc or tenofovir disoproxil fumarate plus darunavir/ritonavir + emtricitabine. The neuropsychological (NP) battery of 15 tests done at baseline, week 24 and week 48 assessed Language, Attention, Executive, Learning, Memory, Speed of Processing, and Fine motor domains. Thirty-one systemic immune, inflammatory and coagulation biomarkers were assessed at baseline and 48 weeks. Analyses were as-treated and included only participants who remained on randomized study arms through week 48. Spearman correlations evaluated associations between NP scores and biomarkers. Adjustment for multiple testing was not applied to this exploratory analysis.
Results: Of the 230 participants, 220 individuals with both baseline and week 48 NP and biomarker data were included in this analysis. Most (91%) were male; median age was 33 yrs, 44% White, 31% Black, 22% Hispanic; >12 years education 70%; median VL was 4.5 log10 c/mL (IQR:4.5-5.0) and CD4 count was 389 (IQR:293-508) cells/mm3. At baseline (pre-ART), there were weak correlations between NP total z score and IP10 (r=-0.19), CD38+/HLA-DR+(CD4+)% (r=-0.22), and CD38+/HLA-DR+(CD8+)% (r=-0.25). At week 48, weak total z score and biomarker correlations were found for CD14++CD16-(classical monocytes)% (r=0.25), and CD14+CD16++ (non-classical monocytes)% (r=-0.26) as expected. All other biomarkers showed even weaker or no correlation with NP at baseline and week 48. We found no significant association between the changes in NP and changes in immune or inflammatory biomarkers from baseline to week 48.
Conclusion: We found no significant association between changes in systemic immune and inflammation biomarkers during ART and neurocognitive functioning. This suggests that systemic responses may poorly reflect changes within the CNS. The correlations between NP and monocyte subsets after ART initiation, though modest, are consistent with a role for monocytes in HAND persistence during ART.

343 IMPACT OF ADVANCING AGE ON COGNITION IN HIV+ PERSONS ON A FIRST SUPPRESSIVE REGIMEN

Hamza Coban[1], Kevin Robertson[2], Kunling Wu[3], Ronald Bosch[3], **Ronald J. Ellis**[4]
[1]Univ of California San Diego, La Jolla, CA, USA, [2]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]Harvard Univ, Boston, MA, USA, [4]Univ of California, San Diego, CA, USA

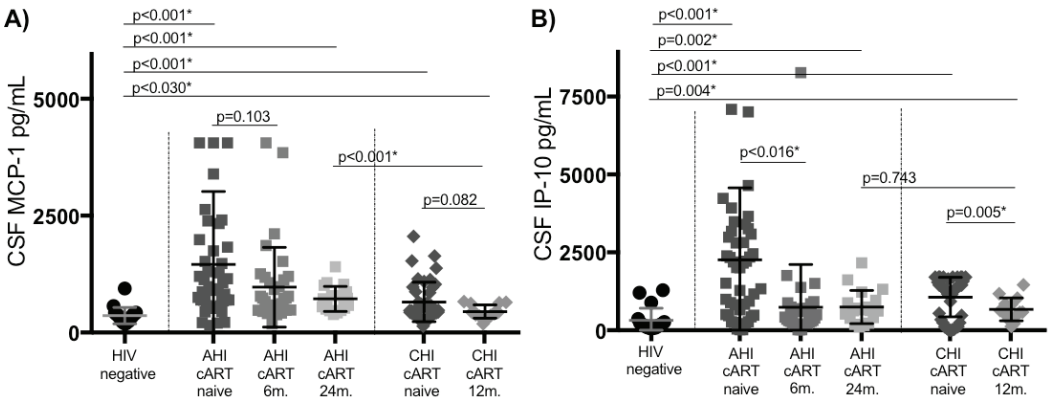
Background: We evaluated the relationship of advancing age to neurocognitive (NC) performance over time in a large cohort of individuals who had initiated their first virologically suppressive antiretroviral therapy (ART) regimen.
Methods: This analysis included ART-naïve individuals from 7 randomized ART parent trials of the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort. All underwent annual NC testing with the ACTG NeuroScreen. Only assessments done after the participants had been on ART for at least 2 years were included in this analysis. Overall performance, calculated by comparison to normative data from HIV negative individuals, was summarized using mean z-scores across the 4 tests (NPZ-4). Impairment was defined as ≤ -2.0 SD on one test or ≤ -1.0 SD on two tests. Uni- and multi-variable repeated measures regression models evaluated predictors of NC performance. Predictors evaluated included entry demographics, smoking, injection drug use (IDU), hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) serostatus, history of stroke, ART regimen type, pre-ART nadir CD4 and plasma viral load (PVL) and as well as time-updated PVL and CD4. Variables significant at p≤0.10 were eligible to enter the multivariable models.
Results: The cohort comprised 3,313 individuals with a median age at parent entry of 38 [IQR 31, 45; 12% over age 50], 36% Black, non-Hispanic; 22% Hispanic; CD4 nadir median 221 [IQR 82, 324]. Median duration of NC follow-up was 3.4 years (range 0-6.4). Considering the cohort as a whole, NC performance improved year on year such that 23% were classified as impaired at the first analyzed visit compared to only 13% in the last analyzed visit. After adjusting for the expected effects of age using norms from HIV–negative individuals, the odds of NCI impairment at a visit among HIV+ participants increased for each decade of advancing age (OR 1.18 [1.1,1.25]). Virologic suppression, which was maintained at 91% of follow-up visits, was not related to NC worsening.
Conclusion: Despite continued virologic suppression and overall NC improvement in the cohort as a whole, older individuals tended to have worse NC performance, after consideration of concurrent predictors, than younger individuals. Future studies should evaluate potential mediators of the adverse effects of age on NC trajectories, such as inflammation and vascular risk factors.

344 CNS IMMUNE ACTIVATION PERSISTS IN ACUTE AND CHRONIC HIV DESPITE EXTENDED CART

Joanna Hellmuth[1], John Best[2], Carlo Sacdalan[3], Shelly J. Krebs[4], Duanghathai Suttichom[5], Serena Spudich[6], Nisakorn Ratnaratorn[3], Jintanat Ananworanich[4], Victor Valcour[1], for the SEARCH 010/RV254 Study Group
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Univ of Pennsylvania, Philadelphia, PA, USA, [3]SEARCH, Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [4]US Military HIV Rsr Prog, Silver Spring, MD, USA, [5]SEARCH, South East Asia Rsr Collab with Hawaii, Bangkok, Thailand, [6]Yale Univ, New Haven, CT, USA

Background: Continued immune activation in the cerebrospinal fluid (CSF) after prolonged combination antiretroviral therapy (cART) may indicate the existence of a persistent CNS viral reservoir. This study investigated longitudinal markers of CNS-relevant immune activation in acute and chronic HIV infection (AHI, CHI, respectively) before and after cART initiation.
Methods: Prior to initiation of cART in AHI, neopterin, MCP-1, IP-10 were measured in plasma and cerebrospinal fluid (CSF), and repeated after 6 and 24 months of treatment. The level of these soluble biomarkers were also measured in CHI participants, repeated after 12 months of treatment, and compared to healthy controls. Group comparisons employed t-tests for parametric data and Mann-Whitney U tests for non-parametric data.
Results: Baseline markers of immune activation were available in 82 AHI participants, 60 CHI participants, and 18 healthy controls. Nearly 46% of CHI participants had a diagnosis of HIV-associated neurocognitive disorder (HAND). Prior to starting cART, both AHI and CHI participants had higher plasma and CSF levels for neopterin, MCP-1, and IP-10 (all p<0.001) compared to healthy controls. After 6 months of cART, AHI participants had persistent elevations in plasma neopterin (p<0.001), as well as plasma and CSF MCP-1 (CSF: 971 vs. 362 pg/mL, p<0.001) and IP-10 (CSF: 742 vs. 320 pg/mL, p=0.008). This pattern of immune activation continued after 24 months of cART (all p≤0.002). CHI participants with 12 months of cART had continued elevations in plasma and CSF neopterin (p<0.001; p=0.037), MCP-1 (p<0.001; p=0.030) and IP-10 (p<0.001; p=0.004) compared to healthy controls.
Conclusion: We identified elevated CNS-relevant plasma and intrathecal immune activation markers in AHI and CHI that do not fully resolve after extended cART. The continued CSF immune activation despite prolonged cART may imply the presence of a CNS viral reservoir.

Figure 1. Longitudinal CSF MCP-1 and IP-10 in acute and chronic HIV infection before and after cART



CSF: cerebrospinal fluid; MCP-1: monocyte chemoattractant protein-1; IP-10: interferon gamma-induced protein 10; AHI: acute HIV infection; CHI: chronic HIV infection; cART: combination antiretroviral therapy

345 IMMUNE MARKERS OF CRYPTOCOCCAL REACTIVATION IN HIV INFECTION

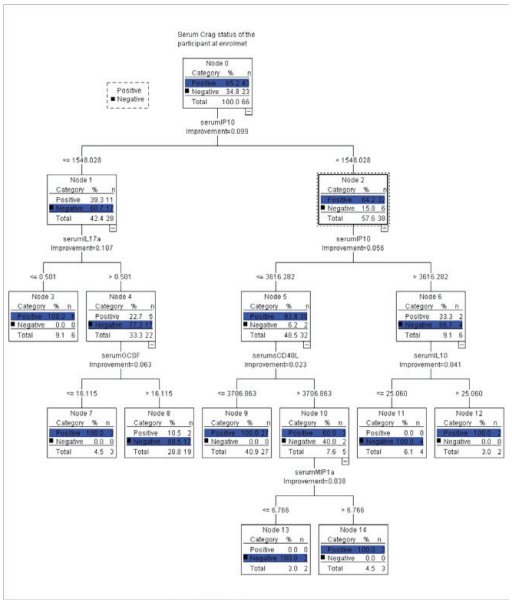
Admire Hlupeni[1], Kathryn F. Boyd[2], Azure T. Makadzange[3], Chiratidzo E. Ndhlovu[1]
[1]*Univ of Zimbabwe, Harare, Zimbabwe,* [2]*Infectious Disease Rsr Lab, Harare, Zimbabwe,* [3]*Massachusetts General Hosp, Cambridge, MA, USA*

Background: Cryptococcal infection establishes latent stage that can be reactivated in the setting of advanced HIV infection particularly in individuals with CD4+ T cells ≤100 cells/µl. Reactivation of subclinical infection can be detected by a positive serum cryptococcal antigen (sCrAg) prior to disease dissemination and cryptococcal meningitis (CM). Host factors governing reactivation remain unclear. In animal models, innate, Th17 and Th1immune responses are associated with disease containment. Human studies have focused on patients with disseminated cryptococcal disease.

Methods: We determined the factors associated with reactivation by studying a cohort in Zimbabwe of sCrAg+ individuals prior to the onset of symptomatic meningitis. We analyzed serum from 43 sCrAg+ and 23 sCrAg- individuals; paired CSF was available for 38 sCrAg+ participants, 7 of whom were also CSF CrAg+. A panel of 26 cytokines (Flt-3L, G-CSF,GM-CSF, IL-10,IL-12(p40), IL-12(p70), IL-13, IL-15, IL-17α, IL-1α,IL-1β , IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-8, INF- α 2, INF-γ, IP-10, MCP-1, MIP-1α, MIP-1β, sCD40L,TNF-α,TNF-β) was measured (in pg/ml) using multiplexed Luminex sandwich immunoassays.

Results: Median age and CD4 count were 38 years (IQR: 33-42) and 17 cells/mm3 (IQR: 10-32) respectively; most participants were male (66.7%). Median serum IL-17α (1.2 (0.64-3.3) vs 0.64 (0.64-1.8)pg/ml, p=0.032) and MIP-1β (32.6 (24.4-99.4) vs 18.7(2.5-47.1) pg/ml, p=0.02) levels were significantly higher in sCrAg- compared with CrAg+. Serum IP10 levels were higher in the CrAg+ (2041 (1510.6-2666.6)pg/ml) than in the CrAg- (1207 (757.7-1797.6pg/mL), p=0.028). There were no significant differences in the expression of the other cytokines. A model comprising of serum IP-10, IL-17α, G-CSF, sCD40L and IL-10 had a 97% predictive accuracy of an individual's serum CrAg status (95.3% PPV and 100% NPV). There was no difference in serum and CSF cytokine expression levels between those who were CSF CrAg+ and those that were CSFCrAg-

Conclusion: Serum IL-17α, MIP-1β and IP10 are important regulators of cryotococcal disease reactivation in patients with advanced HIV infection. IFNγ was not associated with reactivation, however IP10 which is produced in response to IFNγ and is associated with poor outcomes in HIV infection, was associated with disease reactivation. A model of serum IP-10, IL-17α, G-CSF, sCD40L and IL-10 predicts reactivation and suggests important immunomodulatory roles of these cytokines in cryptococcal reactivation.



346 THE ROLE OF PRESTROKE IMMUNE STATUS IN STROKE MECHANISMS IN HIV+ INDIVIDUALS

Jose Gutierrez[1], Camilla Ingrid Hatleberg[2], Henry W. Evans[1], Michael T. Yin[1]
[1]Columbia Univ, New York, NY, USA, [2]CHIP, Copenhagen, Denmark

Background: Autopsy studies from HIV+ individuals suggest an association between intracranial atherosclerosis with lower nadir CD4 but higher CD4 count at the time of death. It is unknown whether the same association applies to HIV+ individuals with ischemic stroke.

Methods: A retrospective chart review of inpatient admissions for ICD-9 defined ischemic stroke in HIV+ individuals from 2002-2016 at a tertiary care center was performed. Stroke mechanisms were ascertained based on radiographic and clinical presentation, and adjudicated by examining the diagnostic results by pre-defined criteria. The prevalence of vascular risk factors, use of antiretroviral drugs (ARVs), nadir CD4 and absolute CD4 counts (cells/mm3) at the time of stroke were captured. Logistic regressions were used to calculate the odds ratios (OR) and 95% confidence intervals (CIs) adjusting for age, sex, ethnicity, vascular risk factors and ARVs.

Results: Among 115 cases of stroke, the median age was 52 ± 12 years, and 64% were men. The distribution of stroke mechanisms were 26% intracranial atherosclerosis, 12% small artery disease, 14% infectious, 8% cardioembolic, 31% cryptogenic, and 9% other etiologies. The median nadir CD4-count was 154 (IQR 22-300), and 351 (IQR 103-546) at the time of stroke, and 53% were on ARVs. At the time of stroke; infectious etiologies were less common with increasing CD4 counts (OR 0.44 per each 50 cells/mm3 , 95%CI 0.70-0.99) while intracranial atherosclerosis stroke were more common with vascular risk factors (OR 1.5, 95%CI 1.00-2.18) and higher CD4 counts (OR 1.08, 95%CI 1.00-1.18). Statistical interaction was found between lower nadir CD4-count and greater absolute gain in CD4 count at the time of stroke (P=0.01) for stroke due to intracranial atherosclerosis. Among individuals with nadir CD4 counts < 200, but absolute CD4 counts gains > 200 from nadir to the time of stroke, intracranial atherosclerosis was the more common stroke mechanism (OR 4.44, 95%CI 1.31-15.07).

Conclusion: In one of the largest studies of HIV+ individuals focused on ischemic stroke mechanisms, intracranial atherosclerosis was the most frequent stroke mechanisms among those with lower nadir CD4 counts but higher CD4 counts at the time of stroke. Determining the association between pre-stroke immune status and stroke mechanisms may allow a targeted approach to stroke prevention.

347 TYPES OF ISCHEMIC STROKES AMONG HIV-INFECTED INDIVIDUALS ACROSS THE UNITED STATES

Heidi M. Crane[1], Robin M. Nance[1], Felicia C. Chow[2], Christina Marra[3], Joseph Zunt[1], Emily Ho[1], Richard D. Moore[4], Daniel Drozd[1], Mari Kitahata[1], David Tirschwell[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Univ of California San Francisco, San Francisco, CA, USA, [3]Harborview Med Cntr, Seattle, WA, USA, [4]The Johns Hopkins Univ, Baltimore, MD, USA

Background: Most of the evidence for an increased risk of cardiovascular disease (CVD) in HIV is from studies of myocardial infarction. Estimates of stroke risk are less well-defined, in part because of the lack of a standard approach to identifying stroke in HIV. We developed a protocol to identify and validate stroke type (ischemic vs. hemorrhagic), ischemic sub-types, etiologies and risk factors including CNS infection and illicit drug use to address questions specific to HIV.

Methods: Using comprehensive diagnosis and procedure codes, we first identified potential stroke events at 5 sites in CNICS, a US multisite clinical cohort of HIV-infected individuals receiving longitudinal care. Sites then assembled de-identified packets of provider notes and neuroimaging results for each potential event. Two neurologists reviewed each packet, followed by a 3rd if discrepancies occurred. Each neurologist identified stroke type, subtype and whether the stroke was associated with infection or illicit drug use. We compared demographic and clinical characteristics, including those related to HIV and CVD risk, by ischemic stroke subtype.

Results: Among 20,973 HIV-infected individuals, 312 had a stroke, 253 (81%) of which were ischemic. Of these, 41% occurred in the setting of illicit drug use or infection. Ischemic stroke subtypes included large vessel atheroembolic (23%); cardioembolic (30%); small vessel (31%); and other/unknown (15%). Those with cardioembolic strokes were younger (21% vs. 8% <40 years, p<0.01) and more likely to be associated with illicit drug use or CNS infection (50% vs. 27%, p<0.01) compared with individuals with small vessel strokes. Small vessel strokes were associated with use of antihypertensive medications, higher systolic blood pressure (mean 138 vs. 129 or 130mmHg, p=0.02), and higher total cholesterol (mean 196 vs. 168 or 183 mg/dL, p=0.03) compared to those with cardioembolic or atheroembolic stroke respectively.

Conclusion: Ischemic stroke, particularly small vessel and cardioembolic subtypes are most common in HIV. A high proportion of ischemic and particularly cardioembolic strokes were related to illicit drug use or infection. Those with small vessel strokes had a more severe CVD risk profile. Rigorous stroke type and subtype definitions allowed for clear elucidation of traditional and non-traditional risk factors associated with stroke types which will better inform interventions designed to improve clinical management and reduce risk.

348 ASSOCIATION OF HIV AND OPPORTUNISTIC INFECTIONS WITH INCIDENT STROKE

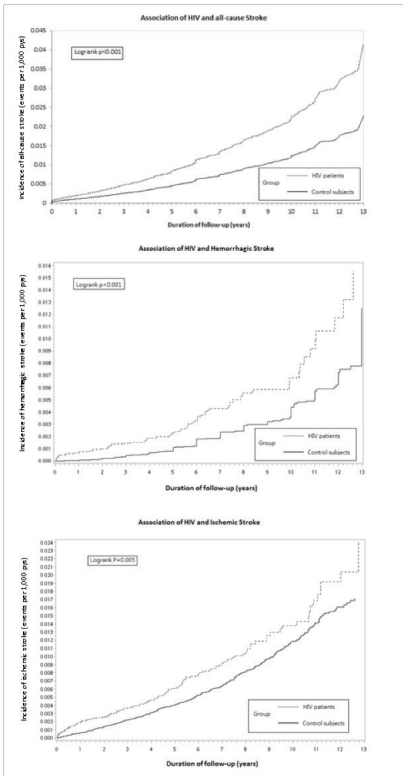
Yung-Feng Yen[1], I-An Jen[2], Yi-Ming A. Chen[3]
[1]Taipei City Hosp, Taipei, Taiwan, [2]Natl Yang-Ming Univ, Taipei, Taiwan, [3]Kaohsiung Med Univ, Kaohsiung, Taiwan

Background: HIV-associated vasculopathy and opportunistic infections (OIs) might cause vascular atherosclerosis and aneurysmal arteriopathy, which could increase the risk of incident stroke. However, few longitudinal studies have investigated the link between HIV and incident stroke. This nationwide population-based cohort study evaluated the association of HIV and OIs with incident stroke.

Methods: We identified adults with HIV infection in 2000-2012, using the Taiwan National Health Insurance Research Database. A control cohort without HIV infection, matched for age and sex, was selected for comparison. Stroke incidence until December 31, 2012 was then ascertained for all patients.A time-dependent Cox proportional hazards model was used to determine the association between HIV, opportunistic infections, and incident stroke.

Results: Among a total of 106 875 patients (21 375 HIV patients and 85 500 matched controls), stroke occurred in 927 patients (0.87%) during a mean follow-up period of 5.44 years, including 672 (0.63%) ischemic strokes and 255 (0.24%) hemorrhagic strokes. After adjusting for age, sex, and comorbidities, HIV infection was an independent risk factor for incident all-cause stroke [adjusted hazard ratio (AHR) 1.83; 95% confidence interval (CI) 1.58-2.13]. When type of stroke was considered, HIV infection increased the risks of ischemic (AHR 1.33; 95%CI 1.09-1.63) and hemorrhagic stroke (AHR 2.01; 95%CI 1.51-2.69). The risk of incident stroke was significantly higher in HIV patients with cryptococcal meningitis (AHR 4.40; 95%CI 1.38-14.02), cytomegalovirus disease (AHR 2.79; 95%CI 1.37-5.67), and Penicillium marneffei infection (AHR 2.90; 95%CI 1.16-7.28).

Conclusion: This study suggested that HIV patients had an increased the risk of stroke, particularly those with cryptococcal meningitis, cytomegalovirus, or P. marneffei infection.



349 HIV NEUROLOGICAL DISORDERS CAN OCCUR IN PATIENTS WITH SUPPRESSED HIV-1 VL IN PLASMA

Cathia Soulie[1], Maxime Grudé[2], Corinne Amiel[3], Laurence Morand-Joubert[4], Stephanie Raymond[5], Coralie Pallier[6], Pantxika Bellecave[7], Diane Descamps[8], Anne-Geneviève Marcelin[1], for the ANRS Resistance AC11 Group

[1]Pitié Salpêtrière Hosp, Paris, France, [2]INSERM, Paris, France, [3]Tenon Hosp, Paris, France, [4]Saint Antoine Hosp, Paris, France, [5]Toulouse Univ Hosp, Toulouse, France, [6]Paul Brousse Hosp, Villejuif, France, [7]Pellegrin Hosp, Bordeaux, France, [8]Bichat Hosp, Paris, France

Background: HIV antiretroviral (ARV) therapy is successful in reducing the cerebrospinal fluid (CSF) HIV RNA levels and also in preventing HIV associated dementia or disorders related to HIV encephalitis. However, associated brain disorders could persist despite antiretroviral therapy. Contributing factors remain poorly understood. We studied a large population of antiretroviral treated patients who had a HIV RNA viral load (VL) >1.7 log10 copies/mL in CSF associated with cognitive impairment.

Methods: Blood and CSF samples were collected at time of neurological disorders for 227 patients in 22 centers in France and 1 center in Switzerland. Demographic data and ARV treatment were collected. Bulk genotypic HIV resistance tests were realized on CSF. The genotypic susceptibility score (GSS) of current treatment was calculated according to the last ANRS AC-11 genotype interpretation algorithm: 0 (resistant), 0.5 (intermediate) or 1 (susceptible). Comparisons between groups were performed by using non-parametric tests.

Results: 227 patients (65% male, median age 45 years) were studied. Current and nadir CD4 cell counts were 230 (110-452) and 67 (24-165) cells/mm3, respectively. Overall, median CSF HIV RNA was 3.8 (3.1-4.6) log10 copies/mL. Among the 227 patients, 195 had a VL also detectable in plasma (median VL = 3.7 (2.7-4.7) log10 copies/mL) and 32 were discordant with a VL undetectable in plasma (VL<1.7 log10 copies/mL). The clinical and virological factors were then compared between these two groups of patients. The CSF VL was lower (2.8 vs 4.0 log10 copies/mL; p=3.34 109) and the CD4 cell count was higher (476 vs 214; p=0.0003) in the group of patients with VL<1.7 log10 copies/mL in plasma compared with patients with plasma VL>1.7 log10 copies/mL. The CD4 nadir tended to be higher (92 vs 63; p=0.0640) in the group of patients with undetectable VL in plasma. No difference was observed between the 2 patient's groups for GSS (2) and Charter score (8 and 7 for patients with plasma HIV VL<1.7 and >1.7 log10 copies/mL, respectively).

Conclusion: 14% of patients with cognitive impairment and HIV RNA > 1.7 log10 copies/mL in CSF were well controlled in plasma. Thus, it is important to explore HIV CSF (VL and resistance genotype) even if the HIV VL is controlled in plasma because HIV resistance could be observed. Indeed, an optimization of antiretroviral treatment could be necessary using fully active drugs with improved central nervous system penetration.

350 COGNITIVE TRAJECTORIES OVER 4 YEARS AMONG HIV+ WOMEN WITH OPTIMAL VIRAL SUPPRESSION

Leah H. Rubin[1], Gayle Springer[2], Pauline M. Maki[1], Kathryn Anastos[3], Deborah Gustafson[4], Maria Villacres[5], Drenna Waldrop-Valverde[6], David Vance[7], Hector Bolivar[8], Victor Valcour[9]

[1]Univ of Illinois at Chicago, Chicago, IL, USA, [2]The Johns Hopkins Univ, Baltimore, MD, USA, [3]Albert Einstein Coll of Med, Bronx, NY, USA, [4]SUNY Downstate Med Cntr, Brooklyn, NY, USA, [5]Univ of Southern California, Los Angeles, CA, USA, [6]Emory Univ, Atlanta, GA, USA, [7]Univ of Alabama at Birmingham, Birmingham, AL, USA, [8]Univ of Miami, Miami, FL, USA, [9]Univ of California San Francisco, San Francisco, USA

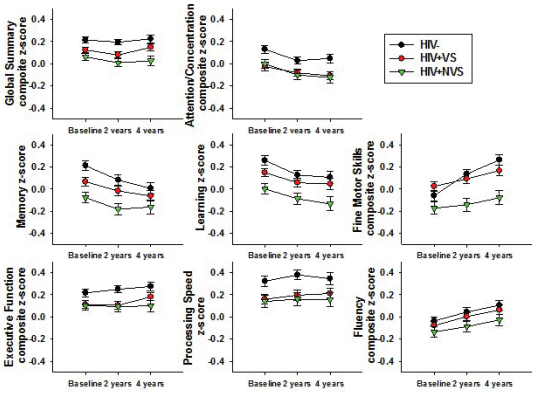
Background: An estimated 50% of HIV-infected individuals will exhibit cognitive impairment during their lifetime despite benefits of combination antiretroviral therapy (cART). Although rates of impairment are lower among virally suppressed HIV-infected (HIV+VS) individuals, impairment still persists even among this subgroup. Little is known about cognitive trajectories among HIV+VS individuals which is needed to provide a framework for understanding mechanisms of detrimental change. Thus, we compared the cognitive trajectories between HIV+VS, HIV-uninfected (HIV-), and HIV+ women without systematic viral control (HIV+NVS). We expected that HIV+VS+ women would perform worse than HIV- women but better than HIV+NVS women on global neuropsychological (NP) test performance, learning, memory, and attention.

Methods: From 2009-2016, 1757 Women's Interagency HIV Study participants underwent neurocognitive testing at baseline and biennially for 4 years (max 3 testing sessions/person). Of 1757 women, there were 661 HIV+VS, 611 demographically-similar HIV-, and 485 HIV+NVS women. VS was defined as consistent HIV RNA in plasma <500ml/cp and cART use across all sessions. Mixed effects regressions were used to examine group differences and group x time interactions on cognition controlling for relevant demographic, behavioral, and clinical factors.

Results: The cohort was 61% non-Hispanic Black, middle-aged (mean=46yrs, SD=9), and 54% had high school or less education. HIV+VS women demonstrated lower scores on global NP performance, memory, attention, executive function, and speed versus HIV- women (p's<0.05; Figure 1). HIV+NVS women showed lower scores versus HIV+VS women on global NP performance, memory, learning, and motor skills (p's<0.05). HIV- women showed improved motor skills whereas HIV+VS women did not improve (p<0.01). HIV+NVS women did not demonstrate global NP performance gains as those seen among HIV+VS women (p<0.05). HIV+NVS women showed less improvement on motor skills and executive function as compared to the HIV- women (p's<0.05).

Conclusion: Cognitive difficulties remain present even among women with consistent viral suppression. While there are some differences in trajectories between groups, cognitive difficulties persist in HIV+VS women over time. Findings reinforce a need to identify mechanisms bypassing the direct and indirect effects of the virus on the CNS and the importance of developing novel therapies to attenuate cognitive problems.

Fig 1. Longitudinal trajectories (raw Mean, SE) among HIV+VS, HIV+NVS, and HIV- women.



Note. VS=Virally suppressed; NVS= not virally suppressed

351 COGNITIVE TRAJECTORIES IN SUPPRESSED HIV INFECTION INDICATE EVOLVING DISEASE ACTIVITY

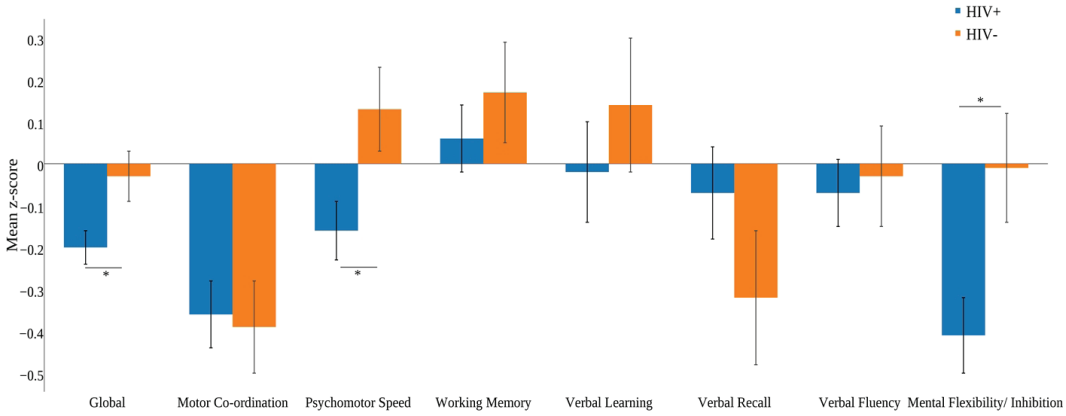
Chloe Gott[1], **Thomas Gates**[2], Nadene Dermody[1], Bruce Brew[3], Lucette Cysique[4]
[1]Macquarie Univ, North Ryde, NSW, Australia, [2]St Vincent's Hosp, Sydney, Darlinghurst, NSW, Australia, [3]Univ of New South Wales, Darlinghurst, NSW, Australia, [4]NeuroSci Rsr Australia, Randwick, NSW, Australia

Background: While the cross-sectional profile of HIV-associated neurocognitive disorder (HAND) is well described, the longitudinal rate and profile of cognitive decline in persons with stable, treated and virally-suppressed HIV infection is far from established. The aims of the current study were to: 1) quantify incident neurocognitive decline in HIV+ persons relative to controls. 2) determine the profile of cognitive trajectories as a function of historical and baseline HAND status. 3) determine which HIV disease biomarkers contribute to cognitive decline.

Methods: Ninety-six HIV+ (97% virally undetectable; median current cART duration=24 months; median HIV duration=19 years, mean age=56 years) and 44 demographically comparable HIV- participants underwent standard neuropsychological testing assessing 7 cognitive domains at baseline and 18-month follow-up. We defined clinically relevant cognitive trajectories based on historical and baseline HAND status and cognitive decline using norms for change corrected for practise effect. Cognitive decline was defined using a continuous global change score (GCS) and dichotomous definition of clinically meaningful cognitive decline (decline/stable; 95% confidence interval, 1-tailed around the HIV- group mean GCS).

Results: Relative to HIV- controls (4.5%), 14% of HIV+ participants were defined as having declined (p=.11). However, the HIV+ group scored significantly lower on global change scores (GCS) (p=.03), and showed greater decline in processing speed (p=.02) and mental flexibility/inhibition (p=.02) compared to controls. Having HAND at baseline significantly predicted cognitive decline at follow up (p=.005). We determined seven clinically relevant cognitive trajectories which in order of prevalence were: 1) Always neurocognitively-normal (39%), 2) Baseline impairment, stable (35%), 3) Long-term impairment, stable (9%), 4) Baseline impairment, decline (7%), 5) History of HAND, fully recovered (3%), 6) Incident decline at 18 months (3%), 7) Consistent decline (3%). There was no relationship between cognitive decline (accounting for historical and baseline HAND) and traditional HIV disease biomarkers.

Conclusion: Despite long-term viral suppression, we found mostly subclinical levels of decline in psychomotor speed and executive functioning - well-established markers of HAND progression. Moreover, 57% of our cohort were undergoing slow evolution of their disease, challenging the prevalent notion of neurocognitive stability in virally-suppressed HIV infection.



352LB LONGITUDINAL ANALYSIS SHOWS NO EVIDENCE FOR ACCELERATED BRAIN AGEING IN TREATED HIV

James H. Cole[1], Matthan W. Caan[2], Jonathan Underwood[1], **Rosan van Zoest**[3], Davide De Francesco[4], Alan Winston[1], Caroline Sabin[5], David J. Sharp[1], Peter Reiss[6], for the COmorBidity in Relation to AIDS (COBRA) Collaboration
[1]Imperial College London, London, United Kingdom, [2]Academic Medical Center Amsterdam, Amsterdam, Netherlands, [3]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands, [4]UCL, London, United Kingdom, [5]University College London, London, United Kingdom, [6]Stichting HIV monitoring and Academical Medical Center Amsterdam, Amsterdam, Netherlands

Background: A major concern for people living with HIV is the reportedly high prevalence of cognitive impairment, which may reflect an exacerbation of the effects of ageing on the brain. Using longitudinal neuroimaging and neuropsychological data from participants in the EU-funded COBRA collaboration, we determined whether successfully treated HIV infection is associated with accelerated age-related changes to brain structure and function.

Methods: HIV+ve people with plasma HIV RNA <50 copies/ml on antiretroviral therapy for >1 year and demographically comparable HIV-ve controls were recruited at centres in Amsterdam and London. Participants were assessed at baseline and two years using multi-modal magnetic resonance imaging (T1-weighted, diffusion, resting-state fMRI, arterial spin labelling, spectroscopy), processed to generate global and regional summary metrics of brain structure and function. Neuropsychological assessments (reported as domain T-scores adjusted for age, sex, education) tested the cognitive domains of attention, executive function, language, memory, motor function and processing speed. Between-group comparisons of baseline values and change over time were assessed using linear and mixed-effects regression respectively, with models accounting for age, time between assessments and (for neuroimaging only) intracranial volume and scanner type.

Results: At baseline, the 134 HIV+ve people (mean age 57.4 [SD=7.4] years, 6.7% female) had smaller grey matter volume, abnormal white matter microstructure and poorer cognitive function compared to 79 HIV-ve controls (58.8 [7.8] years, 7.6% female). Age-related declines in neuroimaging measures were observed in both groups, e.g., HIV+ve people lost 0.82% of brain volume per year, while HIV-ve controls lost 0.77%. Importantly, there were no group differences in the rates of brain volume loss or change in any neuroimaging measure (p>0.1, Table). Measure of cognitive function showed limited change. In fact global cognition T-score increased in both groups (HIV+ve 0.79, HIV-ve 0.45). There were no group differences in rates of change in cognition (p>0.1), with the exception of attention T-score, where the groups became more similar.

Conclusion: While HIV+ve persons had abnormal measures of brain structure and function at baseline, we found no difference in the dynamics of these measures over time between HIV+ve and HIV-ve persons. Our findings suggest that there is no evidence for accelerated brain ageing in successfully treated HIV+ve people.

Table. Mean [standard deviation] values of neuroimaging and neuropsychological measures at baseline and changes over two years in HIV-positive and HIV-negative individuals

Measure	*Baseline*		*Baseline comparison p-value*	*Longitudinal change*		*Longitudinal comparison p-value*
	HIV-positive	HIV-negative		HIV-positive	HIV-negative	
N	134	79		120	76	-
NEUROIMAGING						
T1-MRI						
Grey matter volume (L)	0.65 [0.06]	0.68 [0.06]	0.02	-0.01 [0.02]	-0.01 [0.02]	0.93
White matter volume (L)	0.48 [0.06]	0.48 [0.05]	0.61	-0.01 [0.02]	-0.01 [0.02]	0.37
Cortical thickness (mm)	2.37 [0.10]	2.38 [0.10]	0.05	-0.03 [0.06]	-0.02 [0.06]	0.51
Diffusion-MRI						
Whole-brain FA	0.55 [0.02]	0.55 [0.02]	<0.01	-0.01 [0.01]	-0.01 [0.01]	0.63
Whole-brain MD ($10^{-3}mm^2/s^{-1}$)	0.74 [0.04]	0.73 [0.04]	0.01	0.02 [0.02]	0.01 [0.02]	0.11
Corpus callosum FA	0.65 [0.04]	0.66 [0.04]	0.02	-0.01 [0.02]	-0.01 [0.02]	0.69
Corpus callosum MD ($10^{-3}mm^2/s^{-1}$)	0.81 [0.07]	0.80 [0.06]	0.03	0.02 [0.04]	0.01 [0.03]	0.13
Resting-state MRI						
Default mode network	4.64 [1.47]	5.05 [1.60]	0.12	0.31 [1.73]	0.44 [1.94]	0.75
Executive control network	7.12 [2.17]	7.38 [1.99	0.68	0.08 [2.38]	0.39 [2.88]	0.49
Fronto-parietal network - left	4.89 [1.43]	4.80 [1.33]	0.36	0.25 [1.62]	0.54 [1.29]	0.24
Fronto-parietal network - right	6.09 [1.85]	6.08 [1.37]	0.80	-0.01 [1.95]	0.34 [1.60]	0.34
MRS						
NAA	1.37 [0.26]	1.44 [0.26]	0.30	-0.03 [0.33]	-0.08 [0.31]	0.31
Myo-inositol	0.65 [0.16]	0.66 [0.20]	0.23	-0.06 [0.27]	-0.03 [0.32]	0.54
Choline	0.35 [0.07]	0.37 [0.07]	0.09	0.00 [0.08]	-0.02 [0.08]	0.14
Glutamate/Glutamine	0.98 [0.56]	1.07 [0.51]	0.54	-0.02 [0.80]	-0.02 [0.70]	0.85
ASL						
Grey matter perfusion	62.54 [14.11]	63.46 [13.09]	0.83	-5.38 [14.56]	-5.47 [11.32]	0.51
NEUROPSYCHOLOGICAL TESTS						
Language	52.0 [9.0]	52.9 [8.9]	0.36	0.2 [5.6]	0.5 [6.3]	0.97
Attention	49.9 [11.5]	56.1 [9.0]	<0.01	0.6 [8.1]	-2.2 [6.5]	0.02
Processing speed	50.6 [7.9]	54.4 [7.1]	<0.01	0.9 [4.7]	0.2 [3.4]	0.43
Executive function	48.3 [8.5]	51.3 [7.3]	0.01	0.2 [5.2]	0.8 [6.5]	0.31
Memory	55.3 [7.8]	56.5 [7.7]	0.17	2.2 [5.2]	3.2 [4.8]	0.12
Motor function	46.8 [8.3]	50.8 [7.7]	<0.01	0.5 [6.3]	0.2 [5.3]	0.96
Global cognitive performance	50.5 [6.3]	53.7 [5.1]	<0.01	0.8 [2.8]	0.5 [2.6]	0.60

Regression models included adjustment for age, scanner, intra-cranial volume (neuroimaging) and study site (neuropsychology). Resting-state fMRI values represents relative measures of within-network connectivity. MRS values are reported as a ratio of creatine.

353 DECREASE IN EXECUTIVE FUNCTION IS ASSOCIATED WITH DETECTABLE PLASMA HIV DURING CART

Albert Anderson[1], Josue Perez-Santiago[2], Andrea Knezevic[1], Xiaohe Yang[1], Eugene Huang[1], Jennifer Iudicello[3], David Moore[2], Ronald J. Ellis[2], Robert K. Heaton[3], Scott Letendre[2]
[1]Emory Univ, Atlanta, GA, USA, [2]Univ of California San Diego, San Diego, CA, USA, [3]Univ of California at San Diego, La Jolla, CA, USA

Background: HIV- associated neurocognitive impairment (NCI) continues to be prevalent, even in patients on combination antiretroviral therapy (cART). Growing evidence shows that NCI is associated with adverse clinical outcomes. To assess the influence of neurocognition (NC) on virologic suppression, we pooled data from multiple studies in which participants underwent comprehensive NC testing. We hypothesized that worse NC would be associated with detectable plasma HIV RNA despite self-reported adherence to cART.
Methods: Longitudinal data from multiple studies nested within the HIV Neurobehavioral Research Program were analyzed. Subjects were included in the analysis if, at all visits, the following criteria were met: 1) on cART with ≥3 drugs; 2) ≥ 95% cART adherence reported for the prior two weeks; 3) Use of plasma HIV RNA assay with lower limit of ≤50 copies/ml. Data were analyzed using generalized estimating equation (GEE) models for repeated measures. Covariates included demographic characteristics, global and domain-specific neurocognitive performance, and the use of addictive drugs. Variables significant in univariate analysis at alpha 0.05 were included in multivariable modeling, which was performed using backward stepwise selection.
Results: The 1,943 included participants had a total of 5,555 visits. In the univariate analysis, the variables associated with HIV RNA ≤ 50 included white race, older age, higher nadir CD4+ count, higher CD4+/CD8+ ratio, and higher mean T score for the executive function domain. Hepatitis C virus seropositivity as well as current use of illicit drugs and opioids were associated with HIV RNA >50. In the final multivariate model, undetectable plasma HIV RNA was associated with: white race (OR 1.46, 95%CI 1.08-1.98); increasing age per 5 years (OR 1.10, 95% CI 1.01-1.19), higher CD4/CD8 ratio (OR 1.13, 95% CI 1.08-1.18), and better executive function (OR 1.16 per T-score increase of 10, 95% CI 1.03, 1.31). Current use of cocaine (OR 0.31, 95% CI 0.2-0.48), opiates (OR 0.59, 95% CI 0.38-0.93), or methamphetamine (OR 0.52, 95% CI 0.33-0.83) were associated with decreased odds of undetectable plasma HIV.
Conclusion: HIV-infected adults on cART who report excellent adherence are more likely to have undetectable plasma HIV RNA if they have better executive functioning, even after accounting for traditional risk factors. These findings provide more evidence that neurocognition is important in the management of HIV-infected individuals.

354 DAAS IMPROVE VACS BUT DO NOT INFLUENCE COGNITIVE IMPAIRMENT IN HIV/HCV COINFECTED

Ilaria Mastrorosa, Patrizia Lorenzini, Martina Ricottini, Gabriele Fabbri, Pietro Balestra, Alessandra Vergori, Carmela Pinnetti, Mauro Zaccarelli, Adriana Ammassari, Andrea Antinori
Natl Inst for Infectious Diseases, Rome, Italy

Background: The role of HCV as an independent risk factor for HIV-associated neurocognitive impairment (NCI) is still controversial. VACS Index, a composite marker of disease severity, has been associated with increased risk for mortality and with concurrent risk for NCI. Aim was to evaluate changes over time after DAA treatment on neurocognitive performance and VACS index in HIV/HCV co-infected (HIV/HCV) patients (pts).
Methods: HIV/HCV pts starting DAA treatment were enrolled in a prospective study. All patients underwent neuropsychological assessment (NPA) before starting DAA (T1) and 12-24 weeks after (T2) end of treatment (EOT). NPA was carried out through a standardized battery of 14 tests on 5 different domains. We used NPZ-8 as a summary measure of z-scores of neuropsychological testing performance. Pts were classified as having NCI if they scored >1 standard deviation (SD) below the normal mean in at least 2 tests, or >2 SD in 1 test. HAND was classified according to Frascati's criteria. VACS Index was calculated through standard methods at T1 and 6 months after EOT. Paired Wilcoxon and Mc Nemar test were used for statistical comparisons.
Results: A total of 62 patients included: male 74.2%, median age 54 years (IQR 51-56); injection drug users (IDUs) 85.4%; on cART 100%; median CD4 563 cell/mmc (IQR 340-761); HIV-RNA not detectable 83.3%; baseline log10 HCV RNA 5.8 (IQR 5.3-6.3). Fibrosis was F1/F2 in 11, F3 in 12, F4 in 39 pts. Half of the patients was HCV treatment experienced. DAA regimen was SOF-based for 32 pts and non-SOF-based for 30 pts. At baseline 23/62 were neurocognitively impaired. HAND criteria were limited by high frequency of confounding comorbid conditions (substance use). No significant changes over time in NPA was observed after DAA (Table). Similarly, when considering only pts achieving SVR12, neurocognitive performance did not improve. For 51 pts, VACS index was calculated at T1 and 6 month after EOT: at month 6 compared to T1, median values were significantly lower after DAA treatment (Table).

Conclusion: In our experience, DAA treatment strongly improved VACS Index, but did not impact on neurocognitive performance in HIV/HCV co-infected. These results could be explained by a poor contribution of HCV to neurocognitive impairment in HIV co-infected population, even though the elevated frequency of confounding factors in this highly vulnerable population may have masked benefit effect of DAA on neurocognition.

Table. Results of neurocognitive performance and VACS Index during DAA therapy

Total patients treated with DAA (n=62)	before HCV therapy	post HCV therapy (SVR12)	p
Pts neurocognitively impaired	23 (37.1%)	26 (41.9%)	0.317
NPZ-8, median (IQR)	-0.57 (-0.97; -0.04)	-0.41 (-0.85; 0.01)	0.195
VACs Index, median (IQR)	42 (23-52)	27 (17-45)	<0.001
Patients with SVR12 (n=58)	**before HCV therapy**	**post HCV therapy (SVR12)**	**p**
Pts neurocognitively impaired	23 (39.7%)	23 (39.7%)	0.781
NPZ-8, median (IQR)	-0.57 (-0.97; -0.04)	-0.40 (-0.85; 0.07)	0.096
VACs Index, median (IQR)	42 (23-52)	27 (17-45)	<0.001

355 LIMITATIONS OF THE INTERNATIONAL HIV DEMENTIA SCALE IN THE CURRENT ERA

Benedetta Milanini[1], Emmanuel Bahemana[2], Babajide Keshinro Keshinro[3], Francis Kiweewa[4], Rither Langat[5], Winnie Rehema[6], Isabel E. Allen[1], Christina Polyak[7], Julie Ake[7], Victor Valcour[1]

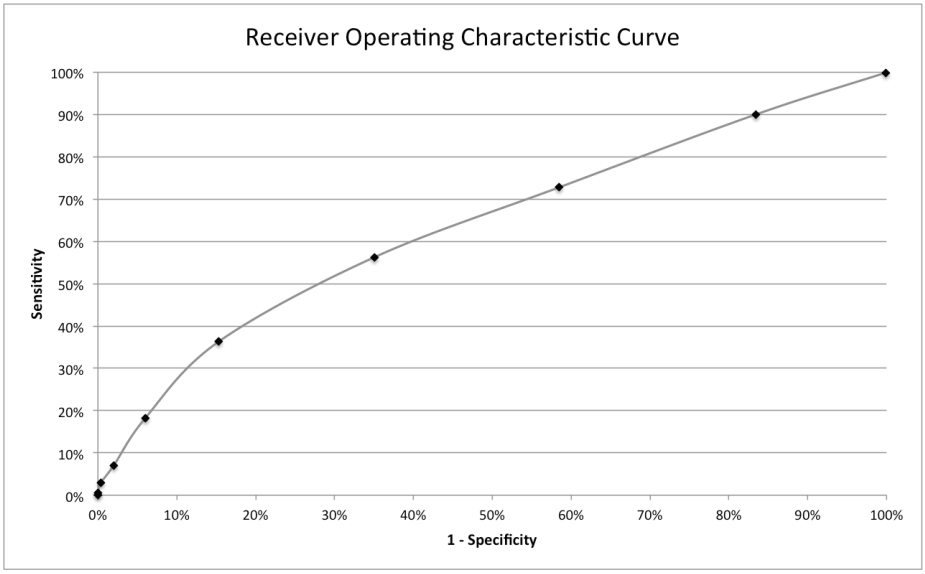
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Walter Reed Prog–Tanzania, Mbeya, Tanzania, United Republic of, [3]Walter Reed Prog–Nigeria, Abuja, Nigeria, [4]Makerere Univ Walter Reed Proj, Kampala, Uganda, [5]KEMRI/Walter Reed Proj, Kericho, Kenya, [6]KEMRI/Walter Reed Proj, Kisumu, Kenya, [7]US Military HIV Rsr Prog, Bethesda, MD, USA

Background: The International HIV Dementia Scale (IHDS) was developed as a tool for HIV dementia in both the industrialized and developing world. As initially described, a cut-point of 10 on this 12-point scale had sensitivity of 80% with specificity of 55% in Uganda. Recent publications from Uganda identify very high rates of probable HIV dementia (64%, BMC Psychiatry 2013) using this screening instrument, prompting us to examine performance characteristics for the current era.

Methods: 2414 individuals from East Africa underwent testing with the IHDS and a 30-minute cognitive battery that included the World Health Organization (WHO) auditory verbal learning test (AVLT) trial 1, sum of 1-5, and recall; the Trails A test; the grooved pegboard test; and action fluency task. We defined impairment among HIV+ participants as - 1 SD on two tests or - 2 SD on one test when performance was compared to concurrently enrolled controls stratified by age (=35) and education (<6 years, 6-12 years, >12 years). We examined predictive capacity of the IHDS using receiver operator characteristic (ROC) curve. Psychometrists underwent initial certification with re-certification every 6 months.

Results: We enrolled participants from Uganda (n=531), Kenya (n=1466) and Tanzania (n=417) with mean (SD) age for HIV+ (n=2009) and HIV-negative (n=405) groups: 39.8 (10.8) and 37.6 (10.5), respectively (p=0.006). Among HIV+, 1651 (67%) were on cART, 979 (51%) had plasma viral loads <50 copies/ml and 702 (36%) met criteria for impairment. The mean (SD) IHDS score was 8.5 (1.7) and 9.0 (1.6) for HIV+ and HIV-negative, respectively (p=0.001). Using the cut-point of 10, 1290 (64%) of HIV+ subjects would be classified as having dementia as well as 215 (53%) of HIV negative controls. The ROC area under the curve (AUC) was maximally 60% offering a sensitivity of 66% and specificity of 66% at a cut point of 9 among HIV+.

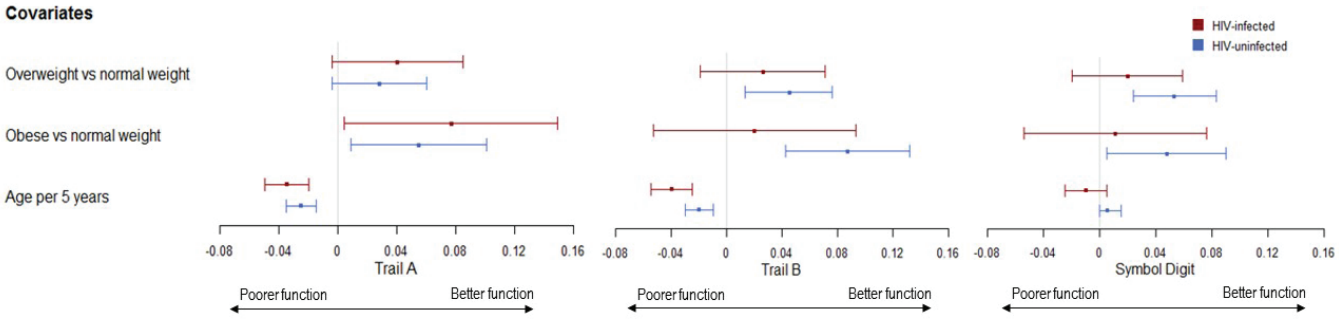
Conclusion: The IHDS has poor performance characteristics for the identification of impairment in East Africa in the current era. Performance for the most severe form of impairment, HIV Dementia, typically constituting < 5% of patients with access to cART, cannot be assessed from these data. Our data raise concerns for continued use of the IHDS in the era of cART.



356 EFFECTS OF AGE AND OBESITY ON NEUROCOGNITIVE PERFORMANCE IN THE MACS COHORT

Kristine Erlandson[1], Long Zhang[2], Lisa Jacobson[2], James T. Becker[3], Cynthia Munro[2], Jordan E. Lake[4], Eileen Martin[5], Andrew Levine[6], Todd Brown[2], Ned Sacktor[2]
[1]Univ of Colorado, Aurora, CO, USA, [2]The Johns Hopkins Univ, Baltimore, MD, USA, [3]Univ of Pittsburgh, Pittsburgh, PA, USA, [4]Univ Texas Houston, Houston, USA, [5]Rush Univ, Chicago, USA, [6]Univ of California Los Angeles, Los Angeles, CA, USA

Background: Age and obesity are both risk factors for dementia and associated with impaired neurocognitive (NC) performance, independent of age or obesity-associated comorbidities. We hypothesized that the effects of age and obesity on NC performance would be greater among HIV+ persons.
Methods: Men with or at risk for HIV infection in the Multicenter AIDS Cohort Study (MACS) with 1) no diagnosed dementia or psychosis, 2) receipt of ≥2 antiretroviral drugs from ≥2 classes, 3) HIV-1 RNA <400 copies/mL at >80% of visits and 4) complete NC assessments from ≥ 1 visit were included. BMI was categorized as underweight (BMI <18.5 kg/m2), normal weight (18.5-24.9), overweight (25-29.9), or obese (≥30); under- and normal weight were combined for analyses. Log-transformed Trail Making Test, parts A and B (TrA, TrB) and the Symbol Digit Modalities test (SDMT) scores were adjusted for age, education, race, and repeat administrations. Mixed methods regression models determined associations of age and BMI with neurocognitive testing, adjusted for covariates.
Results: HIV+ (n=795) and HIV- (n=1605) men contributed 10,023 and 23,204 visits, respectively. HIV+ men contributed to 5148 under/normal weight, 3612 overweight, and 1263 obese visits; HIV- men to 10,157 under/normal weight, 8072 overweight, and 4975 obese visits. Baseline characteristics among HIV+ vs HIV- men, respectively, included: mean age 43.0 (standard deviation 10.1) vs 42.9 (10.9) years; BMI 25.7 (4.3) vs 26.0 (4.7) kg/m2. In multivariate models (Figure), increasing age was associated with poorer NC performance among both HIV+ and HIV- men on TrA and TrB (p<0.001) but not SDMT; there was no HIV by age interaction (p≥0.20). Obesity was associated with improved performance on TrA, TrB, and SDMT among HIV-uninfected participants (all p<0.05), and TrA among HIV-infected participants (p=0.038). There was no age by obesity or HIV serostatus by obesity interaction (all p≥0.11).
Conclusion: Increasing age was associated with poorer NC performance on TrA and TrB among both HIV+ and HIV- men, with no difference by HIV serostatus. Furthermore, an unexpected protective effect of obesity on NC performance was observed, and most significant among HIV- controls. These findings could be the result of unbalanced drop-out or mortality differences at the BMI extremes, or may reflect physiologic processes associated with improved psychomotor speed. Further studies are needed to clarify the mechanisms underlying these findings.



All models were adjusted for age, cohort, race/ethnicty, education, smoking, alcohol and other substance use, hepatitis C, cancer, depression, and hypertension. Additional models for HIV-infected individuals (not included above) also included CD4, HIV-1 viral suppression, history of AIDS, and duration of exposure to ART, EFV, and D4T; for the association between obesity and Trails A among HIV, the estimate and p value were unchanged with these additional variables.

357 CSF TO PLASMA HIV-RNA RATIO ≥1 IS ASSOCIATED WITH HAND IN UNTREATED HIV PATIENTS

Francesca Bai, Francesca Iannuzzi, Esther Merlini, Lidia Borghi, Teresa Bini, Giulia Marchetti, Antonella d'Arminio Monforte
Univ of Milan, Milan, Italy

Background: The association between cerebrospinal fluid (CSF) HIV-RNA and mild forms of HIV-associated neurocognitive disorders (HAND) is still controversial. We aimed to explore the association between plasma and CSF viral load and HAND in a cohort of untreated HIV+ patients (pts).
Methods: We consecutively enrolled untreated HIV+ pts from 01/2011 to 08/2016 to undergo a neurocognitive evaluation (10 tests on 6 cognitive domains to diagnose HAND by Frascati's criteria), lumbar puncture (CSF HIV-RNA) and blood sample (plasma HIV-RNA, CD38/CD45RA/CD45R0/CD127 on CD4/CD8 by flow cytometry). Pts were divided into HAND (including asymptomatic neurocognitive impairment [ANI], mild neurocognitive disorder [MND] or HIV associated dementia [HAD]) and noHAND (normal cognitive performances). Chi-square, Mann-Whitney test and logistic regression were used.
Results: 155 pts were enrolled. HAND was diagnosed in 50/155 (32%) pts: 40 (80%) ANI, 10 (20%) MND; no HAD. Globally, median plasma HIV-RNA was 4.7 log10 cp/ml (IQR 4.11-5.3) with a CSF HIV-RNA approximately 1 log lower than plasma levels (3.65 $\log_{10}$ cp/ml, IQR 3-4.16). No differences in age, sex, hepatitis coinfections and time since HIV diagnosis were described between HAND and noHAND group; however, HAND pts were characterized by a higher frequency of AIDS events and CD4+ nadir <200 cells/mmc, in comparison to noHAND pts. No differences in median plasma and CSF HIV-RNA were observed with similar median CSF to plasma HIV-RNA ratio in the two groups; however, HAND was more frequently associated with ratio ≥1, in comparison to noHAND group (CSF to plasma HIV-RNA ratio ≥1: HAND 13, 26%-noHAND 11, 10.5%; p=0.013). Regarding T-cells immunophenotypes, lower naïve CD45RA+CD4+% and central memory CD127+CD4+% T-cells were associated with HAND (Table 1). In multivariate analysis, adjusting for CD4+ nadir <200 cells/mmc, CSF to plasma HIV-RNA ratio ≥1 (AOR 3.088, IC95% 1.172-8.138, p=0.023) and AIDS events (AOR 3.446, IC95% 1.173-10.123, p=0.024) were confirmed associated with HAND.
Conclusion: in our cohort of untreated HIV+ pts, we reported a 32% of HAND prevalence with a higher frequency in pts with AIDS and CD4+ nadir <200 cells/mmc. Interestingly, mild forms of HAND were independently associated with a CSF to plasma HIV-RNA ratio ≥1, suggesting a compartmentalization of systemic infection into central nervous system with subsequent neuronal damage and neurocognitive impairment.

TABLE 1: Comparison between subjects with normal neurocognitive function and patients with neurocognitive impairment

Total population n=155	No HAND (n=105)	HAND (n= 50)	*p value*
Female, n (%) *	9 (8.6)	4 (8)	0.905
Age (years), median (IQR)°	38 (30-45)	39 (33-48)	0.225
Time since first HIV diagnosis (months), median (IQR)°	2 (1-12)	2 (0.5-24)	0.786
AIDS events, n (%)*	12 (11.5)	18 (36)	**0.0001**
Plasma HIV-RNA, Log_{10} cp/ml median (IQR)°	4.63 (4.09-5.39)	4.79 (4.21 -5.3)	0.571
CSF HIV-RNA, Log_{10} cp/ml median (IQR)°	3.61 (3-4.11)	3.67 (3.19-4.4)	0.16
CSF to plasma HIV-RNA ratio, median (IQR)°	0.76 (0.61-0.86)	0.79 (0.62-1.01)	0.245
Pts with CSF to plasma HIV-RNA ratio ≥1, n (%)*	11 (10.5)	13 (26)	**0.013**
Nadir CD4+ T-cells, cell/mmc median (IQR)°	381 (249-492)	274 (74-411)	**0.004**
Pts with nadir CD4+ T-cells <200 cell/mmc, n (%)*	20 (19.6)	21 (43.8)	**0.002**
CD8+% T-cells, median (IQR)°	56 (48-65)	59 (49-70)	0.127
Ratio CD4/CD8, median (IQR)°	0.38 (0.21-0.5)	0.3 (0.15-0.47)	0.133
CD38+CD8+%, median (IQR)°	12 (7-20)	12 (8-20)	0.702
CD45R0+CD38+CD8+%, median (IQR)°	7 (4-15)	8 (4-15)	0.747
CD127+CD4+%, median (IQR)°	13 (8-17)	10 (5-14)	**0.008**
CD127+CD8+%, median (IQR)°	29 (24-37)	28 (23-37)	0.89
CD45RA+CD4+%, median (IQR)°	8 (5-12)	6 (2-9)	**0.002**
CD45RA+CD8+%, median (IQR)°	19 (13-24)	18 (14-25)	0.835
CD45R0+CD8+%, median (IQR)°	23 (17-31)	21 (16-33)	0.667

Note: °Data are median (IQR). Statistical analyses: Mann-Whitney U Test. *Data are n (%). Statistical analyses: Pearson Chi squared or Fisher Exact Test. p value for comparison between HAND and noHAND patients. IQR: Interquartile range; CFS: cerebrospinal fluid; Pts: patients; HAND: HIV-associated neurocognitive disorders; cp/mL, copies/mL.

358 POST-TRAUMATIC STRESS AND NEUROCOGNITIVE IMPAIRMENT IN A US MILITARY COHORT

Robert Deiss[1], Raeanne Moore[2], Nancy Crum-Cianflone[1], Scott Letendre[2], Anuradha Ganesan[1], Jason Okulicz[3], Mary F. Bavaro[4], David J. Moore[2], Brian K Agan[1]
[1]Uniformed Services Univ of the Hlth Scis, Rockville, MD, USA, [2]Univ of California San Diego, San Diego, CA, USA, [3]Infectious Disease Service, San Antonio, TX, USA, [4]Naval Med Cntr of San Diego, San Diego, CA, USA

Background: Neurocognitive impairment (NCI) is a well-known complication of HIV infection and may be influenced by mental health disorders. We examined the relationship between NCI and mental health disorders including post-traumatic stress disorder (PTSD) in a cohort of HIV-infected military personnel.
Methods: We analyzed data from 189 HIV+ active-duty (72%) and retired (28%) US military men. Participants completed selected modules of the Composite International Diagnostic Interview to ascertain the presence of PTSD, major depressive disorder (MDD), alcohol use disorder (AUD) and other mental health diagnoses. NCI functioning was assessed with a comprehensive battery of standardized neuropsychological tests. We performed chi-square and logistic regression to characterize the relationship between NCI and mental health disorders.
Results: The median age of study subjects was 36 years (interquartile range [IQR] 28-43) and median total years of education was 14 (IQR 12-16). NCI was diagnosed in 19% of subjects. The lifetime prevalence of serious head trauma (12%), MDD (25%) and AUD (37%) did not significantly differ between individuals diagnosed with or without NCI. However, individuals with a lifetime history of PTSD (PTSD+) were more likely to be diagnosed with NCI than those without PTSD (PTSD-); (43% vs 16%, $p<0.01$). While we found no significant differences between PTSD(+) and PTSD(-) with respect to total years of education, current or nadir CD4 count, or highest HIV RNA level, PTSD(+) were more likely to have a prior AIDS diagnosis (29% vs 4.0%, $p<0.01$) than PTSD(-). In multivariate analysis adjusting for age, education, race, history of AIDS diagnosis and history of head trauma, lifetime history of PTSD remained independently associated with NCI (OR 4.2; 95% CI 1.5, 15.3).
Conclusion: Among US HIV-infected military personnel, individuals with a history of PTSD were four-times more likely to be diagnosed with NCI than those without a PTSD diagnosis. PTSD may be an under-appreciated determinant of cognitive functioning, an important finding given its high prevalence among military personnel and vulnerable populations living with HIV. HIV-infected individuals with cognitive difficulties should be screened for mental health disorders including PTSD. Prospective studies of the longitudinal relationship between PTSD and NCI as well as the impact of PTSD treatment on future NCI should be evaluated.

359 ANTIRETROVIRALS IMPROVE HAND STAGE IN HIV+ PATIENTS WITH SUBTYPE D AND A IN UGANDA

Ned Sacktor[1], Deanna Saylor[1], Gertrude Nakigozi[2], Kevin Robertson[3], Noeline Nakasujja[4], Ronald H. Gray[1], Maria Wawer[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Rakai Hlth Scis Prog, Kalisizo, Uganda, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]Makarere Univ, Kampala, Uganda

Background: The predominant HIV subtypes in Rakai, Uganda are D (45%), A (35%) and D/A recombinants (20%), in contrast to the US where subtype B predominates. Combination antiretroviral therapy (CART) improves HIV-associated neurocognitive disorder (HAND) stage in the US, but the effect of CART on HAND stage in individuals with subtypes D and A is largely unknown. The objective of this study was to evaluate the change in HAND stage after CART initiation in 400 HIV+ individuals in Rakai, Uganda.
Methods: 400 ART naive HIV+ individuals and 400 HIV seronegative (HIV-) individuals in Rakai, Uganda received detailed medical, neurological, and functional assessments, neurological examination, and neuropsychological testing. As of September 28, 2016, 277 of the 312 HIV+ individuals (89%) who had reached their 2 year follow-up visit had returned for evaluation. 233 of these HIV+ individuals were on CART with data available for HAND classification. HAND stage was determined at each visit based on normative data developed from the 400 HIV- age-, gender- and community-matched controls. Baseline frequencies of cognitive impairment between HIV+ and HIV- individuals were assessed with chi square tests. Among HIV+ patients on CART, baseline and follow-up HAND stages were compared using Wilcoxon sign rank tests.
Results: Demographic characteristics of the 400 HIV+ individuals were as follows: Age [mean (SD)] = 35 (8) years, Education [mean (SD)] = 5 (3) years, Gender (male, %) = 53]. At baseline HIV+ individuals had more dementia (HAD) (dementia frequency % for HIV+'s =16%) than HIV- individuals {dementia frequency % for HIV-'s = 6%), ($p<0.001$), but there were no differences in asymptomatic neurocognitive impairment (ANI) [HIV+ (10%) vs HIV- (8%)], or mild neurocognitive disorder (MND) [HIV+'s (20%) vs HIV-'s (21%)]. At

the 2 year follow-up, HAND stage frequencies (%) for HIV+ individuals on CART were 3% for ANI, 9% for MND, and 2% for HAD (p<0.001 compared to the matched pre-CART HAND stages of the same 233 HIV+ individuals). HAND stage improved in 44% of HIV+ individuals and worsened in 8% of HIV+ individuals on CART.
Conclusion: Individuals with HIV subtypes D and A showed significant improvement in HAND stage after 2 years of CART treatment compared to their pre-CART status, with a marked decrease in the frequency of HAD. These are similar to results in the US. CART should be initiated in early HIV infection to treat and potentially prevent neurocognitive complications in Sub-Saharan Africa.

360 ADDITIONAL SCREENING TESTS FOR HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS

Mattia Trunfio[1], Chiara Montrucchio[1], Daniela Vai[2], Daniele Imperiale[2], Alessandro Livelli[2], Giancarlo Orofino[3], Alice Trentalange[1], Stefano Bonora[1], Giovanni Di Perri[1], Andrea Calcagno[1]
[1]Univ of Torino, Torino, Italy, [2] Maria Vittoria Hosp, Torino, Italy, [3]Amedeo di Savoia Hosp, Torino, Italy

Background: The diagnosis of HIV-associated neurocognitive disorders (HAND) relies on complete neurocognitive tests (NCT) that are time-consuming. Appropriate screening tests are lacking since both the three questions (3Qs, EACS Guidelines) and the International HIV Dementia Score (IHDS) are associated with poor sensitivity and intermediate/good specificity in different population groups.
Methods: Consecutive HIV-positive patients screened for neurocognitive impairment were prospectively enrolled. Clinical and biochemical data were recorded. 3Qs, IHDS, Clock Drawing Test (CDT) and Frontal Assessment Battery (age and education adjusted, aFAB) were administered: 3Qs≥1, IHDS≤10, CDT>2 and aFAB≤14 were deemed abnormal. Patients showing abnormal IHDS or with open cognitive symptoms underwent full NCT including eight NC domains afterwards: HAND was diagnosed according to the Frascati's criteria. Data are expressed as medians (interquartile ranges) and tested through non-parametric tests.
Results: 669 patients were enrolled (87% on cART, 76% male, median age 50 years): screening tests were abnormal in 171 (26.6%), 266 (42.3%), 70 (15.4%) and 20 (7.9%) patients, according to 3Qs, IHDS, CDT and aFAB, respectively. 279 patients underwent full NCT (84% on cART, 72% male, median age 51 years). Plasma HIV-RNA was <50 copies/mL in 186 subjects (81.6%), median and nadir CD4+ T-cell/uL count were 516 (304-777) and 153 cells/uL (57-285). HAND was diagnosed in 141 patients (50.5%): 100, 32 and 9 subjects with ANI, MND or HAD. A significant correlation was observed between IHDS (p<0.0001) and aFAB (p<0.0001) with HAND diagnosis. Sensitivity, specificity and correct classification rate (CCR) of screening test for HAND diagnosis were as follows: 3Qs (36.5%, 56.4%, 46.4%), IHDS (72.8%, 55.7%, 64%), aFAB (24.5%, 100%, 61.9%), CDT (30.1%, 71.6%, 52.2%). Considering only symptomatic neurocognitive disorders, aFAB presented the highest CCR (84.9%). The concomitant use of aFAB or CDT with IHDS did not substantially improve screening tests' accuracy.
Conclusion: All screening tests showed incomplete accuracy in predicting HAND. While IHDS presented the highest sensitivity, aFAB was associated with a very high specificity and the highest correct classification rate for symptomatic HAND. The 10-minute, easy-to-administered, FAB test warrants further studies in HIV-positive patients.

361 COGNITIVE COMPLAINTS AND DEVELOPMENT OF FALLS AMONG HIV+ AND HIV- WOMEN

Anjali Sharma[1], Donald R. Hoover[2], Qiuhu Shi[3], Michael Plankey[4], Phyllis Tien[5], Kathleen M. Weber[6], Michelle Floris-Moore[7], Hector Bolivar[8], Marica M. Holstad[9], Michael T. Yin[10]
[1]Albert Einstein Coll of Med, Bronx, NY, USA, [2]Rutgers, the State Univ of New Jersey, Piscataway, NJ, USA, [3]New York Med Coll, Valhalla, NY, USA, [4]Georgetown Univ, Washington DC, USA, [5]Univ of California San Francisco, San Francisco, CA, USA, [6]Cook County Hlth & Hosps System, Chicago, IL, USA, [7]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [8]Univ of Miami, Miami, FL, USA, [9]Emory Univ, Atlanta, GA, USA, [10]Columbia Univ, New York, NY, USA

Background: We previously reported greater fracture rates in aging HIV+ vs. HIV- women in the Women's Interagency HIV Study (WIHS). Because fracture may be due to reduced bone strength combined with greater risk of falls, we compared rates of falls and evaluated relationships between subjective cognitive complaints and fall in HIV+ and HIV- women
Methods: We analyzed 1876 (1289 HIV+, 587 HIV-) women with 18 months of data on self-reported falls during the 6 months prior to each study visit. The primary exposure of interest was subjective cognitive complaints (self-reported major problems with memory or concentration, confusion, or inability to perform routine mental tasks). Hierarchical models evaluated associations between subjective cognitive complaints (and HIV status) and having any fall (vs. none), after adjusting for: (1) demographics, (2) co-morbid conditions, (3) substance use/CNS active medications, and (4) HIV-specific factors. Logistic regression models for prediction of falls were fit, with covariates associated with any fall in univariate analysis (p<0.1) included in multivariable models. Associations with falls did not vary across the three visits, thus visits were pooled together and generalized estimating equations with logit link adjusted for within-person correlation due to use of repeated measures.
Results: HIV+ women were older than HIV- women (median 49 vs. 47yr, p<0.0001), and more likely to report neuropathy (21% vs. 14%, p=0.0003); 11% of all women reported cognitive complaints. On average, at least one fall was reported in 17.5% of HIV+ and 17.6% of HIV-women. HIV remained unassociated with incident falls in multivariate analyses. Subjective cognitive complaints were associated with increased odds of having any fall (Table models 1-2), however this association was reduced by 45% after fully adjusting for covariates associated with falls, in particular medical comorbidities (Table models 3-4). Similar patterns were seen in HIV+ women.
Conclusion: HIV+ women did not have more frequent falls compared with HIV- women. Subjective cognitive complaints were associated with greater odds of having a fall; this risk was reduced by 45% with full adjustment of covariates. Among HIV+ women, the association between cognitive complaints and falls appears to be mediated by comorbid medical illness. Additional studies are needed to understand which comorbid illnesses are most influential and whether management of those conditions can prevent falls among aging HIV+ women.

Table: Relationship between Subjective Cognitive Complaints and Odds of Any fall in WIHS

	HIV+ and HIV- women		HIV+ women only	
	AOR (95% CI)	P value	AOR (95%CI)	P value
Model 1: Subjective Cognitive Complaints adjusted for HIV status	2.60 (2.06, 3.28)	<0.0001	N/a	N/a
Model 2: Adjusted for Model 1 + Demographics	2.30 (1.78, 2.96)	<0.0001	2.03 (1.49, 2.76)	<0.0001
Model 3: Adjusted for Model 2 + Comorbidities	1.46 (1.12, 1.91)	0.006	1.23 (0.89, 1.71)	0.20
Model 4: Adjusted for Model 3 + Substance Abuse & CNS active agents	1.42 (1.08, 1.86)	0.01	1.18 (0.85, 1.64)	0.33
Model 5: Adjusted for Model 4 + Prior AIDS	N/a	N/a	1.09 (0.83, 1.42)	0.55

362 PREVALENCE OF NEUROCOGNITIVE DISORDERS IN A WELL-TREATED AND AGING SWISS HIV-COHORT

Melanie Metral[1], Isabella Locatelli[1], Peter Brugger[2], Klemens Gutbrod[3], Ursula Kunze[4], Isaure Nadin[5], Marc Schwind[6], Riccardo Pignatti[7], Matthias Cavassini[1], Renaud Du Pasquier[1]
[1]Univ of Lausanne, Lausanne, Switzerland, [2]Univ Hosp of Zürich, Zürich, Switzerland, [3]Univ Hosp of Bern, Bern, Switzerland, [4]Felix Platter Hosp, Basel, Switzerland, [5]Univ Hosps of Geneva, Geneva, Switzerland, [6]Klinik für Neuro, St. Gallen, Switzerland, [7]Servizio di Malattie Infettive, Lugano, Switzerland

Background: The prevalence of HIV-infected associated neurocognitive disorders (HAND) remains high. In particular, the prevalence of HAND and the contribution of confounding factors in a well-treated aging population are unknown. This study aims to determine the prevalence and incidence of neurocognitive disorders (NCD) through longitudinal neurocognitive assessment over a 4 years period in a large well-treated and aging HIV cohort. In the present abstract, findings of the baseline milestone are presented.
Methods: This is an ongoing, prospective, longitudinal, multicenter and multilingual (German, French and Italian) study within the Swiss HIV Cohort Study called the NAMACO study (Neurocognitive Assessment in the Metabolic and Aging COhort). So far, we have analysed 899 HIV-infected subjects older than 45 years who have undergone a thorough standardized neuropsychological assessment inspired by the tests used in the START study covering 7 cognitive domains (memory, attention, speed of information processing, executive functions, language, motor skills and sensory-perceptive abilities). To diagnose HAND, we referred to the Frascati criteria.
Results: Our cohort (mean age 55±7.5 years, 80% men, 92% Caucasian) had a high proportion of undetectable viral load (96%, VL<50 copies/ml; median current CD4 632 cell/mm3 and median nadir CD4 180 cell/mm3). At baseline, the prevalence of NCD was 41%, with 27% of patients suffering from HAND (26% asymptomatic neurocognitive impairment (ANI), 0.7% mild neurocognitive disorder, and 0.7% HIV-associated dementia) and 14% due to"other"factors (mostly psychiatric disorders). Lower employment status (36%) was associated with a higher prevalence of ANI (31%) and"other"(25%). Motor skills (42% of our population), speed of processing (33%) and attention/working memory (33%) were the most frequently impaired domains.
Conclusion: We were able to implement a standardized neuropsychological testing in three national languages, which provides a unique comprehensive view of the cognitive status of older HIV-infected patients in Switzerland. Despite the fact that HIV in this cohort is very well controlled (96% aviremic), the prevalence of HAND remains high (27%). However, the HAND population is composed mostly of ANI. Psychiatric disorders represent the most important confounding factor, accounting for one third of cognitive disorders. The most affected domains were motor skills, speed of processing and attention/working memory.

363 CNS MONITORING OF CART INTERRUPTION IN INDIVIDUALS TREATED DURING FIEBIG I ACUTE HIV

Phillip Chan[1], Donn Colby[1], Victor Valcour[2], Napapon Sailasuta[3], Shelly J. Krebs[4], Linda Jagodzinski[4], Robert Paul[5], Jintanat Ananworanich[4], **Serena Spudich**[6], for the RV411 and RV254/SEARCH 010 Study Groups
[1]SEARCH, The Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [2]Univ of California San Francisco, San Francisco, USA, [3]Univ of Hawaii, Honolulu, HI, USA, [4]US Military HIV Rsr Prog, Silver Spring, MD, USA, [5]Univ of Missouri–St. Louis, St. Louis, MO, USA, [6]Yale Univ, New Haven, CT, USA

Background: Monitored treatment interruption (TI) of combination antiretroviral therapy (cART) is a frequent strategy in studies of HIV remission. We assessed the central nervous system (CNS) effects of TI after sustained treatment started in early acute HIV infection (AHI) to monitor for adverse consequences of inflammation or dysfunction in the CNS and examine sources of viral rebound following withdrawal of cART.
Methods: Eight participants with >24 months of viral suppression after a median of 2.8 (range 2.5-5.5) years of treatment initiated during Fiebig I (HIV RNA+, p24-, IgM-) AHI elected for TI followed by plasma HIV RNA monitoring every 3-7 days and cART resumption once plasma HIV RNA >1,000 cps/ml. Optional CNS measures during stable therapy prior to TI (pre-TI) and after post-TI rebound viremia (any plasma HIV RNA of >20 cps/ml) included cerebrospinal fluid (CSF) HIV RNA (LLOD 80 cps/ml), soluble CSF and plasma immune activation markers, and cerebral metabolites via 3T brain magnetic resonance spectroscopy (MRS). Participants completed a novel tablet-based measure of attention and inhibitory control from the NIH-Toolbox (Flanker test) during screening (wk -4), pre-TI wk 0, post-TI wk 1, after rebound viremia, and at 2, 4, and 12 weeks after resuming cART.
Results: Plasma HIV rebound occurred at a median 26 (range 13-48) days after TI. Four participants underwent CSF sampling, revealing no detectable CSF HIV RNA (<80 cps/ml) pre-TI and during rebound viremia (corresponding plasma HIV RNA 30, 78, 739 and 13,462 cps/ml). Levels of CSF and plasma neopterin, MCP1, IP10, and sCD14 did not significantly change from pre-TI to rebound viremia. Brain MRS in basal ganglia and frontal white matter in 5 participants similarly revealed no significant changes in neuronal or inflammatory measures from pre-TI to rebound viremia. Flanker task performance remained similar across intervals of pre-TI wk 0 to plasma rebound (p=0.30). Flanker scores improved from the end of the TI to 12 weeks after resumption of cART (p=0.045) to levels exceeding performance at pre-TI.
Conclusion: Longitudinal monitoring of the CNS did not reveal evidence of adverse CNS effects of TI after cART started during very early acute HIV infection. All of the four participants who had CSF sampling had no detected HIV RNA in the CSF during rebound plasma viremia. Examination of the CNS is feasible to integrate in systemic HIV studies and critical for a comprehensive understanding of the impact of interventions aimed at viral remission.

364 CSF HIV-1 COMPARTMENTALIZATION BY ENV DEEP SEQUENCING: RELATION TO NEURONAL INJURY

Richard W. Price[1], Magnus Gisslén[2], Laura P. Kincer[3], Ean Spielvogel[3], Amy Lin[1], Jaser Eusuff[4], Serena Spudich[5], Ronald Swanstrom[3], Sarah Beth Joseph[3], for the THINC Study Group
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Sahlgenska Academy at the Univ of Gothenburg, Gothenburg, Sweden, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]Univ of California Berkeley, Berkeley, CA, USA, [5]Yale Univ, New Haven, CT, USA

Background: HIV-1 infection of the central nervous system (CNS) is a constant feature of systemic infection and HIV RNA is detectable in cerebrospinal fluid (CSF) of virtually all untreated viremic individuals. CSF HIV can derive from circulating blood (equilibrated) but also from locally replicating populations (compartmentalized) due to either clonal expansion or sustained replication and evolution of diverse populations. We used partial HIV env deep sequencing to survey matched CSF and blood from untreated individuals grouped by blood CD4+ T cell counts, clinical status, and concentrations of CSF neurofilament light chain (NFL), a sensitive biomarker of neuronal injury.
Methods: We cross-sectionally examined 43 archived CSF and blood sample pairs from untreated individuals from Gothenburg and San Francisco, and successfully generated sequences from 33 pairs divided into 4 groups: 1. neuroasymptomatic (NA) CD4 >200 cells/µL (N=8); 2. NA CD4 <200 with normal CSF NFL (NFL-) (N=8); 3. NA CD4 <200 with elevated NFL (NFL+) (N=10); and 4. clinically diagnosed HAD (N=7), all with elevated CSF NFL. Viral RNA was used to generate cDNA, and the V1/V3 region of env amplified and sequenced using Illumina MiSeq deep sequencing with PrimerID. Neighbor joining phylogenetic trees were constructed for each subject and visually segregated into 3 types: A. genetically diverse compartmentalized CSF populations comprising >1/3 of CSF env genes; B. CSF clonal expansions with limited diversity of CSF env genes; and C. fully equilibrated CSF and plasma populations.
Results: Compartmentalization of CSF HIV populations was common through the course of infection, though its character changed (Table). Whereas clonal expansion predominated in early infection and in later infection without neuronal injury (Groups 1 and 2), diverse compartmentalized populations predominated in late infection with neuronal injury (Groups 3 and 4). However, all groups contained some individuals with diverse compartmentalization or equilibrated infection.
Conclusion: Diverse compartmentalization in most individuals with elevated CSF NFL supports the importance of local CNS HIV replication to CNS injury. However, clonal expansion and equilibrated infection in some with elevated CSF NFL suggests that either it is not the sole or simple determinant of neuronal injury and that additional pathogenic factors are also involved, or that CSF sample and sequencing selection did not fully represent local replication in brain.

TABLE CSF:blood HIV Population Relationships

Subject Group	N	Diverse compartment A	Clonal expansions B	Equilibrated C
1. >200 CD4	8	25.0%	50.0%	25.0%
2. NA <200 CD4 NFL-	8	25.0%	62.5%	12.5%
3. NA <200 CD4 NFL+	10	60.0%	20.0%	20.0%
4. HAD	7	85.7%	0.0%	14.3%

365 EARLY EMERGENCE OF MAC-TROPIC HIV VARIANTS IN BRAIN OF PATIENTS WITH NORMAL NEUROLOGY

Maria Paz Gonzalez-Perez, Paul P. Peters, Paul Clapham
Univ of Massachusetts, Worcester, MA, USA

Background: Highly mac-tropic R5 variants are predominant in brain tissue of AIDS patients with neuroAIDS including HAD. Proviral load in brain tissue is low before neuro-disease develops making it difficult to amplify HIV env sequences. However, if envs could be amplified, they may provide insights into Env genotypes and properties associated with HIV colonization of brain tissue, before the highly mac-tropic, neurovirulent variants develop. Here, we investigated sequences of HIV-1 envs derived from immune and brain tissue of 12 AIDS patients with normal neurology or minor complications (N/MC), before expressing Envs on pseudoviruses and evaluating their properties.
Methods: Envelopes were amplified from DNA or RNA from single genomes present in brain and spleen, bone marrow or plasma. Envs were cloned into the pcDNA 3.1D/V5-His-TOPO and sequenced. Env+ pseudovirions were prepared by cotransfection of env vectors with env- pNL4.3 into 293T cells and titrated on HeLa TZM-BL (CD4+ CCR5+ CXCR4+), HIJ (CD4+ CCR5- CXCR4+) and on macrophages. Phylogenetic analyses were undertaken with MEGA v6.
Results: N/MC subjects had lower levels of HIV proviral DNA in the brain, with viral sequences difficult to detect in most subjects. However, a substantial number of envs were amplified from brain tissue DNA and/or RNA of seven subjects. Mac-tropic Envs were detected in brain tissue of four N/MC subjects. These mac-tropic R5 Envs in brain tissue formed distinct phylogenetic clusters from most non-mac-tropic envs from spleen or brain. PCR of env sequences from brain tissue RNA indicated that there was evidence of active replication in brain tissue of some subjects. Envs from immune tissue of the N/MC subjects were nearly all tightly non-mac-tropic contrasting with our previous data for neuroAIDS subjects where Envs derived from immune tissue mediated a range of macrophage infectivity from background levels to modest infection, with a small number of Envs mediating high macrophage infection.
Conclusion: Macrophage-tropic variants are established and likely to be replicating in the brain of a percentage of HIV+ subjects early in disease, well before serious neurological dysfunction becomes apparent. These mac-tropic variants may represent viruses early in their adaptation for infection and replication in brain, perivascular macrophages. Our data provide new insights into HIV replication and evolution of mac-tropic Envs in brain tissue of AIDS patients before the onset of serious neurological complications.

366 BLOOD BRAIN BARRIER FUNCTION, ART NEUROACTIVITY, AND RISK OF CSF HIV ESCAPE

Carmela Pinnetti, Massimo Tempestilli, Patrizia Lorenzini, Valentina Fedele, Stefania Carta, Valentina Mazzotta, Chiara Agrati, Adriana Ammassari, Carlo F. Perno, Andrea Antinori
Natl Inst for Infectious Diseases, Rome, Italy

Background: It is debated whether HIV cerebrospinal fluid (CSF) escape (HIVE) may be linked to patients' features or to ineffective antiretroviral (ARV) CSF penetration. Aim was to assess CSF penetration and activity of ARVs and correlation with blood brain barrier (BBB) and to estimate risk and predictors of HIVE.
Methods: Retrospective study on CSF/plasma paired samples from HIV+ patients taking cART undergoing lumbar puncture (LP) because neurologically symptomatic or for CNS staging. HIVE was: a) detectable CSF HIV-RNA with concurrent plasma <50 cp/mL; b) CSF HIV-RNA >1.0 log10 higher than in concomitant plasma. ARVs concentrations in CSF and plasma were measured by mass spectrometry methods. CSF/plasma concentration ratio was calculated and 95% CSF inhibitory quotients (IQ95) derived, and considered optimal if >1. Impaired BBB was defined by CSF/plasma albumin quotient x 103 (Qalb), according to age-normalized reference ranges (Reiber, Clin Chem, 1995). Adjusted ORs of HIVE were estimated by fitting a logistic multivariable regression model.
Results: 133 CSF/plasma pairs from 120 patients (2000-2014). Male 79.7%; median age 47y (IQR 40-51); CD4 count <200 cells/mm3 47.4%. At LP, 58.7% was on TDF/FTC, 3% ABC/3TC, 10.5% ZDV/3TC, 36.8% EFV, 27.1% LPV/r, 13.5% ATV/r, 11.3% DRV/r. Proportion of samples with IQ95 >1 was lower for LPV/r and ATV/r (p=0.014). After stratification by Qalb, the proportion of CSF with IQ95 >1 in the two strata was still similar for EFV, ATV/r and DRV/r, but not for LPV/r (p=0.05 at interaction test). A positive correlation between Qalb and CSF/plasma ARV concentration ratio (R=0.686, p<0.001) and ARV IQ95 (R=0.658, p<0.001) was found. HIVE was detected in 19/133 samples (14.4%). Only in a subset of 73 asymptomatic pts, duration of current cART [AOR 1.98 per year more (95%CI 1.27-3.12)] and CSF log10 HIV-RNA [AOR 17.91 (95%CI 1.04-307.55)] was associated to an increased HIVE risk by multivariable logistic regression. IQ95 of third drug was not associated with HIVE [AOR 0.84 95%CI 0.20-3.50], whereas Qalb was associated to increased HIVE risk [AOR 5.75; 95%CI 1.10-30.1].
Conclusion: BBB dysfunction may influence neuropenetration (CSF/plasma drug concentration ratio) and efficacy (IQ95) of ARVs and play a role on asymptomatic HIVE mechanism. Despite the fact that action of ARVs in the CNS, except for DRV/r, was far below, the role of drug exposure and activity in CSF on HIVE pathogenesis remains controversial.

Drugs^	Samples No.	HIV escape	CSF PK, ng/mL, median (IQR)	CSF/plasma ARV drug ratio, median (IQR)	IQ_{95}, median (IQR)	Samples with IQ_{95}>1	Samples with IQ_{95}>1	
							Q_{alb} normal (intact BBB) §	Q_{alb} abnormal (altered BBB)#
EFV	49	5 (10.2%)	10.1 (5.9-17.0)	0.7% (0.2%-1.0%)	2.1 (1.2-3.6)	39 (79.6%)	28/35 (80.0%)	11/14 (78.6%)
LPV/r	36	8 (22.9%)	20.5 (13.8-51.0)	0.3% (0.2%-0.6%)	1.2 (0.8-3.0)	22 (61.1%)	7/19 (36.8%)	15/17 (88.2%)
ATV/r	18	4 (22.2%)	9.1 (4.0-15.6)	0.9% (0.5%-1.3%)	1.4 (0.6-2.4)	11 (61.1%)	8/13 (61.5%)	3/5 (60.0%)
DRV/r	15	2 (13.3%)	39 (12.7-104.2)	0.7% (0.5%-1.9%)	20.5 (6.7-54.8)	15 (100.0%)	4/4 (100.0%)	11/11 (100.0%)
^Drugs with <5 samples collected were not showed in Table (nevirapine=4, nelfinavir=4, etravirine=2, raltegravir=2, rilpivirine=1, maraviroc=1, tipranavir=1)								

*p at chi square test=0.014; §p at chi square test=0.006; #p at chi square test=0.171

367 SEX-BASED DIFFERENCES IN HIV RESERVOIRS IN BRAIN AND NEUROCOGNITION

Michelli Faria de Oliveira[1], Masato Nakazawa[1], Andrej Vitomirov[1], Mitchell Zhao[1], Ben Gouaux[2], David Moore[2], Ronald J. Ellis[2], Davey M. Smith[1], Sara Gianella[1]
[1]Univ of California San Diego, La Jolla, CA, USA, [2]Univ of California San Diego, San Diego, CA, USA

Background: While antiretroviral therapy (ART) can reduce HIV RNA below the limit of detection in plasma, HIV DNA reservoirs can persist in anatomic compartments, as the central nervous system. The clinical and biological factors that influence HIV reservoirs in the brain are unknown.
Methods: Paired autopsy tissues from frontal cortex [FC, N=61], occipital cortex [OCC, N=53], basal ganglia [BG, N=30]) and peripheral lymph tissue (LT, N=37) were collected from 63 HIV+ adults as part of the National NeuroAIDS Tissue Consortium between 1999-2014. All participants died with documented virologic suppression on ART (<50 or 400 copies/ml, assay-dependent) without evidence of major neurologic conditions. Genomic DNA was extracted by magnetic beads; levels of HIV DNA were measured by ddPCR and normalized by RPP30. Neurocognitive (NC) functioning was assessed at the last visit (median 3 months before death) and participants were categorized as: (1) no NC impairment (NCI) (2) subclinical NCI, (3) mild NCI (4) severe NCI (all HIV-associated), (5) non-HIV associated NCI. Bayesian hierarchical regression model was used to evaluate the relationship between brain regions, sex, and NC functioning after adjusting for significant covariates. Significance of an effect is assessed with the Bayesian p-value and the difference in Leave-One-Out (LOO) criteria: positive value = greater fit.
Results: The study cohort is composed of 12 female and 51 males with a median age of 45 years. Median CD4+ at the last visit was 164 [IQR: 80-390] and median estimated duration of infection (EDI) was 14 years [IQR: 10-19]. HIV DNA was detected in 69% of all brain and 100% of peripheral LT samples. BG had higher levels of HIV DNA (17.5 copies/106 cells) compared to FC (15.1, p=0.13) and OC (11.9, p=0.04). Females had higher levels of HIV DNA than males across all brain regions (p=0.05, Figure) but not in peripheral LT (P>0.2) after adjusting for CD4+, EDI, age and year of death. We found a robust significant interaction between sex, HIV DNA, and NC functioning (LOO Difference=1.4). Preliminary results indicate that increased HIV DNA differentially affected NC functioning in women and men, depending on the severity of the impairment.
Conclusion: HIV DNA was detected in the majority of brains despite virologic suppression. While levels of HIV DNA were comparable in peripheral LT, women presented higher brain HIV DNA levels than men. These brain HIV reservoirs might differentially affect neurocognition in women and deserve investigation.

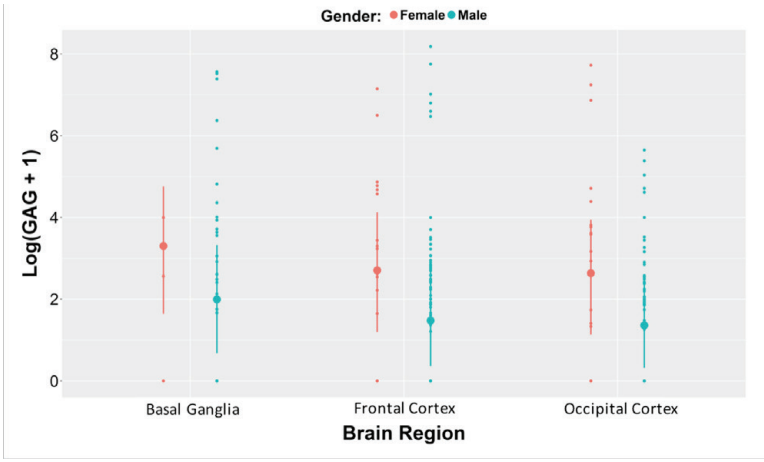


Figure. Difference in levels of HIV DNA (gag) across brain regions between females and males. Females had greater levels of HIV DNA than men in brain regions.

368 THE EFFECT OF CRYPTOCOCCAL MENINGITIS ON THE HIV RESERVOIR IN THE CNS

Maura Manion[1], Camille Lange[2], Kathy Huppler Hullsiek[3], Brandon Keele[4], Helene Highbarger[5], David Meya[6], Frank Maldarelli[4], David Boulware[3], Irini Sereti[1]
[1]NIAID, Bethesda, MD, USA, [2]NIH, Frederick, MD, USA, [3]Univ of Minnesota, Minneapolis, MN, USA, [4]NCI, Frederick, MD, USA, [5]Leidos Biomed, Inc, Frederick, MD, USA, [6]Makerere Univ, Kampala, Uganda

Background: Opportunistic central nervous system (CNS) infections are postulated to influence the formation and persistence of a HIV CNS reservoir through trafficking of infected and activated cells. Viral compartmentalization present at initiation of antiretroviral therapy (ART) initiation may affect the establishment of a reservoir. We investigated the role CNS infections have in seeding the HIV reservoir by characterizing viral populations and compartmentalization of virus in blood and cerebrospinal fluid (CSF).
Methods: Paired CSF and plasma samples from 73 HIV-infected persons with cryptococcal meningitis were obtained prior to ART during two clinical trials in Uganda. In a subset of patients (N=14), single genome sequences (SGS) of HIV-1 envelope were obtained from paired plasma and CSF samples, aligned (MEGA), and subjected to phylogenetic and population genetic analysis, including geographic subdivision to determine panmixia between populations, and Slatkin-Maddison population migration studies to determine structural shifts between populations. Geno2Pheo algorithm was used to predict co-receptor utilization.
Results: Participants (Table) had median CD4 =21 cells/μL and pre-ART HIV-1 viral load (VL) of 5 log10 RNA copies/mL in plasma and 4.6 log10 copies/mL in CSF. CSF VL was lower by a median of 0.3 (IQR: -0.2, 0.9) copies/mL than in plasma. Median CSF VL was higher by 0.42 log10 copies/mL in those with CSF WBC ≥ 5 than in < 5 cells/μL (p=0.03). Single genome sequences (length 21818nt) were obtained. Geographic subdivision and migration studies demonstrated viral compartmentalization between CSF and plasma in 43% (6/14) patients, 4 of 6 with higher plasma VL than CSF and 2 of 8 with higher CSF VL than plasma. Analysis of predicted co-receptors identified X4 variants in CSF and plasma, including patients with compartmentalization; CSF may have predominantly X4 virus even when plasma has predominantly R5 variants.
Conclusion: This is the first description of HIV-1 compartmentalization in the CNS during AIDS-related infections. The difference between HIV VL in plasma and CSF in these persons was less than expected. Persons with greater CSF pleocytosis had higher CSF VL. Of cryptococcal meningitis participants, 40% had distinct HIV populations in CSF and in plasma, with a trend of compartmentalization that varied with CSF VL. This provides insights into the seeding of the HIV reservoir during CNS opportunistic infections.

Characteristics of Participants with Cryptococcal Meningitis	
n	73
Age, years	37 [29, 43]
Male Sex	34 (68%)
CD4 count/μL	21 [10, 70]
CSF WBC cells/μL	<5 [<5, 25]
CSF WBC < 5 cells/μL	30 (70%)

Distribution of HIV-1 Viral Loads				
	N	Median [IQR]	Mean	P-value
CSF Viral Load	73	4.61 [3.6, 5.15]	4.26	0.03
CSF WBC <5 cells/μL	30	4.74 [3.79, 5.22]	4.54	
CSF WBC ≥5 cells/μL	13	5.16 [4.71, 5.37]	5.06	
Plasma Viral Load	58	4.99 [4.27, 5.47]	4.61	0.26
CSF WBC ≤5 cells/μL	25	5.13 [4.46, 5.46]	5.05	
CSF WBC ≥5 cells/μL	10	5.41 [5.02, 5.63]	5.32	

Values are median [IQR] or N (%); P-value by independent *t*-test.
Viral loads are $\log_{10}$ copies/mL.

369 HIV CNS COMPARTMENTALIZATION AMONG SUBJECTS WITH HIV-1 SUBTYPES G AND CRF02_AG

Olubusuyi M. Adewumi[1], Elena Dukhovlinova[2], Nathan Shehu[3], Shuntai Zhou[2], Maxwell Akanbi[3], Babafemi Taiwo[4], Adesola Ogunniyi[1], Kevin Robertson[2], Ronald Swanstrom[2]
[1]Univ of Ibadan, Ibadan, Nigeria, [2]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]Jos Univ Teaching Hosp, Jos, Nigeria, [4]Northwestern Univ Feinberg Sch of Med, Chicago, IL, USA,

Background: HIV-1 compartmentalization in the central nervous system (CNS) and its contribution to neurological disease are incompletely understood. Previous studies were conducted among subjects infected with subtypes B or C. Little is known about other HIV-1 subtypes. We investigated HIV-1 compartmentalization in the CNS of subjects infected with HIV-1 subtypes G and CRF02_AG, the most prevalent subtypes in parts of sub-Saharan Africa.
Methods: A cross-sectional study was conducted among HIV-infected subjects with suspected cryptococcal meningitis at Jos University Teaching Hospital, Nigeria. Paired plasma and cerebrospinal fluid (CSF) samples were collected from 13 (M-6, F-7; age range: 23-45yrs) subjects with a clinical indication for lumbar puncture. Viral RNA extraction, cDNA synthesis, and amplification of the V1/V3 region of env and the full-length HIV-1 env gene were done by PCR techniques using specific sets of primers. Pooled libraries of VI/V3 amplicons (tagged with Primer ID) and full length HIV env genes were analyzed by deep sequencing and single genome amplification (SGA) assays respectively, followed by phylogenetic analysis to determine evolutionary association.
Results: Plasma and CSF viral RNA of the subjects ranged between <400 - 1.0 x106 copies/mL and <400 - 5.1 x106 copies/mL, respectively. Six of the subjects had sufficient levels of virus in the CSF to allow comparison to virus in the blood. All recovered isolates were most closely related to HIV-1 subtypes G or CRF02_AG. Deep sequencing demonstrated HIV-1 compartmentalization in the CNS in subjects A02, A04 and A10, and equilibrated virus populations in the plasma and CSF in subject A13. Further analysis by SGA assay confirmed the findings and showed a diverse level of compartmentalization in the subjects (Figure 1). Determination of the method of entry of the phenotype of the compartmentalized variants is ongoing.
Conclusion: We have provided the first documentation of CNS compartmentalization of HIV-1 subtypes G and CRF02_AG. Improved understanding of effects compartmentalization on CNS HIV drug susceptibility, viral reservoir, and neurological disorders in sub-Saharan Africa where these subtypes are dominant is imperative. Extremely high viral RNA levels observed in the CSF of subject A13 may be due to the transfer of infected T cells into the CSF/CNS indicating a possible contribution of the meningitis that is prevalent in HIV-1 patients in the region.

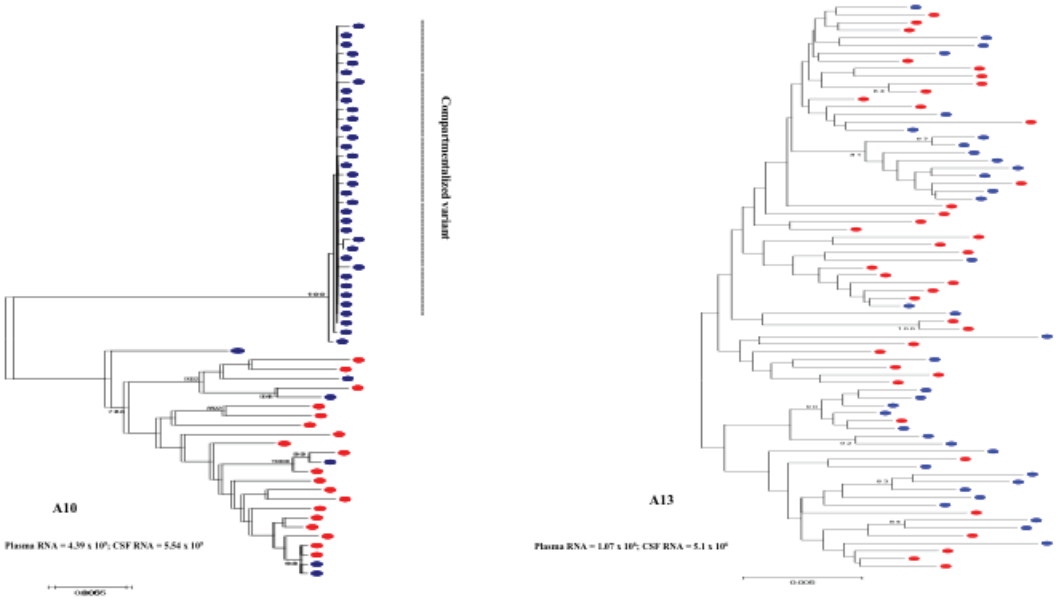


Figure 1: Phylogenetic trees showing evidence of compartmentalization of HIV in the CNS in subject A10, and suspected pleocytosis in subject A13. Test of phylogeny was done by Neighbor-joining statistical method and bootstrap values are indicated if >75%. Legend: - CSF - Plasma

370 EXPRESSION OF UNIQUE AND DIVERSE HIV VARIANTS IN CEREBROSPINAL FLUID DURING ART

Jeffrey A. Johnson[1], Sarah Malik[1], Sam Nightingale[2], Jin-fen Li[1], Apostolos Beloukas[2], Tom Solomon[2], Saye Khoo[3], Anna Maria Geretti[2]
[1]CDC, Atlanta, GA, USA, [2]Univ of Liverpool, Liverpool, UK, [3]Univ of Liverpool Inst of Translational Med, Liverpool, UK

Background: The central nervous system (CNS) may become a sanctuary site for HIV during stable antiretroviral therapy (ART). The determinants and mechanisms of viral persistence in CNS remain poorly understood. Using a particle immunocapture algorithm targeting cell proteins within HIV envelopes, we investigated the possible cellular sources of HIV persisting in cerebrospinal fluid (CSF) and examined the phylogenetic relatedness of plasma and CSF viruses.

Methods: From the PARTITION Study, we examined 6 HIV-positive persons on stable ART who underwent lumbar puncture for neurological disease (n=4) or a history of intermittent plasma viremia (n=2). Virions expressed in CSF were segregated by source cell type by targeting 10 different host cell proteins that may embed in HIV envelopes during budding. Virions from each capture step were sequenced for evidence of reverse transcriptase (RT) drug-resistant variants (DRVs), and for relatedness to other viruses in the CSF and in plasma. Drug concentrations in plasma and CSF were measured by HPLC.

Results: At sampling, HIV-1 RNA levels in CSF were median 1.2 log10 c/ml (range 0.4-2.0) higher than in paired plasma (Table). The captures identified distinct HIV variants in the CSF of 4/6 individuals. Two subjects (ID 01A and 14A) with no reported NNRTI exposure expressed NNRTI-DRVs in CSF, while plasma viremia was suppressed. One person on an efavirenz (EFV)-containing regimen (ID 04A) expressed 3 different NNRTI-DRVs in the CSF, with no evidence of plasma DRVs. One person with prior abacavir (ABC)/lamivudine (3TC) and current emtricitabine (FTC) exposure (ID 01B) expressed M184I in CSF, whereas one other individual with prior ABC exposure (ID 14A) had a K65E variant. CSF DRVs found in captures were associated with CD45RA-/CD45RO+ and CD3-/CD2+ and/or CD10+ particles, suggesting perivascular macrophage or TH17 cells and NK cells, respectively, as the sources. ID 10A with unsuppressed viremia had phylogenetically distant wildtype viruses in the plasma and CSF, and ART drugs were undetectable.

Conclusion: We found evidence of diverse CSF HIV variants that were distinct from plasma viruses suggesting CNS HIV evolution and maintenance that is separate from blood. Lower CNS drug concentrations and/or activity may allow for compartmentalized selection, persistence and evolution of drug-resistant variants. The capture data suggest different resident cell types were lending to ongoing CNS HIV expression under ART.

Table. Characteristics at time of paired plasma and CSF at sampling and HIV RT DRMs

Participant ID	01A	01B	04A	05B	10A	14A
ART regimen	TDF FTC MVC RAL	TDF FTC DRV/r	AZT 3TC EFV	ABC 3TC DRV/r	TDF FTC RAL	3TC MVC RAL DRV/r
Other (prior) ARVs	None	3TC ABC	None	AZT SQV/r LPV/r	None	ABC
CPE score	10	7		8	7	6
Plasma/CSF drug concentration ng/mL	TDF 146/- FTC 1984/- RAL 123/18	TDF -/38 FTC -/63 DRV 1196/20	AZT 298/103 3TC 866/182 EFV 996/22	3TC 35/- DRV 1933/25	RAL <LLQ/<LLQ	MVC 118/48 RAL 1237/171 DRV2667/177
CD4 cells/mm^3	185	660	449	734	342	374
Nadir CD4 cells/mm^3	-	44	390	323	-	30
Plasma/CSF VL c/mL	52/1231	88/1569	3443/13088	258/3518	10817/63010	<40/1981
DRMs						
CSF	K103N [mϕ, $_m$NK]	M184I ($_h$Mc: None)	K103N [NK], V108I, E138A	L74V, M184V	None	K65E [T_H17], V108I, V179D [T_N], M184V
Plasma current	-	-	None	M184V	None	-
Plasma historic	-	K103R M184I	None	-	-	-

-, not available; CPE, CNS penetration effectiveness; <LLQ, below the limit of quantitation; [], cell source suggested by capture: mϕ, macrophage; $_m$NK, mature natural killer cells; $_h$Mc, homing monocyte; T_N, naïve thymocyte

371 CSF ESCAPE IN TREATED HIV INFECTION SHOWS X4 TROPISM AND DEFECTIVE VIRAL SEQUENCES

Bryan Smith[1], Guanhan Li[1], Hiromi Imamichi[2], Brad Sherman[2], Manori De Alwis[1], Govind Nair[1], Joseph Snow[1], Daniel S. Reich[1], H. Clifford Lane[3], Avindra Nath[1]
[1]NIH, Bethesda, MD, USA, [2]NIH, Frederick, MD, USA, [3]NIAID, Bethesda, MD, USA

Background: There is often clinical concern when HIV is detectable in cerebrospinal fluid despite virologic suppression in plasma in well-treated patients with HIV infection. We describe such "asymptomatic" CSF escape in participants enrolled in a cohort study at the National Institutes of Health (NIH) and sequenced the envelope gene.
Methods: Participants with HIV infection and a plasma viral load less than the limit of detection for at least 12 months were enrolled in a natural history study at the NIH evaluating cognitive and neurologic outcomes. All participants completed thorough neurologic and psychiatric evaluations, brain magnetic resonance imaging, a detail neuropsychological battery, and lumbar puncture. MRI brain volumes were determined using Freesurfer. CSF HIV RNA was determined using Roche COBAS Taqman HIV-1 v2.0 and plasma HIV was determined using the Abbott RealTime PCR. CSF escape was defined as a CSF HIV RNA level ≥40 copies/ml with a plasma level <40 copies/ml. Measures of cognition (HIV-associated neurocognitive disorder [HAND], average T-score, and Global Dementia Scale [GDS]) were determined using consensus criteria as previously described. Pac Bio system was used for sequencing of envelope gene, and viral outgrowth assay for detection of replicating virus.
Results: All participants had a plasma viral load <40 copies/ml at the time of evaluation. Of 62 participants who completed all procedures, 9 (14.2%) had CSF escape with a mean CSF viral load of 74.2 copies/ml (range 41-289). Of demographic variables, there were no differences in age (mean 53.3 years without CSF escape and 54.4 years with escape) or sex (36% female without escape and 50% female with escape. There were no significant differences in brain volume or measures of cognition or depression between the two groups. In two individuals, defective viral sequences were predominantly found and analysis of V3 loop showed X4 tropic virus. In one patient, X4 tropic virus capable of infecting astrocytes was found by viral outgrowth assay.
Conclusion: X4 tropic viral sequences predominate in the CSF in asymptomatic CSF escape, the clinical significance of which needs to be determined by longitudinal monitoring of changes in neurologic, cognitive, and psychiatric outcomes.

372 NEUROPSYCHIATRIC ADVERSE EVENTS ASSOCIATED WITH INTEGRASE STRAND TRANSFER INHIBITORS

Prabha Viswanathan, Elande Baro, Guoxing Soon, Adam Sherwat, Kimberly Struble
FDA, Silver Spring, MD, USA

Background: The increased use of INSTI based regimens over PI or NNRTI based regimens is largely due to the potency and safety of INSTIs. Case reports of new-onset or worsening of neuropsychiatric conditions, particularly depression and suicidality, have emerged with INSTIs. These reports prompted FDA to investigate the relationship between INSTIs and neuropsychiatric adverse events (NPAE), and compare the frequency of NPAEs with INSTIs, PIs and EFV.
Methods: FDA conducted a meta-analysis of 6 randomized, active-controlled Phase 3 trials in treatment-naïve subjects (TN) comparing raltegravir, dolutegravir or elvitegravir to: EFV, PIs (atazanavir or darunavir) or another INSTI. These trials were submitted by industry to FDA to support approval of the INSTIs. The frequency of NPAEs in each treatment group was assessed over 96 weeks. NPAEs were identified using the Standardized MedDRA Query (SMQ) Version 18.0. A broad search for terms in the Depression and Suicide/Self-Injury (DSS) SMQ and the Psychosis and Psychotic Disorders (PPD) SMQ was done. The event of highest toxicity grade was counted for each subject. Overall risk difference for INSTI vs EFV and INSTI vs PI was computed based on fixed effects and random effect analyses using inverse variance weights in both models. In the random effects model (DerSimonian-Laird estimate), the study variable was included as a random effect. Analyses were also performed by demographic subgroups (age, sex, race, region, and IV drug use).

Results: The meta-analysis (primary analysis) shows the risk of NPAE in TN patients was similar for INSTI vs EFV and INSTI vs PI. Risk difference (95% CI) for DSS AEs and PPD AEs: INSTI vs EFV -3% (-5,0) and -1% (-2,1) and INSTI vs PI -1% (-2,4) and 0% (-2,1). Results were identical for the fixed and random effects analyses. Grade 3 and 4 events occurred in 1% of INSTI and PI subjects and 2% of EFV. Subgroup analyses were not interpretable due to small sample size.
Conclusion: This meta-analysis shows the risk of NPAE when analyzed at the level of pooled DSS and PPD SMQs is similar for INSTIs vs EFV, with a trend toward lower risk with INSTIs compared with EFV. The risk for NPAEs is similar between INSTIs and PIs. Although NPAEs were infrequent and risk was not increased with INSTIs, providers should be aware of the association between HIV infection, ART, and NPAEs.

Table 1: Summary of Frequently Reported NPAEs (Secondary Analysis: Raw Counts, Unweighted Totals)

	INSTI vs PI			INSTI vs EFV		
NPAEs Pooled by Preferred Terms (All Grades, All Cause)	**INSTI N=2461**	**PI N= 597**	**Risk Difference (95% CI)**	**INSTI N=2461**	**EFV N=1053**	**Risk Difference (95% CI)**
Depression	174 (7.1%)	51 (8.5%)	-1.4% (-3.9%, 1.1%)	174 (7.1%)	101 (9.6%)	-2.5% (-4.5%,-0.5%)
Sleep Disorders	10 (0.4%)	0	0.4% (0.2%, 0.6%)	10 (0.4%)	12 (1.1%)	-0.7% (-1.4%, 0%)
Suicidal Thoughts and Behaviors	14 (0.6%)	1 (0.2%)	0.4% (-0.1%, 0.9%)	14 (0.6%)	2 (0.2%)	0.4% (0%, 0.8%)
Memory Impairment	13 (0.5%)	5 (0.8%)	-0.3% (-1.1%, 0.5%)	13 (0.5%)	3 (0.3%)	0.2% (-0.2%, 0.6%)

373 PROGRESSIVE HIPPOCAMPAL NEURONAL LOSS IN PEDIATRIC SIV INFECTION

Heather Carryl[1], Koen Van Rompay[2], Kristina De Paris[3], Mark W. Burke[1]
[1]Howard Univ, Washington, DC, USA, [2]Univ of California Davis, Davis, CA, USA, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: As of 2013, there are 3.2 million children under the age of 15 living with HIV, globally, with an estimated one new diagnosis every 2 minutes. The devastating neurological impact of HIV on children includes loss of brain growth, motor abnormalities and cognitive dysfunction. Despite early antiretroviral treatment (ART) intervention to suppress viral load, neurological consequences of perinatal HIV-1 infection persist. Utilizing the pediatric simian immunodeficiency virus (SIV) infection model, we tested the hypothesis that early life SIV infection depletes neuronal population in the hippocampus.
Methods: A total of 22 infant rhesus macaques (Macaca mulatta) were divided into three groups: Group 1 received intravenous inoculation of SIVmac251 on postnatal day 3 (n=3) with a survival time of 6-10 weeks; Group 2 was orally challenged with SIVmac251 at week 9 of age (n=15) with a survival period of 12 weeks post-infection; and Group 3 served as uninfected controls with a survival time of 15-22 weeks. Systematic sections through the hippocampus regions CA1 to CA3 were Nissl stained and hippocampal pyramidal neurons were quantified using design-based stereology.
Results: We have previously reported that intravenously SIV-infected neonatal infant macaques (Group 1) displayed a 42% neuronal reduction throughout the hippocampal CA fields. The orally infected infant macaques in Group 2 displayed a 75% neuronal reduction in the CA1 compared to controls and 54% fewer neurons than Group 1 infants. The CA2 region showed a similar pattern with a 67% reduction between Group 2 and controls and a 40% difference between Group 1 and 2. In the CA3 region there were no significant differences between Groups 1 and 2, however both SIV-infected groups had significantly fewer pyramidal neurons than control subjects. Volume differences were found only in the CA1 region between the three groups. Plasma viral load ranged from 170,000 to 650,000,000 copies/ml plasma vRNA, however there were no correlation between plasma viral load and neuronal populations in any of the CA fields.
Conclusion: The loss of hippocampal neurons may contribute to the rapid neurocognitive decline associated with pediatric HIV infection. While each subfield showed vulnerability to SIV infection, the CA1 and CA2 subregions demonstrated a potentially enhanced vulnerability to perinatal SIV infection. These data underscore the need for early diagnosis and treatment including therapeutics targeting the CNS.

374 HIV GENE VARIANTS ALTERING CORECEPTOR BINDING & DRUG RESISTANCE PREDICT CNS PHENOTYPES

Debashis Sahoo, **Sarah Dabydeen**, Kumud K. Singh
Univ of California San Diego, La Jolla, CA, USA

Background: Independently evolved HIV subspecies develop gene variants that provide selective advantage to viral survival and pathogenicity. We hypothesized that unique variants in HIV envelope gp120 (Env) and reverse transcriptase (RT) gene sequences from brain may predict HIV related central nervous system (CNS) disease phenotypes.
Methods: Publicly available database (HANDDB, handdatabase.org) with 5,783 non-redundant HIV subtype B sequences (n=163) from brain and non-brain tissues was assessed for HIV associated neurocognitive disorders (HAND). After aligning sequences by clustalw algorithm, we identified unique nucleotide variants and determined their association with the CNS phenotypes.
Results: Using commonly used HIV genome HXB2 sequence as a reference, we found that specific variants at Env 7144T nucleotide position or amino acid position 307 (aa307, Ile) were associated with HAND phenotype (97% of HAND, n=1016 vs. none in non-HAND sequences, n=661; $p < 0.001$). Also, position 6979G (aa252, Arg) had similar association (76% of HAND, n=816 vs. 17% in non-HAND sequences, n=590; $p < 0.001$). These variants were common in brain and CSF, present predominantly in males, and were associated with lower CD4 cell count, HIV associated dementia/ AIDS dementia complex, and minor cognitive motor disorder. For RT gene, 2754A (aa224, Thr) was predictive of HAND phenotype

(99% of HAND, n=116 vs. 55% in non-HAND sequences, n=51; p < 0.001). Also, nucleotide position 3137G (aa351, Gly) in the RT gene was associated with HAND phenotype (95% of HAND, n=125 vs. 51% in non-HAND sequences, n=51; p < 0.001). Furthermore, 7443A (aa407, Asn), 6676A (aa151, Lys) and 6656G (aa144, Ser) were significantly associated with HIV encephalitis (HIVE) phenotypes (p < 0.001). Despite majority of these individuals being on azidothymidine for at least 20 months, they developed HAND and HIVE phenotypes. Biologically, Env gene variants were associated with alteration in binding site to CCR5/CXCR4 coreceptor (7144T), gp41 (6979G), or development of drug resistance in RT gene (2754A and 3137G).
Conclusion: Presence of unique Env and RT gene variants predicted the CNS phenotypes in HIV infected adults. These studies will help in developing advanced predictive models for identification of individuals at the risk of developing CNS phenotypes and in finding novel viral sequence targets for personalized therapeutics.

375 IFNγ-INDUCED PROTEASOMAL DEGRADATION OF ASTROCYTIC HO-1 IN HIV NEUROPATHOGENESIS

Alexander J. Gill[1], Colleen E. Kovacsics[1], Suren A. Ambegaokar[2], Benjamin B. Gelman[3], Dennis L. Kolson[1]
[1]Univ of Pennsylvania, Philadelphia, PA, USA, [2]Ohio Wesleyan Univ, Delaware, OH, USA, [3]Univ of Texas Med Branch, Galveston, TX, USA

Background: We previously demonstrated that heme oxgyenase-1 (HO-1) protein expression is significantly reduced within the prefrontal cortex of HIV+ individuals and correlated with neurocognitive dysfunction and central nervous system immune activation. We also demonstrated that HIV-infection of macrophages in vitro reduces HO-1 protein expression. Because macrophages are a small cellular component of the brain, the reduction of macrophage HO-1 expression likely accounts for a small part of the total brain HIV-associated HO-1 loss. We therefore investigated the potential contribution of astrocytes, the major reservoir of HO-1 protein in the brain, to this HIV-associated HO-1 loss.
Methods: HO-1 protein and mRNA were quantified by Western blot and qPCR respectively, in two relevant tissue sources: primary human fetal astrocytes treated with interferon-gamma (IFNγ) and brain prefrontal cortex from HIV- and HIV+ brains (n =156) from subjects enrolled in the National NeuroAIDS Tissue Consortium. Pulse-chase HO-1 protein degradation experiments were performed in U251 astrocytic cells transiently expressing FLAG-HO-1.
Results: HO-1 protein is decreased (p<0.01) and HO-1 mRNA is increased (p<0.01) in the prefrontal cortex of HIV+ individuals compared with HIV- controls. HO-1 protein correlates negatively with HO-1 RNA (p<0.05). This HO-1 protein reduction correlates with increased expression of immunoproteasome subunits (LMP7 and PA28α; p<0.05). Prolonged exposure of fetal astrocytes to IFNγ, an HIV-associated immune activator, selectively reduces HO-1 protein expression (p<0.05), increases immunoproteasome subunit (LMP2, LMP7, and PA28α; p<0.001) expression, while decreasing constitutive proteasome subunit (β1 and β2; p<0.001) expression. This IFNγ-mediated reduction of astrocyte HO-1 protein was associated with a non-significant increase in HO-1 RNA expression. Finally, prolonged IFNγ exposure reduced HO-1 protein half-life in astrocytic cells (p<0.001) and this HO-1 degradation was reduced by proteasome inhibitors.
Conclusion: Immunoproteasome-mediated HO-1 degradation in astrocytes is a potential mechanism driving brain HO-1 loss in the HIV-infected brain, in addition to HIV-induced HO-1 loss in infected macrophages. Our data suggest unique causal links among HIV infection, IFNγ-mediated immunoproteasome induction, and enhanced HO-1 degradation, which likely contribute to the neuropathogenesis of HIV-associated neurocognitive disorders (HAND).

376 IFN-B REDUCES MACROPHAGE HEME OXYGENASE-1 EXPRESSION: ROLE IN HIV NEUROPATHOGENESIS

Fiorella P. Rossi[1], **Alexander J. Gill**[1], Rolando Garza[2], Dennis L. Kolson[1]
[1]Univ of Pennsylvania, Philadelphia, PA, USA, [2]Univ of Texas at San Antonio, San Antonio, TX, USA

Background: Chronic HIV infection induces persistent inflammation within the central nervous system (CNS). We have previously demonstrated a deficiency of the highly inducible anti-inflammatory enzyme heme oxygenase-1 (HO-1) in the brains of HIV+ individuals that correlates with markers of neuroinflammation and clinical neurocognitive impairment. Despite a reduction in HO-1 protein expression, HO-1 RNA is increased in the brains of HIV+ individuals. Additionally, we have shown that HIV infection decreases HO-1 protein expression within infected macrophages in association with increased release of neurotoxic levels of glutamate. We hypothesize that HIV-associated pro-inflammatory factors released from HIV-infected macrophages or other activated resident CNS cells drive the decrease in brain HO-1 protein expression.
Methods: We stimulated human monocyte derived macrophages (MDMs) with HIV-associated proinflammatory factors including GM-CSF, TNF-alpha, IFN-beta, and IL-18 for 24 hours and 7 days to resemble acute and chronic exposure in the brain respectively. We determined protein and mRNA levels of HO-1 and heme oxygenase-2 (HO-2), a constitutive isoform of heme oxygenase, by western blot and qPCR, and quantified neurotoxicity by MAP2 ELISA. We also quantified glutamate levels in MDM supernatants using Amplex Red Glutamic acid/glutamate oxidase kit.
Results: Chronic stimulation of MDMs with GM-CSF or TNF-alpha resulted in a marked reduction of HO-1 protein of -3.7 and -2.1 fold, respectively (p<0.001) and mRNA expression of -2.0 and -1.5 fold, (p<0.01) but not a significant difference in HO-2 expression (p>0.1). Surprisingly, while IFN-beta reduced HO-1 protein by 50% (p<0.0001), it increased HO-1 mRNA levels by 15.8 fold (p=0.1); suggesting a post-translational mechanism of HO-1 protein loss. Additionally, supernatants from IFN-beta stimulated MDMs had increased levels of glutamate and associated neurotoxicity (p<0.0001).
Conclusion: Our results demonstrate that chronic stimulation with inflammatory cytokines can drive down HO-1 mRNA and protein in macrophages. However the mechanism of HO-1 protein loss in IFN-beta-stimulated macrophages differs from other inflammatory stimuli. These IFN-beta effects resemble our previous observations of HO-1 expression in the brains of HIV-infected individuals, where HO-1 protein loss was associated with increased HO-1 mRNA. This suggests that IFN-beta can play a major role in HIV neuropathogenesis by reducing HO-1 protein expression.

377 CNS IRON STATUS IS ASSOCIATED WITH NEUROCOGNITIVE FUNCTION OVER TIME IN HIV+ ADULTS

Harpreet Kaur[1], William S. Bush[2], Scott Letendre[3], Ronald J. Ellis[3], Robert K. Heaton[3], Stephanie M. Patton[4], James R. Connor[4], David C. Samuels[5], Todd Hulgan[5], Asha R. Kallianpur[1]
[1]Cleveland Clinic, Cleveland, OH, USA, [2]Case Western Reserve Univ, Cleveland, OH, USA, [3]Univ of California San Diego, San Diego, CA, USA, [4]Penn State, Hershey, PA, USA, [5]Vanderbilt Univ, Nashville, TN, USA

Background: Dysregulated central nervous system (CNS) iron transport has been implicated in neurocognitive (NC) disorders. We hypothesized that cerebrospinal fluid (CSF) biomarkers of CNS iron status are associated with changes in NC function over time in HIV-infected (HIV+) adults.
Methods: CSF iron, heavy-chain ferritin (H-ferritin) and transferrin were quantified in 403 participants in CHARTER, a prospective observational study of HIV+ adults who underwent comprehensive NC testing and assignment of a Global Deficit Score (GDS) at baseline and 6-month intervals up to 42 months (mos.). NC change status (improved/stable/declined) was defined at specific visits or last follow-up compared to baseline. Non-parametric statistical tests were used to test associations at baseline with GDS as a continuous variable, HIV disease or demographic factors. Biomarker associations with NC change status were evaluated by analysis of variance (ANOVA) or logistic regression to adjust for potential confounders such as age, comorbidity, and zidovudine (ZDV) use, which impacts iron transport. Repeated-measures ANOVA was performed to assess biomarker-GDS associations at 30, 36, and 42 mos. Analyses stratified by age and APOE-ε4 carrier status were also explored.
Results: Of 403 HIV+ adults with CSF biomarker data (22% aged≥50, 73% on ART, 68% with undetectable virus, 19% women), 157 completed follow-up at 30 mos., 131 at 36 mos., and 110 at 42 mos. CSF transferrin and H-ferritin were higher in men and participants aged≥50 years but were unrelated to APOE-ε4 status. Higher H-ferritin at baseline was associated with NC improvement at last follow-up in HIV+ adults aged<50, adjusting for age, comorbidity, ZDV use, and APOE-ε4 status, with relative risk 1.17 vs. stable status [p=0.01, 95% CI=1.03-1.33]. H-ferritin and transferrin were also associated with GDS differences at 30, 36 and 42 mos., adjusting for comorbidity [p<0.05 for both H-ferritin and transferrin; 0.5-1.1% of total GDS variance explained]. H-ferritin at baseline was also associated with better GDS in participants aged<50 at 30, 36, and 42 mos. (1.3% of GDS variance over 42 mos. explained). In APOE-ε4 carriers aged≥50 (N=10), CSF transferrin was associated with better GDS at 30 mos., explaining 11.6% of the total GDS variance.
Conclusion: CSF transferrin and ferritin are independently associated with NC change status and longitudinal GDS differences in HIV+ adults. Larger studies, including more older HIV+ adults, are needed to confirm these findings.

378 DIFFERENTIAL IN VITRO NEUROTOXICITY OF ANTIRETROVIRAL DRUGS

Cagla Akay-Espinoza, Anna L. Stern, Rebecca I. Nara, Nina Panvelker, Jiean Li, Kelly L. Jordan-Sciutto
Univ of Pennsylvania, Philadelphia, PA, USA

Background: Mounting evidence suggests antiretroviral drugs (ARVs) may potentially contribute to the persistence and evolution of clinical and pathologic presentation of HIV-associated neurocognitive disorders (HAND), which impacts 30%–50% of HIV+ patients in the post-antiretroviral (ART) era. We previously reported that two first generation HIV protease inhibitors (PIs), ritonavir and saquinavir, led to oxidative stress and induced the unfolded protein response (UPR), with subsequent synaptic damage and neuronal death in vitro. Intriguingly, augmentation of the endogenous antioxidant response (EAR) by monomethyl fumarate (MMF) reversed PI-induced neurotoxicity. In this study, we determined whether two newer PIs, darunavir and lopinavir, were deleterious to neurons in vitro. Further, we expanded our assessment to include two integrase inhibitor (IIs) class ARVs, dolutegravir and elvitegravir.
Methods: Primary rat neuroglial cultures at 14–21 days in vitro were treated with increasing therapeutically relevant doses of ARVs for 4 h–8 days, and oxidative stress, mitochondrial membrane potential, UPR activation and neuronal viability were assessed.
Results: Within the II class, elvitegravir but not DTG was neurotoxic in a dose dependent manner after 2, 4, and 8 days of treatment. Within the PI class, lopinavir but not darunavir was neurotoxic after 2d. Moreover, lopinavir increased BiP, a UPR marker, and heme-oxygenase 1 (HO-1), an EAR protein induced in response to oxidative stress, whereas mitochondrial membrane potential was decreased with lopinavir treatment. Preliminary results indicated that two HO-1 inducers, MMF and 1-(2-Cyano-3,12,28-trioxooleana-1,9(11)-dien-28-yl)-1H-imidazole (CDDO-Im), partially ameliorated lopinavir-induced neurotoxicity.
Conclusion: These findings support our previous observations that PI-induced neurotoxicity could be alleviated by EAR induction. Intriguingly, ARV-mediated deleterious effects were observed with certain PIs and IIs, providing support for the potential class- and drug-specific neurotoxic effects of ARVs. Future in vivo studies are needed to confirm the neurotoxicity profiles of ARVs for potential incorporation into patient management. Furthermore, the EAR may be a potential access point for the development of adjunctive therapies to complement ART to limit their contribution to HAND persistence.

379 DISCORDANT HIV RNA IN OLFACTORY MUCOSA OF HIV-POSITIVE PATIENTS

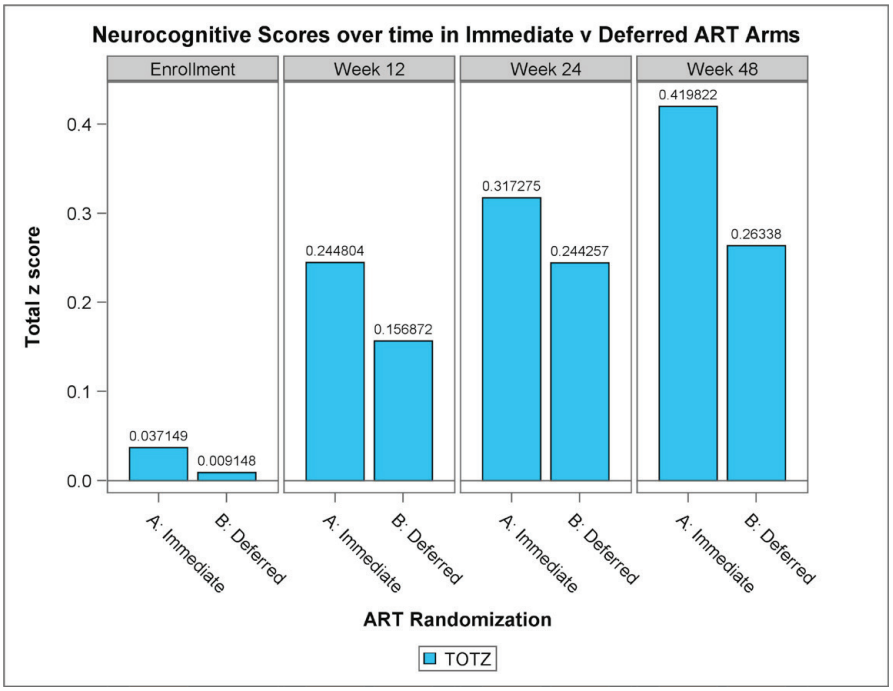
Andrea Calcagno[1], Tiziano Allice[2], Luca Bertero[1], Mattia Trunfio[1], Maria Enrica Amasio[3], Daniele Imperiale[3], Valeria Ghisetti[2], Giovanni Di Perri[1], Paola Cassoni[1], Stefano Bonora[1]
[1]Univ of Torino, Torino, Italy, [2]Ospedale Amedeo di Savoia, Torino, Italy, [3]Ospedale Maria Vittoria, Torino, Italy

Background: Central nervous system (CNS) HIV infection may have relevant long-term consequences for HIV-positive patients. Compartmental viral suppression is tested on cerebrospinal fluid (CSF) samples, although the latter might represent a surrogate marker of brain tissue. The olfactory mucosa (OM) is the only CNS tissue that is easily accessible and its collection may represent a non-invasive diagnostic technique.
Methods: Treated and untreated HIV-positive patients undergoing a lumbar puncture for clinical reasons were included. After signing a written informed consent, patients underwent (<72 hours from the spinal tap) a nasal brushing: after local epinephrine application, 4 swabs (Copan diagnostics) were consequently inserted (2 for each nostril) and a 360-degree rotation performed. Swabs were either inserted in 4% formaldehyde (stained with monoclonal anti-olfactory marker protein, OMP, clone B-6, Santa Cruz Biotechnology, Inc.) or in Copan UTM viral transport medium. Plasma and CSF HIV RNA were quantified with CAP/CTM v.2.0 HIV-1 (Roche Molecular, USA, detection limit 20 copies/mL). HIV RNA was measured in OM (1mL) with a modified CAP/CTM procedure. Data are expressed as medians (interquartile ranges).
Results: 19 patients were included (52.6% male, 68.4% Caucasian, 63.2% on treatment): median age was 49 years (43-58). Median CD4+ T lymphocytes were 174 cells/uL (30-375). Plasma and CSF HIV RNA were 5.2 Log10 copies/mL (4.9-5.7) and 2.2 Log10 copies/mL (1.3-3) in untreated and <1.3 Log10 copies/mL (<1.3-1.8) and <1.3 Log10 copies/mL (<1.3-1.7) in treated subjects; CSF escape was observed in 3 patients (15.8%). Patients' diagnoses included HAND (9 patients, 5 asymptomatic and 4 mild neurocognitive disorders), late-presentation (5), or other conditions. Mild discomfort and sneezing were the only reported side effects. All samples showed a high cellularity, anti-OMP intensity and a median of 45% (30-72) anti-OMP positive cells. OM HIV RNA was detectable in 10 samples [2.43 Log10 copies/mL (1.97-3.21] and it showed a significant correlation with plasma (rho=0.67, p=0.001), but not CSF HIV RNA (rho=0.26, p=0.273).
Conclusion: Nasal brushing is a safe and promising procedure that allows a non-invasive collection of olfactory mucosa cells, including olfactory neurons. HIV RNA can be measured in most samples and it correlated with plasma viral load: studies are ongoing to understand the clinical relevance and source of this mucosal HIV RNA.

380 CAN WE AFFORD TO WAIT? ART AND THE CNS

Kevin Robertson[1], Javier R. Lama[2], Christopher D. Pilcher[3], Jessica Rios[2], Peter Brandes[2], Eduardo Ruiz[2], Eline Appelmans[4], Serena Spudich[5], Ann Duerr[4], for the SABES Team
[1]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Asociacion Civil Impacta Salud y Educacion, Lima, Peru, [3]Univ of California San Francisco, San Francisco, CA, USA, [4]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [5]Yale Univ, New Haven, CT, USA

Background: The central nervous system (CNS) is an early target of HIV infection and inflammation. The prevailing belief is that early identification and treatment are crucial to preventing HIV-associated cognitive impairment. However, the optimal timing of antiretroviral therapy (ART) initiation required to prevent these neurological outcomes remains unknown.
Methods: The SABES study followed high-risk HIV- MSM and transgender women (TW) with monthly HIV testing (serology and RNA). We enrolled MSM/TW with acute (seronegative but HIV RNA+) and recent (seropositive with negative HIV RNA test within past 3 months) HIV infection. Participants were randomized to initiate ART (FTC/TDF/EFV and FTC/TDF/COBI/EVG) immediately after diagnosis or 24 weeks later. They underwent a neurocognitive assessment of 8 functional domains.
Results: Participants with acute HIV (N=31: 16 immediate arm; 15 deferred arm) and recent HIV (N=57: 26 immediate arm; 31 deferred arm) underwent assessments at baseline (N= 31 assessments in immediate arm & 57 in deferred arm), week 12 (N=30 & 57), week 24 (N=27 & 53), and week 48 (N=23 & 34). Participant demographics at enrollment were mean age 26.8 years, education 12.4 years, CD4+ cell count 463 and HIV RNA 5.68 log cps/ml. Overall neurocognitive (total z) and domain scores were derived from site-specific normative data (positive scores reflect better performance). Overall, there was significant improvement over time in total z score among participants ($F(3,188)= 27.15$, $p<.0001$), reflecting the positive effects of entrance to care, practice/learning and ART initiation. There was a trend for greater neurocognitive improvement among participants in the immediate arm at the 48 week time point ($F(1,46)=2.84$, $p=.09$) (See Fig. 1).
Conclusion: This unique randomized cohort offers a rigorous assessment of the consequences that delays in ART initiation may have on neurocognitive function. These preliminary results suggest that HIV care that includes ART initiation very shortly after HIV acquisition resulted in greater improvement in participants' neurocognitive performance over time. Long term follow-up of these participants will provide valuable insights on the further evolution of these early differences in neurocognitive functioning.



381 CENICRIVIROC IMPROVES NEUROCOGNITION AND REDUCES MONOCYTE ACTIVATION IN TREATED HIV

Lishomwa C. Ndhlovu[1], **Michelle L. D'Antoni**[1], Robert Paul[2], Kalpana J. Kallianpur[1], Laurent Fischer[3], Eric Lefebvre[3], Star Seyedkazemi[3], Beau K. Nakamoto[1], Debra Ogata-Arakaki[1], Cecilia Shikuma[1]
[1]Univ of Hawaii, Honolulu, HI, USA, [2]Univ of Missouri–St. Louis, St. Louis, MO, USA, [3]Tobira Therapeutics, Inc, South San Francisco, CA, USA

Background: Our current understanding of the pathogenesis of HIV-associated neurocognitive impairment (NCI) centers on the migration of activated inflammatory monocytes (MO) into the central nervous system (CNS). We hypothesized that antagonizing CCR2 and CCR5 will improve NCI by decreasing MO activation and transmigration.
Methods: A single arm, 24-week, antiretroviral (ART) intensification trial of cenicriviroc (CVC, a dual CCR2 and CCR5 antagonist) in HIV-infected subjects on stable ART>1 year with plasma HIV RNA <50 copies/ml. CVC, a CYP3A4 and P-gp substrate, was dosed based on co-administered ART. Neuropsychological (NP) performance included measures of psychomotor speed (PM), executive function (EF), learning and memory (LM), and working memory (WM). Domain-specific standardized scores (NPZ) were determined and a global NPZ was defined by aggregating the domain scores. At enrollment, subjects were classified as either having low cognitive performance if the NPZ for one or more domains was -0.5 or lower (n=11). All others were classified as cognitively normal (n=6). Plasma markers of monocyte activation (neopterin, soluble (s)CD14 and sCD163) were measured by ELISA. Wilcoxon signed rank test and Pearson correlations were performed for nonparametric and parametric analyses, respectively.
Results: Seventeen subjects, 94% male, median age 55 [IQR 47, 58], and median CD4 count, 545 [404, 731] were included. Significant 24-week improvements in NPZ_global (median change 0.255; p=0.017) and NPZ_WM (median change 0.44; p=0.015) were observed independent of baseline cognitive status. Improvements in NPZ_LM (median change 0.07; p=0.430), NPZ_EF (median change 0.23; p=0.207) and NPZ_PM (median change 0.33; p=0.0797) after 24 weeks were not significant. Significant 24-week decreases were observed for sCD163 (median change -1.54ng/ml; p=0.001), sCD14 (median change -1.17ng/ml; p=0.003) and neopterin (median change -0.87ng/ml; p=0.0004). A 24-week decrease in neopterin predicted an increase from entry to week-24 in NPZ_WM (r=-0.52; p=0.03). Separate analyses in subjects with low vs normal cognitive performance at baseline did not show any appreciable differences in results.
Conclusion: Intensification of ART with CVC may lead to an improvement in NCI, which is associated with a reduction in monocyte immune activation in virally suppressed subjects with chronic HIV. Further study of CVC in a randomized controlled study is warranted.

382 CSF INFLAMMATORY MARKERS AFTER ADDING MARAVIROC TO MONOTHERAPY DARUNAVIR/RITONAVIR

Tristan Barber[1], Arkaitz Imaz[2], Marta Boffito[1], Daniel Podzamczer[2], Anton Pozniak[1], Rosa Fortuny[2], Nicholas Davies[1], Jordi Niubo[2], Sundhiya Mandalia[3], Brian Gazzard[1]
[1]Chelsea and Westminster NHS Fndn Trust, London, UK, [2]Hosp Univ de Bellvitge, Barcelona, Spain, [3]Imperial Coll London, London, UK

Background: Alternative ART strategies such as protease inhibitor monotherapy have raised concerns about CNS penetration. CINAMMON is a phase IV, open-label, single-arm, pilot study to assess the role of maraviroc (MVC) addition to darunavir/ritonavir monotherapy (mono-DRV/r) in virologically suppressed patients.
Methods: Subjects on mono-DRV/r with VL<40 in London and Barcelona were recruited if showing a CCR5 tropic results and remained on mono-DRV/r for 12w before adding MVC. Lumbar puncture (LP) and neurocognitive (NC) function (Cogstate) examinations were performed at baseline, w12 and following 24w of MVC (w36). CSF and plasma DRV/r concentrations were measured at w12 and w36, and MVC at w36. The primary study endpoint was week (w) 12 to w36 CSF inflammatory markers changes (neopterin, S100b, neurofilament heavy chain (NFH), CSF ferritin) following MVC 150mg qd addition to mono-DRV/r 800/100mg qd for 24w. Secondary endpoints included changes in neurocognitive function (Cogstate), and CSF drug levels, following addition of MVC.
Results: Nineteen patients were recruited and 15 completed the study (17M, 2F). Drop outs were for headache (2), knee problem meaning could not attend (1), and personal reasons (1). Mean age (range) was 45.4 years (27.2-65.1), 13/19 were white and 10/19 MSM. No changes in S100b, NfH, CSF ferritin, neopterin were seen between w12 and w36. Overall NC function improved between w12 and w36 following MVC addition: total age adjusted z score improved by 0.27 (weighted paired t-test; p=0.11). Looking at tests for executive function only, in this group age adjusted z score improved by 0.54 (weighted paired t-test; p=0.03). This compared to tests for other (non-executive) cognitive function where the age adjusted z score showed no significant change between w12 and w36 (weighted paired t-test; p=0.25). Darunavir plasma:CSF concentration ratio did not change between w12 (132) and w36 (112; p=0.577, Wilcoxon signed rank). Maraviroc plasma:CSF concentration ratio was 35 at w36.

Conclusion: No change in neuroinflammatory markers were observed. Whilst a learning effect cannot be entirely excluded, in this small study the addition of 24 weeks of MVC 150mg to stable DRV/r monotherapy showed a tendency to improvement in overall NC function overall at w36, and a significant improvement in executive function. The mechanism of this improvement should be further evaluated.

383 CSF LEVELS OF THE GLIAL MARKER YKL-40 STRONGLY ASSOCIATED WITH NEURONAL INJURY IN HIV

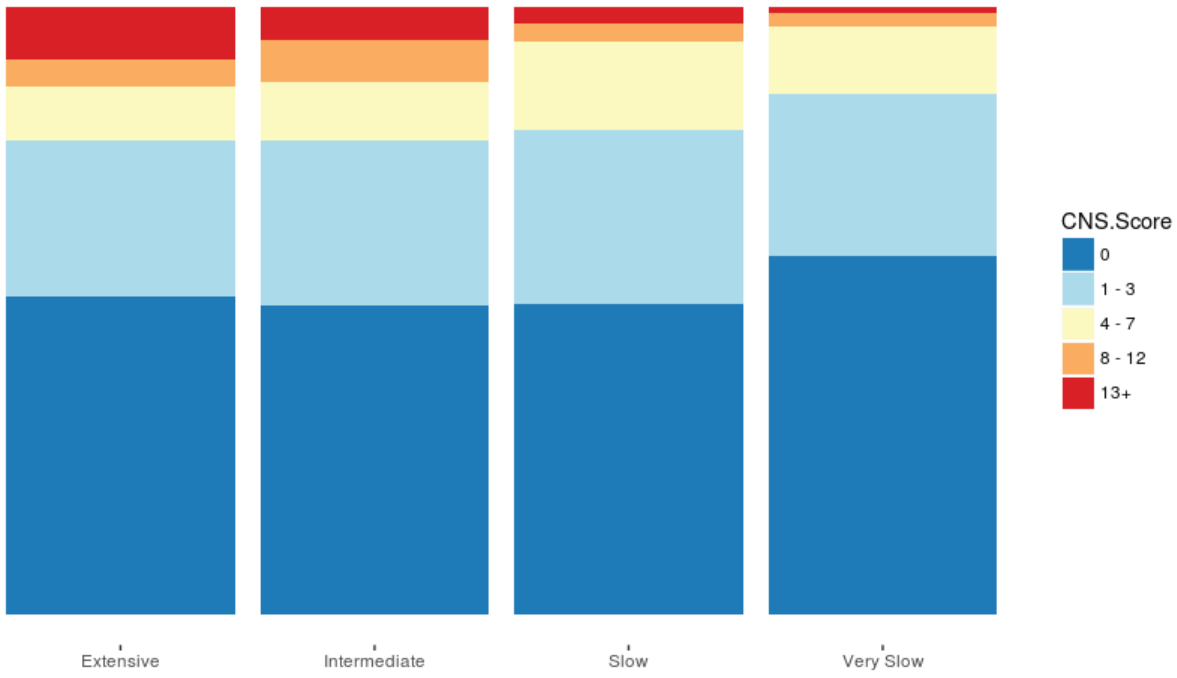
Linn Hermansson[1], Markus Axelsson[1], Kaj Blennow[2], Dietmar Fuchs[3], Lars Hagberg[1], Jan Lycke[1], Henrik Zetterberg[1], Magnus Gisslén[1]
[1]Sahlgrenska Academy at the Univ of Gothenburg, Gothenburg, Sweden, [2]Sahlgrenska Univ Hosp, Gothenburg, Sweden, [3]Innsbruck Med Univ, Innsbruck, Austria

Background: CNS inflammation is a nearly universal component of HIV-1 infection present throughout the entire infectious course. The objective of this study was to characterize cerebrospinal fluid (CSF) YKL-40, a biomarker that reflects activation of astroglial and microglial cells, in chronic HIV infection, with and without antiretroviral treatment (ART).
Methods: YKL-40, neopterin, and neurofilament light protein (NFL) were analyzed with ELISA in archived CSF samples from 120 HIV-infected (85 untreated neurological asymptomatic (NA) patients; 7 with HIV associated dementia (HAD); and 28 on effective ART), and 39 HIV-negative controls.
Results: YKL-40 was significantly higher in HAD compared to all other groups, but was also higher in untreated NA patients with CD4 <350 compared to HIV-negative controls. NA patients with CD4 >350 and persons on ART didn't have significantly different CSF YKL-40 levels compared to controls. Significant correlations were found between CSF YKL-40 and age ($r=0.38$, $p<0.001$), CD4 ($r=-0.36$, $p<0.001$), plasma HIV-RNA ($r=0.35$, $p<0.001$), CSF HIV-RNA ($r=0.35$, $p<0.001$), CSF neopterin ($r=0.40$, $p<0.001$), albumin ratio ($r=0.44$, $p<0.001$), and CSF NFL ($r=0.71$, $p<0.001$). Age, CD4, albumin ratio, and CSF HIV RNA were found as independent predictors of CSF YKL-40 concentrations in a multivariable analysis. CSF YKL-40 was shown to be a strong independent predictor of CSF NFL in a multivariable analysis, together with age, CSF neopterin, and CD4 cell count.
Conclusion: This study suggests that CSF YKL-40 could be a valuable marker in understanding HIV neuropathogenesis. The strong correlation between CSF YKL-40 and NFL give support to a pathogenetic association between glial activation and neuronal injury and suggest the utility of further exploring the prognostic value of YKL-40.

384 EXTENSIVE EFAVIRENZ METABOLISM IS ASSOCIATED WITH GREATER CNS TOXICITY

Marijana Vujkovic[1], Scarlett Bellamy[2], Athena Zuppa[1], Marc Gastonguay[3], Xiaoyan Han[4], Mosepele Mosepele[5], Gregory Bisson[4], Richard Aplenc[1], **Robert Gross**[4]
[1]Children's Hosp of Philadelphia, Philadelphia, PA, USA, [2]Drexel Univ, Philadelphia, PA, USA, [3]Metrum Rsr Group, Tariffville, CT, USA, [4]Univ of Pennsylvania, Philadelphia, PA, USA, [5]Univ of Botswana, Gaborone, Botswana

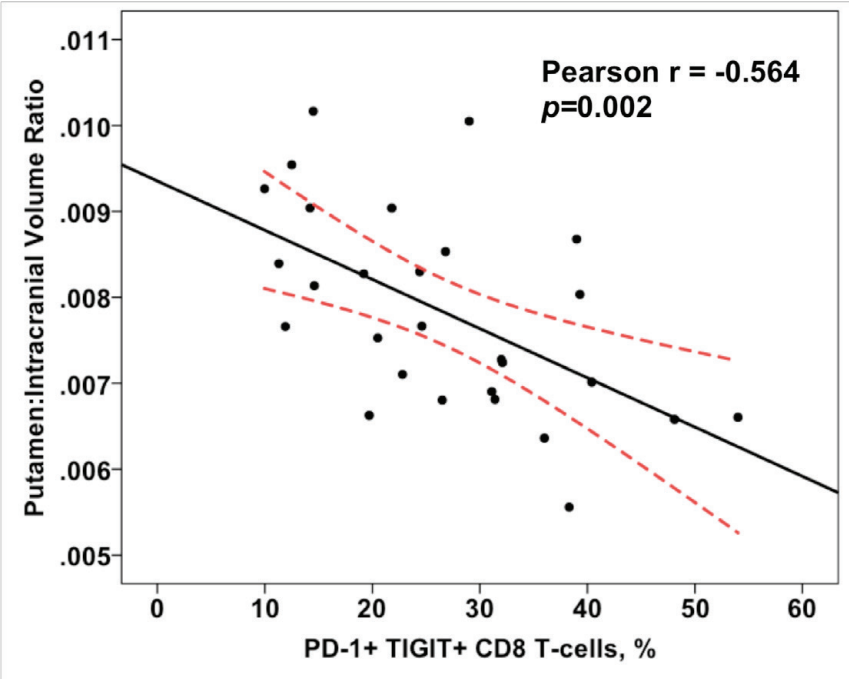
Background: Efavirenz causes central nervous system adverse effects (CNS AEs) including sleep disturbance, somnolence, vivid dreams and others. The relation between efavirenz clearance and CNS AEs has been unclear, particularly when stratified by race. P450 (CYP) isoenzyme 2B6 G516T confers slower metabolism and is more common with African origin. We hypothesized that this allele and additional CYP polymorphisms that affect efavirenz clearance mediate CNS AEs.
Methods: We included 842 HIV infected adults initiating efavirenz + 2 nucleoside analog reverse transcriptase inhibitors in a cohort study in Botswana. DNA was genotyped for 21 variants in CYP 2B6, 2A6, 3A4, and 3A5 genes and mid-dose EFV plasma samples were collected at 1 month of therapy. AEs were measured using 21 CNS symptoms in the ACTG Subject Experience Questionnaire. We used a one-compartment population PK model with nonlinear mixed effect modeling in NONMEM 7 to estimate EFV clearance, including the fixed covariates of allometrically scaled weight, G516T genotype, and visit number. SNPs that resulted in the greatest statistically significant decrease in the minimum objective function value (MOFV) were regarded as either extensive or slow metabolizers. Associations between metabolizer groups and CNS AEs were evaluated using negative binomials in a generalized linear regression model including the covariates: plasma EFV concentration, CYP2B6 G516T genotype, age, gender, alcohol intake, baseline CD4 count and viral load.
Results: The initial covariate model showed a MOFV of 2075. Two SNPs showed a reduced apparent oral EFV clearance: rs28399499 (8.0, 4.7, and 1.4 L/hr/70kg for TT, CT, CC, MOFV=1768) and rs28399433 (7.6, 5.9, and 4.9 L/hr/70kg for TT, GT, GG, MOFV=2015). Four SNPs showed extensive apparent clearance: rs2279345 (6.5, 8.0, and 8.4 L/hr/70kg for TT, CT, CC, MOFV=1995), rs4803417 (6.8, 8.3, and 9.4 L/hr/70kg for AA, AC, CC, MOFV=2015), rs4802101 (7.3 and, 8.6 L/hr/70kg for AA, AG, MOFV=2037), and rs61663607 (7.2, 7.2, and 8.7 L/hr/70kg for TT, CT, CC, MOFV=2021). Faster efavirenz clearance was associated with greater reported CNS AEs ($\beta=0.42$, $p=0.01$, see Figure).
Conclusion: In a model including multiple fast and slow clearance polymorphisms, faster clearance was associated with more CNS AEs. These findings implicate metabolites rather than parent drug as the cause of efavirenz-related CNS AEs. Assays for extensive CYP polymorphisms may permit avoidance of EFV in HIV-infected Africans at high risk of CNS AEs.



385 EXHAUSTED T CELLS AND INFLAMMATORY MONOCYTES ARE LINKED TO BRAIN ATROPHY IN HIV

Brooks I. Mitchell[1], Glen Chew[1], Kalpana J. Kallianpur[1], Mary Margaret Byron[1], Robert Paul[2], Beau K. Nakamoto[1], Dominic Chow[1], Scott A. Souza[1], Cecilia Shikuma[1], Lishomwa C. Ndhlovu[1]
[1]Univ of Hawaii, Honolulu, HI, USA, [2]Univ of Missouri–St. Louis, St. Louis, MO, USA

Background: We have previously reported that T-cell exhaustion associated with neurocognitive impairment among HIV-infected adults on stable antiretroviral therapy (ART). Here, we investigated the relationship between immune populations and regional brain volumes.
Methods: We utilized flow-cytometry to assess markers of CD8 T-cell activation (CD38+HLA-DR+), senescence (CD57+CD28-), and exhaustion (TIM-3, PD-1 and TIGIT) in peripheral blood mononuclear cells in HIV-infected individuals on stable ART with available regional brain volume data measured by T1-weighted magnetic resonance imaging at 3T as well as monocyte counts for classical (CD14+CD16-), intermediate (CD14+CD16+) and non-classical/inflammatory (CD14+/lowCD16++) subsets. Multivariable linear regression was utilized to assess the relationships between the immunophenotypes and regional brain volumes while controlling for intracranial volume and age. Pearson correlations were used in the analysis.
Results: Thirty-three HIV+ participants were mostly male (84%) with a median age 52 years, and median current CD4 T-cell count of 479 cells/mm3. Detectable viral load (>50 copies/ml) was noted in 12% of the participants. Higher PD-1+ CD8 T-cell frequencies (%) were associated with lower volumes in the putamen (β= -0.522, p=0.005), nucleus accumbens (β= -0.426, p=0.023), cerebellar cortex (β= -0.389, p=0.042), and subcortical gray matter (β= -0.368, p=0.037) brain regions. Higher % of PD-1+TIM-3+ CD8 T-cells were associated with lower volumes in the putamen (β= -0.533, p=0.003) and nucleus accumbens (β= -0.371, p=0.046), while higher % of PD-1+TIGIT+ CD8 T-cells were only associated with lower volumes in the putamen (β= -0.488,p=0.008). Higher % of PD-1+, PD-1+TIM-3+ and PD-1+TIGIT+ CD8 T-cells were associated with higher counts of inflammatory monocytes (all p<0.05). Even with the exclusion of individuals with detectable viremia, all findings remained significant. No associations were observed for regional brain volumes with % of TIM-3+, TIGIT+, or TIM+TIGIT+ CD8 T-cells or with any of these markers on CD4 T-cells.
Conclusion: T-cell exhaustion was associated with lower brain volumes and increases in inflammatory monocytes, suggesting monocyte-T-cell exhaustion may be interrelated processes involved in brain atrophy during ART-treated HIV. Immunotherapy targeting PD-1 in combination with other negative checkpoint receptors may be considered as treatment modalities for HAND and associated structural brain atrophy.



386 CSF AND SERUM BIOMARKERS OF NEURONAL INJURY AND AGING IN HIV-INFECTED PARTICIPANTS

Sergio M. de Almeida[1], Clea E. Ribeiro[1], Indianara Rotta[1], Mauro Piovesan[1], Sonia M. Raboni[1], Scott Letendre[2], Bin Tang[2], Florin Vaida[2], Ronald J. Ellis[2]
[1]Univ Fed do Paraná, Curitiba, Brazil, [2]Univ of California San Diego, San Diego, CA, USA

Background: The profile of neural injury biomarkers is not well defined in HIV infection, the majority of the studies are on HIV subtype B (HIV1-B). In vitro, HIV1-B Tat protein, inhibits neprilysin, an important amyloid β (Aβ)-degrading enzyme, causing Aβ accumulation. Effects of HIV subtype C (HIV1-C) have not been yet characterized. This study aimed to compare Aβ and related biomarkers between HIV1B (n=27) and C (n=26). Additional comparisons were made to healthy HIV negative (n=18) and Alzheimer disease (AD) patients (n=24).
Methods: Immunoassays were used to measure soluble amyloid precursor protein α and β (sAPPα, sAPPβ); Aβ38,40,42 and total; tau phosphorylated at threonine 181(P-tau181); Total tau (T-tau) and neurofilament light(NFL). Comparisons between HIV(+) and HIV(-) were adjusted by linear regression for gender and age. HIV subtype comparisons were adjusted for nadir CD4 and plasma viral load suppression.
Results: CSF Aβ42 was lower in HIV1-C than B(p= 0.03); the subtypes did not differ in serum biomarkers. Compared to AD, all HIV(+) together (n=68) had lower CSF levels of T-tau, P-tau181,NFL (p <0.001) and sAPPα(p= 0.02); All HIV(+) together had higher CSF levels of Aβ42 (p<0.001) and higher CSF indexes: [Aß42/ (240 + 1.18 T-tau)], P-tau181/AB42, T-tau/Aβ42, P-tau181/T-tau, sAPPα/β (all p<0.01) than AD. In serum HIV(+)<="" div="">
Conclusion: There was impact of HIV infection on amyloidal metabolism, with difference between subtypes B and C and difference with AD. The finding that Aß42 levels were lower in HIV1C than HIV1B, suggests that there may be greater deposition of Aß42 in HIV1-C than B.

387 CSF S100B AND CX3CR1 MONOCYTES IN ACUTE HIV INFECTION PREDICT PUTAMEN ATROPHY

Lishomwa C. Ndhlovu[1], **Kalpana J. Kallianpur**[1], Eugene Kroon[2], Thep Chalermchai[3], Khunthalee Benjapornpong[4], Shelly J. Krebs[5], Serena Spudich[6], Jintanat Ananworanich[5], Victor Valcour[7], for the RV254/SEARCH010 Study Group

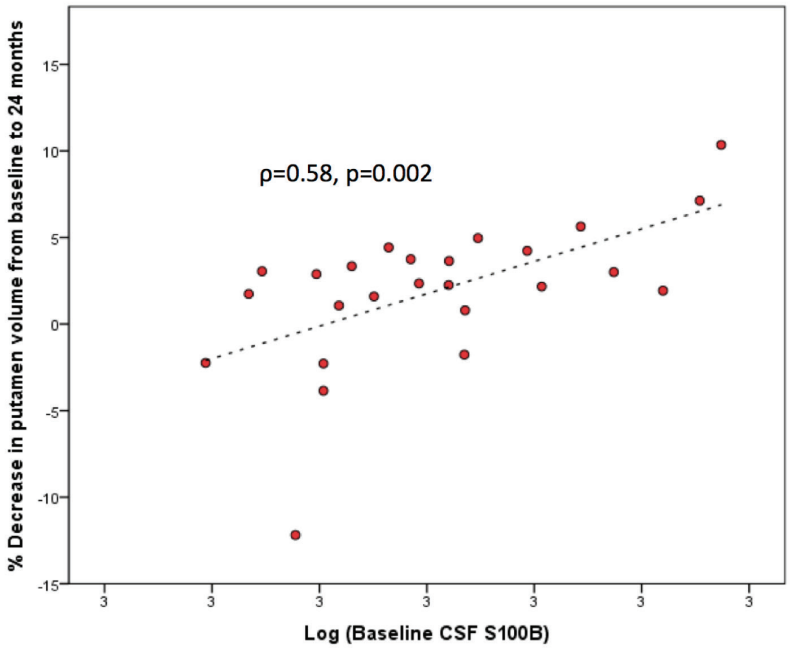
[1]Univ of Hawaii, Honolulu, HI, USA, [2]SEARCH, The Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [3]SEARCH, Bangkok, Thailand, [4]Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [5]US Military HIV Rsr Prog, Silver Spring, MD, USA, [6]Yale Univ, New Haven, CT, USA, [7]Univ of California San Francisco, San Francisco, CA, USA

Background: We previously reported decreases in brain regional gray matter (GM) volumes over 24 months in individuals who initiated combination antiretroviral therapy (cART) during acute HIV infection (AHI). Here we examined relationships of caudate, putamen, pallidum and total subcortical GM volumetric reductions to peripheral immune activation/inflammation (sCD163, sCD14, IL-6, TNF-α, MCP-1) and neuronal (S100B and neurofilament light protein) markers and to monocyte phenotypes implicated in HIV neuropathogenesis.

Methods: We prospectively enrolled individuals with AHI (Fiebig stages I-IV) who underwent brain magnetic resonance imaging (MRI) at 1.5T and then immediately initiated cART. MRI was repeated at 24 months. Biomarkers in cerebrospinal fluid (CSF) were assayed by ELISA or Luminex. Peripheral blood mononuclear cells were assayed by flow cytometry to measure monocyte frequencies based on CD14, CD16, CCR5, CCR2 and CX3CR1 expression. Nonparametric statistics were used.

Results: Biomarkers and monocyte frequency data at baseline prior to cART and at 24 months were obtained for 15 participants [14 male; baseline median (range) age=28.0 (19-45) years; exposure time=15 (8-28) days; CD4 count=339 (132-740) cells/mm3; plasma HIV RNA=5.53 (2.78-7.56) log10 copies/mL]. Regional volumes at both timepoints were available for 13 individuals. S100B increased from 966 (540-1493) pg/mL at baseline to 1024 (649-1590) pg/mL at 24 months post-ART initiation (p=0.009). At baseline, higher S100B correlated with higher frequencies (%) of non-classical (patrolling/inflammatory) monocytes (ρ=0.56, p=0.029), and on a per cell basis for non-classical monocytes expressing CX3CR1, a receptor that facilitates monocyte migration and survival (ρ=0.64, p=0.010). % decrease in putamen volume from baseline to 24 months post-cART correlated positively with baseline S100B (ρ=0.58, p=0.002) and with baseline % CX3CR1+ monocytes (ρ=0.76, p=0.004).

Conclusion: S100B, serves as a marker of brain damage and AHI participants exhibited an increase in CSF S100B over 24 months despite immediate initiation of cART. CSF S100B in AHI may predict atrophy of the putamen, a region which has been suggested to be preferentially susceptible to early HIV-related damage (Wright et al, 2016). CX3CR1 monocytes may penetrate the brain and be involved in neuronal-microglial interactions that contribute to brain volumetric changes ultimately reflected by elevated CSF S100B.



388 TELOMERE LENGTH: NEUROCOGNITIVE BIOMARKER IN HIV-1–INFECTED SUBJECTS

Marília L. Araújo[1], Maria Rita. P Gascón[2], Raquel Paiva[3], Bárbara Santana[3], Rodrigo Calado[3], Wellington Duarte[1], Luiz A. Fonseca[1], Augusto César P. Oliveira[2], Jorge Casseb[1]

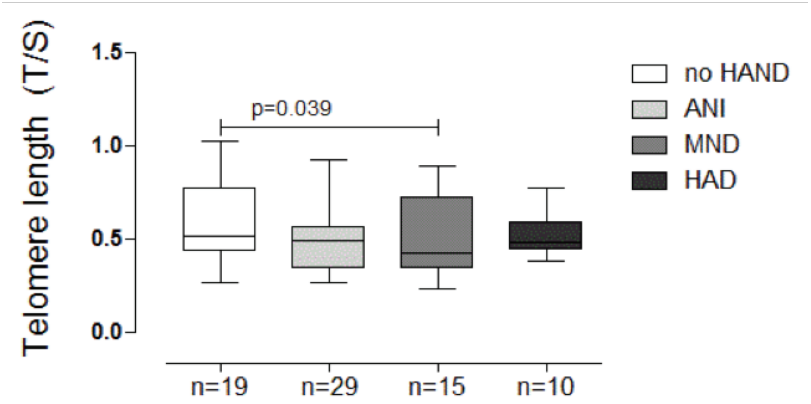
[1]Univ de São Paulo, São Paulo, Brazil, [2]Inst de Infectologia Emílio Ribas, São Paulo, Brazil, [3]Univ de São Paulo Ribeirão Preto, Ribeirão Preto, Brazil

Background: HIV associated neurocognitive disorders (HAND) remain a serious problem today because of the high prevalence of their milder forms. HIV-positive individuals have substantially shorter telomeres in peripheral blood mononuclear cells and in CD8 + T cells compared to HIV negative individuals. Given the above, the objective of this study was to evaluate the association of telomere length of leukocytes (LTL) in HIV-infected individuals with cognitive disabilities, since it remains a very controversial subject.

Methods: A total of 73 patients of both sexes, infected with HIV-1 and aged 20 to 60 years, participated in this study: Nineteen HIV-1-positive patients without cognitive impairment and 54 HIV patients (+) with neurocognitive disorders, namely: 29 with asymptomatic neurocognitive disorder (ANI), 15 with mild to moderate neurocognitive disorder (MND) and 10 with HIV-associated dementia (HAD); 118 HIV-negative individuals made up the control group. All participants underwent a series of previously validated neuropsychological tests. HIV-1 viral load was determined in cerebrospinal fluid cells (CSF) and in PBMC. We used DNA from peripheral leukocytes to calculate the length of telomeres by real time PCR. Statistical analysis: We used Mann Whitney test for the analysis of nonparametric variables, and the Spearman and Pearson's r tests for analysis of correlation where appropriate.

Results: Telomere length was not associated with sex (p=0.85) and decreased with age (p=0.0001), irrespective of HIV status. HIV-1-infected individuals with milder forms of neurocognitive impairment had a significantly shorter telomere length as compared with HIV-positive patients without neurocognitive impairment (p=0.038). There was no correlation between plasma viral load and the size of telomere (p=0.66).

Conclusion: Our results suggest that telomere length can be a cell senescence marker in subjects with HAND.



389 CEREBROSPINAL FLUID CONCENTRATION OF THE SYNAPTIC MARKER NEUROGRANIN IN HIV

Maria C. Brühl[1], Aylin Yilmaz[2], Lars Hagberg[2], Dietmar Fuchs[3], Kaj Blennow[1], Henrik Zetterberg[2], Richard W. Price[4], Magnus Gisslén[2]
[1]Sahlgrenska Univ Hosp, Gothenburg, Sweden, [2]Sahlgrenska Academy at the Univ of Gothenburg, Gothenburg, Sweden, [3]Innsbruck Med Univ, Innsbruck, Austria, [4]San Francisco General Hosp, San Fransisco, CA, USA

Background: HIV-associated dementia (HAD) that represents the most advanced stage of HIV-associated neurocognitive disorders (HAND) is characterized by evident neuronal damage and loss. The incidence of HAD has decreased substantially since the introduction of combination antiretroviral therapy (cART) but milder forms of HAND persist also in patients on otherwise effective cART. Several biomarkers in CSF have been shown to mirror the late neuronal damage and intrathecal immune activation in people living with HIV (PLHIV), in particular neurofilament light protein (NFL) and neopterin. We hypothesize that synapses are involved early in the neuropathogenic pathways. To test this hypothesis, we have analyzed the synaptic marker neurogranin (NG) in a cohort of PLHIV thoroughly classified by systemic disease progression, CNS symptomatology, and ART.
Methods: A cross-sectional study using archived CSF samples from two academic centers: Sahlgrenska University Hospital, Gothenburg, Sweden and San Francisco General Hospital, CA, USA was performed. The study population consisted of 149 PLHIV divided into 6 subgroups in regard to neurological symptoms and CD4 counts and 16 HIV-negative controls. CSF NG, NFL, and neopterin concentrations were measured by ELISA.
Results: There were no significant differences in CSF NG levels between the various subgroups, although there was a relatively wide range within each group (figure 1a). CSF NFL concentrations were highest in the HAD group. The results also showed a trend of increased concentrations in participants with lower CD4 counts, all in agreement with earlier studies (figure 1b). A significant correlation was found between CSF NG and CSF NFL concentrations ($r = 0{,}38$, $p < 0{,}0001$) (figure 1c).
Conclusion: With an ageing population of PLHIV on cART it is essential to early identify neurological impairment and discriminate between HAND and other forms of cognitive disorders. CNS immune activation and axonal injury, the latter mirrored by increased CSF NFL levels, are common features in HIV CNS disorder but the HAND neuropathogenesis is still not completely understood. Our hypothesis of early synaptic injury could not be confirmed by increased CSF concentration of the synaptic marker neurogranin in our study population with CNS symptoms. This either indicate that synaptic injury does not precede axonal injury in HIV-associated CNS disease or that CSF neurogranin is not a sensitive enough biomarker for synaptic impairment in HAND, which would contrast its utility in AD.

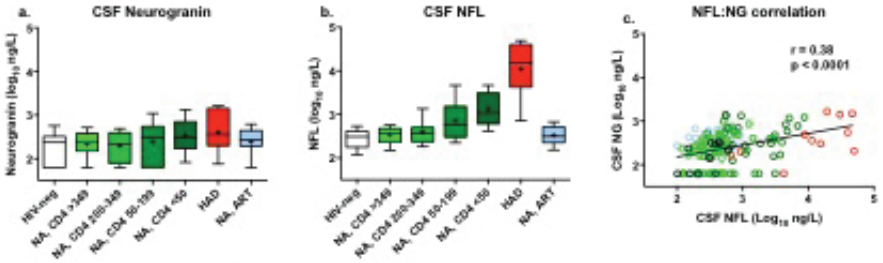


Figure 1. Panels a–b, illustrates log concentrations of respective marker for the 7 subject groups (HIV-neg (n=16), NA – neuroasymptomatic, sub grouped by the level of blood CD4+ T-cell counts into CD4+ <50 T-cells/mL (n=25), CD4+ 50-199 T-cells/mL (n=25), CD4+ 200-349 T-cells/mL (n=25) and CD4+ >349 T-cells/mL (n=30); diagnosed HAD (n=11); subjects on suppressive cART without signs of neurological impairment (n=33)). **Panel c,** illustrates the correlation between CSF NFL and CSF NG, color-coded by subject group.

390 THE HUMAN GUT MICROBIOME AND HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS

Josue Perez-Santiago[1], Sara Gianella[2], Ajay Bharti[1], Debralee Cooksonv[1], Robert K. Heaton[2], Igor Grant[2], Scott Letendre[1], Scott N. Peterson[3]
[1]Univ of California San Diego, San Diego, CA, USA, [2]Univ of California San Diego, La Jolla, CA, USA, [3]Sanford Burnham Prebys Med Discovery Inst, La Jolla, CA, USA

Background: Although advances in antiretroviral therapy (ART) have dramatically improved longevity, up to half of HIV+ adults still develop HIV associated neurocognitive (NC) disorders (HAND), even after achieving viral suppression. The mechanisms leading to HAND remain unclear, limiting the development of effective interventions. The gut microbiome has been implicated in the development and function of brain circuits that support emotion and cognition. Here we investigated the association between the gut microbiome of subjects with or without HAND.

Methods: We retrospectively evaluated the gut microbiome from 47 HIV+ male adults enrolled the HIV Neurobehavioral Research Program cohort. HAND was diagnosed using standardized criteria, including activities of daily living as follow: HIV Associated Dementia (HAD, n=4), asymptomatic NC impairment (ANI, n=16), mild NC disorder (MND, n=7), and NC unimpaired (NC-U, n=20). Stool, sociodemographic, and clinical data were collected for each participant. Stool DNA was extracted and the V3-V4 hypervariable region of the 16S ribosomal RNA gene was amplified by PCR and sequenced. Microbiome and statistical analyses were performed using Qiime and R statistical software.
Results: There were no significant group differences on age or clinical characteristics (see Table). Analysis of variance followed by a Tukey post-hoc adjustment identified that participants with HAD showed significantly higher levels of Bacteroidetes (median=0.59) compared to ANI (median=0.39, p=0.02), MND (median=0.47, p=0.03), and NC-U (median=0.42, p=0.08). Conversely, participants with HAD showed significantly lower levels of Firmicutes (median=0.28) compared to ANI (median=0.56, p<0.01), MND (median=0.48, p<0.01), and NC-U (median=0.47, p=0.06). While older age was associated with higher levels of Firmicutes (rho=0.35, p=0.01) and trending to lower levels of Bacteroidetes (rho=-0.25, p=0.08), in a multivariate analysis the associations of both Bacteroidetes (p<0.01) and Firmicutes (p<0.01) remained significant after adjusting for age.
Conclusion: The gut microbiome, particularly Bacteroidetes and Firmicutes, is associated with the most severe form of HAND, HAD. While this sample was relatively small, these microbial signatures may be important for identifying individuals with increased risk of developing HAND and may lead to new therapeutic options for individuals with HAND after successful ART.

Table: Clinical and demographic characteristics by study group

Clinical/Demographical Variable	(n=20)	ANI (n=17)	MND (n=7)	HAD (n=4)
Ethnicity (% White)	40%	53%	71%	50%
Age (years)	51 (43.5-56.5)	57 (49-64.5)	59(51-63.5)	50 (44.25-52.75
CD4 absolute (cells/μL)	624 (399-704)	507 (420.5-766.5)	530 (391.75-643.5)	753(421.25-1028.5)
CD8 absolute (cells/μL)	627 (478-923.5)	825 (655-1194)	904 (791.75-1188.75)	994 (872-1317.5)

Note: Values represent Median (IQR) unless otherwise noted. NC-U= Neurocognitive Unimpaired, ANI=Asymptomatic Neurocognitive Impairment, MND=Mild Neurocognitive Disorder, HAD=HIV Associated Dementia

391 HIV ANTIBODIES IN CSF AND SERUM IN UNTREATED AND TREATED INFECTION

Magnus Gisslén[1], Richard W. Price[2], Serena Spudich[3], Lars Hagberg[1], Steven G. Deeks[2], Peter Burbelo[4]
[1]Sahlgenska Academy at the Univ of Gothenburg, Gothenburg, Sweden, [2]Univ of California San Francisco, San Fransisco, CA, USA, [3]Yale Univ, New Haven, CT, USA, [4]NIDCR, Bethesda, MD, USA
Background: HIV likely persists in the CNS during antiretroviral therapy (ART) and may be important in continued neurocognitive impairment. Given that the reservoir in the CNS is small and difficult to access, host-responses to any residual HIV may prove to be a useful biomarker for studies aimed at studying or eradicating the virus. Here we quantitatively analyzed anti-HIV antibodies in matched CSF and serum samples from a diverse cohort of infected adults including long-term treated patients using luciferase immunoprecipitation systems (LIPS).
Methods: Using LIPS, antibody responses against 7 HIV proteins were quantitatively analyzed in paired CSF and serum samples from uninfected controls (n=12), hyperacute HIV infection (n=2), early untreated HIV infection (n=4), elite controllers (n=6), treated acute infection (n=2) and before and after treatment of chronic infection (n=11).
Results: HIV antibodies during early HIV infection emerged in the serum compartment before the CSF, with levels increasing over time in both bodily fluids. Antibodies to HIV were absent during hyperacute infection and low during primary/early infection. Anti-HIV antibodies were detected in CSF of all 11 participants with chronic infection prior to ART. Treatment of chronic infection resulted in significant decreases in CSF antibody levels against many HIV proteins including integrase, protease and gp120. Antibody levels in CSF and serum in the long-term treated were highly associated, with correlation coefficients (R) for integrase, protease, p24, matrix, reverse transcriptase, gp120, and gp41 of 0.87, 0.84, 0.82, 0.69, 0.60, 0.58, and 0.43, respectively. Comparison amongst the heterogeneous group of elite controllers revealed discordant antibody levels against p24 and reverse transcriptase between CSF and serum.
Conclusion: Monitoring antibody response to HIV proteins in the CSF may provide a useful tool to longitudinally monitor the viral reservoir in the CNS before and during treatment. The discordant CSF and serum antibody responses seen in elite controllers and perhaps other groups suggest that the levels of HIV replication in these two compartments may be different. Although our sample size is small, early treatment of acute infection markedly blocked the presence of anti-HIV antibodies in serum and CSF.

392 NUCLEAR-MITOCHONDRIAL INTERACTIONS AND NEUROCOGNITIVE IMPAIRMENT IN HIV+ ADULTS

Sandra P. Smieszek[1], Asha R. Kallianpur[2], David C. Samuels[3], Donald Franklin[4], Robert K. Heaton[5], Scott Letendre[4], Ronald J. Ellis[4], Todd Hulgan[3], **William S. Bush**[1]
[1]Case Western Reserve Univ, Cleveland, OH, USA, [2]Cleveland Clinic Lerner Coll of Med, Cleveland, OH, USA, [3]Vanderbilt Univ, Nashville, TN, USA, [4]Univ of California San Diego, San Diego, CA, USA, [5]Univ of California San Diego, La Jolla, CA, USA
Background: HIV-Associated Neurocognitive Disorder (HAND) is a term that captures a wide spectrum of neurocognitive deficits, ranging from mild to severe, in HIV-infected persons. The genetic underpinnings of this complex phenotype are incompletely understood. Abnormalities of mitochondrial function and iron metabolism have long been implicated in neurodegeneration. In this analysis, we aimed to characterize the mitochondrial DNA (mtDNA) haplogroup interactions with nuclear genes found to be associated with HAND phenotypes.
Methods: Genetic associations with HAND were investigated in the CHARTER cohort, encompassing 1025 individuals of African, European and admixed Hispanic ancestry. CHARTER is a US-based observational study of neuro-HIV outcomes in ambulatory, HIV+ adults who underwent standardized, comprehensive NC assessment (2003-7) and were assigned a Global Deficit Score (GDS) [normal (GDS<0.5) or impaired (GDS≥0.5)]. We employed a polygenic modeling approach to investigate the global effect of previously associated nuclear SNPs, and to examine how the polygenic effect of these SNPs is influenced by mtDNA haplogroups. Subsequently, we performed interaction analysis per SNP by mtDNA haplogroup combination, adjusting for population effects and known clinical covariates (comorbidity status, current CART use, plasma viral load, nadir CD4+ T-cell count).
Results: We found evidence of interactions between nuclear genomic SNPs en masse and mtDNA haplogroups within European and African-ancestry individuals, as shown in Table 1. The analysis of each SNP by mtDNA haplogroup combination identified significant interactions between a region of chromosome 19 (two strongly correlated SNPs, rs17160128 and rs12460243) and European mtDNA haplogroups with continuous GDS after Bonferroni correction, with the SNPs showing a more dominant association in H and J haplogroups versus a more additive association in T and UK haplogroups.
Conclusion: These associations highlight the potential role of FBN3, a nearby gene that belongs to the fibrillin gene family. Fibrillins assemble into microfibrils in many connective tissues and are important in regulating pathways of the immune response, inflammation and are involved in maintenance of blood-brain-barrier integrity. These findings were demonstrated using a novel analytic approach and indicate a new potential genetic mechanism in the pathogenesis of HAND, which may lead to greater understanding of the pathophysiology of this neurocognitive disorder.

393 GENETICALLY PREDICTED GENE EXPRESSION AND HIV-ASSOCIATED NEUROCOGNITIVE DISORDER

Sandra Smieszek[1], William S. Bush[1], Todd Hulgan[2], David C. Samuels[2], Donald Franklin[3], Robert K. Heaton[4], Scott Letendre[3], Ronald J. Ellis[3], Asha R. Kallianpur[5]
[1]Case Western Reserve Univ, Cleveland, OH, USA, [2]Vanderbilt Univ, Nashville, TN, USA, [3]Univ of California San Diego, San Diego, CA, USA, [4]Univ of California San Diego, La Jolla, CA, USA, [5]Cleveland Clinic Lerner Coll of Med, Cleveland, OH, USA

Background: HIV-Associated Neurocognitive Disorder (HAND) is a term established to capture a spectrum of neurocognitive (NC) deficits associated with HIV infection. The genetic underpinnings of HAND are poorly understood. CHARTER is a US-based observational study of neuro-HIV outcomes in ambulatory, HIV+ adults who underwent standardized, comprehensive NC assessment (2003-7) and were assigned a Global Deficit Score (GDS) [normal (GDS<0.5) or impaired (GDS≥0.5)]. In this study, we investigated the impact of genetic variants known to alter the expression of genes in whole blood on GDS outcomes.
Methods: We used CHARTER genome-wide association study (GWAS) data (imputed to the 1000 Genomes reference) to predict gene expression using an approach called PrediXcan. It estimates the genetically regulated component of gene expression using reference panels from studies of expression quantitative trait loci (eQTL). In this study, Gene/Tissue Expression data and CHARTER genome-wide genotype data were used to model the expression profile of 11,000 genes. We then evaluated associations of these "imputed" gene expression traits with two CHARTER NC phenotypes (continuous GDS and GDS impairment). We performed regression analyses to identify predicted gene expression values that associate to continuous GDS and GDS impairment, adjusting for population effects and known clinical covariates (comorbidity status, current CART use, plasma viral load, nadir CD4+ T-cell count).
Results: While no genes were significant after multiple testing corrections, the top genes were Ankyrin Repeat Domain 44 (ANKRD44), insulin receptor substrate 2 (IRS2), and Activating Transcription Factor 3 (ATF3). Using a set of 222 genes associated to CHARTER phenotypes at $p < 0.01$, we performed gene pathway enrichment analysis. Initial analysis suggests overrepresentation of iron ion binding, immune defense response, regulation of inflammatory process and mitochondrial-mediated membrane pathways. Additionally, among the most significant associations ($p < 0.01$), we found 17 genes with known HIV protein interactions.
Conclusion: We identified genes and pathways influencing NC impairment in HIV-infected cases. We hypothesize that individuals with altered regulation of HIV-interacting genes may be predisposed to HAND in the presence of HIV infection. We provide support for a role of iron transport in HAND pathogenesis and evaluates gene expression effects by modeling the mechanisms through which genetic variants influence NC impairment.

394 MRS MEASURES ASSOCIATE WITH IMPAIRED NEUROPSYCHOLOGICAL PERFORMANCE IN ACUTE HIV

Joanna Hellmuth[1], James L. Fletcher[2], Victor Valcour[1], Napapon Sailasuta[3], Somporn Tipsuk[2], Jintanat Ananworanich[4], Bonnie Slike[4], Robert Paul[5], Serena Spudich[6], for the SEARCH 010/RV254 Study Group
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]SEARCH, Bangkok, Thailand, [3]Univ of Hawaii, Honolulu, HI, USA[4]US Military HIV Rsr Prog, Silver Spring, MD, USA, [5]Univ of Missouri-St. Louis, St. Louis, MO, USA, [6]Yale Univ, New Haven, USA

Background: We used magnetic resonance spectroscopy (MRS) to assess the mechanisms underlying impaired neuropsychological performance (defined as ≥1 SD below Thai norms on ≥2 cognitive tests) in untreated acute HIV infection (AHI).
Methods: Participants were prospectively identified through laboratory screening at an HIV testing center in Bangkok, Thailand and diagnosed with Fiebig I-V acute HIV. Prior to starting combination antiretroviral therapy (cART), participants completed neuropsychological (NP) testing (Color Trails I, Color Trails II, Grooved pegboard non-dominant hand, Trail Making A), a PHQ-9 depression inventory, phlebotomy, and optional cerebrospinal fluid (CSF) testing for viral and inflammatory markers. A subset of AHI participants and a group of HIV-uninfected individuals underwent 1.5 Tesla brain MRS.
Results: 297 participants had NP testing during AHI (median estimated HIV infection duration 21 days, IQR: 10). The proportion of AHI participants with impaired NP performance pre-cART was 20.9%, similar to a report from 36 participants in this cohort. Those with impaired NP performance had higher PHQ-9 depression scores (11.8 vs. 9.9; p=0.02), and a trend towards higher plasma log10HIV RNA (6.0 vs. 5.7; p=0.09). In the 30% of participants with MRS (n=90), those with impaired NP performance had higher frontal gray matter glutamate+glutamine (Glx)/creatine (excitotoxocity and/or glial dysfunction; 2.46 vs. 2.27, p=0.008), lower frontal white matter NAA/creatine (neuronal integrity; 1.42 vs. 1.55; p=0.022), and higher posterior cortical gray choline/creatine (inflammation; 0.180 vs. 0.166; p=0.025) compared to those with normal performance. In a general linear model adjusting for age, AHI participants with impaired performance had higher frontal gray matter Glx/creatine compared to healthy controls (p=0.003) and both AHI groups had higher posterior cortical gray choline/creatine compared to controls ($p \leq 0.001$).
Conclusion: AHI participants with NP impairment prior to cART exhibit abnormal MRS metabolite measures suggesting increased cortical and subcortical neuronal dysfunction and inflammation compared to those without impairment. This may reflect brain differences prior to HIV infection, or may be due to a differential impact of AHI in the central nervous system. We confirmed that over 20% of participants in AHI have impaired cognitive performance prior to cART.

395 CIRCULATING HIV DNA IS ASSOCIATED WITH WEAKER INTRINSIC BRAIN CONNECTIVITY

Kalpana J. Kallianpur[1], Bruce Shiramizu[1], Melissa Agsalda-Garcia[1], Robert Paul[2], Cecilia Shikuma[1], Gregory Kirk[3], Rasmus Birn[3]
[1]Univ of Hawaii–Manoa, Honolulu, HI, USA, [2]Univ of Missouri St. Louis, St. Louis, MO, USA, [3]Univ of Wisconsin Madison, Madison, WI, USA

Background: Monocytes constitute a proviral HIV DNA reservoir contributing to HIV-associated neurocognitive disorder (HAND) that persists despite suppressive antiretroviral therapy (ART). Lymphocyte HIV DNA has also been implicated in HAND. Although HIV DNA in peripheral blood has been linked to subcortical and cortical (e.g., insular) gray matter atrophy, brain function has not been examined in relation to HIV DNA.
Methods: We cross-sectionally studied HIV+ and HIV- individuals who underwent resting-state functional connectivity (RSFC) magnetic resonance imaging at 3T and neuropsychological (NP) testing. HIV DNA copy numbers per 106 cells were assessed within CD14+ monocyte and CD14- non-monocyte peripheral blood mononuclear cell subsets in HIV+ subjects. Global (NPZ_14) and composite domain-specific NP z-scores were obtained. Analysis of Functional Neuroimages software was used to analyze RSFC data. Age was a covariate in voxelwise analyses. Whole-brain RSFC was computed for seed regions of interest (ROIs) in the insula, caudate, putamen, amygdala and hippocampus; and RSFC differences between HIV+ and HIV- groups assessed. RSFC correlations with HIV DNA were examined. Voxelwise estimates of RSFC were corrected for multiple comparisons using a cluster-based method to achieve a corrected $p<0.05$.
Results: 44 HIV- individuals (55 ± 8 years old) and 38 HIV+ subjects (53 ± 8 years old; all on ART; 87% with plasma HIV RNA < 50 copies/mL; CD4 count=541 ± 279 cells/mm3), of whom 27 had HIV DNA data (log10CD14+ HIV DNA=3.4 ± 1.1; log10CD14- HIV DNA=2.5 ± 1.2), were evaluated. Insular RSFC to prefrontal cortex (PFC) was lower in HIV+ than in HIV- subjects. Decreased RSFC of the left anterior insula to medial PFC correlated with higher CD14+ HIV DNA (Figure). CD14- HIV DNA correlated negatively with the RSFC of left insular and bilateral caudate ROIs to inferior temporal (IT), parietal, cingulate and PFC regions. Average RSFC strength was related to NP z-scores: e.g., RSFC between right caudate and left IT gyrus correlated with NPZ_14 (R= 0.61, p=0.003). CD14- HIV DNA correlated with NPZ_14 (R= −0.59, $p<0.01$) and with psychomotor speed, working memory and executive function (R~ −0.5, $p<0.05$).
Conclusion: These findings directly link peripheral blood HIV DNA burden to brain and cognitive dysfunction in optimally treated HIV disease, underscoring the need to eradicate circulating HIV reservoirs. Our results for CD14- subsets indicate that the role of HIV DNA in T lymphocytes should be a focus of further study.

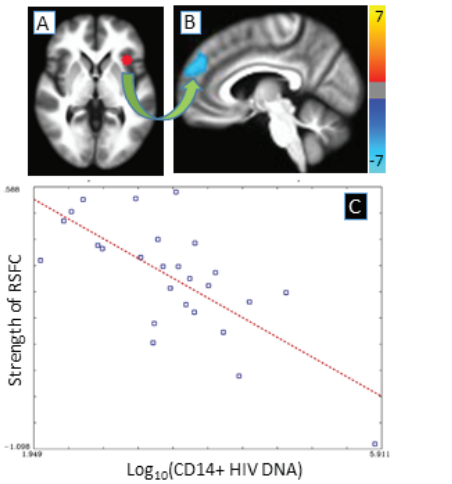


FIGURE. Relationship between resting-state functional connectivity (RSFC) and monocyte HIV DNA. (A) Seed region of interest in left anterior insula. (B) Region in medial prefrontal cortex (PFC) where RSFC to left anterior insula is significantly correlated with monocyte HIV DNA ($p<0.05$, corrected for multiple comparisons at cluster-level with a voxel-level $p<0.005$). (C) Scatterplot showing relationship of monocyte HIV DNA to strength of RSFC between left anterior insula and left medial PFC (averaged over clusters).

396 RETINAL LAYERS THICKNESS AS MARKER OF ACCELERATED NEUROCOGNITIVE DECAY IN HIV DISEASE

Chiara Resnati[1], Alessandro Invernizzi[1], Alessandra Acquistapace[1], Marta Ferrari[1], Sara Bochicchio[1], Valentina Leta[1], Cristina Gervasoni[2], Stefano Rusconi[1], Simone Pomati[2], Agostino Riva[2]

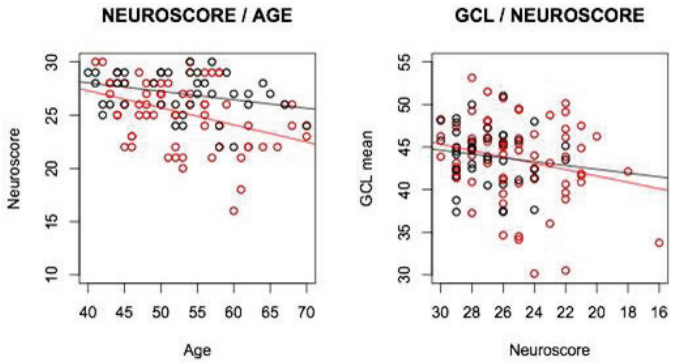
[1]Univ of Milan, Milano, Italy, [2]Luigi Sacco Univ Hosp, Milano, Italy

Background: Asymptomatic/mild HIV associated neurocognitive disorder, in the form of a premature cognitive and brain aging, is a concern despite effective ART. The retina can be considered an extension of the CNS, thus Spectral domain optical coherence tomography (SD-OCT) was used to investigate structural changes of retinal layers in subjects affected by brain diseases. The aim of this study was to investigate the structural changes occurring in different retinal layers visualized by SD-OCT in HIV patients with well controlled disease without retinitis.

Methods: Methods We performed SD-OCT on 69 HIV positive patients on ART with VL<37 cp/ml. To rule out the presence of unknown ocular condition possibly affecting the data collection all subjects underwent a complete ophthalmic examination. SD-OCT images of the retina were collected in both eyes with Heidelberg Spectralis OCT. This technique allowed a detailed visualization of the retinal layers in the macular region, these scans were later used to analyze ganglion cells layer (GCL) and inner plexiform layer (IPL) of the retina. All the enrolled subjects underwent a Montreal Cognitive Assessment Test (MoCA).

Results: Results 69 HIV positive patients (21 females,48 males) with well controlled disease (VL<37 cp/ml) with a mean age of 53 years (SD 7.3, range 41-70) were analyzed with 41 age and sex matched healthy controls. With aging Ganglion Cells Complex (GCL + IPL) thickness decreased significantly in HIV subjects ($p=0.004$) and also in healthy controls but without statistical significance. Splitting GCC into its components: GCL is the most significant layer($r=-0.37$, $p< 0.001$) . GCL thickness did not show significant correlation with gender, disease duration, CD4 nadir, therapy with thymidine analogues. The score achieved in MoCA resulted significantly lower in HIV patients compared to controls ($p=0.0008$). Cognitive Function significantly decreased in HIV patients with age (Fig1); in controls a similar trend was evident with borderline significance ($p=0.058$). However, the correlation between age and MoCA Test resulted significant only in HIV subjects ($p=0.0009$). MoCA was directly correlated with GCL thickness in HIV patients (Fig 1), but was not in healthy controls.

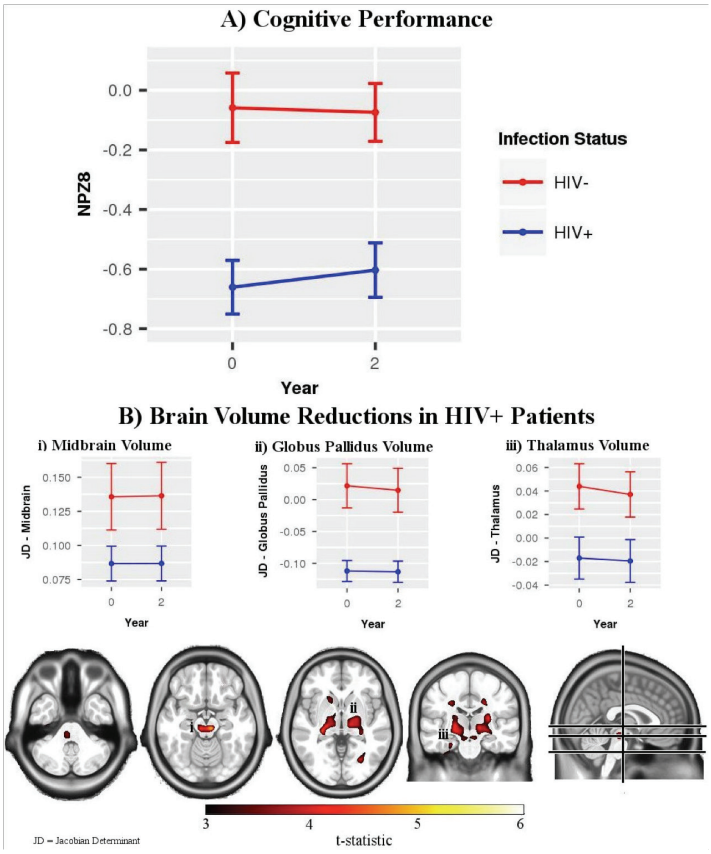
Conclusion: Conclusions Our results suggest premature cognitive impairment in HIV subjects. GCL thickness significantly decrease in HIV with ageing. Decline is similar to cognitive function decrease. GCL thickness could be an indirect marker for CNS premature ageing in HIV.



397 LONGITUDINAL ASSESSMENT OF REGIONALLY SPECIFIC BRAIN VOLUMES IN TREATED HIV+ PATIENTS

Ryan Sanford[1], Lesley K. Fellows[1], Louis Collins[1], Beau M. Ances[2]
[1]Montreal Neuro Inst, Montreal, Canada, [2]Washington Univ, St. Louis, MO, USA

Background: Combination antiretroviral therapy (cART) has shifted HIV from a fatal illness to a chronic condition. However, HIV-associated neurocognitive disorder is still prevalent. The cause of this brain dysfunction remains unclear because results from cross-sectional studies are unable to determine whether there is ongoing brain injury despite cART, or brain injury prior to cART initiation. To explore this issue, we longitudinally assessed regionally specific brain volumes in treated HIV+ patients with well-controlled infections, and demographically-matched HIV- controls.
Methods: 46 HIV+ and 31 HIV- completed two neuroimaging and neuropsychological testing sessions approximately 2 years apart. The neuropsychological battery covered 6 cognitive domains with 8 standard tests. A standardized z-score for each test was derived using appropriate demographic norms. A neuropsychological summary score (NPZ8) was created by averaging z-scores across the 8 tests. Tensor-based morphometry (TBM) estimated brain volumes at both visits, and change in brain volume over time. General linear models assessed the correlation of HIV status, and current and nadir CD4 with brain volumes, change in brain volume, NPZ8 and change in NPZ8.
Results: The two groups were demographically similar (HIV+ age [mean±SD]: 47±13, education: 13±3, sex: 52% male; HIV- age: 51±13, education: 14±2, sex: 48% male). HIV+ patients had worse cognitive performance than controls at both visits. NPZ8 was not associated with current or nadir CD4. No significant changes in NPZ8 were observed over time in either group. No differences in the change in NPZ8 between groups were detected. TBM revealed volume reductions in the thalamus, caudate, putamen, globus pallidus and midbrain in HIV+ patients at both visits. No significant changes in brain volume were observed over time in either group, and no differences in change in brain volume were detected between the groups. Brain volume measures were not correlated with NPZ8, current or nadir CD4.
Conclusion: Regionally specific subcortical volume reductions and poor cognitive performance were observed in the HIV+ group. However, no detectable brain volume loss or cognitive decline were revealed over 2 years in this sample of treated HIV+ patients. These findings support the hypothesis that brain dysfunction most likely occurs before cART initiation suggesting a possible neurocognitive benefit from early cART. Additional longitudinal studies with larger samples are warranted to validate these results.



398 BRAIN HIV LATENCY LEADS TO A COMPLEX PATTERN OF NEUROCHEMICAL DYSREGULATION

Lucette Cysique[1], Michael V. Tobia[2], **Thomas Gates**[3], Lauriane Juge[2], Simon Jones[4], Caroline Rae[2], Bruce Brew[4]
[1]NeuroSci Rsr Australia, Randwick, Australia, [2]Univ of New South Wales, Randwick, Australia, [3]St. Vincent's Hosp, Sydney, Australia, [4]Univ of New South Wales, Darlinghurst, Australia

Background: HIV brain latency may induce neuropathological events in virally suppressed HIV+ persons and persisting HIV-associated neurocognitive disorder (HAND). In the current study, we investigate whether major brain metabolites are impacted by a putative marker of brain HIV latency (CSF BCL11b, a microglia cell transcription factor that inhibits HIV transcription) in conjunction with CSF neopterin, CSF NFL, and CSF tat.
Methods: Sample's characteristics are presented in Table 1. All participants undertook a CSF lumbar puncture at baseline only; a 1H Magnetic Resonance Spectroscopy (MRS) scan, and a neuropsychological testing at both baseline and 18-months later. CSF samples were analyzed for BCL11b, neopterin, NFL, and tat using standard assays. 1H MRS included measurements of N-acetyl Aspartate (NAA), choline (Cho), Creatine (Cr), Myo-inositol (MI), glutamine/glutamate (Glx) in the frontal white matter (FWM), posterior cingulate cortex (PCC), and caudate nucleus area (CA). MRS spectra were measured with reference to the unsuppressed water signal and quantified using JMRUI V.03. Baseline cognitive impairment was based on the Frascati criteria, and cognitive decline was corrected for practice effect.
Results: Baseline adjusted regression models for neopterin, NFL and tat showed that a higher CSF BCL11b was consistently associated with lower FWM Cr (when adjusted for neopterin: Std beta=-.30; p=.15; when adjusted for NFL: Std beta=-.51; p=.03; and when adjusted for tat: Std beta=-.47; p=.02). These analyses also revealed that FWM Cho

was lower as a function of tat detectability (Std beta=-.51; p=.03). In longitudinal analyses, CSF neopterin was predictive of increased FWM Glx at follow-up, but not at baseline (Std Beta=-.33; p=.02). No CSF biomarkers was associated with baseline HAND, but NFL was associated with history of HAND (p=.02). Finally, a higher level of baseline NFL was predictive of cognitive decline (r=-.53; p=.005).
Conclusion: Frontal white matter reduced cellular energy (Creatine decrease), in addition to disruption of cells' membrane homeostasis (Choline decrease) may indicate HIV brain latency-related neuropathogenesis. Over-time, these dysregulations may lead to Glutamate excitotoxicity (Glx increase), and axonal injury (NFL increase). The latter appears to uniquely predict neurocognitive decline. These pilot data need to be further tested in a larger sample.

Table 1: Demographic and clinical characteristics of the study group

N	26
Study period plasma and CSF HIV RNA <50 cp/mL	100%
Mean age	57 years
Current cART stability duration	24 months
Median nadir CD4 cell count cp/mL	135
Baseline CD4 cell count cp/mL	544
Follow-up CD4 cell count cp/mL	849
Median baseline HIV duration	19 years
Baseline HAND (56% ANI; 25% MND; 19% HAD)	61%
Previous HAND History	21%
Clinically meaningful cognitive decline	15%
BCL11b expression	0.20 ± 0.14
CSF neopterin (nmol/L)	14.3 ± 5.1
CSF NFL (pg/mL)	946.1 ± 357.3
CSF tat detectability	19.2% (5/26)

399 CEREBRAL ENDOTHELIAL FUNCTION CORRELATES WITH PERFORMANCE ON COGNITIVE SCREENING TEST

Natasha Mehta[1], Yanling Li[2], Yinghuan Hu[2], Huanling Wang[2], Weihai Xu[2], Taisheng Li[2], Felicia C Chow[1]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Peking Union Med Coll Hosp, Beijing, China

Background: HIV-associated cognitive impairment remains prevalent in people living with HIV infection (PLWH) despite widespread use of combination antiretroviral therapy (ART). Increasing attention has been paid to the role of comorbid vascular disease and cerebrovascular injury in the development of HIV-associated cognitive impairment. We hypothesize that cerebral endothelial dysfunction, a marker of cerebrovascular risk, may be associated with cognitive impairment in PLWH.
Methods: We recruited HIV-infected adults followed in the Peking Union Medical College Hospital HIV clinic in Beijing, China. All participants were on combination ART with undetectable plasma HIV RNA level. We used cerebral vasoreactivity (VR), defined as the percentage change in middle cerebral artery mean flow velocity on transcranial Doppler ultrasound (TCD) in response to breath holding, as the primary measure of cerebral endothelial function. Lower cerebral VR is indicative of worse cerebral endothelial function. Cognitive evaluation was performed on the same day as the TCD using the Montreal Cognitive Assessment (MoCA, Chinese Beijing version), a cognitive screening test commonly used in the clinical setting. We constructed linear regression models to estimate the association between cerebral VR and cognitive function.
Results: Of 46 participants, the mean age was 42 years, and 15% were women. Thirty-three percent (33%) had a high school education or less. Mean cerebral VR was 1.07 [standard deviation (SD), 0.33], and mean MoCA score was 26.5 (SD 4.2). In models adjusted for education level, older age, female sex, and lower cerebral VR were associated with a lower MoCA score. In a multivariable model adjusted for age, sex and education level, we observed a trend toward a 1-point increase in the MoCA score for every 1 SD increase in mean cerebral VR (p=0.066). We did not find a statistically significant association between either traditional vascular risk factors (e.g., hypertension, smoking) or HIV-related variables (e.g., current or nadir CD4, ART class, duration of ART use) and the MoCA score.
Conclusion: Among treated, virally suppressed PLWH, cerebral endothelial function correlated with cognitive performance on the MoCA, independent of age, sex and education level. Further evaluation of TCD-assessed cerebral VR as a potential preclinical marker of cognitive impairment and of cognitive decline in longitudinal studies is warranted.

400 RANDOMIZED TRIAL OF BRAIN FUNCTION CHANGE AFTER STARTING TDF/FTC+ATV/R OR ABC/3TC+EFV

Ignacio Pérez-Valero[1], Alicia Gonzalez-Baeza[1], Lucia Bailon[1], Belén Alejos[2], Rocio Montejano[1], Victor Hontanon[1], Helena Melero[3], Marisa Montes[1], Carmen Bayon[1], Jose R. Arribas[1]
[1]Hosp Univ La Paz, Madrid, Spain, Spain, [2]Instituto de Salud Carlos III, Madrid, Spain, [3]Univ Rey Juan Carlos, Alcorcón, Spain

Background: Implications of ART neuropenetration (NP) on brain function (BF) of HIV patients starting therapy are uncertain.
Methods: Randomized, pilot, open-label, 24-week trial designed to evaluate the effects on BF of starting ART with different NP: ABC/3TC+EFV (high NP) vs. TDF/FTC+ATV/r (low NP). In addition to conventional virological and immunological endpoints, at baseline and week 24, we determined creatinine (Cr) ratios of N-acetyl-aspartate (NAA/Cr), Choline (CHO/Cr) and Mioinositol (MI/Cr) in the frontal lobe (FL), basal ganglia and parietal lobe using 3T Magnetic Resonance Spectroscopy of the brain. Cognition was evaluated with a 7-domain battery of tests. ART type effect on brain metabolite ratios and cognitive changes were determined using linear regression models adjusted by baseline levels.
Results: 25 patients were included: 14 on ABC/3TC+EFV and 11 TDF/FTC+ATV/r. Baseline characteristics were similar in both groups (table). 1 patient on ABC/3TC+EFV was discontinued at week 5 due to severe pneumonia. At week 24, 21 patients achieved HIV suppression (HIV RNA <50 cop/mL) (11 on ABC/3TC+EFV and 10 on TDF/FTC+ATV/r), 19 still on randomized ART and 2 on other regimens (1 per group). By ITT, CHO/Cr and MI/Cr increased with ABC/3TC+EFV (0.073±0.091 and 0.0716±0.223) and decreased with TDF/FTC+ATV/r (-0.034±0.119 and -0.013±0.098) in the white matter of FL (p=0.034 and p=0.088 respectively) and MI/Cr also tended to increase with ABC/3TC+EFV (0.065±0.096) and to decrease with TDF/FTC+ATV/r (-0.003±0.069) in the grey matter of FL (p=0.084). No significant changes of NAA/Cr were observed. Global cognition (NPZ-7 change) slightly improved in both groups (0.28±0.35 vs. 0.21±0.27; p=0.32). By cognitive domains, delayed recall improved with ABC/3TC+EFV (0.31±0.58) and decreased with TDF/FTC+ATV/r (-0.11±0.4) (p=0.01). Learning tended to improve more with ABC/3TC+EFV (0.37±0.79 vs. 0.22±0.63; p=0.085). No other differences were observed in cognitive domains.

Conclusion: Starting ART with high NP as ABC/3TC+EFV vs. starting ART with low NP as TDF/FTC+ATV/r was associated with higher levels of the inflammatory marker CHO/Cr in the FL and had positive effects on delayed recall tasks.

Baseline characteristics of patients who completed follow up

	ABC/3TC + EFV N=13	TDF/FTC ATV/r N=11	P Value
Age: mean (SD)	39.5 (9.8)	34.7 (8.4)	0.17
Gender male: N (%)	13 (100)	11 (100)	1
Ethnicity (Caucasian): n (%)	11 (84.6)	10 (90.9)	0.64
CD4 at baseline: median (IQR)	468 (321-534)	514 (397-660)	0.22
AIDS: n (%)	2 (15.4)	1 (9.1)	0.64
HIV RNA > 10^5 at baseline: n (%)	5 (38.5)	5 (41.7)	0.73
Years since HIV diagnosis: median (IQR)	0.22 (0.14-0.37)	0.15 (0.10-0.36)	0.38
Past neurological Comorbidities: n (%)	2 (15.4)	1 (9.1)	0.64
Past psychiatric Comorbidities: n (%)	3 (23.1)	1 (9.1)	0.36
History of Illicit drug consumption: n (%)	3 (23.1)	0 (0)	0.09
HAD – depression subscale: median (IQR)	3 (2-6)	3 (1-5)	0.69
Neurocognitive impairment; n (%)	2 (15.4)	3 (27.3)	0.48
NPZ-7: mean (SD)	0.26 (0.58)	-0.06 (0.76)	0.27

401 RESTING CEREBRAL BLOOD FLOW AND RISKY DECISION-MAKING IN HIV+ AND HIV– YOUNG ADULTS

Robert S. Smith[1], Anika Guha[2], Aaron Tanenbaum[1], Florin Vaida[3], Robert Paul[4], Beau M. Ances[1]
[1]Washington Univ in Saint Louis, Saint Louis, MO, USA, [2]Univ of California Los Angeles, Los Angeles, CA, USA, [3]Univ of California San Diego, San Diego, USA, [4]Univ of Missouri–St. Louis, St. Louis, MO, USA

Background: Few studies have investigated neuroimaging signatures of risky decision-making in HIV+ young adults. HIV-infected (HIV+) individuals often engage in high-risk behavior. Brain regions involved in executive function mature during adolescence. Many of the same regions experience reduced blood flow in the presence of HIV infection. In response to blood flow deficits, HIV+ individuals may recruit additional regions in task experiments. We studied the relationship between resting state cerebral blood flow (rCBF) and risky decision-making in HIV+ (n=41) and HIV-uninfected (HIV–) (n=62) participants.
Methods: Risky decision-making, measured via the Iowa Gambling Task (IGT), was compared voxel-wise to rCBF, acquired via pseudocontinuous arterial spin labeling. Separate rCBF-IGT relationship maps were obtained for HIV– and HIV+ participants, and for the combination of HIV– and HIV+ participants. Relationship maps comprise voxels with a significant ($p<0.05$) rCBF-IGT relationship that are apart of clusters larger than chance ($p<0.05$). The three maps were evaluated for (un)shared regions. For HIV+ individuals, rCBF was compared to HIV disease factors (recent and nadir CD4, and current viral load). All comparisons were made via Pearson correlation.
Results: HIV+ participants performed worse on the IGT compared to HIV– controls. We observed three spatially distinct regions (Figure 1a), Regions-I, -II, and -III, that defined a decreasing rCBF-IGT relationship in HIV+, which is reversed in HIV– (Figure 1b). Region-I (red), strongest rCBF-IGT link in HIV+ (r=0.51), was comprised of frontal and insular areas. Region-II (yellow) contained middle frontal, insular, and orbitofrontal regions. Region-III (blue), strongest rCBF-IGT link in HIV– (r=0.54), consisted of dorsolateral prefrontal and posterior cingulate areas. We quantified rCBF changes associated with the transition to Region-I from -III and found: HIV+ had significantly reduced rCBF in Region-III compared to HIV- controls, rCBF in Regions-III and -I were negatively associated (r=-0.34) in HIV+, and the difference in Region-I and -III rCBF negatively associated with recent CD4 (r=-0.35).
Conclusion: HIV+ young adults recruited additional executive areas at rest in response to blood flow deficits. Increased CD4 counts may lead to partial blood flow recovery, but may not reinstate functionality in retracted territory. Longitudinal studies are needed to determine whether recovery translates to reduced high-risk behavior at this critical development time.

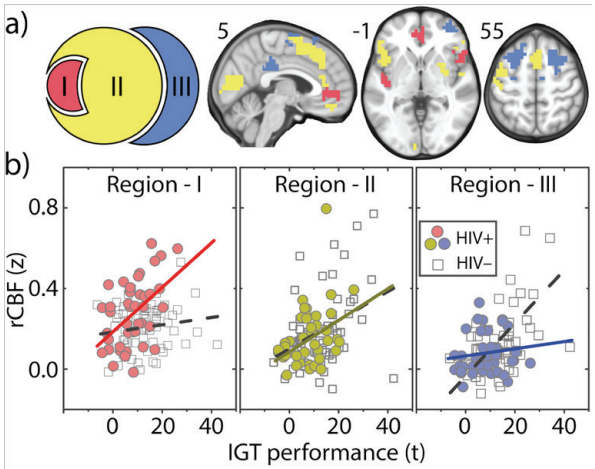


Figure 1. a) Distinct brain territories defined by shared (Region-II) and and unshared (Regions-I and -III) brain regions within resting cerebral blood flow (rCBF) and Iowa Gambling Task (IGT) relationship maps for HIV+ and HIV– young adults. b) The rCBF-IGT relationship strength in each territory for HIV– and HIV+ young adults.

402 MRI REVEALS ENLARGED INTRACRANIAL ARTERIES IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDER

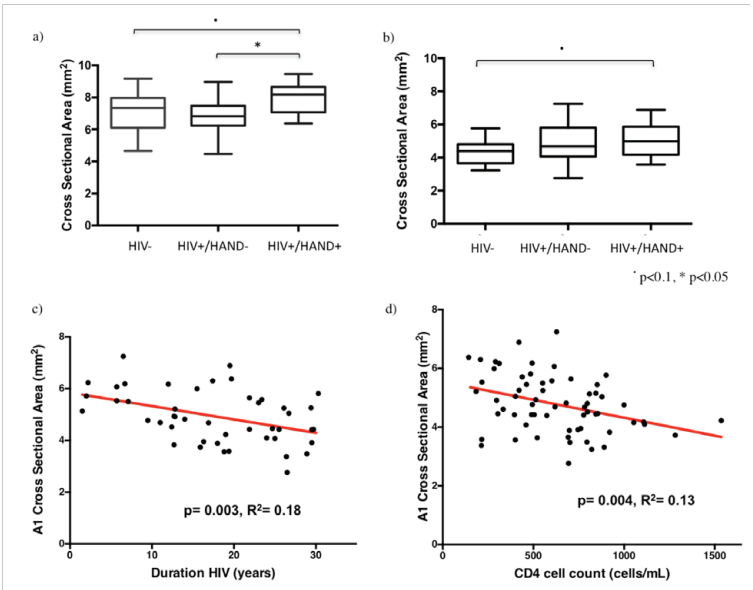
Govind Nair, Angela Summers, Joseph Snow, Daniel S. Reich, Sally Steinbach, Paba M. DeAlwis, **Bryan Smith**, Avindra Nath
NIH, Bethesda, MD, USA

Background: Postmortem studies have demonstrated cerebrovascular remodeling in HIV-infected individuals (HIV+). In this study, intracranial arterial caliber was measured in-vivo in HIV+ with and without cognitive impairment, and compared to controls recruited from similar backgrounds.

Methods: Using high-resolution T2*-weighted magnetic resonance imagining (MRI) sequences and novel analysis methods developed in-house, cross-sectional area of the anterior (A1 segment) and middle (M1 segment) cerebral arteries was studied in 22 HIV- subjects (HIV-), 18 HIV+ with concordant diagnosis of HIV-associated neurocognitive disorder (HIV+/HAND+), and 43 HIV+ without HAND (HIV+/HAND-). Clinical and demographic variables were also assessed in relation to arterial caliber measurements. One-way ANOVA was used for statistical comparison between groups.

Results: HIV+/HAND+ had larger M1 caliber (mean ± SD, 7·9 ± 0·9 mm2) than HIV+/HAND- (7·1 ± 1·0 mm2, p=0·02), and a trend toward larger A1 caliber (5·1 ± 1 mm2) compared to HIV- (4·3 ± 0·7 mm2, p=0·08). Disease duration and current cerebrospinal fluid CD4+ cell count were negatively correlated with A1 caliber (p=0·003 and 0·004, respectively). Figure legend: Group-average plots of vessel caliber from M1 (a) and A1 (b) segments in control (HIV-), HIV infected individuals without cognitive impairment (HIV+/HAND-) and HIV infected individuals with cognitive impairment (HIV+/HAND+) show increase in caliber in the HAND group. Furthermore, median A1 caliber showed significant negative correlation with duration of HIV (c) and current CSF CD4 T-cell levels (d).

Conclusion: Intracranial arterial caliber was measured in-vivo with high sensitivity using this novel method. We hypothesize that failure to recover from acute HIV-induced loss of compliance or thinning of the arterial wall ultimately leads to cognitive impairment. Longitudinal monitoring of vascular caliber in-vivo, ideally from the time of initial infection, could shed further light into the pathophysiology of HAND.



403 WORKING MEMORY IN HIV+ YOUNG ADULTS: FUNCTIONAL IMAGING USING MAGNETOENCEPHALOGRAPHY

Sharon Nichols[1], Ashley R. Swan[2], Annemarie A. Quinto[2], Chris Fennema-Notestine[2], Mingxiong Huang[2]
[1]Univ of California San Diego, La Jolla, CA, USA, [2]Univ of California San Diego, San Diego, CA, USA

Background: Sensitive markers of HIV effects on the central nervous system (CNS) are critical to assess the impact of early treatment or CNS reservoir eradication strategies, particularly in those with suppressed viral load (SVL). This pilot study compared performance on a working memory task with varying load (N-back) between young adults with behaviorally acquired HIV (YWH) and uninfected controls and compared brain activity during N-back between YWH and controls using magnetoencephalography (MEG), a functional imaging technique with fine-grained spatial and temporal resolution.

Methods: Twelve YWH and 13 age- and education-matched controls, males aged 18-24, completed cognitive testing and structural MRI, and performed an N-back task (0, 1 and 2-back) in the MEG scanner. D-prime was computed as the z-score of the hit rate minus the z-score of the false alarm rate for each N-back condition. MEG data were processed using the Fast-VESTAL source imaging program and activation for control participants was subtracted from that for YWH across frequency bands and cortical areas separately for each condition. MEG analyses used cluster analysis with voxel size>500. N-back and MEG analyses used t-tests with p<0.01.

Results: Among YWH, mean CD4 count was 494 and 10 had SVL; mean duration since diagnosis was 36 months. D-prime decreased as working memory load increased, as expected. YWH and controls had comparable 1-back (4.43 and 4.57 for YWH and controls, respectively) and 2-back (2.75 and 2.79) performance but YWH had marginally lower 0-back d-prime (5.39) than controls (6.02). YWH had different patterns of activation during N-back, with both hyperactivation (dlPFC, anterior cingulated/paracingulate gyrus, superior parietal lobe, fusiform and insular cortex across frequency bands, supplementary motor area in beta and gamma) and hypoactivation (bilateral frontal pole across frequencies, and widespread superficial cortical gray in beta and gamma frequencies) compared to controls.

Conclusion: YWH showed striking differences in brain activation from uninfected controls during N-back despite only minor differences in performance, suggesting alterations in substrates underlying working memory functioning. MEG may detect subtle functional changes and warrants study as a marker of early CNS impact in relatively recent infection.

404 LEDIPASVIR/SOFOSBUVIR RAISES TENOFOVIR DIPHOSPHATE CONCENTRATIONS IN RED CELLS

Christine MacBrayne[1], Daniel S. Fierer[2], Kristen M. Marks[3], Peter L. Anderson[1], Lane R. Bushman[1], Kimberly M. Hollabaugh[4], Michael D. Hughes[4], Raymond T. Chung[5], Susanna Naggie[6], Jennifer J. Kiser[1]
[1]Univ of Colorado, Aurora, CO, USA, [2]Icahn Sch of Med at Mt Sinai, New York, NY, USA, [3]Weill Cornell Med, New York, NY, USA, [4]Harvard Univ, Boston, MA, USA, [5]MGH, Boston, USA, [6]Duke Univ, Durham, NC, USA

Background: ACTG 5327 ("SWIFT-C") is an ongoing study of sofosbuvir (SOF)-based treatment of acute Hepatitis C virus (HCV) in HIV-infected individuals. We previously reported that participants in Cohort 1 of SWIFT-C taking SOF and ribavirin had 4.3-fold (range 1.4-15.8) higher intracellular tenofovir-diphosphate (TFV-DP) concentrations in dried blood

spots (DBS), but there are no data with SOF and the HCV NS5A inhibitor, ledipasvir (LDV). The objective of this analysis was to compare TFV-DP concentrations in red blood cells (RBC) measured with DBS and tenofovir (TFV) concentrations in plasma before, during, and after LDV/SOF treatment in participants in Cohort 2 of SWIFT-C.
Methods: Plasma and DBS were obtained from participants taking tenofovir disoproxil fumarate (TDF). TFV-DP was measured in those with available samples at entry, weeks 2 and 8 of LDV/SOF treatment and 2 (EOT+2), 4 (EOT+4), 8 (EOT+8), and 12 weeks (EOT+12) following completion of LDV/SOF treatment. For the 12 participants with data through EOT+12, TFV-DP was also measured at weeks 1 and 4 to provide additional information on the kinetics of the interaction. TFV in plasma was measured at entry, week 8 and EOT+12. TFV and TFV-DP were log transformed for analysis and compared at each visit to study entry using paired t-tests.
Results: 19 participants (5 Hispanic, mean±SD age 43.7±8.4yrs, weight 77.4±10.2kg, and CrCl 106.1±24.4 mL/min) were taking a TDF-based antiretroviral (ARV) regimen prior to commencing 8 weeks of LDV/SOF. Geometric mean TFV-DP and TFV concentrations are shown in the table. At weeks 1, 2, 4 and 8 of LDV/SOF treatment, TFV-DP was 7.1, 9.7, 16.7 and 16.6-fold higher in DBS, respectively compared with study entry (all $p < 0.001$). By EOT + 12, TFV-DP concentrations were similar to baseline ($p=0.39$). Plasma TFV levels were 1.9 fold higher at week 8 vs. study entry ($P=0.0014$) and similar between study entry and EOT+12 ($P=0.56$).
Conclusion: After 8 weeks of LDV/SOF treatment, TFV-DP concentrations in DBS were increased 16.6-fold and TFV in plasma was increased 1.9 fold. TFV-DP accumulated rapidly in DBS after starting LDV/SOF (more than doubling within the first week), but declined consistent with the 17-day half-life in RBC after LDV/SOF therapy was completed. This suggests enhanced RBC loading during LDV/SOF therapy. Additional studies are needed to determine the mechanism, magnitude in other cell types, and clinical significance of this interaction.

Visit (N= number of participants/samples analyzed at visit)	Geometric Mean (%CV) TFV-DP in DBS	Visit (N= number of participants/samples analyzed at visit)	Geometric Mean (%CV) TFV in Plasma
Entry (19)	1533.0 (35.9)	**Entry (17)**	75.9 (77.9)
Week 1 (12)	10,850.9 (71.9)		
Week 2 (19)	14,838.8 (61.0)		
Week 4 (12)	25,547.6 (66.5)		
Week 8 (17)	25,519.5 (54.4)	**Week 8 (15)**	144.6 (129.2)
EOT + 2 (11)	15,138.6 (48.5)		
EOT + 4 (16)	8,333.2 (69.8)		
EOT + 8 (12)	3,893.3 (55.9)		
EOT + 12 (12)	1,970.4 (47.4)	**EOT + 12 (11)**	76.9 (47.5)

405 TENOFOVIR DIPHOSPHATE ARISING FROM TAF IS QUANTIFIABLE IN DRIED BLOOD SPOTS

Jose Castillo-Mancilla, Ryan P. Coyle, Jia-Hua Zheng, Lucas Ellison, Laura Roon, Jordan Fey, Lane Bushman, Jennifer J. Kiser, Peter Anderson
Univ of Colorado, Aurora, CO, USA

Background: Tenofovir diphosphate (TFV-DP) in red blood cells measured with dried blood spots (DBS) is a useful marker of cumulative tenofovir disoproxil fumarate (TDF) dosing, given its long half-life of approximately 17 days. However, studies have not assessed TFV-DP in DBS arising from tenofovir alafenamide (TAF). We aimed to determine whether TFV-DP can also be quantified in DBS during TAF therapy.
Methods: DBS were obtained from HIV-infected individuals on TAF-based therapy, using convenience sampling at various times post dose. Participants were either TDF-naïve or had been off any TDF-based therapy for at least 5 months. TFV-DP in DBS was measured using a validated LC-MS/MS method. The observed concentrations of TFV-DP in DBS from TAF were compared with the expected concentration of TFV-DP from TDF for daily dosing based on a previously published pharmacokinetic model. Data are presented as median (range).
Results: A total of 10 samples from 10 participants (9 White males; 1 Black female) were analyzed. Median age was 40 (26-62) years, and median hematocrit was 46 (41-55) percent. All had HIV-RNA <200 copies/mL. Eight participants were considered to be at steady-state (>8 weeks of therapy) with a median of 14 (9-21) weeks on TAF. The median concentration of TFV-DP in DBS was 224 (83-254) fmol/punch in these individuals. Two participants were pre-steady-state with 16 days of therapy and their values were 54 and 93 fmol/punch, consistent with a long half-life. Of the samples analyzed at expected steady-state, 7 were obtained from individuals taking co-formulated emtricitabine/cobicistat/elvitegravir/10 mg TAF; median TFV-DP was 231 (83-254) fmol/punch. One sample was from an individual taking emtricitabine/25mg TAF; TFV-DP was 216 fmol/punch. All participants had detectable concentrations of FTC-TP in DBS, reflecting recent dosing within the last 48 hours. TFV-DP values arising from TAF therapy were lower than from daily TDF dosing (median 1560 fmol/punch).
Conclusion: TFV-DP arising from TAF-based therapy is quantifiable in DBS, although at lower levels compared with TDF. TAF does not appear to load red blood cells with tenofovir to the same extent as peripheral blood mononuclear cells. Nevertheless, TFV-DP in DBS appears to be promising for use as a measure of cumulative dosing and adherence to TAF-based therapy. A directly observed therapy study is now underway to evaluate the pharmacokinetics and dose proportionality of TFV-DP arising from TAF.

406 EXTRA/INTRA-CELLULAR NUCLEOSIDE/TIDE SEMEN PHARMACOLOGY: IMPLICATIONS FOR ERADICATION

Julie B. Dumond, Stephen A. Greene, Heather M. Asher Prince, Jingxian Chen, Brian Maas, Craig Sykes, Amanda Schauer, Cynthia L. Gay, Angela Kashuba, Myron S. Cohen
Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: The male genital tract (MGT) is a putative HIV reservoir and potential barrier to cure. Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and emtricitabine (FTC) are widely-used NRTIs. Seminal mononuclear cell (SMC) concentrations (C) of TDF, TAF, and FTC may inform effective dosing regimens for HIV cure.
Methods: 8 HIV+, 8 HIV- men receiving TDF/FTC and 4 HIV+ men receiving TAF/FTC for clinical care provided 6 blood (BP) and seminal plasma (SP) samples to construct a composite 24hr C curve. TFV diphosphate (TFVdp), FTC triphosphate (FTCtp), deoxyadenosine triphosphate (dATP), and deoxycytidine triphosphate (dCTP) were measured in peripheral blood mononuclear cells (PBMC) and SMC; SMC for 12 men were pooled due to low cell counts. For PBMC/SMC C below the limit of quantification (LOQ), ½ of the sample LOQ was imputed. Noncompartmental analysis (Phoenix Win Nonlinv6.3, Certara) generated BP and SP area under the curves (AUC) for SP:BP ratios. C over 24h ($C_{ss,ave}$) was computed for each analyte. Data are reported as median (IQR).
Results: Age, BMI for the HIV+ men was 40 (34, 47) yrs and 28.5 (25.8, 32.9) kg/m^2. Age, BMI for the HIV- men was 30.5 (24, 39) yrs and 28.3 (23.9, 32.1) kg/m^2. All had eGFR >50 mL/min. HIV+ TDF men had 39% higher SP C than HIV- TDF men. TAF C were also detected for longer post-dose in SP (12h) than in BP (6h), although they were 80% lower than in BP. TFV SP:BP AUC ratios after TDF dosing were 1.6 (0.8,4.7) [HIV+] and 1.1 (0.8, 2.4) [HIV-]; and 9.4 (7.7, 12) after TAF dosing. $C_{ss,ave}$ are in the table. Despite low TFV C in BP with TAF, TFV SP C were similar to SP C in HIV- TDF men. As expected, TFVdp PBMC C with TAF were 4-fold higher than with TDF. SMC TFVdp C were 94% higher with TAF than with TDF. FTC

SP:BP ratios were ≥3; FTC SP C in HIV+ men were 30-60% higher than HIV- men; FTCtp SMC C were 8-fold higher with TAF. Small changes in median dATP and dCTP SMC C between groups were seen.

Conclusion: High TFV C in SP after TAF dosing was unexpected. Cathepsin A in the MGT and differing drug transporter affinities for TAF and TFV may explain these findings. Increased SMC TFVdp C after TAF dosing may reflect both high TFV penetration and increased PBMC C; these data suggest TAF's MGT distribution differs from TDF. Differing SP/SMC C between HIV+/HIV- men and TFV dosage form suggest drug and disease-specific mechanisms of MGT penetration.

	Tenofovir (TFV)					
	TFV BP $C_{ss,\ ave}$ (ng/mL)	TFV SP $C_{ss,\ ave}$ (ng/mL)	TFVdp PBMC $C_{ss,\ ave}$ (fmol/10^6 cells)	TFVdp SMC $C_{ss,\ ave}$ (fmol/10^6 cells)	dATP PBMC $C_{ss,ave}$ (fmol/10^6 cells)	dATP SMC $C_{ss,\ ave}$ (fmol/10^6 cells)
HIV- TDF/FTC	117 (57, 153)	113 (73, 373)	114 (94, 298)	16 (4.7, 53)	121 (98, 180)	65 (3.8, 76)
HIV+ TDF/FTC	110 (89, 164)	167 (87, 300)	199 (137, 429)	21 (4.7, 51)	168 (119, 193)	26 (12, 46)
HIV+ TAF/FTC	12 (10,13)	120 (89, 173)	784 (677, 1112)	58 (30, 119)	125 (102, 281)	72 (61, 76)
	Emtricitabine (FTC)					
	FTC BP $C_{ss,\ ave}$ (ng/mL)	FTC SP $C_{ss,\ ave}$ (ng/mL)	FTCtp PBMC $C_{ss,\ ave}$ (fmol/10^6 cells)	FTCtp SMC $C_{ss,\ ave}$ (fmol/10^6 cells)	dCTP PBMC $C_{ss,ave}$ (fmol/10^6 cells)	dCTP SMC $C_{ss,\ ave}$ (fmol/10^6 cells)
HIV- TDF/FTC	379 (248, 460)	976 (380, 1726)	5782 (4380, 12169)	76 (52, 152)	546 (509, 1059)	55 (34, 81)
HIV+ TDF/FTC	313 (289, 353)	1342 (1071, 1511)	5803 (4403, 8799)	43 (24, 103)	593 (526, 630)	104 (7.5, 219)
HIV+ TAF/FTC	387 (375, 410)	1760 (1598, 2125)	6679 (5484, 17164)	376 (276, 925)	626 (445, 1240)	176 (155, 196)

407 INTEGRASE AND PROTEASE INHIBITOR CONCENTRATIONS IN LYMPHOID VS GI TISSUES

Sulggi Lee[1], Hiroyu Hatano[1], Angela Kashuba[2], Mackenzie L. Cottrell[2], Teri Liegler[1], Sophie Stephenson[1], Ma Somsouk[1], Peter W. Hunt[1], Steven G. Deeks[1], Radojka M. Savic[1]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: The majority of persistently HIV-infected cells in patients on suppressive antiretroviral therapy (ART) are in lymphoid tissue. Limited drug uptake by lymphoid tissues may contribute to sustained viral persistence. Identifying tissue sources with differential drug uptake may help guide future HIV eradication strategies.

Methods: We measured plasma, gut mucosa, and peripheral lymph node drug concentrations from HIV-infected participants with plasma HIV RNA<40 copies/mL for ≥12 months on integrase (raltegravir, RAL) or protease inhibitor (daranavir, DRV, or atazanavir, ATV)-based regimens. Tissue samples were collected in duplicate, homogenized, and quantified using a validated liquid chromatography-mass spectrometry assay. We developed compartmental plasma-tissue PK models used nonlinear mixed effects modeling incorporating previously reported PK parameters for these drugs. Monte Carlo simulations were performed to estimate plasma and tissue PK profiles, and reported IC95 (RAL) or IC90 (DRV, ATV) values were used to calculate Ctrough:IC95/90 ratios.

Results: Rectal biopsies were collected from 19 participants (8 RAL, 7 DRV, 4 ATV), with a subset with ileal (2 RAL, 1 DRV, 1 ATV) and lymph node (2 RAL, 1 DRV) samples. The median age was 44 years and median duration of ART suppression was 4.4 years. Tissue:plasma concentration ratios (TPRs) were higher in ileum vs. rectum for RAL and ATV (Table 1A). Median Ctrough:IC95/90 ratios for RAL, DRV, and ATV were: 97.9, 1622, and 2.67, respectively (Table 1B), corresponding to a predicted 100% of RAL and DRV and 80% of ATV participants with rectal concentrations >IC95/90. Adequate lymph node samples were only available for RAL (1 DRV participant demonstrated evidence of nonadherence). Among RAL participants, median Ctrough:IC95 ratios for rectum, ileum, and lymph node were 97.9, 99.9, and 3.20, suggesting lower drug penetration in lymphoid vs. gut tissues. Based on this model, we predict ~15% of patients will have lymph node concentrations<="" div="">

Conclusion: The relative concentrations of both integrase (RAL) and protease (ATV) inhibitors were higher in ileum compared to rectum. In a limited number of participants, concentrations of RAL were significantly lower in lymph nodes compared to gut mucosa, confirming prior observations. These results support and add to the current limited data on tissue ART drug concentrations and have potential implications on HIV cure strategies.

408 PLASMA AND INTRACELLULAR PK OF TENOFOVIR IN PATIENTS SWITCHED FROM TDF TO TAF

Anthony Podany, Sara H. Bares, Joshua Havens, Ravi Dyavar Shetty, Jennifer O'Neill, Sarah Lee, Courtney Fletcher, Susan Swindells, Kimberly K. Scarsi
Univ of Nebraska, Omaha, NE, USA

Background: Tenofovir alafenamide (TAF), a pro-drug of tenofovir (TFV), has higher intracellular penetration and lower plasma concentrations than tenofovir disoproxil fumarate (TDF). Intraindividual comparisons of plasma and intracellular pharmacokinetics (PK) of TFV and its intracellular metabolite, tenofovir-diphosphate (TFV-DP) have not been described in patients switching from TDF to TAF.

Methods: We conducted a prospective, non-randomized, cross-over, PK study in participants receiving a TDF-based antiretroviral therapy (ART) regimen (TDF 300mg/FTC 200mg/COBI 150mg/EVG 150mg) who were switching to a TAF containing regimen (TAF 10mg/FTC 200mg/COBI 150mg/EVG 150mg). Single, sparse plasma and PBMC samples were collected prior to switching therapy and 4 to 8 weeks post-switch to TAF. Plasma TFV and cell associated TFV-DP concentrations were determined with validated liquid chromatography tandem mass spectrometry methods. PBMC cell enumeration was performed by quantification of RNase P (RPP30) copy numbers by a highly sensitive droplet digital PCR assay. Patient characteristics are summarized as median (interquartile range, IQR); PK data are summarized as geometric mean (IQR), and compared pre- and post-switch using a geometric mean ratio (GMR) of TAF:TDF, and Wilcoxon signed rank test.

Results: 30 participants completed both study visits: 4 (13%) female, 10 (33%) black non-hispanic, and 39 (25-58) years of age. All participants had undetectable (<20cpm) HIV-1 RNA prior to switching ART and median CD4+ count of 632 (429-713) cells/mm3. Time of blood sampling post dose was 11.2 (4.1-18.6) hrs during TDF-based ART and 10.8 (2.7-17.4) hrs during TAF-based ART. TFV plasma concentrations during TDF-based ART were 100.0 (57.1-147.3) ng/mL and 10.2 (9.8-13.7) ng/mL during TAF-based ART (GMR 0.10; p<0.001). TFV-DP concentrations during the TDF-based regimen were 346.9 (149.3-617.4) fmol/million cells and 834.7 (526.0-1110.9) fmol/million cells in participants receiving TAF-based ART (GMR = 2.4, p=0.004).

Conclusion: Plasma TFV concentrations significantly decreased after switching to TAF, coinciding with the lower dose of tenofovir contained in the TAF-based ART regimen. Conversely, intracellular TFV-DP concentrations were significantly increased with the TAF-based regimen. This study provides the first intraindividual plasma and intracellular PK data in virologically suppressed HIV+ individuals switching from TDF to TAF.

409 COBICISTAT, BUT NOT RITONAVIR, INCREASES DABIGATRAN EXPOSURE

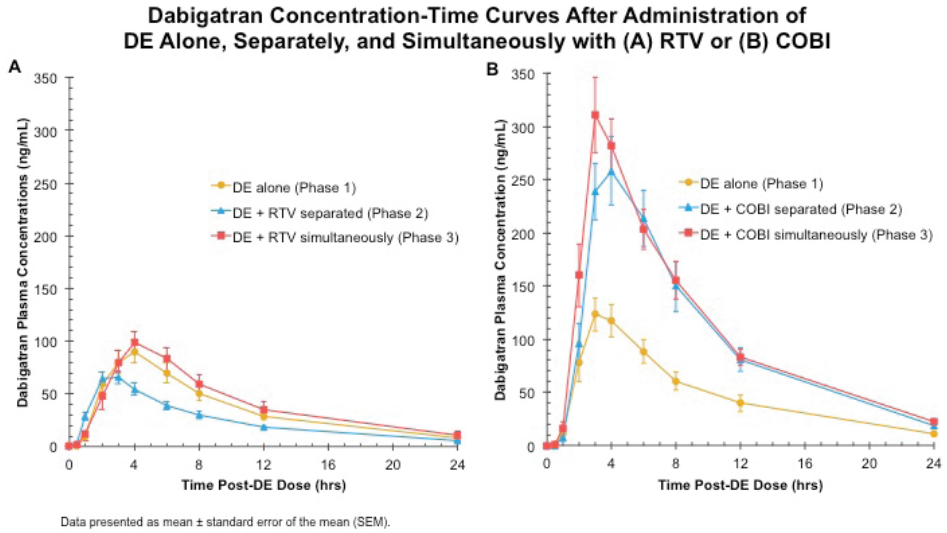
Kristina M. Brooks[1], Lori A. Gordon[2], Scott Penzak[3], Anela Kellogg[4], Maryellen McManus[1], Khanh Nghiem[1], Jay Lozier[1], Jomy M. George[1], Colleen Hadigan[5], Parag Kumar[1]
[1]NIH, Bethesda, MD, USA, [2]Xavier Univ of Louisiana, New Orleans, LA, USA, [3]Univ of North Texas, Fort Worth, TX, USA, [4]Leidos Biomed Rsr, Inc, Bethesda, MD, USA, [5]NIAID, Bethesda, MD, USA

Background: Ritonavir (RTV) and cobicistat (COBI) are antiretroviral pharmacokinetic (PK) enhancers that can inhibit several drug transporters, including P-glycoprotein (P-gp) and renal multidrug and toxin extrusion-1 (MATE-1). Dabigatran etexilate (DE) is the prodrug form of the oral direct thrombin inhibitor, dabigatran, and is a substrate for these transporters. Thus, this study aimed to evaluate the effects of separated and simultaneous administration of RTV and COBI on dabigatran PK.

Methods: This was a single-center, open-label, fixed-sequence study in HIV-negative healthy volunteers. Subjects received either RTV 100 mg (Arm A) or COBI 150 mg (Arm B) once daily (Days 5 - 26±1). Each arm was comprised of 3 phases (Ph): (1) DE 150 mg x1 alone (Day 0) followed by a 5-day washout, (2) DE 150 mg x1 2 hours before RTV or COBI (Day 19±1), and (3) DE 150 mg x1 simultaneously with RTV or COBI (Day 26±1). Blood samples were collected serially over 24 hours after each DE dose, and were analyzed using a UPLC-MS/MS method. PK parameters were determined using noncompartmental methods (Phoenix WinNonlin, v6.4). Geometric mean ratios with 90% confidence intervals (CI) were compared between phases and p-values were calculated using a 2-tailed paired t-test.

Results: A total of 36 subjects were enrolled, with 16 fully completing each arm. With RTV, dabigatran area-under-the-concentration-time curve from 0 to ∞ (AUC0-∞) and peak concentrations (Cmax) were decreased by 29% (p<0.01, 90% CI [0.60-0.82]) and 27% (p<0.01, [0.61-0.85]), respectively, between Ph 2 vs. 1, with no change in half-life (t1/2). No significant changes in dabigatran PK were observed in Ph 3 vs. 1. In contrast, COBI increased dabigatran AUC0-∞ by 110% (p<0.0001, [1.65-2.54]) and Cmax by 99% (p<0.0001, [1.42-2.56]) in Ph 2 vs. 1, and increased both dabigatran AUC0-∞ and Cmax by 127% in Ph 3 vs. 1 (p<0.0001 for both, [1.81-2.73] and [1.59-2.96], respectively). The t1/2 in Ph 2 and 3 was reduced marginally by 7% and 8%, respectively, vs. Ph 1 (p<0.05 for both).

Conclusion: No significant changes in dabigatran exposure were observed with simultaneous RTV administration, possibly due to mixed induction and inhibition of P-gp by RTV. Conversely, COBI resulted in significant increases in dabigatran exposure that persisted despite separating administration, most likely due to intestinal P-gp inhibition. These findings suggest RTV and DE can likely be coadministered, whereas use of DE and COBI may require reduced dosing and prudent clinical monitoring.



409a EARLY TERMINATION OF A PK STUDY BETWEEN DOLUTEGRAVIR AND WEEKLY ISONIAZID/RIFAPENTINE

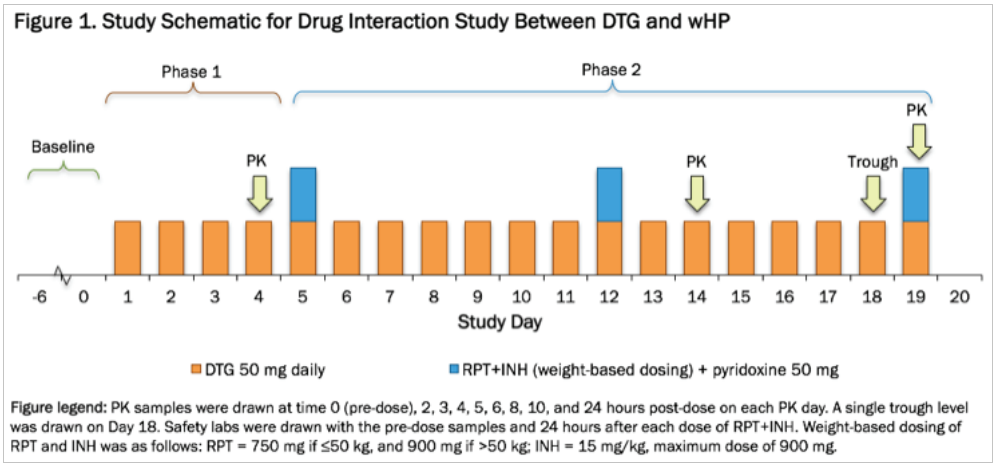
Kristina M. Brooks[1], Alice K Pau[2], Jomy M. George[1], Raul Alfaro[1], Anela Kellogg[3], Mary McLaughlin[2], Maryellen McManus[1], Colleen Hadigan[2], Joseph A. Kovacs[1], Parag Kumar[1]
[1]NIH Clinical Center, Bethesda, MD, [2]National Institute of Allergy and Infectious Diseases, Bethesda, MD, [3]Leidos Biomedical Research, Inc., Bethesda, MD

Background: Once-weekly isoniazid (INH) and rifapentine (RPT) (wHP) for 3 months is a recommended regimen for latent tuberculosis infection (LTBI). Limited drug interaction data exist on the use of this regimen with antiretroviral agents. This study sought to characterize the effects of wHP on the steady-state pharmacokinetics (PK) of dolutegravir (DTG).

Methods: This was an open-label, intrasubject drug interaction study in HIV-negative healthy volunteers comprised of 2 phases: (1) DTG once daily alone and (2) DTG once daily with wHP. The study design is detailed in Figure 1. DTG levels were measured at all PK visits, and RPT and INH levels on Day 19. DTG, RPT, and INH PK parameters were determined by non-compartmental methods (Phoenix WinNonlin, v6.4). Geometric mean ratios with 90% confidence intervals [CI] were compared between PK days. Adverse events (AEs) were graded via the DAIDS AE Toxicity Table (v2.0).

Results: Of 4 enrolled subjects (3 males, 1 female, age 22-46 years), 3 completed the study and 1 withdrew prior to the 3rd dose of HP. The study was stopped prematurely due to the development of multiple AEs in 2 subjects. In both subjects, flu-like syndrome with symptoms of nausea, vomiting, and fever (Grades 2 and 3) began ~8 hours after the last doses of DTG, RPT, and INH and lasted 24-48 hours. One subject required a 24-hour hospitalization for management of orthostatic hypotension (Grade 3). Transaminase elevations (Grades 2-4) occurred in both subjects. Following wHP initiation, DTG exposure was decreased by 46% on Day 14 vs. 4 (p=0.134, 90% CI [0.27-1.10]) and Cmin was decreased by 74% on Day 15 (p=0.017) (n=4). The Cmin was 5.3x DTG's protein-adjusted IC90 (0.064 µg/mL) at this time point (range 0.9-11.0). One subject had multiple Cmin values <0.3 µg/mL following wHP initiation, a level associated with higher rates of DTG treatment failure. Day 19 exposure to RPT and its active metabolite were similar to reference PK data, but INH exposure was 67-92% higher than expected in the 2 subjects who developed AEs.

Conclusion: Serious toxicities, possibly related to high INH exposure, were observed in 2 of 3 subjects receiving 3 doses of wHP with once daily DTG, leading to early termination of our study. Limited PK data from these subjects showed decreased DTG exposure and Cmin values with wHP co-administration. Given that flu-like syndrome was reported in <4% of subjects in studies of the efficacy of wHP alone, these data suggest that co-administration of DTG and wHP should be avoided.



410 INCREASED DOLUTEGRAVIR EXPOSURE IN HIV PATIENTS SWITCHED FROM RITONAVIR TO COBICISTAT

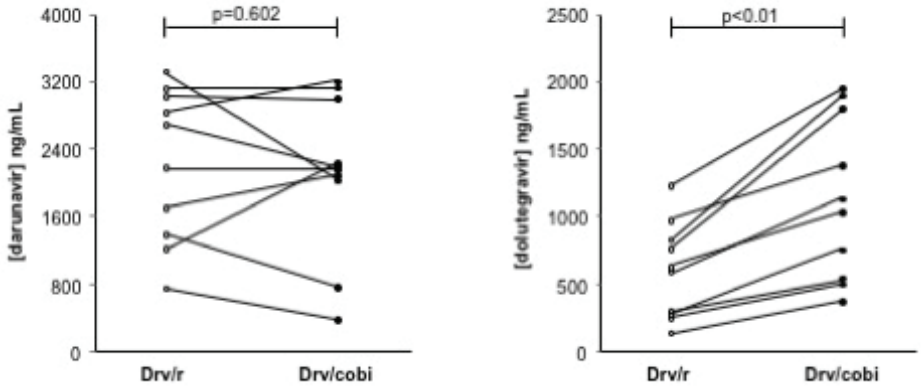
Cristina Gervasoni, Agostino Riva, Amedeo Capetti, Valeria Cozzi, Giuliano Rizzardini, Massimo Galli, Emilio Clementi, Dario Cattaneo
Luigi Sacco Univ Hosp, Milan, Italy

Background: Cobicistat is a new pharmacoenhancer which is now replacing ritonavir thanks to its more selective inhibition on cytochrome P450-mediated hepatic metabolism. Here we carried out a pharmacokinetic survey in HIV-infected patients switching from darunavir/ritonavir (800/100 mg/daily) to darunavir/cobicistat (800/150 mg/daily) and given dolutegravir (50 mg/daily) as part of their antiretroviral therapy

Methods: A consecutive series of HIV-infected patients undergoing therapeutic drug monitoring (TDM) of dolutegravir and darunavir plasma trough concentrations before (visit 1) and after (visit 2) the switch from ritonavir to cobicistat were considered. Collected blood samples had to be taken 24 hours after the last drug intake (a time window of ±20 min was considered acceptable), immediately before drug administration. Drug concentrations were assessed by high performance liquid chromatography method with UV detection previously developed in our lab. Comparisons between the two visits were performed by paired t-tests

Results: Patients (n=10) were all Caucasians, highly pretreated, mainly males (80%), with mean age of 54±6 years and with good immunological status (CD4 cell count: 650±399 cells/mL, viral load <37 copies/mL). As shown in Figure 1, the switch from ritonavir to cobicistat resulted in a 100% increase of dolutegravir trough concentrations (from 591±373 to 1130±634 ng/mL, p<0.01), whereas no difference on darunavir trough concentrations were observed (from 2249±989 to 2122±1032 ng/mL, p=0.602). The second visit was performed at 79±64 days after the fist TDM assessment. During this period no significant increment in serum creatinine concentrations was recorded (visit 1: 1.14±0.33 mg/dL, visit 2: 1.22±0.29 mg/dL, p=0.655)

Conclusion: We confirmed in a real-life setting that the switch from ritonavir to cobicistat resulted in a comparable boosting effect on darunavir exposure. We also documented for the first time that cobicistat significantly increased dolutegravir trough concentrations. It is likely that such pharmacokinetic interaction may be the result of a higher degree of inhibition of cobicistat than ritonavir on intestinal efflux transporters P-glycoprotein and breast cancer resistance protein, ultimately resulting in increased dolutegravir absorption. Interestingly, concomitant administration of dolutegravir and cobicistat – both drugs reported to potentially affect kidney function – has no effect on serum creatinine concentrations



411 EFFECT OF COBICISTAT ON TENOFOVIR PLASMA CONCENTRATION: A CROSS-SECTIONAL STUDY

Cristina Gervasoni[1], Davide Minisci[1], Sara Baldelli[1], Cristina Mazzali[2], Andrea Giacomelli[1], Laura Milazzo[1], Paola Meraviglia[1], Emilio Clementi[1], Massimo Galli[1], Dario Cattaneo[1]
[1]*Luigi Sacco Univ Hosp, Milano, Italy,* [2]*Politecnico di Milano, Italy, Milano, Italy*

Background: The dose of tenofovir alafenamide (TAF) is reduced from 25 to 10 mg daily when given with cobicistat (COBI) or ritonavir due to the boosting effects of these drugs on tenofovir levels. However, such dose reduction has never being adopted for tenofovir disoproxil fumarate (TDF). Accordingly, the observed less nephrotoxicity of TAF versus TDF could have been driven, at least in part, by inappropriate dose selection for drugs comparison. We aim at providing data on the effect of COBI on tenofovir concentrations in real-life settings.

Methods: A cross-sectional analysis was conducted in HIV-positive patients from our database receiving TDF-containing antiretroviral therapies (ART) for at least one month and with at least one assessment of tenofovir plasma trough concentrations. Uni- and multivariate regression analyses were carried out considering tenofovir concentration as the dependent variable and clinical characteristics of the enrolled patients as independent covariates. A general linear model to analyze the effect of independent variables on tenofovir concentrations was applied. Independent variables with p-values < 0.20 at univariate analysis where introduced in the multivariate model
Results: Overall, 510 HIV-infected patients were identified from our dataset. These patients were given TDF in combination with PIs/ritonavir (n=212, 41.6%), NNRTIs (n=176, 34.5%), INIs (dolutegravir or raltegravir, n=46, 9.0%) or with elvitegravir/COBI coformulation (n=76, 14.9%). As shown in Table 1, the covariates that resulted significantly associated with elevated tenofovir plasma trough concentrations were patients' age, body weight, sex, serum creatinine levels and concomitant ART. The highest drug concentrations were measured in patients given elvitegravir/COBI (161±113 ng/mL), being significantly higher than values measured in patients given PIs/ritonavir (147±125 ng/mL), INIs (113±74 ng/mL) or NNRTIs (109±62 ng/mL)
Conclusion: We firstly confirmed the importance of some clinical covariates in predicting tenofovir overexposure. We also provided solid evidence that coadministration with COBI, ihibiting specific influx/efflux drug transporters , resulted in significantly higher tenofovir concentrations compared with all other ART. Accordingly, it could be hypothesized that the lack of dose adjustment for TDF when given with COBI (or with ritonavir) could have introduced a bias in the comparison of safety between TAF and TDF in the current randomized trials

	Univariate analysis			Multivariate analysis		
	beta	**std dev**	**p-value**	**beta**	**std dev**	**p-value**
Concomitant ART			**<.0001**			**<.0001**
COBICISTAT vs PI	0.21	0.08	*0.0113*	0.29	0.08	*0.0005*
INI vs PI	-0.18	0.10	*0.0635*	-0.20	0.10	*0.0458*
NNRTI vs PI	-0.17	0.06	*0.0075*	-0.12	0.06	*0.0561*
SEX (F vs M)	0.14	0.06	**0.0259**	0.20	0.08	**0.0107**
Co-infections (*NO vs YES*)	0.08	0.06	0.1872	0.08	0.06	0.1534
CD4			0.8881			
[0-250] vs [250-500]	0.04	0.09	*0.6283*			
[250-500] vs [>500]	0.004	0.06	*0.9503*			
Viral load (*>=37 vs <37*)	-0.0004	0.08	*0.9963*			
Days of TDF therapy			0.6695			
<= 1y vs > 6y	-0.04	0.08	*0.5989*			
(1y-3y] vs > 6y	0.06	0.08	*0.4568*			
(3y-6y] vs > 6y	-0.03	0.08	*0.7183*			
Age	0.01	0.002	**0.0002**	0.01	0.003	**0.0002**
Weight	-0.006	0.002	**0.0015**	-0.01	0.002	**0.0136**
Creatinine	0.53	0.10	**<.0001**	0.57	0.11	**<.0001**

ART: antiretroviral therapy; PI: protease inhibitors; INI: integrase inhibitors (excluding elvitegravir); NNRTI: non nucleoside reverse transcriptase inhibitors

412 MULTIPLE-DOSE TREATMENT WITH RITONAVIR INCREASES THE EXPOSURE OF DORAVIRINE

Sauzanne Khalilieh[1], Matt Anderson[1], Tine Laethem[2], Kelly Yee[1], Rosa Sanchez[1], Li Fan[1], Monali Sura[1], Luc Van Bortel[3], Greit Van Lancker[3], Marian Iwamoto[1]
[1]Merck & Co, Inc, Kenilworth, NJ, USA, [2]MSD Belgium, Brussels, Belgium, [3]Ghent Univ Hosp, Ghent, Belgium

Background: Doravirine is a novel, potent, HIV-1 non-nucleoside reverse transcriptase inhibitor in development that is primarily metabolized by oxidation via CYP3A4. Ritonavir (RTV) is both an inhibitor of CYP3A and a general inducer of enzymes that may metabolize doravirine. The objective of this study was to assess the effect of multiple doses of RTV on the pharmacokinetics (PK) of doravirine.
Methods: This was an open-label, 2-period, fixed-sequence study in healthy adult subjects. In Period 1 (P1), a single dose of doravirine 50 mg was administered on Day 1. In Period 2 (P2), following a 7-day washout, RTV 100 mg was administered twice daily for 20 days and co-administered with doravirine 50 mg the morning of Day 14. Blood samples to measure doravirine concentrations were collected through 120 and 168 hours post doravirine dose in P1 and P2, respectively.
Results: Eight adult male subjects were enrolled and completed the study. Following co-administration with multiple-doses of RTV, doravirine AUC, Cmax, and C24hr increased. The geometric mean (GM) ratios (90% confidence intervals) [(doravirine +RTV)/doravirine] for doravirine AUC0-∞, Cmax, and C24hr were 3.54 (3.04, 4.11), 1.31 (1.17, 1.46), and 2.91 (2.33, 3.62), respectively. The apparent GM (GCV%) half-life (hr) of doravirine was increased when co administered with RTV, 13.97 (10.59%) and 35.16 (12.27%), respectively. The median (range) Tmax (hr) values following a single dose of doravirine alone and when co administered with RTV were 3.50 (2.00, 5.00) and 5.00 (1.00, 16.00), respectively. Eight subjects reported a total of 22 adverse events (AEs); all AEs, with the exception of one headache of moderate intensity, were mild. There were no serious AEs and no discontinuations due to an AE.
Conclusion: Consistent with the metabolic profile of doravirine, co-administration of doravirine with the CYP3A inhibitor RTV significantly increased doravirine AUC0-∞ and C24hr, with a more modest increase in Cmax, via CYP3A inhibition. Doravirine was generally well tolerated when administered alone or with RTV.

413 GLECAPREVIR AND PIBRENTASVIR INTERACTIONS WITH COMBINATION ANTIRETROVIRAL REGIMENS

Matthew P. Kosloski, Sandeep Dutta, Rolando M. Viani, Xin Qi, Roger Trinh, Andrew Campbell, Wei Liu
AbbVie, North Chicago, IL, USA

Background: The direct acting antiviral combination of glecaprevir (GLE; formerly ABT-493), a NS3/4 protease inhibitor discovered by AbbVie and Enanta, and pibrentasvir (PIB; formerly ABT-530), a NS5A inhibitor, is being developed to treat chronic hepatitis C virus (HCV) genotype 1 to 6 infection. Current guidelines recommend that HCV/HIV co-infected patients be treated the same as HCV mono-infected patients, with considerations for potential drug-drug interactions (DDI) with antiretrovirals. Elvitegravir (ELV)/cobicistat (COBI)/ emtricitabine (FTC)/tenofovir alafenamide (TAF) or abacavir (ABC)/dolutegravir (DTG)/ lamivudine (3TC) are recommended combination antiretroviral regimens . A Phase 1 DDI study was conducted to evaluate pharmacokinetics, tolerability, and safety of GLE + PIB coadministered with ELV/COBI/FTC/TAF or DTG/ABC/3TC.
Methods: An open label, multiple-dose study was conducted in healthy adult subjects receiving GLE 300 mg QD + PIB 120 mg QD with ELV/COBI/FTC/ TAF 150/150/200/10 mg QD (n=24, Arm 1) or ABC/DTG/3TC 600/50/300 mg QD (Arm 2, N=24) alone or in combination. Intensive pharmacokinetic assessments were performed for GLE, PIB, and anti-retroviral drugs on multiple days. Effects of GLE + PIB on the pharmacokinetics of the antiretroviral drugs and vice versa were assessed by a repeated-measures analysis using SAS. Safety was evaluated via assessment of adverse events, vital signs, ECGs and clinical laboratory tests.
Results: In Arm 1, Cmax and AUC were increased by 150% to 205% for GLE and by 24% to 57% for PIB, when co-administered with ELV/COBI/FTC/TAF. GLE + PIB increased Cmax and AUC of ELV and COBI by 29% to 47%, but not of FTC or tenofovir (≤ 12% change). In Arm 2, GLE and PIB Cmax and AUC were slightly lower (25% to 28%) when coadministered with ABC/DTG/3TC. Cmax and AUC of ABC, DTG, and 3TC were not impacted by GLE + PIB (≤ 13% difference). No clinically significant vital signs or laboratory measurements were

observed during the study with the exception of one subject in Arm 1 who discontinued from the study due to a Grade 3 decrease in neutrophil count during ELV/COBI/FTC/ TAF and GLE-PIB coadministration.

Conclusion: Results from the study supported coadministration of GLE/PIB with these combination antiretroviral regimens in ongoing Phase 3 studies in HIV/HCV co-infected subjects. No dose-adjustment is required when GLE/PIB are coadministered with ELV, FTC, TAF, ABC, DTG, or 3TC.

414 EFFECT OF LOW-DOSE METHOTREXATE ON THE PHARMACOKINETICS OF TENOFOVIR

David Gingich[1], Heather Ribaudo[2], Amy Kantor[2], James H. Stein[3], Judith S. Currier[4], Priscilla Hsue[1], Francesca Aweeka[1]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Harvard Univ, Boston, MA, USA, [3]Univ of Wisconsin, Madison, WI, USA, [4]Univ of California Los Angeles, Los Angeles, CA, USA

Background: HIV infected individuals have increased risk of premature cardiovascular disease in spite of effective antiretroviral therapy (ART). Low dose methotrexate (LDMTX) is being evaluated to counter HIV-associated inflammation (ACTG 5314). Methotrexate and tenofovir (TFV) are both eliminated by the kidneys, so a pharmacokinetic (PK) substudy investigated whether LDMTX alters TFV PK.

Methods: In the parent trial, participants were randomized LDMTX or placebo weekly for 24 wks with close monitoring for viral load (VL) and CD4 count. Eligible PK sub-study participants were on stable TFV containing ART. Intensive PK sampling occurred at wk 2, at the time of the 2nd dose of either LDMTX 10 mg or placebo which was dosed with TFV. Serial PK sampling was at 0, 0.5, 1, 2, 4 and 6 hrs post-dosing with a subgroup having extended sampling at 8, 12 and 24 hrs. PK parameters were the area under the concentration time curve (AUC0-6hr and AUC0-24hr) and peak concentration (Cmax). The study had 95% power to detect a 40% increase in AUC with a relaxed type-one error rate (1-sided 5%). Analyses were conducted on natural log scale. Statistical tests (two sample t-tests) are 2-sided and interpreted at the 10% level consistent with the study design.

Results: 48 participants had PK sampling (20 LDMTX, 28 placebo); all were taking TFV in the form of tenofovir disoproxil fumarate. Participants were 92% male, 48% white and 46% black; characteristics were balanced across treatment arms with the exception of concomitant PI-use (25% LDMTX, 43% placebo). For TFV, there was a 22% reduction in the geometric mean (GM) AUC0-6hr in the context of LDMTX; a similar reduction was apparent for AUC0-24hr and Cmax (Table). Analysis by concomitant protease inhibitor (PI) use, suggested a greater difference in the absence of a PI that appeared driven by 5 participants in the LDMTX arm with low TFV concentrations over the sampling period. A formal interaction test was not significant (P>0.3). For PK of LDMTX, the AUC0-6hr and Cmax are summarized descriptively (Table). A5314 follow-up is ongoing; interim safety analyses of VL have raised no concerns.

Conclusion: During TFV and LDMTX co-administration, decreases in the TFV AUC0-24hr and Cmax are apparent. These decreases appear driven by a subset of participants in the LDMTX arm who were not on PI's. The results suggest alterations in TFV dosing during co-treatment with LDMTX are likely unnecessary for patients on PI. Further study of an interaction in patients not on PIs is warranted.

Geometric Mean Pharmacokinetic Parameters of MTX and TFV

	MTX	TFV						
	(with TFV, n=20)	(with Placebo, n=28)		(with LDMTX, n=20)		(LDMTX/Placebo)		
Parameter	GM [90% CI]	GM [90% CI]		GM [90% CI]		GMR [90% CI]		P-value
Cmax (NG/ML)	144 [127, 164]	315	[284, 349]	231	[188, 283]	0.73	[0.60, 0.90]	0.027
PI	-	341	[291, 400]	314	[234, 420]	0.92	[0.69, 1.22]	0.62
No PI	-	296	[256, 343]	209	[162, 268]	0.70	[0.53, 0.93]	0.045
$AUC_{0\text{-}6hr}$ (HR*NG/ML)	492 [434, 558]	1239	[1105, 1390]	967	[802, 1166]	0.78	[0.64, 0.96]	0.06
PI	-	1343	[1127, 1600]	1275	[874, 1859]	0.95	[0.68, 1.32]	0.80
No PI	-	1167	[992, 1372]	882	[706, 1101]	0.76	[0.58, 0.98]	0.08
$AUC_{0\text{-}24hr}$[1] (HR*NG/ML)	-	3481	[2948, 4110]	2235	[1511, 3306]	0.64	[0.45, 0.91]	0.08
$AUC^{I}_{0\text{-}24hr}$[2] (HR*NG/ML)	-	3503	[3087, 3975]	2647	[2218, 3160]	0.76	[0.61, 0.93]	0.033
PI	-	3873	[3205, 4679]	3331	[2202, 5039]	0.86	[0.60, 1.23]	0.52
No PI	-	3249	[2718, 3883]	2452	[1995, 3014]	0.75	[0.58, 0.98]	0.08

GM: geometric mean; CI: confidence interval; GMR: geometric mean ratio; *[1]7 participants for TFV+placebo and 10 participants for TFV+LDMTX; [2]Imputed the pre-dose concentration as the 24hr concentration since participants were at steady state.*

415 PHARMACOKINETICS ANALYSIS OF VRC01, A BROADLY NEUTRALIZING HIV-1 MONOCLONAL ANTIBODY

Yunda Huang[1], Lily Zhang[1], Nicole Grunenberg[1], Robert Bailor[2], Abby Isaacs[1], Julie Ledgerwood[3], Kelly Seaton[4], Kenneth Mayer[5], Larry Corey[1], Peter Gilbert[1]
[1]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [2]NIAID, Gaithersburg, MD, USA, [3]NIAID, Bethesda, MD, USA, [4]Duke Human Vaccine Inst, Durham, NC, USA, [5]The Fenway Inst, Boston, MA, USA

Background: VRC01 is a monoclonal antibody targeting the CD4 binding site of the HIV envelope. Eighty-four HIV-uninfected adults received multiple-dose intravenous (IV) VRC01 at 10, 20, 30 or 40 mg/Kg every 4 or 8 weeks, or subcutaneous (SC) VRC01 at 5 mg/Kg every 2 weeks, and were followed for 8 months in HVTN 104. We conducted the first population pharmacokinetics (popPK) analysis of VRC01, providing important understanding of the inter-individual variability (IIV) of the drug disposition process and the effects of covariates on systemic drug exposure for ongoing and planned HIV prevention efficacy trials of VRC01.

Methods: VRC01 serum concentration-time data were described using an open 2-compartment disposition model with first-order elimination from the central compartment. A depot compartment with a first-order absorption rate constant was included for SC VRC01. Nonlinear mixed effect models with exponential random effects and combined proportion/ constant residual error were used. Baseline demographic and safety laboratory values were screened and considered as potential covariates of different functional forms in the popPK model via a stepwise model selection procedure. The PK model was parameterized in terms of clearance (CL), central volume of distribution (Vc), peripheral volume of distribution (Vp), distribution clearance (Q), and absorption rate constant (Ka).

Results: All available 1117 serum concentrations were modeled. Dose-normalized area under the time-concentration curve showed linearity of PK following IV VRC01. IIV of the PK parameters was moderate (23-31% CV) except for that of Vp (40% CV) and Ka (48% CV) in the base model that did not account for covariates (Table). Relative to IV administration, bioavailability (F1) after SC administration was 71%. Population mean estimates for CL and Vc were 0.39 Liter/day and 1.83 Liter, with an estimated terminal half-life of 15 days. The correlations between the individual-level PK parameters ranged from 0.12 (Vc and Q) to 0.97 (Vp and Q). In the final model, body weight was identified to have a significant influence on CL (0.7% fold increase per Kg) and Vc (1.1% per Kg). All parameters were estimated with acceptable precision.

Conclusion: A robust popPK model for VRC01 was developed, supporting the weight-dependent dosing regimens. This model could be used to simulate concentration data for correlates research, and with given protective VRC01 levels to guide dose and target population selections in efficacy trials.

Table: popPK parameter estimates of VRC01 based on the modeling of all five IV infusion and SC groups (n=84 participants). %RSE: relative standard error (SE) of the fixed effect estimate calculated as 100* the ratio of the standard error and estimate, both for log-transformed PK parameters. %CV: coefficient of variation for exponential random effects calculated as $\sqrt{variance}$* 100. R: correlation coefficient of the random effects.

Parameter (units)	Base model of all IV and SC groups			
	Fixed effects: Population Parameter		Random effects: Inter-individual/ Covariance/Residual error	
	Estimate	%RSE	Estimate (%CV)	%RSE
F1 (-) – bioavailability after SC administration	0.71	12.50	0.00*	--
Ka (1/day) - absorption rate constant	0.35	5.90	0.23 (47.6)	0.49
CL (Liter/day) – clearance from the central compartment	0.39	3.76	0.096 (31.0)	4.44
Vc (Liter) – volume of the central compartment	1.83	6.71	0.052 (22.7)	0.045
Q (Liter/day) – inter-compartmental distribution clearance	0.79	16.30	0.097 (31.2)	0.645
Vp (Liter) – volume of the peripheral compartment	4.76	3.00	0.16 (39.6)	0.498
Covariance between CL and Q	--	--	0.057 (R=0.59)	10.4
Covariance between CL and Vp	--	--	0.082 (R=0.67)	8.79
Covariance between Q and Vp	--	--	0.12 (R=0.97)	0.497
σ^2 (proportional)	--	--	0.041 (20.1)	5.69
σ^2 (additive)	--	--	0.450	18.3

*Inter-subject random variance was fixed at 0 in the base model.

416 EFFECT OF CYP3A4*22 ON ORAL RILPIVIRINE PLASMA CONCENTRATIONS

Rana Abutaima[1], Marta Boffito[2], Andrea Calcagno[3], Jessica Cusato[3], Antonio D'Avolio[3], Laura Else[1], Chris Higgs[2], Saye Khoo[1], Marco Siccardi[1], Andrew Owen[1]
[1]Univ of Liverpool, Liverpool, UK, [2]St. Stephen's AIDS Trust, Chelsea and Westminster Hosp, London, UK, [3]Univ of Turin, Turin, Italy

Background: Rilpivirine (RPV) is mainly metabolised by cytochrome P450 (CYP) enzymes but less is known about the importance of transporters in its disposition. Many enzymes and transporters are transcriptionally regulated by the pregnane-X-receptor (PXR; NR1I2). In this study, we sought to determine associations between genetic variants within the genes coding for these proteins and RPV plasma concentrations.

Methods: Blood samples were collected 12 hours post dose (C_{12}) from 150 patients receiving RPV-containing regimens recruited in Turin (Italy) and London (UK). Plasma concentrations of RPV were analysed by validated LC-MS/MS methods. Genotyping was conducted by real-time PCR-based allelic discrimination using standard methods for the following polymorphisms: *CYP3A4*22* (rs35599367), *CYP2C19*2* (rs4244285), *CYP2C19*17* (rs12248560), *NR1I2* (rs2472677), *SLC22A1* (rs628031, rs72552763, rs622342 and rs683369), *SLCO2B1* (rs1077858, rs12422149, rs35199625, rs2712807 and rs2851069). Data were log transformed, and univariate and multivariate linear regression was used to investigate associations. All data are given as mean with standard deviation.

Results: Patients were 42.7 (11.1) years old, with height 173.5 (8.3) cm, weight 72.3 (12.4) kg and C_{12}171.4 (80.9) ng. mL^{-1}. 86% were male, 98% were white, 74.7% received emtricitabine with tenofovir disoproxil fumarate (FTC/TDF), 23.3% received ritonavir-boosted darunavir (DRV/r), and 2% received abacavir with lamivudine (ABC/3TC). All SNPs were in Hardy-Weinberg equilibrium and carrier/non-carrier analyses were applied in regression analyses. In univariate linear regression, differences in C_{12} were associated with height (P= 0.01) and *CYP3A4*22* (P= 0.01). Differences in C_{12} were also seen between patients receiving different backbone therapies. *CYP3A4*22* (P= 0.02, β= -0.17), and concomitant drugs (P= 0.02, β= -0.09) remained significant in multivariate linear regression (see table).

Conclusion: These results indicate that *CYP3A4*22* (c.522-191 C>T; rs35599367) is associated with RPV pharmacokinetics but further studies are required to confirm this association. While the impact of *CYP3A4*22* on C_{12} was relatively minor, a more marked effect would be expected after administration of the RPV long-acting depot and this warrants further investigation.

Variable	Mean C_{12} value (ng. mL^{-1}) (SD)	Multivariate linear regression (Backward method)			
		β	95% CI		P value
Height		-0.004	-0.01	0.001	0.09
TDF/FTC	182.3 (93.9)	-0.09	-0.16	-0.01	0.02
DRV/r	140.2 (62)				
ABC/3TC	171.4 (89.9)				
*CYP3A4*22* T allele carrier	221.2 (50.6)	-0.17	-0.30	-0.03	0.02
*CYP3A4*22* Non-carrier	167.98 (89.9)				
rs1789693 T allele carrier	163.43 (82.5)	0.06	-0.01	0.14	0.09
rs1789693 Non-carrier	183.59 (97.4)				

417 EFFECT OF CYP3A5 GENOTYPE ON THE PK OF MARAVIROC AND METABOLITES IN HEALTHY SUBJECTS

Manoli Vourvahis[1], Sunil Nepal[2], Annie Fang[1], Gwendolyn Fate[3], Linda S. Wood[3], Jean-Claude Marshall[3], Andrew Clark[4], Jayvant Heera[3]
[1]Pfizer, New York, NY, USA, [2]Pfizer, Biostatistics, Collville, PA, USA, [3]Pfizer, Groton, CT, USA, [4]ViiV Hlthcare, London, UK

Background: Maraviroc (MVC) is a substrate for CYP3A, P-gp and OATP1B1. Previous data demonstrated that MVC average exposures (Cavg) are lower in subjects with the CYP3A5 (3A5)*1/*1 wild-type/extensive metabolizer (EM) genotype (GT) (n=8) compared to those with 3A5 mutant alleles (*3, *6 and/or *7; poor metabolizer (PM); n=8). While rare in Caucasians (CAU), the prevalence of EMs is substantial (39-70%) in Blacks. Thus, the aim was to describe the prevalence and assess the effect of 3A5 GT on the pharmacokinetics

(PK) of MVC and metabolites in healthy African-American (AA) and CAU subjects when MVC was dosed alone or with darunavir/cobicistat (DRV/c). MVC and metabolite PK comparisons were assessed by 3A5 GT with and without DRV/c and between race.

Methods: This was an open-label, parallel group study targeting 12 healthy adults per cohort. Subjects were enrolled by 3A5 GT and race into: Cohort 1–AA with no 3A5*1 alleles (PM); Cohort 2–AA with one 3A5*1 allele (intermediate metabolizer; IM); Cohort 3–AA with two 3A5*1 alleles (EM); or Cohort 4–CAU with no 3A5*1 alleles (PM). For Part 1, all subjects received MVC 300 mg BID for 5 days. For Part 2 (Cohorts 1 and 3), subjects received MVC 150 mg QD in combination with DRV/c for 10 days. Serial PK sampling followed the last dose of MVC in Part 1 and 2.

Results: 47 subjects were enrolled. MVC and metabolite PK, when dosed alone, are summarized in the Table. Mean MVC Cavg were ranked highest to lowest by 3A5 GT, PM>IM>EM. EMs had 37% and 26% lower MVC Cavg compared to AA PMs and CAU PMs, respectively. Comparing the impact of race, AA PMs had 17% higher exposures as compared to CAU PMs. PF-06857639 was the only MVC metabolite shown to be affected by 3A5 GT. When MVC was co-administered with DRV/c, AA EMs had an 18% lower MVC Cavg compared to AA PMs and metabolites were undetectable in most samples. There were no serious or severe adverse events.

Conclusion: 3A5 GT, not race, had the most influence on MVC exposure and the magnitude of the 3A5 GT effect on MVC Cavg was reduced in the presence of DRV/c, a potent CYP3A inhibitor. Lower MVC PK associated with 3A5 EMs are not expected to be clinically relevant for treatment of HIV, regardless of 3A5 GT, as MVC exposures associated with MVC efficacy (Cavg ≥75 ng/mL) was achieved in all subjects with MVC 300 mg BID alone and MVC 150 mg QD with DRV/c and was not shown to impact efficacy in a previous presentation of the Phase 3 MERIT study. Maraviroc dosing with/without DRV/c was well tolerated.

	Maraviroc			PF-06857639	PF-06857640	PF-06927572	PF-06927573
	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{12h} (ng/mL)	MR_{AUC}	MR_{AUC}	MR_{AUC}	MR_{AUC}
Cohort	Geometric mean						
Cohort 1 (AA PM; n=11)	287	864	59.8	0.022	0.026	0.028	0.020
Cohort 2 (AA IM; n=12)	246	754	63.1	0.036	0.026	0.029	0.024
Cohort 3 (AA EM; n=12)	182	529	45.3	0.043	0.028	0.028	0.020
Cohort 4 (CAU PM; n=12)	246	731	63.1	0.016	0.023	0.028	0.021
Test/ Reference	GMR (p-value)						
AA EM/PM ratio	0.63* p<0.001	0.61* p<0.001	0.76* p=0.033	1.98* p<0.001	1.09 p=0.391	1.01 p=0.936	1.00 p=0.971
AA EM/CAU PM ratio	0.74* p=0.004	0.72* p=0.014	0.72* p=0.010	2.72* p<0.001	1.20 p=0.059	1.01 p=0.954	0.97 p=0.791
AA IM/PM ratio	0.86 p=0.137	0.87 p=0.295	1.05 p=0.677	1.64* p<0.001	1.02 p=0.858	1.05 p=0.697	1.19 p=0.126
AA EM/IM ratio	0.74* p=0.004	0.70* p=0.007	0.72* p=0.010	1.21 p=0.106	1.07 p=0.487	0.96 p=0.752	0.84 p=0.110
AA PM/CAU PM ratio	1.17 p=0.132	1.18 p=0.200	0.95 p=0.676	1.37* p=0.011	1.10 p=0.308	1.00 p=0.982	0.98 p=0.824

* statistically significant (p<0.05)

AA - African-American; CAU – Caucasian; CI – confidence interval; EM – extensive metabolizers; IM – intermediate metabolizers; PM – poor metabolizers; GMR – geometric mean ratio; MR_{AUC} – AUC metabolic ratio (calculated as $AUC_{metabolite}/AUC_{parent} \times MW_{parent}/MW_{metabolite}$); MW – molecular weight; PF-06857639, PF-06857640, PF-06927572 and PF-06927573 represents the CYP3A-derived maraviroc metabolites

418 ABCG2 RS2231142 INFLUENCES TFV CONCENTRATIONS IN PLASMA AND URINE

Margherita Bracchi[1], **Megan Neary**[2], Nicole Pagani[1], Laura Else[2], Saye Khoo[2], Zaheer Abbas[1], David Hawkins[1], Graeme Moyle[1], Andrew Owen[2], Marta Boffito[3]
[1]Chelsea and Westminster Hosp, London, UK, [2]Univ of Liverpool, Liverpool, UK, [3]Chelsea and Westminster NHS Fndn Trust, London, UK

Background: Tenofovir (TFV) disoproxil fumarate (TDF) is recommended by WHO as a first-line antiretroviral therapy and its use post-patent expiry is predicted to increase. This study investigated the association between pharmacogenetic variants linked to TFV metabolism / excretion, and TFV plasma and urine concentrations in patients receiving TFV as part of different regimens.

Methods: This prospective, longitudinal, PK evaluation studied a total of 56 HIV positive patients receiving TFV combined with raltegravir (RAL) (n = 18), dolutegravir (DTG) (n = 19) or elvitegravir and cobicistat (EVG/COBI) (n = 19). Whole blood, plasma and urine samples were taken for pharmacogenetic and pharmacokinetic analysis at study week 4. TFV concentration in blood plasma and urine at steady state were determined using validated LC-MS/MS. ABCC4 4131T>C (rs3742106), ABCC10 2843T>C (rs2125739), ABCC10 526G>A

(rs9349256), ABCC2 1249G>A (rs2273697), ABCC2 -24C>T (rs717620), ABCC2 3563T>A (rs17222723), ABCC2 3972C>T (rs3740066) and ABCG2 421C>A (rs2231142) were genotyped using TaqMan assays. Associations between patient genotype and TFV concentrations were determined through univariate and multivariate linear regression.
Results: The study group included HIV-infected adults (53 men, 3 women). Patient ethnicities were Caucasian (n = 42), Black (n = 2), Asian (n = 4), Mixed Race (n = 2) and Other (n = 3), 3 patients had unspecified ethnicity. All genotypes were in Hardy-Weinberg equilibrium. ABCG2 421C>A (rs2231142) was associated with lower TFV plasma (P = 0.030, β = -0.213) and urine (P = 0.001, β = -0.473) concentrations (log10 ng/mL). No other genetic associations were observed. Ethnicity classification of 'Other' was associated with lower plasma (P = 0.047, β=-0.353) and urine (P = 0.030, β = -0.476) TFV concentrations compared to the Caucasian ethnicity group but the extremely small number of these patients should be considered. Patients receiving EVG/COBI were associated with lower urine (P = 0.006, β = -0.325) TFV concentration compared to the RAL group.
Conclusion: This is the first study to demonstrate that ABCG2 421C>A (rs2231142) influences TFV plasma and urine concentrations. TDF but not TFV has previously been demonstrated to interact with ABCG2 and thus further investigation is warranted to confirm and elucidate the mechanism of this association.

419 TFV-DP IN DRIED BLOOD SPOTS (DBS) FOLLOWING DIRECTLY OBSERVED THERAPY: DOT-DBS STUDY

Peter Anderson[1], Albert Y. Liu[2], Jose Castillo-Mancilla[1], Sharon Seifert[1], Cricket McHugh[1], Theresa Wagner[2], Susan Buchbinder[2], Lane Bushman[1], Jennifer J. Kiser[1], Samantha MaWhinney[1]
[1]Univ of Colorado Denver, Aurora, CO, USA, [2]San Francisco Dept of Pub Hlth, San Francisco, CA, USA

Background: Tenofovir-diphosphate (TFV-DP) in red blood cells measured with DBS is a useful marker of cumulative tenofovir disoproxil fumarate (TDF) adherence, given its ~17 day half-life. To date, adherence interpretations were based on pharmacokinetic (pk) modeling from 17 individuals who received 30 days of daily TDF/emtricitabine (FTC). DOT-DBS prospectively evaluated TFV-DP pk at steady-state, dose-proportionality, and comparability with earlier pk modeling.
Methods: HIV negative subjects were recruited from Denver and San Francisco (SF). Subjects were randomized to 2 of 3 TDF/FTC doses (as a % of daily dosing) for 12 wks each; 100%, 67%, and 33%, separated by a 12-wk washout. Arms 33% and 67% were balanced by; "intermittent" (skipping days) and "holiday" (skipping wks). Doses were observed in person or by live video. DBS from wk 12 were analyzed. Demonstration that TFV-DP was directly proportional with cumulative dosing (dose proportionality) required the 90% CI for slope of ln dose on wk 12 ln TFV-DP to be within 0.80-1.20. Mixed models were used. Subgroup analyses were univariate.
Results: 48 adults were included, 24 from each site; 23 males, 26 white, 8 black, 14 Hispanic (2 black). Median (range) age was 29 (21-49) years, weight 77 (51-155) kg, CrCl 98 (69-156) ml/min, HCT 43% (35-49). Two subjects completed only the 1st dosing period and two were within 4 wks of finishing the 2nd. TFV-DP was dose-proportional; slope 1.02 (90% CI 0.94-1.09). Table shows results for each dose. Sub-group analyses showed no statistical differences in dose proportionality. TFV-DP did not vary substantially by "Intermittent" vs "holiday", CrCl, or HCT. SF and blacks trended towards lower TFV-DP compared with Denver and whites, -12% (95% CI, -24, 0.4) and -14% (-27, 2.3), respectively. TFV-DP was 22% (7, 39) higher in females than males. Study estimates were comparable with the earlier pk model, which assumed dose proportionality and used rounded 25th percentiles for 28.6%, 57.1%, and 100% dosing (2, 4, 7 doses/wk); results were 355 vs 350, 719 vs 700, and 1271 vs 1250 fmol/punch, respectively.
Conclusion: TFV-DP in DBS was dose proportional and estimates matched a previous pk model used for adherence interpretations. Some variability may be explained by SF (sea level) vs Denver (5280 feet), blacks vs whites and females vs males. These differences should be explored further. TFV-DP in DBS provides an estimate of cumulative dosing that can be used to interpret average adherence to TDF-based therapy.

420 IN VITRO AND IN VIVO EVALUATION OF BIODEGRADABLE IMPLANT CONTAINING TAF FOR HIV PREP

Phillip G. Durham[1], Greg Gatto[1], Leah Johnson[1], Mark A. Marzinke[2], Stephanie Swarner[1], Ginger Rothrock[1], Tejal Desai[3], Ian McGowan[4], Ida Washington[5], Ariane van der Straten[6]
[1]RTI Intl, Durham, NC, USA, [2]The Johns Hopkins Univ, Baltimore, MD, USA, [3]Univ of California San Francisco, San Francisco, CA, USA, [4]Univ of Pittsburgh, Pittsburgh, PA, [5]Magee-Womens Rsr Inst, Pittsburgh, PA, USA, [6]RTI Intl, San Francisco, CA, USA

Background: Subcutaneous implants for Pre-exposure prophylaxis (PrEP) could provide constant protection from HIV over several months. Polycaprolactone (PCL) is used as a biodegradable thin film for membrane controlled, zero-order drug release kinetics from implantable devices. We assessed in vitro and in vivo release of Tenofovir (TFV) Alafenamide Fumarate (TAF) from PCL devices, to demonstrate sustained levels of TAF and its metabolites in rabbits.
Methods: PCL films (25 µm) were solvent-cast, formed into an open-end hollow rod and loaded with TAF and PEG_{300} (2:1 ratio). Three TAF dosing groups targeted to deliver 0.98, 0.49 and 0.1 mg/day for 30 days (high [H], medium [M] and low dose [L], respectively) were fabricated by scaling device size and surface area. In vitro, 6 devices/group were evaluated (PBS, 37°C) and TAF release was measured at 2-day intervals by UV visible spectroscopy. Six rabbits/group were implanted with a single device. We collected blood samples (days 0-45) and peripheral blood mononuclear cells (PBMCs; days 21-45). Devices were retrieved from all animals for further analysis. Drug and metabolite concentrations were determined via liquid chromatographic-tandem mass spectrometric analysis. Here we report plasma TFV and TAF concentrations (ng/ml) and PBMC TFV diphosphate (TFVdp) concentrations (fmol/10^6 cells).
Results: *In vitro* TAF devices showed linear release (R^2 >0.95) for a mean of 17.4 days (H group) and 21 days (M and L groups). The average release of TAF was proportional to the device sizes over 15.92 days, with observed releases 24%-47% faster than targeted. In the H group, plasma TAF was quantifiable for ≤ 21 days, TFV for ≤ 30 days, and PBMC TFVdp at 21-day only (Table 1). TAF release *in vitro* highly correlated (R^2 >0.98) to both TAF and TFV levels *in vivo* as determined by the average *in vitro* release rate for each group at 15.92 days and TAF and TFV plasma concentrations at 14 days.
Conclusion: Devices showed dose dependent sustained plasma TAF and TFV levels that correlated with *in vitro* release of TAF. *In vitro* data suggests *in vivo* depletion occurred between days 14-21, coincident with the disappearance of TAF from plasma. After depletion, TAF, TFV and TFVdp levels quickly reduced to below quantification. This short end-of-dose resolution may avoid long sub-effective drug PK tail. Using the *in vitro/in vivo* correlation as a reference, additional experiments are planned to evaluate the PK of maximally loaded devices to release TAF for a much longer duration.

Dose group	Target TAF release over 30 days (mg/day)	Actual TAF in vitro release over 15 days (mg/day)	In vivo plasma TAF levels on day 14 (ng/mL) [# animals]	In vivo plasma TFV levels on day 14 (ng/mL) [# animals])	In vivo PBMC TFVdp on day 21 (fmol/10^6 cells) [# animals]
High (H)	0.98	1.22 (±0.17)	0.33 (±0.20) [6]	20.45 (±8.76) [6]	295.8 (±59.0) [4]
Medium (M)	0.49	0.72 (±0.03)	0.14 (±0.10) [3]	9.73 (±6.29) [5]	- [0]
Low (L)	0.1	0.13 (±0.02)	- [0]	1.81 (±0.58) [5]	152.9 [1]

421LB HPTN 076: TMC278 LA SAFE, TOLERABLE, AND ACCEPTABLE FOR HIV PREEXPOSURE PROPHYLAXIS

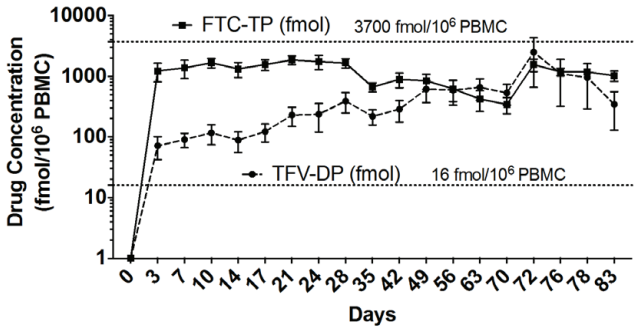
Linda-Gail Bekker[1], Shuying S. Li[2], Betsy Tolley[3], Mark A. Marzinke[4], Nyaradzo Mgodi[5], Jessica E. Justman[6], Shobha Swaminathan[7], Adeola Adeyeye[8], Jennifer H. Farrior[3], Nirupama Sista[3]
[1]Univ of Cape Town, Cape Town, South Africa, [2]FRCHC, Seattle, WA, USA, [3]FHI 360, Durham, NC, USA, [4]Johns Hopkins Univ, Baltimore, MD, USA, [5]Univ of Zimbabwe, Harare, Zimbabwe, [6]ICAP at Columbia Univ, New York, NY, USA, [7]Rutgers Univ, Newark, NJ, USA, [8]NIH, Rockville, MD, USA

Background: Adherence to daily pre-exposure prophylaxis (PrEP) is difficult for many people so finding alternative strategies is a priority. HPTN 076 evaluated safety and acceptability of the long-acting injectable form of rilpivirine (TMC278 LA) for PrEP.
Methods: HPTN 076 is a phase 2, double-blind, 2:1 randomized trial comparing the safety of 1200mg TMC278 LA (LA) to placebo (P). Injectable product was administered to low risk, sexually active HIV-uninfected women in two gluteal, intramuscular (IM) injections every eight weeks over a 48-week period. Injections followed 28-days of self-administered daily oral rilpivirine (RPV, 25mg). Acceptability, safety and pharmacokinetic data were collected throughout the study. Product was paused for any participant with Grade (Gr) ≥2 related or Gr ≥3 unrelated adverse events (AEs).
Results: A total of 136 (100 African, 36 US) women were enrolled; median age 31 years (IQR: 25,38), median weight 75kg (IQR: 64, 89), 46% married, 94% Black and 60% unemployed. Ten women withdrew (8 RPV, 2 P) and four had product discontinued (3 RPV, 1 P) during the oral phase (Weeks 0-4). A total of 122 (80 LA, 42 P) women received ≥ one injection; 98 (64 LA, 34 P) received all six injections. During the injection phase (Weeks 4-52), one woman withdrew (P) and 16 product discontinuations (10 LA, 6 P) occurred. Of the product discontinuations, 6 (8%) LA and 2 (5%) P were due to AEs including one P arm participant with prolonged QTc interval. Transient Gr ≥2 liver abnormalities occurred in 9 (11%) of the LA participants compared with 4 (10%) in the P arm. Three LA arm participants developed Gr ≥3 injection site reactions compared with none in the P arm. No significant difference was observed between the two arms. Among participants who received ≥ one injection, the median trough concentration (CTrough) of RPV was 68.2 ng/mL. At Week 52 (eight weeks after last injection), the CTrough was 91.9 ng/mL. The concentration two weeks (C2WK) after the first and second injections (at Weeks 6 and 14) was 85.5 ng/mL and 113 ng/mL, respectively. At the last injection visit, 61% of women strongly agreed that they would definitely use and 73% that they would think about using a PrEP injectable in the future.
Conclusion: TMC278 LA IM injections administered every eight weeks in this clinical trial cohort of African and US women were safe, overall well tolerated and acceptable. The lower quartile RPV concentrations were consistently above the PA-IC90 at all times through eight weeks post injection.

422LB TRANSCUTANEOUS REFILLABLE NANOFLUIDIC IMPLANT FOR CONSTANT DELIVERY OF HIV PREP

Corrine Xuan Chua[1], Priya Jain[1], Ming Hu[2], Peter L. Anderson[3], Jason T. Kimata[4], Jagannadha Sastry[5], Roberto Arduino[5], **Alessandro Grattoni**[1]
[1]Houston Methodist Rsr Inst, Houston, TX, USA, [2]Univ of Houston, Houston, TX, USA, [3]Univ of Colorado Denver, Aurora, CO, USA, [4]Baylor Coll of Med, Houston, TX, USA, [5]Univ of Texas, Houston, TX, USA

Background: Antiretroviral drugs such tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), are effective as HIV preventive, pre-exposure prophylaxis (PrEP). Unfortunately, poor patient adherence has rendered treatment less effective. TDF success motivated development of tenofovir alafenamide (TAF), which is more potent with reduced side effects. However, patient adherence remains a concern. To address this, we developed a novel transcutaneously refillable nanochannel system (nDS) for the delivery of TAF and FTC for HIV PrEP. We hypothesized that the nDS implant could deliver sustained doses of TAF and FTC as PrEP to prevent infection from SHIV challenge in non-human primates long term.
Methods: We microfabricated silicon nanochannel membrane with channels as small as 2.5 nm in compliance with FDA requirement for implantable devices. nDS implants achieved constant release therapeutics in small and large animal models for over 6 months. In this study, nDS was tailored for the controlled delivery of TAF and FTC (received in kind from Gilead). Ti implants were designed for transcutaneous refilling to extend the duration of treatment. Implants loaded with TAF and FTC were tested in vitro for 3 months to assess release rates and drug stability. PK studies were then performed in vivo in three rhesus macaques with implants subcutaneously inserted in the dorsum and transcutaneous refilling tested at day 70. Plasma and biopsy samples were collected at different timepoints and TFVpp and FTCtp concentration quantified in PBMCs.
Results: The implant demonstrated sustained release of both TAF and FTC for over 83 days. Both TAF and FTC maintained bioactivity over the duration of the study. PK data (figure 1) showed that nDS achieved sustained preventative levels of TFVpp above 70 fmol/million PBMCs over 83 days. For FTCtp levels of approximately 1.5 pmol/million PBMCs were sustained for 28 days followed by a decrease in PBMC levels due to a decline of FTC in the implant reservoir. Transcutaneous refilling proved successful with FTCtp levels again reaching above 1.5 pmol/million PBMCs. Implants were well tolerated by the animals and surrounding tissues.
Conclusion: nDS achieved sustained delivery of TAF and FTC at approximately 2 and 100 mg/day, respectively, compatible with HIV PrEP. Successful transcutaneous refilling was achieved. Current studies supported by NIH and Gilead are examining the potential of nDS as a breakthrough delivery system addressing the current limitation of HIV PrEP.



423 AN IN VITRO–IN SILICO STUDY OF REDUCED-DOSE EFAVIRENZ INTERACTION WITH LEVONORGESTREL

Owain Roberts[1], Paul Curley[1], Rajith Kumar Reddy Rajoli[1], Darren M. Moss[1], Mohammed Lamorde[3], Andrew Owen[1], Kimberly K. Scarsi[3], Marco Siccardi[1]
[1]Univ of Liverpool, Liverpool, UK, [2]Infectious Diseases Inst Ltd, Kampala, Uganda, [3]Univ of Nebraska, Omaha, NE, USA

Background: Efavirenz (EFV)-based ART remains the preferred first-line ART regimen in low- and middle-income countries and progestin-containing implants are recommended forms of hormonal contraception for HIV-infected women. However, a recent drug-drug interaction (DDI) study showed 57% lower LNG concentrations, along with unintended pregnancies, when the implant was combined with EFV 600 mg. The aim of this study was to quantify the extent of DDI between EFV and LNG using an in vitro approach, and to apply a physiologically-based pharmacokinetic (PBPK) model to simulate the effects of reduced-dose EFV on LNG pharmacokinetics (PK).
Methods: Primary human hepatocytes were incubated with EFV (0.033–0.33 μM) in Williams' E medium over 72 hours, followed by co-incubation with LNG (1 nM) for one hour. Resultant LNG concentrations were quantified using LC-MS/MS, and mean ± SD LNG apparent intrinsic clearance (CLint.app; μl/min/million hepatocytes) from two separate donors

performed in triplicate was calculated. The in vitro data and published PK data were used to inform a PBPK model using MATLAB R2013b to simulate LNG plasma concentrations during co-administration of a 150 mg sub-dermal LNG implant plus 400 mg or 600 mg daily EFV in 100 individuals at 4, 12 and 24 weeks.
Results: Under control conditions where cells were treated with LNG alone, LNG CLint.app was 27.1 ± 7.6 µl/min. Incubation of hepatocytes with 0.033 µM EFV increased LNG CLint.app to 39.2 ± 9.3 µl/min (+44% compared to control), whilst incubation of hepatocytes with 0.1 µM and 0.33 µM resulted in increases in LNG CLint.app of 41.0 ± 7.5 µl/min and 39.2 ± 6.4 µl/min (+51% and +44% compared to control), respectively. Using a PBPK model, LNG PK was calculated at 4, 12 and 24 weeks (Table 1). Compared to the control group, simulated LNG concentrations were 56-57% lower in patients receiving 600 mg EFV and 49-50% lower in patients receiving 400 mg EFV.
Conclusion: Using concentrations spanning the therapeutic range of EFV, DDIs between EFV and LNG were quantified using an in vitro model of drug metabolism. At each concentration tested, incubation with EFV significantly increased LNG CLint.app. PBPK simulations found that reducing the EFV dose from 600 mg to 400 mg only modestly decreased the magnitude of the EFV-LNG DDI; therefore, reduced-dose EFV may not mitigate the risk of contraceptive failure when combined with standard dose LNG. These data will be useful to aid in the optimisation of dosing strategies for combining LNG implants with ART.

Table 1: PBPK simulation of the effects of administering EFV (600 mg once daily) or EFV (400 mg once daily) on LNG plasma concentrations over 4, 12 and 24 weeks compared to a control group treated with a 150 mg LNG sub-dermal implant alone. The geometric means of LNG plasma concentrations are shown with 90% confidence intervals provided in parentheses.

	Control Group (pg/ml)	EFV 600 mg (pg/ml)	EFV 400 mg (pg/ml)
Week 4	566 (503—632)	254 (228—283)	291 (263—317)
Week 12	511 (453—576)	229 (204—256)	262 (239—287)
Week 24	456 (402—516)	203 (180—229)	233 (211—257)

424 PHARMACOKINETICS, SAFETY & EFFICACY OF E/C/F/TAF IN HIV-INFECTED CHILDREN (6-12 YRS)

Aditya Gaur[1], Eva Natukunda[2], Pope Kosalarksa[3], Jag Batra[4], Natella Rakhmanina[5], Amy Coluci[6], Yongwu Shao[6], Heather Zhang[6], Cheryl Pikora[6], Martin Rhee[6]
[1]St. Jude Children's Rsr Hosp, Memphis, TN, USA, [2]Joint Clinical Rsr Cntr, Kampala, Uganda, [3]Khon Kaen Univ, Khon Kaen, Thailand, [4]Miller Children's Hosp, Long Beach, CA, USA, [5]Children's Rsr Inst–Children's Natl Med Cntr, Washington, DC, USA, [6]Gilead Scis, Inc, Foster City, CA, USA

Background: Currently, no once-daily (QD) single-tablet regimen (STR) is available for HIV-infected children <12 years of age. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF; E/C/F/TAF) is a QD integrase strand transfer inhibitor (INSTI)-based STR approved for use in adults and adolescents ≥12 years of age.
Methods: We conducted a prospective, single-arm, open-label, 2-part, 48-week clinical trial to evaluate the pharmacokinetics (PK), safety and efficacy of switching to the adult formulation of E/C/F/TAF (150/150/200/10 mg) QD in virologically suppressed children (6 to <12 years) weighing ≥25 kg. Intensive PK was evaluated and compared with adult values. Adverse events (AE), laboratory tests, including HIV-1 RNA, were assessed. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry. We report intensive PK and follow up data through Week 24.
Results: We enrolled 23 children; median age 10 y (range 8-11y), median weight 31 kg (range 25.5-58.2 kg), 61% female, 78% Black, median CD4 count 969 cells/µL. All (100%) had HIV-1 RNA <50 c/mL at Week 24. Plasma PK of EVG, COBI, FTC, and TAF (and its metabolite tenofovir) were modestly higher (20-80%) than in adults, but were within safe and efficacious ranges of adults. No subject had a serious AE or AE leading to study drug discontinuation. No subject had proximal renal tubulopathy. Estimated GFR (Schwartz formula) decreased at Week 4 and remained stable (median change at Week 24: -6.5 mL/min/1.73 m2), consistent with inhibition of renal tubular creatinine (Cr) secretion by COBI. Measures of proteinuria generally improved: median % change at Week 24 in urine protein to Cr ratio, retinol binding protein to Cr ratio, and beta-2-microglobulin to Cr ratio were -30%, -31%, and -6%, respectively. Median % change in BMD at Week 24 was +4.2% for spine and +1.2% for total body less head (TBLH). BMD decreases of ≥4% occurred in 2 subjects for spine and none for TBLH. Median change in BMD height-adjusted Z-score was +0.10 for spine and -0.12 for TBLH. No subject had a bone fracture.
Conclusion: In HIV-infected children 6 to <12 years of age, E/C/F/TAF uniformly maintained virologic suppression through Week 24. Using the adult formulation, plasma PK of all components were higher than adults; however, E/C/F/TAF was generally well tolerated through 24 weeks with a favorable renal and bone safety profile. These findings support use of E/C/F/TAF as the first QD and INSTI-based STR in children 6 to <12 years of age.

	Parameter, GLSM	Children[a] (6 to < 12 yrs; ≥ 25 kg)	Adults[b]	%GLSM Ratio (90% CI)
EVG	AUC_{tau}(ng*h/mL)	28892	21554	134 (104, 173)
	C_{max} (ng/mL)	2822	1998	141 (115, 173)
	C_{tau} (ng/mL)	212	248	86 (55, 133)
COBI	AUC_{tau} (ng*h/mL)	14156	8976	158 (126, 198)
	C_{max} (ng/mL)	1778	1400	127 (98, 165)
	C_{tau} (ng/mL)	29	17	171 (95, 310)
FTC	AUC_{tau} (ng*h/mL)	20262	11577	175 (160, 192)
	C_{max} (ng/mL)	3295	2014	164 (145, 184)
	C_{tau} (ng/mL)	112	89	125 (107, 146)
TAF	AUC_{last} (ng*h/mL)	304	178	171 (147, 199)
	C_{max} (ng/mL)	263	145	182 (146, 225)
TFV	AUC_{tau} (ng*h/mL)	432	284	152 (142, 163)
	C_{max} (ng/mL)	26	15	173 (161, 186)
	C_{tau} (ng/mL)	15	10	143 (132, 155)

GLSM, Geometric least-squares mean
[a] n=22 for EVG and FTC AUC_{tau}, n=20 for COBI AUC_{tau}, n=23 for other PK parameters
[b] From GENVOYA product label; n=19 for EVG, FTC and COBI, n=539 for TAF, and n=841 for TFV

425 PHARMACOKINETICS, SAFETY, AND EFFICACY OF ATV OR DRV WITH COBI IN ADOLESCENTS

Elizabeth J. McFarland[1], Gloria P. Heresi[2], Jag Batra[3], Torsak Bunupuradah[4], Kulkanya Chokephaibulkit[5], Pope Kosalarksa[6], Pamela Wong[7], Heather Zhang[7], Cheryl Pikora[7], Martin Rhee[7]
[1]Univ of Colorado, Aurora, CO, USA, [2]Univ of Texas, Houston, TX, USA, [3]Miller Children's Hosp, Long Beach, CA, USA, [4]HIV-NAT,Thai Red Cross AIDS Rsr, Bangkok, Thailand, [5]Mahidol Univ, Bangkok, Thailand, [6]Khon Kaen Univ, Khon Kaen, Thailand, [7]Gilead Scis, Inc, Foster City, CA, USA

Background: Cobicistat (COBI) is a potent, mechanism-based inhibitor of CYP3A, thus, when coadministered, can increase the systemic exposure of CYP3A substrates. It is approved for use as a pharmacoenhancer for atazanavir (ATV) or darunavir (DRV) and for elvitegravir (EVG) within EVG-containing single-tablet regimens (e.g. EVG/COBI/emtricitabine/tenofovir alafenamide).
Methods: We conducted a prospective, single-arm, open-label, 2-part, 48-week trial to explore the pharmacokinetics (PK), safety, and efficacy of switching from ritonavir (RTV) to COBI as a boosting agent for ATV or DRV. We enrolled virologically-suppressed adolescent participants (12 to <18 years) on a stable regimen consisting of either RTV-boosted ATV or RTV-boosted DRV plus 2 NRTIs. The adult dosage of COBI 150 mg was administered and plasma exposures of ATV and DRV were evaluated by intensive PK on Day 10. We report data from Part A, in which all participants participated in intensive PK sampling and were followed through Week 12.
Results: We enrolled 22 adolescents; median age 14 years (range 12-17), median body weight 52.7 kg, 36% female, 23% Black, mean CD4 count 989 cells/μL. Participants received COBI with ATV (n=14) or DRV (n=8). In adolescents (vs adult historical intensive PK data), steady-state plasma exposures of ATV and DRV were modestly higher (24-71%) (ATV) or similar (DRV), except DRV C_{tau} was slightly lower when combined with COBI (Table). Exposures to both protease inhibitors fell within safe and efficacious ranges of adults. No participant experienced treatment-related serious adverse events (AEs) or AEs leading to study drug discontinuation. Small decreases in eGFRSchwartz (median -6.7 mL/min/1.73m^2) were seen at Week 12, consistent with the inhibitory effect of renal creatinine secretion by COBI. Most participants, 21 of 22 (95%), had HIV-1 RNA <50 c/mL at Week 12.
Conclusion: In adolescents, when boosted with adult dosage strength of COBI, plasma exposures of ATV and DRV were within safe and efficacious ranges as seen in adults. Virologic suppression was maintained and treatment was generally well tolerated through 12 weeks. These findings support ongoing evaluation of COBI 150 mg as a pharmacoenhancer of ATV or DRV in adolescents 12 to <18 years of age.

Table. PK Parameters of ATV or DRV boosted by COBI

ATV PK parameter	Adolescents (n=14) (GLS mean)	Adults (n=30) (GLS mean)	GMR (90% CI)
AUC_{tau} (ng*h/mL)	51654	39961	129.3 (101.0, 165.5)
C_{max} (ng/mL)	4375	3538	123.7 (97.9,156.2)
C_{tau} (ng/mL)	987	576	171.2 (100.2, 292.3)

DRV Parameter	Adolescents (n=7)[a] (GLS mean)	Adults (n=59-60) (GLS mean)	GMR (90% CI)
AUC_{tau} (ng*h/mL)	77514	77534	100.0 (79.2,126.2)
C_{max} (ng/mL)	7379	7422	99.4 (83.6,118.3)
C_{tau} (ng/mL)	740	947	78.1 (35.1, 173.9)

GLS = geometric least squares
Adult exposures are from intensive PK sub-studies of COBI-boosted ATV vs ritonavir-boosted ATV, each with FTC/TDF (216-0105 and 216-0114), N=30
[a]One participant in the DRV group had missing PK data.

426 EFFECT OF DOLUTEGRAVIR PLASMA CONCENTRATION ON CENTRAL NERVOUS SYSTEM SIDE EFFECTS

Hiroki Yagura[1], Dai Watanabe[1], Takao Nakauchi[1], Kosuke Tomishima[1], Daisuke Kasai[1], Yasuharu Nishida[1], Munehiro Yoshino[2], Tomoko Uehira[1], Kunio Yamazaki[1], Takuma Shirasaka[1]
[1]Natl Hosp, Osaka, Japan, [2]Natl Hosp Org Osaka Minami Med Cntr, Osaka, Japan

Background: Dolutegravir (DTG), a second-generation HIV integrase inhibitor that can easily be administered once daily, was shown to have apparent non-inferior efficacy in comparison with other medications in phase III trials. At present, it is being prescribed increasingly, especially in developed countries, including Japan, and has been previously reported to induce side effects in the central nervous system (CNS), such as insomnia and headache. However, its mechanism including association between DTG plasma concentration and CNS side effects remains unknown.
Methods: We recruited 162 HIV-infected patients who had undergone anti-retroviral treatment, including DTG treatment, from Osaka National Hospital, Japan, from April 2014 to March 2016. DTG plasma trough concentration was measured, and the association between DTG concentration and CNS side effects was statistically analyzed within 6 months of DTG introduction.
Results: Of the 162, 154 (95%) were male and 8 (5%) were female. Their age at enrollment was median 43 years old (inter quartile range 38-52). 36 (22%) patients introduced DTG in the first antiretroviral treatment.In the rest of 126 (78%), DTG was switched from other antiretroviral agents. At least one of the CNS side effects was observed in 41 (25%) patients, which include dizziness [14/41 (34%)], headache [11 (27%)], insomnia [11 (27%)], restlessness [4 (10%)], and anxiety [3 (7%)]. According to the analyses: 1) patients with CNS side effects scored higher trough DTG plasma concentration compared with the subjects without symptoms (median 1.34 vs 1.03 ug/ml, p=0.003 by univariate Mann-Whitney U-test, and p=0.005 by multivariate binary regression test); 2) positive correlation was observed between DTG concentration and frequency of CNS side effects (p=0.002;Figure) ; and 3) no significant difference in DTG concentration was observed among CNS symptoms (p=0.56).
Conclusion: In this study, a positive correlation between trough plasma DTG concentration and CNS side effects was identified among Japanese population. This implied the importance of DTG concentration measurement for the evaluation of CNS side effects.

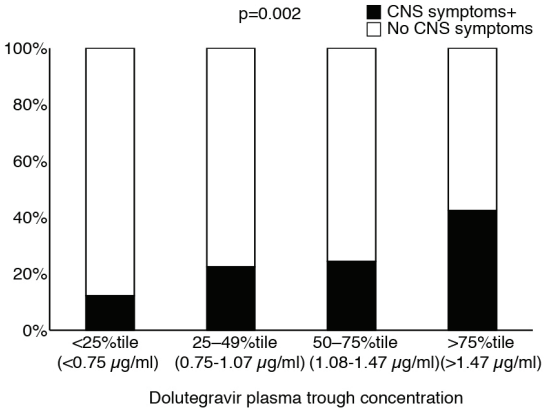


Figure. Association between trough Dolutegravir concentration and CNS side effects rate. P value by Cochran-Armitage test is shown.

427 EVALUATION OF RPV/FTC/TAF EXPOSURE-EFFICACY AND EXPOSURE-SAFETY RELATIONSHIPS

Sophia R. Majeed[1], Kavitha Bhasi[1], Yongwu Shao[1], William Garner[1], Jenna Scott[1], Carlos P. Ruixo[2], Devi SenGupta[1], Huyen Cao[1], Brian P. Kearney[1], Joseph M. Custodio[1]
[1]*Gilead Scis, Foster City, CA, USA,* [2]*Janssen Rsr and Development, Beerse, Belgium*

Background: Tenofovir alafenamide (TAF) is a tenofovir (TFV) prodrug that achieves markedly lower plasma TFV exposures compared to tenofovir disoproxil furmarate (TDF), reducing risks of renal and bone toxicities. Efficacy and safety of switching from TDF-based single-tablet regimens (STRs), rilpivirine (RPV)/emtricitabine (FTC)/TDF or efavirenz (EFV)/FTC/TDF to the TAF-based STR, RPV/FTC/TAF, was evaluated in 2 randomized, double-blind, active-controlled Phase 3 studies in virologically suppressed HIV-1 infected adults.

Methods: Area under the curve over 24 hours (AUCtau), maximum concentration (Cmax) and/or concentration at 24 hours (Ctau) were estimated from sparsely sampled pharmacokinetic (PK) data from the RPV/FTC/TAF arm of both studies for RPV (4 visits), TAF (1 visit), and its metabolite TFV (4 visits) using established population PK models. The PK-pharmacodynamic (PKPD) efficacy endpoint, proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 (FDA snapshot algorithm), was assessed by RPV and TAF exposure quartiles. Logistic regression was performed on log-transformed PK exposures of subjects with HIV-1 RNA <50 copies/mL. Exposures of subjects with HIV-1 RNA >=50 copies/mL and HIV-1 RNA <50 copies/mL were compared by a one-way analysis of variance. PKPD safety endpoints for RPV, TAF and TFV included most frequently reported AEs of upper respiratory tract infection (URI), nasopharyngitis, diarrhea, and headache, and were evaluated by quartiles of RPV, TAF and TFV exposures.

Results: 754 subjects were treated with RPV/FTC/TAF. RPV, TAF and TFV PK parameters were available for 749, 545 and 748 RPV/FTC/TAF-treated subjects, respectively. Mean (% coefficient of variation) RPV AUCtau was 2551 (33.7), with a range of 502.0 to 5824 ng*h/mL and TAF AUCtau was 173.9 (28.2), with a range of 91.7 to 413.1 ng*h/mL. Virologic success was high across RPV and TAF exposure quartiles (Table 1). No exposure-efficacy trend was seen for TAF. A significant trend was noted with virologic success and RPV exposure, driven by higher frequency of subjects lost to follow up and missing data in the lowest quartile. This was not considered clinically relevant as RPV exposures were similar irrespective of virologic outcome. No clinically relevant relationships with AEs were observed across wide ranges of RPV, TAF and TFV exposures (Table 1).

Conclusion: RPV/FTC/TAF was safe and efficacious, with no clinically relevant relationships between exposure and efficacy or safety noted across RPV, TAF and TFV exposures.

Table 1. Percentage of Virologic Success by FDA Snapshot Algorithm and Percentage of Subjects with Selected Adverse Events at Week 48 by RPV, TAF and/or TFV AUCtau Quartile Subgroups

RPV AUCtau Quartile Range (ng*h/mL)	Quartile 1 (502.0 to 1934) (N=187)	Quartile 2 (1938 to 2436) (N=187)	Quartile 3 (2442 to 3057) (N=188)	Quartile 4 (3058 to 5824) (N=187)
Virologic Success (HIV-1 RNA <50 copies/mL)	88.8%	92.0%	91.5%	96.3%
URI	5.9%	9.1%	11.7%	11.2%
Nasopharyngitis	5.9%	8.0%	11.2%	4.8%
Diarrhea	3.2%	6.4%	7.4%	5.9%
Headache	4.8%	6.4%	4.3%	4.8%
TAF AUCtau Quartile Range (ng*h/mL)	**Quartile 1 (91.7 to 138.5) (N=136)**	**Quartile 2 (138.6 to 164.4) (N=136)**	**Quartile 3 (164.7 to 195.5) (N=137)**	**Quartile 4 (195.8 to 413.1) (N=136)**
Virologic Success (HIV-1 RNA <50 copies/mL)	96.3%	95.6%	94.2%	95.6%
URI	14.0%	8.8%	5.1%	10.3%
Nasopharyngitis	8.8%	7.4%	8.0%	8.8%
Diarrhea	5.9%	6.6%	4.4%	2.9%
Headache	7.4%	5.1%	2.9%	6.6%
TFV[a] AUCtau Quartile Range (ng*h/mL)	**Quartile 1 (147.9, 275.2) (N=187)**	**Quartile 2 (275.8, 337.7) (N=187)**	**Quartile 3 (337.8, 404.8) (N=187)**	**Quartile 4 (404.9, 1287) (N=187)**
URI	10.2%	9.1%	5.9%	12.8%
Nasopharyngitis	7.5%	9.1%	7.5%	5.9%
Diarrhea	8.0%	6.4%	2.7%	5.9%
Headache	4.8%	3.2%	7.5%	4.8%

a. Only exposure-safety relationships were evaluated for TFV, as efficacy is not associated with this metabolite of TAF

428 EFFECT OF SORBITOL ON 3TC PK AFTER ADMINISTRATION OF LAMIVUDINE SOLUTION IN ADULTS

Kimberly K. Adkison[1], Cynthia McCoig[2], Allen Wolstenholme[3], Yu Lou[4], Zhiping Zhang[4], Amy Eld[3], Katy Hayward[5], Mark Shaefer[1]
[1]ViiV Hlthcare, Rsr Triangle Park, NC, USA, [2]ViiV Hlthcare, Tres Cantos, Madrid, Spain, [3]GlaxoSmithKline, Collville, PA, USA, [4]PAREXEL Intl, Durham, NC, USA, [5]ViiV Hlthcare, Brentford, UK

Background: Several relative bioavailability studies of lamivudine (3TC) in HIV-infected children (0.5-12y) showed that EPIVIR® oral solution yielded 30-57% lower plasma 3TC exposures than various tablet formulations. It was hypothesized that the lower 3TC concentrations observed in these pediatric studies could be due to an interaction between 3TC and sorbitol, an excipient in co-administered liquid medications. This study was conducted to evaluate the effect of sorbitol on the single dose pharmacokinetics (PK) of 3TC oral solution.

Methods: Study 204857 (NCT02634073) was an open label, randomized, 4-way William's crossover study in healthy adult subjects. Subjects were randomized to receive each treatment in 1 of 4 sequences with a ≥7 day between-treatment washout period. Treatments included a single dose of 3TC 300 mg (Treatment A; reference), 3TC 300 mg + sorbitol 3.2 g (Treatment B), 3TC 300 mg + sorbitol 10.2 g (Treatment C), and 3TC 300 mg + sorbitol 13.4 g (Treatment D). 3TC was administered as EPIVIR 10mg/mL oral solution following an 8-hour fast. Serial PK samples were collected after each treatment. Test/reference geometric least squares (GLS) means ratio and associated 90% confidence intervals (CI) of non-compartmental PK parameters (log-transformed) were determined by analysis of variance using a mixed effects model. Safety assessments were performed throughout the study.

Results: Of 37 subjects screened, 16 were randomized and completed the study. Selected 3TC PK parameters and statistical comparisons to reference are summarized in the Table. Sorbitol had a dose-dependent effect on 3TC PK with 28%, 52%, and 55% lower Cmax, 20%, 39%, and 44% lower AUC(0-24), and 14%, 32%, and 36% lower AUC(0-∞) when co-administered with 3.2 g, 10.2 g, and 13.4 g sorbitol, respectively. The median 3TC Tmax occurred between 0.75 to 1.26 h post dose, with later Tmax associated with sorbitol co-administration. 3TC with and without sorbitol containing solutions were well tolerated. There were no deaths or SAEs. A total of 3 subjects reported 5 AEs; 1 was drug-related.

Conclusion: Co-administration of single doses of 3TC and sorbitol solutions under fasted conditions resulted in decreased 3TC plasma exposures. Sorbitol had the greatest impact on 3TC Cmax and AUC(0-24), suggesting that an absorption-based interaction is the likely mechanism for the reduction in 3TC exposures observed in this study.

PK Parameter	Geometric Mean (%CV)				Ratio of GLS Means [90% CI]		
	Tmt A (N=16)	Tmt B (N=16)	Tmt C (N=16)	Tmt D (N=16)	B vs A (N=16)	C vs A (N=16)	D vs A (N=16)
Cmax (µg/mL)	3.34 (34.9)	2.42 (32.7)	1.60 (27.2)	1.52 (30.9)	0.724 [0.657, 0.798]	0.479 [0.434, 0.527]	0.454 [0.412, 0.500]
AUC(0-24) (µg.h/mL)	12.4 (23.6)	9.96 (22.6)	7.54 (23.7)	6.91 (28.9)	0.803 [0.747, 0.864]	0.608 [0.566, 0.655]	0.557 [0.518, 0.599]
AUC(0-∞) (µg.h/mL)	13.2 (22.3)	11.3[1] (21.2)	8.93 (22.1)	8.60[2] (24.1)	0.855[1] [0.799, 0.914]	0.677 [0.635, 0.721]	0.637[2] [0.594, 0.682]
Tmax[3] (h)	0.75 (0.50-1.50)	1.00 (0.50-1.50)	1.00 (0.50-2.50)	1.26 (0.50-3.00)	N/A	N/A	N/A

Tmt A: EPIVIR Oral Solution 300 mg
Tmt B: EPIVIR Oral Solution 300 mg + Aqueous solution containing Sorbitol 3.2 g
Tmt C: EPIVIR Oral Solution 300 mg + Aqueous solution containing Sorbitol 10.2 g
Tmt D: EPIVIR Oral Solution 300 mg + Aqueous solution containing Sorbitol 13.4 g
[1]n=14; [2]n=13; [3] median (range)

429 CRUSHING OF DOLUTEGRAVIR COMBINATION TABLETS INCREASES DOLUTEGRAVIR EXPOSURE

Marieke Roskam-Kwint[1], **Pauline Bollen**[1], Angela Colbers[1], Marjolijn Duisenberg-van Essenberg[2], Veroniek Harbers[1], Reinout van Crevel[1], David M. Burger[1]
[1]Radboud Univ Med Cntr, Nijmegen, Netherlands, [2]Elisabeth–TweeSteden Ziekenhuis, Tilburg, Netherlands

Background: If HIV-patients are unconscious or cannot swallow tablets for other reasons, antiretroviral medication is often crushed and dissolved prior to administration. Crushing can influence pharmacokinetics (PK) leading to altered drug exposure, possibly leading to treatment failure, development of resistance or toxicity. Currently, there is no information about crushing the branded fixed-dose combination of dolutegravir/abacavir/lamivudine (TRI), therefore crushing TRI is not recommended. In addition, a PK interaction between dolutegravir (DTG) and enteral nutrition is possible, based on the known interaction between DTG and cations in antacids and supplements.

Methods: An open-label, 3-period, randomized, cross-over, trial in 22 healthy volunteers was conducted. Subjects randomly received a single dose of TRI with a 7-day washout period. Reference treatment A: TRI whole tablet fasting, intervention treatments B: crushed and suspended TRI fasting and C: crushed and suspended TRI, followed by drinking drip feed (250kcal) within 5 minutes after TRI intake. To show bioequivalence between reference A and B and C a 48-h PK profile was measured for DTG. Geometric mean ratios (GMR) with 90% confidence interval (CI) for AUC0-inf and Cmax were calculated. Bioequivalence was accepted when the 90% CI was within 80-125% for AUC and Cmax. Safety and tolerability were evaluated.

Results: 22 healthy volunteers (21 Caucasian and 1 mixed-race, 10 female), 25 (18-54) years and BMI 23 (20-27) kg/m2 (median (range)) completed the trial. For crushed TRI vs whole tablet, the GMR (90% CI) of DTG Cmax was 129% (123-136), of DTG AUC0-inf 126% (119-132) and DTG half-life 101% (97-104). For crushed TRI with enteral nutrition vs whole tablet, the GMR (90% CI) of DTG Cmax was 122% (115-128), of DTG AUC0-inf 118% (112-125) and DTG half-life 98% (95-102). No SAEs were reported during the trial.

Conclusion: AUC0-inf and Cmax fell outside the predefined bioequivalence range. DTG exposure was 26% higher after crushing and 18% higher after crushing and intake with enteral nutrition. The maximum concentrations showed the same trend. The half-life was similar in all treatments, therefore increased DTG exposure is probably caused by enhanced absorption. Enteral nutrition did not negatively affect DTG absorption. Although no dose-limiting toxicity of DTG is observed to date, caution is warranted if chronic administration of crushed TRI is needed.

430 EFFECT OF SEVERE RENAL IMPAIRMENT ON DORAVIRINE PHARMACOKINETICS

Wendy Ankrom[1], Kelly Yee[1], Rosa Sanchez[1], Adedayo Adedoyin[1], Li Fan[1], Thomas Marbury[2], Richard A. Preston[3], Sauzanne Khalilieh[1], Marian Iwamoto[1]
[1]Merck & Co, Inc, Kenilworth, NJ, USA, [2]Orlando Clinical Rsr Cntr, Orlando, FL, USA, [3]Univ of Miami, Miami, FL, USA

Background: Doravirine is a novel, potent, HIV-1 non-nucleoside reverse transcriptase inhibitor that is primarily metabolized by oxidation via CYP3A4 with limited renal excretion. As the HIV-infected population ages, the number of HIV-infected patients with chronic kidney disease will also increase. Even drugs with limited renal excretion have exhibited altered pharmacokinetics (PK) in patients with severe renal impairment. This study assessed the impact of severe renal impairment on the PK of doravirine.
Methods: This was an open-label, single-dose study in subjects with severe renal impairment and healthy matched control subjects. The healthy control subjects were matched within +/-10 kg and +/-10 years of the mean weight and age, respectively, of the severe renal impairment cohort. A single dose of 100 mg doravirine was administered to subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and to healthy matched controls (eGFR ≥ 80 mL/min/1.73 m^2). Blood samples to measure doravirine concentrations were collected through 96 and 72 hours postdose in renally impaired subjects and healthy controls, respectively.
Results: Sixteen (16) adult subjects were enrolled; 8 (2 female, 6 male) with severe renal impairment and 8 (3 female, 5 male) healthy matched control subjects. In the subjects with severe renal impairment, AUC0-inf, and C24hr were modestly increased, while Cmax was minimally impacted. The geometric mean ratios (90% confidence intervals) [severe renal impairment/healthy] for doravirine Cmax, AUC0-inf, and C24hr were 0.83 (0.61, 1.15), 1.43 (1.00, 2.04), and 1.38 (0.99, 1.92), respectively. Terminal t1/2 was increased from 17 for healthy matched control subjects to 25 hrs for the subjects with severe renal impairment. There were no serious adverse experiences (AEs). Three (19%) subjects reported one AE each; only 1 of these (mild nausea) occurring in a subject with renal impairment was considered drug related. No subjects discontinued.
Conclusion: Severe renal impairment had a modest, but not clinically meaningful, effect on the PK of doravirine. A single dose of 100 mg doravirine was generally well tolerated in subjects with severe renal impairment.

431 HIGHER PLASMA LEVELS AND MORE SIDE EFFECTS IN ELDERLY DARUNAVIR-TREATED PATIENTS

Erika Ahlgren[1], Arvid Edén[1], Jaran Eriksen[2], Staffan Nilsson[3], Carl Johan Treutiger[2], Anders Thalme[4], Anders Blaxhult[5], Åsa Mellgren[6], Magnus Gisslén[1], Lars-Magnus Andersson[1]
[1]Univ of Gothenburg, Gothenburg, Sweden, [2]Karolinska Inst, Stockholm, Sweden, [3]Chalmers Univ of Tech, Gothenburg, Sweden, [4]Karolinska Univ Hosp, Stockholm, Sweden, [5]Sodersjukhuset, Stockholm, Sweden, [6]South Älvsborgs Hosp, Borås, Sweden

Background: An increasing proportion of people living with HIV-1 are 50 years or older. In older patients comorbidities and concomitant medications are more frequent, increasing the risk for potentially dangerous drug interactions (PDDIs). Data on the pharmacokinetics of PIs and NNRTIs in individuals 65 years and older are scarce. The aim of this study was to investigate differences in drug levels, PDDIs and side effects in people living with HIV-1 65 years or older, compared to individuals 49 years or younger in Sweden.
Methods: From the Swedish HIV-cohort, we cross-sectionally included patients 65 years or older and controls 49 years or younger on stable treatment with atazanavir (ATV), darunavir (DRV) or efavirenz (EFV) since ≥6 months. Plasma drug levels were analyzed with high-performance liquid chromatography (HPLC). Comorbidities, concomitant medication, adherence and adverse effects were registered by a standardized questionnaire and structured medical record review. PDDIs were analyzed using drug interactions databases.
Results: Between 2013 and 2015, we included 99 individuals 65 years or older (ATV n=19, DRV n=34, EFV n=46) and 97 younger controls (ATV n=18, DRV n=36, EFV n=43). Individuals with a two-dose DRV-regimen (n=10 in the study group and n=5 controls) were excluded from the drug level analysis. Steady state DRV concentrations were significantly higher in individuals 65 years or older compared to controls, (p=0.047) analyzed with ANCOVA adjusting for time, with log-transformed concentrations of DRV. The geometrical mean was 48% higher in the individuals ≥65 years. No significant difference was found in the ATV or EFV arms. The ≥65 group had a significantly higher median (IQR) number of concomitant medications, 3 (1-5) vs. 0 (0-2) (p <0,0001), and significantly more (median, IQR) PDDIs, 2 (0-3) vs. 0 (0-1) (p <0,0001) compared to controls. In individuals 65 years and older the DRV group had significantly more (median, IQR) PDDIs than the ATV and EFV study groups 3 (1-6) vs. 2 (0-3) and 1 (0-2) (p=0,002). The DRV group had a higher frequency of reported side effects than the ATV and EFV groups ≥65 years 37.9% vs. 0% and 23.8% (p=0.012).
Conclusion: Higher steady state plasma levels of darunavir but not of atazanavir or efavirenz were found in people living with HIV-1 who are 65 years or older compared to matched younger controls. Consistent with this finding, the frequency of reported side effects were higher in the darunavir group than in the atazanavir and efavirenz groups.

432 PHARMACOKINETICS OF DOLUTEGRAVIR IN PEOPLE LIVING WITH HIV OVER THE AGE OF 60

Emilie Elliot[1], Xinzhu Wang[2], Nicole Pagani[1], Alison Jenkin[1], Jaime Vera-Rojas[3], Isaac Day-Weber[2], Graeme Moyle[4], Myra McClure[2], Marta Boffito[1]
[1]St. Stephen's AIDS Trust–Chelsea and Westminster Hosp, London, UK, [2]Imperial Coll, London, UK, [3]Brighton and Sussex Med Sch, Brighton, UK, [4]Chelsea and Westminster Hosp, London, UK

Background: Antiretroviral (ARV) pharmacokinetics (PK) and pharmacodynamics (safety and efficacy) may differ in older versus younger patients. The aim of this study was to evaluate dolutegravir (DTG) PK in people living with HIV (PLWH) ≥60 years following an ARV combination (cART) switch to abacavir (ABC)/lamivudine (3TC)/DTG fixed dose combination (FDC).
Methods: The study protocol required the enrolment of PLWH aged ≥60 years (30%) and ≥65 years (70%), with HIV-RNA<50 copies/mL on any cART, HLAB5701 negative and no history of treatment failure. On day 1, all switched to ABC/3TC/DTG and, on day 28, intensive PK sampling was undertaken in a fasted state. DTG plasma concentrations were determined by UPLC and DTG steady-state PK parameters compared to those obtained from the PK sub-study of SPRING-1, where PLWH younger than 50 years underwent full DTG PK determination following ABC/3TC/DTG intake in a fasted state (control group). Non-parametric testing (Mann–Whitney U test) was used to compare DTG exposure in the two groups.
Results: Full PK profiles were available from 28 PLWH over the age of 60 years (median/range age: 66/60-79 years; 1 female) and from 16 younger controls (median/range age: 37/22-50 years; 1 female). No differences in DTG PK parameters were observed between the two groups: geometric mean (95%CI) DTG Cmax, Ctrough and AUC0-24 were 4284 (3875-4951), 1104 (922-1286) ng/mL and 54386 (48051-60721) ng.h/mL in the over 60 years group and 3409 (2854-4184), 1130 (780-1480) ng/mL and 51124 (40461-61787) ng.h/mL in the control group (p=0.66). The studied FDC was well tolerated, with no grade 3 or 4 side effects or laboratory abnormalities and no virological failures at week 4 post-switch.
Conclusion: No significant changes in DTG exposure were observed, suggesting that advanced age does not affect DTG metabolism. ABC/3TC/DTG was well tolerated by PLWH over the age of 60 during the first month of treatment.

433 NOVEL HIV PI WITH HIGH RESISTANCE BARRIER AND POTENTIAL FOR UNBOOSTED QD ORAL DOSING

John O. Link, Darryl Kato, Michael Moore, Andrew Mulato, Bernard Murray, Judy Mwangi, Nathan D. Shapiro, George Stepan, Yujin Wang, Zheng-Yu Yang
Gilead Scis, Inc, Foster City, CA, USA

Background: Background: HIV protease inhibitors (PIs) represent an important antiretroviral class largely due to their low potential to select for clinical resistance. Despite extensive discovery and development efforts over the past 30 years, all marketed PIs suffer from high rates of hepatic oxidative metabolism, leaving none that are suitable for once-daily (QD) dosing without pharmacokinetic boosting. Here we describe a novel, potent HIV PI that exhibits a high resistance barrier, exceptional metabolic stability, and has the potential for use as an unboosted, QD oral agent for the treatment of HIV infection.
Methods: Methods: Antiretroviral EC_{50} and Hill-coefficient values were measured in a cytopathic MT4 T-cell assay. PI cross-resistance was assessed against a panel of atazanavir (ATV) and darunavir (DRV) resistance-associated HIV-1 mutants (RAMs). Predicted drug clearance (CL) was measured in human liver microsomes with added cofactors. Oral and intravenous pharmacokinetic studies were conducted in rat and dog.

Results: Results: GS-PI1 is a potent inhibitor of HIV replication in MT4 cells with an EC_{50} of 4.9 nM (ATV and DRV EC_{50} values are 10.7 and 7.5 nM, respectively), a Hill-slope of 5.0, and a protein-adjusted EC_{95} of 310 nM. Similar antiretroviral potency was observed in PBMCs. GS-PI1 potency was reduced <2-fold against major PI RAMs, whereas ATV and DRV potency shifts are as high as 56 and 35-fold, respectively. GS-PI1 retains a high barrier to resistance emergence *in vitro*, as evidenced by the lack of viral breakthrough in HIV-infected MT2 cells at a fixed drug concentration equal to 2x its EC_{50}. GS-PI1 has oral bioavailabilities of 37% and 18%, and half-lives of 13 and 14 hours in rat and dog respectively. The *in vivo* half-lives of GS-PI1 are 10 to 40-fold longer than those of ATV (0.37 h rat, 1.3 h dog) or DRV (0.32 h rat, 0.34 h dog). The human predicted clearance (CL) for GS-PI1 is 0.05 L/h/kg (4% hepatic extraction) compared to predicted CLs of 1.20 and 1.07 L/h/kg for DRV and ATV (92% and 83% hepatic extraction), respectively.
Conclusion: Conclusion: GS-PI1 represents a new class of HIV protease inhibitor possessing favorable potency, resistance barrier, and *in vivo* half-lives relative to marketed HIV PIs and has been designed to achieve metabolic stability without pharmacokinetic boosting. GS-PI1 has the potential for once-daily oral dosing without boosting in the treatment of HIV infection.

434 NOVEL NON-CATALYTIC SITE INTEGRASE INHIBITOR WITH IMPROVED RESISTANCE PROFILE

Michael L. Mitchell, Mini Balakrishnan, Gediminas Brizgys, Ruby Cai, Eric Lansdon, Andrew Mulato, Mark Osier, Jianhong Wang, Helen Yu, Roman Sakowicz
Gilead Scis, Inc, Foster City, CA, USA

Background: Non-catalytic site integrase inhibitors (NCINIs) are a promising class of novel antiretrovirals (ARV). Here we describe the search for an NCINI with the potential for low-dose, unboosted once-daily oral dosing, potency against NCINI binding-pocket variants, a high barrier to resistance, and a favorable safety profile.
Methods: Novel NCINIs were evaluated against wild-type (WT) and integrase (IN) polymorphic variants of HIV-1, and DMPK properties. Resistance associated mutations were identified through dose-escalation resistance selection. Barrier to resistance was evaluated in a viral breakthrough assay at fixed drug concentrations. Interactions of NCINIs with WT and mutant catalytic core domains of IN were elucidated by X-ray crystallography. Pre-clinical toxicology was assessed in rats and cynomolgus monkeys.
Results: GS-9695 was identified as an initial lead with excellent potency against WT HIV-1 (EC50: 1.2 ± 0.2 nM) and majority of IN polymorphic variants (fold shift: 0.2 to 4.7). However, GS-9695 resistance associated with the IN T174I mutation emerged rapidly in vitro. Subsequent NCINI compound optimization screened against the T174I mutant and lead to the identification of GS-9822 with similar antiviral potency (EC50: 3.0 ± 0.9 nM) and superior profile against IN polymorphic variants (fold shift: 0.4 to 1.3). Potent antiviral activity was observed against HIV-1 clinical isolates (mean EC50: 0.7 nM, range: 0.13 to 3.1 nM). GS-9822 had improved potency against the T174I mutant compared to GS-9695 (EC50: 143 vs 917 nM, respectively). Viral breakthrough assays also demonstrated a superior resistance profile for GS-9822 relative to GS-9695. GS-9822 but not GS-9695 maintained interactions with W131 in both wild-type and T174I mutant IN. GS-9822 had high in vitro metabolic stability and favorable oral pharmacokinetic profiles with low systemic clearance in rat, dog and monkeys. However, a key unexpected finding in cynomolgus monkey toxicology studies was a dose-dependent vacuolation of the urothelium of kidney, bladder and ureter.
Conclusion: GS-9822 is a novel, potent NCINI with a higher barrier to resistance relative to early prototype NCINIs, and a resistance profile orthogonal to existing antiretroviral agents. GS-9822 exhibited potential for once-daily oral dosing, making it suitable for combination with other ARVs. However, a unique and difficult-to-monitor urothelial toxicity observed in cynomolgus monkeys poses a formidable challenge for further development of GS-9822.

435 MK-8591 CONCENTRATIONS AT SITES OF HIV TRANSMISSION AND REPLICATION

Jay Grobler, Carolyn McHale, Carol Freddo, Dan Dreyer, Li Sun, Marissa Vavrek, Sheila Breidinger, Kerry Fillgrove, Daria Hazuda, Ming-Tain Lai
Merck & Co, Inc, West Point, PA, USA

Background: MK-8591 is a long acting nucleoside reverse transcriptase translocation inhibitor (NRTTI) that has demonstrated potent antiviral activity in HIV-1 infected subjects administered a once-weekly (QW) 10 mg dose as monotherapy in a clinical trial and in SIV-infected rhesus macaque models. MK-8591 extended duration dosing potential was suggested by the long-intracellular half-life of MK-8591-triphosphate (MK-8591-TP) in peripheral blood mononuclear cells (PBMCs) in vitro and in preclinical models. Here we describe the tissue distribution of MK-8591 and its anabolites in rats by quantitative whole body autoradiography and in rhesus vaginal and rectal mucosa by biopsy.
Methods: Wistar Hannover rats dosed orally at 50 mpk (mg/kg) of [14C]-MK-8591 were sacrificed at 0.5 hr and 24 hr, cryo-sectioned (40 µm thick sagittal), and phosphor imaged for 4 days. Radioactivity in tissues was quantified using the blood standards along with Raytest AIDA image analysis software. For rectal and vaginal tissue distribution studies, monkeys were dosed 3.9 mpk orally on days 1 and 8. PBMCs were isolated from blood collected at day 1, 7, 14, and 21. Colorectal and vaginal biopsies were collected on days 7 (pre-dose) and 14, pooled separately, and snap-frozen with liquid nitrogen. PBMC and biopsy samples were analyzed by LC-MS/MS.
Results: In rats, MK-8591 distributed widely within 30 min of dosing and was notably enriched in lymphoid tissue (75.9 nmol-eq/g) compared to blood (lymph node:blood ratio = 2.7). MK-8591 remained enriched in lymphoid tissue at 24 hr (11.1 nmol-eq/g; lymph node:blood ratio = 7.1). In rhesus macaques, on days 7 and 14, levels of MK-8591-TP in rectal tissues (36 pmol/g and 31 pmol/g) were similar to those measured in vaginal tissue (49 pmol/g and 78 pmol/g).
Conclusion: The levels of MK-8591-TP achieved in both rectal and vaginal tissue are comparable to the levels of tenofovir diphosphate observed in rectal tissue from human subjects treated with tenofovir disoproxil fumarate. Given the significantly greater potency of MK-8591 (IC50=0.2 nM) compared to TDF (IC50=73 nM), these data suggest utility of MK-8591 for prophylaxis in both men and women. In addition, as lymphoid tissues are sites of active HIV replication and persistence, the observation that MK-8591 is enriched in lymphoid tissues in rats suggests the potential to address the ongoing replication of HIV in lymph nodes.

436 GS-9131 IS A NOVEL NRTI WITH ACTIVITY AGAINST NRTI-RESISTANT HIV-1

Kirsten L. White, Nicolas Margot, Kirsten Stray, Helen Yu, George Stepan, Constantine Boojamra, Richard Mackman, Adrian Ray, Michael D. Miller, Tomas Cihlar
Gilead Scis, Inc, Foster City, CA, USA

Background: There remains a need for an NRTI with potent activity against HIV-1 virus with NRTI resistance. GS-9131 is a monoamidate prodrug of the nucleotide analog GS-9148 (phosphonomethoxy-2'-fluoro-2',3'-dideoxydidehydroadenosine). GS-9131 undergoes conversion in lymphocytes to GS-9148 diphosphate, a potent inhibitor of HIV-1 RT. GS-9148 has a low potential for mitochondrial toxicity and renal accumulation. Here we report on the antiviral activity and resistance profile of GS-9131.
Methods: GS-9131 was subjected to extensive in vitro evaluation of antiviral activity and resistance profile. The PhenoSense HIV assay was used to compare the activity of GS-9131 and the NRTIs (ZDV, ddI, d4T, FTC, ABC, and TFV) against HIV-1 variants with all major types of NRTI resistance mutations. GS-9131 activity was also determined against 14 HIV-1 clinical isolates and 1 HIV-2 isolate in peripheral blood mononuclear cells.
Results: GS-9131 had potent activity against laboratory strains of HIV-1 both in primary cells and T-cell lines (EC50 = 25-200 nM) and exhibited potent antiretroviral activity against HIV-1 isolates of subtypes A, B, C, D, E, F, group O and N (EC50 0.29-113 nM). GS-9131 also had potent activity against HIV-2 (EC50 = 21 nM) and showed low cytotoxicity in multiple cell types including renal cells (CC50 > 100 µM). The activity of GS-9131 was not affected by the presence of RT mutations K65R, L74V, M184V or their combinations (EC50 fold change < 1). Viruses with 4 or more thymidine analog mutations (TAMs), including one with the T69-insertion, showed minimal changes (0.68 to 1.5-fold) in susceptibility to GS-9131, a change smaller than any other tested NRTI. Passaging of HIV-1 in the presence of the parent drug GS-9148 selected for a primary K70E mutation in combination with D123N and T165I, or the poorly fit Q151L mutation in combination with K70E, L74I, and L187F/M in RT; these variants conferred <3-fold and 50-fold reduced susceptibility to GS-9131, respectively. GS-9131 (GS-9148) was synergistic in combination studies with AZT, FTC, ABC, efavirenz, the integrase inhibitors bictegravir and dolutegravir, and the PI lopinavir, and additive with TFV and TAF.
Conclusion: GS-9131 exhibits potent in vitro antiretroviral activity and a favorable resistance profile including lower levels of resistance than approved NRTIs. GS-9131 is an attractive candidate for further clinical development with a potential for once daily dosing and efficacy in patients with NRTI resistance.

437 PRO140 SINGLE-AGENT MAINTENANCE THERAPY FOR HIV-1 INFECTION: A 2-YEAR UPDATE

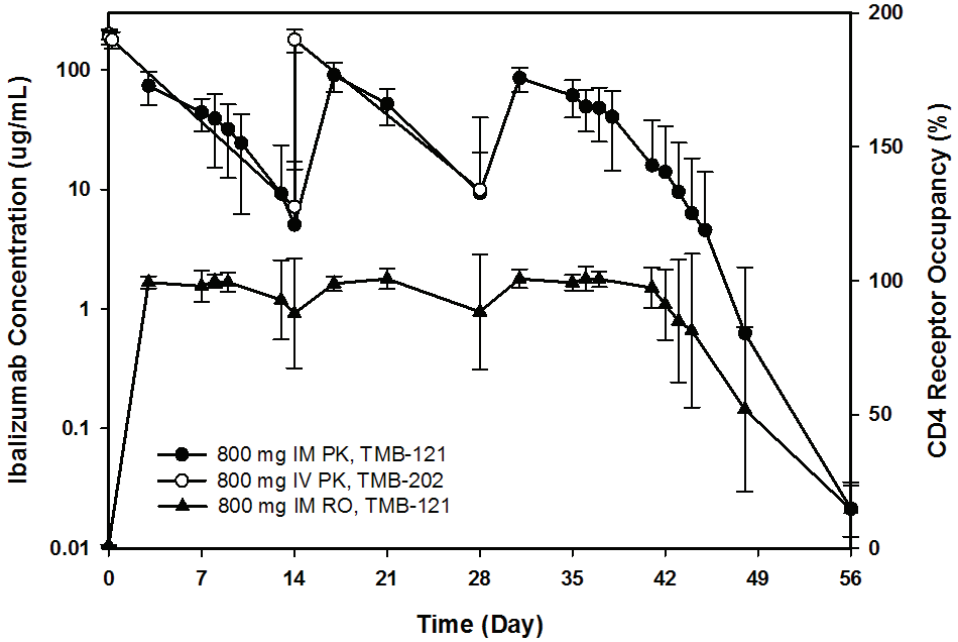
Jay Lalezari[1], **Kush Dhody**[2], Ula Kowalczyk[1], Kazem Kazempour[2], Nader Pourhassan[3], Paul J. Maddon[4]
[1]Quest Clinical Rsr, San Francisco, CA, USA, [2]Amarex Clinical Rsr, LLC, Germantown, MD, USA, [3]CytoDyn Inc., Vancouver, WA, USA, [4]Maddon Advisors LLC, Scarsdale, NY, USA

Background: PRO140 is a humanized CCR5 mAb with potent antiviral activity of ≥1.65 log10 mean viral load (VL) reduction as a weekly subcutaneous injection (SC) in patients infected with only CCR5-tropic HIV-1. This open-label, single-arm phase 2b extension study evaluated long-term suppression of HIV-1 replication by PRO140 SC monotherapy (MT) following initial antiretroviral therapy (ART).
Methods: 42 adult patients on ART and infected with only CCR5-tropic HIV-1 (11-cohort 1, 28-cohort 2, 3-cohort 3) with VL <40 c/mL (LabCorp) were switched to weekly PRO140 350 mg SC MT. Following maintenance of viral suppression for 13 weeks, 17 subjects in cohort 2 and 3 were trained to self-administer PRO140 SC and offered continuation of MT in an ongoing extension study.
Results: 16 eligible subjects (87.5% male, 19% non-white) with median age of 54.9 years (26-68) and median CD4 T-cell count of 593 cells/mm3 (365-1059) were enrolled. One patient discontinued at week 47 (with VL <40 c/mL) due to relocation and 5 subjects experienced virologic failure (VF) (2 consecutive VL ≥400 c/mL). The mean time to VF was 329 days (106-691). 10 subjects are currently on PRO140 SC MT of which 9 subjects have completed nearly 2 years of treatment (93–106 weeks). 7 patients reported single-copy HIV-1 RNA values of <1 c/mL; 3 subjects reported values of 4, 10, and 19 c/mL (bioMONTR Labs). Prior to study entry, all subjects were infected with only CCR5-tropic HIV-1 by Trofile® DNA Co-receptor Tropism Assay (LabCorp). Co-receptor tropism was reassessed at VF by Trofile® RNA Assay and no change was reported. PhenoSense® Entry (LabCorp) results for PRO140, maraviroc, and AMD3100 showed no significant change in post-treatment IC50, IC90 and fold change values compared with baseline results in VF and non-VF group of subjects. Anti-PRO140 antibodies were not detected in any subject. PRO140 was generally well tolerated with no drug-related major adverse events or treatment discontinuation reported.
Conclusion: In this phase 2b extension study, patients infected with only CCR5-tropic HIV-1 and virologically suppressed on ART were switched to weekly self-administered PRO140 350 mg SC MT. For nearly 2 years, PRO140 SC MT provided maximal virologic suppression, was well tolerated, and enabled the avoidance of potential toxicity of ART while preserving drug options. These results support further development of PRO140 SC as a simple, long-acting, single-agent maintenance therapy after initial ART in selected HIV-1 infected patients.

438 INTRAMUSCULAR IBALIZUMAB: PHARMACOKINETICS, SAFETY, AND EFFICACY VS IV ADMINISTRATION

Hsi-Hsun Lin[1], Susan Shin-Jung Lee[2], Ning-Chi Wang[3], YingAn Lai[4], Kuei-Ling Kuo[4], Steven Weinheimer[5], **Stanley Lewis**[5]
[1]E-Da Hosp, Kaohsiung City, Taiwan, [2]Kaohsiung Veterans General Hosp, Kaohsiung, Taiwan, [3]Tri-Service General Hosp, Taipei City, Taiwan, [4]TaiMed Biologics, Taipei City, Taiwan, [5]TaiMed Biologics USA, Irvine, CA, USA

Background: Ibalizumab (IBA) is a humanized monoclonal antibody that binds to a conformational epitope on the domain 2 region of human CD4 receptors thereby blocking entry of HIV into CD4 lymphocytes. It is a long-acting HIV entry inhibitor currently in Phase 3 development for the treatment of multi-drug resistant (MDR) HIV infection via intravenous (IV) administration. In this ongoing adaptive design study, we aimed to investigate the pharmacokinetics (PK), safety, antiretroviral activity, and pharmacodynamics (PD) of intramuscular (IM) administration of different doses of IBA. This report presents results of the 800 mg IM dose group as it offers the most direct comparison to the previous IV administration trial in patients with MDR HIV.
Methods: A Phase 1/2, randomized study of IBA injection was conducted, which enrolled HIV positive patients with HIV-1 RNA ≥5000 copies/mL who have not received antiretroviral (ARV) treatment for the preceding year. Injections of 800 mg IBA were administrated intramuscularly every two weeks with no other ARVs on three occasions.
Results: All eight patients enrolled in the 800 mg dose group were males with a mean age of 28 years. At Baseline (BL), mean viral load (VL) was 55,000 copies/mL and mean CD4+T cell count was 314 cells/μL. Starting ~3 days post-injection, after serum concentrations peaked, the PK profile of 800 mg IM IBA was comparable to that of IV IBA infusions (from study TMB-202, Figure 1). The terminal half-life (T1/2) was 0.86 day and distribution T1/2 was 3.47 days. The mean trough concentration was 5-14 μg/mL and the mean CD4 receptor occupancy (RO) was greater than 80% during the dosing period. The mean maximum VL reduction was 1.23 log10 at Day 7 following the first administration, followed by a return toward BL at the end of dosing. After three doses, CD4+ T cell counts were 51% higher than Baseline, on average. No serious adverse events or discontinuations were reported during the study period. No injection site reactions were reported.
Conclusion: The PK profile of biweekly 800 mg IBA administered IM was comparable to the IV PK profile from a previous study. IBA at 800 mg was safe, well tolerated, and produced clinically significant viral load reductions at Day 7 as monotherapy.



439 A LONG-ACTING NANOFORMULATED CABOTEGRAVIR PRODRUG FOR IMPROVED ANTIRETROVIRAL THERAPY

Tian Zhou, Benson Edagwa, JoEllyn McMillan, Howard E. Gendelman
Univ of Nebraska, Omaha, NE, USA

Background: Significant interest in long-acting parenteral (LAP) antiretroviral drugs (ARVs) has set the bar for future HIV/AIDS care. LAP ARVs can improve treatment adherence and positively affect drug resistance and systemic toxicity patterns. Cabotegravir (CAB), a potent HIV integrase inhibitor, now in phase II clinical trials as a LAP (CAB-LAP), currently demonstrates sustained plasma drug levels in humans up to 52 days after single intramuscular dose. We proposed that CAB-LAP could be modified to further reduce injection volumes and improve pharmacokinetic (PK) profiles. To this end, a nanoformulated prodrug of CAB (called NMCAB) was made to extend the drug half-life and antiretroviral activities and enabled the creation of a long-acting dolutegravir (DTG).
Methods: CAB was chemically conjugated to myristoyl chloride, increasing its hydrophobicity. NMCAB was produced by high-pressure homogenization with poloxamer 407. Uptake and retention were tested in human monocyte-derived macrophages (MDM). Antiretroviral activity was evaluated by HIV reverse transcriptase (RT) activity and HIV-1p24 expression. Pharmacokinetics of NMCAB was evaluated in Balb/C mice and compared to parent drug formulations after a single intramuscular injection of 15 or 45 mg/kg. The plasma drug levels were monitored for two months.
Results: NMCAB was efficiently taken up by MDM with sustained slow release of up to 30 days. Notably, the parent drug formulations were eliminated after a single day of treatment. Drug crystals were observed by transmission electron microscopy in NMCAB treated MDM, but not in cells treated with parent drug. NMCAB showed sustained antiretroviral activity in MDM as determined by both RT activity and HIV-1p24 staining for up to 30 days after drug removal. In contrast, parent drug formulations failed to inhibit viral growth one day after drug loading. In in vivo studies, NMCAB showed reduced burst release but was cleared more slowly, resulting in drug levels at later time points being up to 100 times higher than the parent drug formulations (Figure). Replicate results were seen for a created DTG prodrug and will be discussed.
Conclusion: Both CAB and DTG prodrugs were successfully synthesized and encapsulated into nanoparticles with clear improvements as a LAP formulation for antiretroviral therapy.

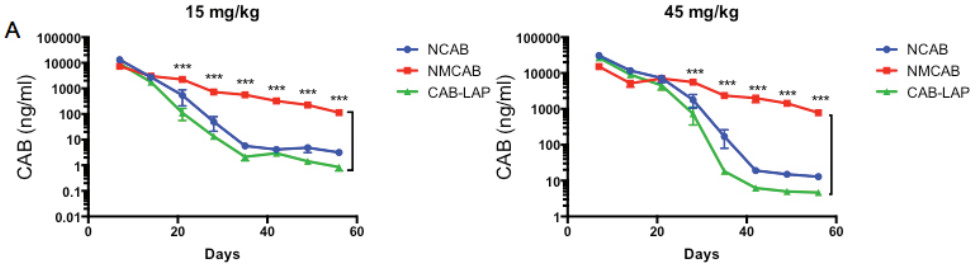


Figure. Pharmacokinetics profiles of NMCAB (red) in Balb/C mice compared to parent drug formulations, including CAB-LAP (provided by ViiV Healthcare) and NCAB (manufactured by high-pressure homogenization with the same excipients as for NMCAB). The figure shows plasma CAB levels for up to 8 weeks after a single intramuscular injection of 15 mg/kg (left) and 45 mg/kg (right). (*** P<0.001)

440 ANTIVIRAL ACTIVITY OF EFDA AGAINST NRTI-SENSITIVE AND -RESISTANT STRAINS OF HIV-2

Vincent Wu[1], Robert Smith[1], Sara Masoum[1], Dana Raugi[1], Selly Ba[2], Moussa Seydi[2], Jay Grobler[3], Geoffrey Gottlieb[1], for the University of Washington–Dakar HIV-2 Study Group
[1]Univ of Washington, Seattle, WA, USA, [2]CHU de Fann, Dakar, Senegal, [3]Merck & Co, West Point, PA, USA

Background: EFdA (4′-ethynyl-2-fluoro-2′-deoxyadenosine; MK-8591; Merck & Co.) is an investigational NRTI that blocks HIV-1 replication in culture with 50% effective concentrations (EC50) in the low-nanomolar to picomolar range. EFdA is highly active against HIV-1 and SIV in humanized mice and rhesus macaques, respectively, and a single 10-mg dose of EFdA demonstrated potent antiviral activity for 10 days in a phase 1b proof-of-concept clinical trial. However, studies evaluating the activity of the EFdA against HIV-2 are lacking, and the ability of the drug to inhibit NRTI-resistant mutants of HIV-2 is unknown.
Methods: HIV-1 and HIV-2 isolates from antiretroviral-naïve individuals were tested against EFdA in single-cycle infections of MAGIC-5A cells. Site-directed mutants of HIV-2 reverse transcriptase (RT) were generated in a full-length plasmid clone (pROD9) and were evaluated for EFdA resistance in the single-cycle assay. 50% cytotoxic concentrations (CC50) for EFdA were determined using a CellTiter-Glo® luminescence kit.
Results: EFdA inhibited HIV-2 infection of MAGIC-5A cells with mean EC50 values (± SD) of 0.58 ± 0.13 nM for 6 group A isolates and 0.55 ± 0.16 nM for 6 group B isolates (range = 0.34–0.83 nM for all 12 HIV-2 strains tested). In contrast, the mean EC50 for 6 HIV-1 isolates, including group M subtype A, B, C and D strains and the group O isolate MVP5180-91, was 2.0 ± 0.43 nM (range = 1.29–2.54 nM; $p < 0.0001$ for HIV-1 vs. HIV-2, Mann-Whitney test). In spreading infections of CEMss cells, EC50 values for HIV-2 ROD9 and HIV-1 NL4-3 were 38 and 120 pM, respectively. EFdA was fully active against HIV-2 RT mutants K65R and Q151M (EC50 = 0.17 ± 0.04 nM and 0.31 ± 0.05 nM, respectively), whereas the M184V variant was 10-fold resistant to the drug. Similar levels of resistance (12–16-fold) were seen for HIV-2 mutants that harbored M184V plus one or more additional NRTI resistance-associated changes in RT, including a patient-derived clone encoding K65R+N69S+V111I+Q151M+M184V. The CC50 for EFdA in MAGIC-5A cells was >100 nM.
Conclusion: EFdA is the most potent inhibitor of HIV-2 replication described to date and is more active against HIV-2 than against HIV-1 in culture. EFdA also inhibits multi-NRTI–resistant HIV-2 mutants with single-cycle EC50 values ≤ 10 nM. These data indicate that EFdA should be evaluated in clinical studies involving HIV-2–infected individuals.

441 WITHDRAWN

442 LONG-TERM SAFETY AND EFFICACY OF CAB AND RPV AS 2-DRUG ORAL MAINTENANCE THERAPY

David A. Margolis[1], Cynthia Brinson[2], Graham H. Smith[3], Joseph J. Eron[4], Gary J. Richmond[5], Roger P. LeBlanc[6], Peter E. Williams[7], William Spreen[1], Kenneth Sutton[8], Britt S. Stancil[9]
[1]ViiV Hlthcare, Rsr Triangle Park, NC, USA, [2]Central Texas Clinical Rsr, Austin, TX, USA, [3]Maple Leaf Med Clinic, Toronto, Ontario, Canada, [4]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [5]Gary J Richmond MD PA, Ft Lauderdale, FL, USA, [6]Clinique OPUS, Montréal, Québec, Canada, [7]Janssen Rsr and Development, Beerse, Belgium, [8]ViiV Hlthcare, Raleigh, NC, USA, [9]PAREXEL Intl, Durham, NC, USA

Background: Cabotegravir (CAB), an HIV INSTI is under development in both oral and long-acting (LA) injectable formulations. LATTE was designed to select a daily oral dose of CAB and to evaluate a two drug ART regimen with rilpivirine (RPV), as suppressive maintenance therapy. Results enabled the LATTE-2 study to evaluate CAB LA + RPV LA dosed once every 1 or 2 months.

Methods: Phase 2b, multicentre, partially-blinded dose-ranging study in ART-naïve HIV infected adults, randomized 1:1:1:1 to the induction regimen of once daily oral CAB 10, 30, or 60 mg or efavirenz (EFV) 600 mg with TDF/FTC or ABC/3TC through W24. CAB patients (Pts) with VL <50 c/mL immediately prior to W24 discontinued NRTIs and began RPV 25 mg as a two drug oral maintenance regimen through W96. No change was made to the EFV arm. After W96, at the start of the open-label (OL) phase, all Pts randomized to CAB were given the option to continue on the sponsor selected dose (30 mg) of CAB. EFV arm Pts completed the study at W96. The OL phase is ongoing and CAB Pts have completed W144, 120 weeks on a two-drug ART regimen as of this analysis.
Results: 243 Pts were randomized and initiated treatment (ITT-E). Of those randomized to CAB (n=181), 160 Pts began the maintenance regimen (W24) and138 continued into OL phase (W96). Amongst Pts who began CAB + RPV at W24, 76% maintained <50 c/mL, and 8% were virologic non-responders by Snapshot at W144 (ITT-ME). There were 9 protocol defined virologic failures (PDVF) on CAB, 3 occurred after W96. One Pt developed treatment emergent (TE) NNRTI resistance mutations at W132. No Pts developed TE major INI resistance mutations since W96. In total, 5 Pts developed TE resistance to one or both agents during the study. During the maintenance and OL phases, 7 (4%) reported drug-related AEs ≥ Grade 2. SAEs occurred in 15 (9%) CAB Pts (none drug related) and 4 (3%) withdrew due to AEs. Maintenance TE maximum lab abnormalities ≥ Grade 3 occurred in 25% of CAB Pts, with lipase and creatine kinase only having ≥5% of Pts (5% and 9% respectively). 17% of CAB Pts had a maintenance TE graded ALT, <1% were ≥ Grade 3.
Conclusion: As maintenance therapy in virologically suppressed Pts, the two drug regimen CAB + RPV provided durable viral suppression through W144. CAB + RPV continues to be generally safe and well tolerated; these data support progression to phase 3 studies.

443 EFFICACY & SAFETY OF SWITCHING TO EVG/COBI/FTC/TAF IN VIROLOGICALLY SUPPRESSED WOMEN

Sally Hodder[1], Kathleen Squires[2], Cissy Kityo[3], Debbie Hagins[4], Anchalee Avihingsanon[5], Yulia Plotnikova[6], Shuping Jiang[7], Rima Kulkarni[7], Andrew Cheng[7], Huyen Cao[7]
[1]West Virginia Clinical and Translational Sci Inst, Morgantown, WV, USA, [2]Thomas Jefferson Univ, Philadelphia, PA, USA, [3]Joint Clinical Rsr Cntr, Kampala, Uganda, [4]Chatham CARE Cntr, Savannah, GA, USA, [5]HIV-NAT, Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [6]Irkutsk Regional Cntr for Prevention and Control of AIDS and Infectious Diseases, Irkutsk, Russian Federation, [7]Gilead Scis, Inc, Foster City, CA, USA

Background: The integrase inhibitor regimen (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate [E/C/F/TDF]) demonstrated superior efficacy when compared to a protease inhibitor regimen (atazanavir boosted by ritonavir [ATV/r] plus F/TDF) in 575 treatment naïve women at Week (W) 48. We now report the safety and efficacy of subsequent switching to E/C/F/tenofovir alafenamide (TAF) versus remaining on ATV/r+F/TDF.
Methods: After completing the initial randomized, blinded 48-week trial, women on ATV/r+F/TDF were randomized 3:1 to receive open label E/C/F/TAF versus remaining on their current regimen. Viral suppression (HIV-1 RNA <50 and <20 copies [c]/mL) by FDA snapshot analysis, pre-defined bone and renal safety, and tolerability endpoints 48 weeks after switch are reported. Women who become pregnant while on study are given the option to continue study drug.
Results: 212 HIV-infected, virologically suppressed women were randomized (E/C/F/TAF n=159, ATV/r+F/TDF n=53). Virologic suppression (<50 c/mL) was maintained in 94.3% on E/C/F/TAF vs 86.8% on ATV/r+F/TDF (weighted difference: 7.5%; 95% CI: -1.2% to 19.4%), with virologic failure in 1.9%, 3.8%, respectively. More women on E/C/F/TAF achieved <20 c/mL at W48 compared to ATV/r+F/TDF (84.9% versus 71.7%, weighted difference: 13.2% [-0.0% to 27.5%], p=0.041). No treatment emergent resistance was detected in either study groups. Mean % increase in BMD was higher in the TAF group for both lumbar spine and total hip (Table). Multiple markers of renal safety were improved for participants randomized to TAF (Table). No cases of proximal renal tubulopathy were reported. Participants on TAF had greater increases in lipids (Table), with no difference in TC:HDL ratio (Table). 19 women became pregnant during the switch study, 13 E/C/F/TAF and 6 ATV/r+F/TDF) and 3 normal infants have been delivered in each group to date.
Conclusion: These data demonstrate that women who switch to an integrase inhibitor + TAF-based regimen maintain high levels of virologic suppression with improvement in BMD and renal function biomarkers, as compared with those remaining on their ritonavir boosted atazanavir+TDF-based regimen.

Table. Changes in Renal, Bone, and Lipid Safety Parameters from Baseline at Week 48

Parameters[a]	E/C/F/TAF (n=159)	ATV/r+F/TDF (n=53)	Significance
eGFR, mL/min (Cockcroft-Gault)	4.2 (-6.0, 13.6)	-1.8 (-8.4, 7.2)	0.060
β-2 microglobulin/Cr (β-2M/Cr), %	-47.7 (-79.7, -13.6)	20.7 (-11.1, 113.0)	<0.001
Retinol Binding Protein/Cr (RBP/Cr), %	-33.6 (-54.6, 1.5)	23.4 (-6.8, 93.3)	<0.001
Lumbar Spine BMD, %	2.82 (3.158)	0.00 (3.383)	<0.001
Total Hip BMD, %	2.08 (3.327)	1.33 (3.242)	0.29
Total cholesterol, mg/dL	27 (7, 46)	5 (-7, 24)	<0.001
LDL cholesterol, mg/dL	16 (1, 34)	8 (-10, 18)	0.002
HDL cholesterol, mg/dL	5 (-1, 12)	0 (-4, 7)	0.009
Total cholesterol:HDL ratio	0.1 (-0.1, 0.5)	0.0 (-0.3, 0.4)	0.075
Rate of initiation of lipid-modifying agents	2 (1.3%)	0	1.00

[a] Mean (SD) used to summarize BMD; otherwise, median (Q1, Q3) is used.

444 THE FDA SNAPSHOT ALGORITHM MAY OVERESTIMATE THE EFFICACY OF INITIAL ART

Stephen J. Kerr[1], Andrew Carr[2]
[1]The Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [2]St. Vincent's Hosp, Sydney, Australia

Background: The FDA Snapshot algorithm defines success of antiretroviral therapy (ART) by viral load < 50 cp/mL without ART change (mostly for adverse events [AEs]). Notably, a viral load <50 cp/mL but with a drug-related AE is regarded as treatment success. However, drug-related AEs might increase the risk of ART failure.
Methods: We hypothesised that an efficacy algorithm incorporating ART-related AEs would be clinically meaningful, as they would predict ART failure. We analysed individual-patient data from SINGLE, a placebo-controlled trial of abacavir-lamivudine-dolutegravir (ABC-3TC-DTG) vs. tenofovir-emtricitabine-efavirenz (TDF-FTC-EFV). Data were obtained via clinicalstudydatarequest.com/ after independent protocol review by the Wellcome Trust (but not the study sponsor). We investigated if drug-related AEs through Week 12 predicted subsequent ART failure, and failure rates using the Snapshot algorithm vs. a 'Snapshot-Plus' algorithm that additionally regards Grade-2+ drug-related AEs as ART failure. Groups were compared through Week 144, as were strata ≥ or <100,000 cp/mL at baseline. Data were analysed by calculating the proportion of responders (95%CI) with both algorithms. Chi-square and McNemar tests compared responders within and between algorithms, respectively. Logistic regression determined the odds of failure by the Snapshot algorithm for subjects experiencing drug-related AEs to week 12.

Results: Grade 2-4, drug-related AEs through Week 12 significantly increased the risk of ART failure at Week 48 by Snapshot (OR 2.68 [95%CI 1.75, 4.11]), and at Weeks 96 and 144; the relationship with any-grade, drug-related AEs through Week 12 was not significant. At Week 48, Snapshot efficacy was 87.9% with ABC-3TC-DTG and 80.1% with TDF-FTC-EFV (Table). 'Snapshot-Plus' response rates were substantially lower (76.6% and 62.8%, respectively). DTG minus EFV group differences were significantly greater with 'Snapshot-Plus' at each time point (13.8% vs. 7.3% at Week 48; McNemar's P<0.001), including in the stratum with baseline viral load <100,000 cp/mL (15.0% vs. 7.7% at Week 48; P<0.001).
Conclusion: In this trial, grade 2-4, AE-free ART efficacy was lower than estimated by the standard Snapshot algorithm. The 'Snapshot-Plus' algorithm may be a more clinically relevant measure of ART efficacy, and may better distinguish regimens when used in patients with viral load <100,000 cp/mL. The algorithms should be compared using data from other trials.

Algorithm	Snapshot algorithm				'Snapshot-Plus' algorithm (includes grade 2-4, study drug-related AEs)			
	Responders				Responders			
All subjects	ABC-3TC-DTG N=414	TDF-FTC-EFV N=419	Mean diff. (95%CI)	P	ABC-3TC-DTG N=414	TDF-FTC-EFV N=419	Mean diff. (95%CI)	P
Wk 48	87.9%	80.1%	7.3 (2.3,12.2)	0.004	76.6%	62.8%	13.8 (7.6, 20.0)	<0.0001
Wk 96	80.4%	72.3%	8.1 (2.4, 13.9)	0.006	70.3%	56.6%	13.7 (7.3, 20.2)	<0.0001
Wk 144	71.5%	63.2%	8.3 (1.9, 14.6)	0.01	62.6%	50.4%	12.2 (5.5, 18.9)	0.0004
HIV RNA <100,000	N=280	N=288			N=280	N=288		
Wk 48	90.4%	82.6%	7.7 (2.1, 13.3)	0.007	77.9%	62.9%	15.0 (7.6, 22.4)	<0.0001
Wk 96	85.0%	72.6%	12.4 (5.8, 19.1)	0.0003	73.2%	55.6%	17.7 (9.9, 25.4)	<0.0001
Wk 144	72.9%	64.2%	8.6 (1.0, 16.2)	0.03	63.6%	50.4%	13.2 (5.2, 21.3)	0.002

445 CELLULAR HIV-1 DNA LEVELS AFTER 96 WEEKS OF SWITCH TO ATV/R +3TC IN THE ATLAS-M TRIAL

Francesca Lombardi[1], Simone Belmonti[1], Eugenia Quiros-Roldan[2], Alessandra Latini[3], Chiara Picarelli[1], Arianna Emiliozzi[1], Massimiliano Fabbiani[4], Roberto Cauda[1], Andrea De Luca[5], for the AtLaS-M Study Group
[1]Catholic Univ of Sacred Heart, Rome, Italy, [2]Spedali Civili di Brescia, Brescia, Italy, [3]IFO S. Gallicano Inst (IRCCS), Rome, Italy, [4]Univ of Milan, Milan, Italy, [5]Siena Univ Hosp, Siena, Italy

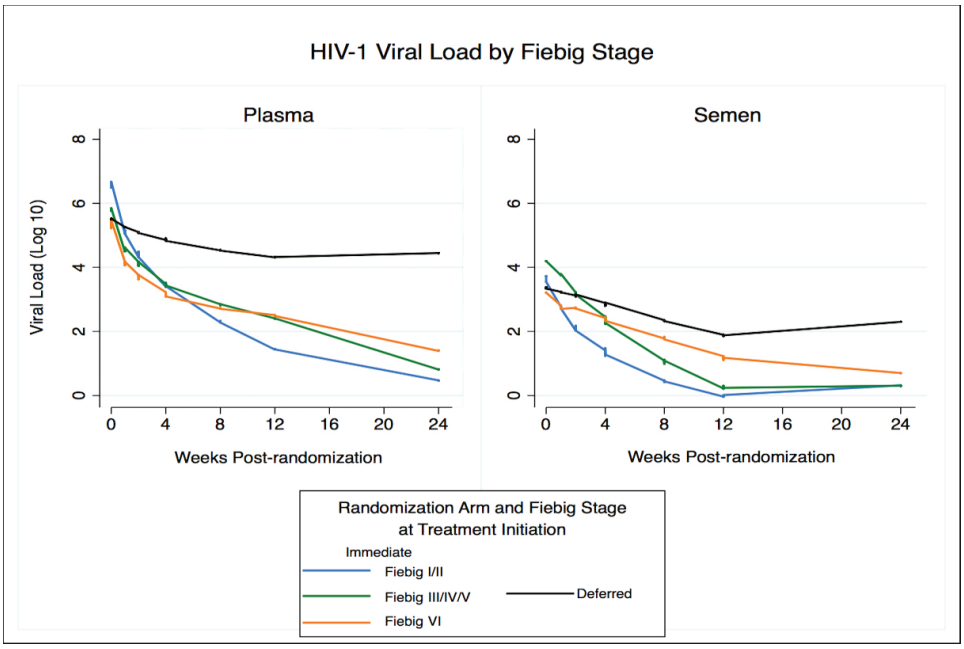
Background: The AtLaS-M randomized trial showed that in virologically suppressed patients (pts) on atazanavir/ritonavir (ATV/r) with 2 NRTIs, switching to a dual therapy (DT) with ATV/r plus lamivudine (3TC) had superior efficacy as compared to continuing the previous triple therapy (TT). This sub-study was designed to evaluate the impact at 96 weeks of the DT versus the TT on the HIV-1 cellular reservoir as reflected by the quantification of the blood-associated HIV-1 DNA levels.
Methods: Total HIV-1 DNA levels in whole blood were quantified at baseline (BL) and after 96 weeks (W96) by a TaqMan real-time PCR assay targeting the HIV-1 5' LTR region. Plasma residual viremia (RV) (HIV-1 RNA <50 cps/mL) was categorized as detectable (1-49 cps/mL) or undetectable (<1 cp/mL). Logistic regression and Cox proportional hazard models were used to predict the effects of BL HIV-1 DNA levels on risk of RV at W96 and viral rebound (VR)(HIV-1 RNA ≥50 cps/mL during 96 weeks), respectively.
Results: A representative subset of 140 of 266 randomized pts was analyzed: 86.4% males, mean age 43.2 yrs and mean CD4 count 657 cell/μL. Main BL characteristics did not differ between pts in DT-arm (n=75) and TT-arm (n=65). The mean BL HIV-1 DNA levels (log10 cps/10^6 leukocytes) in DT (2.42, 95% CI 2.32;2.54) vs TT-arm (2.37, 95% CI 2.24;2.51) were comparable (p=0.570). A significant mean decrease in log10 HIV-1 DNA cps/10^6 leukocytes was observed between BL and W96 in both arms: -0.15 (95% CI -0.23;-0.07, p<0.001) in DT vs -0.18 (95% CI -0.27;-0.08, p<0.001) in TT, without significant differences between the two arms (p=0.703). No demographical, clinical and viro-immunological variable was associated with HIV-1 DNA changes by using linear regression analysis. No significant change in RV levels was observed in both arms (McNemar test, p=ns); detectable W96 RV was associated with higher BL HIV-1 DNA levels compared to undetectable RV (OR: 2.47; 95% CI 1.17;5.19, p=0.017). BL HIV-1 DNA levels was not a predictor of time to VR (p=0.128); pts in the DT-arm had a lower risk of VR (aHR vs TT-arm: 0.29; 95 % CI 0.11;0.83, p=0.021).
Conclusion: When compared to continuing 3-drug therapy, DT with ATV/r+3TC resulted in similar decline of HIV-1 DNA levels in pts with sustained viral suppression. HIV-1 DNA load predicted residual viremia but not viral rebound in this setting. These findings support the safety of simplification to ATV/r+3TC on the cellular HIV-1 reservoir.

446 DYNAMICS OF VIRAL LOAD AND CYTOKINES WHEN ART IS INITIATED SOON AFTER HIV ACQUISITION

Trupti I. Gilada[1], Javier R. Lama[2], Rachel A. Bender Ignacio[3], Ricardo Alfaro[2], Carmela Ganoza[2], Angela K. Ulrich[4], Socorro M. Harb[3], Rogelio M. Valdez[4], Robert Coombs[3], Ann Duerr[4]
[1]Unison Medicare and Rsr Cntr, Mumbai, India, [2]Asociacion Civil Impacta Salud y Educacion, Lima, Peru, [3]Univ of Washington, Seattle, WA, USA, [4]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA

Background: We analyzed dynamics of HIV-1 viral load (VL) in plasma and semen, and pro-inflammatory cytokines in plasma after ART initiation soon after HIV acquisition. We hypothesized that both cytokine levels and HIV-1 VL would decay more quickly when ART was initiated during Fiebig stages I/II (F I/II) as compared to Fiebig stages III/IV/V (F III/IV/V) and stage VI (F VI).
Methods: This study was conducted in a subset of participants (n=57 MSM/transgender women) from the ongoing ¿Sabes? study in Lima, Peru . All participants tested negative for HIV RNA ≤3 months prior to diagnosis; roughly 1/3rd were diagnosed in F I/II. They were randomized to initiate ART immediately after diagnosis (Immediate) or 24 weeks later (Deferred). HIV-1 RNA in plasma and seminal fluid and cytokine levels in plasma were measured at 0, 1, 2, 4, 8, 12 and 24 weeks after HIV diagnosis. Statistical methods included general estimating equations and a nonlinear mixed effects model.
Results: As expected, both plasma and seminal VL declined faster in the Immediate arm (n=26, 7 in F I/II, 11 in F III/IV/V, 8 in F VI at ART initiation) than in untreated participants in the Deferred arm (n=31), after controlling for Fiebig stage (p<0.0001). The decay rate was significantly faster in plasma than in semen (p<0.0001) after controlling for baseline

VL. Moreover, in those treated immediately, F I/II had markedly faster rates of seminal VL decay compared to F III/IV/V and F VI (p=0.072 and p=0.022, respectively) (Figure). There was no difference in rate of VL decay in plasma by Fiebig stage. Immediate ART was associated with significantly greater decline over 24 weeks in plasma IL-16, IP-10, TNFα, IL-1α, IL-2, IL-6,IL-10 and MIP1α, and IL-23p40 (p<0.05) but not TNFβ, SDF1α, MIP1β, MCP1, IL-8, IL-4, IL-1β, IFNα2a, IL-7, IL-12p70, or IFNγ. Change in cytokine levels was not strongly predicted by Fiebig stage, except for IL-23p40 and IL-16.
Conclusion: ART initiation at the very earliest time point (in F I/II) has the greatest potential to impact HIV transmission through rapid reduction in seminal viral shedding. Semen VL decays slowly especially when ART is initiated in F VI, and is imperfectly predicted by plasma VL. The effects on plasma VL and inflammatory cytokines highlight the potential benefit of early ART initiation for individuals. These results underscore the need for frequent HIV testing with algorithms that detect acute infection in high-risk populations as part of treatment and treatment-as-prevention efforts.



447 VALACYCLOVIR DOES NOT ATTENUATE CD4 COUNT DECLINE IN CART-UNTREATED HIV INFECTION

Darrell H. Tan[1], Janet M. Raboud[2], Leah Szadkowski[3], Beatriz Grinsztejn[4], Jose Valdez Madruga[5], Pedro Cahn[6], Simon Barton[7], Amanda Clarke[8], Wendy Zubyk[9], Sharon Walmsley[10]
[1]St. Michael's Hosp, Toronto, Ontario, Canada, [2]Univ of Toronto, Toronto, Ontario, Canada, [3]Toronto General Rsr Inst, Toronto, Ontario, Canada, [4]Inst Nacional de Infectologia (INI-Fiocruz), Rio de Janeiro, Brazil, [5]Centro de Referência e Treinamento em DST/AIDS-SP, Sao Paulo, Brazil, [6]Fundación Huesped, Buenos Aires, Argentina, [7]St. Stephen's AIDS Trust, London, UK, [8]Brighton & Sussex Univ Hosps NHS Trust, Brighton, UK, [9]Canadian HIV Trials Network, Vancouver, British Columbia, Canada, [10]Univ of Toronto, Toronto, Ontario, Canada

Background: Valacyclovir, a nucleoside analogue used for herpes simplex virus type 2 (HSV-2) infection, has been shown to decrease plasma HIV viral load (VL) regardless of HSV-2 serostatus. We studied the impact of valacyclovir on HIV disease progression in treatment-naïve HIV-infected adults.
Methods: VALIDATE (VALacyclovir In Delaying Antiretroviral Treatment Entry, CTN-240) was a fully blind, multicenter, international 1:1 randomized controlled trial among treatment-naïve HIV-1-infected adults with CD4 counts of 400-900 cells/mm3 and not meeting contemporaneous recommendations for antiretroviral treatment (ART). Participants received valacyclovir 500 mg twice daily or placebo and were followed quarterly until there was documentation of either two consecutive CD4 counts ≤350 cells/mm3 or ART initiation for any reason. The primary analysis was a random effects model comparing the annual rate of CD4 count decline by study arm after adjusting for baseline CD4 count. Secondary analyses compared the rate of CD4 count percentage decline, HIV VL, HSV reactivations and drug-related adverse events. Upon recommendation by the DSMC, the trial was closed after release of the START trial results in August 2015.
Results: We randomized 198 participants at 23 sites in Canada, Brazil, Argentina and the United Kingdom, including 72% MSM and 20% women. Median (IQR) age was 35 (30, 43) years. Baseline CD4 count was 592 (491, 694) cells/mm3 or 28% (23%, 33%), and VL was 4.04 (3.5, 4.5) log10 copies/mL. Over 276 person-years of follow-up, the CD4 count declined by 50 cells/mm3/year in the valacyclovir arm vs 59 cells/mm3/year in the placebo arm (p=0.65). Annual rates of decline in CD4 percentage were 1.2% and 1.69% for valacyclovir and placebo respectively (p=0.34). Valacyclovir decreased HIV VL by -0.22 log10 copies/ml overall (p=.01), but annual rates of change in plasma HIV VL were not different at 0.08 and 0.15 log10 copies/mL/year respectively (p=0.23). The proportions of patients with microbiologically confirmed HSV reactivations were not significantly different between study arms (1% vs 2%, p=.58). Grade 2 or higher drug-related adverse events occurred in 6% of valacyclovir and 7% of placebo participants (p=0.83).
Conclusion: Valacyclovir did not slow HIV disease progression in ART-untreated adults, in contrast to trials using acyclovir in Sub-Saharan Africa, but did lower HIV VL by a small amount. These results provide further justification for early ART initiation in treatment naïve patients.

	CD4 count		CD4 percent		log10 viral load	
	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value
Intercept	186 (107,264)	<0.0001	3.18 (0.93,5.43)	<.01	0.51 (0.11,0.90)	0.01
Valacyclovir	25 (-15, 65)	0.22	0.66 (-0.46,1.78)	0.25	-0.22 (-0.38,-0.05)	0.01
Years	-59 (-86,-32)	<0.0001	-1.69 (-2.42,-0.96)	<.0001	0.15 (0.07,0.23)	<.001
Valacyclovir*years	8.7 (-29, 46)	0.65	0.49 (-0.52,1.50)	0.34	-0.07 (-0.19,0.04)	0.23
Baseline value	68 (56, 80)	<0.0001	0.91 (0.83,0.98)	<.0001	0.85 (0.75,0.94)	<.0001

448 RALTEGRAVIR/EMTRICITABINE/TENOFOVIR IN HIV-2 INFECTION (ANRS 159 VIH-2 PILOT TRIAL)

Sophie Matheron[1], Diane Descamps[1], Sébastien Gallien[2], Amel Besseghir[3], Roland Tubiana[4], Florence Damond[1], Fideline Collin[3], Francoise Brun-Vezinet[1], Genevieve Chene[3], for the ANRS 159 VIH2 trial Study Group

[1]Hopital Bichat-Claude Bernard, AP-HP, Paris, France, [2]Hopital Saint Louis, AP-HP, Paris, France, [3]INSERM, Bordeaux, France, [4]Hopital Pitié-Salpétrière, AP-HP, Paris, France

Background: We hypothesized that cART involving an integrase inhibitor (raltegravir) and 2 NRTIs (emtricitabine, tenofovir) could improve the gain in CD4 lymphocytes count (CD4) in HIV-2.

Methods: This multicenter non-comparative trial included ARV-naïve adults infected with HIV-2 only, with either previous CDC group B or C defining event, or a CD4 count <500/µL or CD4 decrease >50 cells/µL/year over the last 3 years or confirmed plasma HIV-2 RNA (pVL) ≥100 copies/mL. The primary endpoint was a composite criterion: proportion of participants surviving at 48 weeks (W48) without any of the following events: CD4 gain <100/µL at W48 compared to baseline (W0) CD4 count, pVL ≥40 cp/mL from W24 confirmed within the next 4 weeks, raltegravir permanent discontinuation, new B or C event. Missing data were considered as failure. Ultrasensible pVL (uspVL) and total DNA were determined using "in-house" PCR assays

Results: From August 2012 to February 2015, 30 patients (67% women) were included. At baseline, they were aged 49 years, had HIV-2 infection diagnosed for 11 years (InterQuartile Range [IQR]=8 to 14) and median CD4 nadir of 351/µL; median CD4 count was 436/µL (IQR=314 to 507); pVL was ≥40 copies/mL in 20/30 (67%) participants (median=2.5 log10 copies/mL); uspVL was ≥5 copies/mL in 23/25 participants (92%); total DNA was >6 copies/PCR in 8/25 participants (32%) (median=225.5 copies/106 PBMC). At W48, the composite endpoint of success was reached in 12/30 patients (40%; 95% Confidence Interval 22.7 to 59.4). Eighteen patients failed due to CD4 gain <100/µL (n=15), pVL ≥40 copies/mL (n=1) or withdrawal before W48 (n=2). pVL was ≥5 copies/mL in 2/15 patients (13%). Total DNA was >6 copies/PCR in 3/26 (11.5%). Among the 22 patients with baseline CD4 <500/µL and the 8 with CD4 ≥500/µL, 36% and 50% experienced treatment success, respectively. Median CD4 change was +87/µL (IQR +38 to +213) in the 28 patients with complete follow-up; +115/µL and +70/µL in those with baseline pVL ≥40 and <40 copies/mL, respectively. No serious adverse reaction was reported.

Conclusion: Overall, first line raltegravir-containing cART was well tolerated and yielded therapeutic success in 40% of HIV-2 patients at one year, comparable to that reported with a PI containing-regimen. Failure was mainly explained by a lower CD4 gain than expected. At W48, uspVL and total DNA were undetectable in about 90% of participants with available measurement.

449LB LONG-ACTING IBALIZUMAB IN PATIENTS WITH MULTI-DRUG RESISTANT HIV-1: A 24-WEEK STUDY

Stanley Lewis[1], Jeffry Fessel[2], **Brinda Emu**[3], Shannon Schrader[4], Princy Kumar[5], Gary J. Richmond[6], Steven Weinheimer[1], Christian Marsolais[7]

[1]TaiMed Biologics USA, Irvine, CA, USA, [2]Kaiser Permanent Med Cntr, San Fransisco, CA, USA, [3]Yale Univ, New Haven, CT, USA, [4]Schrader Clinic, Houston, TX, USA, [5]Georgetown Univ, Washington, DC, [6]Gary J Richmond MD PA, Ft Lauderdale, FL, USA, [7]Theratechnologies, Inc, Montreal, Canada

Background: Multi-drug resistant (MDR) HIV-1 has been associated with a higher risk of disease progression and death. Antiretroviral agents (ARVs) with new mechanisms of action are necessary for patients with MDR HIV-1. The humanized monoclonal antibody, ibalizumab (IBA), is a long-acting ARV with a unique binding specificity allowing it to block viral entry into host cells. In the registrational Phase 3 study in MDR HIV-1 patients, TMB-301, IBA previously showed significant viral load (VL) reductions 7 days after initial dosing when added to a failing ARV regimen. Here, we describe the sustained efficacy, safety and tolerability of IBA through Week (wk) 24 of treatment.

Methods: TMB-301 is an open-label study investigating the antiviral activity and safety of IBA plus an optimized background regimen (OBR) in treatment-experienced patients with MDR HIV-1. Following a 7-day monitoring period of patients on a failing ARV regimen, an intravenous (IV) loading dose of 2000 mg IBA was administered (functional monotherapy). On Day 14, an OBR was added with at least one additional sensitive agent and patients continued on an IV maintenance dose of 800 mg IBA every two wks for 24 wks. Efficacy and safety endpoints were evaluated.

Results: Enrolled patients (n=40) had a median Baseline (BL) VL of 4.6 log10 (18% BL VL ≥100,000 copies/mL) and a median BL CD4+ T cell count of 73 cells/µL. Resistance testing at BL showed 53% and 35% of patients had exhausted ≥3 and 4 ARV classes, respectively, and 16% of patients had HIV-1 resistant to all approved ARVs. 43% of patients required an investigational agent in OBR. At Wk 24, using the ITT – Missing Equals Failure (ITT-MEF) analysis, the mean change from BL VL was -1.6 log10 with 55% and 48% of patients having a ≥1 log10 and ≥2 log10 reduction, respectively. Viral load <50 and <200 HIV RNA copies/mL was reached in 43% and 50% of patients, respectively. Other efficacy outcomes are presented on Table 1. Most treatment-emergent adverse events reported were mild to moderate in intensity. Nine patients had a serious adverse event, of which one (immune reconstitution inflammatory syndrome) was considered drug-related. Nine patients discontinued the study prior to completion.

Conclusion: Bi-weekly IBA plus OBR maintained virologic efficacy and was well tolerated through Wk 24 in patients with very limited treatment options due to resistance to approved ARV agents.

450LB A PHASE 2 OPEN-LABEL TRIAL OF ANTIBODY UB-421 MONOTHERAPY AS A SUBSTITUTE FOR HAART

Chang-Yi Wang[1], **Wingwai Wong**[2], Hung-Chin Tsai[3], Yen-Hsu Chen[4], Mei-June Liao[5], Shugene Lynn[6], for the United BioPharma UB-421 Clinical and Research Team
[1]United Biomed, Inc, Hauppauge, NY, USA, [2]Taipei Veterans General Hosp, Taipei, Taiwan, [3]Kaohsiung Veterans General Hosp, Kaohsiung, Taiwan, [4]Kaohsiung Med Univ and Hosp, Kaohsiung, Taiwan, [5]United Biopharma, Inc, Hsinchu, Taiwan, [6]UBI Asia, Hsinchu, Taiwan

Background: The antiviral activity of UB-421, a monoclonal antibody that binds to CD4 receptor to block HIV-1 entry, was demonstrated in a prior Phase 2a trial of 29 antiretroviral-naïve HIV-1(+) adults in Taiwan (Trial No. NCT01668043); the average (and SD) of maximum viral load (VL) reduction was 2.27 (0.6) and 2.45 (0.46) log10 copies/mL after 8-week monotherapy on 10mg/Kg/weekly or 25mg/Kg/biweekly, respectively.
Methods: Efficacy and safety of UB-421 monotherapy was examined in this Phase 2 trial among HAART-stabilized HIV-1(+) Asian adults whose VLs had been recorded as undetectable (< 50 copies/mL) at least twice in the past year (NCT02369146); 14 and 15 such adults interrupted HAART to receive 8 doses of UB-421 infusions on 10mg/Kg/weekly (Arm 1) or 25mg/Kg/biweekly (Arm 2) regimens, respectively, with prompt return to HAART if viral rebound (VR, > 400 copies/mL at 2 consecutive visits). Efficacy was assessed as the percentage of and the time to VR; changes in laboratory parameters were compared to baseline.
Results: Twenty-seven of 29 enrolled subjects completed all 8 doses of UB-421 with no VR during the monotherapy period, which was 8-week for Arm 1 and 16-week for Arm 2. Two subjects in Arm 2 did not complete (1 lost to follow-up, 1 withdrew due to skin rash), but had undetectable VL for all trial visits. At the end of treatment (EOT), 22 subjects resumed HAART and were monitored for 8 weeks with continuous viral suppression. Five subjects (3 in Arm 1 and 2 in Arm 2) refused to resume the scheduled HAART, and viral rebound was detected 35-62 days after the last UB-421 dose; all 5 re-started HAART right after rebound, and their VL were monitored until undetectable. At the end of study for both arms, CD4+ T cell counts remained stable (p>0.17 Wilcoxon signed-rank (WSR) test), while CD8+ T cell counts increased (p<0.05). The 27 completers exhibited significant reductions (interquartile =1.7% - 3.1%) of CD4+ T regulatory cell percentage at EOT (p<0.001 WSR test). In 11 subjects with proviral DNA > 100 copies/10^6 PBMC at baseline, 10 showed a mean 2.24-fold reduction at EOT. The most common drug-related (possible or probable) adverse event (AE) was mild to moderate skin rash (48.3% of 29 subjects), and no death or drug-related SAE occurred.
Conclusion: No viral rebound occurred during the UB-421 monotherapy period; the regimen was safe and well tolerated. UB-421 warrants further evaluation for an indication as monotherapy for HAART substitution in virally suppressed HIV-1 adults.

451LB DOLUTEGRAVIR AS MAINTENANCE MONOTHERAPY FOR HIV-1: A RANDOMIZED CLINICAL TRIAL

Ingeborg Wijting[1], Casper Rokx[1], Charles Boucher[1], Dorine de Vries - Sluijs[1], Karin Schurink[1], Elrozy Andrinopoulou[1], Eric van Gorp[1], Wouter Bierman[2], Bart Rijnders[1], for the DOMONO Study-Group
[1]Erasmus Univ Med Cntr Rotterdam, Rotterdam, Netherlands, [2]Univ Med Cntr Groningen, Groningen, Netherlands

Background: The development of integrase (IN) inhibitor resistance during dolutegravir (DTG) containing cART is exceedingly rare. This high genetic resistance barrier may make DTG suitable as maintenance monotherapy. We hypothesized that DTG monotherapy is non-inferior to cART in maintaining viral suppression.
Methods: Multicenter randomized trial comparing DTG 50mg QD (DOLUMONO) with continued cART(con-cART). Pts included were HIV-1+ and on cART with a viral load (VL)<50c/ml for >6months, a CD4 nadir >200cells/ul, a pre-cART peak VL<100.000c/ml and no history of virological failure (VF). 24wks after randomization, the con-cART group switched to DOLUMONO as well (delayed switch), fig1. The primary endpoint was the on-treatment proportion of pts with a VL<200c/ml at W24. Assuming 95% viral suppression, 104 pts were needed for a study with β=80%, δ=-0.12, and α=0.025. Secondary endpoints were VL<200c/ml and <50c/ml at W24 and W48 in all pts on DOLUMONO (immediate+delayed switch group combined). Due to the "W24 delayed switch" study design, no randomized con-cART control group is available to compare the W48 DTG monotherapy results with. Therefore, a concurrent control group of 152 pts on cART was included (fig1). These pts fulfilled the same in -and exclusion criteria but continued their cART. NCT02401828.
Results: 104 pts were included and on cART for 40 months with CD4 nadir of 340cells/ul. One pt discontinued DTG at W12 for adverse events. At W24, DOLUMONO was non-inferior to con-cART: VL<200c/ml in 49/50 vs 53/53 (Δ2%, Exact 95%CI +12% to -5%) with no IN resistance in the single VF. Also 46 of 53 pts randomized to con-cART switched to DOLUMONO 24 weeks after randomization. Consequently, a total of 96 pts received DTG monotherapy, of whom 94 have reached W24. 92/94 had a VL<200c/ml with no resistance in the 2 VF. However, when 77 of the 96 pts had reached W48 of monotherapy, VF had developed in 8 (2 before W24, 6 after W24). IN genotyping was successful in 6 and resistance found in 3: the 155H and 263K in 1 pt each and the 230R, a mutation not previously described during DTG therapy, in 1 pt. As per predefined stopping rule, this led to the premature study discontinuation. In the concurrent control group on cART, VF was observed significantly less (3/152 vs 8/96, p=0.03).
Conclusion: Although DTG monotherapy was non-inferior to cART at W24, VF continued to occur after W24 and led to DTG resistance in 3. The genetic barrier of DTG monotherapy is insufficient to allow for maintenance monotherapy.

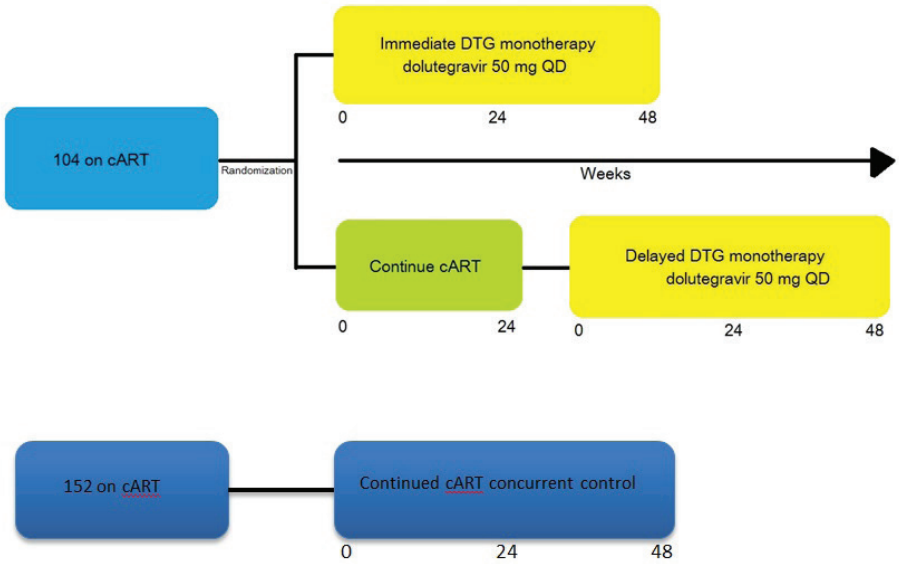


Figure 1. Flowchart of study scheme

452LB ELSULFAVIRINE AS COMPARED TO EFAVIRENZ IN COMBINATION WITH TDF/FTC: 48-WEEK STUDY

Robert Murphy[1], Alexey V. Kravchenko[2], Elena Orlova-Morozova[3], Firaya Nagimova[4], Oleg Kozirev[5], Tatyana Shimonava[6], Marina Deulina[2], Natalia Vostokova[7], Olga Zozulya[7], Vadim Bichko[8]

[1]Northwestern Univ, Chicago, IL, USA, [2]Russia AIDS Federal Cntr, Moscow, Russian Federation, [3]Moscow Region AIDS Cntr, Moscow, Russian Federation, [4]Republic Tartarstan AIDS Cntr, Kazan, Russian Federation, [5]Volgograd Region AIDS Cntr, Volgograd, Russian Federation, [6]Moscow City AIDS Cntr, Moscow, Russian Federation, [7]IPHARMA Moscow, Moscow, Russian Federation, [8]Viriom, Inc, San Diego, CA, USA

Background: Elpida® (VM1500) is the prodrug of Elsulfavirine (VM1500A), a new potent non-nucleoside reverse transcriptase inhibitor with unique pharmacokinetic properties (T1/2 is ~8 days). A 20 mg once daily dosing was chosen for further study based on 12-week efficacy, pharmacology and safety data.

Methods: Compare the efficacy and safety of an ART regimen including Elpida or Efavirenz (EFV) plus tenofovir/emtracitabine (TDF/FTC). Phase IIb randomized, placebo-controlled, double-blind, multicenter study in ART-naïve HIV-1-infected patients treated for 48 weeks. Patients were randomized 1:1 to receive; 1) Elpida 20 mg QD, or 2) EFV 600 mg QD. All patients were treated with TDF/FTC.

Results: 120 patients enrolled, 60 Elpida/60 EFV. Baseline plasma HIV RNA median was 4.7-4.8 log10 copies/ml; median CD4+ T lymphocyte count was 349 and 379 cells/mm3 for Elpida and EFV respectively. A total of 55/60 (91.7%) Elpida and 47/60 (78.3%) EFV (p=0.041) completed treatment. At Week 48 of therapy 45/55 (81%) of Elpida and 35/47 (73.7%) of EFV patients had HIV-1 RNA values <50 copies/ml (MITTI-analysis) and all patients in both groups who completed treatment had HIV-1 RNA value < 400 copies/ml. Patients with baseline HIV-I RNA > 100 000 copies/ml, with HIV RNA <50 copies/mL at week 48 were 14/18 (77.7%) and N15/22 (68.2%) of patients respectively after 48 weeks of therapy. No patient demonstrated virologic failure defined as two consecutive HIV RNA plasma levels of >400copies/ml. CD4+ T lymphocyte counts increased at Week 48 by 179 and 182 cells/mm3 respectively. Median CD4/CD8 ratio increased in both groups from 0.41 to 0.78 and from 0.34 to 0.63 respectively. Study drug-associated adverse events were observed in N22/60 (36.7%) of Elpida patients and 45/58 (77.6%) of EFV patients (p <0.0001). AEs of special interest (CNS disorders, skin disorders) with a frequency > 5% occurred in 31.7% and 62.1% of patients respectively (p = 0.008). The most frequent were headache (15% and 24.1%), dizziness (6.7% and 27.6%), sleep disorders (5% and 20.7%). Only EFV patients had abnormal dreams (17.2%), skin rash (17.2%), and pruritus (5.2%). Only 5 patient discontinued Elpida (2 AE [1 pregnancy], 1 lack of compliance, 1 LTFU, 1 withdrew consent), and 13 patients discontinued EFV (7 AE, 5 LTFU, 1 withdrew consent) because of drug-related AEs.

Conclusion: Elpida was significantly better tolerated than EFV-based therapy offering a safer alternative to EFV-based ART.

453 SIGNIFICANT EFFICACY & LONG-TERM SAFETY DIFFERENCE WITH TAF-BASED STR IN NAÏVE ADULTS

Jose R. Arribas[1], Melanie Thompson[2], Paul E. Sax[3], Bernhard Haas[4], Cheryl McDonald[5], David Wohl[6], Edwin DeJesus[7], Amanda Clarke[8], Moupali Das[9], Scott McCallister[9]

[1]Hosp Univ La Paz, Madrid, Spain, [2]AIDS Rsr Consortium of Atlanta, Atlanta, GA, USA, [3]Brigham and Women's Hosp, Boston, MA, USA, [4]Hosp Graz West, Graz, Austria, [5]Tarrant County Infectious Disease Associates, Fort Worth, TX, USA, [6]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [7]Orlando Immunol Cntr, Orlando, FL, USA, [8]Brighton & Sussex Univ Hosps NHS Trust, Brighton, UK, [9]Gilead Scis, Inc, Foster City, CA, USA

Background: Two randomized, controlled, double-blinded multinational Phase 3 trials compared tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF), each in single-tablet regimens coformulated with elvitegravir/cobicistat/emtricitabine (E/C/F). At Week (W) 48, E/C/F/TAF was statistically noninferior to E/C/F/TDF for the proportion of subjects with HIV-1 RNA <50 copies(c)/mL and had significant improvements in renal and bone safety endpoints. We now describe follow up of blinded data through W144, including longer-term safety data and prespecified <20 c/mL secondary endpoint.

Methods: ARV naïve participants randomized 1:1 to receive E/C/F/TAF (TAF) or E/C/F/TDF (TDF). W144 viral suppression (HIV-1 RNA <50 and <20 c/mL) by FDA snapshot analysis, predefined bone and renal safety, and tolerability endpoints are reported.

Results: 1,733 HIV-infected adults were randomized and treated: 15% women, 43% non-white, 23% viral load >100,000 c/mL. Median baseline characteristics: age 34 yrs, CD4 count 405 cells/μL, and VL 4.58 log10 c/mL. At W144, TAF met prespecified criteria for both noninferiority and superiority to TDF by FDA snapshot algorithm (HIV-1 RNA <50 and <20 c/mL) (Table 1). Mean % decrease in BMD was significantly less in the TAF group for both lumbar spine and total hip (Table 1). As shown in Table 1, multiple measures of renal safety were significantly better for participants randomized to TAF. There were no cases of renal tubulopathy in the TAF arm vs 2 on TDF. No participants on TAF had renal-related discontinuations vs 12 on TDF (p<0.001). Participants on TAF had greater increases in TC, LDL, and HDL (Table 1), with no difference in the rate of initiation of lipid-modifying agents (TAF: 5.5% vs TDF: 5.8%).

Conclusion: Through W144, participants on E/C/F/TAF had a significantly higher rate of virologic suppression (<50 c/mL) than those on E/C/F/TDF, driven by fewer participants on E/C/F/TAF with no W144 data. Participants on E/C/F/TAF also had a significantly higher rate of virologic suppression (<20 c/mL), driven by fewer participants on E/C/F/TAF with viral load ≥20 c/mL. E/C/F/TAF continued to have a statistically superior bone and renal safety profile compared to E/C/F/TDF, demonstrating significant safety advantages over E/C/F/TDF through 3 years of treatment. Individuals on TAF had greater plasma lipid changes, but proportions starting lipid-lowering therapy were comparable.

Table 1. W144 Efficacy and Changes from Baseline in Renal, Bone, and Lipid Safety Parameters

Efficacy Parameter	E/C/F/TAF (n=866)	E/C/F/TDF (n=867)	Significance
HIV-1 RNA <50 c/mL, n (%)	729 (84.2%)	694 (80.0%)	p=0.021 (diff in percentages [95% CI]: 4.2% [0.6% to 7.8%])
HIV-1 RNA ≥50 c/mL, n (%)	40 (4.6%)	34 (3.9%)	—
Virologic failure or lack of efficacy	17 (2.0%)	17 (2.0%)	—
Other[a]	23 (2.7%)	17 (2.0%)	—
No Virologic Data in W144 Window	97 (11.2%)	139 (16.0%)	—
HIV-1 RNA <20 c/mL, n (%)	702 (81.1%)	657 (75.8%)	0.006 (diff in percentages [95% CI]: 5.4% [1.5% to 9.2%])
Safety Parameter[b]			
Renal Safety, change from baseline			
eGFR, mL/min (CG)	-1.6 (-11.4, 9.4)	-7.7 (-18.4, 4.2)	All p<0.001
UPCR	-10.5% (-43.9%, 38.0%)	25.2% (-23.8%, 95.2%)	
β-2M/Cr	-25.7% (-58.2%, 13.7%)	53.8 (-26.0%, 305.1%)	
RBP/Cr	34.8% (-4.6%, 83.3%)	111.0% (38.4%, 264.9%)	
Bone Density, % change from baseline			
Lumbar Spine	-0.92% (4.12%)	-2.95% (4.29%)	Both p<0.001
Total Hip	-0.75% (4.45%)	-3.36% (4.33%)	
Fasting lipid parameters, change from baseline			
Total Cholesterol (mg/dL)	31 (13, 49)	13 (-5, 30)	All p≤0.006
LDL (mg/dL)	19 (2, 36)	6 (-8, 21)	
HDL (mg/dL)	6 (0, 13)	2 (-3, 9)	
Total cholesterol: HDL ratio	0.2 (-0.3, 0.7)	0.1 (-0.4, 0.6)	

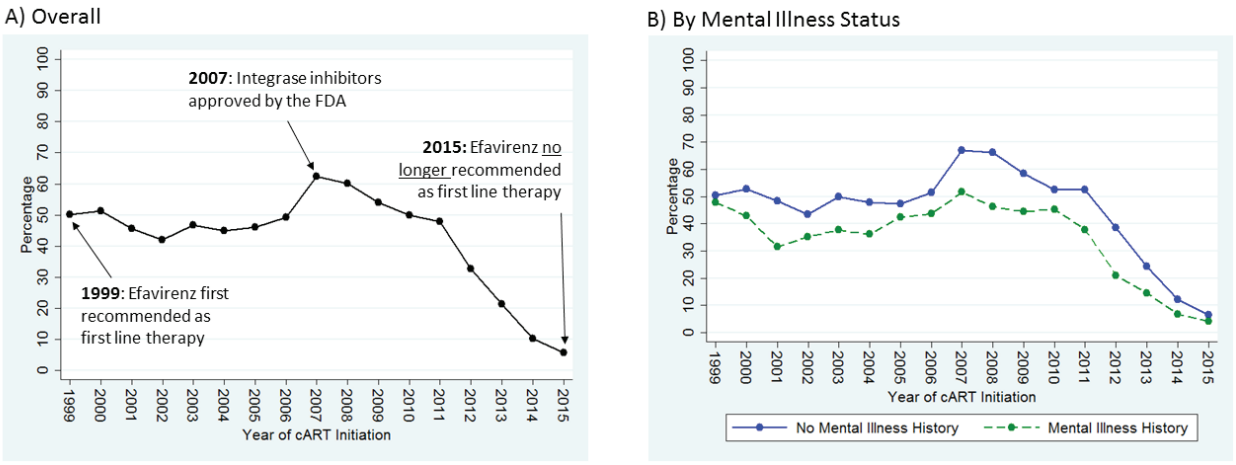
β-2M/Cr = urine beta-2-microglobulin to creatinine ratio; c/mL = copies/mL; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; UPCR = urine protein to creatinine ratio; RBP/Cr = urine retinol binding protein to creatinine ratio
Renal safety: all parameters are % change from baseline, except eGFR, which is actual change from baseline
[a] Other includes discontinued drug due to other reasons and last available HIV RNA ≥50 c/mL or added another ARV.
[b] For safety parameters, mean (SD) used to summarize BMD; otherwise, median (Q1, Q3) is used.

454 PATTERNS OF EFAVIRENZ USE AS FIRST-LINE THERAPY IN THE UNITED STATES: 1999–2015

Angela Bengtson[1], Brian W. Pence[1], Ellen F. Eaton[2], Jessie K. Edwards[1], Joseph J. Eron[1], W. C. Mathews[3], Katie Mollan[1], Richard D. Moore[4], Connall O'Cleirigh[5], Michael J. Mugavero[2]
[1]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Univ of Alabama at Birmingham, Birmingham, AL, USA, [3]Univ of California San Diego, San Diego, CA, USA, [4]Johns Hopkins, Baltimore, MD, USA, [5]Massachusetts General Hosp, Boston, MA, USA

Background: Between 1999 and 2014 efavirenz was recommended as first-line therapy for HIV-infected adults in the US, and continues to be recommended globally by the WHO. However, efavirenz has been linked to suicidal behavior and may not be appropriate for patients with mental illness.
Methods: We examined the patterns of initiating efavirenz-containing first line combination antiretroviral therapy (cART) overall and by mental illness status using data from CNICS, a cohort of 31,000 HIV-infected adults in care at 8 sites in the US. Participants were included if they initiated cART between 1999 and 2015 and were followed from cART initiation until initial cART regimen or cART discontinuation, death, loss to care (>12 months with no HIV appointment), or administrative censoring (Oct 2014-Sept 2015, depending on site), whichever date came first. We used multivariable log binomial models to examine factors associated with initiating and discontinuing efavirenz-containing cART.
Results: We included 9,775 new cART users. Of those, 4,239 (43%) initiated efavirenz-containing cART; and 772 of those participants (18%) discontinued efavirenz. At cART initiation, 2,492 (25%) of participants had a history of a mental illness associated with suicidal behavior, including depression, psychosis, post-traumatic stress disorder, or obsessive compulsive disorder. Efavirenz initiation peaked in 2007 and declined rapidly thereafter (Figure). Over time, persons with a history of a mental illness were modestly less likely to initiate efavirenz-containing cART, compared to those with no history of mental illness. In a multivariable analysis adjusted for site and year of cART initiation, factors associated with initiating efavirenz-containing cART were: prior mono or dual therapy use (prevalence ratio (PR) 0.74, 95% CI 0.66, 0.83), being female (PR 0.80, 95% CI 0.74, 0.86), intravenous drug use (PR 0.83, 95% CI 0.77, 0.90), history of mental illness (PR 0.79, 95% CI 0.75, 0.84) and CD4 cell count >350 (PR 0.91, 95% CI 0.86, 0.95). History of mental illness (PR 1.18, 95% CI 1.02, 1.37) and CD4 cell count >350 (PR 0.86, 95% CI 0.73, 0.98) were associated with discontinuing efavirenz.
Conclusion: Until recently, efavirenz was widely used as first line therapy for HIV-infected adults in the US, including among individuals with a history of mental illness. Given the widespread use of efavirenz globally, greater clarity about the implications of efavirenz use among persons with mental illness is needed.

Figure. Proportion of 9, 775 HIV-infected Adults Initiating Efavirenz-containing cART A) Overall and B) by Mental Illness Status in the United States: 1999-2015.



455 ART INITIATION, REGARDLESS OF COMPOSITION, IMPROVES PATIENT-REPORTED DEPRESSION

Ellen Eaton, Ashutosh Tamhane, Michael J. Mugavero
Univ of Alabama at Birmingham, Birmingham, AL, USA

Background: More than 50% of persons living with HIV (PLWH) have depression. Co-morbid HIV and depression yield reduced rates of antiretroviral therapy (ART) adherence and higher rates of HIV viral progression and mortality. We hypothesized that patient and ART-specific factors are associated with depression 12 months after ART initiation.
Methods: This retrospective study included treatment-naïve PLWH initiating ART between January 2007 and December 2012 at the HIV clinic of the University of Alabama at Birmingham (Alabama, USA). In addition to baseline (at ART initiation) sociodemographic and clinical characteristics, PHQ9 scores (self-reported depression) were obtained both at baseline and while receiving ART at 12-month. Patients were categorized as having depression (PHQ score ≥10) or mild/no depression (score ≤9) and receiving Efavirenz or Non-Efavirenz-based regimens. Associations were examined using univariate and multivariable logistic regression analyses.
Results: 291 patients were included: 61 (21%) had depression at 12 months, 83% were male, 60% were Black/African American, and mean age was 35 years. Odds of depression were higher at baseline than at 12 months (30% vs 21%, p=0.003), more so in the Non-Efavirenz regimen (39% vs 24%, p<0.001) than in Efavirenz-based regimen (20% vs 17%, p=0.48). Differential baseline depression between the regimens (20% vs 39%, p<0.001) was indicative of channeling bias. Depression at 12 months was higher among uninsured patients (30/142=27%) than in public (4/22=18%) or privately insured (18/127=14%). Overall, baseline median PHQ score decreased from 6 to 3 at 12 months (Efavirenz: 4 vs 2, Non-efavirenz: 7.5. vs 4.0). In univariate analysis, recipients of the Efavirenz-based regimen were at lower odds of having 12-month depression than Non-efavirenz regimens (OR=-0.7, 95% CI 0.4-1.2) (Table 1); after adjusting for baseline depression (channeling bias), the difference in 12 month depression between the regimens decreased (OR=0.9; 95% CI: 0.5-1.8). In multivariable analysis, baseline depression (ORadjusted=7.6; 95% CI: 3.7 – 15.5) and lack of insurance (ORadjusted=2.8; 95% CI: 1.3 – 6.0) were significantly associated with greater odds of 12 month depression; no difference was observed between ART regimens (Table 1).
Conclusion: In addition to aggressively treating existing depression, initiating ART and enrolling PLWH in insurance has the potential to improve depression and HIV health outcomes.

Table 1. Univariate and multivariable analyses examining association of socio-demographic and clinical characteristics with 12-month depression in treatment naïve HIV-infected patients initiating ART

Baseline Characteristic[b]	Total N=291	12-month Depression N=61	Univariate analysis[c]	Multivariable analysis[c]
	N	N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Efavirenz-based ART	143	25 (41)	0.7 (0.4, 1.2)	0.9 (0.4, 1.7)
Depression[a]	87	38 (62)	**6.1 (3.3, 11.2)**	**7.6 (3.7, 15.5)**
Female	48	14 (23)	1.7 (0.9, 3.5)	1.5 (0.5, 4.6)
White	116	27 (44)	1.3 (0.7, 2.2)	1.5 (0.7, 3.1)
Insurance: Public	22	4 (7)	1.3 (0.4, 4.4)	0.9 (0.2, 3.7)
Uninsured	142	39 (64)	**2.3 (1.2, 4.3)**	**2.8 (1.3, 6.0)**
CD4 (cells/uL) <200	89	21 (34)	1.3 (0.7, 2.4)	1.3 (0.6, 2.9)
VL (copies/mL), log, $<10^5$	143	29 (48)	0.9 (0.5, 1.7)	1.5 (0.7, 3.4)

NOTE: Reference categories not shown in the table. Bold numbers indicate statistical significance at 0.05 level.
ART=antiretroviral therapy, CD4= CD4 cell count, CI=confidence interval, IVDU= intravenous drug use, OR=odds ratio, VL= HIV viral load.
[a]Using PHQ-9 questionnaire (self-reported).
[b]Baseline characteristics defined as present at the time of ART initiation.
[c]Unconditional logistic regression.
Patient-reported Age, Alcohol Abuse and Substance Use are not listed but were included in the model

456 THE CLINICAL AND ECONOMIC IMPACT OF DOLUTEGRAVIR-BASED FIRST-LINE ART IN INDIA

Amy Zheng[1], Nagalingeswaran Kumarasamy[2], Mingshu Huang[1], A. David Paltiel[3], Kenneth H. Mayer[4], Bharat Bhushan Rewari[5], Rochelle P. Walensky[1], Kenneth Freedberg[1]
[1]Massachusetts General Hosp, Boston, MA, USA, [2]YR Gaitonde Cntr for AIDS Rsr and Educ, Chennai, India, [3]Yale Univ, New Haven, CT, USA, [4]Fenway Hlth, Boston, MA, USA, [5]WHO, New Delhi, India

Background: Dolutegravir (DTG)-based antiretroviral therapy (ART) has proven superior or non-inferior to other regimens and is recommended first-line treatment in the US. Efavirenz (EFV)-based regimens remain the standard of care (SOC) in India and other resource-limited settings, where DTG is not yet available. Anticipating generic DTG availability, we examined the clinical outcomes, cost-effectiveness, and budgetary impact of DTG-based 1st-line ART in India.
Methods: We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) International microsimulation model of HIV disease and treatment to evaluate two 1st-line ART strategies: 1) SOC: EFV/TDF/3TC; and 2) a DTG-based regimen: DTG+TDF/3TC in an HIV-infected cohort (mean age 37 years, 48% male, and median CD4 235 cells/μL). Regimen-specific model inputs included 48-week HIV RNA suppression (82% [SOC] vs. 90% [DTG]) and CD4 count increase in the first 2 months (83 vs. 107 cells/μL), from clinical trial data. Annual cost/person of SOC was USD$144; in the base case we assumed a DTG-based ART cost of $174/person/year (range $60-$264), from WHO-projected costs of generic DTG regimens. 2nd-line PI-based ART cost was $255/person/year. Life years and costs were discounted in the ICERs; program costs were undiscounted. Strategies with incremental cost-effectiveness ratios (ICERs, $/year of life saved [YLS]) <1X Indian annual per capita GDP ($1,600) were considered cost-effective. We examined parameter uncertainty in sensitivity analysis.
Results: A DTG-based regimen improved 5-year survival from 80% to 84% and extended life expectancy from 14.5 to 15.7 years, compared with SOC (Table). The proportion of patients on 1st-line ART at 5 years increased from 92% (SOC) to 96% (DTG). At a cost of $174/person/year, a DTG-based regimen had an ICER of $500/YLS compared to SOC. The ICER remained below $1,600/YLS across wide ranges of 1st-line ART cost, CD4 count increase in the first 2 months, 48-week HIV suppression rate, CD4 count at ART initiation, and 2nd-line ART cost. Program treatment costs were similar for newly ART-eligible patients at 2 years ($169 million [SOC] vs. $175 million [DTG]).
Conclusion: A generic DTG-based option for 1st-line ART in India will increase survival, decrease the proportion of patients switching to 2nd-line ART, and be cost-effective, with little additional outlay over the current standard of care. DTG-based 1st-line ART, once generic pricing is available, should become the standard of care for ART initiation in India.

457 QUALITY OF LIFE IMPROVEMENT DURING SECOND-LINE THERAPY IN RESOURCE-LIMITED SETTINGS

Thiago S. Torres[1], Linda J. Harrison[1], Alberto M. La Rosa[2], Lu Zheng[1], Sandra W. Cardoso[3], Selvamuthu Poongulali[4], McNeil Ngongondo[5], Ann Collier[6], Michael D. Hughes[1], for the AIDS Clinical Trials Group (ACTG) A5273 Study Group
[1]Harvard Univ, Boston, MA, USA, [2]Asociación Civil Impacta Salud y Educación, Lima, Peru, [3]Inst Nacional de Infectologia (INI/Fiocruz), Rio de Janeiro, Brazil, [4]YRGCARE Med Cntre, Chennai, India, [5]UNC-Proj Malawi, Lilongwe, Malawi, [6]Univ of Washington, Seattle, WA, USA

Background: Health-related quality of life (QoL) improves on first-line antiretroviral therapy (ART). However, at first-line failure, we have previously described poorer QoL among people in resource-limited settings (RLS) with higher viral load (VL). Change in QoL after starting second-line ART in RLS has not been evaluated.
Methods: ACTG A5273 was a randomized clinical trial of second-line ART comparing lopinavir/ritonavir (LPV/r) + raltegravir (RAL) with LPV/r + nucleos(t)ide reverse transcriptase inhibitors (NRTI) in participants failing a non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen at 15 sites in 9 RLS conducted between 2012 and 2014. The primary analysis of the trial showed no difference in virologic outcome between the two regimens. Participants completed the ACTG SF-21, which has 8 QoL domains with a standard score ranging from 0 (worst) to 100 (best): general health perceptions (GHP), physical functioning (PF), role functioning (RF), social functioning (SF), cognitive functioning (CF), pain (P), mental health (MH), and energy/fatigue (E/F). All participants were followed for at least 48 weeks. In a secondary analysis, differences in mean change in QoL between baseline (week 0) and week 48 by treatment arm and baseline VL were evaluated in intent-to-treat analysis using generalized estimating equation methods.
Results: 512 eligible adults (49% male, median age 39 years) from India (31%), Malawi (22%), South Africa (20%), Zimbabwe (9%) Kenya (9%), Tanzania (3%), Brazil (2%), Peru (2%), and Thailand (1%) were included. Median baseline CD4 count was 135 (IQR: 53; 271) cells/mm3 and VL 33,360 (IQR: 8,033; 138,153) cp/mL; 31% had VL >100,000 cp/mL. 512 and 492 participants had QoL assessments at baseline and week 48, respectively. QoL improved significantly from week 0 to 48 ($p<0.05$ for all domains for both treatments) with larger increases in GHP and RF. There was no significant difference between treatment arms for any domain (Table 1). Individuals with VL >100,000 cp/mL at baseline had lower mean QoL at week 0 than those with VL ≤100,000 cp/mL (3.6 to 12.1 lower; $p<0.02$ for each domain) but larger improvements such that mean QoL was similar at week 48 (1.3 lower to 1.7 higher across domains; $p>0.2$).
Conclusion: Improvements in QoL were similar after starting second-line ART with LPV/r + RAL or LPV/r + NRTI in RLS. QoL scores were worse among participants with higher VL prior to starting second-line, but after one year similar QoL scores were achieved.

Table 1. Mean QoL at week 0 and mean increase in QoL to week 48.

QoL Domain	Mean QoL at Week 0 (95%CI) (n=512)	Mean increase in QoL to week 48		Treatment comparison: LPV/r+RAL vs. LPV/r+NRTIs	
		LPV/r+RAL (95%CI)	LPV/r+NRTIs (95%CI)	Difference in mean increase (95%CI)	p-value
General Health Perception (GHP)	67.1 (65.3; 68.9)	6.1 (3.5; 8.8)	7.9 (5.0; 10.7)	-1.7 (-5.6; 2.1)	0.38
Physical Functioning (PF)	91.5 (89.9; 93.0)	3.6 (1.4; 5.8)	5.1 (2.2; 7.9)	-1.5 (-5.1; 2.1)	0.42
Role Functioning (RF)	80.4 (77.9; 83.0)	8.6 (5.0;12.1)	9.1 (5.2;13.0)	-0.5 (-5.8; 4.8)	0.85
Social Functioning (SF)	91.2 (89.8; 92.5)	4.1 (2.0; 6.3)	2.8 (0.5; 5.0)	1.3 (-1.8; 4.4)	0.40
Cognitive Functioning (CF)	91.0 (89.6; 92.3)	3.2 (1.3; 5.1)	5.3 (3.0; 7.6)	-2.1 (-5.1; 0.9)	0.17
Pain (P)	82.9 (81.0; 84.7)	3.8 (0.9; 6.7)	5.2 (2.1; 8.3)	-1.4 (-5.7; 2.8)	0.51
Mental Health (MH)	84.9 (83.6; 86.2)	3.6 (1.6; 5.6)	5.3 (3.0; 7.6)	-1.7 (-4.7; 1.4)	0.28
Energy/Fatigue (E/F)	79.9 (78.2; 81.6)	3.4 (0.6; 6.1)	4.8 (1.7; 7.7)	-1.4 (-5.4; 2.7)	0.51

458 PROMISING RESULTS OF DOLUTEGRAVIR + LAMIVUDINE MAINTENANCE IN ANRS 167 LAMIDOL TRIAL

Veronique Joly[1], Charles Burdet[2], Roland Landman[3], François Raffi[4], Christine Katlama[5], André Cabié[6], Aida Benalycherif[3], Gilles Peytavin[1], Diane Descamps[1], Yazdan Yazdanpanah[2]
[1]Hôpital Bichat, Paris, France, [2]INSERM, Paris, France, [3]IMEA, Paris, France, [4]CHU Hotel-Dieu Nantes, Nantes, France, [5]Pierre and Marie Curie Univ, Paris, France, [6]CHU Fort de France, Fort de France, Martinique, France

Background: Dolutegravir (DTG) is a potent INSTI with high genetic barrier. The once-daily (QD) DTG-3TC combination is attractive, both drugs being safe, highly efficient and convenient.

Methods: ANRS 167 LAMIDOL trial is an ongoing open-label, single-arm, multicenter trial assessing the efficacy and tolerance of DTG (50mgQD) - 3TC (300mgQD) in HIV-1 virologically suppressed patients (Pts) on first line cART with 2 NRTIs and either a PI, a NNRTI, or an INSTI. Inclusion criteria were age ≥18yrs, CD4 nadir >200/mm3, normal standard biological parameters, plasma HIV-RNA (pVL)≤50 cps/mL for at least 2 yrs, and wild-type HIV genotype prior to cART initiation (including for INSTI when tested). History of cART modification for intolerance or simplification was allowed. From Wk0 to Wk8 (Phase 1), third agent was switched to DTG, the 2 NRTIs being unchanged. From Wk8 to Wk56 (Phase 2), Pts received QD combination of DTG 50mg-3TC 300mg except if intolerance or pVL>50cps/mL during Phase 1. Virologic failure was defined as pVL>50cps/mL on 2 consecutive samples during Phase 2.

Results: 110 Pts were enrolled in Phase 1 in 19 HIV clinics in France from 10/1/2015 to 02/29/2016. Six Pts were not included in Phase 2 (intolerance to DTG in 3 Pts, pVL>50cps/mL in 3 Pts). 104 Pts initiated DTG-3TC combination with following characteristics at inclusion: 86% male, 72% MSM, median age 45yrs (min-max 24-70), 87% stage A, median CD4 nadir 339/mm3 (min-max 203-1155), median time since HIV diagnosis 6.3 yrs (min-max 2.3-24.5), median time on actual cART 4.0 yrs (min-max 0.5-11.3), median CD4 743/mm3 (min-max 373-1115). The baseline regimen contained PI, NNRTI and INSTI in 22%, 58% and 20% Pts, respectively. On 9/26/2016, 103 Pts reached Wk32 corresponding to 24 Wks DTG-3TC combination. No Pt withdrew from study treatment. One protocol-defined virologic failure occurred (pVL=77cps/mL at Wk16) despite adequate plasma C12h of 3TC (299ng/mL) and DTG (2,401ng/mL). Three SAEs occurred in 3 Pts: 2 biological including one 10-fold ALT elevation related to an acute hepatitis C infection and one > 10-fold elevation in creatinine kinase concomitantly with fitness activity, and one depression leading to hospitalization in a Pt with previous psychiatric disorders. DTG-3TC combination was maintained in these 3 Pts with improvement of abnormalities.

Conclusion: When used as 2-drug maintenance therapy, DTG-3TC combination was efficient and well tolerated after 24 Wks of follow-up in highly selected, virologically suppressed Pts.

459 ADVERSE DRUG REACTIONS AMONG PATIENTS RECEIVING SECOND-LINE ART IN SOUTH AFRICA

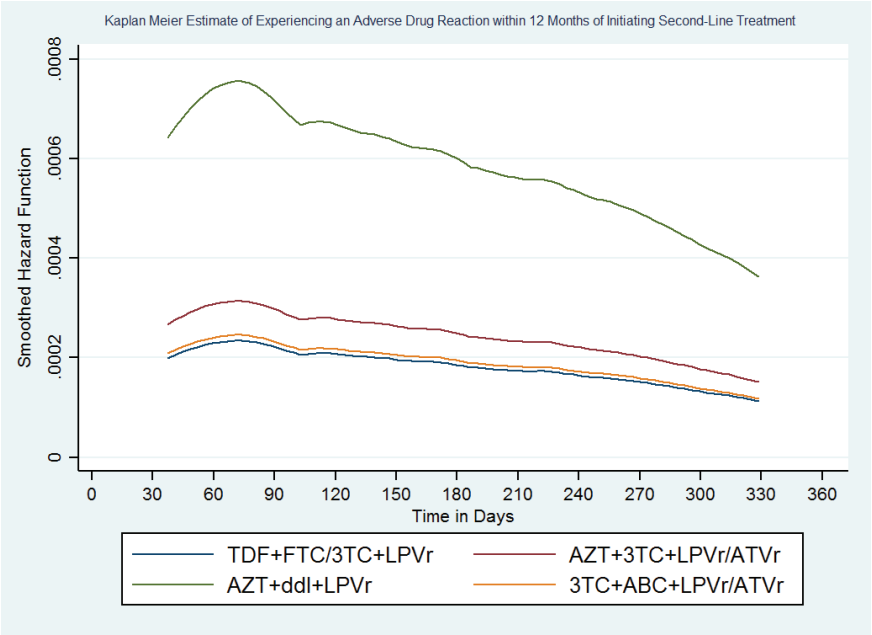
Dorina Onoya[1], Kamban Hirasen[1], Lawrence Long[1], Matthew Fox[2]
[1]Univ of the Witwatersrand, Johannesburg, South Africa, [2]Boston Univ, Boston, MA, USA

Background: As first-line antiretroviral therapy (ART) programmes mature, an increasing number of patients are being switched to second-line regimens. Adverse drug reactions (ADRs) which result primarily from medicines toxicity and drug interactions may compromise the effectiveness of treatment programs through its potential impact on treatment adherence and retention. Understanding the timing and rate of ADRs among patients on second-line ART is important in preventing switches to more expensive third-line regimens, particularly in resource limited settings.

Methods: Retrospective cohort study of HIV positive adult patients (≥18 years) who initiated standard second-line ART at a large urban clinic in Johannesburg, South Africa, from 01 April 2004 – 31 March 2015. Our primary outcome was the development of an ADR defined as one of the following diagnosed conditions within 12 months of initiating second-line ART: dyslipidaemia, diarrhoea, pain, skin conditions, neuropathy, gynecomastia/breast conditions, hepatitis and lactic acidosis. Kaplan Meier survival analysis was used to determine ADR incidence in the first 12 months on second-line ART. Models were controlled for age and sex. Person-time accrued from second-line treatment initiation to earliest of ADR, 12 months post second-line initiation or last clinic visit date.

Results: A total of 2907 patients initiated standard second-line ART. Of these patients, 12.7% (369/2907) had developed an ADR during the 12 months of follow-up. The highest ADR incidence was observed among patients receiving AZT+ddl+LPVr (23.0/100 PY, 95% CI: 19.3-27.5) and AZT+3TC+LPVr/ATVr (9.4/100 PY; 95% CI: 7.6-11.7) while the lowest rate was observed among patients receiving TDF+FTC/3TC+LPVr (7.1/100 PY, 95% CI: 5.5-9.1). These ADRs occurred in a median time of 4.2 months (IQR: 2.9-7.2), 5.5 months (IQR: 2.0-8.1) and 2.8 months (IQR: 0.9-7.1) respectively.

Conclusion: Patients on recently recommended regimens such as TDF+FTC/3TC+LPVr show lower rates of ADRs which is encouraging. The declining ADR incidence over time indicates that single/multi-drug substitutions may have taken place. The occurrence of ADRs early on in treatment (within 6 months) may indicate poor tolerability and require early drug substitution. This earlier substitution may facilitate greater adherence and retention in treatment.



460 LONG-TERM EFFICACY OF DOLUTEGRAVIR 50 MG BID IN INI-RESISTANT FAILING HIV-1 SUBJECTS

Antonella Castagna[1], Micol Ferrara[2], Laura Galli[3], Laura Comi[4], Gaetana Sterrantino[5], Giovanni Cenderello[6], Mauro Zaccarelli[7], Emanuele Focà[8], Andrea Roncadori[9], Adriano Lazzarin[10]

[1]Univ Vita-Salute San Raffaele, Milan, Italy, [2]Univ di Torino, Torino, Italy, [3]Ospedale San Raffaele, Milano, Italy, [4]Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy, [5]Azienda Ospedaliero Univ Careggi, Firenze, Italy, [6]Galliera Hosp, Genoa, Italy, [7]Natl Inst for Infectious Diseases, Rome, Italy, [8]ASST Spedali Civili di Brescia, Brescia, Italy, [9]CINECA, Casalecchio di Reno, Italy, [10]San Raffaele Vita-Salute Univ, Milan, Italy

Background: No data are available on long-term efficacy of dolutegravir (DTG, 50 mg twice daily) as rescue therapy in treatment-experienced patients (pts) infected with HIV strains with resistance mutations to raltegravir or elvitegravir. Here we evaluated long-term efficacy of DTG 50 mg twice daily in combination with optimized background therapy (OBT) using data from clinical practice.

Methods: The Italian Medicines Agency (AIFA) prospectively collects since 2014 demographic, clinical, virological and immunological data associated with DTG 50 mg BID prescription from all the Italian Infectious Diseases Centers (www.progettoprestigio.it). Highly treatment-experienced failing patients, with integrase inhibitor resistant virus, who started DTG 50 mg twice daily plus OBT were included in the analyses. Patients' follow-up accrued from the start of DTG 50mg+OBT until DTG discontinuation or last visit. Virological efficacy was defined by a viral load [VL] <50 cps/mL at last observed visit. Results were described as median (IQR) or frequency (%).

Results: 174 HIV-1 infected failing patients: 71% males, age 51 (47-55) years, 93% Italian, HIV-infection since 22 (16-26) years, 35% HCV positive, baseline (BL) VL 3.81 (2.75-4.64) log_{10}cps/mL, BL CD4+ 295 (138-509) cells/μL. At baseline, OBT included >3 drugs in 29% of the pts; 78% were PI-based regimens, 29% NNRTI-based, 47% included NRTIs in the regimen, 6% included enfuvirtide. 37% participated to the VIKING studies or Early Access Program. Twenty-five (14%) pts discontinued (9 virological failure, 9 clinical reasons, 3 patient's decision, 2 lost to follow-up, 2 deaths due to disease progression). At last follow-up visit, 70% had VL<50 cps/mL, with a median CD4+ of 456 cells/μL (267-733) and a CD4+ change from BL of +100 (8-270) cells/μL. 52 (30%) subjects at last visit had VL≥50 cps/ml, 31 (18%) of whom >200 cps/ml. Efficacy results according to DTG exposure are reported in the Table. Up to date, BL and follow-up genotypic drug-resistance tests are available in 9 subjects with VL>200 cps/mL at last visit; new INI mutations were selected as follows: G140S (+2 pts), Q148H (+1 pt), E138K (+6 pts), S147G (+1 pt), N155H (+1 pt), T97A (+6 pts), G140N (+1 pt), Q148R (+1 pt), L74M (+1 pt), H51Y (+1 pt), N165I (+1 pt).

Conclusion: Remarkable long-term efficacy of DTG 50 mg BID in association with OBT was observed in this setting. Joint efforts are needed to set out suitable therapeutic interventions in subject failing this regimen.

Table - Efficacy results in 174 INI-resistant HIV-1 failing subjects treated with DTG 50 mg BID plus OBT

DTG 50 mg BID exposure	Number of subjects	Baseline		Last visit			
		HIV-RNA (log_{10}cps/mL)	CD4+ (cells/μL)	HIV-RNA <50 cps/mL	HIV-RNA ≥50 cps/mL	Change in CD4+ among subjects with last VL<50 cps/mL (cells/μL)	Change in CD4+ among subjects with last VL≥50 cps/mL (cells/μL)
≤2 years	118	3.4 (2.6-4.4)	330 (174-587)	81 (69%)	37 (31%)	+80 (+8/+160)	+65 (-13/+151)
>2 to ≤4 years	30	4.0 (3.4-4.9)	336 (122-506)	20 (67%)	10 (33%)	+290 (+119/+415)	+17 (-33/+107)
>4 to ≤6 years	26	4.4 (3.9-5.1)	185 (82-301)	21 (81%)	5 (19%)	+333 (+253/+507)	+86 (-15/+96)

461 VIROLOGICAL RESPONSE TO ANTIRETROVIRAL TREATMENT IN AN EASTERN EUROPEAN COHORT STUDY

Radko Avi, Merit Pauskar, Heli Rajasaar, Eveli Kallas, Ene-Ly Jõgeda, Pilleriin Soodla, Irja Lutsar, Kristi Huik, for the Estonian HIV Positive Patients Database
Univ of Tartu, Tartu, Estonia

Background: Viral suppression (VS) of first line combined ART (cART) ranges from 53–80% in North America and Western Europe. However, corresponding data from Eastern Europe is not available. We evaluated virological response to first line ART and defined factors that influence this response.
Methods: All patients participating in the Estonian HIV cohort study (E-HIV) who initiated cART between 2000 and 2014 were included. Primary VS was achieved if two consecutive viral loads (VLs) were below 400 c/ml after initiation of cART. Virologial failure (VF) was defined by two consecutive VLs over 400 c/ml or a major treatment regimen switch after primary VS. Hazard ratios (HR) were calculated using Cox proportional hazard models or Breslow test as appropriate.
Results: Of a total of 4507 patients in the E-HIV, 3396 (61% men) met the study criteria and were followed-up for a median of 2.4 years; a total of 7890 person-years. Overall, 1325 patients were lost to follow-up. At initiation of cART the median age was 30 years (IQR 26–32), CD4 count 211 (124–230) cells/µl, and VL 4.9 (4.3–4.8) log10 copies/ml. In total, primary VS was achieved in 58% (95% CI:56%–60%) of patients (1967/3396). At months 6, 9, and 12 after cART initiation, VS was achieved in 40% (1363/3396), 46% (1567/3396) and 49% (1667/3396) of patients, respectively. Overall, the VF occurred in 25% of patients (492/1967) - 12% (236/1967), 21% (413/1967) and 24% (472/1967) at year 1, 3, and 5 after VS achievement, respectively. Intravenous drug use (IDU) as the transmission route (adjusted HR [aHR] 0.87, 95% CI:0.76–0.99), higher VL at cART initiation (aHR per log10 0.80, 95% CI:0.77–0.84), earlier calendar year of HIV diagnosis (aHR per year 0.96, 95% CI:0.95–0.97), and HCV seropositivity (aHR 0.73, 95% CI:0.64–0.84) decreased the probability of achieving VS. Female gender and IDU route were associated with an increased risk of VF (aHR 1.84, 95% CI:1.43–2.38, and 1.40, 95% CI:1.04–1.90, respectively), while older age at cART initiation and later calendar year of HIV diagnosis were related to a reduced risk of VF (aHR per year 0.96, 95% CI:0.94–0.97, and aHR per year 0.95, 95% CI:0.91–0.99, respectively).
Conclusion: In the first large cohort study of the Eastern European HIV epidemic, we showed that the overall virological response to cART is comparable to the lower end of rates in Western countries. Our results indicate that special strategies are needed for younger patients, the HCV co-infected, females, and IDUs in order to reduce cART failure.

462 DURABILITY OF NNRTI BASED REGIMENS AFTER 7 YEARS OF TREATMENT IN RURAL UGANDA

Mastula Nanfuka[1], Zishan Cui[2], Stephen Okoboi[1], Josephine Birungi[1], Pontiano Kaleebu[3], Julia Zhu[2], Samuel Tibengana[1], David Moore[4]
[1]The AIDS Support Organization, Kampala, Uganda, [2]BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada, [3]Med Rsr Council, Entebbe, Uganda, [4]Univ of British Columbia, Vancouver, British Columbia, Canada

Background: Most ART programs in low-income countries in Africa have predominantly used NNRTI-based regimens with limited access to routine viral load (VL) testing. For individuals who have maintained long term adherence to first line therapy and have been documented to have a suppressed VL on at least one occasion, it is unknown how frequently treatment failure would arise over the long-term. We measured the incidence of virologically defined failure among individuals who have been successfully treated on first line NNRTI based regimens for nearly seven years in rural Uganda.
Methods: We analyzed data from a prospective cohort study of participants who had been on NNRTI based first line ART for ≥4 years and had a measured VL <1000 copies/mL at enrollment and followed up for an additional three years. All were clients of TASO in Jinja, Uganda. We collected clinical and behavioural data every six months and samples for VL testing were drawn annually. The main outcome of interest was VL > 1000 copies at 36 months after enrollment. We compared factors associated with virologic failure (VF) at 36 months using Wilcoxon Rank Sum, Chi square and Fisher's Exact Test.
Results: We enrolled 503 participants (75.9% females) with a median age of 45years and median duration of ART of 6.8years (Q1-Q3 = 6.0 -7.6 years). A total of 69.0% of participants were receiving nevirapine, lamivudine and zidovudine at enrollment , 22.5% were receiving efavirenz, lamivudine and zidovudine and 8.6% were receiving other regimens. After three additional years of follow up, 3.0% (15) died, 0.6% (3) were lost to follow up, 1.0% (5) voluntarily withdrew. Of the 479 who were followed up for 36 months and with complete information, 2.5% (12) had VL ≥ 1000 copies/mL, of whom 83% (10) had an enrollment VL <50 copies/mL and 1.7% (2) had VL between 50-500 copies. VF was inversely associated with reporting never missing pills (41.7% of failure patients vs. 72.8% non-failure patients p=0.034). There were differences in distribution of the previous ART regimens before enrollment (p=0.005), but there were no clear associations with specific regimens. There was no association between having a VL>50 copies/mL at enrollment and later VF (p=0.160).
Conclusion: Incidence of VF among individuals who had been taking ART for nearly 7 years was very low in the subsequent three years. NNRTI-based regimens appear to be very durable among those with good adherence

463 LONG-TERM VIRAL SUPPRESSION DURING INITIAL ANTIRETROVIRAL THERAPY IN HANOI, VIETNAM

Junko Tanuma[1], Shoko Matsumoto[1], Sebastien Haneuze[2], Cuong Do Duy[3], Thanh Thuy Pham Thi[3], Dung T. Nguyen[4], Kinh V. Nguyen[4], Shinichi Oka[1]
[1]Natl Cntr for Global Hlth and Med, Tokyo, Japan, [2]Harvard Univ, Boston, MA, USA, [3]Bach Mai Hosp, Hanoi, Vietnam, [4]Natl Hosp for Trop Diseases, Hanoi, Vietnam

Background: Achieving viral suppression is key in the global strategy to end the HIV epidemic. However, the levels of viral suppression have yet to be described in many resource-limited settings.
Methods: Analyses were conducted with a longitudinal dataset from a cohort of adult HIV-infected individuals who initiated ART in two large hospitals in urban Hanoi, Vietnam from October 2007 to April 2013 and whose viral load was measured every 6 months until April 2015. The time to treatment failure from ART initiation was analyzed using two endpoints: (1) the virologic failure (VF) defined as having an HIV viral load of ≥1000 copies/mL during first-line ART and (2) a combined clinical endpoint that included death, loss to follow-up, and a change in antiretroviral drugs due to lack of efficacy or identification of VF, whichever occurred first after 6 months of first-line ART. The mean CD4 count and mean CD4 count change trajectories were estimated using linear regression with the outcome as a function of time. Factors related to the time to VF and impaired early immune recovery, which was defined as not attaining an increase of 100 cells/µl in CD4 counts at 24 months, were further analyzed.
Results: In 1806 eligible participants, 225 were identified as having VF with a median of 50 months of first-line ART. The combined clinical endpoint was noted in 313 individuals, which included 225 VFs, 36 deaths, 50 loss to follow-ups, and 2 changes of ART for lack of efficacy. The viral suppression rate at 12 months was 95.5% and 80% for thresholds of 1000 and 50 copies/mL, respectively. The survival without VF was maintained above 90% until 42 months and was 86% at 5 years and 78% at 10 years. The mean change of CD4 count was 155 cells/µl in the first year and 255 cells/µl at 24 months and 164 out of 1013 failed to achieve early immune recovery. A younger age (hazard ratio [HR] 0.75, vs. <30), HCV-antibody positivity (HR 1.43), and d4T-containing regimens (HR 1.4, vs. AZT) were associated with earlier VF. Factors associated with impaired early immune recovery included the male sex (odds ratio [OR] 1.78), HCV-antibody positivity (OR 1.72), d4T-based regimens (OR 0.51, vs. AZT), and NVP-based regimens (OR 0.53, vs. EFV) after controlling for baseline CD4 counts.
Conclusion: Durable high-rate viral suppression was noted in the cohort of patients on initial ART in Vietnam. Our results indicated that the 90% target of viral suppression could be achieved in Vietnam.

464 OUTCOMES AND SIDE EFFECTS OF PATIENTS ON ART FOR MORE THAN 10 YEARS IN MALAWI

Sekai C. Mathabire[1], Alia Tayea[1], Joseph Bitilinyu-Bangoh[2], Elkin H. Bermudez[1], Leon Salumu[3], Isabel A. Quiles[4], Elisabeth Szumilin[3], Zengani Chirwa[5], Fernanda Rick[1], David Maman[6]
[1]MSF France, Chiradzulu, Malawi, [2]Queen Elizabeth Central Hosp, Blantyre, Malawi, [3]MSF France, Paris, France, [4]MSF France, Lilongwe, Malawi, [5]Ministry of Hlth, Malawi, Lilongwe, Malawi, [6]Epicentre, Cape Town, South Africa

Background: With the support of MSF, antiretroviral drugs (ART) have been available in Chiradzulu district, Malawi, since 2001. We conducted a cross-sectional study among individuals on ART for more than 10 years to assess long term clinical, immunological, virological outcomes and prevalence of major side effects.
Methods: Participants from Chiradzulu, on ART for more than 10 years were identified using a routine electronic HIV cohort monitoring database and invited to participate in the cross-sectional study. Following informed consent, individual patient data was collected using a standard questionnaire, clinical examination was conducted and blood was collected for CD4 and viral load tests. The ACTG Brief Peripheral Neuropathy Screening Tool was used to assess peripheral neuropathy.
Results: Of 7,117 patients who initiated ARV in Chiradzulu, between February 2001 and February 2006, 1,405(19.8%) died, 1,508 (21.2%) were lost to follow-up, 1,070(15.0%) transferred out and 3,134 (44.4%) were still alive and followed-up. Of them, 379 were randomly included in the study. They were mostly women (73.1%) and their median age was 47[IQR 42-53]. The median time on ART was 11.6 years (IQR 10.6-12.1) and 344 patients (91%) were on first line/alternative 1st line regimens, mostly on TDF based regimen (86.6%). At the time of the survey, most of the patients were WHO Stage 1 (89.3%; 95%CI 86.6-91.4), had a CD4 count above 500 cells/µL (61.4%; 95%CI 57.8-64.9) and were virally suppressed (92.7%; 95%CI 90.6-94.4). A total 239 patients (63.1%) had a history of ART related toxicities that led to drug changes, with 176 (46.4%) and 53 (14.0%) due to Lipodystrophy and peripheral neuropathy, respectively. Facial atrophy was still common (55.3%) and was higher among those who started with D4T than those who started on AZT regimens (57.4% [95%CI: 52.0-62.6] versus 42.5% [95%CI: 28.3-58.1], p=0.02). Regarding peripheral neuropathy, 35.1% (95%CI 30.5-40.0) had at least one symptom (95%CI 30.5-40.0). Of them, 52.2% (95%CI 44.1-61.1) and 63.5% (95%CI 54.7-71.5) had abnormal reflexes and perceptions of tuning fork vibrations, respectively.
Conclusion: Good clinical and virological outcomes were achieved among those retained in care. Probably due to long exposure to D4T, Lipodystrophy and peripheral neuropathy were common side-effects.

465 INCREASED PERSISTENCE OF INITIAL ART WITH INSTI-CONTAINING REGIMENS

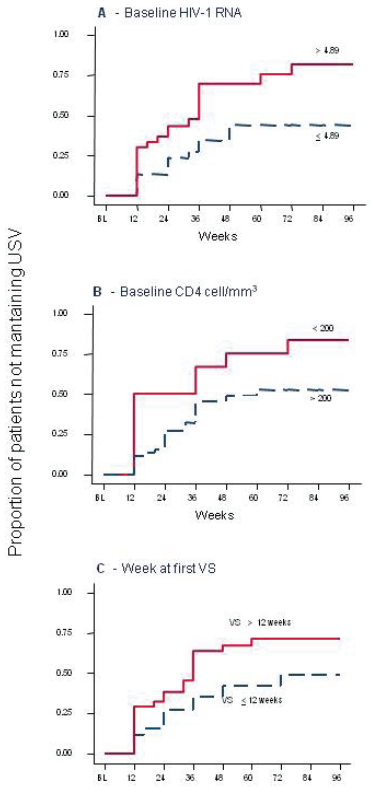
Thibaut Davy, Sonia Napravnik, Oksana Zakharova, Joseph J. Eron
Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: The durability of a first combination antiretroviral (cART) regimen is important to long-term sustained virologic suppression and immunologic recovery and influences treatment selection. In this study we aimed to estimate and compare the durability of the first cART regimen received by antiretroviral-naïve patients from 1996 through 2014.
Methods: All HIV-infected patients participating in the UNC Center for AIDS Research Clinical Cohort (UCHCC) and initiating ART between 1996 and 2014 were included. Separate time-to-event analyses with regimen discontinuation and virologic failure as outcomes were used, including Kaplan-Meier survival curves and Cox proportional hazards models adjusted for baseline age, sex, race, CD4 cell count, HIV RNA level, and calendar year.
Results: The study population comprised 1,624 patients with a median age of 37 years (Interquartile Range [IQR]: 29, 46) at therapy initiation, CD4 cell count of 277 cells/mm3 (IQR: 104, 463), and a majority of African-American (60%) and male (72%) patients. Eleven percent initiated INSTI, 33% NNRTI, 20% bPI, 27% Other, and 9% NRTI-only regimens. Less than half of patients initiating INSTI experienced discontinuation or virologic failure with median times to event greater than 7.4 years for both outcomes; compared to 3.5 years for discontinuation and 5.1 years for virologic failure among patients initiating NNRTI (Figure, both log-rank p<0.01). Compared to NNRTI-containing regimens, INSTI-containing regimens had an adjusted hazard ratio of 0.49 (95% confidence interval, 0.35, 0.69) for discontinuation and 0.70 (95% confidence interval, 0.46, 1.06) for virologic failure. All other regimen types were associated with increased rates of discontinuation and failure compared to NNRTI.
Conclusion: In the last 20 years, new agents with greater potency, safety and tolerability used in first regimens have led to notable increases in the durability of a first regimen. The recent introduction of INSTI based regimens as initial treatment in routine clinical care has led to substantial increases in first line regimen durability and decreased virologic failure.

466 DYNAMICS OF ULTRA-DEEP SUPPRESSED HIV VIREMIA (<5 CP/ML) IN CART-TREATED PATIENTS

Alessandra Amendola, Adriana Ammassari, Assunta Navarra, Giulia Bibbolino, Carmela Pinnetti, Isabella Abbate, Gabriella Rozera, Annalisa Mondi, Enrico Girardi, Maria R. Capobianchi
Natl Inst for Infectious Diseases Lazzaro Spallanzani, Rome, Italy

Background: Residual viremia (RV; <50 c/ml HIV RNA) persists in up to 70-90% patients under successful cART over extended periods. Its role in loss of virologic control is controversial, since it has been found to predict virological rebound in some, but not all studies. Further, RV dynamics are still largely unknown. Our aim was to monitor RV in effectively cART-treated patients for one year after viral suppression (VS; <50 c/ml) to assess the proportion of patients reaching ultra-deep suppressed viremia (USV; <5 c/ml) and the ability to maintain this condition.
Methods: Sixty HIV-infected patients (49 with chronic HIV infection, 11 with primary HIV infection) on first-line cART, reaching and maintaining stable VS, were analysed (M/F 54/6; mean age 36 y; pre-cART median HIV RNA 4.89 log10 c/ml and mean CD4+ 382/mm3). HIV RNA viral load (VL) and RV were measured with standard and ultrasensitive (US) protocols of Abbott Real-Time HIV-1 assay (LLOD: 40 and 5 c/ml, respectively) at baseline (BL), at VS (T0), at month 6 (T1) and 12 (T2) after T0. Cox proportional hazard models were carried out to analyze factors associated with time to first USV and USV maintenance.
Results: Overall, during first year of cART-induced continuous VS, a steady decrease of the median RV occurred: median RV log10 c/ml (IQR) at T0, T1 and T2 were 0.81 (0.40-1.23), 0.39 (0.00-0.78) and 0.18 (0.00-0.068), respectively. A significant difference was found for T0 vs T1 and To vs T2: p<0.0005. All patients achieved USV: 27 (45%) maintained USV throughout the study and, among them, 88.2% showed undetected HIV RNA with US at the end of follow-up. The remaining 33 patients, although with continuous VS, showed fluctuating levels of RV between 5-10 c/ml HIV RNA. Factors associated with the inability to maintain USV were [aHR, 95%IC]: pre-cART higher VL [2.14, 1.23-3.72], pre-cART CD4+ <200/mm3 [3.97, 1.61-9.77], >12 weeks to achieve VS [2.51, 1.07-5.89] (Figure).
Conclusion: After VS on first-line cART, a steady and significant reduction of RV is observed, suggesting progressive purging of viral reservoirs. In almost half of successfully-treated patients, USV is achieved and maintained throughout the first year of continuous VS. Pre-cART lower VL and higher CD4+ cells, together with faster VS achievement, were all associated to USV attainment. Early start of cART and use of potent cART are essential to lower RV and viral reservoirs in HIV-positive patients.



467 SUBOPTIMAL IMMUNE RECOVERY DESPITE SUPPRESSIVE ANTIRETROVIRAL THERAPY IN AFRICA

Stefanie Kroeze[1], Pascale Ondoa[1], Cissy Kityo[2], Margaret Siwale[3], Sonia Boender[1], Peter Reiss[4], Ferdinand Wit[4], Tobias F. Rinke de Wit[1], Raph L. Hamers[1], for the PASER Study Group
[1]Amsterdam Inst for Global Hlth and Development, Amsterdam, Netherlands, [2]Joint Clinical Rsr Cntr, Kampala, Uganda, [3]Lusaka Trust Hosp, Lusake, Zambia, [4]Stichting HIV Monitoring and Academic Med Cntr Amsterdam, Amsterdam, Netherlands

Background: Suboptimal immune recovery (SO-IR), during suppressive antiretroviral therapy (ART), is associated with an increased risk of HIV-related illnesses, but has not been well-documented in African populations. We assessed SO-IR occurrence, defined by failure to attain clinically relevant thresholds of CD4 cell counts, factors associated with SO-IR, and incidence of tuberculosis (TB), AIDS or death during 6 years of ART within a large cohort.
Methods: The Pan-African Studies to Evaluate Resistance (PASER) cohort comprises HIV-1 infected adults from Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe. Participants included in this analysis initiated first-line non-nucleoside reverse transcriptase inhibitor-based ART and had viral load (VL) <50 cps/mL after 1 year. VL testing was done annually. SO-IR was defined as proportions of participants with CD4<200, <350 and <500 cells/µL after 6 years of ART. Participants were censored at death, loss to follow-up, or at their last VL<50 cps/mL (if subsequent VL≥50 cps/mL). Incidence of TB, AIDS, or death was calculated per CD4 category and factors associated with SO-IR were assessed using Cox-regression.
Results: 1,581 participants initiated ART, had VL<50 cps/mL after 12 months, and ≥1 CD4 count available; 61% were women, median age was 37 years (IQR 31-43), and median pre-ART CD4 count was 148 cells/µl (IQR 77-215), with 99% <350 and 70% <200 cells/µL. Total follow-up time was 5245 person-years (PYR). Proportions of SO-IR<200, <350, <500 cells/µL were 7.4, 27.2, 57.6% after 6 years. Per CD4 category <200, 200-350, 350-500 and >500 cells/µl, AIDS incidence was 4.4 (95%CI 3.2-5.6), 1.3 (0.9-2.0), 0.5 (0.2-1.1) and 0.4 (0.2-1.0) events/100PYR; TB incidence 3.3 (2.4-4.6), 0.8 (0.5-1.4), 0.4 (0.2-1.0) and 0.2 (0.1-0.8) events/100PYR; mortality 0.7 (0.4-1.4), 0.5 (0.2-1.0), 0.1 (0.0-0.6) and 0.7 (0.3-1.3)/100PYR. Baseline factors associated with failure to attain CD4≥500 were increasing age, male sex, and pre-ART CD4<200 cells/µL; additionally, subtype A, C or other (compared to D) was associated with failure to attain CD4≥350 and CD4≥200 (table).
Conclusion: SO-IR is frequent in African adults, with the majority not attaining the CD4>500 cells/µL threshold after 6 years of ART. In our cohort, persons with SO-IR had an increased risk of TB and AIDS, but not death. This warrants close clinical and laboratory monitoring and emphasizes the importance of early ART initiation.

468 CURRENT STATIN USE REDUCES RISK OF VIRAL REBOUND ON SUPPRESSIVE CART

Henning J. Drechsler[1], Colby Ayers[2], James Cutrell[1], Naim Maalouf[3], Pablo Tebas[4], Roger Bedimo[1]
[1]VA North Texas Hlth Care Cntr, Dallas, TX, USA, [2]Univ of Texas Southwestern, Dallas, TX, USA, [3]Univ of Texas Southwestern Med Cntr, Dallas, TX, USA, [4]Univ of Pennsylvania, Philadelphia, PA, USA

Background: Pleiotropic effects of statins include improvement of endothelial dysfunction, increased nitric oxide, antioxidant and anti-inflammatory properties, and stabilization of atherosclerotic plaques. Statins are also active against HIV-1 in vitro; however, they have never been shown to have an antiviral effect in clinical studies. Given their short half-lives, a modest virologic effect of statins is difficult to prove during cART and may require the analysis of continuous exposure. We hypothesized that continuous use of statins would increase the durability of successful cART.
Methods: We examined the time to virologic rebound after reaching an undetectable viral load (VL) in all HIV infected US-veterans who started successful cART 1995-2011, had a VL >1000 copies/mL before, and had ≥1 follow up VL within 13 months of reaching undetectability. We defined virologic failure (VF) as any VL >1,000 copies/mL or the first of 2 consecutive VL >200 copies/mL. To address bias by indication and control for adherence, we used pharmacy refill data to build a time-updated drug exposure model for cART, statins, and other cardiovascular drugs (CVMs). We determined ever use, current use, and 30-day use rate [percentage of days covered (PDC)] We used both multiply adjusted and inverse-probability-weighted (IPW) Cox models to explore the association between statin use and VF.
Results: We included 19,324 veterans. Median follow-up until the first viral rebound was 15 months (IQR: 6-40); 55% experienced VF. Almost 1/3 patients ever used statins but exposure was discontinuous with only 41% of follow-up time covered after initial exposure. The unadjusted hazard ratio (HR) for VF for current statin use was 0.60 (95%CI: 0.56-0.65). This association persisted after multivariate adjustment for demographics, HIV and cART parameters [HR 0.81 (CI: 0.75-0.88), p<0.001] and IPW [HR: 0.86 (CI: 0.78-0.96), p=0.001, see Table]. This was not observed for current use of other CVMs. The PDC model yielded similar results (not shown). There was no independent association between ever-statin use and VF.
Conclusion: Current statin exposure reduces the risk of VF in univariate, multivariate and inverse-probability-weighted models suggesting that statins have a modest antiviral activity in vivo. Whether this effect is direct or mediated by their anti-inflammatory properties merits further evaluation. In addition to their cardiovascular benefits, statins could increase the durability of successful antiretroviral therapy.

469 HIV-RELATED PILL AVERSION: CHARACTERIZING A NOVEL BARRIER TO ADHERENCE

Robin Dorman, Sarah H. Sutton, **Lynn M. Yee**
Northwestern Univ, Chicago, IL, USA

Background: Pill aversion, defined as difficulty swallowing pills without identifiable medical cause as well as anxiety associated with pill swallowing, is a poorly-characterized barrier to sustained viral suppression in HIV-infected adults. We aimed to determine the prevalence of pill aversion in an adult outpatient HIV population and describe the relationship between symptoms and skipping pills.
Methods: This was an observational study of HIV-infected individuals at a single urban tertiary care center. Participants attending HIV clinic were asked to complete anonymous questionnaires about their experience of swallowing HAART pills. The primary outcome was skipping pills due to pill aversion symptoms; this was defined as any affirmative response regarding skipping pills due to feeling uncomfortable taking them, problems swallowing them, or pill qualities. Descriptive statistics and bivariable analyses were used as appropriate. Multivariable logistic regression was utilized to determine factors associated with skipping pills.
Results: Of 312 participants (mean age 47.8y), a majority were male (74.8%) and identified as white (48.4%) or non-Hispanic black (NHB; 40.8%). Nearly a quarter (24.8%) skipped pills due to pill aversion symptoms. Younger age, being NHB or Hispanic compared to white and having public insurance were associated with skipping pills due to pill aversion. Depression (27.6%) and anxiety (21.2%) were common and associated with pill aversion on bivariable analyses, but this association did not persist on multivariable analysis. Individuals who skipped pills were more likely to report a detectable viral load (25.7% vs. 8.5%, p=0.001) and have a lower self-reported adherence (79.4% vs. 94.9%, p<0.001). Importantly, participants who skip pills were more likely to report negative or fear-based emotions about their pills (Table). Participants who skipped pills were more likely to report sensations of gagging (13.5% vs 5.0%, p=0.013), choking (9.5% vs 1.8%, p=0.003), pills getting stuck in the throat (24.3% vs 9.0%, p=0.001), a heavy feeling in the stomach (18.9% vs 0.9%, p<0.001), as well as being bothered by the taste, smell, and size of pills (all p<0.001).
Conclusion: HIV-related pill aversion is surprisingly frequent. Symptoms of pill aversion are a significant and novel barrier to adherence in an adult HIV population. Further investigation regarding generalizability, prevalence, and characterization of pill aversion is essential and may have implications for the cascade of care.

470 LONG-TERM EFFECTS OF IMMEDIATE VERSUS DEFERRED C-ART IN PRIMARY HIV INFECTION (PHI)

Kees Brinkman, Sebastian Tawil, Guido van den Berk, Daoud Ait Moha, Willem Blok
OLVG, Amsterdam, Netherlands

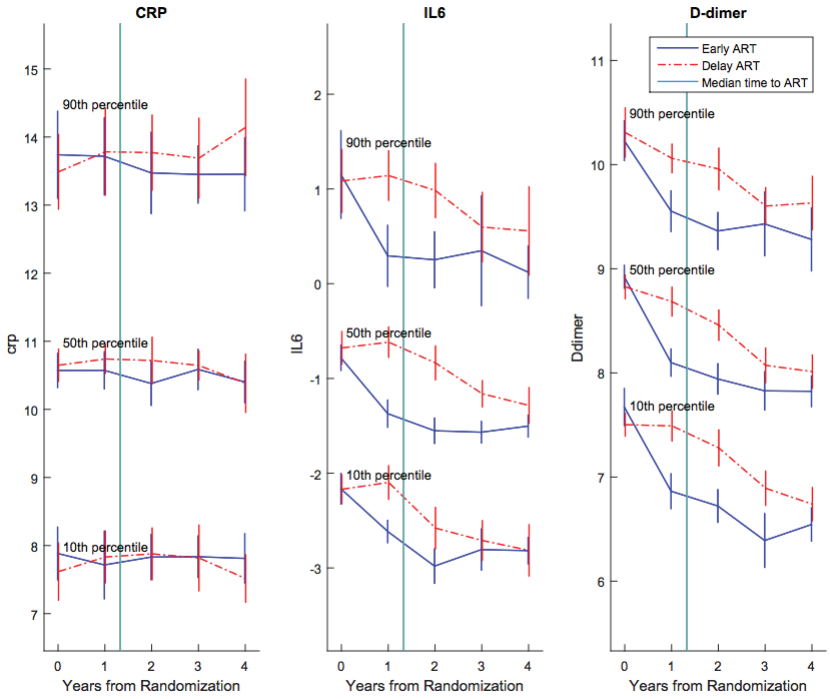
Background: In primary HIV infection Immediate (but transient) cART suggests an immunological benefit over deferred cART; clinical benefits have not been reported. There are no studies on continuous cART in this setting. Here we studied the long-term effects of immediate (continuous) cART on immune recovery, mortality and clinical events in comparison with deferred cART in persons with PHI.

Methods: From 1996 all individuals in the OLVG with a documented hiv seroconversion within 1 year (=PHI) were identified and divided in two groups: immediate cART (initiated < 3 mo. after Dx) versus deferred cART (initiated > 3 mo. after Dx). Differences in outcomes between groups were analysed for the following outcomes: immune recovery at 2, 5, and 10 years after diagnosis (CD4 counts and CD4-CD8 ratios), mortality, AIDS-related events, cardiovascular events and malignancies. Statistical analysis: Fishers Exact, Mann Whitney U test; Kaplan-Meier curves and the log rank test to compare survival curves between groups.
Results: A total of 370 patients with PHI were included: 91 initiated cART within 3 months (median 1 mo., IQR 0-2 mo.)(9 interrupted cART temporarily) and 279 initiated cART after 3 months (median 25 mo., IQR 14-44 mo.). Median follow-up was longer for the deferred group (6 yrs (IQR 4-10)) compared with the immediate group (3 yrs (IQR 2-7)) (p<0,001). No significant differences between groups were found in CD4 and CD4/CD8 ratio at 5 years (median 560.0 cells/mm3 vs. 590.0 cells/mm3, p=0.572; median 0.71 vs. 0.62, p=0.084) and 10 years after diagnosis (median 550.0 cells/mm3 vs. 580.0 cells/mm3, p=0.264; median 0.74 vs. 0.66, p=0.329). Outcome rates (and KM curves) did not differ significantly between groups for mortality (2.2% vs. 5.4%, p=0,261), AIDS-related events (5.5% vs. 9.7%, p=0.218) and cardiovascular events (2.2% vs. 4.3%, p=0.532). A total of 25 malignancies (12 AIDS related; 13 non AIDS related) occurred only in the deferred group and differed therefore significantly with the immediate group (0% v. 9,0%, p=0.003) (Figure). Results remained similar when the 9 interrupters in the immediate group were excluded from the analyses.
Conclusion: Immediate cART provided no benefits over deferred cART in primary HIV infection for immune recovery, mortality, AIDS-related events, and cardiovascular events. However, immediate cART significantly reduced the risk of AIDS-defining and non-AIDS-defining malignancies in this setting.

471 IL-6 AND D-DIMER PREDICT MORTALITY AND ARE ELEVATED AFTER DELAYED HIV TREATMENT

Ashita S. Batavia[1], Myung Hee Lee[1], Patrice Severe[2], Julie Reust[1], Yuan-Shan Zhu[1], Marc Antoine Jean Juste[2], Kathryn Dupnik[1], Jean W. Pape[1], Daniel Fitzgerald[1]
[1]Weill Cornell Med Coll, New York, NY, USA, [2]GHESKIO, Port-au-Prince, Haiti

Background: In HIV-infected individuals nonspecific inflammation is associated with disease progression and increased mortality. The effect of the timing of antiretroviral therapy (ART) in mitigating inflammation at lower CD4 counts is still unclear. We investigated longitudinal trends in C-reactive protein (CRP), interleukin (IL)-6 and D-dimer following delayed ART initiation and identified predictors of mortality.
Methods: CIPRA HT001 was a randomized controlled clinical trial conducted at the GHESKIO Center in Port-au-Prince, Haiti. Between August 2005 and July 2008, 816 HIV-infected adults with CD4 between 200-350 cells/mm3, no prior ART exposure, and no AIDS history were randomized to either early (immediate; N=408) or delayed ART initiation (CD4 ≤200 cells/mm3 or with development of an AIDS-defining condition; N=408). This study is institutional review board approved. Biomarker and HIV-1 RNA levels were measured from banked plasma specimens collected at enrollment and annually. The plasma concentrations of CRP and IL-6 were measured with V-PLEX assay kits (Meso Scale Discovery. Gaithersburg, MD). D-dimer was measured with IMUCLONE D-dimer ELISA kits (Sekisui Diagnostics, LLC, Stamford, CT). HIV-1 RNA levels were assayed using the NucliSens EasyQ HIV-1 PCR Test, v1.2 (BioMérieux, Lyon, France). The 10th, median and 90th percentile biomarker levels were assessed at enrollment and updated annually by treatment group. Cox proportional hazards regression models were used to estimate the risk of all cause mortality from enrollment. Only p-values <0.05 were considered significant.
Results: Figure 1 shows representative percentile curves and 95% confidence intervals for CRP, IL-6 and D-dimer in the early and delayed groups from randomization. The longitudinal trends in IL-6 and D-dimer were significantly different in the early and delayed groups. The observation period was 4853 person-years, with 31 and 51 deaths in early and delayed groups respectively. In multivariate analysis significant enrollment predictors of all cause mortality are log2IL-6 (Hazard ratio, HR, 1.23), log2D-dimer (HR 1.30), log2HIV-1 RNA level (HR 1.69), World Health Organization HIV Clinical Stage 3 (HR 2.22) and randomization to the delayed group (HR 2.08).
Conclusion: Delayed ART initiation is associated with increases in IL-6 and D-dimer that are incompletely reversed with treatment. In multivariate analysis these biomarkers are strong predictors of all-cause mortality



472 EARLY TREATMENT IS LIKELY MORE IMPORTANT THAN PREVIOUSLY THOUGHT

Katherine E. Schlusser[1], Shweta Sharma[2], Julia A. Metcalf[3], Angie N. Pinto[4], Rika Draenert[5], Pola de la Torre[6], Giuseppe Tambussi[7], James Neaton[2], Oliver Laeyendecker[8]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Univ of Minnesota, Minneapolis, MN, USA, [3]NIAIDs, Bethesda, MD, USA, [4]Kirby Inst, Sydney, Australia, [5]Klinikum der Univ Munich, Munich, Germany, [6]Cooper Univ Hosp, Camden, NJ, USA, [7]Ospedale San Raffaele, Milano, Italy, [8]NIAID, Baltimore, MD, USA

Background: The Strategic Timing of Antiretroviral Treatment (START) trial randomized persons with CD4+ >500 cells/μL to immediate or deferred antiretroviral treatment (ART). START demonstrated that early ART for HIV is more beneficial than waiting until CD4+ count drops below 350 cells/μL. We examined whether CD4+ count response differed between those recently infected and those infected for a longer duration.

Methods: START participants were classified into groups by duration of HIV infection (self-report)/diagnosis (documented) at study entry: 1) recently infected (<6 months) by self-report or recently infected using a multi-assay algorithm (MAA) based on serologic markers of early infection (group 1; n=373); 2) diagnosis date <6 months but recent infection not confirmed by MAA or diagnosis date 6-24 months (group 2; n=2,635); or 3) diagnosis date ≥2 years (group 3; n=1,605). Longitudinal regression was used to compare CD4+ count levels during follow-up for the immediate and deferred ART arms by duration of infection. In the deferred arm, time to CD4+ <350 cells/μL or AIDS (threshold for initiating ART) was compared by duration of infection, with and without censoring for ART initiation.

Results: At entry, individuals recently infected (group 1) were younger than those in groups 2 and 3 (31 vs 34 vs 40 (years), p<0.001); and more likely to be MSM (75% vs 59% vs 44%, p<0.001). Those recently infected had a higher median baseline viral load than the other two groups (27199 vs 13550 vs 9744 (copies/mL), p<0.001). The mean CD4+ difference (immediate minus deferred) over follow-up was significantly greater for those in the recent infection group compared to the two other groups (230 vs 202 and 171 cells/μL; p<0.001). Time to CD4+ decline to 350 cells/μL or AIDS was faster among those recently infected compared to those who were not (Figure). Rates for the three groups with ART censoring were 19.7, 16.0, and 11.7 per 100 person-years (p<0.001).

Conclusion: Our results demonstrate that the CD4+ count difference over follow up between the immediate and deferred ART arms was greater among those recently infected. Immediate treatment after HIV infection likely has a greater impact than previously thought, as selection into the START trial required individuals to have two CD4s > 500 cell/μL and those enrolled were less likely to be recently infected and more likely to be individuals with decreased pathogenic progression as measured by CD4+ decline.

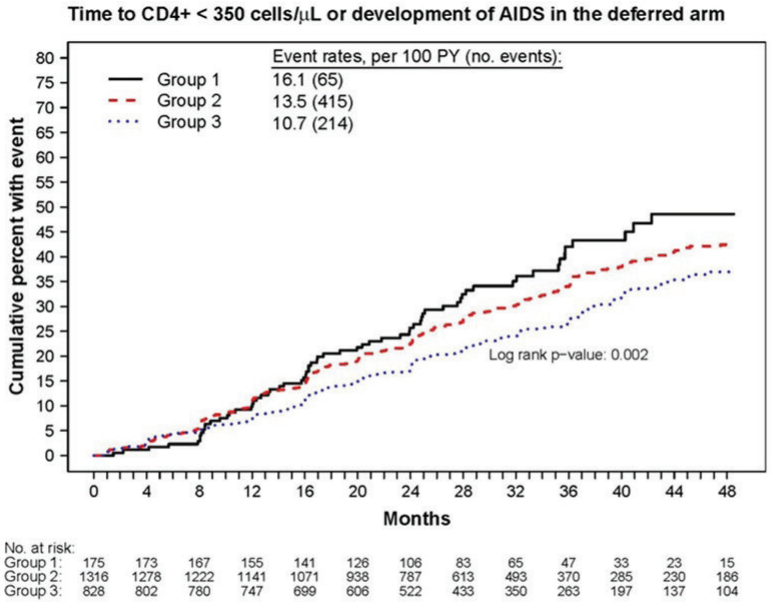


Figure 1. Kaplan-Meier plot for time to CD4+ < 350 cells/μL or AIDS in the deferred arm by duration of infection group. The threshold for initiating ART in the deferred arm was reaching a CD4+ < 350 cells/μL or developing AIDS.

473 ART IN HIV PERSONS WITH PRETREATMENT VIREMIA ≤3000 C/ML: THE START STUDY

Irini Sereti[1], Roy M. Gulick[2], Sonya Krishnan[1], Stephen A. Migueles[1], Adrian Palfreeman[3], Veronique Touzeau-Römer[4], Waldo Belloso[5], Sean Emery[6], Matthew Law[6]
[1]NIAID, Bethesda, MD, USA, [2]Weill Cornell Med, New York, NY, USA, [3]Leicester Royal Infirmary, Leicester, UK, [4]Med Univ of Vienna, Vienna, Austria, [5]Hosp Italiano de Buenos Aires, Buenos Aires, Argentina, [6]Kirby Inst, Sydney, Australia

Background: The benefit of immediate antiretroviral therapy (ART) was established in the strategic timing of antiretroviral treatment (START) study. This benefit was evident across a number of baseline subgroups including plasma viral load (pVL). The aim of this sub-analysis of the START trial was to assess the effects of immediate versus deferred ART on CD4+ count and pVL during follow-up, outcomes for which there is greater power, among participants with pVL ≤3000 c/mL (lowest quartile). This is an important subgroup due to their low risk of clinical outcomes.

Methods: Participants with pre-ART pVL ≤3000c/mL were included in this sub-analysis provided they had no current or previous history of ART use (N=1138 including 347 with pVL≤400c/mL and 94 with pVL≤50 c/mL). All analyses were ITT. We compared immediate (Imm) with deferred (Def) ART in terms of the CD4 cell count and pVL results at study time points.

Results: Participants with pVL≤3000c/mL had a pre-ART median age of 37 years and 40% were female. 4% of participants were HCV antibody + and 3% were HBsAg+. The median CD4 cell count was 714 cells/μL (IQR 617, 854) and median pVL was 971 c/mL (IQR 293, 1830). 538 out of 557 (97%) in the Imm arm started ART at a median of 6 days (IQR 1, 14) and 168 out of 581 (29%) in the Def arm at a median of 694 days (IQR 396, 1033) after randomization respectively. Primary endpoints were observed in 11 (0.67 per 100 person years) and 12 (0.72 per 100 person years) participants in the Imm and Def arms respectively (hazard ratio=0.92, 95% confidence interval 0.41 to 2.08). Mean CD4 counts and percentage of participants with pVL≤200 c/mL and >3000 c/mL by randomization arm at 12 and 24 months are shown in Table 1. The mean CD4 count difference between treatment arms at 12 months was 126 cells/μL (95% confidence interval 94 to 157).

Conclusion: In this sub-analysis of START participants with pre-treatment pVL <3000 c/mL randomized to Imm vs Def ART. The Imm ART group had higher CD4 cell counts and greater suppressed viremia during follow-up. The clinical benefits of these differences will require long-term follow-up.

Table 1. Mean CD4 cell counts and percentage participants with pVL≤200 c/mL and >3000 c/mL by randomization arm at 12 and 24 months.

	Immediate		Deferred	
	N	Mean (SD)	N	Mean (SD)
Month 12	517	821 (269)	540	696 (247)
Month 24	433	874 (275)	434	670 (241)

	Immediate			Deferred		
	N	%≤200	%>3,000 c/mL	N	%≤200	%>3000 c/mL
Month 12	516	93%	3%	538	22%	32%
Month 24	432	95%	1%	433	29%	34%

474 BENEFIT OF CONTINUOUS/IMMEDIATE ART ON DISEASE RISK: SMART & START COMBINED ANALYSIS

Álvaro H. Borges[1], Jacqueline Neuhaus[2], Shweta Sharma[2], James Neaton[2], Keith Henry[3], Olga Anagnostou[4], Therese Staub[5], Sean Emery[6], Jens D. Lundgren[1], for the INSIGHT SMART & START Study Groups

[1]RigsHosp, Copenhagen, Denmark, [2]Univ of Minnesota, Minneapolis, MN, USA, [3]Hennepin County Med Cntr, Minneapolis, MN, USA, [4]Univ of Athens, Athens, Greece, [5]Cntr Hosp de Luxembourg, Luxembourg, Luxembourg, [6]Kirby Inst, Sydney, Australia

Background: The SMART and START trials established continuous/immediate ART as the standard of care for HIV+ persons. The CD4 difference between treatment groups during follow-up in each trial was approximately 200 cells/μL. We hypothesized that treatment hazard ratios (HRs) were similar in each trial and the pooled analysis of the two studies would better estimate the effect of continuous/immediate ART on disease risk.

Methods: The drug conservation arm in SMART and the deferred ART arm in START were pooled as the "immune impairment group" (IIG) and the viral suppression arm in SMART and the early ART arm in START as "immune preservation group" (IPG). Endpoints assessed were AIDS or AIDS-death (AIDS), serious non-AIDS or non-AIDS-death (SNA), cardiovascular disease (CVD), cancer, and all-cause death. HRs from Cox models were obtained for IIG vs IPG for each study and heterogeneity assessed. For the pooled cohort we 1) obtained estimated HRs, 2) assessed mediators of IPG benefit from models adjusting for baseline demographics, CVD and cancer risk factors, and time-updated CD4 and HIV RNA, and 3) performed subgroup analyses based on baseline demographics, CVD and cancer risk factors, CD4 count and geographical region.

Results: Among 10157 participants (median age 40y; 27% female; 51% MSM; median baseline CD4 634 cells/μL; 37% smokers), there were 123 AIDS, 244 SNA, 117 cancers, 103 CVD, 118 deaths, and 359 AIDS or SNA. Nadir median CD4 counts in SMART and START were 250 and 553 cells/μL, respectively. HRs for endpoints were similar for both trials without evidence of heterogeneity (Figure). Unadjusted pooled HRs (95% CI) of IIG vs IPG were for AIDS 3.60 (2.35, 5.51); SNA 1.59 (1.23-2.06); CVD 1.60 (1.07-2.37); cancer 1.86 (1.27-2.72); death 1.82 (1.25-2.65), and AIDS or SNA 2.03 (1.63-2.53). Adjustment for time-updated CD4 and HIV RNA attenuated the pooled HRs for SNA (1.35, 1.00-1.82) and death (1.21, 0.78-1.87). IIG was consistently associated with increased risk of the various endpoints across all subgroups investigated (interaction p>0.1), except that the risk of cancer associated with IIG was higher among those ≤ 35 years (HR 3.16 vs 1.86, interaction p=0.05).

Conclusion: Continuous/immediate ART use reduced the risk of AIDS and SNA events among HIV+ persons consistently in SMART and START despite a difference in nadir CD4 count of 300 cells/μL. Pooled treatment differences were similar across a number of subgroups except for age and cancer risk.

475 NO PER-PATIENT COST INCREASE UNDER IMMEDIATE ART FOR ALL: EVIDENCE FROM SWAZILAND

Shaukat Khan[1], Emma Mafara[1], Pascal Geldsetzer[2], Salinda Phanitsiri[3], Cebele Wong[1], Charlotte Lejeune[1], Fiona Walsh[3], Velephi Okello[4], Till Baernighausen[5]

[1]Clinton Hlth Access Initiative, Mbabane, Swaziland, [2]Harvard Univ, Boston, MA, USA, [3]Clinton Hlth Access Initiative, Boston, MA, USA, [4]Swaziland Ministry of Hlth, Mbabane, Swaziland, [5]Heidelberg Univ, Heidelberg, Germany

Background: Swaziland has one of the highest adult HIV prevalence rates (26%) worldwide. As Swaziland and many other countries in sub-Saharan Africa are moving to universal test-and-treat (UTT), or Early Access to ART for All (EAAA), policies, it is critical to understand the cost implications of this change to inform long-term financial planning. The study presented here is one of the first empirical costing study of EAAA in a public-sector health setting. We compare average patient costs under standard-of-care (SOC) vs. under EAAA.

Methods: From September 2014 through July 2016, we collected comprehensive data on facility-level ART costs from 7 facilities prior to and after transitioning to EAAA as part of a large-scale randomized stepped-wedge health systems trial of EAAA. We used a "bottom-up costing" approach extracting data from facility budgets, expenditure reports, and patient records. SOC ART eligibility threshold was ≤350 cells/ml until December 2015, when it changed to ≤500 cells/ml. We used an activity-based allocation method for costs shared with non-ART patients. The costs include medications, laboratory services, direct and indirect personnel, equipment and administrative services. Total costs were divided by the total number of ART patient-years over the period the facility experienced SOC and EAAA to derive ART cost per patient per year (PPPY).

Results: The average facility-level cost for ART patients was $277 PPPY (95%CI: 184-371) in SOC compared to $254 PPPY (95%CI: 209-298) in EAAA (p=0.66). The cost of ARVs was $113 PPPY (95%CI: 111-116) in SOC and $110 PPPY (95%CI: 108-112) in EAAA (p=0.04). The personnel costs were $130 PPPY (95%CI: 43-217) in SOC and $96 PPPY (95%CI: 51-141) in EAAA (p=0.51). Laboratory costs were $22 PPPY (95%CI: 11-33) in SOC and $37 PPPY (95%CI: 29-44) in EAAA (p=0.05).

Conclusion: We present the first direct comparison of public-sector patient costs under EAAA and SOC. Even though we would expect ART patients under EAAA to be on average healthier than patients under SOC, average public-sector costs per ART patient are essentially the same under the two treatment policies. Differences in funding requirements for SOC vs. EAAA will thus be largely driven by the number of patients receiving treatment. The larger average laboratory costs in EAAA were explained by increased uptake of viral load monitoring.

Table1: Cost of Treatment per Patient-Year by facility ($USD)

	Standard of Care[a] Cost per patient per year ($USD) (Simple Mean[b] ± SE)	Early Access to ART Cost per patient per year ($USD) (Simple Mean ± SE)	p value[g]
Total Cost	**$277.48 ± 47.60**	**$253.65 ± 22.60**	**p=0.66**
ARV[c]	$113.47 ± 1.17	$109.72 ± 1.12	p=0.04
Personnel[d]	$130.22 ± 44.42	$96.39 ± 22.97	p=0.51
Lab[e]	$21.87 ± 5.58	$36.70 ± 3.83	p=0.05
Other[f]	$11.92 ± 2.16	$10.84 ± 1.53	p=0.69

[a]Standard of Care was CD4≤350 cells/ml till Dec 31st, 2015 when it changed to CD4≤500 cells/ml. 6 facilities transitioned before guideline change while last facility transitioned on Jan 1st, 2016

[b]Simple mean calculated across facilities in the sample

[c]ARV costs does not include cost of delivery to the facility

[d]Direct and indirect personnel costs are included

[e]Lab costs include consumables and reagents

[f]Other costs include building, equipment, training, and Opportunstic infections

[g]student t-test

476 COST-EFFECTIVENESS AND BUDGET IMPACT OF IMMEDIATE ART INITIATION IN CÔTE D'IVOIRE

Eric N. Ouattara[1], Rachel L. MacLean[2], Christine DANEL[3], Ethan D. Borre[2], DELPHINE GABILLARD[3], Mingshu Huang[2], A. David Paltiel[4], xavier anglaret[3], Serge EHOLIE[5], Kenneth Freedberg[2]

[1]Prog PAC-CI, ANRS Rsr site, Abidjan, Cote d'Ivoire, [2]Massachusetts General Hosp, Boston, MA, USA, [3]INSERM, Bordeaux, France, [4]Yale Univ, New Haven, CT, USA, [5]Service des Maladies Infectieuses et Tropes, Abidjan, Côte d'Ivoire

Background: In 2015, the Temprano and START trials provided evidence supporting early ART initiation, prompting the WHO to recommend ART at diagnosis for HIV-infected persons. Our objective was to project the clinical and economic outcomes, cost-effectiveness, and 5yr budget impact of immediate ART initiation in Côte d'Ivoire, the setting of Temprano.

Methods: We used a mathematical model of HIV (CEPAC-I), informed by the Temprano trial, to assess three ART initiation criteria in Côte d'Ivoire: 1) CD4 count <350/μL; 2) CD4 count <500/μL; and 3) Immediate ART. We reported outcomes from the payor perspective for the entire HIV-infected population currently in care in Côte d'Ivoire (All-in-care, mean CD4 259/μL; 170,000 persons) and for only those in care with CD4 counts >500 cells/μL (>500/μL-in-care, mean CD4: 666/uL; 22,000 persons). We assumed viral load-dependent transmission rates (0.16-9.03/100PY). ART 48-week efficacy was 80% and adherence-dependent loss to follow-up rates were 1.9-13%/month. 1st- and 2nd-line ART costs were $122 and $391/year. Outcomes included transmitted HIV cases, life expectancy in life-years (LY), 10yr incremental cost-effectiveness ratios (ICERs), and 5yr budget impact. We labeled a strategy "cost-effective" if its ICER, in $/year of life saved (YLS), was less than the annual per capita GDP in Côte d'Ivoire ($1,530). We conducted extensive sensitivity analyses to assess the impact of parameter uncertainty on our findings.

Results: For All-in-care, Immediate ART decreased 10-year transmissions from 93,900 to 84,800 (-9.7%) compared to ART<350/μL and increased life expectancy by 17,000 LYs over 10 years, yielding an ICER of $300/YLS (<0.25x per capita GDP). Immediate ART increased total 5yr costs from $515.5M to $523.4M (+1.4%) compared to ART<350/μL. Increasing mean CD4 at linkage to care to 500/μl and varying transmission rates over their 95% confidence interval, the 5yr cost difference for Immediate ART compared to ART<350/μL ranged from -11.1% to +3.1%. For the >500/μL-in-care, Immediate ART was cost-saving over 10yr, with small increases in 5yr costs (+2.3%). Cost-effectiveness and budget impact findings were most sensitive to 1st-line ART cost.

Conclusion: In Côte d'Ivoire, Immediate ART compared to later initiation reduces HIV transmissions, increases survival, and is very cost-effective, all with modest increase in program costs. Immediate ART initiation should be the standard of care in Côte d'Ivoire and similar settings.

Table 1. Outcomes of comparing different ART initiation strategies for HIV-infected patients in Côte d'Ivoire: Cost-effectiveness and budget impact analyses*

	Transmission	Cost-effectiveness			Budget impact over 5 years	
	Transmissions caused, 10yr	Total costs ($M), 10yr†	Total life years, 10yr‡	ICER, 10yr ($/YLS)	Total costs ($M)	Budget change % ($)§
All-in-care (CD4 at linkage: 259/μL (SD: 196), n=170,000)						
ART<350/μL (SOC)	93,900	757.4	1,373,000	---	515.5	---
ART<500/μL	88,300	762.2	1,385,000	Dom	520.6	+1.0 (4.9M)
Immediate ART	84,800	763.3	1,390,000	300	523.4	+1.5 (7.9M)
>500/μL-in-care (CD4 at linkage: 666/μL (SD: 160), n=22,000)						
ART<350/μL (SOC)	10,500	120.7	198,000	Dom	74.0	--
ART<500/μL	8,900	120.9	201,300	Dom	75.3	+1.8 (1.3M)
Immediate ART	7,400	119.3	203,600	Cost-saving	75.7	+2.3 (1.7M)

Abbreviations: yr: year; M: million; ICER: incremental cost-effectiveness ratio; ART: antiretroviral therapy; YLS: year of life saved; Dom: dominated - more costly and less effective than some combination of other strategies; SOC: standard of care

*All results are reported as undiscounted, except for cost-effectiveness results which are discounted at 3%/year.

†Cumulative costs include all costs from transmitted cases.

‡Cumulative survival for all prevalent and transmitted cases.

§Budget change is relative to standard of care (*ART<350/μL*) and from the payer perspective.

477 CORRELATES OF DRUG RESISTANCE MUTATIONS IN ART-NAÏVE INDIVIDUALS WITH HIV INFECTION

Sarah E. Porter[1], Ellsworth Campbell[1], Emily Westheimer[2], Cynthia L. Gay[3], Stephanie E. Cohen[4], Anupama Shankar[1], Jin-Fen Li[1], Jeffrey A. Johnson[1], William M. Switzer[1], Philip J. Peters[1]
[1]CDC, Atlanta, GA, USA, [2]New York City DHMH, New York, NY, USA, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]San Francisco Dept of Pub Hlth, San Francisco, CA, USA

Background: Testing for HIV transmitted drug resistance mutations (TDRM) is recommended for persons with newly diagnosed HIV infection to aid selection of antiretroviral therapy (ART). In order to assess the potential of drug resistance testing to inform public health interventions, we evaluated the correlates of TDRM in ART-naïve patients using data from a multi-state study of acute HIV infection conducted between 2011 and 2013.
Methods: This analysis included 539 of 1326 (44%) HIV-positive study participants with available genotypic HIV drug resistance results and first HIV-positive test ≤91 days prior to study enrollment. A diagnostic testing algorithm was used to classify all infections as acute HIV infection (AHI) or established HIV infection (EHI), and 499 (93%) participants were interviewed about HIV risk behaviors. HIV transmission clusters were identified through genetic distance-based cluster analysis of HIV-1 polymerase sequences. We used logistic regression to assess correlation of TDRM in NRTI, NNRTI, or PI classes with AHI, cluster size, and HIV risk behaviors. Results are reported as odds ratios adjusted for study site and demographic factors (aOR) and 95% confidence intervals (CI).
Results: The characteristics of individuals in the analysis were: median age 30 years, 95% male, 83% men who have sex with men, and race/ethnicity distribution was 35% white, 32% black, and 20% Hispanic. Overall, 129 (24%) individuals had acute HIV infection, and 135 (25%) were part of a transmission cluster with ≥2 participants. NNRTI class resistance was most common (12%), followed by resistance to NRTI (6%) and PI (4%) classes. TDRM was found in 20% (95% CI: 13-27%) of AHI and in 17% (95% CI: 13-21%) of EHI (aOR: 1.0, 95% CI 0.6-1.8). Persons in transmission clusters with ≥3 individuals were more likely to have TDRM compared to those with fewer genetic links (aOR: 2.5, 95% CI 1.3-4.8). We found no association between TDRM and sex with an HIV-positive partner in the study (aOR: 0.8, 95% CI: 0.4-1.4), meeting a sex partner online (aOR: 0.9, 95% CI 0.5-1.6), or reporting ≥10 sex partners in the past 12 months (aOR: 1.6, 95% CI 0.8-2.9).
Conclusion: Among ART-naïve HIV-positive individuals, persons within larger transmission clusters had a higher risk of TDRM in our analysis. We found no association between TDRM and AHI or the HIV risk behaviors we assessed. Enhanced partner services may be warranted for persons with TDRM to improve HIV case finding, particularly for those with drug-resistant HIV infection.

478 HIV INTEGRASE GENOTYPIC TESTING AND RESISTANCE IN THE UNITED STATES—9 JURISDICTIONS

Angela L. Hernandez[1], M. Cheryl B. Ocfemia[1], Neeraja Saduvala[2], Alexandra Oster[1], Walid Heneine[1], Jeffrey A. Johnson[1], Irene Hall[1]
[1]CDC, Atlanta, GA, USA, [2]ICF Intl, Atlanta, GA, USA

Background: In 2016, national drug resistance testing guidelines were updated to recommend providers include integrase (IN) genotypic testing at entry into HIV care if transmitted resistance to integrase strand transfer inhibitors (INSTI) is a concern. We used National HIV Surveillance System (NHSS) data to assess the prevalence of IN genotypic testing and INSTI-associated resistance.
Methods: We analyzed HIV-1 sequences from persons with HIV infection diagnosed through 2014 and reported to NHSS by December 2015 from 9 surveillance jurisdictions (Colorado, Connecticut, California [Los Angeles County], Michigan, New York, Philadelphia, South Carolina, Texas, and Washington). We describe (1) overall prevalence and timing of IN genotypic tests after HIV diagnosis (≤3 months and >3 months) by sex, age, race/ethnicity, transmission category, stage of HIV disease, population of area of residence at diagnosis, and antiretroviral use (ARV) at diagnosis, and (2) prevalence of INSTI-resistant associated mutations using the updated CDC HIV-1 surveillance mutation list.
Results: We analyzed 14,468 IN sequences; 7,107 (49%) sequences were IN only. IN genotypic testing was more common among males, persons aged 20-29 years, blacks; by transmission category, more common among males with HIV infection attributed to male-to-male sexual contact, heterosexual females, persons who were not stage 3 of HIV disease (AIDS), and persons residing in areas with a population of >500,000. Prevalence of INSTI-resistant mutations among all IN sequences was extremely low (65/14,468; 0.4%). Of these, the most prevalent mutations were N155H (38%), followed by E92Q (29%) and G140S (25%). IN genotypic testing was performed ≤3 months after diagnosis for 5,240 (36%) persons, of which 4,631 (88%) had no evidence of ARV use; 2 (0.04%) had transmitted INSTI-associated resistance (N155H [100%]; E92Q [50%]).
Conclusion: INSTI-resistant mutations are rare and indicate that current INSTI-based regimens remain effective. A majority of genotypic testing for resistance to INSTIs occurs more than 3 months of HIV diagnosis likely after initiation of antiretroviral therapy. NHSS provides the opportunity to monitor IN genotypic testing and prevalence of INSTI-associated resistance at a population level.

479 PREDICTORS OF HIV GENOTYPE TESTING AMONG NEW DIAGNOSES LINKED TO CARE IN PHILADELPHIA

Melissa Miller, Tanner Nassau, Makeda Carroll, Coleman Terrell, Kathleen Brady
Philadelphia Dept of Pub Hlth, Philadelphia, PA, USA

Background: Genotypic testing (GT) is recommended by Public Health Service treatment guidelines and used as part of routine HIV surveillance to assess trends in HIV drug resistance and transmission patterns. Despite increasing rates of linkage to care (LTC), GT ≤90 days post diagnosis remains stable around 50%. This analysis aims to identify and address barriers to timely GT among persons who have successfully LTC.
Methods: Data were extracted from Philadelphia's Enhanced HIV/AIDS Reporting System on individuals aged >18+ newly diagnosed with HIV from 2013-2015 and LTC within 90 days of diagnosis. LTC was defined as having a viral load (VL) or CD4 < 90 days after diagnosis. Multivariable logistic regression models predicted timely GT, defined as GT < 90 days of diagnosis. Models were adjusted for race, sex at birth, age at diagnosis, exposure category, type of diagnosing facility (testing/linkage site, outpatient medical facility, inpatient facility, correctional facility, other), year of diagnosis, insurance status, concurrent HIV/AIDS diagnosis, LTC within 30 days, and viral suppression (VS, defined as a VL <200 copies/ml at the last measure in the year after diagnosis).
Results: 1,383 Philadelphia residents that LTC < 90 days of diagnosis were included in the analysis. Of these, 56% received timely GT. New diagnoses aged 45+ were less likely to have evidence of timely GT compared to diagnoses aged 18-24 (AOR, 0.6; 95% CI:0.4-0.8). Those diagnosed at correctional facilities (AOR,0.4; 95% CI:0.2-0.7), inpatient facilities (AOR, 0.5; 95% CI:0.3-0.8), and outpatient medical facilities (AOR, 0.6; 95% CI:0.4-0.9) were all less likely to have timely GT compared to those diagnosed at testing and linkage sites. Individuals without insurance at diagnosis were 45% less likely to have timely GT compared to privately insured individuals (AOR, 0.5; 95%CI:0.4-0.8) Individuals who achieved VS within 1 year post diagnosis were 1.6 times as likely to have received timely GT as those who did not (95%CI:1.3-2.0).
Conclusion: Our data show poor adherence to recommendations for baseline GT in persons newly diagnosed with HIV. Timely GT is critical in improving long term care outcomes and in creating local transmission networks that provide entry points for intervention to reduce new HIV infections, both in keeping with National HIV/AIDS Strategy efforts. Age, insurance status, diagnosing facility, and VS are all factors that should be considered when targeting efforts to increase GT at the patient and provider level.

480 PRETREATMENT DRUG-RESISTANCE INCREASE IN 3 FOCAL POINTS OF MEXICO, 2012–2015

Claudia García-Morales[1], Santiago Avila-Rios[1], Daniela Tapia-Trejo[1], Verónica S. Quiroz-Morales[1], Samuel Navarro[2], Carlos A. Barrera-Arellano[3], Jesús Casillas-Rodríguez[4], Akio Murakami-Ogasawara[1], Gustavo Reyes-Terán[1], for the HIV MexNet Group
[1]Natl Inst of Respiratory Diseases, Mexico City, Mexico, [2]Hosp General Tijuana, Tijuana, Baja California, USA, [3]Capasits Cancún, Cancún, Quintana Roo, Mexico, [4]Clínica Especializada Condesa, Mexico City, Mexico

Background: Pre-treatment drug resistance (PDR) is a concern for the management of HIV infection, with several low- and middle-income countries recently reporting levels of HIVDR above 10% amongst antiretroviral treatment (ART) naïve individuals. In Mexico, a nationally representative survey estimated a 16% PDR level in 2015. Following up on this study, we longitudinally assessed HIV PDR in three focal points of the Mexican HIV epidemic.

Methods: HIV-infected ART-naïve individuals were recruited from 2008 to 2015: 589 from Tijuana, 1,142 from the central Metropolitan Zone (MZ), including Mexico City and the State of Mexico, and 547 from Cancun. Plasma HIV pol sequences were obtained. PDR was estimated using the Stanford HIVdb tool (v.7.0).
Results: From 2012 to 2015, the overall PDR was 13.5% (95%, CI 10.7%-16.7%) in Tijuana, 14.9% (95%, CI 12.0%-18.2%) in Cancun and 16% (95%, CI 12.9%-19.4%) in the MZ. PDR to NNRTI was higher than to NRTI and PI in the MZ (10.6%) and Cancun (7.9%) ($p<0.05$), but not in Tijuana (5.7%) ($p>0.05$). No differences in overall or drug class-specific PDR were observed between the geographic zones. An increasing trend in overall PDR was observed in the MZ from 2008 to 2015 (10.2% to 16.1%, p=0.04), particularly associated with increasing PDR to NNRTI (3.6% to 12.3%, p=0.0072). Aditionally, PDR to TDF+FTC+EFV, the most widely used ART regimen in Mexico, significantly increased in this region (2.2% to 10.7%, p=0.0022), with PDR to EFV increasing from 0.6% to 10.0% (p=0.0011). Cancun also showed an increasing trend in PDR to NNRTI (4.7% to 13.3%, p=0.0167), TDF+FTC+EFV (6.3% to 13.3%, p=0.0167), and EFV (3.2% to 11.1%, p=0.0048) from 2012 to 2015. Similarly, Tijuana showed an increasing trend in overall PDR (11.6% to 17.5%, p=0.0167), but not to NNRTI. K103N was the most frequent DR mutation in the MZ (4.4%) and Cancun (4.2%), but not in Tijuana (1.4%). Clusters of drug-resistant viruses mostly from males were observed in the MZ. The proportion of females in clusters increased in Tijuana and to a lesser extent in Cancun.
Conclusion: HIV PDR significantly increased in the three focal points, but PDR showed zone-specific characteristics. NNRTI PDR significantly increased in Cancun and the MZ, but not in Tijuana. Importantly, PDR to the most widely used ART regimen in Mexico reached levels over 10% in Cancun and the MZ warranting immediate programmatic actions. Our observations also underscore the importance of implementing sub-national PDR surveys.

481 HIV DRUG RESISTANCE: A UNIQUE PERSPECTIVE ACROSS 4 AFRICAN COUNTRIES

Brook Danboise[1], Christina Polyak[1], Alex Kasembeli[2], Samoel Khamadi[3], Babajide Keshinro Keshinro[4], Hannah Kibuuka[5], John Owuoth[6], Sheila A. Peel[1], Julie Ake[1], Trevor Crowell[1]
[1]US Military HIV Rsr Prog, Bethesda, MD, USA, [2]Walter Reed Proj–Kericho, Kericho, Kenya, [3]Walter Reed Prog–Tanzania, Mbeya, Tanzania, United Republic of, [4]Walter Reed Prog–Nigeria, Abuja, Nigeria, [5]Makerere Univ Walter Reed Proj, Kampala, Uganda, [6]Walter Reed Proj, Kisumu, Kenya

Background: The World Health Organization (WHO) has identified HIV drug resistance (HIVDR) as a significant threat to ending the AIDS pandemic and has called for increased surveillance for drug resistance. We evaluated HIVDR patterns among participants with and without a history of antiretroviral therapy (ART) in the prospective, multinational African Cohort Study (AFRICOS).
Methods: AFRICOS enrolls adults at 11 PEPFAR-supported facilities in Uganda, Kenya, Tanzania, and Nigeria. At enrollment, all HIV-infected participants with viral load ≥1000 copies/mL receive HIVDR testing with pol subtype. We tallied mutations classified as conferring high-level or low-level resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) according to the Stanford HIVDB 7.0.1 and SmartGene IDNS software. For participants with no history of ART use, WHO surveillance drug resistance mutations (SDRMs) were also noted.
Results: From 21 January 2013 to 9 December 2015, 1915 HIV-infected participants enrolled in AFRICOS. Of these, 746 had a viral load ≥ 1000 copies/mL and 253 had baseline HIVDR testing results available for inclusion in this analysis. Ninety-four (37%) were male and the median age of participants was 35 (interquartile range 28-41) years. One hundred eighty-eight (74.3%) participants were ART-naïve and 65 (25.7%) were ART-experienced at enrollment. Table 1 summarizes HIVDR for ART-naïve and ART-experienced participants in each country and the overall cohort. SDRMs among ART-naïve participants were rare (10/188, 5.3%), with K103N as the most frequent major mutation (8/188, 4.3%). HIVDR among ART-experienced participants was mostly driven by mutations conferring resistance to NRTIs (29/65, 44.6%) and NNRTIs (42/65, 64.6%), including a 10.8% rate of K65R. PI resistance was noted but uncommon (4/65, 6.2%).
Conclusion: The prevalence of SDRMs among ART-naïve participants was low in Uganda and Nigeria, whereas moderate rates in Kenya and Tanzania suggest the need for evaluation of clinics, educational efforts and screening programs. Continued surveillance will inform local guidelines about HIVDR testing prior to ART initiation. Among ART-experienced participants, NRTI and NNRTI mutations were common, particularly in Kenya, Tanzania and Nigeria. Although currently uncommon, emerging resistance to PIs in these countries may eventually limit the effectiveness of current empiric second-line therapy.

Table 1. Summary of Drug Resistance in AFRICOS: Major Resistance to Drug Classes and Key Mutations among Participants with HIV RNA ≥1000 copies/mL at enrollment

	Uganda	Kenya	Tanzania	Nigeria	Total
ART-Naïve Participants	(n=75)	(n=24)	(n=58)	(n=31)	(n=188)
Any SDRM	3 (4.0)	1 (4.2)	5 (8.6)	1 (3.2)	10 (5.3)
Any NRTI Resistance	0 (0.0)	0 (0.0)	0 (0.0)	3 (9.7)	3 (1.6)
K65R	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
M184V/I	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)	1 (0.5)
M41L	0 (0.0)	0 (4.2)	0 (0.0)	1(3.2)	1 (0.5)
Any NNRTI Resistance	7 (9.3)	1 (4.2)	11 (19.0)	3 (9.7)	22 (11.7)
K103N	3 (4.0)	1 (4.2)	4 (6.9)	0 (0.0)	8 (4.3)
Y181C	1 (1.3)	0 (0.0)	1 (1.7)	0 (0.0)	2 (1.1)
Any PI Resistance	1 (1.3)	2 (8.3)	10 (17.2)	0 (0.0)	13 (6.9)
ART-Experienced Participants	(n=16)	(n=13)	(n=17)	(n=19)	(n=65)
Any NRTI Resistance	2 (12.5)	8 (61.5)	10 (58.8)	9 (47.4)	29 (44.6)
K65R	0 (0.0)	2 (15.4)	1 (5.9)	4 (21.1)	7 (10.8)
M184V/I	2 (12.5)	8 (61.5)	10 (58.8)	6 (31.6)	26 (40.0)
M41L	0 (0.0)	1 (7.7)	3 (17.6)	1 (5.3)	5 (7.7)
Any NNRTI Resistance	5 (31.3)	10 (76.9)	14 (82.4)	13 (68.4)	42 (64.6)
K103N	1 (6.3)	6 (46.2)	7 (41.2)	8 (42.1)	22 (33.8)
Y181C	0 (0.0)	2 (15.4)	4 (23.5)	2 (10.5)	8 (12.3)
Any PI Resistance	0 (0.0)	1 (7.7)	2 (11.8)	1 (5.3)	4 (6.2)

Abbreviations: ART, antiretroviral therapy; SDRM, World Health Organization surveillance drug resistance mutation; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

482 HIV PRETREATMENT DRUG RESISTANCE IN CAMEROON: FIRST NATIONWIDE STUDY

Gaëlle F. Tchouwa[1], Jenny Domyeum[1], Sabrina Eymard-Duvernay[2], Amandine Cournil[2], Eric Delaporte[2], Martine Peeters[2], Elliot Raizes[3], Eitel Mpoudi-Ngole[1], Avelin F. Aghokeng[4]
[1]CREMER, Yaoundé, Cameroon, [2]Univ de Montpellier, Montpellier, France, Montpellier, France, [3]CDC, Atlanta, GA, USA, [4]IRD, Yaoundé, Cameroon

Background: The ongoing scale-up of antiretroviral treatment (ART) in sub-Saharan Africa has now moved to a new era with the recent WHO recommendations to test and immediately treat HIV-positive individuals. Pre-treatment drug resistance (PDR) may significantly compromise ART efficacy if high PDR frequency is found for common first-line antiretrovirals (ARVs). We present here the first nationally-representative PDR study conducted in Cameroon, West Africa.
Methods: We adapted the recently published WHO PDR protocol to the situation of Cameroon. HIV-infected individuals eligible for first-line ART initiation as per national recommendations were recruited from 24 clinics that were randomly selected in urban and rural regions. Recruitments were conducted during a period of six months, from February to July 2015, and the dried blood spot specimens (DBS) collected were centralized in a WHO-accredited laboratory in Yaoundé, Cameroon, for genotyping and sequencing. HIV drug resistance (HIVDR) mutations were identified using the Stanford algorithm.
Results: Overall, 379 participants were recruited and 335 pol sequences were successfully obtained. Two hundred and eighteen sequences were from patients attending urban ART sites and 117 from patients seen at rural facilities. Ten percent (32/335) were from participants with reported previous exposure to ARVs, through PMTCT intervention or ART. PDR frequency among all initiators was 9.7% (95% CI: 6.6-14.2%) overall, 13.3% (8.3-20.4%) in urban regions and 4.1% (1.7-9.5%) in rural regions. Among participants with no

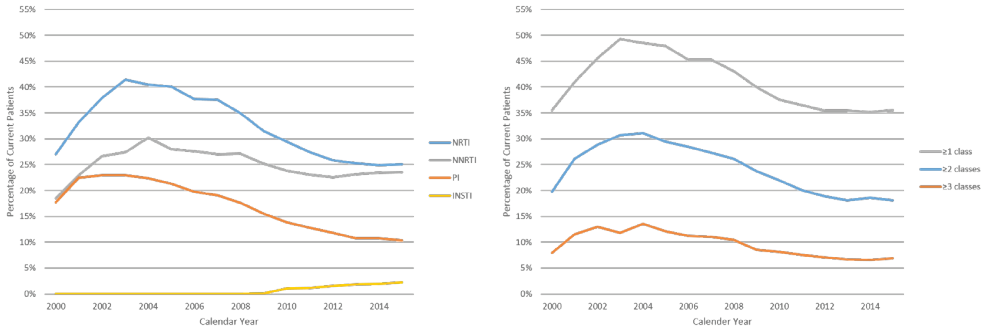
prior exposure to ARVs, PDR frequency was 9.8% (6.2-15.1%) overall, and 12.9% (7.5-21.2%) and 5.1% (2.1-11.7%) in urban and rural regions, respectively. Ninety-three percent of major PDR mutations were NNRTI mutations, essentially K103N and Y181C, and only a few (<3%) major NRTI and PI mutations were found.
Conclusion: Our study is the first nationwide evaluation of PDR in Cameroon and indicates that 10% of patients initiating the first-line ART carry a mutated virus and may be at risk of premature treatment failure. Before implementing the test and treat strategy in Cameroon as recommended by WHO, interventions to prevent HIVDR must be urgently implemented, especially in urban regions where higher levels of PDR prevalence were observed.

483 LOW PREVALENCE OF HIV DRUG RESISTANCE WITH MODERN AGENTS

Thibaut Davy, Laurence Brunet, Sonia Napravnik, Oksana Zakharova, Ann M. Dennis, Joseph J. Eron
Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: Resistance to antiretrovirals limits the impact of potent combination therapy. The resistance profile of patients has evolved with the introduction of new drugs. In this study, we estimated the annual prevalence of cumulative HIV drug resistance between 2000 and 2015 by drug class and year of ART initiation.
Methods: We included ART-experienced patients in the UNC CFAR HIV Clinical Cohort (UCHCC) with at least 1 HIV RNA viral load between 2000 and 2015. For each year, we calculated the prevalence of total drug resistance burden by class. We examined mutations associated with reduced susceptibility based on the 2015 IAS-USA guidelines. Resistance profile was imputed for years when genotype testing had not been performed. Patients with viral load ≤ 1000 and no prior resistance detected were assumed to have no resistance, while the resistance profile of those with a viral load > 1000 after 90 days of ART was multiply imputed using age, sex, race, HIV risk factor, CD4 cell count, HIV RNA and initial ART regimen. Prevalence time trends were tested using linear regression with year as the predictor. The prevalence of resistance burden was also estimated in a subgroup analysis of patients initiating ART in 2007 or later.
Results: The study population comprised 3,681 patients who were 71% male, 60% African-American, 41% men who have sex with men, and 13% injection drug users. Of all participants, 2,234 (61%) had at least 1 viral load > 1000 after 90 days of ART, and 2,301 (63%) had at least 1 genotype test performed. The prevalence of resistance to NRTIs, NNRTIs, any drug class, and 2 or more classes increased between 2000 and 2005 and subsequently decreased until the end of the study period (Figure, all $p<0.05$). The prevalence of resistance to PIs and to 3 or more classes remained stable between 2000 and 2005 ($p=0.34$ and 0.13, respectively) but decreased in the following years (both $p<0.01$). The prevalence of INSTI resistance increased slightly between 2009 and 2015 but remained low ($p<0.01$). Among 685 patients initiating ART in 2007 or later, the 2015 resistance prevalence was 21% for any class (95% CI 17%, 24%), 17% for NNRTIs (14%, 20%), 6% for NRTIs (4%, 8%), 2% for PIs (1%, 4%), 1% for INSTIs (0%, 2%), 5% for 2 or more classes (3%, 7%), and 1% for 3 or more classes (0%, 2%).
Conclusion: The prevalence of drug resistance has declined in the last decade and is very low for patients who initiated antiretroviral therapy in the modern treatment era. Little resistance to INSTI agents has emerged.

Figure. Prevalence of cumulative drug resistance by class and multi-class, 2000-2015



484 LOW PREVALENCE OF NRTI, NNRTI, AND PI DRUG RESISTANCE MUTATIONS IN BOTSWANA

Sikhulile Moyo[1], Simani Gaseitsiwe[1], Melissa Zahralban-Steele[2], Dorcas Maruapula[1], Phillimon P. Sebogodi[1], Madisa Mine[3], Elliot Raizes[4], Shahin Lockman[2], Max Essex[2], Vlad Novitsky[2]
[1]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, [2]Harvard Univ, Boston, MA, [3]Natl Hlth Lab, Gaborone, Botswana, [4]CDC, Atlanta, GA, USA

Background: Monitoring of HIV-1 drug resistance is essential in the era of expanded access to antiretroviral treatment. This study aimed to survey the population prevalence of HIV-1 mutations associated with resistance to nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) in a cohort of HIV-1 clade C-infected patients in Botswana.
Methods: Blood samples were collected from HIV-positive participants in the Botswana Combination Prevention Project (BCPP) who reside in 15 communities, predominantly in the southern region of Botswana. A long-range HIV genotyping protocol was applied. Both viral RNA and proviral DNA templates were used for amplification, as the majority of participants were receiving ART. NRTI, NNRTI and PI resistance mutations were analyzed according to the WHO 2009 and IAS-USA 2015 lists. All viral sequences were screened for G-to-A hypermutations (HM). Mutations in sequences with adjusted HM rate above the 3rd quartile of the subset of viral sequences without mutations were considered to be generated by HM, and were not counted toward drug-resistant mutations. Viral suppression was considered at HIV-1 RNA 400 copies/mL.
Results: The majority of genotyped individuals, 413 of 665 (62.1%; 95% CI 58.3–65.8%), were receiving ART and 405 (60.9%; 95% CI 57.1–64.6%) had undetectable HIV-1 RNA 400 copies/mL. Among individuals on ART who were virologically suppressed (n=391), NRTI-, NNRTI- and PI-associated mutation were found in 2.8%, 4.1% and 1.3%, respectively. Among individuals on ART who were not suppressed (n=20), NRTI-, NNRTI- and PI-associated mutation were found in 25%, 25% and 0%, respectively. Among HIV-infected individuals not on ART (n=221), NRTI-, NNRTI- and PI-associated mutation were found in 1.8%, 3,2% and 0%, respectively. The overall distribution of specific mutations to 3 classes of drugs are presented in the Table.
Conclusion: This is the first large surveillance for the prevalence of NRTI, NNRTI and PI resistance mutations on a population level in Botswana. The low prevalence of primary and secondary resistance mutations supports the rationale for a treat-all strategy as the national policy in Botswana. HM analysis and proviral DNA amplification is critical for surveillance in the era of highly suppressive ART scale-up.

NRTI mutations		NNRTI mutations		PI mutations	
M41L	0.46%	K101E	0.76%	M46I/L	0.46%
K65R	0.15%	K103N/S	2.59%	I54V	0.30%
D67N	0.46%	V106M	0.46%	G73S	0.15%
K70R/E	0.61%	Y181C/I	0.61%	L76V	0.15%
Y115F	0.15%	Y188L/C	0.61%	V82A	0.30%
M184V/I	1.67%	G190A/S/E	0.91%	I85V	0.15%
T215Y/I/S	0.61%	P225H	0.15%	N88S	0.15%
K219E	0.15%				

485 ARV RESISTANCE MUTATIONS IN PATIENTS RECEIVING A WHO TDF-CONTAINING 1ST-LINE REGIMEN

Soo-Yon Rhee[1], John Gregson[2], Ravindra K. Gupta[3], Robert Shafer[1], for the TenoRes Study Group
[1]Stanford Univ, Stanford, CA, USA, [2]London Sch of Hygiene and Trop Med, London, UK, [3]Univ Coll London, London, UK

Background: TDF has replaced thymidine analogs (TAs) as the preferred NRTI for the initial treatment of HIV in LMICs. However, few data are available on the NRTI drug resistance mutations (DRMs) associated with virological failure (VF) in pts receiving TDF-containing 1st-line regimens in such settings.
Methods: We assembled sequences from 2,233 pts with VF on a 1st-line regimen of TDF + 3TC/FTC + NVP/EFV that included 1,573 sequences from the TenoRes collaboration and 660 sequences from recently published studies. 61% of pts were from a LMIC; 39% from an UIC. Virus load (VL) was available at VF in 61% of pts. 247 sequences with >=1 canonical TA mutation (TAM) were excluded. We compared the proportions of mutations in TDF pts with those in 50,801 ARV-naïve pts to identify significant TDF regimen-associated mutations (TRAMs) following adjustment for multiple comparisons and subtype composition. We then compared the proportion of each TRAM in TDF pts with its proportion in 7,283 pts receiving a TA-containing 1st-line regimen and assessed the association of TRAMs with VL at time of VF.
Results: We identified 78 TRAMs including 31 NRTI-TRAMs, 39 NNRTI-TRAMs, and 8 novel mutations. The 31 NRTI-TRAMs included 16 established NRTI DRMs (62V, 65RN, 69del, 70EQTN, 74VI, 75MIL, 115F, 184VI), 10 mutations at 5 positions previously associated with NRTI therapy (68GDN, 69I, 88SC, 165LV, 228RQ), and 5 non-canonical TAMs (67G, 203K, 218E, 219NR). Ten NRTI-TRAMs (62V, 65RN, 68GN, 70EQN, 74I, 115F, 184I) and 2 NNRTI-TRAMs (100I, 190E) were more common in the TDF compared to the TA pts. The most strongly correlated TRAM pairs were 65R-62V, 65R-68GN, 65R-184V, and 70E-228R. 65R was positively correlated with 70T but negatively correlated with 70QE. In a univariate analysis, being from an LMIC, 3TC use, non-B subtype, no. of NRTI-TRAMs, no. of NNRTI-TRAMs, 65R, 184V, and 70EQNT were associated with an increased VL. In a multivariate analysis, being from an LMIC ($p<1e-6$) and no. of NNRTI-TRAMs ($p<1e-6$) remained associated with an increased VL.
Conclusion: TDF-containing 1st-line regimens select for many RT mutations of which 39 are associated with NNRTIs and 31 with NRTIs. The spectrum of NRTI-TRAMs extends beyond 65R to also include 62V, 65N, 68GDN, 69del, 70EQTN, 74I, and 115F. VL was associated with being from an LMIC and the no. of NNRTI-TRAMs.

486 VIRAL SUPPRESSION AND ACQUIRED HIV DRUG RESISTANCE IN CAMEROON: A NATIONWIDE STUDY

Gaëlle F. Tchouwa[1], Jenny Domyeum[1], Sabrina Eymard-Duvernay[2], Amandine Cournil[2], Eric Delaporte[2], Martine Peeters[2], Eitel Mpoudi-Ngole[1], Elliot Raizes[3], **Avelin F. Aghokeng**[4]
[1]CREMER, Yaoundé, Cameroon, [2]Univ de Montpellier, Montpellier, France, [3]CDC, Atlanta, GA, USA, [4]IRD, Yaoundé, Cameroon

Background: Acquired HIV drug resistance (ADR) can significantly compromise antiretroviral treatment (ART) efficacy. In resource-limited countries where decision to treat or to switch treatment is mostly based on clinical assessment and access to virological monitoring is still limited, population-based studies on viral load suppression and HIV drug resistance (HIVDR) rates could inform programs. We present here the first nationally-representative ADR study in Cameroon.
Methods: We adapted the protocol from the recently published WHO generic ADR protocol. Eligible participants were patients on ART for 12 to 24 months (ADR1) or 48 to 60 months (ADR2). ADR1 participants were recruited in 25 clinics that were randomly selected in urban and rural regions. ADR2 participants were from 7 urban clinics. Recruitment was from February to August 2015 and collected dried blood spots (DBS) and plasma specimens were sent to a WHO accredited laboratory in Yaoundé, Cameroon for viral load (VL) testing and genotyping. Specimens with VL≥1000 copies/ml were considered for HIVDR genotyping and drug resistance mutations were identified using the Stanford algorithm.
Results: Overall, 1052 ADR1 and 387 ADR2 participants were recruited. Women predominated, representing 76% and 74% of patients in each group, respectively. Median ages were 39 (32-47) years and 42 (35-51) years in the ADR1 and ADR2 groups, respectively. Almost all participants were on first-line ART, predominantly TDF+3TC+EFV/NVP, and only 2% of ADR1 and 6% of ADR2 were receiving PI-based drugs. Viral suppression in the ADR1 group was 72.0% (95% CI: 70.3-73.7) overall, 74.9% (73.2-76.6) in urban sites and 67.7% (63.3-71.7) in rural sites. In the ADR2 group, viral suppression was 67.5% (62.9-71.7). HIVDR was identified in 66.6% (60.6-72.1) of ADR1 patients with VL≥1000 copies/ml, 63.1% (56.3-69.4) and 72.5% (58.1-83.4) in urban and rural sites, respectively. In the ADR2 group, HIVDR frequency was 83.6% (67.3-92.6) in participants with VL≥1000 copies/ml.
Conclusion: This study represents the first nationwide assessment of virological failure and HIVDR frequency in West Africa. Results indicates that important efforts will be required to achieve the 2020 UNAIDS target of 90% viral suppression. Better ART management is urgently needed, and should focus on preventing drug stock-outs, reduction in lost to follow-up, improved access to VL testing and clinical use of the VL results.

487 HIGH HIV DRUG RESISTANCE OF FIRST-LINE ART TREATMENT IN BENIN PEDIATRIC POPULATION

Djeneba Bocar Fofana[1], Marcelline d'Almeida[2], Pierre-Marie Girard[1], Bernabé Lafia[3], Sidonie Lambert[1], Lutecia Zohoun-Guidigbi[2], Rene Keke[4], Cathia Soulie[5], Anne-Geneviève Marcelin[5], **Laurence Morand-Joubert**[1]
[1]Saint-Antoine Hosp, Paris, France, [2]Univ d'Abomey–Calavi, Benin, [3]CNHU–HKM, Cotonou, Benin, [4]Reference Lab of the Natl Cntr for the Treatment of HIV, Cotonou, Benin, [5]Pitie-Salpetriere Hosp, Paris, France

Background: In recent years, the pediatric Highly Active Antiretroviral Therapy (HAART) has shown enormous progress in Africa. However, a high percentage of children continue to experience treatment failure. In Benin (West Africa), there are currently no data on human immunodeficiency virus drug resistance (HIVDR) in pediatric populations. This study aimed to assess the prevalence of HIVDR among children with continued virological ART failures in this country.
Methods: Dried blood spots from sixty two HIV-infected children were collected at clinical pediatric of national hospital center in Cotonou between April and September of 2015. These were children with at least two detectable viral loads during treatment. Reverse transcriptase, protease and integrase genes were amplified, sequenced, analyzed for the presence of HIV drug resistance and interpreted according to the latest version of the National Agency for HIV and Hepatitis Research algorithm. Demographic data and treatment received were collected.
Results: The characteristics of the population show a median age of 10 years (IQR 6 - 13), a median duration on ART of 5 years (IQR 3-7), and a median HIV-1 RNA level of 54000 copies/mL (IQR 5543 - 170000 copies/mL). We observed a very few diversity of HIV in this population of CRF02_AG at 82%. At treatment failure, 92% of patients were on first-line

with an ART combination of two, NRTIs (zidovudine or abacavir and lamivudine) and one non-NRTI (nevirapine or efavirenz) or PI-based regimen (lopinavir/ritonavir). Only 8% of the patients were on second line. Of thefifty one sequences amplified. NRTIs, non-NRTI, and dual-class resistance was present in 71%, 84% and 65%, respectively. The proportion of patients with intermediate resistance to TDF (tenofovir) and ETR (etravirine) and RPV (rilpivirine) was, 24%, 42% and 36%, respectively. None major mutations of resistance to PI observed, except two children who presented resistance to all drugs with a low sensibility to darunavir. None of the children had major mutation of resistance to Integrase Inhibitors

Conclusion: Our results had shown that the development of drug resistance could be one of the main consequences of high and continuous viral replication in children in Benin. Thus, the inadequate attention in monitoring lifelong ART in children can prevent to achieve the goal of viral suppression by 90% of UNAIDS.

488 DRUG-RESISTANT HIV-1 DURING LONG-TERM SECOND-LINE ANTIRETROVIRAL TREATMENT IN KENYA

Seth Inzaule[1], Raph L. Hamers[1], Irene Mukui[2], Kennedy Were[3], Preston Owiti[3], Daniel Kwaro[3], Tobias R. de Wit[1], Clement Zeh[4]
[1]Academic Med Cntr of the Univ of Amsterdam, Amsterdam, Netherlands, [2]Natl AIDS and STI Control Prog, Nairobi, Kenya, [3]Kenya Med Rsr Inst, Kisumu, Kenya, [4]US CDC, Kisumu, Kenya

Background: We performed a nationwide assessment of HIV drug resistance (HIVDR) among patients with virological failure (VF) on 2nd-line boosted-protease-inhibitor (PI)-based antiretroviral therapy (ART) in Kenya, and predicted susceptibility to WHO-recommended 3rd-line regimens.

Methods: We included all patients who were referred for HIVDR testing from facilities in western Kenya (2010-2012) and nationally (2013-2015). VF was defined as either two sequential viral loads (VL)>1000 cps/ml or immunological failure plus confirmatory VL>1000 cps/ml. We performed Sanger pol sequencing, scored drug resistance mutations (DRMs) with the IAS-USA list, and assigned genotypic susceptibility scores (GSS) based on the Stanford algorithm. GSS of WHO-recommended 1st, 2nd and 3rd-line regimens were calculated as the arithmetic sum of the individual-drug GSS, with GSS<2 considered complete loss of activity to the available drug options. Factors associated with PI-resistance were assessed using multivariable logistic regression.

Results: Of 126 patients, 123 viral isolates were successfully genotyped. Median age and CD4 counts were 24 (IQR 10-36) years and 114.5 (IQR 24-251) cells/μL respectively. Mean VL was 4.8 (SD0.1) log10 cps/mL. Prior median ART duration was 6.4 (IQR 4.3-8.1) years, of which 3.1 (1.9-4.6) on 2nd-line. 119 (97%) patients were on lopinavir/ritonavir-based 2nd-line. 111 (82%) of patients had ≥1 DRM, of whom 77 (63%) to nucleoside reverse-transcriptase inhibitors (NRTIs) (63 M184V, 51%; 46 ≥1 thymidine analogue mutations (TAMs), 37%; 8 K65R, 7%; 7 L74I, 6%; 6 Y115F, 5%; 2 each for F116Y, Q151M and T69i, 2%) and 39 (31%) to PIs (29 M46I/L, 24%; 27 I54V, 22%; 24 V82A/T/F/S, 20%; 11 L76V, 9%; 7 each for Q58E and L74S, 6%; 4 I84V, 3%; 3 I50V, 2.4%, 2 each for N83D and V32I, 2%; 1 D30N, 1%). 28 (23%) patients had GSS<2 for all 1st and 2nd-line drugs. Factors associated with PI-resistance were high VL at failure, presence of >4NRTI mutations and >1 TAMS. For 3rd-line regimens, probability of GSS≥2 was highest if boosted-darunavir plus integrase inhibitor was combined with etravirine (0.70), followed by AZT+3TC (0.61, p=0.219), TDF+3TC (0.55, p=0.102), 3TC/FTC (0.48, p=0.04), ABC (0.48, p=0.04), TDF (0.42, p=0.013), AZT (0.39, p=0.04) (Figure)

Conclusion: 1 in 4 Kenyans failing 2nd-line ART may have completely exhausted the available 1st and 2nd-line regimens, highlighting the need for increased access to 3rd-line regimens.

489 ELIMINATING DRUG RESISTANCE IN SOUTH AFRICA BY USING DOLUTEGRAVIR

Katie Sharp[1], Thibault Mesplede[2], Mark A. Wainberg[2], Sally Blower[1]
[1]Univ of California, Los Angeles, Los Angeles, CA, USA, [2]McGill Univ, Montreal, Quebec, Canada

Background: Approximately 6.2 million individuals are living with HIV infection in South Africa, where only half are receiving antiretroviral treatment. The non-nucleoside reverse transcriptase inhibitor Efaverinz (EFV) has been widely used in first-line therapies since 2007, which has led to high levels of acquired and transmitted resistance; the predominant mutation being K103N. Testing for resistance strains in South Africa is seldom offered upon virological failure. In resource-rich countries, Dolutegravir (DTG) a new integrase inhibitor, has replaced EFV in first-line regimens. DTG has the highest clinical barrier against resistance of any antiretroviral, however it can occasionally lead to the mutation R263K if used in second-line therapies. We model the impact of (i) introducing resistance testing upon HIV diagnosis and during treatment, and (ii) switching first-line treatment from EFV to DTG, on reducing HIV drug resistance in South Africa.

Methods: We use a transmission model, parameterized with epidemiologic data from South Africa to reconstruct treatment history, including acquired and transmitted resistance. We conduct an uncertainty analysis using Latin Hypercube Sampling and a multivariate sensitivity analysis based on response hypersurface modeling. Input variables are treatment rates for different CD4-stages of infection, drug adherence/efficacy and the frequency of testing for resistance.

Results: If current treatment conditions are maintained, incidence will decrease from 300,000 in 2016 to 170,000 in 2030, but the number of individuals with the K103N mutation will increase to 1,400,000. Introducing resistance testing will prevent 330,000 new K103N infections by 2030 (pink curve). Introducing testing and switching to DTG will prevent 860,000 new K103N infections (blue curve) and also ~1,200,000 cases of acquired resistance. Notably, only a small number of individuals with the R263K mutation will be seen by 2030, and DTG will prevent the greatest number of new infections compared to current conditions and introducing testing.

Conclusion: Introducing resistance testing into South Africa will substantially reduce the transmission of drug resistant strains, but have no effect on acquired resistance. Introducing testing and switching to DTG-based first-line therapies, reduces TDR even further and essentially prevents the development of acquired resistance, indicating that DTG has the potential to eliminate drug resistance in South Africa.

490 IMPACT OF PRETREATMENT HIV-DRUG RESISTANCE ON VIROLOGIC OUTCOME OF FIRST-LINE ART

Ingrid A Beck[1], Molly Levine[1], Ross Milne[1], Isaac So[1], Nina Andersen[1], Michael Watling[2], Michael H. Chung[2], James Munyao[3], Catherine Kiptinness[4], Lisa Frenkel[2]
[1]Seattle Children's Rsr Inst, Seattle, WA, USA, [2]Univ of Washington, Seattle, WA, USA, [3]Coptic Hope Cntr, Nairobi, Kenya, [4]Univ of Washington, Nairobi, Kenya

Background: Pre-treatment HIV-drug resistance (PDR) to WHO-recommended 1st-line antiretroviral treatment (ART) is increasing in low-resource communities. Data on the risk that specific PDR mutations confer for virologic failure (VF) of ART could inform policy makers in their management of HIV resistance. We assessed the risk that PDR at single or multiple codons conferred for VF during EFV- or NVP-based ART.

Methods: Kenyans initiating 1st-line ART within studies in 2006, 2010 and 2014 were evaluated for PDR mutations K103N, Y181C, G190A, M184V and K65R by an oligonucleotide ligation assay (OLA) sensitive to 2% mutant within a subject's viral population. Consensus sequencing and 454-pyrosequencing or Illumina assays confirmed OLA results in those with PDR and/or VF. VF was defined as plasma viral load ≥ 400 HIV RNA copies/mL at month-12 of NNRTI-ART. Rates of VF at month-12 were compared (Fisher's exact) between ART regimens and between mutants and wild-type (WT) genotypes during EFV- or NVP-based ART.

Results: A total of 1228 individuals given NNRTI-ART had month-12 virologic outcome and PDR data for mutations K103N, Y181C, G190A and M184V, and a subset of 922 for K65R. 30/518 (5.8%) subjects on EFV-ART had VF compared to 97/710 (13.7%) on NVP-ART (p<0.0001). PDR was detected in 63/1228 (5.1%) individuals; among these, 23.8% (5/21) given EFV-ART had VF vs. 69% (29/42) given NVP-ART (p=0.001). No VF was observed in subjects with low frequency mutants (2-9%) in the EFV-ART group (0/5) compared to 63.6% (7/11) in the NVP-ART group (p=0.034). Among subjects with PDR, single NNRTI mutations were detected in 39 (61.9%), single NRTI mutations in 3 (4.8%), and multiple NNRTI/NRTI mutations in 21 (33.3%). In subjects given NVP-ART, those with single or multiple mutations had higher rates of VF compared to those with WT genotype (p<0.0001). In contrast, in subjects given EFV-ART, those with multiple mutations had increased rates of VF compared to those with WT (p=0.003), but those with a single NNRTI mutation had rates of VF similar to those with WT HIV (p=0.165) (Fig 1).

Conclusion: The lower rate of VF among subjects receiving EFV-ART compared to NVP-ART, regardless of whether infected with WT or DR HIV, emphasizes the greater potency of EFV-ART. A lower risk of VF conferred by single NNRTI mutations during EFV-ART suggests that use of assays to detect and manage PDR could maximize viral suppression and extend the use of EFV-ART in low-resource settings.

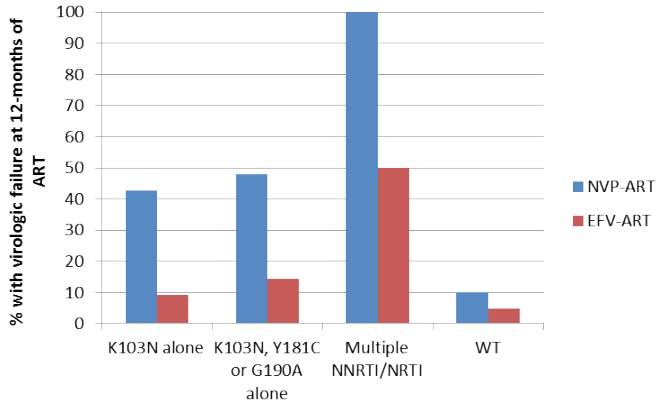


Figure 1. Virologic failure at 12 months of NVP- vs. EFV-ART by HIV drug resistance mutations detected by OLA

491 RESPONSE TO FIRST-LINE ART IN ADULTS WITH DRUG RESISTANT HIV, ANRS 12249 TASP TRIAL

Collins C. Iwuji[1], Anne Derache[2], Kathy Baisley[3], Siva Danaviah[4], Tulio de Oliveira[5], François Dabis[6], Kholoud Porter[1], Deenan Pillay[2], for the ANRS 12249 TasP Study Group
[1]Univ Coll London, London, UK, [2]Africa Hlth Rsr Inst, Mtubatuba, South Africa, [3]London Sch of Hygiene and Trop Med, London, UK, [4]Africa Cntr for Pop Heath, Mtubatuba, South Africa, [5]Univ of KwaZulu-Natal, Durban, South Africa, [6]Univ de Bordeaux, Bordeaux, France

Background: Mathematical models suggest that high levels of transmitted drug resistance (TDR) could compromise ART programmes. We assessed the impact of pre-treatment drug resistance (PDR) on viral suppression (VS) [viral load [VL] <400 copies/mL] in adults who initiated 1st-line ART within the cluster randomised TasP trial in rural KwaZulu-Natal
Methods: HIV-positive adults enrolled from March 2012–June 2016 and initiated ART with VL data available were eligible. HIV whole genome sequences (WGS) were generated on Illumina MiSeq in recently-infected (RIn) adults with available plasma samples and chronically-infected (CIn) ART-naïve adults. WGS were assembled using Geneious software; a 2% threshold was used to assess minority drug resistant variants defined as representing <20% of the viral population. TDR was assessed using the WHO 2009 list of mutations. Cox regression was used to estimate hazard ratios. Adherence was measured by visual analogue scale
Results: 921 (854/1064 CIn (81%); 67/81 (83%) RIn) of 1,145 adults with sequences initiated ART. 838 (783/854 CIn (92%); 55/67 RIn (82%)) had follow up VL and contributed to the analysis. Median age was 35 years (y) (IQR 28, 47) in CIn and 27 y (23, 38) in RIn; 71% and 84% were female, respectively; 97% were on fixed dose combination of tenofovir/emtricitabine/efavirenz. In RIn, the prevalence of any TDR was 14.6%(95%CI 8.3-24.2) in majority virus and 23.6%(95% CI 15.2-34.9) in minority virus. In CIn, PDR prevalence was 8.8%(7.2-10.7) and 18.7%(16.2-21.3) in majority and minority virus, respectively. The K103N mutation was the most common in majority and minority viruses. Cumulative suppression at 12 months (m) was 97%. Median time to VS was 2.96m (IQR 2.76-3.94). After adjusting for sex, age, baseline VL and adherence, there was no evidence that PDR was associated with VL suppression (adjusted (a)HR 0.96, 95%CI 0.75-1.23 and aHR=1.12, 95%CI 0.89-1.42, for majority virus and minority virus, respectively, vs no mutations). High baseline VL (>100,000 vs <10,000) was associated with a decreased rate of VS (aHR 0.75; 0.62-0.91) and good adherence (≥95% vs <95%) was associated with an increased rate of VS (aHR 1.36; 1.11-1.66)
Conclusion: The prevalence of TDR is above the WHO threshold of 5% in this rural South African setting. With local guidelines recommending test and treat, strengthening early warning TDR indicators is required. However, our data suggest the clinical impact of this may be limited, if adherence to current 1st-line ART is good

492 ASSOCIATION BETWEEN HIV DRUG RESISTANCE AND BASELINE FAILURE IN THE ACTG PEARLS STUDY

Rami Kantor[1], Saran Vardhanabhuti[2], Srikanth Tripathy[3], Mariza Morgado[4], Shanmugam Saravanan[5], Carole Wallis[6], Sarah E. Hudelson[7], Susan H. Eshleman[7], Thomas Campbell[8]
[1]Brown Univ, Providence, RI, USA, [2]Harvard Univ, Cambridge, MA, USA, [3]Natl Inst for Rsr in TB, Chennai, India, [4]Oswaldo Cruz Inst, Rio de Janeiro, Brazil, [5]YRG CARE, Chennai, Tamilnadu, [6]Lancet Labs and BARC-SA, Johannesburg, South Africa, [7]The Johns Hopkins Univ, Baltimore, MD, USA, [9]Univ of Colorado Denver, Aurora, CO, USA

Background: Pre-therapy genotyping is recommended in developed countries but supporting data in global settings are lacking. We examined the association of pre-therapy baseline (BL) DR mutations (DRMs) with resistance at virologic failure (VF) in a multi-national, prospective, randomized trial, in 9 countries on 4 continents.
Methods: 1571 drug-naïve HIV-infected adults were randomly assigned to 3 Arms: efavirenz+lamivudine+zidovudine (Arm A; World Health Organization (WHO) alternative option), atazanavir+didanosine+emtricitabine (Arm B), or efavirenz+emtricitabine+tenofovir (Arm C; WHO preferred option). VF was defined as confirmed viral load (VL) >1000 copies/mL at/after 14 weeks. Reverse transcriptase and protease genotyping was performed with the ViroSeq HIV Genotyping System. DR was assessed using the 2015 International Antiviral Society-USA list. Clinically significant DR was defined as intermediate/high resistance to ≥1 drug based on the Stanford Database. Associations of DR at VF were estimated by Chi-Square or Wilcoxon tests for baseline dichotomous or continuous variables respectively.
Results: BL and at-failure genotypes were available for 238/270 participants with VF (74 Arm A, 95 Arm B, 69 Arm C); 44% women; median age 32 years; median BL-at failure CD4 162-240 cells/μL and VL 5.2-4.2 log10 copies/mL; median time to VF 32 weeks; subtypes: 56% C, 39% B, 5% other. At least one DRM was found at VF in 70% of participants across Arms; 47% NRTI, most common M184V (40%), 51% NNRTI, most common K103N (31%); 7% PI in Arm B, most common I50L (6%); 38% single, 29% dual, 3% triple-class. Of those with BL DR, 98% (42/43) had any DR at VF and 63% had DRMs at failure that were not detected at BL. Of those without BL DR, 63% (122/195) had any DR at VF. DR at VF was associated with low BL CD4, greater CD4 change from BL, high BL VL, low at-failure VL and BL DR (p≤.002 for all). Of those with any DR at VF 63% had clinically significant DR to study regimens and 15% had DR to future options; and was associated with males, low BL CD4, greater CD4 change from BL, low BL VL, low at failure VL and BL DR (p≤.003 for all).
Conclusion: In this multi-national clinical trial with 60% non-subtype B HIV-1 infection, BL DR was associated not only with VF as previously reported, but also with clinically-significant DR at VF that impacted treatment options.

493 SHOULD WE BE TESTING FOR BASELINE INTEGRASE RESISTANCE?

Yiannis Koullias[1], Paul E. Sax[1], Rochelle P. Walensky[2], Emily P. Hyle[2]
[1]Brigham and Women's Hosp, Boston, MA, USA, [3]Massachusetts General Hosp, Boston, MA, USA

Background: Treatment guidelines recommend baseline genotype resistance testing in new HIV diagnoses to guide selection of 1st-line therapy. While integrase strand transfer inhibitors (INSTIs) are recommended for initial treatment, most genotype tests do not assess INSTI resistance (INSTI-R). Given the low rate of transmitted INSTI-R, it is unclear if baseline testing would provide value. We examine the conditions under which INSTI-R testing might be cost-effective.

Methods: We use a decision tree to examine the incremental cost-effectiveness ratio (ICER) of INSTI-R testing vs. no testing. Results are based on differences in 96-wk quality-adjusted life expectancy (QALE), assuming equivalent outcomes thereafter. In the base case, the prevalence of transmitted INSTI-R is 0.1%, derived from published studies. Those who undergo INSTI-R testing and have resistance detected at baseline start a DRV/r-based regimen. The FLAMINGO trial provides estimates of 96-wk HIV RNA suppression rates with DTG (80.1%) and DRV/r (67.8%)-based regimens. For those with INSTI-R but without an INSTI-R test, we presume a 30% probability of success on DTG, since many INSTI-R isolates remain susceptible to DTG. In the base case, we presume a quality of life (QoL) reduction for those experiencing virologic failure (~3%). Costs include: INSTI-R $250/test; DTG-based ART ($38,150/yr) and DRV/r-based ART ($44,400/yr). In sensitivity analyses, we examine how changes in these parameters influence the conclusions.
Results: Compared to a no test strategy, the INSTI-R test decreased QALE by 1.23x10^-6 QALY and increased per person costs by $250 at 96-wk; hence, not performing the test was the preferred strategy. Reducing QoL for DRV/r treatment further strengthened the preference for no test, even at implausibly high levels of transmitted INSTI-R. In sensitivity analyses, reducing DTG suppression with undiagnosed INSTI-R to <20% and increasing PI-regimen efficacy to >80% yielded improved clinical outcomes, but the ICER of INSTI-R testing was not cost effective, well exceeding $1 million/QALY. Base-case results were similar when an NNRTI was substituted for DRV/r.
Conclusion: At an estimated INSTI-R prevalence of 0.1% and a current INSTI-R test cost of $250, baseline INSTI-R testing results in worse clinical outcomes and higher costs than no test. A no test strategy remains preferred if there is a possibility of INSTI-suppression despite detected INSTI-R, or if there is a QoL benefit to PI avoidance, regardless of the prevalence of INSTI-R.

494 COST-EFFECTIVENESS ANALYSIS OF PRE-ART HIV DRUG RESISTANCE TESTING IN KENYA

Horacio A. Duarte[1], Joseph Babigumira[2], David Stauffer[3], Robert Shafer[3], Ingrid Beck[4], Louis Garrison[2], Michael H Chung[2], Lisa Frenkel[1], Eran Bendavid[3]
[1]Univ of Washington/Seattle Children's Rsr Inst, Seattle, WA, USA, [2]Univ of Washington, Seattle, WA, USA, [3]Stanford Univ, Stanford, CA, USA, [4]Seattle Children's Rsr Inst, Seattle, WA, USA
Background: The prevalence of pre-treatment HIV drug resistance (PDR) is increasing in East Africa, which may decrease the effectiveness of antiretroviral therapy (ART) programs. Testing for PDR with an oligonucleotide ligation assay (OLA), a low-cost point mutation assay, is a potential strategy to address the challenges posed by PDR in resource-poor settings.
Methods: We developed an HIV drug resistance model that simulated the emergence and transmission of resistance mutations, calibrated to the Kenyan epidemic. We implemented 6 care strategies for PDR testing: no testing (NT), OLA, or consensus sequencing (CS), each with initial viral load (VL) testing at either 6 or 12 months (NT+VL6, NT+VL12, OLA+VL6, OLA+VL12, CS+VL6, and CS+VL12). We assumed the cost of OLA and CS were $30 and $300, respectively, per test. This model was used to evaluate the health outcomes, lifetime costs, and cost-effectiveness of the strategies over a 15-year time horizon. Health outcomes included quality-adjusted life years (QALYs), new HIV infections and opportunistic infections, rates of ART suppression of HIV replication, and rates of drug resistance.
Results: The OLA+VL12 strategy provided 23 additional QALYs at an additional cost of $5,297 per 1,000 population, compared to NT+VL12 (an incremental cost-effectiveness ratio (ICER) of $230/QALY gained). The current Kenyan practice (NT+VL6) resulted in 22 fewer QALYs and cost an additional $3,889 per 1,000 population, compared to OLA+VL12. Strategies that used CS for PDR testing were not cost-effective by national income standards. OLA+VL12 resulted in more patients maintaining viral suppression than NT+VL6 (73% vs. 60%, respectively). OLA+VL12 also had 7.6% fewer new HIV infections than NT+VL6. Initial PDR prevalence was 8.0% in 2013. By 2028, this prevalence increased to 34.8% with NT+VL6, but only to 25.5% with OLA+VL12. The probability of virologic failure at 12 months among patients with PDR is an important factor in the cost-effectiveness of OLA+VL12. When this probability was decreased from 47% to 34% in a one-way sensitivity analysis, the ICER associated with OLA+VL12 increased to $562/QALY gained, compared to NT+VL12.
Conclusion: Low-cost pre-treatment drug resistance testing with initial VL test at 12 months is very cost-effective compared to NT+VL12, in Kenya. Over time, testing for PDR has the potential to reduce the growth of PDR prevalence in resource-poor settings.

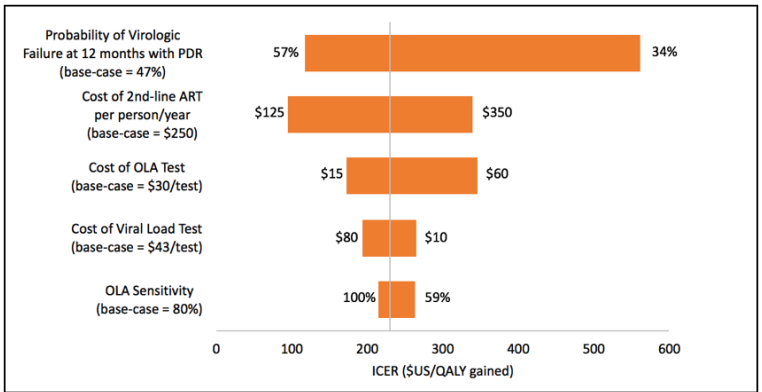


Figure 1: One-Way Sensitivity Analysis of Key Model Parameters
ICER values are for OLA+VL12 compared to NT+VL12. Each horizontal bar represents the range of ICER values for the specified range of the tested parameter. The vertical bar represents the $230/QALY base-case analysis ICER.

495 EVOLUTION OF ARCHIVED HIV-1 QUASISPECIES IN INDIVIDUALS TREATED WITH DOLUTEGRAVIR

Pierre Gantner[1], Guinevere Q. Lee[2], David Rey[1], Thibault Mesplede[3], Marialuisa Partisani[1], Geneviève Beck-Wirth[4], Jean-Pierre Faller[5], Martin Martinot[6], Mark Wainberg[3], Samira Fafi-Kremer[1]
[1]Hôpitaux Univ de Strasbourg, Strasbourg, France, [2]BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada, [3]McGill Univ, Montreal, Quebec, Canada, [4]Groupe Hosp Regional–Mulhouse Sud Alsace, Mulhouse, France, [5]Hôpital Nord Franche Comté, Belfort, France, [6]Hôpital Civil de Colmar, Colmar, France
Background: Integrated proviral DNA persists for decades even when antiretroviral therapy (ART) prevents active replication. Residual replication on ART and cell trafficking should increase the proviral DNA genetic variability over time. We assessed the dynamics of archived HIV quasispecies over 48 weeks in patients starting successful dolutegravir-based regimen (DBR) using an ultra-deep sequencing technique.
Methods: The DRONE study is an ongoing multicenter prospective longitudinal study including patients starting a DBR (NCT02557997). In the present substudy we enrolled 20 participants divided into four groups: treatment-naïve individuals who initiated a DBR during primary (PI, n=5) or chronic (CI, n=5) infection, and treatment-experienced individuals who started a DBR while in virological success for ≥10 years (VS, n=5) or in the aftermath of virological failure (VF, n=5). Peripheral blood mononuclear cells were

collected at baseline and weeks 4, 24 and 48. HIV-DNA Integrase (IN) and V3 loop sequences were obtained by 454/pyrosequencing (Roche) and analyzed for resistance and viral diversity (Shannon entropy).
Results: All patients achieved or maintained HIV-RNA < 50 copies/mL from weeks 4 to 48. We detected emerging resistance mutations in the proviral DNA from five individuals, including the R263K substitution in one individual from the CI group at week 4. Proviruses from three patients from the VS group harbored various substitutions at position 50 (Patient 1: T50I at week 48; Patient 2: M50I (+ A124T) at weeks 4, 24 and 48; Patient 3: I50T at weeks 4 and 48, and I50M at week 24) and the N230S substitution was observed in one individual from the PI group at weeks 4 and 48. DBR was associated with a transient decrease in the proviral genetic diversity of either IN or V3 sequences at week 4, even in individuals who were previously successfully treated (Student's t-test $p<0.05$).
Conclusion: Our result show that (i) the R263K substitution can emerge and get archived under DBR (ii) the detection of R263K in proviruses is not associated with virological failure and (iii) multiple changes at position 50 can be detected over time in proviruses of individuals using DBR. Given that the R263K and M50I substitutions have been specifically associated with resistance against dolutegravir (and more recently, bictegravir), the identification of those emerging mutations in the proviral DNA and the transient decrease in viral diversity suggest that archived viral quasispecies continue to evolve on ART.

496 IMPACT OF CLINICALLY OBSERVED INTEGRASE MUTATIONS ON DOLUTEGRAVIR RESISTANCE

Atsuko Hachiya, Masaaki Nakashima, Yoko Ido, Urara Shigemi, Masakazu Matsuda, Reiko Okazaki, Junji Imamura, Yoshiyuki Yokomaku, Yasumasa Iwatani
Natl Hosp Org Nagoya Med Cntr, Nagoya, Japan

Background: Dolutegravir (DTG), the second-generation integrase strand transfer inhibitor (INSTI), displays potent antiretroviral effects and superior resistance profiles. To date, HIV-1 integrase (IN) mutations associated with high-level DTG resistance have not yet been reported in the clinical settings. To explore potential DTG resistance mutations, we analyzed impacts of the IN mutations detected in clinical isolates.
Methods: We set out isolation of raltegravir (RAL) resistant viruses from clinical samples during virological failure under RAL-based regimen. The clinically suspected resistance mutations were introduced into the IN region of HIV-1 DNA clone by site-directed mutagenesis. Drug susceptibility of the recombinant viruses was evaluated in a single-round replication assay using TZM-bl cells. Structural analyses of the IN-INSTI complexes were performed *in silico*.
Results: Genotypic and phenotypic analyses demonstrated that over the time course of clinical samples, a novel combination of L74F/V75I mutations in the IN region conferred resistance to first-generation INSTIs. Next, we evaluated whether the addition of L74F alone or L74F/V75I to the major resistance mutations impacts on INSTI resistance level. The results showed that the addition of L74F to the major mutations, G140S/Q148H, increased the DTG resistance level (15-fold). In contrast, the L74F/V75I drastically enhanced the level of DTG resistance when combined with either N155H (>385-fold) or G140S/Q148H (100-fold). Notably, these combinational mutations also increased the resistance magnitude to cabotegravir (CAB) that is currently an investigational second-generation INSTI. DTG efficiently chelates two divalent metal ions of the IN catalytic center that are coordinated by the DDE motif (D64-D116-E152). On the IN-INSTI structure, the L74 and V75 residues are located at the β2 strand, which is juxtaposed to the β1 strand containing the D64 residue. This suggests an indirect structural impact of the L74F/V75I mutations to the catalytic center, leading high resistance to the second-generation INSTIs.
Conclusion: This is the first report to demonstrate that clinically detected L74F/V75I mutations enhance the resistance level of the major mutations to all four currently available INSTIs. These findings will help understanding of superior resistance profiles of the second-generation INSTIs and providing insights into rational design of the next generation INSTIs.

497 BICTEGRAVIR DISSOCIATION HALF-LIFE FROM HIV-1 G140S+Q148H INTEGRASE/DNA COMPLEXES

Kirsten L. White, Anita Niedziela-Majka, Nikolai Novikov, Michael D. Miller, Haolun Jin, Scott E. Lazerwith, Manuel Tsiang
Gilead Scis, Inc, Foster City, CA, USA

Background: Long dissociation half-life (t1/2) of HIV integrase strand transfer inhibitors (INSTI) correlates with high antiretroviral activity and barrier to resistance. The dissociation t1/2 of bictegravir (BIC) from wild-type (WT) integrase (IN)/DNA complexes is longer than that of elvitegravir (EVG), raltegravir (RAL), and dolutegravir (DTG). BIC has improved activity against HIV isolates with INSTI resistance mutations, particularly the 140/148 combination. Here, we evaluate phenotypic resistance and dissociation kinetics using G140S+Q148H mutant IN.
Methods: INSTIs were phenotyped with 17 G140S+Q148H clinically-derived isolates with or without other IN mutations. The apparent association and dissociation t1/2 of 3H-labelled RAL, EVG, DTG, and BIC were measured using WT and G140S/Q148H mutant HIV IN/DNA complexes with a scintillation proximity assay. The association and dissociation kinetics were analyzed using both a single exponential decay function and an equilibrium binding model that generates half-lives that may be more representative of the t1/2 in cells.
Results: HIV isolates with G140S+Q148H in IN had mean phenotypic fold-change values of 3.6±1.9 for BIC, 8.1±4.7 for DTG ($p<0.01$ for DTG vs BIC), and >100 for RAL and EVG. The apparent association t1/2 of BIC and DTG to G140S+Q148H mutant HIV IN/DNA complexes were 37±4 min and 34±5 min, respectively, and similar to that for WT. For BIC and DTG, the dissociation t1/2 from G140S+Q148H IN/DNA complexes were both shorter compared to WT ($p\leq0.01$). The BIC apparent t1/2 from the mutant IN/DNA complexes using single exponential fit was longer than DTG (5.5±0.1 h vs 2.0±0.01 h, respectively, $p<0.01$). Similarly, dissociation t1/2 determined from equilibrium binding models were longer for BIC than DTG (2.5±0.07 h vs 0.65±0.2 h, respectively, $p<0.01$). In contrast, EVG and RAL had no measurable association or dissociation with the mutant IN/DNA, consistent with high-level resistance.
Conclusion: BIC has improved activity compared to DTG, EVG, and RAL against HIV isolates with the 140+148 INSTI resistance mutations. BIC dissociates more slowly than DTG from the G140S+Q148H mutant IN/DNA complex and may explain the improved in vitro activity of BIC compared to other INSTIs against this mutant.

498 PHENOTYPIC SUSCEPTIBILITY OF SIV AND HIV-1 VARIANTS TO BICTEGRAVIR, A NOVEL INSTI

Said Hassounah, Thibault Mesplede, Bonnie Spira, Nathan Osman, Mark A. Wainberg
McGill Univ, Montréal, Quebec, Canada

Background: Animal models are essential to answer key questions pertaining to antiretroviral therapy that include studies on novel drugs, drug resistance-associated mutations (RAMs), and treatment interruption. Given the high cost of animal-based research for the study of drug resistance, there is a need to validate and extend findings in tissue culture that were first obtained with HIV. A novel next generation integrase strand transfer inhibitor (INSTI), Bictegravir (BIC), has shown promising results against HIV-1 infection in vitro and in vivo, and against clinical isolates with INSTI resistance. BIC possesses a higher barrier to resistance than raltegravir (RAL) and elvitegravir (EVG). Our objective was to compare the susceptibilities of SIV and HIV-1 to BIC and to characterize the susceptibility of mutational patterns in HIV-1 IN against BIC.
Methods: We constructed 7 SIV IN mutants (E92Q, T97A, G118R, Y143R, N155H, R263K, and G140S/Q148H) by site-directed mutagenesis (SDM). Mutations conferring resistance to INSTIs, some of which had not been investigated until now, were introduced into wild-type (WT) HIV-1 pNL4.3 by SDM (Y143R, N155H, R263K, R263K/M50I, R263K/H51Y, R263K/E138K, and G140S/Q148H). Single-cycle infection assays (in TZM-bl reporter cells) were used to quantify the sensitivities of WT and IN variants of SIV and HIV-1 against BIC. Both cabotegravir (CTG) and dolutegravir (DTG) were included as controls.
Results: BIC showed comparable activity against SIV and HIV-1 in a single cycle infection with EC50s in the low nanomolar range (~2-3 nM). Amino acid changes E92Q, T97A, Y143R, N155H in SIV did not have major impact on BIC susceptibility (≤3-fold increase in EC50) whereas G118R and R263K in SIV conferred ~13-fold and ~ 6-fold increases in EC50, respectively. HIV-1 IN mutants Y143R, N155H, R263K, R263K/M50I, R263K/E138K, and G140S/Q148H remained susceptible to BIC (≤3-fold increase in EC50). However, R263K/H51Y conferred low resistance to BIC (~8-fold). BIC exhibited a comparable resistance profile to CTG and DTG against SIV and HIV-1 IN mutants and displayed an improved resistance profile compared to RAL and EVG.

Conclusion: Altogether, our results show that the same mutations that are associated with drug resistance in HIV exhibit similar profiles in SIV. The resistance profiles of BIC and DTG in SIV are also similar. Our data provide an important reference point for interpretation of additional mutational patterns that may emerge in HIV-1.

499 A HIGH-LEVEL RESISTANCE TO INTEGRASE INHIBITORS SELECTED OUTSIDE INTEGRASE HIV-1 GENE

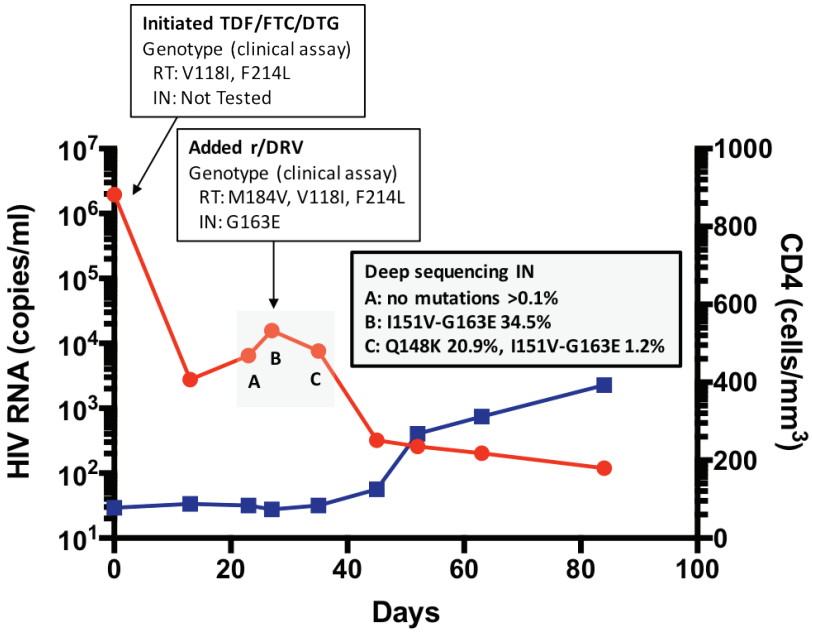
Isabelle Malet[1], Frédéric Subra[2], Charlotte Charpentier[3], Gilles Collin[4], Diane Descamps[4], Vincent Calvez[1], Anne-Geneviève Marcelin[1], **Olivier Delelis**[2]
[1]Pitie-Salpetriere Hosp, Paris, France, [2] Ecole Normale Supérieure de Cachan, Cachan, France, [3]INSERM, Paris, France, [4]Bichat Hosp, Paris, France

Background: Dolutegravir (DTG), a strand-transfer integrase inhibitor, seems to have, as in vitro and in vivo, a higher genetic barrier to resistance than raltegravir (RAL) and elvitegravir (EVG). Most in vitro experiments for selecting resistance to DTG were conducted increasing progressively DTG concentrations and showed difficulties for the virus to select mutations in the integrase gene under DTG pressure. In this study, we tried to select resistance to DTG using, from the beginning, high-level DTG concentrations.
Methods: In vitro resistance selection was performed by infecting 2.106 MT4 cells with the HIV-1 Laï virus, using an equivalent of 1200 ng of p24 antigen. Twenty-four hours post-infection, cells were washed and DTG was added (500 nM), this concentration maintained all along the in vitro selection during three months. Phenotypic susceptibility assays were performed in HeLa-P4 cells in the presence of increasing concentrations of DTG, up to 500nM at 48 h post-infection. RNA virus extracts from supernatants, collected during selection, were used for genotypic analysis. Site-directed mutagenesis experiments were performed using pNL43 plasmid.
Results: After three months of culture, we detected highly resistant viruses to DTG. Phenotypic analyses showed that viruses had a constant viral replication level in the presence of DTG, up to 500 nM (IC95 > 500nM). These results were confirmed using phenotypic PBMC assays. Analyses of different samples throughout the whole selection steps during three months did not show any mutation selection in the integrase gene compared to the baseline virus. The whole HIV-1 genome sequencing found the emergence of five mutations, all located in the nef region. The A9053C mutation situated six nucleotides upstream the 3'PPT motif (located between nucleotides 9069 to 9083, numbered relative to HxB2 sequence) and the four other changes clustered in the 3' end of the 3'PPT motif, inside the G-tract. The motif is represented below, including the mutations in brackets 5'AAAAGAAAAG(G9079C)(G9080A)G(G9082T)(G9083deleted)3'. Site directed mutagenesis experiments introducing all mutations/deletion described above in NL43 HIV-1 showed a high-level of resistance to DTG but also to RAL and EVG, comparing to the wildtype.
Conclusion: Mutations selected in vitro by DTG and located outside the integrase gene can confer themselves very high-level of resistance to all strand-transfer integrase inhibitors.

500LB EMERGENCE OF INTEGRASE RESISTANCE MUTATIONS DURING INITIAL THERAPY WITH TDF/FTC/DTG

Jennifer A. Fulcher[1], Yushen Du[1], Ren Sun[1], Raphael J. Landovitz[2]
[1]Univ of California Los Angeles, Los Angeles, CA, USA, [2]UCLA Cntr for Clinical AIDS Rsr & Educ, Los Angeles, CA, USA

Background: Dolutegravir (DTG) with two NRTIs has emerged as a preferred regimen for initial treatment of HIV-infected individuals due to high efficacy, tolerability, and previously unreported INI drug resistance when used as initial therapy. We present genotypic information during a period of virologic failure in a 46 year old treatment naive man who initiated tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) plus DTG with a high viral load.
Methods: Longitudinal patient samples (3 time points) covering an eight day period of increasing viral load were used for deep sequencing analysis of integrase (IN) genotypes. Plasma RNA was isolated and reverse transcribed, then target regions of IN pre-amplified using nested PCR. Paired end sequencing was performed using Illumina HiSeq 2000. Population sequencing was performed by standard clinical genotype assay (Quest Diagnostics) at the start of antiretroviral therapy and time of virologic inflection.
Results: The patient was treated with TDF/FTC plus DTG as initial therapy (HIV RNA 1,970,000 copies/ml and CD4 78 cells/mm^3) Population sequencing showed no clinically significant resistance mutations in reverse transcriptase (RT) or protease (PR). Baseline IN genotype was not performed. HIV RNA initially decreased to 2,770 copies/ml after two weeks, but then increased to 15,700 copies/ml and plasma samples were collected serially over an eight day period. Deep sequencing of these samples generated a mean of 2,483,155 reads covering the region IN amino acids 142-165. The initial time point showed no significant IN mutations, however the next two time points showed rapid evolution of mutations as shown in Figure, notably the emergence of Q148K. Population sequencing corresponding to the middle time point showed RT mutations M184V and V118I and confirmed IN mutation G163E.
Conclusion: Rapid emergence of known integrase inhibitor resistance mutations during failure of virologic suppression suggest that INI resistance may have contributed to failure on the initial regimen in this case. To our knowledge, this is the first description of potential DTG-resistance in a treatment naive individual.



501 CROSS-RESISTANCE PROFILES OF THE NNRTIS IN DEVELOPMENT TO PREVENT HIV-1 INFECTION

Nicholas S. Giacobbi, Nicolas Sluis-Cremer
Univ of Pittsburgh, Pittsburgh, PA, USA

Background: The NNRTIs dapivirine (DAP), rilpivirine (RPV) and the phenylethylthiazolylthiourea analog MIV-150 are in development as pre-exposure prophylaxis (PrEP) modalities to prevent the acquisition of HIV-1 infection. Currently, there is a paucity of information in regard to the resistance and cross-resistance profiles of DAP and MIV-150, which we addressed in this study.

Methods: Twenty-eight subtype B HIV-1LAI infectious viruses containing single NNRTI resistance mutations spanning 17 different codons (V90I; L100I/V; K101E/P; K103N/S; V106I; V108I; E138A/K; V179D/F, G190A/S; I181C/I/V; Y188C/H/L; H221Y; P225H; F227C/L; M230L; P236L; N348I) were constructed by site-directed mutagenesis. Drug susceptibility in a single cycle assay using TZM-bl cells was determined for RPV, DAP and MIV-150. Low-, intermediate- and high-level resistance was defined as 2-8, 8-20, and >20-fold changes in drug susceptibility compared to the wild type virus.

Results: Of the 3 NNRTIs studied, RPV exhibited the best antiviral activity across the panel of HIV-1 variants tested. RPV was found to be active against 19 of 28 variants, with low-level resistance conferred by the E138A/K, F227C, K101E, Y188L and M230L mutant viruses, and high-level resistance conferred by Y181I/V and K101P. DAP was active against only 15 of the 28 viruses. The K101E, E138K, K103N/S, F227C, Y181C and L100V viruses conferred low resistance to RPV; whereas the L100I and M230L and Y188L, K101P and Y181I/V viruses were found to confer intermediate and high-level resistance, respectively. MIV-150 was also active against only 15 of the HIV-1 variants tested: K101E and L100I/V; F227C and Y181C; and M230L, K103N/S, Y181I/V, Y188L and K101P mutations conferred low-, intermediate and high-level resistance, respectively.

Conclusion: DAP and MIV-150 activity is compromised by many HIV-1 variants containing a single NNRTI resistance mutation. Both NNRTIs exhibit decreased susceptibility toward the K101E, K103N and Y181C mutations which are major NNRTI transmitted drug resistance mutations in all geographic regions and HIV-1 subtypes.

502 DRUG RESISTANCE AFTER CESSATION OF EFAVIRENZ-BASED ANTIRETROVIRAL TREATMENT

Gbolahan Ajibola[1], Christopher Rowley[2], Kathleen M. Powis[3], Sikhulile Moyo[1], Jean Leidner[4], Kara Bennett[5], Florence Chilisa[1], Joseph Makhema[1], Roger L. Shapiro[2], Shahin Lockman[2]
[1]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [2]Harvard Univ, Boston, MA, USA, [3]Massachusetts General Hosp, Boston, MA, USA, [4]Goodtables Consulting, Oklahoma, OK, USA, [5]Bennett Statistical Consulting Inc, New York, NY, USA

Background: Little is known about the risk of antiretroviral resistance following cessation of efavirenz (EFV)-based antiretroviral treatment (ART), particularly when an NRTI "tail" is administered. Until 2015, Botswana's Option "B" program for preventing mother-to-child transmission (PMTCT) recommended discontinuation of efavirenz (EFV)/emtricitabine (FTC)/tenofovir (TDF) after delivery (with an FTC/TDF tail) for women with higher CD4, allowing a unique opportunity to study resistance patterns following discontinuation of
this regimen.

Methods: Resistance testing was performed on specimens obtained from a subset of HIV-infected women participating in the Botswana Mpepu study. Women with CD4>350 cells/mm3 initiated EFV/FTC/TDF in pregnancy for PMTCT, and discontinued at 6 weeks postpartum if formula-feeding or 6 weeks after last breastfeeding. A 7-day tail of FTC/TDF was recommended after stopping EFV. ART provision and management decisions occurred at government clinics. HIV-1 RNA and partial pol sequencing were performed on samples obtained 4-6 weeks after stopping EFV/FTC/TDF (regardless of whether an ARV tail was received). Stanford HIV Drug Resistance Database was used to identify major mutations.

Results: From 2014 to 2015, 74 women discontinued EFV/FTC/TDF postpartum (median CD4 571 cells/mm3, IQR 327), and had sample drawn for genotyping at median 5 weeks (IQR, 2) after EFV/FTC/TDF was stopped. Thirty-two (43%) women received a 1-week tail of FTC/TDF after stopping EFV, while 42 (57%) received no tail. Among 70 women with HIV-1 RNA at delivery, 58 (83%) had HIV-1 RNA<40cp/mL, while 45 (63%) of 71 women with HIV-1 RNA available 5 weeks post-EFV/FTC/TDF cessation had HIV-1 RNA<40cp/mL. Genotyping was attempted for all 74 women, and 35 (47%) were successfully sequenced; 4 (11%) of 35 had a major drug resistance mutation (K103N [n=2] and V106M [n=2]). None of the 4 women with drug resistance had received a FTC/TDF tail and 1 had received ARVs for PMTCT prior to this pregnancy.

Conclusion: A high proportion of postpartum women remained virally suppressed at a median of 5 weeks from EFV/FTC/TDF cessation. Drug resistance mutations were detected in a small proportion of women after cessation of EFV/FTC/TDF. None of the women with drug resistance had received an FTC/TDF tail, which may help prevent selection of drug resistance when discontinuing EFV-based ART.

503 4′-MODIFIED NRTIS' POTENT ANTI-HIV ACTIVITY STEMS FROM STRONG RT ACTIVE-SITE BINDING

Kenji Maeda[1], Yuki Takamatsu[2], Debananda Das[2], Satoru Kohgo[3], Shinichiro Hattori[1], Hironori Hayashi[1], Kouki Matsuda[1], Stefan G. Sarafianos[4], Hiroaki Mitsuya[2]
[1]Natl Cntr for Global Hlth and Med Rsr Inst, Shinjuku, Tokyo, Japan[2]NIH, Bethesda, MD, USA, [3]Sojo Univ, Kumamoto, Japan, [4]Univ of Missouri, Columbia, MO, USA

Background: 4′-Ethynyl-2-fluoro-2′-deoxyadenosine (EFdA or MK-8591), a novel nucleoside reverse transcriptase inhibitor (NRTIs) under clinical trials, is one of the most extremely potent and long-acting anti-HIV-1 agents (Grobler et al. CROI 2016: abstr# 98). EFdA and its derivatives, unlike other conventional NRTIs, possess a modified 4′-moiety while retaining the 3′-OH group in the ribose, and potently inhibit HIV-1 strains resistant to currently available NRTIs.

Methods: We newly synthesized various 4′-modified NRTIs (4′-NRTIs) and tested their antiviral activity against a variety of NRTI-resistant HIV-1 strains. Anti-HIV-1 activity of EFdA and other 4′-NRTIs were examined using various cell-based assays including the MTT and p24 assays. Cytotoxicity of such NRTIs was also determined. Structural analyses were conducted using a recently defined crystal structure of EFdA-TP complexed with RT (Salie, Mitsuya, & Sarafianos. PNAS, 113:9274-9, 2016).

Results: We found that EFdA and NRTIs with 4′-ethynyl- or 4′-cyano retain activity against HIV-1M184V and a multi-NRTI-resistant HIV-1 (HIV-1EFdAR), but not NRTIs with other moieties examined (e.g., 4′-methyl). Structural study revealed that EFdA and 4′-ethynyl/cyano-NRTIs (but not other 4′-modified NRTIs examined), had strong vdW interactions with RT's residues such as F160, and the binding persisted even in the presence of the broadly resistance-endowing V184, thus potently exerting activity against drug-resistant HIV-1s.

Conclusion: EFdA-derivatives with 4′-cyano- or 4′-ethynyl moiety exerted potent activity against HIV-1EFdAR, suggesting that EFdA and its derivatives with 4′-cyano- or 4′-ethynyl moiety should serve as promising candidates for further clinical development with potent activity against various multi-drug-resistant HIV-1 variants, high genetic barrier and QD- (or QW-) possible NRTIs.

504LB RISING TRANSMITTED RESISTANCE FORCES ABANDONMENT OF WHO-RECOMMENDED THERAPY IN ARUBA

Laura Marije Hofstra[1], Elena Sánchez Rivas[2], Monique Nijhuis[1], Eduan Wilkinson[3], Karina Kelly[2], Tania Mudrikova[1], Rob Schuurman[1], Tulio de Oliveira[3], Jaclyn De Kort[2], Annemarie Wensing[1]
[1]Univ Med Cntr Utrecht, Utrecht, Netherlands, [2]Dr. Horacio E. Oduber Hosp, Oranjestad, Aruba, [3]Univ of KwaZulu-Natal, Durban, South Africa

Background: In Western countries emergence of HIV drug resistance has tremendously decreased and transmission of drug resistance has merely stabilized in recent years. However, in many endemic settings with limited resources rates of emerging and transmitted drug resistance are not regularly assessed.

Methods: In Aruba, a highly endemic HIV area in the Caribbean, baseline resistance testing was randomly performed from 2010 on. We performed a survey including >50% of all newly diagnosed HIV-infected individuals in the country. Transmitted HIV drug resistance was determined using WHO-criteria. Transmission dynamics were investigated using phylogenetic analyses. In a subset, baseline samples were re-analyzed using next generation sequencing (NGS).

Results: Baseline resistance was assessed in 104 newly diagnosed untreated individuals (54% of all newly diagnosed individuals in 2010-2015); 86% was men, 39% was foreign-born, and 22% had AIDS at diagnosis, which was in line with the overall HIV-infected population of 2010-2015. The prevalence of transmitted drug resistance was 33% (95% CI:

24-42%). Mutations associated with nucleoside reverse transcriptase inhibitors (NRTIs) or protease inhibitors were rare (both 2%; 95% CI: 0-5%). The prevalence of resistance to non-NRTIs (NNRTIs) reached 45% (95% CI: 27-64%) in 2015, all based on the prevalence of mutation K103N. NGS did not demonstrate additional minority K103N-variants in patients diagnosed with wild-type virus. In patients diagnosed with a K103N-variant, NGS showed persistence of K103N at high frequencies (range: 94.9-98.8%) despite long-term infection in some cases, underlining its potential to become widespread among therapy-naïve individuals. K103N-harboring strains were introduced into the therapy-naïve population via at least 6 independent transmissions which were epidemiologically linked to surrounding countries. Virological failure of the WHO-recommended first-line NNRTI-based regimen was higher in the presence of K103N.

Conclusion: The prevalence of NNRTI-resistant HIV in Aruba has increased to alarming levels, compromising the WHO-recommended first-line regimen. Local and regional public health authorities have been informed and local guidelines have reinforced baseline resistance testing and have replaced the WHO recommended first-line regimen by an integrase inhibitor-based regimen. As adequate surveillance as advocated by the WHO is currently very limited, the Caribbean region could face an unidentified rise of NNRTI-resistant HIV.

505 LOW HIV-1 RESISTANCE IN SUBJECTS USING DARUNAVIR ONCE-DAILY REGIMENS ACROSS STUDIES

Erkki Lathouwers[1], Eric Y. Wong[2], Donghan Luo[2], Sareh Seyedkazemi[2], Sandra De Meyer[1], Kimberley Brown[2]
[1]Janssen Infectious Diseases BVBA, Beerse, Belgium, [2]Janssen Scientific Affairs, LLC, Titusville, NJ, USA

Background: Across Phase 2/3 studies evaluating once-daily (QD) darunavir (DRV) regimens, treatment-naïve (TN) or treatment experienced (TE), including virologically suppressed, HIV-1–infected subjects were treated for 48-192 wk. We summarize treatment-emergent drug resistance-associated mutations (RAMs) for subjects receiving DRV QD dosing from 7 studies.

Methods: Sponsored studies with available genotypes were assessed. TN studies: ARTEMIS (N=343; DRV+ritonavir [r]+emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF]; 192 wk); GS-US-299-0102 (N=103 [DRV/cobicistat (c)/FTC/tenofovir alafenamide]; N=50 [DRV+c+FTC/TDF]; 48 wk). TE studies: ODIN (N=294; DRV+r+≥2 nucleos[t]ide reverse transcriptase inhibitors [NRTIs]; 48 wk); MONET (N=127 [DRV+r]; N=129 [DRV+r+2 NRTIs]; 144 wk); PROTEA (N=137 [DRV+r]; N=136 [DRV+r+2 NRTIs]; 96 wk). TN and TE studies: GS-US-216-0130 (295 TN, 18 TE; DRV+c+2 NRTIs; 48 wk); INROADS (42 TE, 12 TN; DRV+r+etravirine; 48 wk). Across studies, eligible TE subjects did not have DRV RAMs at screening. Criteria for post-baseline resistance testing and evaluation of treatment-emergent or presence of on-treatment RAMs (respective IAS-USA mutations) varied slightly across studies. Genotypic analyses were conducted at baseline except for switch studies enrolling virologically suppressed subjects (MONET, PROTEA).

Results: Within the 7 studies, 2329 subjects were enrolled; 1687 (804 TN, 883 TE) subjects were treated with DRV QD and 193 (65 TN, 128 TE) subjects with protocol-defined virologic failure and post-baseline genotypes were analyzed. None of the TN subjects and 3 TE subjects displayed ≥1 primary protease inhibitor (PI) RAM (**Table**): 1 each from GS-US-216-0130 (I84I/V), MONET (monotherapy arm; L33F detected at Wk 12 with HIV-1 RNA of 63 copies/mL, but was resuppressed at subsequent visits until Wk 144), and ODIN (V32I+M46I+L76V+I84V). DRV phenotypic susceptibility was lost in only the ODIN subject, possibly related to previous lopinavir+r virologic failure. 7 TN and 5 TE subjects developed ≥1 NRTI RAM; 2 TE subjects from INROADS developed non-nucleoside reverse transcriptase inhibitor RAMs (**Table** footnote).

Conclusion: Among HIV-1–infected subjects treated with DRV QD regimens for 48-192 wk (N=1687), development of emergent resistance was rare. Overall, no TN subjects and 0.3% of TE subjects developed primary PI RAMs. Only 1 subject across studies lost DRV phenotypic susceptibility, confirming the high genetic barrier to DRV resistance development.

Table. Summary of Post-Baseline Primary PI RAMs

Treatment experience	Number of subjects treated with DRV QD, n	Number of subjects with ≥1 (emergent) primary PI RAM, n (%)
TN	804[a]	0 (0%)
TE	883[b]	3 (0.3%)

PI, protease inhibitor; RAM, resistance-associated mutation; DRV, darunavir; QD, once-daily; TN, treatment-naïve; TE, treatment-experienced.
[a]For 7 TN subjects (ARTEMIS [n=4],GS-US-299-0102 [n=1],GS-US-216-0130 [n=2]), the following NRTI RAMs were observed: M184V (n=3), K65R+M184V (n=1), M184I/V (n=1), M184V+K70E (n=1), and K65K/R+M184M/I (n=1).
[b]For 5 TE subjects (GS-US-216-0130 [n=1], ODIN [n=4]), the following NRTI RAMs were observed: M184V (n=2), V75I+M184V (n=1), T215F (n=1), and T215Y (n=1). For 2 TE subjects (INROADS [n=2]), the following non-nucleoside reverse transcriptase inhibitor RAMs were observed: E138K+M230L (n=1) and L100L/I+E138E/G+Y181Y/C (n=1).

506 EVOLUTION OF GAG AND GP41 IN PATIENTS RECEIVING FIRST-LINE PI AND NNRTI REGIMENS

Justen Manasa[1], Vici Varghese[1], Soo-Yon Rhee[1], Jeffry Fessel[2], Karen S. Jang[1], Elizabeth White[1], David Katzenstein[1], Robert Shafer[1]
[1]Stanford Univ, Stanford, CA, USA, [2]Kaiser Permanent Med Cntr, San Francisco, CA, USA

Background: Several groups have proposed that genotypic determinants in HIV-1 gag matrix (MA) and the gp41 cytoplasmic domain (gp41-CD) cause PI resistance. However, MA and gp41-CD mutations selected by PI therapy have not been identified.

Methods: We sequenced PR, RT, complete gag and/or gp41 (codons 35-345) before and after therapy in 60 pts with VF on an initial PI (n=40) or NNRTI (n=20) regimen including 34 pts from ACTG A5202 and 26 California clinic pts. To detect selective evolutionary pressure on gag and gp41, we calculated the dn/ds ratios in these genes for each sequence pair. Additionally, each gag and gp41 amino acid was characterized by its prevalence in subtype B sequences from PI-naïve pts in the LANL HIV Sequence Database. We then identified mutations in our dataset at which conserved or relatively common amino acids changed to an amino acid that was >10-fold less prevalent and defined these as having a high selection index.

Results: Of 40 pts with VF on an initial PI regimen, we sequenced gag + gp41 in 12 pts, gag alone in 12 pts, and gp41 alone in 16 pts. The median duration of PI therapy was 24.5 months. 36 received ATV/r and 4 received LPV/r. 37 pts attained plasma VL <100 copies/ml at some time during therapy. 3 developed PI DRMs and 10 developed NRTI DRMs. Of 20 pts with VF on an initial NNRTI regimen, we sequenced gag + gp41 in 13 pts, gag alone in 3 pts, and gp41 alone in 4 pts. There were no significant differences between the PI and NNRTI pts in the median number of gag (6 vs 6), gag-MA (4 vs 4), gp41 (4 vs 3), or gp41-CD (1 vs 3) mutations or in the gag dn/ds (0.14 vs 0.22), gag-MA dn/ds (0.20 vs. 0.39), gp41 dn/ds (0.27 vs 0.27), or gp41-CD dn/ds (0.36 vs. 0.30) ratios. In PI pts, there were 27 gag changes (12 in MA) with a high selection index including two in 2 pts: A115T and the P2/NC cleavage site mutation M378I. There were also 38 gp41 changes (27 in CD) with a high selection index including two in 2 pts: A268V and S293N. However, there was no significant difference in the number of highly selected gag, gag-MA, gp41, or gp41-CD changes between the PI and NNRTI pts.

Conclusion: There was no evidence for an overall difference in selective pressure in gag-MA or gp41-CD between patients receiving an initial PI or NNRTI regimen. The accumulation of additional sequences obtained before and after PI therapy will make it possible to determine whether individual gag-MA or gp41-CD mutations are selected by PIs.

507 RESISTANCE TO POTENT AND BROADLY ACTIVE HIV-1 MATURATION INHIBITORS

Justin A. Kaplan[1], Emiko Urano[1], Sherimay Ablan[1], Nishani Kuruppu[1], David Martin[2], T.J. Nitz[2], Ritu Gaur[3], Carl Wild[2], Eric Freed[1]
[1]NCI, Frederick, MD, USA, [2]DFH Pharma, Inc, Gaithersburg, MD, USA, [3]South Asian Univ, Akbar Bhawan, Chanakyapuri, New Delhi, India

Background: Maturation Inhibitors (MI), a new class of anti-HIV-1 compounds, act by blocking the maturation of virions into infectious particles. Bevirimat (BVM), a first-in-class betulinic acid-based compound, acts by blocking a late step in protease-mediated Gag processing: the cleavage of the capsid-spacer peptide 1 (CA-SP1) intermediate into mature CA. BVM was shown to be safe and effective in reducing viral loads in patients. However, polymorphisms in the SP1 region of Gag reduced HIV-1 susceptibility to BVM in patients, effectively halting BVM's clinical development.
Methods: We carried out extensive screening to identify BVM derivatives with both increased potency against multiple HIV-1 clades and activity against primary isolates containing polymorphisms in SP1. Compound activity was tested in biochemical and biological assays measuring CA-SP1 processing and virus replication kinetics. Selection experiments with both clade B and clade C isolates were performed to identify mutations that confer resistance. Virological, structural, and molecular approaches were applied to elucidate the mechanism of resistance for each mutant. Further, combination assays with MIs alongside protease or integrase inhibitors were performed to determine inhibitor synergy or antagonism.
Results: We identified a set of BVM derivatives that are markedly more potent than BVM against clade B HIV-1 and show robust activity against SP1 polymorphic strains, clinical isolates, and some BVM-resistant mutants. Selection experiments with a clade B isolate identified an SP1-A1V mutation, and a CA-P157A mutation located in the major homology region (MHR) of CA. Selections with a clade C isolate identified several mutations in SP1. The P157A mutant was resistant to not only BVM and the second-generation BVM analogs but also to the structurally distinct maturation inhibitor PF-46396. Analysis of the HIV-1 database reveals that Ala1 of SP1 and Pro157 of CA are conserved in ~99.95% of available sequences. To date, combination assays with potent MI candidates have shown no antagonism with protease or integrase inhibitors.
Conclusion: This study identifies a panel of BVM derivatives that display improvements upon BVM in antiviral potency and breadth of activity. The characterization of resistant mutants provides insights into the structure of the maturation inhibitor binding site and the role of SP1 and the CA MHR in virus assembly and maturation. This study supports ongoing clinical development of this class of inhibitors.

508 CLINICAL VALIDATION OF A NOVEL DIAGNOSTIC HIV-2 TOTAL NUCLEIC ACID QUALITATIVE ASSAY

Ming Chang[1], Audrey J. Wong[1], Dana Raugi[1], Robert Smith[1], Jose Ortega[1], Selly Ba[2], Moussa Seydi[2], Geoffrey Gottlieb[1], Robert Coombs[1], for the University of Washington-Dakar HIV-2 Study Group
[1]Univ of Washington, Seattle, WA, USA, [2]CHU de Fann, Dakar, Senegal

Background: The current 4th-generation HIV diagnostic screening algorithm utilizes HIV-1/2 antigen/antibody combination immunoassays. Reactive samples are then tested by orthogonal immunoassays to confirm and discriminate between HIV-1 and HIV-2 antibodies. Additional HIV nucleic acid testing (NAT) is often required to resolve indeterminate or undifferentiated HIV seroreactivity. Undetectable HIV-2 plasma RNA (<10 copies/mL) is reported in one-third of treatment-naïve HIV-2-infected patients; as such, a second-line NAT that detects HIV-2 DNA/RNA in peripheral blood mononuclear cells (PBMC) is essential to confirm HIV-2 infection in this circumstance.
Methods: We developed and validated an HIV-2 total nucleic acid (TNA) test using the Abbott m2000 platform. Amplification of human DNA and internal control RNA was used to assess for sample quality and assay inhibitors. Assay sensitivity was evaluated by testing known copies of HIV-2 plasmid DNA mixed with 1 million PBMC. Matched plasma and PBMC samples were collected from 25 HIV-1, 30 HIV-2, 8 HIV-1/2 dual-seropositive and 25 HIV-seronegative participants. Diagnostic performance was evaluated by comparing the outcome of the HIV-2 TNA assay with the results obtained by the Abbott HIV Ag/Ab Combo assay (Combo) and the Bio-Rad Multispot HIV-1/HIV-2 Rapid Test.
Results: The assay sensitivity was 26 TNA copies/million cells (95% CI, 18-55 copies/million cells). Thirty of thirty (100%; 95%CI lower bound 88.4%) PBMC samples from HIV-2 seropositive participants tested positive for HIV-2 TNA, including 21 samples from participants with undetectable HIV-2 plasma RNA. All thirty matching plasma samples from the HIV-2 TNA-positive participants were reactive for Combo. Among these thirty Combo-reactive samples, twenty nine were confirmed HIV-2 Ab positive and one was nonreactive by Multispot. Plasma samples from 50 HIV-2 TNA-negative individuals were confirmed non-reactive for HIV-2 Ab. Thus, the overall agreement between the HIV-2 TNA assay and the combined results of the immunoassays was 98.8% (79 of 80). The TNA assay also detected HIV-2 in 7/8 PBMC samples from HIV-1/-2 dually infected participants with undifferentiated Multispot and Geenius HIV-1/HIV-2 assays seroreactivity.
Conclusion: Our HIV-2 TNA assay detected HIV-2 in PBMC from serologically HIV-2 reactive, HIV indeterminate, and HIV undifferentiated individuals with undetectable plasma HIV-2 RNA, and is suitable for confirming HIV-2 infection in the CDC HIV testing algorithm.

509 EVALUATION OF FDA-APPROVED RAPID HIV TESTS FOR LABORATORY DIAGNOSIS OF HIV INFECTION

Kevin P. Delaney, Steven Ethridge, Hongwei Jia, Silvina Masciotra, Laura Wesolowski
CDC, Atlanta, GA, USA

Background: The 2014 revised CDC/APHL Guidelines for Laboratory Diagnosis of HIV infection recommend that reactive antigen/antibody (ag/ab) screening tests be followed by a supplemental antibody test capable of differentiating HIV-1 from HIV-2. However, there is currently only one such supplemental test approved and available for use in the United States. We investigated the performance of other FDA-approved single-use HIV tests when used in this step in an HIV testing algorithm.
Methods: Stored plasma or serum specimens from a study conducted in Los Angeles, California from 2003-2007 were used in this analysis. 707 specimens previously reactive on at least one FDA-approved ag/ab screening test, from 5,470 persons screened for HIV and 403 persons recruited with known HIV infection, were tested with 8 FDA-approved rapid HIV tests. We compared these test results with those from the Geenius HIV-1/HIV-2 differentiation assay. As in the guidelines, specimens with non-reactive results on the supplemental test after a reactive ag/ab test were categorized as HIV-infected or false-reactive on the screening test based on the Aptima HIV-1 qualitative RNA test result.
Results: All FDA-approved rapid tests performed similarly to the Geenius assay in terms of ability to differentiate true infection from false-reactive results for specimens from persons without early HIV infection (Table 1). The Insti HIV-1/HIV-2 antibody test and Determine HIV-1/HIV-2 Combo correctly identified 5/8 early infection specimens; all had been non-reactive using Geenius and all other rapid tests. However, these two tests also returned reactive results in 3-4 specimens (<1/1000 screened) that were HIV-1 Western blot and Aptima negative.
Conclusion: All FDA-approved rapid tests could serve the role of a supplemental test in the HIV-1 diagnostic algorithm. Although they don't differentiate HIV-1 from HIV-2, HIV-2 remains rare in the US and would be identified when a quantitative HIV-1 viral load was performed at HIV care initiation. Likewise, the few false-reactive rapid tests could also be resolved during clinical follow-up. Factors such as speed with which results can be returned and care initiated and simplicity of both testing and result reporting make these other rapid tests good alternatives for the second step in the HIV diagnostic algorithm. These data suggest other rapid tests should be considered as options for this step in future updates to laboratory testing algorithm guidelines.

Table 1: Comparison of rapid test results when performed after reactive antigen/antibody screening tests in the CDC/APHL Algorithm for Laboratory Diagnosis of HIV infection

	CDC/APHL laboratory algorithm result					
	Negative		Early infection[a]		Established infection[a]	
	Rapid test result					
Rapid HIV Test	False Positive[b]	True Negative	False Negative[c]	True Positive	False Negative[c]	True Positive
Total		42		9		656
Geenius HIV-1/HIV-2	0	37	8	0	0	655
Insti HIV-1/HIV-2	4	12	4	5	1	655
DPP HIV-1/HIV-2	2	14	9	0	1	655
StatPak HIV-1/HIV-2	0	37	8	0	8	636
Oraquick HIV-1/HIV-2	0	42	9	0	4	651
Determine HIV-1/HIV-2 Combo	3	39	3	5	1	651
Multispot HIV-1/HIV-2	1	39	8	0	1	626
Unigold HIV-1	0	37	8	0	4	642
Reveal HIV-1	0	36	8	0	1	646

[a]Early infection are those specimens with HIV-1 Western blot negative, APTIMA HIV-1 Qualitative RNA assay positive results; Established infection are those with an HIV-1 Western blot positive result. [b]This would end the algorithm and results would be reported (incorrectly) as HIV-positive. [c]These specimens would continue in the algorithm to nucleic acid testing and be resolved at that step.

510 PERFORMANCE OF DRIED BLOOD SPOTS AS A SAMPLE TYPE FOR HIV AG/AB COMBO ASSAY

Vera Holzmayer, Kelly Coller, Jill Fuhrman, Mary Rodgers, Gavin Cloherty
Abbott Labs, Abbott Park, IL, USA

Background: In resource limited settings, the use of Dried Blood Spots (DBS) for HIV viral diagnosis and monitoring has become a necessity for improved patient management. In this study, we evaluated the performance of the Abbott ARCHITECT HIV Ag/Ab Combo assay using DBS samples.
Methods: Whole blood (WB) from matched pairs of HIV infected plasma/WB samples was spotted on the Whatman 903 cards, dried overnight, eluted, and tested with HIV Ag/Ab Combo assay. Reproducibility of the test results was assessed using triplicates of the 12mm and 6mm DBS from four HIV samples. DBS stability was evaluated on samples stored for up to 14 days at -20oC, room temperature (RT) and +37oC. To evaluate sensitivity, DBS from 500 HIV infected subjects were tested and compared to matched plasma. Reproducibility of the DBS results with low plasma signal to cutoff ratio (S/CO) levels was evaluated by testing 12 samples in replicates.
Results: DBS results were reproducible in both 12mm (CV 1-8.3%) and 6-mm (CV 1.9-5.8%). S/CO from 12mm DBS were up to 2 fold higher compared to 6mm. DBS remained HIV reactive after 14 days storage. We observed <7% drop in S/CO at -20oC, <12% at RT and ≤20% at +37oC on day 14. Of 500 DBS samples with HIV Ag/Ab reactive matched plasma, 471 (94.2%) were reactive and 29 (5.8%) nonreactive. All samples with a plasma S/CO>23 (n=465) were reactive by DBS. Of the 35 samples with S/CO<23 only 6 (17%) DBS were reactive. DBS replicates for samples with 7-30 S/CO in plasma were concordant for 11 samples and discordant for only one sample. For 2 samples with 7-10 S/CO in plasma all replicates were nonreactive (n=40, CV 24.7%). Of 9 samples with 11-23 S/CO in plasma, 4 were reactive in all replicates (n=76, CV 2.52-19.97%) and 5 were nonreactive in 78 of 80 (97.5%) replicates (CV 4.99-172.6%); one sample with plasma S/CO>23 was reactive in all replicates (n=20, CV 4.44%).The detection rate for samples with plasma S/CO range of 7-10, 11-23 and >23 was estimated as 0%, 52% and 100% respectively.
Conclusion: The results indicate that Whatman 903 DBS is a suitable specimen type for the ARCHITECT HIV Ag/Ab Combo assay. The assay reliably detects HIV-1 p24 antigen/anti-HIV-1/-2 antibodies in DBS with corresponding plasma S/CO>23. According to the Abbott Global Surveillance Database where samples were collected all over the world and characterized over 15 years, 95.4% of HIV-infected specimens have HIV Ag/Ab results of S/CO>23 in plasma or serum.

511 RECENCY STAGING OF HIV INFECTIONS THROUGH ROUTINE DIAGNOSTIC TESTING

Eduard Grebe[1], Alex Welte[1], Jake Hall[2], Michael P. Busch[3], Shelley Facente[4], Sheila Keating[2], Kara Marson[4], Christopher D. Pilcher[4], **Gary Murphy**[2], for the CEPHIA
[1]Stellenbosch Univ, Stellenbosch, South Africa, [2]Pub Hlth England, London, UK, [3]Blood Systems Rsr Inst, San Francisco, CA, USA, [4]Univ of California San Francisco, San Francisco, USA

Background: Assay based staging of HIV for recency of infection has multiple purposes: at the population level, it enables cross-sectional incidence estimation. At the individual level, at diagnosis (as available in some national programmes and being contemplated in other large scale systems) recent/non-recent infection classification helps guide psychosocial support strategies, contact tracing, or inclusion in clinical trials. However, as recency testing is currently a specialist service using custom incidence assays, there is additional expense, and a delay between HIV diagnosis and the delivery of the recency result. Given the high dynamic range inherent in widely used (primarily chemiluminescent) diagnostic platforms, we explore whether this unutilized information (signal/cutoff ratio, S/CO) can immediately stage new diagnoses as recent/non-recent, or at least identify specimens that need not be referred for specialised recency testing, allowing prioritisation of specimens.
Methods: 2500 specimens with good clinical characterisation were tested diagnostically on the Abbott Architect 4th generation assay and by Sedia Limiting Antigen Assay for recency determination. We compared the recency classifications based on the two platforms through a number of regressions and correlations, and estimated mean duration of recent infection (MDRI) for a number of thresholds on Architect S/CO values.
Results: At Architect S/CO < 150, MDRI was 163 days, and ART naïve False Recent Rate (FRR) was 2.7%, comparable with previously published LAg values. Individual Architect/LAg results were highly correlated (r=0.81). Figure 1 shows the probability of specimens classifying as LAg recent (ODn<1.5) as a function of ARCHITECT S/CO: more than 80% of specimens with S/CO<100, less than 5% with S/CO>400, and less than 1% of specimens with S/CO>500 scored recent by LAg (ODn<1.5).
Conclusion: An unmodified chemiluminent HIV immunoassay assay can provide comparable information to a custom recency staging assay. In the context of population HIV incidence surveillance, this can lead to simple, readily transferable and cheaper testing protocols. At patient diagnosis, this could enirely eliminate the costs and delays associated with additional recency testing, or at least enable selection of a subset of specimens (high- or low- enough reactivity) for which final staging assignments do not require additional testing.

512 DEVELOPMENT OF A HIGH-THROUGHPUT MULTIPLEX ASSAY FOR MEASURING HIV INCIDENCE

Martin Stengelin[1], Daisy Roy[1], Sudeep Kumar[1], Kara Marson[2], Steven G. Deeks[2], Gary Murphy[3], Michael P. Busch[4], **Christopher D. Pilcher**[2]
[1]Meso Scale Diagnostics, LLC, Rockville, MD, USA, [2]Univ of California San Francisco, San Francisco, CA, USA, [3]Pub Hlth England, London, UK, [4]Blood Systems Rsr Inst, San Francisco, CA, USA

Background: In order to assess the impact of HIV prevention strategies, it is critical to measure the rate at which new HIV infections are occurring in populations. To achieve needed performance requirements (e.g., long "mean duration of recent infection" [MDRI], low "false recent rate" [FRR]), most programs currently use multi-assay algorithms including avidity-modified antibody and viral load measurements. MULTI-ARRAY® is a high throughput technology with a wide dynamic range and low non-specific binding that has been used successfully in a variety of applications. We determined feasibility of an improved multiplex HIV incidence assay to discriminate recent from longstanding HIV infection using the MULTI-ARRAY platform.

Methods: Using MULTI-ARRAY technology, we measured antibody quantity and avidity to ten HIV proteins. A total of 28 assays were run: standard serology assays with and without disrupting agent, and an assay format with anti-human IgG capture and detection with SULFO-TAG™ labeled HIV antigens. 96 samples were tested: 75 samples from the CEPHIA Developmental set (http://www.incidence-estimation.com/cephiaqueries/cephiaDB/overview), 15 samples from the SeraCare Incidence/Prevalence Performance Panel, and additional samples from apparently healthy individuals.

Results: Several assays could discriminate recent from longstanding HIV infection even as stand-alone markers if samples from Elite Controllers were excluded: the standard serology format with and without pretreatment for gp120 and gp160, and the antibody capture format for gp120 showed 100% sensitivity and 100% specificity in this sample set. In a ROC analysis, 13 assays had ROC areas of 0.90 or better (elite controllers excluded). None of the tested antibody assays was able to discriminate elite controllers; thus including a (antigen or nucleic acid) viral load assay would be required. The time dependence of the gp120 and gp160 ECL signal as function of time from seroconversion indicates that the signal continues to increase even after two years, indicating that determining an MDRI of well over a year at a low FRR is feasible.

Conclusion: Assays to discriminate recent from longstanding HIV infection have been developed in a 96-well high-throughput assay format for the MESO® SECTOR S 600 Imager and the MESO QuickPlex® SQ 120.

513 IDENTIFYING RECENT HIV INFECTIONS: AN INDIVIDUALIZED ASSESSMENT OF RISK

Jaythoon Hassan[1], Joanne Moran[1], Kate O'Donnell[2], Gary Murphy[3], Derval Igoe[2], Cillian De Gascun[1], for the Monitoring Recently Acquired HIV Infection Group
[1]Univ Coll Dublin, Dublin, Ireland, [2]Hlth Protection Surveillance Cntr, Dublin, Ireland, [3]Pub Hlth England, London, UK

Background: The accurate identification of recent HIV infection remains an important area of research to inform population-based HIV prevention and treatment intervention policies. Methods that use cross-sectional testing and biomarker information might be an alternative to longitudinal testing, as combinations of serological and molecular methods can potentially provide a means to identify recent HIV infections. The aim of this study was to develop a predictive scoring system which was based on combining the results of Schupbach's Line assay algorithm 15.1 and the viral load (VL) to predict the risk of having recently acquired HIV infection.

Methods: New HIV diagnoses in Ireland from January to April 2016 (n=151) were included in the study. All samples were tested on the Sedia limiting antigen avidity assay (LAg). The normalised cut-off in the LAg assay is 1.5. Schupbach's (2015) Algorithm 15.1 was applied to the Line assay results. This algorithm is derived from antibody reaction scores to HIV antigen bands on the LIA strip. Patients on antiretroviral treatment or previously diagnosed (>12 months) were excluded from the analysis (n=43). The Speigelhalter-Knill-Jones method was used to develop a predictive scoring system which is based on the LAg assay as a gold standard as this assay demonstrated 100% accuracy in identifying recency based on samples tested from the CEPHIA repository. Viral loads above the median of the cohort were used as an indicator of recency.

Results: Patient demographics showed that the recent cohort was predominantly male (87.1%) and MSM/bisexual (78.9%). The LAg assay and LIA Algorithm 15.1 identified 32 cases (21.2%) and 19 cases (12.6%) respectively as recently acquired HIV. The median viral load of the cohort was 16,428 copies/ml (log4.2). The results of the regression model including both the LIA and the HIV VL to predict recency are shown in Table 1. Combining both Algorithm 15.1 and VL demonstrated that the observed risk in our cohort of being recent is 100%. Using standard laboratory assays, this predictive scoring system allows an individualised assessment of risk for prediction of recency.

Conclusion: We have developed a predictive scoring system which is based on combining LIA Algorithm 15.1 and the VL. This proof of concept analysis has demonstrated that data such as LIA and VL can be used to develop a multiassay algorithm to accurately predict an individual's risk of recently acquired HIV infection.

Table 1. Regression Model including both the LIA and the Median HIV Viral Load to predict recency.

	Observed Risk of being recent	Risk Predicted in new scoring system
LIA alone - recent	78.9%	78.8%
VL alone - recent	25.5%	24.2%
Both tests suggest recency	100%	81.3%
Both tests suggest non recency	11.9%	10.8%
LIA suggests recency but VL does not	60%	75.3%
VL suggests recency but LIA does not	10.3%	14.9%

514 THE HIV GENOMIC INCIDENCE ASSAY MEETS FRR AND MDRI PERFORMANCE STANDARDS

Sung Yong Park[1], Tanzy Love[2], Kathryn Anastos[3], Jack DeHovitz[4], Chenglong Liu[5], Kord Kober[6], Mardge Cohen[7], Wendy Mack[1], Elizabeth T. Golub[8], **Ha Youn Lee**[1]
[1]Univ Southern California, Los Angeles, CA, USA, [2]Univ of Rochester, Rochester, NY, USA, [3]Albert Einstein Coll of Med, Bronx, NY, USA, [4]SUNY Downstate Med Cntr, Brooklyn, NY, USA, [5]Georgetown Univ, Washington, DC, USA, [6]Univ of California San Francisco, San Francisco, CA, USA, [7]Stroger Hosp, Chicago, IL, USA, [8]Johns Hopkins Univ, Baltimore, MD, USA

Background: HIV incidence is a direct metric of HIV intervention and prevention trial efficacy. Incidence assay performance is evaluated by mean duration of recent infection (MDRI) and false-recent rate (FRR). A low FRR is required for accurate incidence determination and a higher MDRI allows incidence estimation from a smaller sample size. There is an immediate need for an assay meeting performance standards (MDRI > 1 year and FRR < 1%) to estimate incidence using a single measure.

Methods: We conducted a meta-analysis of HIV envelope genes sequenced from 438 incident specimens and 305 chronic specimens representing a wide range of geographic locations, subtypes, risk behaviors, ART experiences, viral loads and CD4 T cell counts. The genomic assay's FRR was measured from chronic specimens collected at least 2 years after documented HIV infection using the genome similarity index (GSI) as a biomarker of recency. The incident specimens included 186 serial HIV sequence samples likely collected within 6 months of infection (Fiebig stage IV). In order to estimate the MDRI, we statistically modeled the average GSI dynamics with a logistic regression assuming individual variabilities in a Beta distribution. We then tested our genomic assay by sequencing 407 HIV envelope gene segments from 15 Women's Interagency HIV Study (WIHS) seroconverters who were followed from HIV negative status. To assess how closely the WIHS cohort GSI dynamics resemble the Beta distribution estimate, each WIHS specimen's standardized residual was evaluated and the Anderson-Darling test was conducted.

Results: All except one chronic specimen had GSIs below 0.67, yielding a FRR of 0.33 [0-1.0] % with a 2-year cutoff. The GSI probability density function estimated from 438 incident specimens peaked close to a GSI of 1 in early infection and a GSI of 0 around 2 years post infection. Around 1 year post infection the GSI probability density function peaked

at both ends of the GSI spectrum. The resulting MDRI was estimated to be 420 [357, 469] days. Both standardized residuals and the Anderson-Darling tests suggest that our WIHS cohort sequence dataset was statistically consistent with the model GSI dynamics.
Conclusion: This is the first incidence assay conforming to FRR and MDRI performance standards. Signatures of HIV gene diversification offer a foundation for a precise genomic assay with a desirable temporal range of incidence detection. Our finding suggests great promise for realizing accurate cross-sectional incidence surveys.

515 DURATION OF ACUTE HEPATITIS C INFECTION AND IMPLICATIONS FOR INCIDENCE ESTIMATION

Eshan Patel[1], Anna Eisenberg[2], Jeffrey Quinn[1], Thomas C. Quinn[3], Aaron Tobian[1], Oliver Laeyendecker[2]
[1]Johns Hopkins Univ, Baltimore, MD, USA, [2]NIAID, Baltimore, MD, USA, [3]NIAID, Bethesda, MD, USA

Background: Accurate measures of HCV incidence are needed for surveillance and prevention efforts. Acute HCV infection is a stage of recent infection (virologically+ but IgG antibody[Ab]-), but the duration of this state may vary depending on the assays used. We compared the duration of acute HCV infection before seroconversion as defined by various assay algorithms, and examined their impact on the precision of biomarker-based incidence estimation.
Methods: Retrospective analysis of data from HCV seroconversion panels of initially uninfected individuals, sampled at a median of 5-day intervals (SeraCare and Zeptometrix), was used estimate the mean duration of acute HCV infection (the average duration between infection and Ab seroconversion). To estimate the date of infection, HCV uninfected individuals were assayed by nucleic acid testing (NAT) for HCV RNA detection and/or by the Abbott Murex HCV Ag/Ab Combo Assay. The estimated date of HCV IgG Ab seroconversion was monitored by various serologic assays. Using days before seroconversion as the unit of analysis, the mean duration of acute HCV infection was calculated using binomial regression with a logit cubic functional form and a maximum likelihood approach.
Results: The range in the mean duration of acute infection was 20 to 35 days depending on the assay used to identify initial infection and IgG Ab seroconversion (Table 1). NAT testing resulted in longer estimated period of acute infection than using the Ag/Ab Combo Assay by approximately 6-9 days (Table 1). Although there is a loss in the mean duration of acute infection by using the Ag/Ab Combo Assay, this did not meaningfully affect sample size considerations for precise incidence estimation in many hypothetical contexts. To achieve a relative standard error of 20% for an expected incidence estimate of 20%, a survey of 1700 individuals would be required for the largest estimated interval of acute infection from these data (35 days). To achieve the same precision with a 20 day acute interval (smallest interval), the survey size would need to be increased to 4400.
Conclusion: Efforts to optimize biomarker-based methods to estimate the population-level incidence of HCV infection may yield a sensitive and powerful tool to actively monitor the progress toward the WHO's goal of HCV elimination by 2030. Employing acute screening in cross-sectional testing algorithms would extend the window period of identifying a 'recent' infection, but this will be dependent on the combination of assays used.

Table 1. Mean Duration of Acute Infection Before Hepatitis C IgG Antibody Seroconversion.

Detection of Infection	Detection of Seroconversion †	Mean Duration of Acute Infection (95% CI) ††	No. of Recent Samples	No. of Subjects Evaluated†††
Architect Combo Ag/Ab	Abbott Architect Anti-HCV Assay	20 (14, 27)	69	18
Positive by NAT (RNA+)	Abbott Architect Anti-HCV Assay	26 (19, 33)	100	25
Architect Combo Ag/Ab	Ortho HCV Version 3.0 ELISA	20 (12, 33)	54	13
Positive by NAT (RNA+)	Ortho HCV Version 3.0 ELISA	28 (21, 37)	89	19
Architect Combo Ag/Ab	Abbott Murex 4.0 ELISA	26 (20, 33)	77	19
Positive by NAT (RNA+)	Abbott Murex 4.0 ELISA	35 (31, 40)	100	20

† *Assays used a signal-to-cut-off ratio of >1 to determine positivity, as recommended by the manufacturer.*
†† *95% confidence intervals were calculated using subject-level bootstrapping (resampling 1,000 replicates).*
††† *The differential sample sizes reflect both discordant testing but also the sensitivity of each assay.*

516 HEPATITIS C VIRUS GENOTYPE AND IG-G AVIDITY RESPONSE DURING RECENT INFECTION

Veronica Bruce[1], Eshan Patel[2], Andrea Cox[2], Shruti H. Mehta[2], Denali Boon[2], Jacob Konikoff[2], David Thomas[2], Thomas C. Quinn[3], Kimberly Page[1], Oliver Laeyendecker[3]
[1]Univ of New Mexico, Albuquerque, NM, USA, [2]The Johns Hopkins Univ, Baltimore, MD, USA, [3]NIAID, Bethesda, MD, USA

Background: Recently declared WHO hepatitis C virus (HCV) elimination goals include a 90% reduction in HCV infection by 2030. However, accurate tools to monitor reduced HCV incidence are lacking. We assessed the association of HCV genotype and the antibody avidity response during recent infection, and evaluated the impact on parameters for cross-sectional incidence estimation.
Methods: Serum or plasma samples from participants with known duration of HCV infection were obtained from participants enrolled in prospective cohort studies: The U Find Out (UFO) Study and the Before and After Acute Study of Hepatitis (BBAASH) Study. We tested HCV IgG antibody positive and HCV RNA positive samples (n=246) from HIV negative participants (n=93) with the HCV Ortho Avidity Assay. The time-scale origin of this analysis was the estimated Ab seroconversion date. The mean duration of recent infection (MDRI) was calculated at varied thresholds of the Ortho Avidity Assay and by the infected visit-specific HCV genotype. The MDRI estimate, indicative of how long an individual appears recently infected within the first two years, was calculated by binomial regression with a logit cubic functional link and a maximum likelihood approach. Subject-level bootstrapping was used to calculate 95% confidence intervals (10,000 replications).
Results: Among 246 samples from HCV infected persons: 173 (70.3%) were genotype 1; 15 (6.1%) were genotype 2; 42 (17.1%) were genotype 3; 3 (1.2%) were genotype 4; and 13 (5.3%) were of an unspecified genotype. Increases in HCV IgG antibody avidity correlated with the days post-seroconversion for both genotype 1 and non-genotype 1 infections (Figure). At an Ortho HCV Avidity Index cut-off of 30%, the MDRI was lower for genotype 1 infections (155 days [95% CI, 127-185]) than for non-genotype 1 infections (287 days [95% CI, 139-415]). Using the same cut-off, the MDRI for all available data was 199 days [95% CI, 146-256]. When reducing the Ortho HCV Avidity Index cut-off to 20%, all MDRI point estimates decreased but the lower limit remained above 100 days. Similar estimates were obtained in a sensitivity analysis using a log-log link function.
Conclusion: When assessed with the HCV Ortho Avidity Assay, we detected shorter MDRI in persons with genotype 1 infection. If confirmed with a larger sample, these results indicate more work is needed to ascertain how to apply MDRI to mixed genotype populations for HCV incidence estimation.

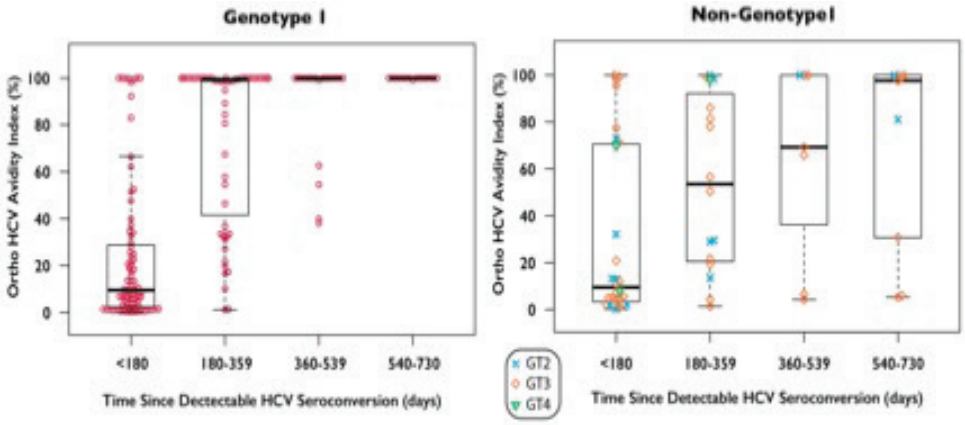


Figure. Differential Increase in HCV IgG Antibody Avidity by Genotype.

517 IDENTIFICATION OF RISK FACTORS FOR HEPATITIS-C TESTING IN NON-BIRTH COHORT PATIENTS

Amanda E. Smart[1], Alexander Geboy[2], Peter Basch[2], Whitney Nichols[2], Alexander Zeymo[2], Idene Perez[2], Maria Hafeez[2], Ilan Fleisher[2], Stephen Fernandez[2], Dawn Fishbein[2]
[1]Georgetown Univ, Washington, DC, USA, [2]MedStar Hlth Rsr Inst, Hyattsville, MD, USA

Background: CDC data from 2012 indicated that 45% of HCV-infected people reported no known risk factors (RFs). However, initiating widespread, automated, RF-based screening outside the Birth Cohort (BC) (b. 1945-1965) is challenging as RFs are often unstructured, not searchable data within Electronic Health Records (EHR). Therefore, testing non-BC patients solely based on RFs has the potential to miss a substantial number of HCV infected patients.

Methods: In July 2015 HCV testing data was collected on non-BC patients who were HCV tested across MedStar Health, as a presumptive marker for high risk. A 1:3 case-control retrospective nested chart review was conducted. HCV RFs and opiate prescriptions were manually abstracted from the EHR; other variables were collected using Explorys. Univariate and multivariate logistic regression models were utilized to determine HCV Ab positive (Ab+) predictors.

Results: Between 7/1/15 and 6/30/16, 329 charts out of 4,741 HCV tested non-BC patients were reviewed; 80 (1.7%) HCV Ab+ or indeterminate patients were compared to 249 randomly selected HCV Ab negative (Ab-) controls (see table for demographics). In bivariate analysis, patients with at least one documented RF were more than twice as likely to have Medicaid ($p = 0.005$) and more than three times as likely to have Medicare than patients without RFs ($p = 0.0034$). Eighteen (23%) HCV Ab+ and 123 (49%) HCV Ab- had no identified RFs; 6 (33%) HCV Ab+ reported RFs only after a positive test result. In multivariate logistic regression, persons were more likely to be HCV Ab+ if they: reported drug use (OR_{adj}26, CI95 6.1-109.8), had Medicaid v. private insurance (3.4, 1.6-7.7), and were white v. other races (3.4, 1.5-7.9), adjusting for demographic factors and opiate prescriptions; sex behavior was no longer significant (ROC = 0.823). There was a significant interaction between age over 40 and opiate prescription use; these groups were 11x more likely to be HCV Ab+ (CI95 1.6-74.8).

Conclusion: In non-BC patients, drug use remained a significant predictor of HCV positivity, as in the BC. However, white race was more significant than black race, which is reversed compared to the BC. The CDC has reported an increase of HCV in opiate abusers, and our data shows some signal for increased risk as well. RF testing in non-BC patients has the potential to miss a significant number of HCV Ab+ patients. Given patient- and provider-level barriers in elucidating RFs, universal HCV Ab testing may be warranted.

	HCV Ab Negative (N = 249)		HCV Ab Positive or Indeterminate (N = 80)		Total (N = 329)		
	RFs [n (%)]	No RFs [n (%)]	RFs [n (%)]	No RFs [n (%)]	HCV Ab- [n (%)]	HCV Ab+ [n (%)]	*p**
Total	126 (50.6)	123 (49.4)	62 (77.5)	18 (22.5)	249 (100)	80 (100)	
Age Below BC (Mean ± SD)	33±8	35±9	38±9	38±9	34±8	38±9	*0.002*
Age Above BC (Mean ± SD)	76±4	78±4	74±2	77±4	77±4	74±3	
Female	62 (24.9)	77 (30.9)	25 (31.3)	11 (13.8)	139 (55.8)	36 (45.0)	
Race: Black	55 (22.1)	65 (26.1)	21 (26.3)	8 (10.0)	120 (48.2)	29 (36.3)	
White	38 (15.3)	40 (16.1)	34 (42.5)	7 (8.8)	78 (31.3)	*41 (51.3)*	*0.014*
Unspecified/Other	33 (13.3)	18 (7.2)	7 (8.8)	3 (3.8)	51 (20.5)	10 (12.5)	
Insurance: Medicare	20 (8.0)	9 (3.6)	11 (13.8)	1 (1.3)	29 (11.6)	12 (15.0)	
Medicaid	23 (9.2)	16 (6.4)	25 (31.3)	5 (6.3)	39 (15.7)	*30 (37.5)*	*< 0.001*
Private	80 (32.1)	92 (36.9)	25 (31.3)	12 (15.0)	172 (69.1)	37 (46.3)	

518 ESTABLISHING EPIDEMIOLOGICAL LINKAGE WITHIN HCV NETWORKS USING GENETIC DISTANCE

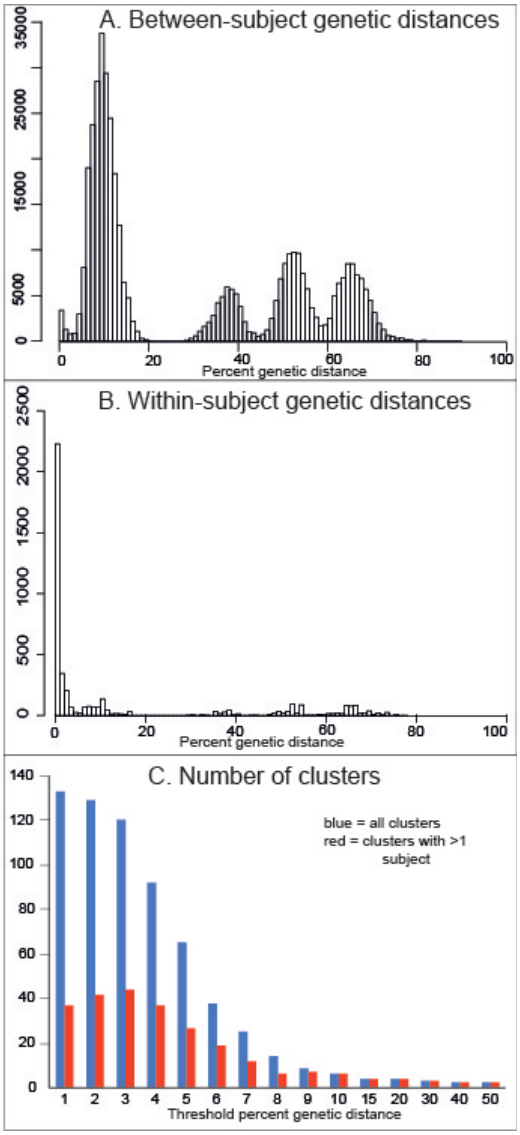
Rebecca Rose[1], Susanna Lamers[2], Guido Massaccesi[3], William Osburn[3], Stuart C. Ray[3], Andrea Cox[3], Oliver Laeyendecker[4]
[1]BioInfoExperts, Norfolk, VA, USA, [2]BioInfoExperts, Thibodaux, LA, USA, [3]Johns Hopkins Univ, Baltimore, MD, USA, [4]NIAID, Baltimore, MD, USA

Background: Viral genetic data can be used for inferring epidemiological networks. We investigated genetic distance thresholds to identify clusters of related viruses among a highly networked population of people who inject drugs (PWID) from Baltimore.

Methods: We used 908 core-E1 bulk sequences from 166 PWID in the Baltimore Before and After Acute Study of Hepatitis (BBAASH) cohort. All subjects had known dates of infection, including chronically infected individuals and those who experienced clearance and re- or co-infection. The number of sequences per subject ranged from 1 to 31, with follow up extending to 14 years post infection. We used HIV-TRACE to calculate genetic distance with the TN93 model and to determine clusters using pairwise genetic distance thresholds of 1-50%. The total number of clusters was calculated using the between-subject distances.

Results: Sequences were predominantly subtype 1a(71%), as well as 1b(7%), 2b(10%) and 3a(11%). 28 subjects were infected with >1 sub/genotype during serial sampling. The largest peak in the distribution of genetic distances between subjects was at 10% (Fig 1A), corresponding to the within subtype comparisons (primarily subtype 1a). A gamma-shaped curve with a peak at 0 and nadir at 2% was present, corresponding to the within-subject comparisons. Four additional peaks were evident at 10%, 35%, 50%, and 65%, which corresponded to comparisons between within genotype, 1a and 1b, 1a/1b and 3a, and 1a/1b/3a and 2b, respectively. In contrast, the bulk (64%) of the distribution of distances within subjects was <3% (Fig 1B). This dataset also showed peaks at 10%, 35%, 50%, and 65%, although these larger distances were much less frequent than in the between-subject dataset. As expected, the number of clusters was highest at 1% (n=133) and decreased slightly at 2% (n=129) and 3% (n=120). A sharp decline was evident until 9% (n=9) and plateaued thereafter (Fig 1C, blue bars). The number of clusters with >1 subject at each threshold was highest at 3% (Fig 1C, red bars). However, the overall proportion of clusters containing >1 subject was lowest at 1% genetic distance (37/133) and increased with distance until all clusters contained >1 subject at 10%.

Conclusion: A threshold of 3% appears to distinguish within versus between-subject distances, for the Core-E1 sequence of HCV. Even at the lowest estimate genetic distance (1%), 28% of clusters contained more than one subject, thus suggesting a high degree of connectivity in this cohort.



519 HIGH PREVALENCE OF HEPATITIS-C VIRUS AMONG HIV NEGATIVE MSM IN AMSTERDAM PREP PROJECT

Elske Hoornenborg[1], Maria Prins[1], Roel C.A. Achterbergh[1], Maarten F. Schim van der Loeff[1], Udi Davidovich[1], Arjan Hogewoning[1], Henry J.C. de Vries[1], Janke Schinkel[2], Thijs J.W. van der Laar[3], for the Amsterdam PrEP Project Team in the HIV Transmission Elimination AMsterdam Consortium (H-Team)
[1]Pub Hlth Service Amsterdam, Amsterdam, Netherlands, [2]Academic Med Cntr, Amsterdam Zuidoost, Netherlands, [3]Stichting Sanquin Bloedvoorziening, Amsterdam, Netherlands

Background: Since 2000, hepatitis C virus (HCV) has emerged as a sexually transmitted infection among men who have sex with men (MSM). Although the reported HCV epidemic has largely been confined to HIV infected MSM, spread to HIV negative MSM might have gone unnoticed.

Methods: HIV negative MSM at high risk for acquiring HIV who enrolled in the Amsterdam Pre-Exposure Prophylaxis (AMPrEP) project at the Public Health Service of Amsterdam were tested for the presence of HCV antibodies and HCV RNA. If positive for HCV RNA, part of the HCV NS5B gene (709 bp) was sequenced. Maximum likelihood phylogenies (GTR substitution model) were constructed to compare HCV sequences from HIV negative AMPrEP participants, Dutch HIV positive MSM with acute or chronic HCV infection (n=246; period 2000-2015) and Dutch risk groups other than MSM (n=153; period 2000-2015). Bootstrap values >70% define robust phylogenetic clusters.

Results: By June, 2016, all 376 HIV negative MSM had been enrolled in AMPrEP; 18 (4.8%, 95%CI 2.8%-7.5%) were positive for anti-HCV or HCV-RNA at baseline. Of those, 15/18 (83%) had detectable HCV-RNA, including one without detectable anti-HCV. HCV genotyping showed genotype 1a (73%), 4d (20%) and 2b (7%). Of the 15 participants with HCV RNA, 13 (87%) were part of 6 robust MSM-specific HCV clades containing MSM with and without HIV. This included 9/11 HIV negative MSM infected with HCV-1a (Figure 1), and all 4 MSM infected with HCV-4d and HCV-2b. Four out of 17 (24%) HCV positive participants reported injecting drugs in the 3 months preceding PrEP start, compared to 11/354 (3.1%) among HCV negative participants, p-value<0.01.

Conclusion: The HCV prevalence of 4.8% among HIV-negative MSM eligible for PrEP was higher than the prevalence around 1% previously observed among Dutch HIV negative MSM attending an STI clinic and not on PrEP. HCV-mono-infected MSM were infected with the same MSM-specific HCV strains circulating among HCV/HIV co-infected MSM, suggesting spread from HIV positive to high-risk HIV negative MSM. Routine HCV testing should be offered to MSM at high risk for HIV and included in PrEP guidelines.

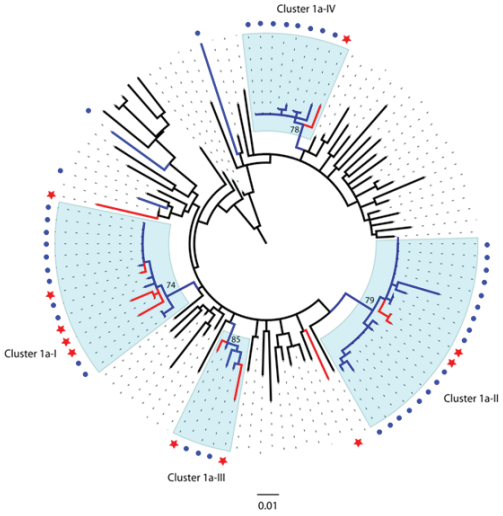


Figure 1: HCV NS5B gene phylogenetic tree for HCV subtype 1a, comparing HCV sequences from HIV negative MSM applying for PrEP (red branches, red stars) with HCV sequences obtained from HIV positive MSM (blue branches, blue dots) and unrelated Dutch risk groups (black branches)

520 HIGH CLUSTERING OF ACUTE HCV INFECTIONS AMONG HIV-POSITIVE MEN WHO HAVE SEX WITH MEN

Eve Todesco[1], Nesrine Day[2], Corinne Amiel[3], Veronique Schneider[4], Georges Kreplak[2], Laurent Roudière[1], Stéphane Hué[5], Christine Katlama[1], Anne-Geneviève Marcelin[1], Marc-Antoine Valantin[1]
[1]Pitié-Salpêtrière Hosp, Paris, France, [2]Cerballiance Lab, Paris, France, [3]INSERM, Paris, France, [4]Tenon Hosp, Paris, France, [5]London Sch of Hygiene & Tropical Med, London, UK

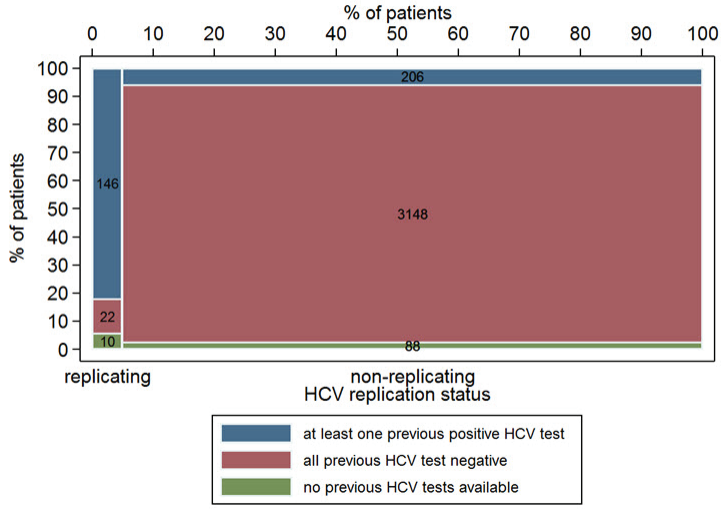
Background: Emerging acute hepatitis C virus (HCV) infections in HIV positive Men having Sex with Men (MSM) has been described in recent years. Moreover, a high rate of reinfection was recently emphasized among these patients, whereas the mode of contamination (sexual or by injecting drug) is still controversial. To study transmissions and better understand the epidemic, we explored virological relationships of acute HCV infections from a restricted geographical area of Paris.
Methods: Polymerase sequences (NS5b) were obtained by Sanger Sequencing (SS) from acute HCV infections, defined as a positive serology and/or a positive viral load < 12 months. Maximum likelihood phylogenies were estimated using FastTree 2.1 under a GTR+CAT model of nucleotide substitution with SH-like tests. More than 400 sequences from Pitié-Salpêtrière hospital HCV patients were used as reference for comparison. Clades with a branch support ≥80% and intra-clade genetic distances <0.03 nucleotide substitution per sites were considered as transmission chains.
Results: Sequencing of 80 acute HCV infections diagnosed during the period 2014-2016 from a neighborhood of center of Paris (« le Marais ») was performed. Patients were infected with HCV genotype 1a (50%), 4d (40%), 3a (7.5%) and 2k (2.5%) and 92.5% of them were coinfected with HIV. At least 81% (n=65) were MSM (15 with unknown sexual orientation). This was a recontamination for 20 patients. Twenty-two transmission chains were identified, including 53 acute Hepatitis C (of which 14 recontaminations) divided in 6 pairs of 2 patients and 14 clusters from 3 to 8 patients. Seven transmission chains were composed by only acute HCV whereas thirteen were mixed acute/chronic.
Conclusion: A high incidence of acute HCV infection has been found in HIV MSM patients in Paris and many of these HCV patients were part of a transmission chain. These results highlight the necessity of frequent HCV testing even after a successfull treatment. In this context of clustering, treatment strategies must be rethought and transmitted drug resistance mutations should be monitored in the future.

521 SYSTEMATIC HCV-RNA SCREEN IN HIV+ MSM REVEALS HIGH NUMBERS OF POTENTIAL TRANSMITTERS

Dominique L. Braun[1], Roger Kouyos[1], Benjamin H. Hampel[1], Christina Grube[1], Huldrych F. Günthard[1], Jürg Böni[2], Jan S. Fehr[1], for the Swiss HIV Cohort Study
[1]Univ Hosp Zurich, Zurich, Switzerland, [2]Univ of Zurich, Zurich, Switzerland

Background: The prevalence of sexually transmitted incident hepatitis C virus (HCV) infections among HIV-positive men who have sex with men (MSM) has increased worldwide, including an epidemic in Switzerland in MSM. The Swiss HCVree Trial (ClinicalTrials.gov NCT02785666) aims to implement a targeted HCV-RNA based assessment of the prevalence of replicating HCV infections in HIV-positive MSM participating in the Swiss HIV Cohort Study (SHCS), and thereafter to treat all HCV-RNA positive MSM with newest anti-HCV direct acting agents. Here we report on preliminary data from the screening period.
Methods: Between October 1st 2015 and May 31th 2016 we offered a systematic, intensified HCV-RNA polymerase chain reaction (PCR) based screening to all MSM participating in the SHCS, which is estimated to represent 75% of all HIV-infected MSM living in Switzerland. Participants were screened at least once at the occasion of their regular clinical HIV visit. Liver transaminases were measured simultaneously, considering >50 U/l as above the upper limit of normal. HCV-RNA testing was done centralized at a single lab using the Abbott RealTime HCV assay with a limit of detection of 12 IU/ml.
Results: Overall, 3'792 individuals are recorded as MSM in the SHCS database, of them we screened 3'620 (95%) by HCV-RNA PCR. Hundred-seventy-eight (4.9%) out of these 3'620 MSM harbored a replicating HCV infection (Figure 1). Mean age of MSM was 49 years and 94% had suppressed HIV viremia, without differences between replicating and non-replicating HCV. Genotype (GT) 1 was the most prevalent GT (72%), followed by GT 4 (22%), GT 3 (5%), and GT 2 (1%). Of the 178 MSM with replicating HCV, 32 individuals (18%) had an incident HCV infection, without prior positive HCV test (e.g, HCV antibodies, HCV-RNA) recorded in the SHCS database. Eight of the MSM with an incident HCV (25%) presented with normal liver enzymes during the screening period.
Conclusion: We identified a high number of replicating HCV infections among HIV positive MSM participating in the SHCS, resulting in 5% prevalence in this population. A substantial proportion of MSM with replicating HCV presented with non-elevated liver enzymes. Thus, an intensified HCV-RNA based screening strategy among sexually active HIV-coinfected MSM is worth to detect potentially transmitters, and to offer universal treatment with DAAs in order to end the epidemic and to achieve a reduction of disease burden on a population level.

Figure 1: Proportion of MSM in the SHCS with a HCV-PCR screen, stratified by HCV replicating status and by newly detected (incident) and previously known HCV infection.



522 HCV IN DEMOCRATIC REPUBLIC OF THE CONGO: THE 2013–2014 DEMOGRAPHIC AND HEALTH SURVEY

Gavin Cloherty[1], **Vera Holzmayer**[1], Jacques Pepin[2], Eric H. Frost[2], Michael Fried[3], Anto Tshefu[4], Franck Fwamba[5], Jérémie Muwanga[5], Steven R. Meshnick[3], Jonathan Parr[3]
[1]Abbott Labs, Abbott Park, IL, USA, [2]Univ of Sherbrooke, Sherbrooke, Quebec, Canada, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC,USA, [4]Univ of Kinshasa, Kinshasa, Democratic Republic of the Congo, [5]Natl AIDS Control Prog (PNLS), Kinshasa, Democratic Republic of the Congo

Background: The burden of HCV in sub-Saharan Africa has been poorly studied, despite estimates indicating that the region harbors some of the highest viral hepatitis rates in the world. The 2013-2014 Demographic and Health Survey (DHS) of the Democratic Republic of the Congo (DRC) offered a unique opportunity to delineate the extent and characteristics of HCV infection in the country. Because the DHS is a nationally representative survey, we could estimate the national burden of infection in the DRC.
Methods: We extracted RNA from a subset of dried blood spots (DBS) collected during the DHS, including 1,009 adults at least 40 years of age, and performed high-throughput HCV viremia testing using the Abbott m2000 instrument (Abbott Molecular, Des Plaines, IL). The Abbott platform reliably identifies HCV RNA extracted from a 6mm punch from DBS prepared using 50uL of whole blood obtained from subjects with viral loads of at least 1,000 IU/mL and allows for high-throughput screening. HCV-positive samples underwent targeted sequencing for genotyping and phylogenetic analyses.
Results: Eleven infections were identified; the country-wide prevalence of HCV viremia was 1.1% among adults ≥ 40 years of age and 5.3% among those with HIV infection. All successfully genotyped cases were due to genotype 4 infection. We identified a cluster of cases in one province, Kasai Occidental, all of which failed initial genotyping attempts. To explore this finding, we are performing additional sampling of adults in this region and employing alternate sequencing approaches.
Conclusion: HCV is common among adults in the DRC and disproportionately affects those living with HIV. Based on recent DRC population estimates, 100,000 to 200,000 adults older than 40 years of age may have active infection and be eligible for treatment. Additionally, there appears to be a cluster of HCV cases in one region with undetermined genotype. Previous sequence analysis of HCV samples obtained from this region of the DRC led to the identification of a novel and rare Genotype 7 strain of HCV. Phylogenetic analyses of these cases may provide further insight into the diversity and evolution of HCV in sub-Saharan Africa. Finally, DBS-based HCV testing represents a useful tool for defining the burden of HCV viremia and can be easily incorporated into population-based surveys.

523 LOW HCV PREVALENCE AMONG HIV+ INDIVIDUALS IN SUB-SAHARAN AFRICA

Anne Loarec[1], Lucas Molfino[2], Kizito Walter[3], Winnie Muyindike[4], Valentina Carnimeo[1], Isabelle Andrieux-Meyer[5], Suna Balkan[6], Yvonne Nzomukunda[3], David Maman[7], Juliet Mwanga-Amumpaire[8]
[1]MSF, Epicentre, Paris, France, [2]MSF, Maputo, Mozambique, [3]MSF, Nairobi, Kenya, [4]Mbarara Univ of Sci and Tech, Mbarara, Uganda, [5]MSF, Geneva, Switzerland, [6]MSF, Paris, France, [7]Epicentre, Cape Town, South Africa, [8]MSF, Epicentre, Mbarara, Uganda

Background: Data on the burden of hepatitis C virus (HCV) in sub-Saharan Africa among HIV patients are critically needed. We present the results of the screening activities among HIV positive cohorts at 5 sites that are supported by MSF in 4 countries in Eastern and Southern Africa, namely Mbarara in Uganda, Kibera and Homa Bay both in Kenya, Maputo in Mozambique, and Chiradzulu in Malawi.
Methods: We included all HIV-positive adults screened between 2014 and 2016 for HCV antibodies at the 5 MSF-supported sites. For each site, a specific screening strategy was implemented in collaboration with the relevant Ministry of Health, according to the context and target population. The screening was done using a single test: OraQuick HCV Rapid Antibody Test (OraSure Technologies, Bethlehem, USA), followed by a viral load (RT-PCR) for confirmation of active infection.
Results: In Mbarara, Uganda, 18 (0.24%) out of 7,500 HIV patients, were tested positive with HCV serology test. In Kibera, Kenya, out of 4,500 patients screened, 10 (0.22%) were tested positive for HCV. In Maputo, Mozambique, the proportion was higher: 30 (1.15%) patients out of 2,600. In this latter site, the screening strategy targeted patients with advanced stage of disease or those belonging to a high-risk group, such as intravenous drug users. In Chiradzulu, Malawi, 385 HIV-positive patients were screened and only 2 (0.52%) tested positive for HCV. In Homa Bay, Kenya, out of 351 HIV-positive in-patients screened, one patient (0.28%) was tested positive. The proportion of patients with a positive HCV serology and a confirmed active infection (PCR-positive) varied across sites. A total of 5 (29%) patients out of 17 and 2 (20%) out of 10 were confirmed to have an active HCV infection in Uganda and Kenya, respectively. This proportion was higher in Mozambique where 26 (86%) out of 30 patients were confirmed to have active infection.
Conclusion: In 4 sub-Saharan countries, HCV prevalence among HIV positive people was low, between 0.05 and 1%. This is lower than found in previous estimates. HCV infection in the broader HIV-infected population does not seem to be a major public health issue in these settings. Nevertheless, data on specific high-risk groups such as intravenous drug users are still lacking. Our results underscore the need to target screening for HCV infection among high-risk groups.

Sites	N° patients screened	N° reactive HCV RDT	Proportion of positive serology	Detectable HCV VL / N° performed VL	Proportion of confirmed HCV active infection out of total screened	Remarks
Mbarara, Uganda	7500	18	0,24%	5/17 (29%)	0,07%	MoH HIV cohort
Nairobi, Kenya	4500	10	0,22%	2/10 (20%)	0,04%	HIV cohort of Kibera
Maputo, Mozambique	2600	30	1,15%	26/30 (86%)	1,00%	Advanced HIV disease or high risk groups
Chiradzulu, Malawi	385	2	0,52%	Not done	Not done	HIV cohort, under ARV Treatment for more than 10 years
Homa Bay, Kenya	351	1	0,28%	Not done	Not done	HIV patients in In-Patients Department

524 EFFECT OF OST AND PSYCHOTHERAPY ON HIV RISK AMONG HCV INFECTED INDIVIDUALS

Zahid A. Butt[1], Nabin Shrestha[1], Naveed Z. Janjua[2], for the BC-HTC Team
[1]Univ of British Columbia, Vancouver, British Columbia, Canada, [2]BC Cntr for Disease Control, Vancouver, British Columbia, Canada

Background: Hepatitis C Virus (HCV) and HIV infections co-occur in certain population groups because of shared risk factors. Limited data on time to HIV infection among HCV infected individuals is available. Understanding differences in HIV incidence among these individuals can help inform strategies to prevent HIV infection. We estimated the time to HIV diagnosis among HCV infected individuals and evaluated factors that could affect HIV infection risk.
Methods: The British Columbia Hepatitis Testers Cohort (BC-HTC) includes all BC residents (~1.5 million) tested for HCV or HIV from 1990 to 2013 and links medical visits, hospitalizations, cancers, prescriptions and deaths. All HCV positive and HIV negative individuals were followed for a positive HIV test to estimate adjusted hazard ratios (aHR) for factors associated with HIV infection using Cox proportional hazards regression.
Results: Of 36,163 individuals who were HCV positive and HIV negative at cohort entry, 2255 (6.2%) acquired HIV over 266,010 years of follow-up for an overall incidence rate of 8.5/1000PY (person years). The HIV incidence rate among HCV seroconverters was 10.7/1000PY versus 8.2/1000PY among those with prevalent HCV infection at diagnosis. Overall median [IQR] time to HIV infection was 3.36 [4.96] years, shorter for seroconverters than prevalent HCV infections (2.78 vs 3.52, p =0.003). In Cox regression, people who injected drugs (PWID) (aHR: 1.42, 95% CI: 1.29-1.57), those with Hepatitis B Virus (HBV) infection (aHR: 1.37, 95% CI: 1.19-1.58), men who have sex with men (MSM) (aHR: 5.91, 95% CI: 4.21-8.29), and urban residence (aHR: 1.40, 95% CI: 1.19-1.65) were associated with higher risk of HIV infection after adjusting for number of HIV tests. Opioid Substitution Therapy (OST) (aHR: 0.39, 95% CI: 0.33-0.45) and psychiatric counseling (aHR: 0.48, 95% CI: 0.44-0.54) were associated with lower risk of HIV infection.
Conclusion: Injection drug use, HBV coinfection, MSM, and urban residence increased the risk of HIV; while engagement in OST and mental health counseling reduced the risk of HIV infection among HCV infected individuals. *The BC-HTC team: Gesink D, Gilbert M, J Wong, M Kuo, A Yu, Alvarez M, Chong M, H Samji, J Buxton, Roth D, Consolacion T, Murti M, Ogilvie G, Balshaw R, M Tyndall, M Krajden

525 PROGRESSION OF LIVER FIBROSIS IN HIV-MONOINFECTED ADULTS WITH ELEVATED TRANSAMINASES

Rebecca Krakora[1], Mary McLaughlin[2], David E. Kleiner[3], Nina Kvaratskhelia[1], Raissa Canales Santos[4], Colleen Hadigan[2], Joseph A. Kovacs[1], Theo Heller[4], **Caryn G. Morse**[1]
[1]NIH, Bethesda, MD, USA, [2]NIAID, Bethesda, MD, USA, [3]NCI, Bethesda, MD, USA, [4]NIDDK, Bethesda, MD, USA

Background: High rates of non-alcoholic steatohepatitis (NASH) and fibrosis have been described in HIV-monoinfected populations. However, data on fibrosis progression in this population are limited. We assessed change in liver fibrosis over time by vibration-controlled transient elastography (VCTE) in a cohort of HIV mono-infected individuals with chronic elevations in serum transaminases.
Methods: Antiretroviral-treated HIV-infected adults with elevated serum transaminases enrolled in a natural history of liver disease and with at least two VCTE measurements ≥1 year apart were included in this analysis. Liver stiffness was assessed by VCTE (Fibroscan, Echosens, Paris). Clinical and laboratory variables at baseline were collected and associations with fibrosis progression, defined as an increase of ≥1 NASH Clinical Research Network (CRN) fibrosis stage as estimated by VCTE, were examined.
Results: Paired VCTE results were available for 42 patients. On baseline liver biopsy, the majority of patients (n=30) had non-alcoholic fatty liver disease (NAFLD), including 23 (55%) with NASH; the remaining had fibrosis without NAFLD (n=2) or non-specific changes, (n=10). Compared with baseline liver biopsy, baseline VCTE had good sensitivity and specificity with an area under the receiver-operating characteristic curve (AUROC) of 90% for detection of any fibrosis (NASH CRN F>0; 95% confidence interval 81-99%). Over a median of 4.8 years (range 1.4-8.6 years), increased liver stiffness consistent with fibrosis progression was seen in 10 (24%) patients, static disease in 25 (59%) and decreased stiffness consistent with fibrosis regression in 7 (17%). No association was seen between fibrosis progression and baseline biopsy findings, transaminase levels, body mass index, or time between measurements. In 15 participants who underwent a second liver biopsy after a median of 4.0 years (range 2.0-8.0 years), fibrosis progression was observed in 3 (20%).
Conclusion: Progression of liver fibrosis is frequently seen in HIV-monoinfected adults with persistent transaminase elevations. Further longitudinal study will help to better characterize the natural history of NAFLD and fibrosis in this population and establish if the natural history differs from that of HIV-negative populations.

526 GUT EPITHELIAL DAMAGE, IMMUNE ACTIVATION & LIVER FIBROSIS IN HIV AND HCV INFECTION

Michael J. Reid[1], Yifei Ma[1], Rebecca Scherzer[1], Jennifer Price[1], Audrey French[2], Michael Plankey[3], Carl Grunfeld[1], Phyllis Tien[1]
[1]Univ of California San Francisco, San Francisco, CA, USA [2]Rush Univ, Chicago, IL, USA, [3]Georgetown Univ, Washington, DC, USA

Background: Markers of gut microbial translocation and innate immune activation have been associated with liver fibrosis progression in HIV/HCV-coinfected persons. Yet, few studies have examined the extent to which immune activation is affected by HIV and HCV infection, gut microbial translocation, and liver fibrosis severity.
Methods: Stored plasma from 120 HIV+/HCV+, 262 HIV+/HCV-, 72 HIV-/HCV+, and 170 HIV-/HCV- enrolled in the Women's Interagency HIV Study and the Study of Visceral Adiposity, HIV, and HCV: Biologic Mediators of Steatosis (VAHH) were tested for intestinal fatty acid binding protein (IFABP, a marker of gut epithelial integrity) and soluble CD14 (sCD14, a marker of monocyte activation). Multivariable linear regression was used to evaluate the association of HIV and HCV with IFABP and sCD14 after adjustment for

demographic, lifestyle factors, body composition, and the AST to platelet ratio index (APRI, a marker of liver fibrosis). In analysis with sCD14, additional adjustment for IFABP was performed.
Results: After adjustment for demographic, lifestyle factors, and body composition, IFABP levels remained 110%, 77%, and 25% higher in the HIV+/HCV+, HIV+/HCV-, and HIV-/HCV+ compared to uninfected HIV-/HCV- controls (Table). APRI had no effect on the associations of either HIV-infected group (HIV+/HCV+ or HIV+/HCV-) with IFABP, whereas the association of HCV monoinfection (HIV-/HCV+) was slightly attenuated. After adjustment for demographic, lifestyle factors, and body composition, sCD14 levels were 37%, 20%, and 11% higher in the HIV+/HCV+, HIV+/HCV-, and HIV-/HCV+ compared to uninfected HIV-/HCV- controls. Additional adjustment for IFABP modestly attenuated the associations of both HIV-infected groups (HIV+/HCV+ and HIV+/HCV-) but to a much lesser extent in HCV monoinfection (HIV-/HCV+). By contrast, additional adjustment for APRI substantially attenuated the association of both HCV-infected groups (HIV+/HCV+ and HIV-/HCV+); but the attenuation was much less in HIV monoinfection (HIV+/HCV-).
Conclusion: HIV monoinfection is strongly associated with higher IFABP and sCD14 levels, HCV monoinfection to a lesser degree, and the contribution of both HIV and HCV infections appears additive. Gut epithelial damage contributes to immune activation in the setting of HIV, whereas liver fibrosis plays a greater role than gut epithelial damage in the setting of HCV. Our findings show that sCD14 is not a specific marker of gut microbial translocation.

527 VERTICALLY HIV/HCV- VS HCV-INFECTED CHILDREN: HCV TREATMENT & PROGRESSION TO FIBROSIS

Carolina Fernández McPhee[1], Talía Sainz[2], Loreto Hierro[3], Antoni Noguera-Julian[4], Maria José Mellado[2], Marta Montero[5], María Isabel González-Tomé[6], Paloma Jara[3], Carmen Díaz[3], Maria Luisa Navarro[1]
[1]Univ Hosp Gregorio Marañon, Madrid, Spain, [2]Hosp La Paz and IdiPAZ, Madrid, Spain, [3]Univ Hosp La Paz, Madrid, Spain, [4]Univ de Barcelona, Barcelona, Spain, [5]Hosp Univ y Politécnico La Fe, Valencia, Spain, [6]Univ Hosp 12 de Octubre, Madrid, Spain
Background: Chronic inflammation and activation of the immune system secondary to HIV infection have been suggested to potentially increase progression of HCV infection in co-infected patients. However, studies addressing the evolution to liver fibrosis and treatment response in vertically HIV/HCV co-infected children are scarce.
Methods: Retrospective, multicenter cohort study that included vertically HIV/HCV co-infected patients (COP) registered in the Spanish National Cohort of HIV-infected children (CoRISpe) and vertically HCV mono-infected patients (MOP) from a National Hepatology Reference Center, paired by sex and age, up to December 2015. Treatment-related characteristics and outcomes and progression to hepatic fibrosis were described. Advanced fibrosis was defined as liver stiffness ≥9.6kPa by transient elastography or fibrosis knodell score ≥3 by liver biopsy.
Results: A total of 142 patients (71 COP and 71 MOP) were included in the study. It was observed that there was no progression to liver fibrosis during childhood and it was after the age of 9 when patients became at risk. At the age of 20, 9/38 (23.7%) COP vs. 3/54 (5.5%) MOP had progressed to advanced fibrosis (p=0.012). Genotype (GT) distribution was as follow: GT1: 50% vs. 88.3%, GT2: 4.5% vs. 1.7%, GT3: 22.7% vs. 6.7% and GT4: 22.7% vs. 3.3% (all p<0.01). A total of 22 (29.7%) COP vs. 52 (70.3%) MOP received treatment against HCV using combined therapy with Peg-IFN/RBV, except 2 COP treated with Peg-IFN/RBV/telaprevir and 1 COP with Peg-IFN/RBV/boceprevir. At treatment initiation, COP were older compared to MOP: 17 years [15.75-19.25] vs.13 [8.25-15] (p<0.001) and HCV-RNA was no different: 5.8 log [5.2-6.6] vs. 5.6 [5-6.1] (p=0.65). COP had a worse hepatic condition: 40% had moderate to advanced fibrosis and 15% cirrhosis vs. 88.6% with no or mild fibrosis in MOP (all p<0.01). The proportion of HCV cured patients was similar in both groups (40.9% COP vs. 42.3% MOP) and although a higher proportion of cured MOP presented a hard to treat genotype, no significant differences were observed when compared to cured COP: 55.5% vs. 86.4% MOP (p=0.15).
Conclusion: No hepatic fibrosis was observed in HIV/HCV co-infected and HCV mono-infected patients during childhood. However, over 20% co-infected patients presented liver disease at the age of 20, suggesting that this population may benefit from early treatment of HCV as soon as new drugs are available for children. HCV treatment outcomes with Peg-IFN/RBV were no different between groups.

528 THE ASSOCIATION BETWEEN HCV AND COMORBID CONDITIONS IN 2 LARGE PATIENT COHORTS

Sarah E. Rowan[1], Joshua Durfee[1], David C. Tabano[2], Suzanne Dircksen[1], Edward Havranek[1], Aimee Truesdale[1], Arthur Davidson[1]
[1]Denver Hlth and Hosp Authority, Denver, CO, USA, [2]Kaiser Permanente Colorado, Denver, CO, USA
Background: Hepatitis C (HCV) causes high rates of liver-related morbidity and mortality. The association between HCV and other common medical conditions has been less well characterized. Further, variations in these HCV associations across health care institutions based on demographic and clinical characteristics have yet to be fully described.
Methods: Electronic medical records of two large integrated health care systems (Denver Health [DH] and Kaiser Permanente Colorado [KP]) were queried to identify all HCV-related testing between January 1, 2008-December 31, 2014. The testing cohorts were stratified by evidence of infection (detectable HCV RNA) versus no HCV infection (no antibody detected or detectable antibody but no detectable RNA). Groups were characterized by demographic variables and comorbid conditions as defined by Elixhauser ICD-9 codes. Comorbid conditions associated with HCV infection were analyzed though multivariate logistic regression using a stepwise approach.
Results: In the DH system, 28,849 individuals were tested for HCV, of whom 2,018 (7%) had evidence of current HCV infection. In the KP system, 81, 419 individuals were tested for HCV; 1,644 (2%) had evidence of HCV infection. Among tested individuals in both systems, HCV-infected individuals were older and more often Black and male. Cirrhosis, liver cancer, HIV, renal disease, cardiovascular disease, mental illness, alcohol abuse, tobacco use, illicit drug use and death were significantly more common among HCV-infected individuals (see Table). Diabetes was more common among HCV-infected individuals in the KP system only; COPD was more common among HCV-infected individuals in the DH system only. In multivariate logistic regression analyses, the adjusted odds ratios for cirrhosis, mental illness and liver cancer were statistically significant for HCV-infected individuals while renal disease, cardiovascular disease and death were not significantly associated with HCV infection.
Conclusion: Among individuals tested for HCV in these two large, integrated health care systems, HCV infection was common. While several comorbid conditions were more frequently observed among HCV-infected individuals, multivariate analysis showed significant associations for cirrhosis, liver cancer and mental illness, suggesting the high prevalence of many comorbid conditions among HCV-infected individuals may be more associated with socio-demographic characteristics, substance abuse and other comorbid conditions than with HCV infection directly.

Table 1. Comorbid Conditions Associated with HCV Infection among Cohorts of Individuals Tested for HCV in Two Large, Integrated Health Care Systems, Denver, CO 2008-2014

Comorbidities	Crude OR (95% CI)		Adjusted OR (95% CI)*	
	DH	KP	DH	KP
Cirrhosis	7.35 (6.55, 8.26)	4.13 (3.47, 4.91)	4.03 (3.53, 4.60)	14.23 (12.34, 16.41)
Renal Disease	1.31 (1.14, 1.52)	0.81 (0.70, 0.95)	0.71 (0.60, 0.837)	0.73 (0.61, 0.87)
Mental Illness	1.95 (1.77, 2.13)	1.22 (1.10, 1.37)	1.40 (1.26, 1.56)	1.24 (1.11, 1.38)
Cardiovascular Disease	1.8 (1.65, 1.99)	1.27 (1.14, 1.41)	0.90 (0.80, 1.00)	0.86 (0.76, 0.98)
Liver Cancer	8.23 (5.87, 11.54)	3.06 (2.05, 4.57)	2.89 (1.97, 4.23)	3.24 (2.33, 4.51)
Death	2.10 (1.68, 2.63)	1.99 (1.60, 2.47)	0.80 (0.63, 1.03)	0.93 (0.76, 1.14)

*controlling for patients' age, gender, race, insurance status and clinical characteristics

529 CAUSE & PREDICTORS OF MORTALITY IN AN HIV/HEPATITIS-C–COINFECTED COHORT IN SCOTLAND

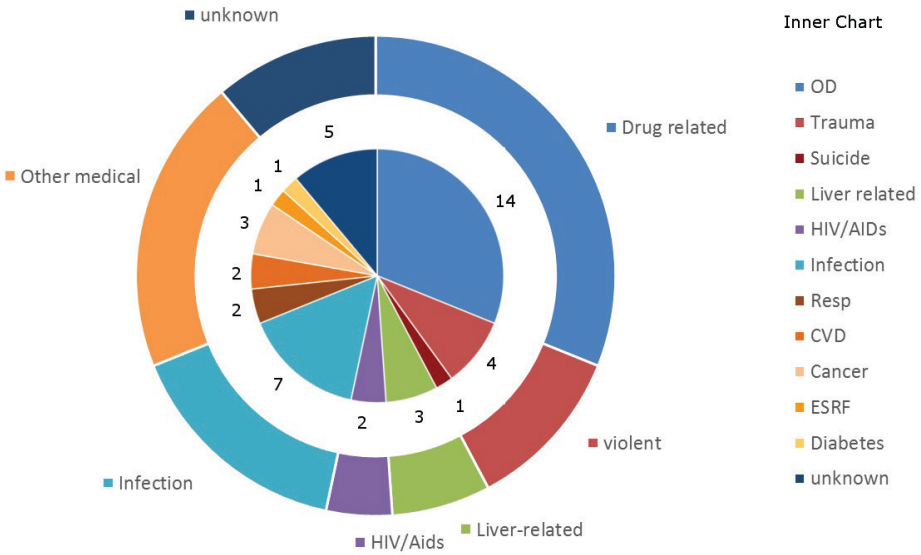
Rebecca Metcalfe[1], Gordon Proctor[2], Joe Schofield[3], Emma Thomson[2]
[1]Brownlee Cntr for Infectious Diseases, NHS Greater Glasgow and Clyde, Glasgow, UK, [2]Univ of Glasgow, Glasgow, UK, [3]Pub Hlth Protection Unit, NHS Greater Glasgow and Clyde, Glasgow, UK

Background: Cohort studies report the prevalence of HIV/hepatitis C (HCV) co-infection to range from 2.4% to 14% across the world and it is recognised that this group are associated with an increased all-cause and liver-related mortality when compared to HIV and HCV mono-infected patients. A few studies have reported on common causes of death in HIV/HCV co-infection but the results are conflicting. We sought to determine the common causes of mortality in our Scottish co-infected cohort and compare the characteristics of this group to the co-infected patients who remain in care, to determine predictive factors to all cause mortality.

Methods: A retrospective cohort review of all patients co-infected with HIV and HCV was carried out, covering a 15 year period. Hospital medical records, coroner records and national registry records were reviewed to collect data on those patients who had died. Data was complied on cause of death, HIV and liver related markers and compared with data of co-infected patients who have not died and statistical analysis performed.

Results: Over 15 years, there were 45 deaths in the HIV/HCV cohort, with a total follow-up time of 540 years and an all-cause mortality rate of 7.78/100 person years. Figure 1 shows the number and primary cause of death recorded for this cohort. Of the drug related deaths, a prescribed opiate substitute (methadone) was a contributor in 93%. Factors that were found to be significant predictors of all cause mortality were low CD4 count, high HIV viral load and even in patients not recorded as having had a liver-related death, lower albumin, higher bilirubin levels* and prolonged INR. *when atazanavir use was excluded

Conclusion: In this study we found that drug related causes were the most common cause of death (31%) in HIV/hepatitis C co-infected patients. Other infections were responsible in 16% and liver-related deaths and HIV/AIDs were responsible for only 11%. We found that liver biochemistry markers can be used to determine risk of all-cause mortality in HIV/HCV co-infected patients and this suggests that liver dysfunction may adversely impact on the likelihood of overdose (even when not recorded as a contributor to death). The majority of drug related deaths were due to a prescribed opiate substitute which raises concerns about opiate prescribing in those with HIV/HCV co-infection.



530 ADAR1 SNPS INVOLVED IN SEVERITY OF LIVER DISEASE IN HIV/HCV-COINFECTED PATIENTS

Luz M. Medrano[1], Amanda Fernández-Rodríguez[1], Juan Berenguer[2], María Á. Jimenez-Sousa[1], Teresa Aldámiz-Echevarría[2], Francisco Tejerina[2], Cristina Diez[2], Lorena Vigón[1], Salvador Resino[1], for the Institute of Health Carlos III (ISCII)
[1]Inst of Hlth Carlos III, Madrid, Spain, [2]Hosp Gregorio Marañon, Madrid, Spain

Background: The adenosine deaminase acting on RNA (ADAR) gene is an interferon-stimulated gene involved in liver injury protection by restraining the development of liver inflammation and fibrosis. ADAR gene encodes for four similar enzymes responsible for RNA editing, which have an antiviral activity against several RNA viruses including hepatitis C virus (HCV). Other viruses such as human immune deficiency virus (HIV) uses ADAR to promote its viral life cycle. Polymorphisms at ADAR gene have been associated with sustained virological response (SVR) in chronic hepatitis B virus and HCV-infected patients. Therefore, we hypothesize that ADAR SNPs could be associated with severity of liver disease in European HIV/HCV coinfected patients.
Methods: 5 SNP at ADAR gene (rs1127326, rs1127317, rs1127314, rs1127313, rs2229857) were genotyped in 220 European HIV/HCV-coinfected naive patients, by GoldenGate® assay (Illumina). Outcome variables liver disease-related were advanced fibrosis (F≥3, APRI≥1.5, and FIB-4≥3.25), severe necroinflammatory activity grade (A3) and fibrosis progression rate (FPR) higher than median (FPR≥0.075). We evaluated the genetic model that best fit our data, and multivariate regression model for analyzing the genetic association was used.
Results: All SNPs were in Hardy-Weinberg equilibrium (HWE) and were associated with severity of liver disease under an additive model of inheritance. After adjusting by the most important clinical and epidemiological covariates, we detected that the presence of rs1127326 T, rs1127317 G, rs1127314 G, and rs2229857 T alleles protects against advanced liver fibrosis measured as F≥3 (adjusted odds ratios (aORs)<0.45; p<0.05), APRI≥1.5 (aORs<0.50; p<0.05) and FPR≥0.075 (aORs<0.45; p<0.05). While rs1127313 G protects against advanced fibrosis measured as F≥3 FIB4≥3.25 and FPR≥0.075 (aOR<0.44; p<0.01). These polymorphisms showed a high linkage disequilibrium (D´=1), but the values of r2 were close to 0.5 in some cases. Three major haplotypes were found (rs1127326, rs1127317, rs1127314, rs1127313 and rs2229857): CTAAC (unfavorable alleles) 51%, TGGGT (favorable alleles) 28.8%, and CTAGC 19.4%. Haplotype association analysis showed similar results to single SNP analyses.
Conclusion: For the first time, we confirm that genetic variants at ADAR gene protect against severity of liver disease in HIV/HCV-coinfected patients. These findings could be used to improve therapeutic decision-making in clinical practice.

531 CB2-RR VARIANT, LINKED TO LIVER DAMAGE IN HIV/HCV CASES, MAY FAVOR HIV ACQUISITION

Caterina Sagnelli[1], Marco Merli[2], Caterina Uberti-Foppa[2], Giulia Bellini[1], Hamid Hasson[2], Nicola Coppola[1], Adriano Lazzarin[2], Evangelista Sagnelli[1], Francesca Rossi[1]
[1]Second Univ of Naples, Naples, Italy, [2]San Raffaele Scientific Inst, Milan, Italy

Background: The possibility that a rs35761398 variant of the CNR2 gene leading to the substitution of Gln (Q) of codon 63 of the cannabinoid receptor 2 (CB2) with Arg (R) may influence the acquisition of HIV infection and the clinical course of chronic hepatitis (CH) C we compared 166 HIV/HCV coinfected with 186 HCV-monoinfected patients
Methods: At enrolment, all patients, naïve for anti-HCV-treatment, underwent a percutaneous liver biopsy graded for fibrosis and necroinflammation (Ishak) by a pathologist unaware of the patients'data, and tested for CB2 rs35761398 polymorphism (TaqMan assay).
Results: In HIV/HCV coinfected setting, 45.8% of patients showed the CB2-RR variant, 38.6% QR and 15.7% QQ, whereas in HCV-monoinfection CB2-RR was 31.2%r, QR 57.5% and for QQ 11.3% (p=0.005). In HIV/HCV coinfection, patients with CB2-RR showed an HAI score >9 more frequently than those with CB2-QQ or QR (65.6 vs. 24.3 and 8.1%, respectively,p<0.001), whereas in HCV-monoinfection setting this score was more frequent in CB2-QQ patients than in those CB2-QQ or QR (p=0.02). Both in HIV/HCV coinfection and HCV-monoinfection, patients with HAI >9 (37 and 43, respectively), compared with those with a lower HAI score (129 and 143, respectively) showed higher AST (p=0.000001 in both) and ALT (p=0.0004 and p=0.000001, respectively), higher fibrosis score (3.6±1.5 vs 1.9±1.4 p<0.0001 in HIV/HCV coinfection and 3.5±1.4 vs 1.9±1.2, p=0.000001 in HCV-monoinfection) and a higher steatosis score (2.0±1.3 vs 1.6±1.3, p=0.03 in HIV/HCV coinfection and 1.6±1.3 vs. 1.1±1.2 in HCV-monoinfection, p<0.03 and 0.08, respectively). Besides, patients HIV/HCV coinfection with HAI>9 more frequently than those with lower scores presented the CB2-RR variant (65.6 vs. 47.3%,p<0.01), whereas no difference and lower prevalences were observed in group B (27.9 vs. 32.2%, respectively). Finally, in ANOVA analysis of HIV/HCV coinfection and HCV-monoinfection, the patients with CB2-RR variant (p=0.003) and male sex (p=0.002) were found prevalently distributed in group A.
Conclusion: The data suggest that the CB2-RR variant is associated with a more severe liver damage in CH patients with HIV/HCV coinfection and, in agreement with some recent experimental data, it might favor the acquisition of HIV infection. The data deserve further investigation.

532 PNPLA3_RS738409 VARIANT INFLUENCES PROGRESSION TO CIRRHOSIS IN HIV/HCV COINFECTION

Luis M. Real[1], Juan Macías[1], María Mancebo[1], Mario Frías[2], Giovanni Dolci[3], Francisco Téllez[4], Dolores Merino[5], Giovanni Guaraldi[3], Antonio Rivero-Juárez[2], Juan A. Pineda[1]
[1]Hosp Univ de Valme, Sevilla, Spain, [2]Hosp Univ Reina Sofía, Córdoba, Spain, [3]Univ of Modena and Reggio Emilia, Modena, Italy, [4]Hosp de La Línea, La Línea de la Concepción, Spain, [5]Complejo Hospario Univ de Huelva, Huelva, Spain

Background: Contradictory data about the impact of the rs738409 steatosis-related polymorphism within PNPLA3 gene on liver fibrosis progression in HIV/hepatitis C virus (HIV/HCV)-coinfected patients have been reported. Our objective was to test whether this, and other polymorphisms previously related to fatty liver disease in HIV infection linked to SAMM50 or LPPR4 genes, influence liver fibrosis progression in HIV/HCV-coinfected individuals.
Methods: 332 HIV/HCV-coinfected patients who consecutively attended four Spanish university hospitals from November 2011 to July 2013 were included. A liver stiffness cut-off of 14.6 kPa, as determined by transient elastography, was used to diagnose cirrhosis. Liver stiffness progression was studied in 171 individuals who had two available LS determinations without anti-HCV treatment between them. Moreover, 28 HIV/HCV-coinfected patients who underwent liver transplant, as well as, 19 non-cirrhotic coinfected individuals used as controls, were included in an additional study.
Results: Only rs738409 was associated with cirrhosis: 45 (29.6%) of 152 G allele carriers versus 36 (20.0%) of 180 CC carriers showed cirrhosis (multivariate p=0.018; adjusted odds ratio=1.98; 95% confidence interval=1.12-3.50). Also, 21 (30.4%) of 69 G allele carriers versus 16 (15.7%) of 102 CC patients showed significant liver stiffness progression (adjusted p-value=0.015; adjusted odds ratio=2.89; 95% confidence interval=1.23-6.83). Finally, the proportion of rs738409_G allele carriers was significantly higher in transplanted individuals than in controls (p=0.044, odds ratio=3.43; 95% confidence interval=1.01-11.70).
Conclusion: The rs738409 polymorphism is associated with liver fibrosis progression in HIV/HCV-coinfected patients.

533 FIB-4 CUTOFFS FOR PREDICTION OF LIVER-RELATED EVENTS IN HIV/HCV COINFECTION

Leire Pérez Latorre[1], Marisa Montes[2], Miguel A. Von Wichmann[3], Manuel Crespo[4], Marta Montero[5], Carmen Quereda[6], María J. Téllez[7], José M. Bellón[1], Juan González-García[2], **Juan Berenguer**[1]
[1]Hosp General Univ Gregorio Marañón, Madrid, Spain, [2]Hosp Univ La Paz, Madrid, Spain, [3]Hosp Univ Donostia, San Sebastián, Spain, [4]Complexo Hospario Univ de Vigo, Vigo, Pontevedra, Spain, [5]Hosp Univ y Politécnico La Fe, Valencia, Spain, [6]Hosp Ramon y Cajal, Madrid, Spain, [7]Hosp Clínico de San Carlos, Madrid, Spain

Background: FIB-4 accurately predicts hepatic fibrosis and is better than liver biopsy as a predictor of clinical outcomes in HIV/HCV-coinfected patients. We designed this study to define clinically useful FIB-4 cutoffs for prediction of liver-related events (LRE) in coinfected patients.
Methods: We analyzed HIV/HCV-coinfected patients with compensated liver disease and a baseline FIB-4 value in the GeSIDA 3603 cohort. The primary outcome was occurrence of LRE (decompensation or hepatocellular carcinoma, whichever occurred first). We used ROC curves to assess the diagnostic capacity of FIB-4 to predict LRE. As sustained viral response (SVR) or end-of-treatment response (ETR) modifies the natural history of hepatitis C, we selected patients without SVR or ETR during follow-up and randomly allocated them to an estimation cohort (EC) or a validation cohort (VC). First, we identified a cutoff value of FIB-4 to recognize patients who would not develop LRE. In order to estimate

the hazard of LRE for values above the cutoff, we assessed the assumption of linearity between FIB-4 and the proportion of LRE and then assessed the hazard of LRE according to different FIB-4 values above the cutoff using the Fine and Gray proportional hazards model and taking into account death as a competing risk.
Results: The study population comprised 657 patients (77% men, median age, 80% prior IDU, 34% advanced fibrosis). After a median follow-up of 5.4 years, 117 patients experienced an LRE, and 70 died. No significant differences in baseline characteristics or outcomes were detected between the EC (n=422) and VC (n=235). The AUROCs (95%CI) of FIB-4 for prediction of LRE in the EC and the VC were 0.77 and 0.79, respectively. Of all the possible values of FIB-4 in the EC ROC curves (min 0.44–max 16.61), we selected the cutoff of 1 with a negative predictive value of 96.9%. Per each unit of FIB-4 increase above 1 in the whole dataset (EC + VC), the sHR of LRE was 1.29 (95% CI: 1.21–1.38); P>0.001. The figure shows cumulative incidence plots of LRE for the various FIB-4 strata.
Conclusion: We found that a FIB-4 value of 1 identified 2 populations at risk of developing LRE. We also found that the hazard of LRE increased proportionally with FIB-4 values above this cutoff. These findings support the role of FIB-4 in the assessment of prognosis in patients with HIV/HCV coinfection. FIB-4 could prove particularly attractive for care or research settings that do not have access to TE.

534 EFFECTIVENESS OF DAAs IN HIV/HCV-COINFECTED PATIENTS WITH DECOMPENSATED CIRRHOSIS

Juan Berenguer[1], Lourdes Domínguez-Domínguez[2], Ángela Gil-Martín[3], Carmen Quereda[4], Teresa Aldámiz-Echevarría[1], Ignacio Santos[5], Pablo Ryan[6], Gabriel Gaspar[7], Inma Jarrin[8], Juan Gonzalez-Garcia[9]
[1]Gregorio Maranon Hosp, Madrid, Spain, [2]Hosp Univ 12 de Octubre, Madrid, Spain, [3]Servicio Madrileño de Salud, Madrid, Spain, [4]Hosp Ramon y Cajal, Madrid, Spain, [5]Hosp Univ de La Princesa, Madrid, Spain, [6]Infanta Leonor Hosp, Madrid, Spain, [7]Hosp Univ de Getafe, Getafe, 28905, [8]Inst of Hlth Carlos III, Madrid, Spain, [9]Hosp Univ La Paz, Madrid, Spain
Background: Clinical trials and real-life studies show high rates of success after all-oral therapy (Rx) with direct-acting antivirals (DAA) in HCV-monoinfected patients with decompensated cirrhosis (De-C). We assessed real-life outcomes of all-oral DAA Rx in HIV/HCV-coinfected patients with De-C.
Methods: MADRID-CoRe is a prospective registry of coinfected adults receiving all-oral DAA in hospitals of the Madrid Regional Health Service (SERMAS). De-C was defined as current/prior Child-Turcotte-Pugh (CTP) stage B or C or current/prior liver decompensation or hepatocellular carcinoma (HCC). The primary endpoint was sustained viral response at week 12 (SVR12). Between Nov. 2014 and Aug. 2016, 2662 coinfected individuals in MADRID-CoRe initiated DAA. Of the 1953 patients who were scheduled to finish treatment on May 31, 2016, severity of liver disease was as follows: no cirrhosis (No-C), 1066 (54.58%); compensated cirrhosis (Co-C), 736 (37.69%); De-C, 146 (7.48%); and unknown, 5 (0.26%).
Results: The main characteristics of the 146 patients with De-C were male sex, (102, 69.86%), median age of 51.58 yr., cART (125, 85.62%), and Rx-naïve (88, 60.27%). One patient had had a liver-transplant (LT), 7 were on the LT waiting list, and 15 had HCC. CTP scores were as follows: A, 75 (51.37%); B, 62 (42.47%); and C, 9 (6.16%). The HCV genotypes were G1a (49, 33.56%), G1b (32, 21.92%), G4 (30, 20.55%), G3 (22, 15.07%), and other (13, 8.90%). The DAA regimens were SOF/LDV (73), SOF+DCV (36), SOF+SMV (26), SOF+RBV (7), PrOD (3), and SMV+DCV (1). RBV was used in 69 patients (47.26%). SVR12 was achieved by 118 patients with De-C (80.82%). This figure was significantly lower than SVR12 achieved by patients with Co-C (91.17%) (P<.001) and patients with No-C (93.53%) (P<.001). The differences between Co-C and No-C were not statistically significant. Of the De-C patients without SVR12, 17 (11.64%) relapsed, 5 (3.42%) died, 2 (1.37%), stopped Rx owing to AE, 1 (0.68%) had breakthrough infection, and 3 (2.05%) stopped for other reasons. The variables associated with SVR12 in the multivariate logistic regression analysis are shown in the table.
Conclusion: The SVR12 rate with all-oral DAAs in coinfected patients with De-C was 81%, ie, significantly lower than in patients with compensated liver disease. Male sex and CTP stage C were associated with treatment failure in De-C. The long-term impact of all-oral DAA Rx in HIV/HCV-coinfected patients with De-C remains to be determined.

535 EFFICACY AND SAFETY OF DAAs IN CIRRHOTIC HCV/HIV COINFECTED PATIENTS

Jordi Navarro[1], Montse Laguno[2], Helem Haydee Vilchez[3], Josep M. Guardiola[4], Jose A. Carrion[5], Luis Force[6], Mireia Cairó[7], Carmen Cifuentes[8], Manuel Crespo[9], for the Catalano-Balear Study Group
[1]Hosp Univ Vall d'Hebron, Barcelona, Spain, [2]Hosp Clínic i Provincial de Barcelona, Barcelona, Spain, [3]Hosp Univ de Son Espases, Palma de Mallorca, Spain, [4]Hosp de la Santa Creu i Sant Pau, Barcelona, Spain, [5]Hosp del Mar, Barcelona, Spain, [6]Hosp de Mataró, Mataró, Spain, [7]Hosp Univ Mútua de Terrassa, Terrassa, Spain, [8]Hosp de Son Llàtzer, Palma de Mallorca, Spain, [9]Hosp Univ de la Vall d'Hebron, Barcelona, Spain
Background: There is scarce data regarding efficacy and safety of new direct antiviral agents (DAA) in cirrhotic HCV-HIV coinfected patients.
Methods: Multicenter prospective cohort analysis carried-out in 13 Spanish hospitals between January and December 2015. Inclusion criteria: 1) Cirrhosis diagnosed by transient elastography (TE>14.6KPa) or by sonographic, endoscopic and/or clinical data. 2) HCV-treatment based on DAA according to drug availability and physician discretion. 3) HCV-HIV coinfection with stable ART and controlled HIV infection. Primary endpoint: Overall efficacy, defined as the percentage of patients with undetectable HCV-RNA at week 12 after treatment (SVRS12). Secondary endpoints: Safety (percentage of withdrawal due to toxicity and/or hepatic decompensation) and efficacy according to regimen used and HCV genotype. Change in TE value after HCV treatment was also evaluated.
Results: A total of 201 patients started treatment. Mostly, male (n=150; 74.3%), Caucasian (n=198; 98%) and ex-IDUs (n=165; 81.7%). Genotypes: Gt-1a, 75 (37.1%); Gt-1b, 27 (13.4%); Gt-4, 51 (25.2%) and Gt-3, 38 (18.8%). Baseline median TE was 20.7KPa (IQR 16.1-33) and HCV-RNA $\log_{10}$ 6.1UI/mL (IQR 5.7-6.6). Most patients had Child-Pugh A class score (n=153; 75.7%) and 36 (17.8%) of them suffered prior hepatic decompensation. There were 104 (51.5%) pretreated patients, of whom 40.4% (n=42) with null response. SVR12 data was available in 170 (84.6%) patients. More commonly used regimens: SOF/LDV+RBV, 43 (25.3%) patients; SOF+SMV+RBV, 34 (20%); SOF/LDV, 26 (15.3%) and SOF+DCV+RBV, 25 (14.7%). Overall, 92.9% (158/170) of patients achieved SVR12, without differences between genotypes (Table 1). A significant lower SVR12 was observed in pretreated as compared to naive patients (88.8% vs. 97.5%; p=0.026). Causes of treatment failure were: 7 (4.1%) relapses, 2 (1.2%) lost to follow-up, 1 (0.6%) toxicity-related discontinuation, 1 (0.6%) hepatic decompensation and 1 (0.6%) viral breakthrough. RBV dose modification was needed in 20 (16.3%) cases, mainly due to anemia (n=17). On-treatment hepatic decompensation was seen in 4 (2.4%) patients (encephalopathy and ascites, 2 each). At week 12 after treatment, TE decreased a mean of 5.6 KPa (95%CI 1.8-9.2; p=0.004) as compared with baseline.
Conclusion: In our cohort, 92.9% of cirrhotic HCV-HIV coinfected patients achieved SVR12, which was associated with a significant decrease in TE. Only 2 (1.2%) patients had to stop treatment due to adverse events.

Table 1.SVRS12 according to genotype and regimen used.

Genotype	Duration	Regimen	SVR12 Yes	SVR12 No
1	12w	3D	3(100%)	
		3D+RBV	2(100%)	
		PR+SOF	1(100%)	
		SOF/LDV	13(100%)	
		SOF/LDV+RBV	23(95.8%)	1(4.2%)
		SOF+DCV	1(100%)	
		SOF+DCV+RBV	5(100%)	
		SOF+SMV	5(62.5%)	3(37.5%)
		SOF+SMV+RBV	18(94.7%)	1(5.3%)
		Total	71(93.4%)	5(6.6%)
	24w	3D+RBV	5(100%)	
		SMV+DCV		1(100%)
		SOF/LDV	1(100%)	
		SOF/LDV+RBV	5(100%)	
		SOF+DCV+RBV	2(100%)	
		SOF+SMV	3(100%)	
		SOF+SMV+RBV	1(100%)	
		Total	17(94.4%)	1(5.6%)
2	12w	SOF+RBV		1(100%)
		Total		1(100%)
3	12w	PR+SOF	3(100%)	
		SOF/LDV	1(100%)	
		SOF+DCV+RBV	3(100%)	
		Total	7(100%)	
	24w	SOF/LDV	1(100%)	
		SOF+DCV	3(100%)	
		SOF+DCV+RBV	14(100%)	
		SOF+RBV	1(100%)	
		Total	19(100%)	
4	12w	PR+SOF	4(100%)	
		SOF/LDV	7(100%)	
		SOF/LDV+RBV	10(76.9%)	3(23.1%)
		SOF+SMV	2(100%)	
		SOF+SMV+RBV	13(92.9%)	1(7.1%)
		Total	36(90%)	4(10%)
	24w	2D+RBV	2(66.7%)	1(33.3%)
		SOF/LDV	3(100%)	
		SOF+DCV+RBV	1(100%)	
		Total	6(85.7%)	1(14.3%)
Mixed (1/4)	12w	SOF/LDV+RBV	1(100%)	
		Total	1(100%)	
Unknown	12w	PR+SOF	1(100%)	
		Total	1(100%)	

536 INFLUENCE OF HIV ON CHANGES IN LIVER FUNCTION IN CIRRHOSIS AFTER ANTI-HCV TREATMENT

Juan Macías[1], Luis E. Morano-Amado[2], Francisca Cuenca-Lopez[3], Dolores Merino[4], Manuel Márquez[5], Karin Neukam[1], Maria J. Rios-Villegas[6], Francisco Téllez[7], Juan A. Pineda[1]
[1]Hosp Univ de Valme, Sevilla, Spain, [2]Hosp Univ Alvaro Cunqueiro, Vigo, Spain, [3]Hosp Univ Reina Sofia, Cordoba, Spain, [4]Complejo Hospario Univ de Huelva, Huelva, Spain, [5]Hosp Virgen de la Victoria, Málaga, Spain, [6]Hosp Univ Virgen Macarena, Sevilla, Spain, [7]Hosp de La Línea, La Línea de la Concepción, Spain

Background: In clinical trials with direct acting antivirals (DAA), improvements in liver function among individuals with cirrhosis have been found in up to two thirds of patients at SVR4. In real life, improvements in MELD score at SVR12 were detected less frequently. However, comparative data of liver function after SVR in patients with cirrhosis due to HCV with and without HIV coinfection are lacking. Therefore, we compared the changes in Child-Pugh-Turcotte (CPT) and MELD scores between the start of treatment with DAA without IFN and SVR12 in patients with cirrhosis due to HCV with and without HIV coinfection.

Methods: Individuals included in the HEPAVIR (NCT02057003), including HIV/HCV-coinfected patients, and GEHEP-MONO (NCT02333292), recruiting HCV-monoinfected patients, cohorts were selected if they met: 1) Cirrhosis; 2) SVR12 to IFN-free AAD. Changes in CPT and MELD indexes between the date of initiation of treatment (BL) and SVR12 in groups with [HIV (+)] and without HIV infection [HIV(-)] were compared.

Results: 309 patients, 195 (63%) of them HIV(+), were included in this analysis. The proportion of patients with CPT> 5 HIV(-) vs. HIV(+) was: BL, 32 (28%) vs. 72 (37%) (p = 0.112) and SVR12, 19 (17%) vs. 47 (24%) (p = 0.124). Among patients with CPT> 5, CPT decreased in 24 (75%) and increased in 3 (9.4%) HIV(-) (BL vs. SVR12, p <0.001), and decreased in 47 (65%) and increased 5 (6.9%) HIV(+) (BL vs. SVR12, p <0.001). The median (Q1-Q3) BL MELD was 7 (6-9) for HIV(-) and 8 (6-10) for HIV(+) (p = 0.003). At the time of the SVR12, the median MELD (Q1-Q3) was 7 (6-9) for HIV(-) and 8 (6-10) for HIV(+) (p = 0.082). In patients with MELD> 6, MELD decreased in 36/70 (51%) and increased in 19/70 (27%) HIV(-) (BL vs. SVR12, p = 0.059), and decreased in 81/143 (57%) and increased in 40/143 (28%) HIV(+) (BL vs. SVR12, p <0.001). The frequency of CPT≥1 and/or MELD≥2 points increase between BL and SVR12 was 18 (16%) HIV(-) and 26 (14%) in HIV(+) (87%) (p = 0.545). After multivariate analysis (adjusted by liver stiffness, albumin, bilirubin, creatinine and INR) HIV was not associated with CPT≥1 and/or MELD≥2 points increase (adjusted OR 1,04, 95% confidence interval: 0,45-2,42; p=0,929).

Conclusion: Although liver function of HIV(+) patients with cirrhosis due to HCV is worse than that of HIV(-) individuals at the start of DAA therapy, at SVR12 both groups show improvements in CPT and MELD. The frequency of liver function worsening after responding to DAA is similar in HIV(+) and HIV(-).

537 LIVER MICRORNA HSA-MIR-125A-5P MAY EXERT AN ONCOSUPPRESSOR EFFECT ON HCC

Lorenzo Onorato[1], Giorgio de Stefano[2], Valentina Lodice[2], Nunzia Farella[2], Nicoletta Potenza[3], Evangelista Sagnelli[1], Aniello Russo[3], Carmine Minichini[1], Mario Starace[1], Nicola Coppola[1]

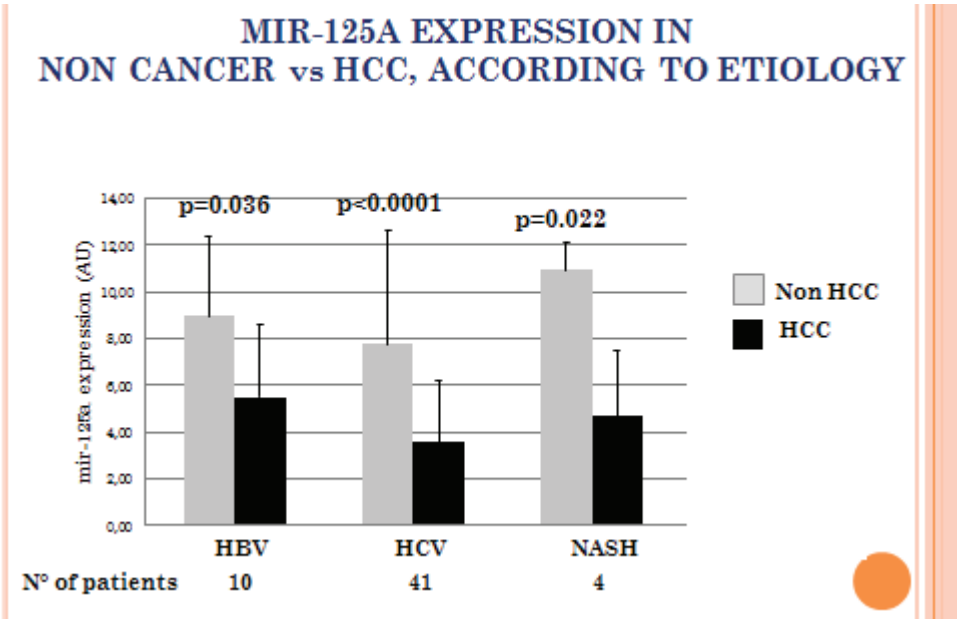
[1]Second Univ of Naples, Naples, Italy, [2]AORN dei Colli, PO Cotugno, Naples, Italy, [3]Second Univ of Naples, Caserta, Italy

Background: MicroRNAs are small non-coding RNAs that modulate gene expression at post-transcriptional level, playing a crucial role in cell differentiation and development. Human miR-125a-5p has been shown to play an anti-proliferative activity toward several cancer cell lines and to be downregulated in some tumors. We aimed to evaluate the hsa-miR-125a-5p concentration and the expression levels of 4 of its validated oncogenic targets in neoplastic and in non-neoplastic liver tissue of patients with HCC.

Methods: All consecutive patients who underwent a diagnostic liver biopsy for HCC at one of two participating Liver Units from June 2013 to May 2014 were enrolled. For each patient, real-time PCR was used to quantify miR-125a-5p and its targeted transcripts in relation to RNU6B and GAPDH, respectively, in HCC and non-HCC liver tissue.

Results: 55 patients were included in the study; the mean age was 70.3±6.0 years and 58.1% of patients were males. The etiologic agent was HCV in 41 patients, HBV in 10 and 4 had NASH-related cirrhosis (Child-Pugh class A in 89.1% of cases and classes-B/C in 10.9%). According to the Barcelona Clinic Liver Cancer (BCLC) class, 47 (85.4%) had class A, 5 (9.1%) class B and 3 (5.5%) class C. Lower levels of hsa-miR- 125a-5p were observed in HCC tissue than in non-HCC liver tissues (M±SD 4.08±2.87 vs. 8.25±4.53 A.U., p<0.00001). This difference was highly significant to statistical analysis in the 41 HCV-patients, 3.75±2.8 vs. 7.97±4.85 AU (p<0.00001) and still significant although at a lower level in the 10 HBsAg positive patients, 5.47±3.13, vs. 8.94±3.46AU (p=0.036), and in the 4 patients with NASH-related cirrhosis, 4.65±2.84 vs. 10.9±1.16 AU (p=0.015) (Figure 1). When patients were stratified according to the epidemiological and clinical characteristics of HCC, no difference was observed between the mean fold-regulation of the miRNA in HCC vs. non-HCC tissue. The analysis of the expression patterns of four validated targets showed an up-regulation of MMP11, SIRT7 and c-Raf, with mean fold regulation values of 3, 2.1 and 1.7, respectively.

Conclusion: These data suggest an oncosuppressor effect of microRNA hsa-miR-125a-5p on HCV, HBV and NASH-related HCC; this effect could be exerted through the regulation of its oncogenic targets MMP11, SIRT7 and c-Raf , an observation deserving further investigation.



538 REAL-LIFE TREATMENT RATES FOR HEPATOCELLULAR CARCINOMA IN HIV-INFECTED PATIENTS

Nicolás Merchante[1], Francisco Rodríguez-Arrondo[2], Esperanza Merino[3], Boris Revollo[4], Sofía Ibarra[5], Miguel García-Deltoro[6], Francisco Téllez[7], Joseba Portu[8], Alberto Romero-Palacios[9], Juan A. Pineda[1]

[1]Hosp Univ de Valme, Sevilla, Spain, [2]Hosp Univ de Donostia, San Sebastián, Spain, [3]Hosp General Univ de Alicante, Alicante, Spain, [4]Hosp German Trias i Pujol, Badalona, Spain, [5]Hosp de Basurto, Basurto, Spain, [6]Hosp General de Valencia, Valencia, Spain, [7]Hosp de La Línea, La Línea de la Concepción, Spain, [8]Hosp de Txagorritxu, Vitoria, Spain, [9]Hosp de Puerto Real, Puerto Real, Spain

Background: The incidence of hepatocellular carcinoma (HCC) in HIV-infected patients is increasing worldwide. It is not known if HIV-infected patients access effective therapy against HCC. Our aim was to assess the proportion of HIV-infected patients with HCC that do not access recommended therapy according to HCC stage.

Methods: The GEHEP-002 multicentric cohort (ClinicalTrials.gov ID: NCT02785835) recruits HCC cases diagnosed in HIV-infected patients from 32 centers from Spain. The Barcelona-Clinic Liver Cancer (BCLC) staging system was used for HCC staging and treatment allocation. The proportion of patients receiving less effective therapy against HCC as indicated by BCLC stage at diagnosis and the evolution of this proportion over time was analyzed.

Results: 317 HCC cases from the GEHEP-002 cohort were included in this study. The distribution of patients according to BCLC stage at diagnosis were: Stage 0= 6 (2%); Stage A: 115 (36.3%); Stage B: 26 (8.2%); Stage C: 111 (35%) and Stage D: 59 (18.5%). Eighty-four (32.5%) out of 258 patients who were potentially candidates to therapy did not received therapy or received treatment less effective as indicated by BCLC (Table 1). The proportion of patients receiving no/less effective therapy varied according to the BCLC stage. Thus, it was 25%, 34.6% and 43% in patients at BCLC stage 0/A, B and C, respectively (p<0.0001) (Table 1). Forty-one (43.6%) out of 94 cases diagnosed prior to 2010 and potentially candidates to HCC treatment received no/less effective therapy than recommended, while this occurred in 45 (27.4%) out of 164 cases diagnosed from 2010 (p=0.03). Conversely, the proportion of HCC cases diagnosed at stage 0/A increased in the second period (36 out of 128 [28%] vs. 85 out of 190 [45%]; p < 0.001).

Conclusion: A high proportion of HIV-infected patients diagnosed of HCC did not receive therapy or receive less effective treatment as recommended by its BCLC stage. This situation becomes more frequent as HCC diagnosis is made in a more advanced stage. However, the access to therapy has improved in the recent years, probably as a consequence of the increase in the proportion of HCC cases that are diagnosed in earlier stages.

Table 1. Treatment received according to BCLC stage at diagnosis (n=317).

	Stage 0/A	Stage B	Stage C	Stage D
	N=121	N=26	N=111	N=59
BCLC recommended therapy	Curative therapies	Chemoembolization	Sorafenib	No therapy
Recommended therapy or more effective, n (%)	91 (75%)	17 (65.4%)	64 (57%)	
More effective	-	4 (15.4%)	35 (31%)	14 (23.7%)
Recommended	91 (75%)	13 (50%)	29 (26%)	-
Less effective therapy or no therapy, n (%)	**30 (25%)**	**9 (34.6%)**	**47 (43%)**	
Less effective	20 (16.5%)	2 (7.6%)	-	
No therapy	10 (8.5%)	7 (27%)	47 (43%)	45 (76.3%)

539 PREDICTORS OF HEPATOCELLULAR CARCINOMA IN HIV/HCV COINFECTED PATIENTS WITH CIRRHOSIS

Aaron P. Thrift, Kathryn E. Royse, Christine Hartman, Jennifer R. Kramer, Elizabeth Chiao
Baylor Coll of Med, Houston, TX

Background: Cirrhosis is the most important risk factor for hepatocellular carcinoma (HCC) in patients with HIV/HCV co-infection. However, even among patients with cirrhosis, HCC risk is not uniform. Indeed, most HIV/HCV co-infected patients with cirrhosis do not progress to HCC. We sought to determine risk factors for progression from cirrhosis to HCC in HIV/HCV co-infected patients.
Methods: We used the Veterans Affairs HIV and HCV Clinical Case Registries and identified HIV/HCV co-infected patients that were diagnosed with cirrhosis (defined by ICD-9-CM codes [571.5, 571.6, and 571.2] or an aspartate aminotransferase to platelet ratio index >2) from 1999-2010. We excluded female veterans (due to small numbers; <2%), as well as patients lacking HCV RNA, follow-up CD4 count or HIV viral load information, and patients diagnosed with cirrhosis within 90 days of HIV diagnosis. The outcome was incident HCC as indicated by ICD-9-CM (155.0 without 155.1). Patients were censored at death, date of last health care encounter or 12/31/2010. We examined associations with age at HIV diagnosis, race/ethnicity, HCV genotype, and HIV-related (combination anti-retroviral therapy era of diagnosis, CD4 cell count, percent time with undetectable HIV viral load, and use of highly active anti-retroviral therapy [HAART]), clinical (ALT and Deyo without AIDS) and behavioral factors (alcohol use, smoking, hard-drug use). Cox proportional hazards analysis was used to estimate Hazard ratios (HR) and 95% confidence intervals (CI) for associations with HCC.
Results: We included 2689 patients; the majority were aged >40y, African American, most recent CD4 count>200, and HCV genotype 1 or 4. Over a median follow-up of 5.0 (SD, 3.4) years, 88 patients (3.3%) developed HCC. In univariate analysis, HCC incidence varied by age at HIV diagnosis, race/ethnicity, ever HAART, alcohol use, and hard-drug use (all p<.10). Older age at HIV diagnosis (>50 vs. <40y; HR=2.19; 95%CI 1.02-4.70), Hispanic ethnicity (vs. non-Hispanic white; HR=2.46; 95%CI 1.05-5.76), and HCV genotype 1/4 (vs. HCV genotype 2/3; HR=1.95; 95%CI 1.06-3.57) were associated with higher risk of HCC in the multivariable model. Percent undetectable HIV viral load and CD4 count <200 (nadir or most recent) were not associated with HCC.
Conclusion: HCC is common in HIV/HCV co-infected patients with cirrhosis (3.3%) and risk varies by age, ethnicity and HCV genotype. If confirmed in other populations, these findings may lead to enhanced HCC prevention and surveillance efforts.

540 IFN-FREE THERAPY IS EFFECTIVE AND SAFE FOR HCV RECURRENCE IN LT HCV/HIV COINFECTION

Christian Manzardo[1], Maria Carlota Londoño[1], Ana Moreno[2], Lluis Castells[3], Victoria Aguilera[4], Jose R. Fernandez[5], Jorge Calvo-Pulido[6], Judith Peñafiel[1], Antoni Rimola[1], Jose M. Miro[1]
[1]Univ of Barcelona, Barcelona, Spain, [2]Hosp Ramon y Cajal, Madrid, Spain, [3]Hosp Univ Vall d'Hebron, Barcelona, Spain, [4]Hosp Univ La Fe, Valencia, Spain, [5]Hosp Univ de Cruces, Barkaldo, Spain, [6]Hosp 12 de Octubre, Madrid, Spain

Background: Interferon (IFN)-based therapy against hepatitis C virus (HCV) recurrence after liver transplantation (LT) has poor effectiveness and tolerability both in HCV-mono-infected (≈30% of sustained virological response [SVR]) and HIV-HCV co-infected LT recipients (≈20% of SVR). Only small case series have reported on the use of direct antiviral agents (DAAs) in LT HCV/HIV co-infected recipients. The aim of this study is to report the effectiveness and safety of IFN-free regimens in a nationwide cohort of HIV HCV co-infected individuals having undergone LT.
Methods: A prospective, multicenter cohort study, including HCV/HIV co-infected LT patients who received IFN-free treatment for recurrent hepatitis C with two or more DAAs (patients receiving DAAs with IFN or Sofosbuvir (SOF) plus ribavirine (RBV) were excluded). For comparison, we included a matched cohort of HCV mono-infected patients who received similar treatment for recurrent HCV. Only patients reaching a follow-up of at least 12 weeks after the end of treatment were analyzed.
Results: Among patients with post-LT HCV recurrence in the FIPSE cohort, 39/228 (17%) of HIV+ and 118/693 (17%) of HCV mono-infected patients received IFN-free regimens containing at least 2 DAAs +/- RBV after a median (IQR) of 42 (16-72) months after LT. No differences in demographics and pre- or peri-transplant characteristics were observed. For HIV-infected individuals, median (IQR) CD4 T-cell count was 367 (200-465) cells/μL. All patients received antiretroviral treatment (ART) and 33 (85%) had a plasma HIV-RNA <50 copies/mL; 19 (48%) were receiving ART based on a non-boosted integrase inhibitor. SVR rates were high (95%) and similar in the HIV-infected and uninfected cohorts (Table). Of note, two failures in HIV+ patients were observed for genotype 4 (SVR 75% vs. 100% among other genotypes, p=0.038). No significant differences in SVR rates among genotypes were observed for HCV mono-infected individuals. Treatment was well tolerated. Only one patient in the mono-infected cohort died because treatment was started in the advanced decompensated cirrhosis stage.
Conclusion: IFN-free regimens for post LT HCV recurrence in HIV infected individuals of our national cohort were highly effective and well tolerated, with results comparable to HCV mono-infected patients. Newer treatment options will probably improve efficacy for genotype 4 in co-infected LT recipients.

Table. IFN-free treatment in HIV-infected and uninfected LT recipients: characteristics and outcomes.

	HIV+	HIV-	P-Value
No. of cases receiving DAAs	39	118	
HCV treatment-naïve patients N(%)	19 (49%)	62 (53%)	0.875
HCV genotype: 1/4 [N]	23/9	96/9	0.462
Log_{10} plasma HCV R viral load [median (IQR)]	6.4 (6.0; 6.6)	6.4 (5.9; 6.7)	0.332
Metavir Fibrosis Stage >=F2 [N(%)]	20 (83%)	51 (57%)	0.035
DAA Regimen [N(%)]			
-SOF + LDV or DCV or SMV +/- RBV	35 (90%)	107 (91%)	0.164
-SMV + DCV +/- RBV	3 (8%)	6 (5%)	
-3D + RBV	1 (3%)	5 (4%)	
Virological response [% (95%CI)]			
-Early response (at week 4)	100 (90; 100)	81 (72; 88)	0.023
-End-of-Treatment	94 (80; 99)	98 (93; 99)	0.239
-12-week SVR	95 (83; 99)	96 (90; 98)	0.239

541 RISK FACTORS OF ACUTE REJECTION AFTER LIVER TRANSPLANTATION IN HIV+/HCV+ PATIENTS

Christian Manzardo[1], Sandra Silva Arrieta[2], Antonio Rafecas[3], Sandra Franco[2], Santos del Campo[4], Elisa Cordero[5], Judith Peñafiel[1], Antoni Rimola[1], Christian Brander[2], Jose M. Miro[1]
[1]Univ of Barcelona, Barcelona, Spain, [2]IrsiCaixa Inst for AIDS Rsr, Badalona, Spain, [3]L'Hosp de Llobregat, Spain, [4]Hosp Ramon y Cajal, Madrid, Spain, [5]Univ of Sevilla, Sevilla, Spain

Background: HCV/HIV-infected liver transplant (LT) recipients have higher rates of acute rejection than recipients without HIV infection (38% vs. 20%; Miro et al. AJT. 2012; Terrault et al. Liver Transplant 2012). However, the causes of rejection have been poorly studied. The aim was to investigate the contribution of clinical, virological and genetic patient and donor variables that may predict acute rejection in HCV/HIV-infected LT recipients.

Methods: We studied 45 HIV/HCV co-infected patients that underwent LT between 2006-2012 in six referral centers across Spain (FIPSE cohort). For 33 of the 45 recipients, organ donor samples or at least some genetic information were available. Recipient and donor gender and age as well as patient's pre- and post LT HCV viral loads, HCV genotype, CD4+ cell count, MELD score, immune suppressive treatment and donor-risk index were recorded. In addition, donor and recipient genetic markers were determined, including HLA-A, -B and DR, genotype and IL28B single nucleotide polymorphisms (SNPs: rs12979860, rs8099917 and ss469415590)

Results: Out of the 45 patients more than a quarter (n=12, 27%) had a histology-proven episode of acute rejection within the first year after transplant. Median (IQR) time between LT and acute rejection was 2.5 (1.6; 6) weeks. Independent risk factors for an acute rejection were infection with HCV genotype 1 (GT1 vs. non-GT1 p=0.015) and mismatches in the HLA class I and II loci. In particular, a complete mismatch across HLA-A, -B and -DR was associated with organ rejection (p=0.001). This was driven by the HLA-A locus, where a complete mismatch resulted in acute rejection in 10 of 18 individuals (56%), whereas among subjects with at least 1 HLA-A match, rejection was observed in only 1 of 11 individuals (9%, p=0.021). Furthermore, patients receiving organs carrying the interferon-λ3 gene (IFNL3, also named IL28B) SNP rs12979860-CC allele (p=0.061) and the interferon-λ4 gene, ss469415590-TT alleles, (p=0.075) tended to suffer increased rates of organ rejection episodes.

Conclusion: Our data in HIV co-infected HCV+ LT recipients show a high rate of organ rejection. While the HCV genotype has been associated with rejection, we identify here additional host and donor genetic markers that may potentially increase the risk of organ rejection and which may help clinical management and organ allocation in liver transplantation in the HIV/HCV co-infected population.

Table. Risk factors associated with acute organ rejection after liver transplantation in HIV/HCV co-infected individuals

Clinical/ virological variables	all subjects (n=45)	subjects without acute rejection (n=33)	subjects with acute rejection (n=12)	p-value
Recipient age	47.9 (4.93)	47.8 (4.66)	47.9 (5.84)	0.971
Recipient gender	38 (84.4%)	28 (84.8%)	10 (83.3%)	1.000
HCV genotype 1	24 (53.3%)	14 (42.4%)	10 (83.3%)	0,036
CD4 T cell counts at transplantation	286 [172;400]	285 [159;400]	342 [230;457]	0.264
Plasma HCV viral load at transplantation	266520 [40652;1932164]	339312 [50882;1932164]	152224 [3964;1592240]	0.385
Donor risk index	1.78 [1.37;1.96]	1.86 [1.35;1.97]	1.52 [1.45;1.95]	0.759
CsA-based immunosuppressive regimen	15 (33.3%)	12 (36.4%)	3 (25.0%)	0.722
Immunogenetic variables				
Complete HLA-A mismatch	18 (62%)	8 (44.4%)	10 (90.9%)	0.019
Complete HLA-A/B/DRB mismatch	10 (43.5%)	1 (7.69%)	9 (90.0%)	0.001
Donor IL28B rs12979860 – CC allele	9 (37.5%)	4 (23.5%)	5 (71.4%)	0,061
Donor IL28B ss469415590-TT alleles	10 (40%)	5(27.8%)	5 (71.4%)	0,075

542LB HCC DEVELOPMENT IN HCV PATIENTS AFTER DAA: THE EXPERIENCE OF THE SCOLTA PROJECT

Barbara Menzaghi[1], Carlo Magni[2], Laura A. Nicolini[3], Giovanni Cenderello[4], Vito Fiore[5], Maria Gussio[6], Roberto Gulminetti[7], Francesca Vichi[8], Paolo Bonfanti[9]
[1]Busto Arsizio Hosp, Busto Arsizio, Italy, [2]ASST Fatebenefratelli, Milan, Italy, [3] Univ of Genova, Genova, Italy, [4]Galliera Hosp, Genoa, Italy, [5]Unit of Infectious Diseases, Sassari, Italy, [6]Garibaldi Hosp, Catania, Italy, [7]IRCCS Policlinico San Matteo Fndn Univ of Pavia, Pavia, Italy, [8]S. Maria Annunziata Hosp, Milan, Italy, [9]A. Manzoni Hospital, Lecco, Italy

Background: Interferon (IFN)-free direct antiviral agents (DAAs) effectively eradicate hepatitis C virus (HCV) and rapidly improve liver residual functions. Recent data have suggested that hepatocellular carcinoma (HCC) risk increases during and after DAAs treatment, in HCV-infected patients with advanced liver disease, but no strong evidence exists.
Methods: The SCOLTA (Surveillance Cohort Long-Term Toxicity of Antiretrovirals/Antivirals)-HCV project is an observational, prospective, multicenter cohort study enrolling patients, either HCV mono- or HIV/HCV co-infected, who started DAA treatment. For HCV treatment and HCC surveillance, patients were followed according to Italian guidelines.
Results: Overall 1,154 pts were included in this study. Males were 69.2%; median age was 56.2 years. HIV/HCV co-infected were 392 (34.0%). Twenty-nine (2.5%) patients had a history of HCC (24, 3.2%, with HCV and 5, 1.3%, with HCV/HIV). At the time of this analysis, median follow-up from initiation of DAA therapy was 16.7 months (IQR 12.7-19.4). Twenty-seven patients developed HCC, as a first diagnosis in 21 cases and recurrence in 6; the incidence rate/100 patient-years was 1.44 (95% CI 0.92-2.16) and 16.61 (95% CI 6.73-34.55) respectively. HCC was diagnosed during DAA treatment in 10 patients (8 new diagnoses and 2 recurrences). All recurrences occurred in HCV mono-infected patients (5 with SVR 12 and 1 with relapse). Among 21 subjects with first HCC diagnosis, 4 were co-infected with HIV: the rate ratio in comparison with HCV mono-infected patients was 0.43 (95% CI 0.13-1.22, p=0.12). In a multivariate Cox model including age, sex, Metavir, HIV co-infection, HCV genotype, and outcome at 12 weeks, age (HR 1.06, 95% CI 1.01-1.12, by 1 year) and Metavir F4 (HR 4.70, 95% CI 1.08-20.44 as compared to F0-F3) were significantly associated to HCC.
Conclusion: In untreated historical controls, HCC incidence rate ranged between 1 and 3/100 patient-years. Our findings indicate that, in cirrhotic patients, the incidence rate of HCC during the first 16 months following initiation of DAA therapy is not different from that expected in untreated patients.

543 HEPATITIS C CASCADE OF CARE IN NON-BIRTH COHORT PATIENTS WITHIN A LARGE HEALTH SYSTEM

Chinyere Ukaegbu[1], Alexander Geboy[1], Whitney Nichols[1], Amanda E. Smart[2], Stephen Fernandez[3], Peter Basch[1], Dawn Fishbein[1]
[1]MedStar Hlth Rsr Inst, Washington, DC, USA, [2]Georgetown Univ, Washington, DC, USA, [3]MedStar Hlth Rsr Inst, Hyattsville, MD, USA

Background: Comprising 75% of all hepatitis C virus (HCV) infected persons in the US, the Birth Cohort (BC) (b. 1945-1965) has been the primary focus in many linkage to care efforts. However, rising HCV incidence in populations born outside of the BC (non-BC), suggest a need to refocus linkage efforts. The Centers for Disease Control and Prevention (CDC) reported that persons aged 30 and younger from nonurban areas compose the majority of acute HCV cases, identifying injection drug use as the main risk factor. This study examines a system- wide HCV cascade of care model for non- BC (HCoC).
Methods: With Gilead FOCUS funding, antibody positive (HCV Ab +) persons were identified across MedStar Health. A retrospective chart review of HCV Ab+ non-BC individuals was conducted.
Results: Between 7/1/2015 and 6/30/2016, 11,874 patients were screened, 60% (n=7,133) in the BC, 40% (n=4,741) comprised the non- BC, with 3% (n=320) testing HCV Ab+. Within the non-BC, 1.6% (n=78) tested HCV Ab +; mean age below the BC was 38.5 +/- 9.5 years and above the BC was 74.5 +/- 2.6 years, and 54% (42/78) were white males. Regarding the HCoC, 87.2% (68/78) of HCV Ab+ persons received clinical orders for HCV RNA tests, 92.6% (63/68) were completed, and 52.4% (33/63) were HCV RNA positive (HCV RNA+). Of this group, 90.9% (30/33) were referred to a specialist, with 50% (15/30) attending a specialist appointment. Of those seen by specialist, 26.7% (8/30) completed hepatocellular carcinoma (HCC) screening, 43.4% (13/30) completed liver staging. Of those HCV RNA+, 18.2% (6/33) received a prescription for HCV, 33% (4/6) started treatment, and 6% (2/33) have completed treatment.
Conclusion: These data are concordant with recent literature suggesting a higher prevalence of HCV infection in non-BC white males. That 40% of HCV testing occurred within the non-BC is encouraging, considering testing in this group is likely driven by direct ascertainment of risk. However, this also presents a barrier to implementing more targeted screening practices as risk-factors for HCV testing are often unstructured data and not yet searchable with current technology. Importantly, primary care providers are obtaining

RNA tests and referring HCV Ab+ patients to care at high rates. Gaps appear in transitioning into specialty care. Work is currently underway to better identify risk associated with testing, and educate providers on HCV linkage and retention using best practices form BC initiatives.

544 STRATEGIES FOR UTILIZING EHR TO IMPROVE BIRTH COHORT TESTING IN THE HOSPITAL SETTING

Lorlette Moir, Shuchin Shukla, Uriel Felsen, Jeffrey Weiss, Kimberly Cartmill, Jonathan M. Schwartz, Paul Meissner, Kimberly Yu, Yuming Ning, Alain H. Litwin
Montefiore Med Cntr, Bronx, NY, USA

Background: Hepatitis C is the leading cause of liver disease in the United States with a 2% prevalence nationally. In 2012 the Centers for Disease Control and Prevention (CDC) released updated recommendations for Hepatitis C testing and screening of persons born between the years of 1945-1965. In 2014 New York State (NYS) expanded on the CDC recommendations by introducing the New York State Hepatitis C Testing Law which mandates that all residents in this birth cohort should be offered Hepatitis C screening within the inpatient or outpatient setting. Accordingly, Montefiore Medical Center implemented birth cohort prompts into Electronic Health Record (EHR) platforms. We describe the impact of EHR prompts on identification of unique Hepatitis C positive patients in the hospital setting.
Methods: Montefiore Medical Center initiated a birth cohort screening prompt across three inpatient settings in March 2015 to encourage providers to test eligible patients. Providers are prompted to test for HCV if the patient had not been previously tested for HCV Antibody. To assess the effect of this prompt, we compared the proportions of patients who received first Hepatitis C tests and the average number per month of newly identified positives before and after the implementation of the EHR prompt (January 2014 through February 2015 and March 2015 through May 2016). Two sample t-tests were used to assess the statistical significance of these observed differences.
Results: From January 2014 through February 2015, an average of 5% of birth cohort patients received HCV testing. Following the implementation of the EHR prompt in March 2015 through May 2016, this increased to 29% ($P<0.0001$). Additionally, the average number of newly identified positives among patients who had not previously been tested rose from 12.2 per month in the pre-implementation period to 32.7 per month in the post-implementation period ($P<0.0001$).
Conclusion: The Hepatitis C screening EHR prompts have had a demonstrable positive effect on the proportion of patients within the birth cohort who are tested, and on the number of Hepatitis C positive patients identified. Given these positive results, EHR implementation of birth cohort strategies should be standardized within inpatient settings.

545 IMPLEMENTATION OF AN EHR PROMPT REVEALS LOW ADHERENCE TO HCV TESTING RECOMMENDATIONS

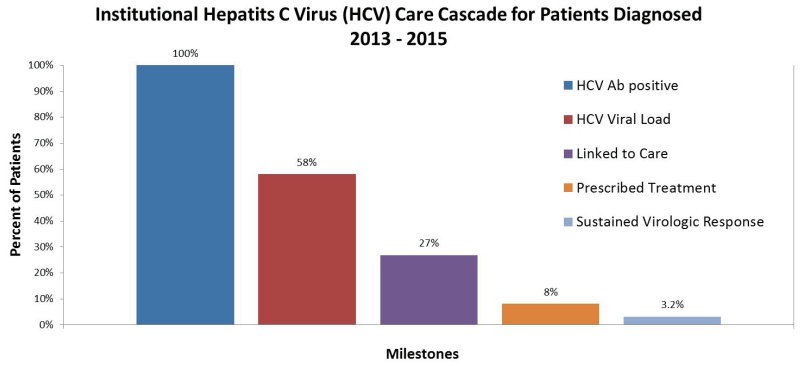
Alexander Geboy[1], Whitney Nichols[1], Chinyere Ukaegbu[1], Stephen Fernandez[2], Peter Basch[3], Dawn Fishbein[1]
[1]MedStar Hlth Rsr Inst, Washington, DC, USA, [2]MedStar Hlth Rsr Inst, Hyattsville, MD, USA, [3]MedStar Hlth, Washington, DC, USA

Background: The prevalence of hepatitis C virus (HCV) among the Birth Cohort (BC) born during 1945-1965 is five times higher than adults born in other years. Though there is a productive discussion about effective linkage to care strategies for this population, healthcare systems are failing to adequately screen eligible patients. Identifying system-wide gaps in adherence to federal screening recommendations is paramount to uncovering the full burden of disease and planning a course toward HCV Elimination.
Methods: Beginning July 2015, MedStar Health (MSH) activated a clinical decision support (CDSS) Electronic Health Record (EHR) prompt. Eligible BC patients were neither previously HCV tested nor positive. The prompt was triggered at primary care visits only upon clicking the "View All Protocols" (VAP) button. It contained seven discrete, actionable options, each traceable and monitored to determine system-wide adherence to HCV BC testing recommendations. A qualitative analysis is presented.
Results: Between 7/1/2015 and 6/30/2016, 77,575 patients were identified as eligible. Testing occurred at 133 primary care sites by 470 providers across MSH. Providers clicked the VAP button for 29,668 (38%) eligible patients seen, accessed the HCV CDSS prompt for 21,675 patients (28% of total denominator; 73% of clicked VAPs), and took an action within the prompt for 20,528 (26% of total; 95% of prompts accessed). Of these: 6,768 patients (9% of total denominator; 33% of prompt actions) were HCV tested, 4,426 patients (5%; 22%) were not screened [1807 (41%) declined, 39 (1%) had a history of HCV positivity, 1912 (43%) previously screened negative, 349 (8%) deferred, and for 319 (7%) it was not indicated]; there were 9,334 actions (45%) that were unaccountable, these were likely printing an HCV handout. There were 1,356 additional tests conducted outside of the CDSS prompt, for a total of 8,124 tests.
Conclusion: Adherence to BC recommendations was low at approximately 11% (8,124/75,305). It is concerning that 62% of providers did not access the VAP. Next steps will provide targeted education to PCPs and a health maintenance dashboard in a new EHR; consideration will be given to implementing standing orders. Barriers to HCoC initiation are evident, and exemplify the observation that only 50% of those infected are ever tested. Creating and implementing new best practices with supporting policy changes are essential if Elimination of HCV is to be a realistic possibility.

546 DEVELOPMENT OF AN EMR-BASED ALGORITHM TO PLACE PATIENTS IN THE HCV CARE CASCADE

Jason Zucker, Justin Aaron, Henry W. Evans, Peter Gordon, Michael T. Yin
Columbia Univ, New York, NY, USA

Background: Disease specific care cascades have become important public health and organizational tools to characterize gaps in care, drive process improvement, and target resources. Their construction is often laborious and to be useful for ongoing process improvement they need to be maintained. Hepatitis C virus (HCV) is the most common blood-borne infection in the United States and the leading cause of cirrhosis, hepatocellular carcinoma, and liver transplant. The advent of highly effective antiviral agents has the potential to end the HCV epidemic if effective and efficient care engagement could be realized. We sought to create an algorithm to electronically derive an individual's location in the HCV care cascade from data available in the electronic medical record (EMR) from a single hospital.
Methods: We included all new institutional diagnosis, defined as patients with a first HCV antibody positive (Ab) test from 2013 to 2015 with positive or no confirmatory testing. Patients with HCV Ab+ tests prior to 2013 and those with negative confirmatory testing were excluded. To create the cascade we identified 5 milestones including: positive HCV Ab, HCV RNA testing, linkage to care defined as an outpatient or inpatient visit with an infectious diseases or gastroenterology provider, prescribed treatment, and sustained virologic response (SVR). An algorithm was developed to categorize patients into each stage of care. To evaluate accuracy we created a reference standard to replicate a clinician's review of the chart. A single researcher without access to the algorithm performed the reference standard review on a random sample of 129 patients.
Results: The algorithm identified 1225 patients with a new institutional diagnosis of HCV infection. The algorithm identified 711 (58%) patients with a detectable HCV RNA, 330 (27%) patients linked to care, 100 (8%) patients prescribed treatment, and 39 (3.2%) with SVR (Figure). The algorithm correctly categorized 117 of 129 (90%) patients compared to 126 of 129 (98%) for the reference standard. 6 of 12 (50%) errors identified were related to physician documentation of outside hospital records.
Conclusion: Using commonly available data from an EMR, our algorithm has a high accuracy for placing individuals in the HCV care cascade, and identified significant gaps at each step of the care cascade at our institution. An electronic care cascade provides a method to readily measure and monitor performance in HCV treatment and care over time.



547 COST-EFFECTIVENESS OF HCV SCREENING AND LINKAGE IN MMT: RELEVANCE OF HIV COINFECTION

Bruce R. Schackman[1], Jared A. Leff[1], Jake R. Morgan[2], Sarah Gutkind[1], Czarina N. Behrends[1], Kevin L. Delucchi[3], Courtney McKnight[4], David C. Perlman[4], Carmen L. Masson[3], Benjamin Linas[5]
[1]Weill Cornell Med Coll, New York, NY, USA, [2]Boston Med Cntr, Boston, MA, USA, [3]Univ of California San Francisco, San Francisco, CA, USA, [4]Icahn Sch of Med at Mt Sinai, New York, NY, USA, [5]Boston Univ, Boston, MA, USA

Background: We evaluated the cost-effectiveness of an HCV screening and linkage to care intervention in US methadone maintenance treatment (MMT) patients using data from a randomized trial conducted in New York City and San Francisco.
Methods: We used a decision analytic model to compare the cost-effectiveness of 4 strategies: 1) no intervention; 2) HCV screening and education (control); 3) HCV screening and education for all and care coordination for all HCV-infected 4) HCV screening and education for all with care coordination only for HCV mono-infected patients (to explore trial results indicating that HIV co-infected participants linked through other systems of care). Trial data include population characteristics (67% male, mean age 48, 50% HCV mono-infected, 8% HCV/HIV co-infected) and linkage rates for HCV mono-infected (34% control, 68% intervention) and HCV/HIV co-infected (79% control, 87% intervention) individuals. Data from published sources include treatment efficacy and HCV re-infection risk. Clinical outcomes include proportions with chronic HCV linked and achieving SVR. We projected quality-adjusted life expectancy (QALYs) and lifetime medical costs using an established model of HCV (HEP-CE). Incremental cost-effectiveness ratios (ICERs) are in 2015 US$/QALY discounted 3% annually.
Results: The control strategy resulted in a projected 34% linking to care within 6 months and 30% achieving SVR (Figure). The cost was $156/person screened. HCV care coordination for HCV mono-infected patients resulted in 57% linkage and 51% achieving SVR at a cost of $470/person screened. Care coordination for all increased projected linkage to 58% and SVR to 52% at a cost of $514/person screened. The care coordination for all strategy was more efficient than (dominated) the care coordination for HCV-mono infected patients only strategy and the control strategy, and had an ICER of $21,600/QALY compared to no intervention. In sensitivity analyses varying the risk of re-infection, results were not highly sensitive to increasing the risk of reinfection (resulting in triple the number of reinfections) as long as re-infected patients were eligible for retreatment (resulting in an additional 8 treatments per 1000 patients treated).
Conclusion: HCV care coordination interventions that include screening, education and linkage to care in MMT settings are likely cost-effective at a conventional $100,000/QALY threshold for both HCV mono-infected and HIV co-infected patients.

548 PROVIDING HCV CURES IN THE MEDICAL HOME: TRAINING A NEW GENERATION OF PROVIDERS

Sarah Rojas, Christian B. Ramers, Stephanie Constantino
Family Hlth Cntrs of San Diego, San Dlego, CA, USA

Background: With the development of non-invasive methods to assess liver fibrosis and HCV Direct Acting Antivirals (DAA's), a major shift is underway in the HCV treatment paradigm. Community Clinics and FQHC's, with their patient-centered medical home (PCMH) model, may be ideal venues for HCV testing, evaluation and treatment, as well as wrap-around primary care services for HCV-infected patients. Much attention has been given to training primary care providers to provide HCV care, but little research has shown effective strategies for doing so.
Methods: Beginning in 2013, we developed an HCV treatment program within an urban FQHC in San Diego. Rapid point-of-care testing in clinics and alcohol/drug treatment programs identified HCV-infected individuals, and test counselors linked them to care. A patient navigator encouraged retention in care and guided patients through complex barriers to access, such as health insurance enrollment and prior authorizations. Fibrosis assessment occurred via non-invasive means. Patients were treated according to published guidelines and clinical outcome data was collected prospectively. Effective HCV screening led to a system bottleneck for assessment and treatment. The necesity for more providers prompted initiation of training programs, created with NIH support. Specifically, we 1) added Hepatitis C assessment, i.e. treatment readiness and preparedness to our HIV/HCV Training track for residents and PCPs, either primary medical Doctors (PMDs) or Nurse Practitioners (NPs) and 2) created a 6-month HCV Training track for PCP providers.
Results: Between 1/1/13 and 8/1/16, 466 patients underwent HCV evaluation; 250 then completed HCV treatment, 58 pts are currently on treatment, 57 are approved; 69 are awaiting insurance approval. In 2013-4, a single ID MD treated 42 pts. Given great need, our ID MD trained one NP the end of 2014; and 2 more NPs & 2 PMDs by the end of 2015. In 2015, 147 patients were treated:106 by ID, 12 by NP. In 2016, 107 patients were treated: 91 by ID, 16 by NP; none had yet been treated by PMDs. 37% (N=113) had stage F3 or F4 fibrosis. 31 (10%) were HIV/HCV co-infected. Of those treated, 208 were >12 weeks post therapy; 144 had labs 12 weeks post-treatment (SVR12) to assess cure rates: 72.5% (per ITT analysis) and 96.7% (per protocol analysis). Of the 7 treatment failures, all had cirrhosis and were managed by ID MD.
Conclusion: Focused training of PCPs can extend HCV treatment access without sacrificing cure rates.

549 HCV RNA DETECTION IN SMALL VOLUME CAPILLARY BLOOD FOR POINT-OF-CARE APPLICATIONS

Mark Hopkins[1], Rachael Dagnall[2], Athanassios Papadimitropoulos[2], Paula Davies[1], Jillian William[1], Eimear Railton[1], Sarah Sarah Hau[1], **Apostolos Beloukas**[2], Anna Maria Geretti[2]
[1]Royal Liverpool Univ Hosp, Liverpool, UK, [2]Univ of Liverpool, Liverpool, UK

Background: The rapid diagnosis of HCV infection is hampered by slow antibody responses and lack of reliable point-of-care tests (POCT). In addition, patients often report preferring blood collection by finger-prick rather than by venous puncture. The Cepheid GeneXpert platform provides a closed system for nucleic acid amplification and detection that makes it suitable for use outside of specialized laboratory settings including POCT; however, there are no published data on the use of small volume capillary blood for HCV RNA detection. This study assessed the performance of the GeneXpert HCV RNA assay in paired blood samples collected by venous puncture and by finger-prick in subjects with known HCV and HIV status.

Methods: Capillary blood was collected by nursing staff using the Roche Accu-Chek Safety Safe-T-Pro Plus Lancet and the Sarstedt Microvette® 100 K3E following established finger-prick procedure. Venous blood was collected in EDTA tubes. The assay was run blind by laboratory staff. Capillary blood (100µl) was transferred directly to the assay cartridge followed by 1ml Xpert diluent. In parallel, plasma (1.1 ml) separated from venous blood was added to another cartridge without sample diluent. Both cartridges were run on the GeneXpert XVI analyzer according to the manufacturer's instructions. Serial dilutions (2-5 log10 IU/ml) of plasma from two HCV RNA positive patients (HCV genotype 1a and 3a) were tested in duplicate to verify sensitivity of the 100ul protocol.
Results: Of 35 subjects undergoing paired blood collection by finger-prick and venous puncture, 2 were excluded due to insufficient sample and cartridge error, respectively. Of the remaining 33 subjects, 24 were HCV antibody and RNA positive, including 5 that were co-infected with HIV. Their plasma HCV RNA load was median 6.0 log10 IU/ml (IQR 5.5-6.4) and HCV genotypes were 1a, 3a, 1b, and 4. A total of 9 subjects were HCV antibody and RNA negative. In all subjects, results obtained with capillary blood matched those of venous blood, and both were in agreement with the patients' known HCV status. With the serial dilutions, the assay showed good linearity (R2 ≥0.99) and 100% detection rate at 2 log10 IU/ml.
Conclusion: The data support the use of small volume capillary blood for HCV RNA detection by GeneXpert, and provide the evidence base for studies evaluating use as POCT in non-specialist laboratory settings.

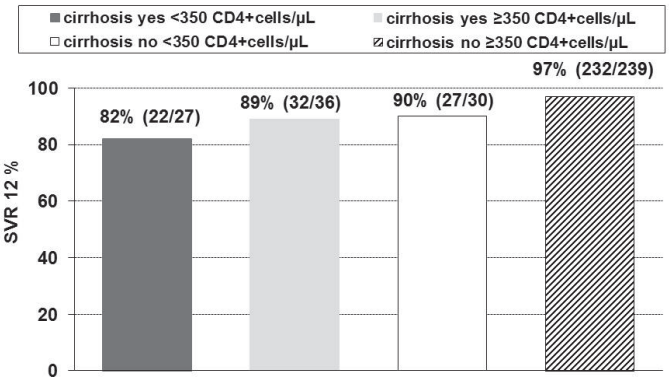
550 HIV/HCV COINFECTION IN THE DAA ERA: "EN ROUTE FOR ERADICATION"?

Laurent Cotte[1], Pascal Puglièse[2], Isabelle Poizot-Martin[3], Marc-Antoine Valantin[4], Lise Cuzin[5], Jacques Reynes[6], Eric Billaud[7], Thomas Huleux[8], Pierre Pradat[1], for the DatAIDS Study Group
[1]Hospices Civils de Lyon, Lyon, France, [2]CHU de Nice, Nice, France, [3]Assistance Publique – Hôpitaux de Marseille, Marseille, France, [4]Assistance Publique - Hôpitaux de Paris, Paris, France, [5]CHU Toulouse, Toulouse, France, [6]CHU de Montpellier, Montpellier, France, [7]CHU de Nantes, Nantes, France, [8]Cntr Hosp de Tourcoing, Tourcoing, France
Background: The HIV-HCV population benefits from a high medical coverage, wide indications to treat HCV and is slowly decreasing over time in European countries. We report the impact of Direct Acting Antiviral agents (DAA) at the population level in French HIV-HCV coinfected patients.
Methods: The DatAIDS cohort covers about 25% of HIV-infected patients in care in France. All HIV-HCV coinfected patients followed between 2012 and 2015 were included. HCV status was defined yearly as naive, spontaneous cure, sustained virological response (SVR), failure or reinfection. The incidence of HCV infection and reinfection and HCV treatment initiation rate were determined yearly.
Results: Among 32,945 HIV-infected patients, 5001 were HIV-HCV coinfected (prevalence 15.2%). Patients were mostly male (71.9%), IVDU (51.0%), of median age 51 years, infected with HCV genotype 1a (39.5%), 3 (21.0%) or 4 (22.0%), with fibrosis F3-4 in 41.4%. From 2012 to 2015, 146 of 17,890 HCV negative patients with serological follow-up acquired HCV. Incident cases were mostly male (98%), MSM (87%) infected with HCV genotype 1a (39%) or 4 (53%). HCV incidence rate increased from 0.35 per 100 person-years (%PY) to 0.69%PY in MSM, while the median incidence in other patients was 0.08%PY. Reinfections occurred in 45 patients (male 93%, MSM 71%, genotype 1a 47% or 4 38%), including 2 patients with another reinfection. Median reinfection rate was 2.56%PY in MSM and 0.22%PY in other patients. Median death rate was 1.4%PY. HCV treatment initiation rate rose from 8.2% in 2012 to 29.4% in 2015, particularly in pre-treated patients (48.0% in 2015 vs 22.6% in naive patients). Pegylated-interferon (PEG-IFN)/ribavirin (RBV) use declined from 37.9% to 0.3%, while RBV+DAAs rose from 0% to 25.0% and DAAs combinations from 0% to 73.7%. SVR rate increased from 68.7% to 95.2%. By the end of 2015, naive patients, spontaneous cure, treatment failure, and SVR accounted for 29.5%, 12.6%, 7.7% and 50.1% of the patients respectively.
Conclusion: HCV treatment dramatically increased in HIV-HCV coinfected patients in France from 2012 to 2015 resulting in HCV cure in more than half of the patients. Combined with a declining HCV prevalence, the prevalence of active HCV infection among HIV patients is expected to drastically decrease in forthcoming years. Since new HCV infections and reinfections mostly occur in MSM, strengthened information and preventive measures are necessary to achieve viral eradication in the HIV-HCV population.

551 SAME SAME BUT DIFFERENT? RISK OF DAA THERAPY FAILURE IN REAL-LIFE HCV/HIV COINFECTION

Christoph Boesecke[1], Patrick Ingiliz[2], Florian Berger[3], Thomas Lutz[4], Knud Schewe[5], Julian Schulze zur Wiesch[6], Axel Baumgarten[2], Stefan Christensen[7], Jürgen K. Rockstroh[1], Stefan Mauss[3]
[1]Univ Hosp Bonn, Bonn, Germany, [2]Cntr for Infectiology, Berlin, Germany, [3]Cntr for HIV and Hepatogastroenterology, Duesseldorf, Germany, [4]Infektiologikum, Frankfurt, Germany, [5]dagnae e.V., Berlin, Germany, [6]Univ Med Cntr, Hamburg–Eppendorf, Hamburg, Germany, [7]CIM Infectious Diseases, Münster, Germany
Background: Directly-acting agents (DAA) against HCV have impressively improved treatment of chronic hepatitis C coinfection. However, relapses still occur. Therefore we assessed the influence of traditional risk factors on treatment outcome in HCV/HIV coinfected patients in the German hepatitis C cohort (GECCO).
Methods: The GECCO cohort is a multicenter cohort from 9 sites in Germany. All HCV/HIV coinfected patients (361/1791) with complete follow-up having received one of the following DAA regimen were analysed: Pegylated interferon plus ribavirin (RBV) + sofosbuvir (SOF); SOF + RBV; SOF + simeprevir; SOF + daclatasvir +/- RBV; SOF + ledipasvir; paritaprevir/ritonavir, ombitasvir +/- RBV and +/- dasabuvir. Treatment outcome was measured as sustained virologic response 12 weeks after end of therapy (SVR12). Fisher's exact, chi-square and Mann-Whitney U test were used for statistical analysis.
Results: 319/361 (88%) patients were male, median age was 48 years (IQR:42-53). HCV genotype (GT) distribution was: GT1 69%, GT2 3%, GT3 10%, GT4 18%. 65/170 (38%) had IL28B C/C polymorphism. 103/361 (29%) had high baseline HCV RNA (>6 Mio IU/mL). Median baseline ALT was 66U/l (44-109). 172/361 (48%) were treatment-experienced (TE). Liver cirrhosis was present in 71/361 (20%). Median CD4 nadir was 218/ul (129-374). 62/361 (17%) had baseline CD4 <350/ul, 54/361 (15%) baseline CD4 <20%. 357/361 (99%) were on cART. 78/361 (22%) were on opiate substitution therapy (OST). Overall SVR rate was 94%. In univariate analysis neither sex (p=0.588), age (p=0.439), GT (p=0.615), high HCV RNA (p=0.749), ALT (p=0.901), DAA regimen (p=0.390), TE (p=0.479), CD4 nadir (p=0.473) or OST (p=0.267) were statistically significantly associated with SVR. However, patients with CD4 <350/ul (p=0.038), CD4 <20% (p=0.017) and with liver cirrhosis (p=0.003) were less likely to achieve SVR (see figure 1). In multivariate analysis only liver cirrhosis (p=0.02, OR 3.5 (95%CI 1.2-9.9)) remained statistically significantly associated with Non-SVR.
Conclusion: Despite considerably improved efficacy of treatment of chronic hepatitis C with DAAs in HCV/HIV-coinfection liver cirrhosis remains as a risk factor for DAA treatment failure. Low CD4 cells were highly correlated with liver cirrhosis probably due to splenomegaly causing lymphopenia. This highlights the need for early initiation of DAA therapy in HCV/HIV coinfection before the onset of higher liver fibrosis/cirrhosis to allow for optimal rates of viral eradication.

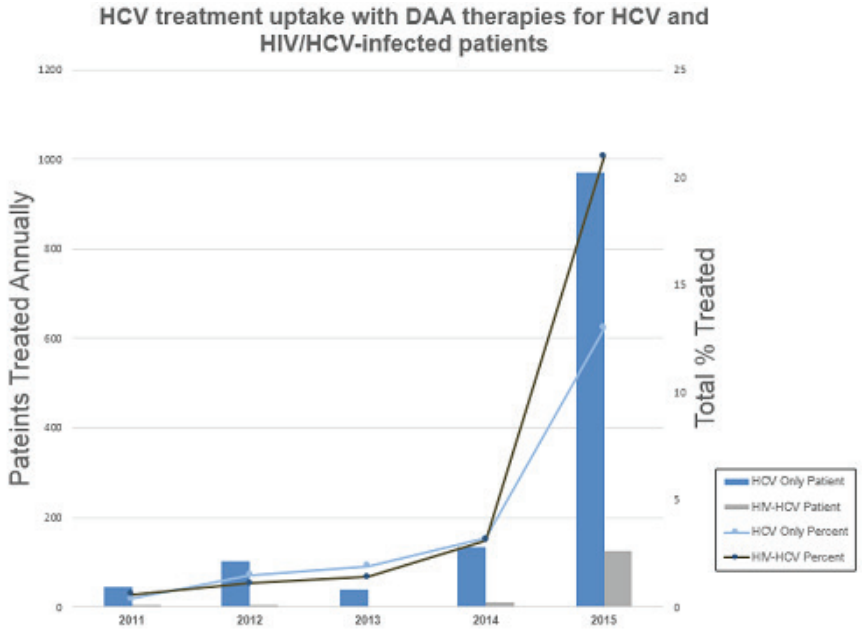
Figure 1. SVR12 according to cirrhosis status and CD4 cell count



552 DIRECT-ACTING ANTIVIRALS IMPROVE ACCESS TO CARE AND CURE FOR PATIENTS WITH HIV-HCV

Lauren F. Collins, Austin Chan, Jiayin Zheng, Shein-Chung Chow, Julius M. Wilder, Andrew J. Muir, Susanna Naggie
Duke Univ, Durham, NC, USA

Background: Prior to the approval of direct-acting antivirals (DAA), uptake of curative hepatitis C virus (HCV) treatment was low, particularly for HIV/HCV co-infected patients. DAA offers >95% sustained virologic response (SVR) for the vast majority of HCV-infected patients, regardless of HIV-1 infection. Although safety and efficacy of HCV therapies have improved, challenges have emerged including high rates of insurance denials and drug interactions between antiretrovirals (ARV) and DAA.
Methods: Using the Duke Enterprise Data Unified Content Explorer, we identified all HIV/HCV co-infected and HCV mono-infected patients engaged (at least one appointment in the system during the study period) in the healthcare system from 2011-2015, reflecting the DAA era. Prescriptions for DAA were queried to determine the treatment numbers. Demographic and clinical data were extracted by database and supplemented by manual record review. We describe the proportion of patients receiving DAA therapy per year of the study. Comparisons among cohorts employed the Fisher's exact test, the chi-square test, and Student's t-test as appropriate.
Results: We identified 9,960 patients with HCV mono-infection and 715 with HIV/HCV co-infection seen at least annually. The description of the HCV mono-infected versus HIV-HCV co-infected patients is as follows: for gender, 60.9% and 69.9% of patients were male; for race, 38.4% and 71.7% were black; 30.6% and 23.9% had cirrhosis; 10.2% and 18.6% had hepatitis B virus co-infection. During the study period, 323/9960 (3.2%) patients with HCV mono-infection were prescribed an interferon-based regimen, compared to 22/715 (2.9%) of HIV/HCV co-infected patients (Figure 1). Comparatively, 970/9960 (9.7%) of HCV mono-infected versus 125/715 (17.4%) of HIV/HCV co-infected patients were prescribed interferon-free DAA regimens (p<0.0001). Patients with HIV/HCV achieved high SVR 12 weeks after therapy completion, with rates of 9/22 (40.9%) compared to 123/125 (98.4%) in the DAA-interferon versus DAA-only era, respectively (p<0.0001). ARV regimens were switched in 21 of 125 (17%) HIV-HCV co-infected patients prior to initiation of DAA.
Conclusion: The introduction of DAA therapy has significantly improved access to HCV treatment and SVR is high in HIV/HCV co-infected patients. Meanwhile <20% of all HCV-infected patients at Duke have received therapy. More studies are needed to understand the barriers to access and how these barriers can be addressed.

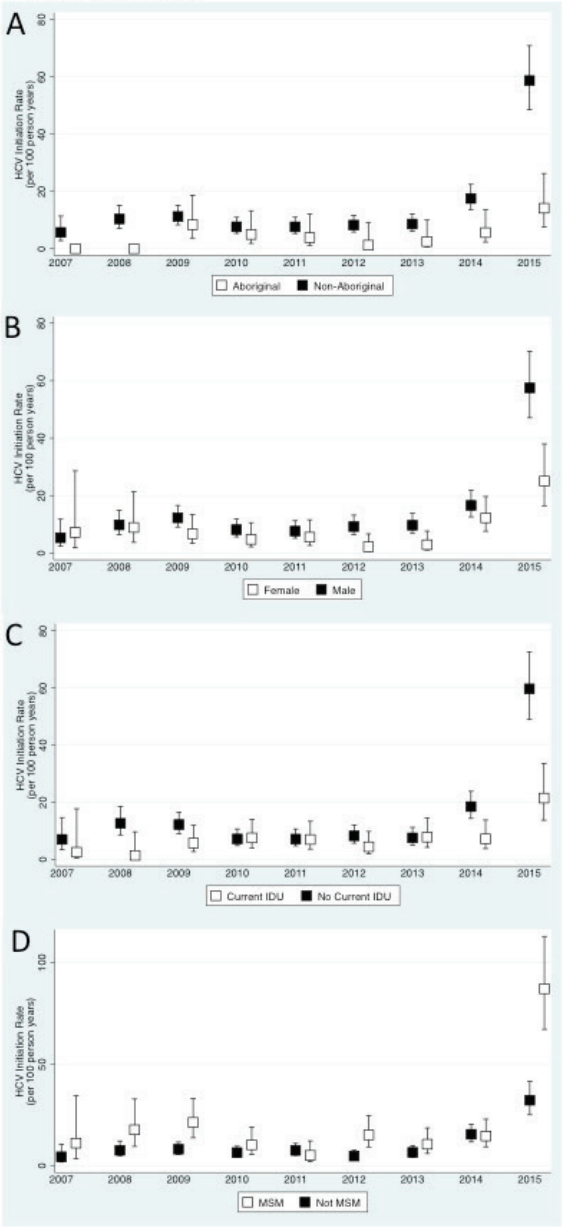


553 DIRECT ACTING ANTIVIRAL UPTAKE DISPARITIES IN HIV/HCV–COINFECTED POPULATIONS

Sahar Saeed[1], Erin C. Strumpf[1], Sharon Walmsley[2], Curtis Cooper[3], Brian Conway[4], Valerie-Martel Laferriere[5], Neora Pick[6], Alexander Wong[7], Marina Klein[8], for the Canadian Co-Infection Cohort Study
[1]McGill Univ, Montreal , Canada, [2]Univ of Toronto, Toronto, Ontario, Canada, [3]Ottawa General Rsr Inst, Ottawa, Ontario, Canada, [4]Vancouver Infectious Diseases Cntr, Vancouver, Canada, [5]Cntr Hosp de l'Univ de Montréal, Montreal, Canada, [6]Oak Tree Clinic, Vancouver, Canada, [7]Regina Qu'Appelle Hlth Region, Regina, Canada, [8]McGill Univ Hlth Cntr Rsr Inst, Montreal, Ontario, Canada

Background: Direct acting antivirals (DAAs) have revolutionized hepatitis C (HCV) treatment with nearly 100% cure rates even in real-world studies, giving hope that HCV can be eliminated. Historically, HCV treatment initiation rates have been low, particularly among people who inject drugs (PWID) an important group to target if the goal is to reduce incident HCV infections. In a publically funded health care setting, we investigated DAA treatment uptake disparities among HIV-HCV co-infected subpopulations.
Methods: The Canadian Co-Infection Cohort Study prospectively follows 1625 HIV/HCV co-infected participants from 19 centers, representing approximately a quarter of the total Canadian co-infected population in care. Among HCV RNA+ participants, we determined the incidence of HCV treatment initiation per year and stratified by different risk profiles (Aboriginals, women, PWID and men who have sex with men (MSM)). Multivariate Cox models were used to estimate adjusted hazard ratios (aHR) for DAA initiation accounting for age, sex, Aboriginal status, active (within 6 months) and past PWID, MSM, alcohol use, advanced fibrosis, HCV genotype, undetectable HIV RNA, province and income (a priori predictors of treatment initiation).
Results: Overall, HCV treatment initiations rose more than five times between 2013 and 2015, from 8 (95% CI: 5-11) to 46 (95% CI: 39-55) per 100 person-years. After stratifying initiation, by risk profiles, uptake was markedly lower among Aboriginals, women and active PWID (Figure 1). Among 854 HCV RNA+ participants, 195 initiated DAAs [128=ledipasvir/sofosbuvir (SOF); 28=SOF/ribavirin; 19=SOF/simeprevir; 13=SOF/ribavirin/interferon; 7=other all-oral regimens]. After adjustment (aHR, 95% CI), Aboriginals (0.56, 0.34-0.94), active PWID (0.54, 0.36-0.84) remained less likely to initiate HCV treatment. Women and past PWID tended to have lower treatment rates (0.80, 0.55, 1.15) and (0.73, 0.53, 1.02). Conversely, MSM were more likely to initiate DAAs (1.89, 1.41- 2.46). SVR rates were high in all sub-groups regardless of uptake: 100% in women and Aboriginals, 95% in active PWID and 91% in MSM compared to 93% for the cohort overall.
Conclusion: Treatment uptake has increased dramatically with the availability of all oral DAAs, but marginalized populations are still failing to access treatment. Barriers to treating these subgroups, who can obtain high SVR rates, need to be addressed if DAAs are to impact HCV incidence and the overall burden of chronic liver disease.

Figure 1: HCV Treatment Initiation Rates (95% CI) per 100 person-years between 2007-2015 by Risk Profile (A: Aboriginal Ethnicity, B: Women, C: Active PWID, D: MSM)



554 HCV TREATMENT IN PEOPLE WHO INJECT DRUGS COLOCATED WITHIN NEEDLE AND SYRINGE PROGRAM

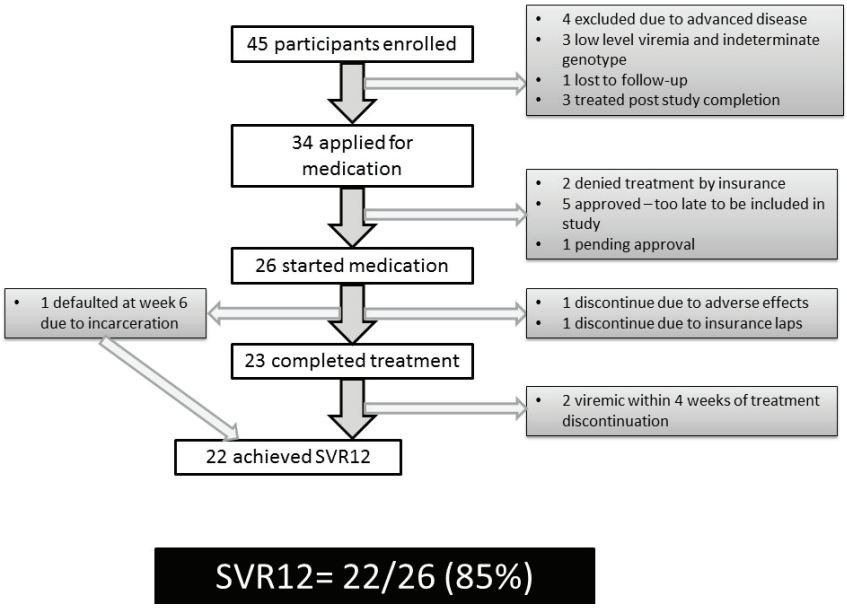
Benjamin Eckhardt[1], Kristen M. Marks[2], Brian Edlin[3]
[1]*New York Univ, New York, NY, USA,* [2]*Weill Cornell Med, New York, NY, USA,* [3]*Natl Development and Rsr Insts, New York, NY, USA*

Background: Hepatitis C (HCV) is a significant public health problem that disproportionately afflicts people who inject drugs. The introduction of direct acting antiviral (DAA) agents for HCV has begun the discussion about potential viral elimination. To maximize the population impact of DAAs on the HCV epidemic, more people who inject drugs need to be cured of their infection.

Methods: Data from two prospective pilot programs was used to describe the clinical outcomes of treating HCV in active injection drug users on-site at a needle syringe program. Participants were eligible if they'd injected drugs within the prior 30 days and were ≥18 years of age. Those with decompensated cirrhosis were excluded for treatment at the needle syringe program and were referred to local hepatology clinics for management. Doctors' visits, blood draws, and medication distribution all occurred within the needle syringe program.

Results: 45 participants were enrolled in the HCV treatment program, 34 had prior authorizations submitted for medication, with 26 participants approved, started on therapy, and included in this analysis. Participants had an average age of 45.9 years, 92% men, 46% homeless, and all had active or were eligible for Medicaid. Participants injected a median of 25 time per month [range 4-150], and had been injecting for a mean of 19.3 years. 58% were currently receiving opioid substitution therapy, and no patients was co-

infected with HIV. 92% of participants were treatment naïve, 58% had genotype 1 infection, 96% received a sofosbuvir-based regimen, and 19% had a fibrosis score ≥F3. Overall, 22/26 (85%) participants achieved a sustained virologic response (SVR12). Three participants discontinued therapy, one due to adverse effects, one due to insurance lapse, and one due to incarceration. Two participants who achieved end of treatment response had return of viremia shortly after treatment discontinuation (both with unique genotypes that were not adequately covered by treatment regimen).
Conclusion: On-site HCV treatment with DAAs of people currently injecting drugs at a needle syringe program is effective, and can achieve high rates of SVR12. Needle syringe program provide a convenient and safe venue to engage HCV infected individuals who are continuing to inject. The rates of re-infection in this population, and the impact of HCV treatment at a needle syringe program on high risk behavior and community wide transmission (cure-as-prevention) need further investigation.



555 HIGH EFFICACY OF IFN-FREE ANTI-HCV REGIMENS FOR INDIVIDUALS ON OPIATE AGONIST THERAPY

Juan Macías[1], Luis E. Morano-Amado[2], Francisca Cuenca-Lopez[3], Miriam Serrano[4], Karin Neukam[1], Francisco Téllez[5], Manuel Márquez[6], Dolores Merino[7], Juan A. Pineda[1]
[1]Hosp Univ de Valme, Sevilla, Spain, [2]Hosp Univ Alvaro Cunqueiro, Vigo, Spain, [3]Hosp Univ Reina Sofia, Cordoba, Spain, [4]Hosp Univ de Gran Canaria Dr Negrín, Las Palmas, Gran Canaria, [5]Hosp de La Línea, La Línea de la Concepción, Spain, [6]Hosp Virgen de la Victoria, Málaga, Spain, [7]Complejo Hospario Univ de Huelva, Huelva, Spain

Background: A large proportion of individuals with HCV infection have been persons who inject drugs (PWID). PWID on opiate agonist therapy (OAT) may frequently use illicit drugs and relapse on injecting drug use. Due to these, clinicians may be reluctant to start anti-HCV therapy in PWID on OAT concerned about adherence and potential lower rates of sustained viral response (SVR). However, there is few data on SVR to direct antiviral agents against HCV (DAA) in patients on OAT. Because of these, we compared the rates of SVR to IFN-free DAA combinations among individuals with and without OAT in real life conditions of use.
Methods: The HEPAVIR-THERAPY cohort, recruiting HIV/HCV-coinfected patients (NCT02057003), and the GEHEP-MONO cohort (NCT02333292), including HCV-monoinfected individuals, are ongoing prospective multicenter cohorts of patients receiving DAA in clinical practice. We compared SVR 4 weeks after treatment (SVR4) among persons who never injected drugs (PWNID), PWID without OAT and PWID on OAT. Analyses were carried out by intention-to-treat.
Results: 914 patients started IFN-free DAA combinations, 370 (40%) PWNID, 443 (49%) PWID without OAT and 101 (11%) PWID on OAT. SVR4 rates were 354 (96%) for PWNID, 397 (90%) for PWID without OAT and 90 (89%) for PWID on OAT (p=0.002). Rates of relapse were: PWNID, 8 (2,2%); PWID without OAT, 21 (4,7%); PWID on OAT, 2 (2%) (p=0,092). Interruptions due to adverse events were: PWNID, 2 (0,5%); PWID without OAT, 3 (0,7%); PWID on OAT, 2 (2%) (p=0,324). Rates of voluntary drop-out were: PWNID, 3 (0,8%); PWID without OAT, 14 (3,2%); PWID on OAT, 4 (4%) (p=0,042). SVR4 rates for individuals without HIV infection were: PWNID 281/289 (97%), PWID without OAT 87/94 (93%) and PWID on OAT 30/34 (88%) (p=0,018). SVR4 rates for HIV-coinfected individuals were: PWNID 73/81(90%), PWID without OAT 310/349 (89%) and PWID on OAT 60/67 (90%) (p=0,938). Multivariate analysis adjusted by HIV, cirrhosis, HCV genotype and baseline HCV RNA showed that PWID without OAT [PWNID as reference, adjusted OR (AOR) 0,58, 95% confidence interval (95%CI): 0,28-1,2, p=0,147] and PWID on OAT [PWNID as reference, adjusted OR (AOR) 0,53, 95% confidence interval (95%CI): 0,21-1,4, p=0,193] were not independently associated with SVR4.
Conclusion: HCV-infected PWID on OAT achieve high SVR4 rates with IFN-free DAA. Because of this real life efficacy, HCV infection treatment should not be deferred among PWID due to ongoing OAT.

556 SVR12 FOR PATIENTS WITH BEHAVIORAL HEALTH CONDITIONS TREATED FOR HEPATITIS C IN FQHCS

Sophy S. Wong, Megan Crowley, Jan Diamond
Alameda Hlth Consortium, San Leandro, CA, USA

Background: Patients with chronic hepatitis C receiving primary care at federally-qualified health centers (FQHCs) often have co-occurring behavioral health conditions, including mental health, substance use and chronic pain diagnoses, which make providers reluctant to offer hepatitis C treatment. Despite increased access to hepatitis C direct-acting antivirals at FQHCs, few studies look at the characteristics and treatment outcomes for such patients. We aim to evaluate outcomes for patients with mental health, substance use and chronic pain diagnoses treated for hepatitis C by primary care providers (PCPs) in non-academic, non-specialist, community health center settings serving a low-income urban population.
Methods: We collected diagnosis, treatment and lab data from the medical records of patients treated for hepatitis C by PCPs at four FQHCs from January 2015 to July 2016. Patients with depression, anxiety, psychotic or organic brain disorders were considered to have a mental health diagnosis. Patients with illicit drug or excessive alcohol use were considered to have a substance use disorder. Medication regimens were determined by PCPs according to guidelines and obtained through usual processes. No study drugs or additional behavioral health staff were provided.

Results: 182 patients completed treatment for hepatitis C with PCPs at the four FQHCs from January 2015 to July 2016. Their genotypes include 1a/b, 2, 3, 4, and 6; 83% had genotype 1. 96% of the 112 patients with a viral load result at least 12 weeks after treatment completion had undetectable viral loads (SVR12). 64% of these patients had co-occurring mental health, substance use and/or chronic pain diagnoses; their SVR12 rate was 94%. There were four treatment failures among patients with behavioral health conditions and one treatment failure among patients without. Two patients stopped treatment early or were lost-to-follow-up, both with mental health conditions and chronic pain. Based on an intention-to-treat analysis, the overall SVR12 rate for this cohort was 94%. No statistically significant differences were found at the $p<0.05$ level. Please refer to the table for details.
Conclusion: These data demonstrate that patients with co-occurring mental health, substance use, and chronic pain diagnoses can achieve similar rates of hepatitis C cure as those without these behavioral health conditions when treated by PCPs in "real world," non-academic, non-specialist, community health center settings.

557 REAL-WORLD OUTCOMES OF HCV TREATMENT IN HOMELESS AND MARGINALLY HOUSED ADULTS

Joshua A. Barocas[1], Marguerite Beiser[2], Casey Leon[2], Molly Ingemi[2], Paul McCabe[3], Lena Cardoso[2], Benjamin Linas[4], James O'Connell[2]
[1]Massachusetts General Hosp, Boston, MA, USA, [2]Boston Hlth Care for the Homeless, Boston, MA, USA, [3]Quinnipiac Univ, North Haven, CT, USA, [4]Boston Univ, Boston, MA, USA
Background: Homeless and marginally housed (HMH) adults have higher rates of HCV than those with stable housing, likely due to a high prevalence of substance use disorder. A national strategy to combat HCV infection requires approaches to reaching and treating HMH adults. We describe the real-world HCV treatment experience of a cohort of HMH adults.
Methods: We retrospectively reviewed HCV treatment outcomes among the initial cohort of HCV-infected HMH adults treated with direct acting antivirals (DAA) at Boston Health Care for the Homeless Program (BHCHP). BHCHP is an urban community health center that provides care to over 12,000 individuals in the greater Boston area annually. BHCHP provides primary care and specialty services, including comprehensive HIV, HCV, and substance use treatment using a patient centered medical home approach. We used the electronic health record and manual chart review to extract demographics, characteristics of HCV and fibrosis, and treatment outcomes. Descriptive statistics were used to characterize the sample.
Results: Sixty-five consecutive individuals who completed DAA therapy were included in this analysis. 51% were male (mean age 55). 60% were non-Caucasian and 23% were in transitional housing or residential treatment programs. 92% reported a history of substance use and 32% had a history of incarceration. 46% were HIV-coinfected with 93% virologic suppression. Most were genotype 1 (89%), 6% were genotype 2. 32% were Metavir ≥F4. Ledipasvir/sofosbuvir (LDV/SOF) was prescribed most often (50/65). Adherence was excellent; only 7 patients reported ≥4 missed doses. 97% of the patients (63/65) achieved SVR12. Patient 1 who failed therapy was genotype 2 with cirrhosis who was treated with SOF/ribavirin for 12 weeks prior to the recommendation that extended treatment in such patients to 16 weeks. Patient had undetectable VL at EOT. Resistance testing was not performed. Patient 2 was genotype 1 with cirrhosis (Fib4=4.3) treated with LDV/SOF for 12 weeks. The patient was undetectable at 4 weeks, but detectable at EOT. Resistance testing following failure showed H58P and L31V mutations.
Conclusion: It is possible to successfully cure HCV in HMH adults with DAA therapy at a rate similar to that seen in clinical trials and other real-world cohorts despite significant additional barriers to health care. The national strategy to combat HCV infection should include treatment of HMH adults and develop best-practices for treating HCV in that population.

558 TREATMENT READINESS FOR HEPATITIS C INFECTION AMONG PWID IN CHENNAI, INDIA

Eshan U. Patel[1], Sunil S. Solomon[2], Allison M. McFall[1], Aylur K. Srikrishnan[2], Amrose Pradeep[2], Jungen Yi[1], Oliver Laeyendecker[3], David Thomas[1], Mark Sulkowski[1], Shruti H. Mehta[1]
[1]Johns Hopkins Univ, Baltimore, MD, USA, [2]YRG CARE, Chennai, India, [3]NIAID, Baltimore, MD, USA
Background: Global hepatitis C virus (HCV) elimination will require widespread treatment of people who inject drugs (PWID). PWID have historically had limited HCV treatment uptake. Little is known, however, about residual barriers in the direct acting antiviral (DAA) era, particularly in low resource settings, some of which are implementing elimination programs. We examined barriers to HCV treatment among PWID in India, where treatment access is rapidly expanding through generic DAAs (current cost of treatment course: $600 USD).
Methods: From 3/15-8/16, participants enrolled in an ongoing community-based cohort of current and former PWID in Chennai, India (n=542) completed a one-time questionnaire on HCV treatment barriers. At biannual follow-up visits, participants underwent a survey and lab testing including HCV & HIV antibody and RNA levels. Descriptive statistics were used to compare characteristics and survey responses.
Results: 214 (39.5%) of 542 were HCV-infected and 162 (30%) HCV RNA positive. 28.5% were HIV/HCV coinfected. In a 13-item survey, we found moderate knowledge about HCV disease and treatment among HCV uninfected (mean score=6.55 [standard deviation (SD)=1.30]), HCV monoinfected (mean=6.75 [SD=1.42]; P=0.12) and HCV/HIV coinfected participants (mean=6.31 [SD=0.94]; P=0.03). Only 30% of HIV/HCV coinfected patients knew HCV was curable (compared to 57% of HCV monoinfected). Only 17 participants reported seeing a doctor and 2 a specialist who could treat HCV (total linked to care - 5.6%), 11 (5.1%) initiated and 10 (4.7%) completed treatment. 10 of the 11 with a treatment history were co-enrolled in a clinical trial of HCV treatment. The primary reasons people were not linked were worries/fears about treatment (HCV monoinfected) and competing financial priorities (HIV/HCV coinfected). Factors that improved willingness were pills (vs. injections), perceived efficacy, cost and location with a higher proportion preferring daily visits to a clinic vs. receiving a month's supply (Figure 1). Willingness to take weekly interferon injections improved substantially with decreasing duration of treatment (60% for 12 weeks vs. 16% for 52 weeks).
Conclusion: These data highlight residual gaps in knowledge and continuing perceptions related to interferon-based therapy, particularly among HIV/HCV coinfected PWID in India. Treatment rollouts need to incorporate educational initiatives and should consider a directly observed therapy (DOT), analogous to what is done for TB.

559 FIELD-BASED DELIVERY OF HCV THERAPY WITH MINIMAL MONITORING TO PWID IN CHENNAI, INDIA

Sunil S. Solomon[1], Amrose Pradeep[2], Mark Sulkowski[1], Aylur K. Srikrishnan[2], Nandagopal Paneerselvam[2], Shanmugam Saravanan[2], Santhanam Anand[2], Muniratnam S. Kumar[2], David Thomas[1], Shruti H. Mehta[3]
[1]Johns Hopkins Univ Sch of Med, Baltimore, MD, USA, [2]YR Gaitonde Cntr for AIDS Rsr and Educ, Chennai, India, [3]Johns Hopkins Univ, Baltimore, USA
Background: In 2016, WHO released elimination targets for hepatitis C virus (HCV), but for these to be achieved, strategies must target those hardest-to-treat in low-and-middle-income countries (LMICs) such as people who inject drugs (PWID). Access in LMICs has improved with generic antivirals (~$200/28 days) but monitoring remains expensive (HCV RNA=$80; genotype=$90). We evaluated the feasibility of field-based directly observed therapy (DOT) with minimal molecular monitoring for delivery of HCV therapy to current and former PWID in Chennai, India, where genotype (GT) 3 or 1 infections are common.
Methods: From 9/2015 – 3/2016, 50 PWID were randomized 1:1 to Arm 1: Sofosbuvir+Peginterferon+Ribavirin (SOF+PR) for 12 weeks or Arm 2: Sofosbuvir+Ribavirin (SOF/RBV) for 24 weeks. HCV RNA testing was done at baseline and 12 weeks after the end of treatment (EOT) to measure sustained virologic response 12 (SVR; HCV RNA<="" div="">
Results: All were male; median age was 46; 2 were HIV co-infected and 20% had an elastography score >12.3 kPA (cirrhosis). Six discontinued (3 per arm) – none due to side effects (treatment completion in each arm: 88%). Of 44 who completed treatment, median missed doses were 2 with SOF+PR (range: 0-18) and 6 (range: 0-39) with SOF/RBV. All 22 who completed treatment with SOF+PR achieved SVR (88%: [22/25]). Of the 16 who completed SOF/RBV treatment and had SVR data at abstract submission, 11 achieved SVR (58% [11/19]). Of the HCV failures with SOF/RBV, 2 had GT1a and 3 GT3a infection; 4 had HCV RNA<="" div="">
Conclusion: Field-based DOT of HCV therapy without real-time molecular monitoring was logistically feasible; however achieving 100% adherence was challenging. SOF+PR appeared superior to SOF/RBV in achieving SVR, especially in those who missed doses with no discontinuations due to side effects. In settings where injections are perceived more effective than pills and adherence may be challenging, there may remain a role for peginterferon in combination with oral direct acting antivirals for short treatment durations.

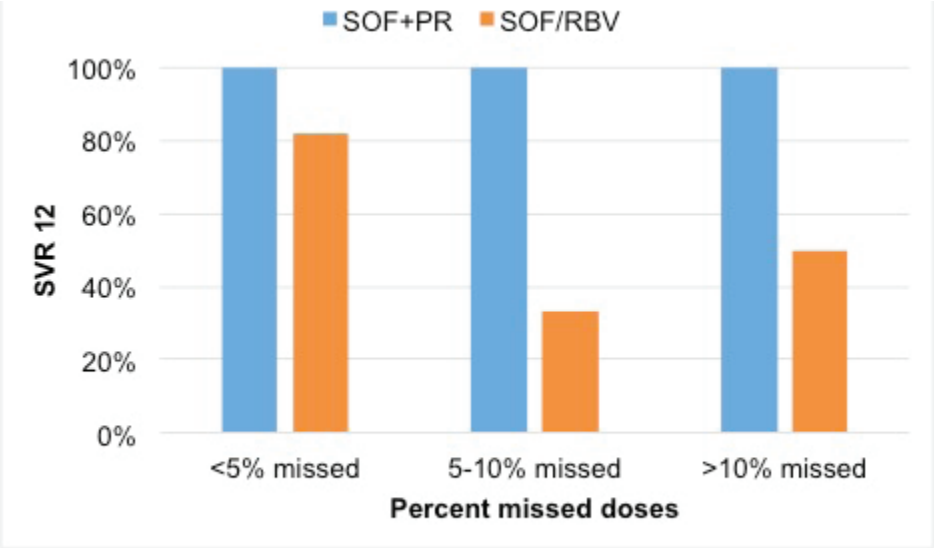


Figure: SVR12 by study arm in participants who completed treatment and had SVR data (n=38)

560 HIGH RATES OF HCV CURE AMONG URBAN BLACK AND NON-BLACK HIV-INFECTED PATIENTS

Oluwaseun Falade-Nwulia[1], Juhi Moon[1], Geetanjali Chander[1], Tanyaporn Wansom[2], Catherine Sutcliffe[1], Shruti H. Mehta[1], David Thomas[1], Richard D. Moore[1], Mark Sulkowski[1]
[1]Johsn Hopkins Univ, Baltimore, MD, USA, [4]US Military HIV Rsr Prog, Bethesda, MD, USA

Background: Generally, HCV cure rates have been similar in patients with and without HIV coinfection; however, in the ION-4 study, black patients treated with sofosbuvir/ledipasvir (SOF/LDV) were significantly less likely to achieve cure (90%) compared to non-black patients (99%). There are limited real world data on the effectiveness of oral direct acting antivirals (DAAs) in predominantly minority HIV/HCV coinfected populations.
Methods: We analyzed HCV treatment outcomes among 255 HCV coinfected patients initiating DAAs between February 2014 and March 2016; all were enrolled in an ongoing prospective HIV cohort in Baltimore, MD. To facilitate adherence, patients received standardized HIV nurse/pharmacy support which included nurse visits and telephone calls. Demographics, laboratory test results and DAAs prescribed were extracted from the electronic medical record.
Results: The median age was 43 years, 87% were black, 73% male, 69% had a history of injection drug use (IDU), 45% a history of hazardous alcohol use and 57% a comorbid psychiatric diagnosis. Median CD4 count was 577 (IQR 397-820) cells/mm3; most (97%) were on antiretrovirals and had HIV RNA <200 copies/ml (95%) and were infected with HCV genotype 1 (98%). Over 60% had significant fibrosis (FIB4 score 1.45-3.25 (44%) and >3.25 (17%, cirrhosis) and 30% were HCV treatment experienced. The majority of patients received SOF/LDV with or without ribavirin (91%) and were treated for 12 weeks (80%) whereas 4% and 15% received treatment for 8 weeks or less and 24 weeks, respectively. Overall, the cure rate was 96% (95% confidence interval [CI] 93-98) and did not vary by race (Black, 96% [95% CI 93-98]; Non-black 97%, [95% CI 83-99]) , HCV treatment experience (Naïve, 96% [95% CI 92-98]; Experienced, 97% [95% CI 91-100], history of IDU, alcohol use or psychiatric diagnosis history. Nine patients did not achieve cure; all were prescribed SOF/LDV without ribavirin for 12 weeks. Of these, 4 discontinued treatment prematurely (< 4 weeks), 3 had decompensated cirrhosis or were treatment-experienced and 2 had genotype 1b infection and did not report missed doses. Treatment was well-tolerated; only 1 patient discontinued due to side effects.
Conclusion: HCV treatment was highly effective among HIV-infected patients who received care using a standard nurse/pharmacist adherence support program. Our results from an urban clinical practice suggest that race and psychosocial comorbidity may not be barriers to HCV elimination

561 GLOBAL ORIGINS OF RESISTANCE-ASSOCIATED VARIANTS IN THE NS5A REGION OF HCV

Bradley R. Jones[1], Jeffrey Joy[2]
[1]BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada, [2]Univ of British Columbia, Vancouver, British Columbia, Canada

Background: Hepatitis C virus (HCV) contains a variety of naturally occurring polymorphisms in the nonstructural protein 5A (NS5A) that reduce susceptibility to currently approved NS5A inhibitors. Previous investigations showed the Q80K mutation in the NS3 region of HCV has a common origin in the world population around 1930 in genotype 1a strongly coupled to substitutions A915/T, S147N or V29A. We sought to reconstruct the evolutionary history of the NS5A resistance-associated substitutions (RASs).
Methods: We collected more than 200,000 HCV sequences from global databases. Sequences were aligned using MAFFT v.7.54b and visually inspected using AliView v.1.18. After discarding sequences from the same patient and sequences that do not cover NS5A by 75%, we were left with 1,613 sequences. RASs were defined as substitutions in the NS5A gene previously identified based on literature sources. We inferred a phylogenetic tree for genotype specific datasets (1a, 1b, and 3a) under approximate maximum likelihood as implemented in FastTree2. Resulting phylogenies were rescaled to units of time using the R package ape. Next, we reconstructed the ancestral sequences at the nodes of the trees using MG94xREV codon model. Finally, NS5A RASs were mapped onto the resulting trees to recover patterns of ancestry.
Results: We found, in contrast to Q80K in NS3, that most NS5A RAVs do not have a common origin, but rather each has evolved independently many times. They are widely dispersed amongst the phylogenetic trees of each genotype. Of the 22 types of RASs found in the total population, only 6 had origins that were not at the tips of the tree, each which had less than 5 RAS descendants. All of these RASs had their origins at tips of the tree, indicating recent origins. While the Q80K polymorphism has a highly localized origin in North America, we find that NS5A RASs have no strong pattern with respect to geography, with the overall prevalence ranging from 0.06% to 5%.
Conclusion: The inferred distribution of RASs in the NS5A region and frequency of their origin suggest that, unlike Q80K, there is a low fitness barrier without the need for co-evolution of compensatory mutations. A low fitness barrier may allow rapid selection of de novo resistance to NS5A inhibitors during therapy.

562 IMPACT OF HCV NS5A RESISTANCE ON TREATMENT RESPONSE IN HIV AND HIV/HCV PATIENTS

Itziar Carrasco Garcia[1], Ana Arias[2], Laura Benitez[2], Silvia Requena[1], Miriam Cuesta[1], Luis Otero[3], Valentin Cuervas-Mons[2], Carmen de Mendoza Fernández[2], for the Internal Medicine Department

[1]Puerta de Hierro Rsr Inst and Univ Hosp, Madrid, Spain, [2]Hosp Puerta de Hierro, Madrid, Spain, [3]Hosp de Cabueñes, Asturias, Spain

Background: Oral DAA have demonstrated high efficacy for the treatment of HCV carriers. However, the presence of resistance–associated substitutions (RAS) at baseline may impair treatment response. Herein, we analyzed baseline RAS at the HCV NS5A gene region in all patients treated with DAA at one large reference clinic in Madrid.

Methods: All HCV patients treated with DAA including NS5A inhibitors were retrospectively examined. Demographics and HCV genotype, baseline serum HCV-RNA, liver fibrosis staging, HIV coinfection, and sustained virological response (SVR) at week 12 were all recorded in a large database built for this study. The HCV NS5A gene region was analyzed using population sequencing at baseline in all patients as well as after 24 weeks of completing therapy in those that failed treatment. All changes recorded at NS5A positions 28, 29, 30, 31, 32, 58, 62, 92 and 93 were considered.

Results: A total of 112 patients were analyzed. HCV genotype distribution was as follows: G1a (47.8%), G1b (23.5%), G3 (14.8%) and G4 (13.9%). Overall, 64 (55.6%) patients were coinfected with HIV and 55% had advanced liver fibrosis (Metavir F3-F4). Overall 57.4% were naive for HCV therapy and more than 60% had baseline HCV-RNA >6 log IU/mL. A total of 46 (41%) patients had at least one RAS at baseline; and 6.2% had 2 or more RAS. Specific changes were as follows: M28A/G/T (4); P29S (1); Q30X (8); L31I/F/M/V (6); T58P/S (19); Q/E62D (16); A92K (1) and Y93C/H (4). Changes at position 58 were only present in genotype 4 whereas changes at position 62 were only present in genotype 3. Eleven (9.8%) patients experienced DAA failure. No association was found with high baseline HCV-RNA, HCV genotype, liver fibrosis stage, HIV coinfection, prior treatment nor specific baseline RAS. However, the presence of two or more RAS at baseline was more frequent in patients who failed compared with those that achieved SVR (18.2% vs 5%, p=0.085; respectively). Baseline NS5A resistance mutations were found at baseline in 4 out of 11 failures. They were recognized in 9 upon failure. Six patients increased the number of RAS after failure, being emerging changes Q30 (3 cases), L31 (1 case), H58 (1 case) and Y93 (2 cases).

Conclusion: Baseline NS5A RAS are frequently seen (41% in our series) in HCV patients, regardless HIV status. The presence of two or more RAS may impair the likelihood of SVR. Treatment failures on NS5A inhibitors may benefit from subsequent HCV resistance testing in order to guide re-treatment options.

563 CATALOGING THE IMPACT OF Y93 SUBSTITUTIONS ON HCV NS5A INHIBITOR SUSCEPTIBILITY

Alicia Newton, Charity Ting, Arne Frantzell, Jennifer Cook, Christos Petropoulos, **Wei Huang**

Monogram BioScis, South San Francisco, CA, USA

Background: Amino acid substitution at position 93 (Y93) of NS5A represents a key pathway to HCV NS5A inhibitor resistance. Multiple substitutions are associated with resistance in genotype 1a (GT1a) viruses, whereas the Y93H substitution predominates in GT1b viruses. In this study, we investigate the impact of different substitutions on NS5A inhibitor susceptibility and replication capacity (RC) in the contextof GT1a and GT1b NS5A sequences.

Methods: A panel of luciferase-reporter replicons containing different Y93 substitution was constructed using H77 (GT1a) and Con1 (GT1b) NS5A sequences. NS5A inhibitor susceptibility (fold change in IC50, FC) and RC relative to the parental replicon was determined.

Results: Y93C/D/F/H/L/N/R/S/T/W substitutions within the GT1a NS5A sequence generally conferred large reductions in susceptibility to ledipasvir (LDV, FC=12.2 to 159321), ombitasvir (OBV, FC=52 to 140593) and daclatasvir (DCV, FC=16 to 16523), as well as elbasvir (EBV, FC=2.6 to 49925) to a lesser extent. In contrast, Y93C/D/F/H/L/N/R/S/T/W substitutions within the GT1b NS5A sequence had much less impact on LDV (FC=0.6 to 2252), OBV (FC=0.6 to 553), DCV (FC=0.4 to 24) and EBV (FC=0.3 to 7.5) susceptibility, including, Y93H (FC=7.5 to 387). Replicons containing Y93C/L/N/R/S/T/W within the GT1a NS5A sequence replicated as well as, or better than, the Y93H replicon in the presence of LDV, OBV or DCV; whereas Y93N/R/S/W replicons replicated as well, or better in the presence of EBV. Among the replicons containing GT1b NS5A sequences, the Y93H replicon replicated better in the presence of each NS5A inhibitor than all of the other replicons containing Y93 substitutions.

Conclusion: Y93 substitutions confer larger reductions in NS5A inhibitor susceptibility in the context of GT1a NS5A sequences compared to GT1b sequences. Reductions in susceptibility were generally larger for LDV, OBV and DCV than EBV. Reductions in NS5A inhibitor susceptibility and RC conferred by Y93 substitutions are consistent with observed prevalence of these substitutions in GT1a and GT1b viruses.

564 NATURAL HCV RESISTANCE IS COMMON IN ITALY AND DIFFERENTLY ASSOCIATED TO GENOTYPES

Valeria Cento[1], Ada Bertoli[1], Giustino Parruti[2], Giuliano Rizzardini[3], Gloria Taliani[4], Caterina Pasquazzi[4], Massimo Andreoni[1], Carlo F. Perno[1], **Francesca Ceccherini Silberstein**[1], for the VIRONET-C

[1]Univ of Rome Tor Vergata, Rome, Italy, [2]Pescara Hosp, Pescara, Italy, [3]Luigi Sacco Univ Hosp, Milan, Italy, [4]Sapienza Univ of Rome, Rome, Italy

Background: Natural resistance associated substitutions (RASs) are reported with highly variable prevalence across different HCV genotypes (GTs) and countries. We investigated the frequency of natural RASs, and the role of NS5A-RASs on treatment efficacy, in a large Italian real-life database including the 4 main HCV-GTs.

Methods: RASs in NS3 (N=1032), NS5A (N=833) and NS5B (N=496) were analysed in 1193 HCV-infected DAA-naïve patients (pts; 68% treatment-experienced; 55% cirrhotic; 5% HIV co-infected). Sanger sequencing was performed by home-made protocols on 714 GT1a, 989 GT1b, 135 GT2c, 333 GT3a, 190 GT4a/d samples. RASs with fold-change >100 were defined as major.

Results: Overall, 415/1193 (35%) pts showed natural RASs, independently by cirrhosis, but with important differences for GT/subtypes. GT1a, GT1b and GT4a frequently showed NS3 RASs (52-20-36%, respectively), with high prevalence of 80K in GT1a (17%). Major RASs 168A/E/T/V had 3-4% prevalence in GT2c-GT4d. Also in NS5A, GT1a, GT1b and GT4a showed the highest prevalence of RASs (10-31-38%, respectively). NS5A RASs prevalence was higher in IFN/RBV experienced patients (35%) vs IFN-naive (22%, p=0.02) only in GT-1b. Major NS5A RASs were detected in 10% GT1a (28V-30H/R-31M-93C/H), 9% GT1b (30R-93H), 5% GT2c (31M-93H), 4% GT3a (93H) and 2% GT4d (30S). In NS5B, the sofosbuvir putative RASs 159F and 316N were exclusively detected in GT1b (13% and 19%) often in association (phy correlation=0.67, p<0.001). Among 372 pts with resistance test in all 3 genes, 10% showed multiple RASs, with frequent NS3+NS5A RASs (mainly in GT1-4). Only 2 GT1b pts showed RASs on 3 drug-targets. Lastly, 138 pts treated with a NS5A-inhibitor were studied to evaluate the potential role of natural RASs. Among 26 non-cirrhotic pts, only 4 showed baseline minor NS5A-RASs (GT1b: 30Q, 31M, 58S, 92T) and all reached a sustained viral response (SVR). Among 112 cirrhotic pts, 4 showed major baseline NS5A RASs (fold-change >1000): two pts (GT1b:93H; GT4d:30S) treated with not-recommended regimens, and without RBV, experienced virologic failure; the other 2 (GT1b:93H; GT1a:30R) received a recommended-regimen with RBV, reached SVR.

Conclusion: Natural RASs are common across all HCV-GTs in Italy, and up to 10% of pts show multi-class RASs, though only the so-called major mutations seem to have a clinical relevance. Thus, qualitative identification of only major RASs (rather than all) is required to properly guide DAA-based therapy.

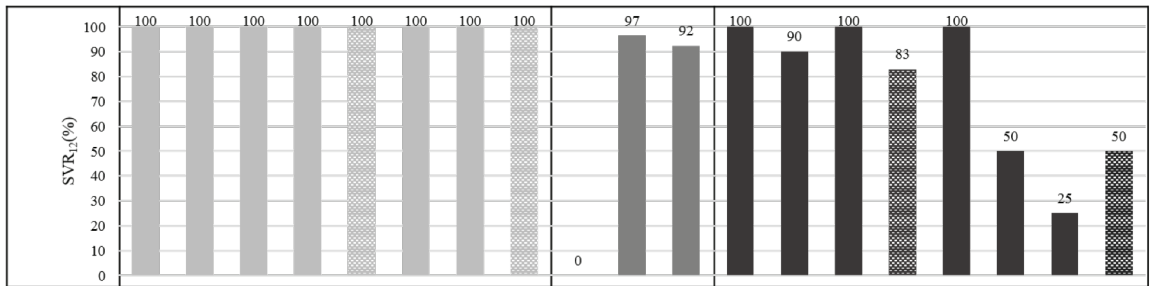
565 OPTIMAL EFFICACY OF HCV-RESISTANCE–BASED RETREATMENTS AFTER PI FAILURE

Valeria Cento[1], Silvia Barbaliscia[1], Stefano Bonora[2], Sergio Babudieri[3], Alessia Ciancio[4], Giuliano Rizzardini[5], Mario Angelico[6], Carlo F. Perno[1], Francesca Ceccherini Silberstein[1], for the VIRONET-C

[1]Univ of Rome Tor Vergata, Rome, Italy, [2]Univ degli Studi di Torino, Torino, Italy, [3]Univ of Sassari, Sassari, Italy, [4]City of Hlth and Sci of Turin, Turin, Italy, [5]Luigi Sacco Univ Hosp, Milano, Italy, [6]Hosp of Rome Tor Vergata, Rome, Italy

Background: We analyzed the efficacy of HCV retreatment strategies after a protease inhibitor (PI) failure with various DAA regimens, and the role of resistance associated substitutions (RASs) on viral failure to a 2nd line regimen.

Methods: This is a multi-center observational real-life study of patients (pts) undergoing HCV retreatment after 1st generation-PI + peg-IFN and ribavirin (RBV) failure. Sustained virological response (SVR) was evaluated at week-12 of follow-up. HCV genotypic resistance testing (GRT) was performed by Sanger-based home made protocols.
Results: 121 pts with chronic HCV infection (GT1b=57%; cirrhosis=87%) were retreated after a median (IQR) of 102 (74-123) weeks from a previous PI failure (telaprevir=69, boceprevir=51, simeprevir=1). Retreatment followed different strategies: A) 18 pts were treated with a GRT-based PI- or NS5A-containing regimen; B) 72 pts were treated with a "switch" regimen of sofosbuvir+NS5A inhibitor+RBV, without baseline GRT, following international guidelines; C) 31 pts received different regimens +/- RBV, neither recommended nor GRT-guided (see figure). Overall SVR rate was 91%, with differences according to strategy choice A), B) or C). All 18 pts treated with GRT-guided regimens (A) reached SVR (100%), despite heterogeneity in treatment duration, PI-inclusion (where indicted by GRT) and RBV use. 68/72 pts (94%) receiving a 2nd line regimen according to guidelines (B) achieved SVR; only 1/4 failing pts was a posteriori tested for natural RASs, revealing a natural L28M NS5A-RAS. On the contrary, SVR rate was strongly reduced (77%) among the 31 pts who received C) (a not recommended, not GRT-guided regimen) (p-trend<0.01). Overall, 37/121 pts were re-treated with a PI (simeprevir or paritaprevir) and 33/37 (90%) achieved SVR. The 4 failing GT-1a cirrhotic patients (all in option C) used a simeprevir-containing regimen; 3/4 showed a posteriori R155K NS3-RAS at baseline (1 had no baseline GRT). All 7 patients treated with a paritaprevir-containing regimen reached SVR, regardless treatment duration and performance of a baseline GRT. When GRT was available both at baseline and at 2nd failure, all pts showed an increase of RASs at the new failure.
Conclusion: DAA's retreatment after 1st generation PI failure can induce a maximal SVR rate if guided by GRT, greater than SOF+NS5A inhibitors+RBV for 24 weeks, as recommended by guidelines. PIs can be fruitfully reconsidered if appropriately chosen after a punctual GRT-based RASs evaluation.



	GRT-guided (N=18)								EASL/AASLD Recommended (N=72)			Not recommended, not GRT-guided (N=31)							
Treatment duration (weeks)	12					24			12	24		12				24			
Ribavirin	Ribavirin				No ribavirin	Ribavirin		No ribavirin	Ribavirin	Ribavirin		Ribavirin			No ribavirin	Ribavirin			No ribavirin
IFN-free regimen	SOF+ LDV	SOF+ DAC	3D	SOF+ SIM	SOF+ SIM	SOF+ DAC	SOF+ SIM	SOF+ DAC	SOF+ LDV	SOF+ LDV	SOF+ DAC	3D	SOF+ SIM	SOF	SOF+ SIM	3D	SOF+ SIM	SOF	SOF+ SIM
SVR12, n/N (%)	1/1 (100)	1/1 (100)	2/2 (100)	5/5 (100)	2/2 (100)	3/3 (100)	3/3 (100)	1/1 (100)	0/1 (0)	56/58 (97)	12/13 (92)	3/3 (100)	9/10 (90)	2/2 (100)	5/6 (83)	2/2 (100)	1/2 (50)	1/4 (25)	1/2 (50)

566 RETREATMENT OPTIONS AFTER FAILING A FIRST LINE OF DAAs AGAINST HEPATITIS C VIRUS

Ana B. Perez[1], Natalia Chueca[1], Miguel García-Deltoro[2], Ana María Martínez-Sapiña[3], Daniel Navarro[4], Dolores Merino[5], Miguel Jiménez[6], Juan Manuel Pascasio[7], Antonio Rivero[8], **Federico García**[1]
[1]Complejo Hospario Univ de Granada, Granada, Spain, [2]Hosp General de Valencia, Valencia, Spain, [3]Hosp Univ Miguel Servet, Zaragoza, Spain, [4]Complejo Hospario Univ de Santiago, Santiago de Compostela, Spain, [5]Complejo Hospario Univ de Huelva, Huelva, Spain, [6]Hosp Regional Carlos Haya, Málaga, Spain, [7]Hosp Univ Virgen del Rocío, Sevilla, Spain, [8]Hosp Univ Reina Sofia, Cordoba, Spain

Background: In Spain, the rollout of interferon-free treatment of HCV infected patients has been implemented since April 2015. In our study, we evluated the retreatment options in a large cohort of patients failing IFN-free direct antiviral agents (DAAs) regimens in Spain (HCVREsp), and the prevalence of HCV resistance associated substitutions (RAS)
Methods: HCVREsp is a prospective multicenter real world cohort enrolling HCV infected patients treated with IFN-free DAA regimens at discretion of the investigators. For patients failing their DAA regimen, population-based sequencing of HCV NS3, NS5A and NS5B genes was performed. When available, a baseline serum sample was analyzed in parallel. Ultra-deep sequencing in NS5B was performed to study mixed infections and to discriminate reinfection from relapse.
Results: HCVREsp includes 5439 patients across Spain, 16.6% treated with SOF/SIM, 16.8% with SOF/DCV, 41.4% with SOF/LD, and 24.5% with Paritaprevir/Ombitasvir/Dasabuvir (3D). We present the data of 255 failing patients, 83% males, median age 53 (IQR 48-58), median log viral load 5,94 logs, IQR 5,49-6,46. Table 1 shows the frequency and characteristics of RAS in the failing cohort. Discordant genotyping from baseline data was observed in 35/255 (13,7%) patients; 4 cases of reinfection and 6 genotyping errors by the commercial methods used at origin were recorded.
Conclusion: In this large Spanish HCV Resistance cohort genotypes 3 & 4 were less prone to the development of RAS, especially GT3 infected patients failing the SOF/LDV combination. Discordant genotype call was a frequent event, and mixed infections and intra- and inter- subtype/genotype reinfection also occurred. From the virological perspective, the recently approved Sofosbuvir-Velaptasvir regimen could be used to retreat a higher number of patients.

		RAS detected	Clinically relevant RAS	Retreatment options
SOF/SIM	51	34(69,4%)	NS3: 29(59,2%)	SOF/DCV ó LED: 84,1% 3D/2D: 50,0% GRZ/EBV: 57,1% SOF/VEL: 97,7%
SOF/DCV	45	39(86,7%)	NS5A: 37(82,2%)	SOF/LED 24W RBV: 17,8% SOF/SIM: GT1 63,6% 3D: 18,2% GRZ/EBV: GT1 27,2% SOF/VEL: 48,9%
SOF/LED	105	74(70,5%)	NS5A/B: 67(63,8%)	SOF/SIM: GT1/GT4 91,4% SOF/DCV ó LED 24W RBV: 36,2% 3D/2D: 27,2% GRZ/EBV: GT1/GT4 21,0% SOF/VEL : 98%
PTV/OMB/DSV	40	34(85,0 %)	NS3/NS5A/NS5B: 33(82,5%)	SOF/SIM: 53,0% SOF/DCV ó LED: 28,2% GRZ/EBV: 21,6% SOF/VEL: 92,3%

567 HCV REINFECTION AFTER SUCCESSFUL DAA TREATMENT: A GECCO ANALYSIS

Patrick Ingiliz[1], Stefan Christensen[2], Florian Berger[3], Torben Kimhofer[4], Knud Schewe[5], Christoph Boesecke[6], Dietrich Hueppe[7], Julian Schulze zur Wiesch[8], Thomas Lutz[9], Stefan Mauss[3]

[1]Cntr for Infectiology, Berlin, Germany, [2]CIM Infectious Diseases, Münster, Germany, [3]Cntr for HIV and Hepatogastroenterology, Duesseldorf, Germany, [4]Imperial Coll London, London, UK, [5]dagnae e.V., Berlin, Germany, [6]Univ Hosp Bonn, Bonn, Germany, [7]Gastroenterology Practice, Herne, Germany, [8]Univ Med Cntr, Hamburg-Eppendorf, Germany, Hamburg, Germany, [9]Infektiologikum, Frankfurt, Germany

Background: Reinfection with the hepatitis C virus has been described in patients with ongoing risk behaviour for HCV acquisition after spontaneous clearance or succesful treatment. The highest incidences have been described in active intravenous drug users (IDUs) and in HIV-positive men who have sex with men (MSM). Among the latter, users of intravenous and non-intravenous drugs (mainly methamphetamine) for sexual enhancement (Chemsex) have been identified as a main risk group for HCV acquisition. In HIV infected MSM in Western Europe in the interferon era, 25% have been found to be reinfected with HCV three years after HCV cure. The frequency of HCV reinfections after treatment with direct-acting antivirals (DAA) is not known. Here, we analysed the reinfection rate in the GECCO cohort.

Methods: The German hepatitis C cohort (GECCO) consists of treatment data on all directly acting antiviral agents from HCV mono- and HIV-HCV coinfected patients from nine centers since February 2014. Reinfection was defined as an detectable HCV RNA in a patient that had an undetectable HCV RNA 12 weeks after the end of treatment (SVR12), or with an HCV genotype switch.

Results: Up to May 2016, 1636 patients have been cured with DAA combinations within the GECCO cohort. Overall, 16 patients (1%) have been identified with an HCV reinfection. All patients were male, the median age was 46 years (IQR 38-52), and 13/16 (81%) were HIV-HCV coinfected. The three HCV mono-reinfections appeared in intravenous drug users (IDU), while all 13 coinfected patients were MSM. Six out of the 13 (46%) MSM declared to have occasional intravenous recreational drug use. The median time from end-of-DAA-treatment to reinfection was 35 weeks (range 5-112). In 9 patients (69%) a genotype switch occured. The reinfection rate in IDUs was 0.5% (3/586), and 0.8% in those on opiate substution treatment (3/355). In MSM, however, it was 7.4% (13/175) ($p<0.001$).

Conclusion: Within the multicentric GECCO cohort, reinfection remains a rare event. Obviously, subgroups with ongoing risk behaviour remain at risk for HCV reinfection, with MSM being more affected than IDUS. In HIV-infected MSM, similar reinfection rates as in the pre-DAA era are observed, again highlighting this subgroup as a target population for close monitoring and specific behavioural interventions.

568LB LEDIPASVIR/SOFOSBUVIR±RIBAVIRIN IN HCV AND HCV/HIV PRIOR SOF-BASED VIROLOGIC FAILURES

Edward Tam[1], Robert S. Brown, Jr[2], Sanjaya Satapathy[3], Gregory Camus[4], Amanda Copans[4], Lorenzo Rossaro[4], Willliam D. Guyer[4], Richard Haubrich[4], Minhee Kang[5], Annie Luetkemeyer[6]

[1]LAIR Cntr, Vancouver, Canada, [2]Weill Cornell Med, New York, NY, USA, [3]Univ of Tennessee, Memphis, TN, USA, [4]Gilead Scis, Inc, Foster City, CA, USA, [5]Harvard Univ, Boston, MA, USA, [6]Univ of California San Francisco, San Francisco, CA

Background: Current AASLD guidance, based on limited data and non-randomized studies, recommends 12-24 weeks (wks) of ledipasvir/sofosbuvir (LDV/SOF)+ribavirin (RBV) for retreatment of patients who failed prior SOF-based therapy.

Methods: Two prospective randomized studies evaluated the efficacy, safety, and duration of LDV/SOF±RBV for treatment of HCV mono- and HCV/HIV co-infected patients who relapsed after simeprevir (SMV)+SOF±RBV or SOF+RBV±pegylated interferon (PEG) regimens. Study 1 (GS-US-337-1746) enrolled 87 genotype (GT)1 and GT4 adult patients. Non-cirrhotics were randomized to Arm 1: LDV/SOF 12 wks or Arm 2: LDV/SOF+RBV 12 wks, and compensated cirrhotics to Arm 3: LDV/SOF+RBV 12 wks or Arm 4: LDV/SOF 24 wks. Study 2 (ACTG A5348) randomized 7 GT1 adults with HCV/HIV co-infection with controlled HIV to Arm A: LDV/SOF+RBV 12 wks or Arm B: LDV/SOF 24 wks. Both studies excluded NS5A-experienced patients, with sustained virologic response (SVR12) as the primary endpoint. NS5A and NS5B resistance associated substitutions (RASs) were analyzed at baseline and, if applicable, at time of virologic failure using deep-sequencing at a 15% cutoff.

Results: Five patients terminated the study prior to starting study drug. All remaining 82 patients in Study 1 and all 7 in Study 2 completed treatment. In Study 1, 69/82 (84%) patients have currently completed 12 week post-treatment follow up: 73% were male, 28% black, mean age 58 years, 52% cirrhotic, 90% GT1 (GT1a=65%), and 94% IL28B non-CC. Overall SVR12 was 87% (range 76-100%, see table). Eight patients experienced virologic failure (relapse) and one was lost to follow up after attaining SVR4. 6/8 with RAS data available developed treatment emergent NS5A RASs. Nine patients (13%) had baseline NS5A RASs and of those 8/9 (89%) achieved SVR12. Of those without baseline NS5A RASs, 52/60 (87%) achieved SVR12. 80% experienced an adverse event (AE); 1 serious AE not related to study drug. In Study 2, 5/7 were male, mean age 55, 1 cirrhotic, 5/7 GT1a. 6/7 have data available at 4 wks follow up, of whom all attained SVR4 with no SAEs or premature discontinuations.

Conclusion: In this SOF-experienced NS5A-naive population, high SVR rates were achieved with LDV/SOF±RBV for 12 or 24 wks, including patients with HCV/HIV co-infection. Highest SVR rates were observed with 12 wks LDV/SOF+RBV in non-cirrhotics and 24 wks LDV/SOF in cirrhotics, suggesting RBV may not be needed when duration is extended in cirrhotics. Baseline RASs did not impact treatment outcome.

Sustained Virologic Response (SVR) by study, drug regimen, & duration of therapy			
Study	Regimen	Duration, weeks	SVR12
Study 1, HCV Non-cirrhotic	Arm 1: LDV/SOF	12	81% (13/16)
	Arm 2: LDV/SOF+RBV	12	100% (17/17)
Study 1, HCV Cirrhotic	Arm 3: LDV/SOF+RBV	12	76% (19/25)
	Arm 4: LDV/SOF**	24	100% (11/11)
			SVR4
Study 2, HCV/HIV	Arm A: LDV/SOF+RBV	12	100% (4/4)
	Arm B: LDV/SOF	24	100% (2/2)

**13/24 patients in Arm 4 have not reached the 12 week post-treatment follow up

569 NINETY-SIX % SVR RATES USING IMPORTED GENERIC DAAs FOR PATIENTS WITH HEPATITIS C

Andrew Hill[1], Giten Khwairakpam[2], James Wang[3], Sergey Golovin[4], Julia Dragunova[5], Rachel Smith[6], Vicky Houghton-Price[6], Roxanna S Korologou-Linden[7], Anton Pozniak[8], Greg Jefferys[9]

[1]St Stephens Cntr, Chelsea and Westminster Hosp, London, UK, [2]TREAT Asia/amfAR, Bangkok, Thailand, [3]Ci Run Hlth Information Consulting Co. Ltd., Kunming, China, [4]Intl Treatment Preparedness Coalition, St. Petersburg, Russian Federation, [5]Intl Treatment Preparedness Coalition and GEPATITKA Community, St. Petersburg, Russian Federation, [6]Metavirology Ltd, London, UK, [7]Imperial Coll London, London, UK, [8]Chelsea and Westminster NHS Fndn Trust, London, UK, [9]Univ of Tasmania, Tasmania, Australia

Background: High prices for Direct Acting Antivirals (DAAs) are a barrier to treatment access. High-income countries such as Russia, China, Southeast Asia and Eastern Europe are not included in voluntary license agreements, and prices of DAAs in these countries are very high. In most of these countries, individual citizens can legally import non-registered medicines for their personal use. An increasing number of individuals are treating their Hepatitis C infection with generic drugs produced in India, China or Egypt. This analysis assessed the effectiveness of generic DAAs imported into 40 countries.

Methods: 568 patients sourced generic versions of sofosbuvir (SOF), ledipasvir (LDV) and daclatasvir (DCV) from suppliers in India, Bangladesh, China and Egypt via established Buyers Clubs and personal connections. The choice of DAAs and the length of treatment were determined based on baseline RNA levels, HCV Genotype and stage of fibrosis. Patient HCV RNA levels were evaluated pre-treatment, during treatment, at end of treatment (EOT) and for SVR 4, 12, and 24 weeks.

Results: Overall, 568 patients submitted results (146 from an Australian Buyers Club, 154 from a Chinese Buyers Club, 200 from a Russian Buyers Club, 68 from a Southeast Asian Buyers Club). Of these, 121 received SOF (59 with RBV), 169 received SOF/LDV (18 with RBV), 279 received SOF/DCV (15 with RBV) and 1 received SOF/LDV/DCV. Overall, the patients were 64% male with a mean age of 43.2 years; 47% were Genotype 1, and 11% cirrhotic. Mean baseline HCV RNA was 6.9 log10 IU/mL. A rapid virological response (RVR) was observed in 94% (29/31) of patients treated with SOF/RBV, 84% (137/163) of the patients treated with SOF/DCV and 80% (75/94) of the patients treated with SOF/LDV. Based on currently available data, the percentage of patients with HCV RNA<="" div="">

Conclusion: Treatment with legally imported generic DAAs achieved high rates of HCV RNA undetectability at the end of treatment and SVR in the majority of patients evaluated to date. The efficacy observed was similar to Phase 3 trials of the branded medicines. Mass treatment with the current generic DAAs is an alternative and feasible route of accessing economical DAAs, where the high-prices for branded DAAs prevent access to treatment.

	SOF/RBV N=59		SOF/LDV N=169		SOF/DCV N=277	
% Cirrhosis	15%	(9/59)	11%	(18/169)	10%	(27/277)
% Genotype 1	32%	(19/59)	80%	(135/169)	25%	(69/277)
HCV RNA <25 IU/mL						
RVR	94%	(29/31)	80%	(75/94)	84%	(137/163)
EOT	100%	(21/21)	97%	(56/58)	98%	(57/58)
SVR 4	100%	(13/13)	93%	(42/45)	100%	(30/30)
SVR 12	100%	(5/5)	100%	(30/30)	92%	(23/25)
SVR 24	100%	(2/2)	100%	(2/2)	100%	(7/7)

570 VIRAL KINETICS PREDICT RESPONSE TO ALL-ORAL THERAPY AGAINST HCV GENOTYPE 3 INFECTION

Juan A. Pineda[1], Luis E. Morano-Amado[2], Rafael Granados[3], Juan Macías[4], Francisco Téllez[5], Miguel García-Deltoro[6], Maria J. Rios-Villegas[7], Antonio Collado[8], Karin Neukam[4], for the GEHEP-MONO/ HEPAVIR-DAA, RIS-HEP07 and RIS-HEP13 Study Groups

[1]Hosp Univ de Valme, Seville, Spain, [2]Hosp Univ Alvaro Cunqueiro, Vigo, Spain, [3]Hosp Univ de Gran Canaria Dr Negrín, Las Palmas de Gran Canaria, Spain, [4]Hosp Univ de Valme, Sevilla, Spain, [5]Hosp de La Línea, La Línea de la Concepción, Spain, [6]Hosp General de Valencia, Valencia, Spain, [7]Hosp Univ Virgen Macarena, Sevilla, Spain, [8]Hosp Univ Torrecárdenas, Almeria, Spain

Background: Rates of sustained virologic response (SVR) to currently recommended therapy against hepatitis C virus (HCV) infection based on all-oral direct-acting antivirals (DAA) are generally high. However, in specific subsets, as it is the case for HCV genotype 3-infected, cirrhotic individuals, SVR rates can be suboptimal. The aim of this study was to determine the predictive capacity of response at week 4 for the achievement of sustained virologic response 12 weeks after the scheduled end of therapy date (SVR12) to treatment against HCV infection with all-oral DAA-based regimens.

Methods: From a prospective multicohort study, patients who completed a course of currently recommended DAA-based therapy at 33 Spanish hospitals and who had reached SVR12 evaluation timepoint were selected. Treatment week 4 HCV-RNA levels were categorized in target not detected (TND), below the lower limit of quantitation (LLOQTD) and ≥LLOQ.
Results: A total of 818 patients were included. SVR12 rates [n/N (%)] for HCV genotypes 1a, 1b, 3 and 4 in an on-treatment approach were 275/282 (97.5%), 283/286 (99%), 114/123 (92.7%) and 123/127 (94.5%). Of the HCV genotype 3-infected patients, 86 (70%) received sofosbuvir/daclatasvir+/-ribavirin, 27 (22%) sofosbuvir/ledipasvir/ribavirin and 10 (8.1%) sofosbuvir/ribavirin, respectively. In this subgroup, in those that achieved TND, LLOQTD and ≥LLOQ, SVR12 was 81 (97.6%), 24 (85.7%) and 9 (75%), respectively; p (linear association)=0.001. Corresponding numbers for HCV genotype 3-infected subjects with cirrhosis were: 52 (96.3%), 14 (77.8%) and 7 (70%); p=0.004. There was no association between response at week 4 and SVR12 for the other HCV genotypes.
Conclusion: Treatment week 4-response indicates the probability to achieve SVR12 to currently used DAA-based therapy in HCV genotype 3-infected individuals. This finding may be useful to tailor treatment strategy in this setting.

571 ALL ORAL DAA THERAPY IN HCV GENOTYPE 4 INFECTION WITH AND WITHOUT HIV COINFECTION

Juan A. Pineda[1], Luis E. Morano-Amado[2], Francisco Téllez[3], Blanca Figueruela López[4], Marcial Delgado-Fernández[5], Antonio Rivero-Juárez[6], Dolores Merino[7], Montserrat Pérez-Pérez[8], Karin Neukam[1], for the GEHEP-MONO/ HEPAVIR-DAA, RIS-HEP07 and RIS-HEP13 Study Groups
[1]Hosp Univ de Valme, Sevilla, Spain, [2]Hosp Univ Alvaro Cunqueiro, Vigo, Spain, [3]Hosp de La Línea, La Línea de la Concepción, Spain, [4]Hosp Univ de Valme, Seville, Spain, [5]Hosp Regional Univ de Málaga, Málaga, Spain, [6]Hosp Univ Reina Sofía, Córdoba, Spain, [7]Complejo Hospario Univ de Huelva, Huelva, Spain, [8]Hosp La Línea, AGS Campo de Gibraltar, La Linea de la Concepcion, Spain

Background: Data on the efficacy of all-oral interferon free combinations in patients with HCV genotype 4 (GT4) infection in real life are scarce, particularly in HIV/HCV-coinfected subjects. The efficacy of direct-acting antiviral (DAA) combinations in HCV-monoinfected and HIV/HCV-coinfected patients with in routine clinical practice is analyzed here.
Methods: Two hundred and fifty-nine, 89 HCV-monoinfected and 170 HIV/HCV-coinfected, subjects harboring GT4 were analyzed. All of them completed a treatment including two DAA with or without ribavirin. Sustained virological response at week 12 of follow-up (SVR) was analyzed on an intention-to-treat basis.
Results: One hundred and fifty-eight (93%) HIV/HCV-coinfected patients and 84 (94%) HCV-monoinfected subjects achieved SVR (p=0.657). Patients with cirrhosis (115 out of 128 [90%], p=0.021), those harboring IL28B genotype TT (22 out of 26 [85%], p=0.05) and those showing baseline plasma LDL-cholesterol ≤ 80 mg/dL (91 out of 100 [90%], p=0.013) responded worse. The impact of IL28B genotype was mainly seen in subjects with HIV coinfection (79% in patients with genotype TT and 94% among those with genotype non-TT [p=0.035] achieved SVR) and in individuals without cirrhosis (SVR 86% in genotype TT versus 100% among those with CC or CT [p=0.002]).
Conclusion: The rate of SVR in HCV GT4 carriers treated with all-oral DAA combinations in real life is similar as in clinical trials, both in HCV-monoinfected and in HIV/HCV-coinfected patients. The response seems to be poorer in patients with cirrhosis and in those with IL28B genotype TT. These parameters could be used to tailor this therapy.

572 EFFECTIVENESS OF ALL-ORAL DAAs FOR HCV GENOTYPE 3 IN HIV/HCV-COINFECTED PATIENTS

Juan González-García[1], Ana Moreno[2], Encarnnnacion Cruz[3], Lourdes Domínguez-Domínguez[4], Victoria Moreno[1], Jorge Vergas[5], Jose Sanz[6], Laura Benitez[7], Beatriz Álvarez[8], Juan Berenguer[9]
[1]Hosp Univ La Paz, Madrid, Spain, [2]Hosp Ramon y Cajal, Madrid, Spain, [3]Subdireccion General de Farmacia, Madrid, Spain, [4]Hosp Univ 12 de Octubre, Madrid, Spain, [5]Hosp Clinico San Carlos, Madrid, Spain, [6]Hosp Príncipe de Asturias, Alcalá de Henares (Madrid), Spain, [7]Clinica Puerta de Hierro, Majadahonda (Madrid), Spain, [8]Hosp Univ Fundación Jiménez Díaz, Madrid, Spain, [9]Hosp General Univ Gregorio Marañón, Madrid, Spain

Background: Infection with HCV genotype 3 (GT3) is common among HIV/HCV-coinfected patients and has more frequently been associated with an increased risk of progression to cirrhosis and development of steatosis or hepatocellular carcinoma than other HCV genotypes. GT3 is currently the most difficult genotype to treat, with fewer therapeutic options based on all-oral direct-acting antivirals (DAAs) than other genotypes. Our aim was to evaluate treatment outcomes of DAA regimens for HIV/HCV-coinfected patients with GT3 and compensated liver disease.
Methods: The Madrid coinfection registry (MADRID-CoRe) is a prospective registry of all coinfected adults (≥18 years) undergoing DAA therapy for HCV in hospitals from the Madrid Regional Health Service (SERMAS). We assessed sustained viral response at week 12 (SVR12), viral relapse, and failure due to treatment discontinuation. Between November 2014 and August 2016, 2662 HIV/HCV-coinfected individuals in MADRID-CoRe initiated DAAs. Here, we present data from HIV/HCV-coinfected patients with GT3 and compensated liver disease who were scheduled to complete treatment on May 31, 2016.
Results: We evaluated 273 patients who met the inclusion criteria. The DAA regimens were as follows: a) daclatasvir/sofosbuvir 196 patients (106 not taking ribavirin [8 wk, 1; 12 wk, 84; 16 wk, 2; 24 wk, 19], and 90 taking ribavirin [12 wk, 43; 16 wk, 1; 24 wk, 46]. B) ledipasvir/sofosbuvir 73 patients (11 not taking ribavirin for 24 wk, and 62 taking ribavirin [12 wk, 5; 24 wk, 57]). C) sofosbuvir/ribavirin for 24 wk, 4 patients. Two patients treated with sofosbuvir/ribavirin achieved SVR12, and 2 discontinued therapy. Patient characteristics and treatment outcomes for daclatasvir/sofosbuvir and ledipasvir/sofosbuvir are shown in the table.
Conclusion: We found daclatasvir/sofosbuvir to be highly effective in HIV/HCV-coinfected patients with GT3 with or without cirrhosis, thus confirming the results of clinical trials. Ledipasvir/sofosbuvir was also highly effective in a particularly difficult-to-treat population composed mainly of patients with liver cirrhosis and very high liver stiffness values. The small sample size precludes any conclusion about the effectiveness of sofosbuvir/ribavirin.

573 SOFOSBUVIR/LEDIPASVIR AS CHOLESTEROL-INCREASE RISK FACTOR IN HIV SUBJECTS

Mario Frías, Antonio Rivero-Juárez, Francisca Cuenca-Lopez, Angela Camacho-Espejo, Diego Rodriguez-Cano, Pedro Lopez-Lopez, Teresa Brieva, Antonio Rivero
Hosp Univ Reina Sofia, Cordoba, Spain

Background: Although HCV viral clearance is clearly linked to a lipid metabolic restoration, could exists other factors which have a direct impact on LDL-cholesterol, regardless of viral suppression. Thus, the objective of our study was to evaluate risk factors associated with serum cholesterol levels increase during IFN-free HCV therapy.
Methods: Prospective, longitudinal study where HIV-infected patients who started and completed a IFN-free therapy for chronic HCV genotype 1 or 4 infection were included. Patients were treated using two different regimens: i) Sofosbuvir + Ledipasvir (SOF/LDV) with/without ribavirin (RBV), or ii) Paritaprevir + Ombitasvir bosted with ritonavir and Dasabuvir (PRT/OMV/rtv/DSB) with/without RBV. In all patients total, HDL and LDL cholesterol, was measured at baseline and at weeks 1, 2, 4, 8 and end of treatment. The changes of cholesterol levels at each week compared with baseline were calculated.
Results: A total of 129 patients completed a full course of therapy and constituted the study population. Of them, 67 (51.9%) initiated therapy with SOF/LDV, 47 (36.4%) with PRT/OMV/rtv/DSB, and 15 (11.6%) with PRT/OMV/rtv. An increase on both total and LDL cholesterol was observed in the overall population at all weeks of therapy. Use of SOF/LDV was associated with both total and LDL cholesterol increase at each time point (Figure 1A and Figure 1B). This effect of SOF/LDV on total and LDL cholesterol was observed in all HCV genotypes, compared with patients receiving PRT/OMV/rtv/DSB. In the linear multivariate analysis, use of SOF/LDV was identified as an associated factor with increasing on both total and LDL cholesterol, adjusted by sex, liver cirrhosis, HCV-viral decline, HIV co-infection, HCV-genotype, and hypolipemiant treatment use.
Conclusion: Our study shows that SOF/LDV increase LDL cholesterol levels during HCV therapy as early as the first week of treatment. Interestingly, this observation was independent of HCV viral clearance, suggesting a direct effect of this combination on LDL cholesterol increase. The clinical impact of this association, overall in high risk cardiovascular patients should be evaluate.

574 LIPID LEVELS AND THE RISK OF ACUTE MYOCARDIAL INFARCTION AMONG HCV+ AND HCV- PERSONS

Adeel A. Butt[1], Peng Yan[2], Kara Chew[3], Judith S. Currier[3], Kathleen Corey[4], Raymond Chung[4], Abdul-Badi Abou-Samra[5], Javed Butler[6], Matthew Freiberg[7], for the ERCHIVES
[1]Hamad Hlthcare Quality Inst and Hamad Med Corporation, Doha, Qatar, [2]VA Pittsburgh Hlthcare System, Pittsburgh, PA, USA, [3]Univ of California Los Angeles, Los Angeles, CA, USA, [4]Massachusetts General Hosp, Boston, USA, [5]Hamad Medica Corporation, Doha, Qatar, [6]SUNY Stonybrook, Stony Brook, NY, USA, [7]Vanderbilt Univ Sch of Med, Nashville, TN, USA

Background: Risk of acute myocardial infarction (AMI) among HCV+ persons compared with HCV- persons with similar lipid levels is unknown.
Methods: We used ERCHIVES to identify two populations of HCV infected and uninfected persons: 1) a propensity score matched (PSM) population, and 2) a low cardiovascular disease (CVD) risk population. We excluded those with baseline CVD, HIV, females (due to small numbers), and those who received HCV treatment. AMI was diagnosed based on previously established ICD-9 codes. We compared AMI rates among lipid strata based on NCEP defined lipid strata.
Results: We identified 85,863 HCV+ and HCV- persons in the PSM population and 55,814 HCV+ and 84,772 HCV- persons in the low CVD risk population. In the PSM population, the incidence rates [95% CI] for AMI among those with TC 200-239 were 5.3 [4.89,5.71] for HCV+ vs 4.71 [4.42,5] for HCV- persons (P=0.02) and for TC>240 mg/dL were 7.38 [6.49,8.26] vs. 6.17 [5.64,6.71] (P=0.02), with a hazard ratio (HR) [95%] CI for AMI for HCV+ vs HCV- of 1.13 [1.02,1.25] and 1.19 [1.03,1.38], respectively. For LDL of 130-159 mg/dL, AMI rates were 5.44 (4.97,5.91) for HCV+ and 4.81 (4.48,5.14) for HCV- persons (P=0.03), with HR [95%] CI for AMI for HCV+ vs HCV- of 1.13 [1.01,1.26]. In the low CVD risk population, the incidence rates among those with TC of 200-239 mg/dL were 4.01 [3.57, 4.44] for HCV+ vs. 3.47 [3.22,3.71] for HCV-, P=0.03) and numerically higher but not statistically significant for those wtih TC of >240 mg/dL (5.13 [4.24, 6.03] vs. 4.35 [3.94,4.77], P=0.12). For LDL of > 160 mg/dL, the rates were higher for HCV+ vs. HCV- persons (5.43 [4.54,6.32] vs. 4.30 [3.88,4.72], P=0.02). For HDL and TG, there were no significant differences among HCV infected vs. HCV infected persons at the higher strata. The rise in risk with increasing lipid levels was greater in younger HCV+ than in HCV- persons, and more profoundly altered in HCV+ persons by lipid lowering therapy.
Conclusion: HCV+ persons may be at a higher risk of AMI than HCV- persons with similar TC and LDL levels, and this risk is more pronounced at a younger age. Lipid lowering therapy significantly reduces this risk, with a more profound reduction among HCV+ vs. HCV- persons at similar lipid levels.

Table. Incidence rate of acute myocardial infarction (per 1,000 patient years) at various lipid levels among HCV infected and uninfected persons in the propensity score matched population.

		HCV+ (N=85,863)			HCV- (N=85,863)			P-value
	Category	Follow up years	N*	AMI rate (95% CI)	Follow up years	N*	AMI rate (95% CI)	
Total cholesterol, mg/dL	<200	424412	1796	4.23 (4.04,4.43)	370421	1693	4.57 (4.35,4.79)	0.02
	200-239	121891	646	5.3 (4.89,5.71)	220430	1038	4.71 (4.42,5)	0.02
	>240	36330	268	7.38 (6.49,8.26)	82290	508	6.17 (5.64,6.71)	0.02
LDL cholesterol, mg/dL	<100	259519	1079	4.16 (3.91,4.41)	187414	882	4.71 (4.4,5.02)	0.007
	100-129	190096	856	4.5 (4.2,4.8)	237368	1061	4.47 (4.2,4.74)	0.89
	130-159	95362	519	5.44 (4.97,5.91)	170974	822	4.81 (4.48,5.14)	0.03
	>=160	37656	256	6.8 (5.97,7.63)	77384	474	6.13 (5.57,6.68)	0.19
HDL cholesterol, mg/dL	<40	228234	1252	5.49 (5.18,5.79)	237457	1479	6.23 (5.91,6.55)	0.001
	40-59	262394	1160	4.42 (4.17,4.68)	326685	1400	4.29 (4.06,4.51)	0.45
	>=60	92006	298	3.24 (2.87,3.61)	108999	360	3.3 (2.96,3.64)	0.83
Triglycerides, mg/dL	<150	390367	1575	4.03 (3.84,4.23)	398761	1603	4.02 (3.82,4.22)	0.93
	150-199	89362	494	5.53 (5.04,6.02)	112019	618	5.52 (5.08,5.95)	1.00
	200-499	97124	590	6.07 (5.58,6.56)	153112	936	6.11 (5.72,6.5)	0.93
	>=500	5781	51	8.82 (6.4,11.2)	9248	82	8.87 (6.95,10.8)	0.95

575 EFFECT OF INTERFERON-FREE TREATMENT ON LIPID AND GLUCOSE METABOLISM IN HEPATITIS C

Elisa Biliotti, Donatella Palazzo, Marco Serani, Rozenn Esvan, Paola Maida, Paola Perinelli, Martina Spaziante, Alessandro Maria Silvestri, Lorenzo Volpicelli, Gloria Taliani
Sapienza Univ of Rome, Rome, Italy

Background: Chronic HCV infection may affect host lipid metabolism and induce hypocholesterolemia, insulin resistance (IR), diabetes, atherosclerosis and steatosis. Low density cholesterol (LDL-C) is an atherogenic lipoprotein, its oxidated form (oxLDL) is involved in the formation of atherosclerotic plaques and is a marker of cardiovascular disease. We investigated the changes of serum lipids, oxLDL and IR during and after DAA treatment of HCV.
Methods: We enrolled 77 HCV pts (57.1% males, age 58.7±11.2 yrs, BMI 24.7±3.9, 74% HCV Genotype 1, 28% with metabolic syndrome, 36% with steatosis) with advanced fibrosis or cirrhosis (liver stiffness 19.1±9.9 KPa) treated with DAA (70% with ribavirin). HOMA-score, total, low and high density cholesterol (TC, LDL-C, HDL-C), tryglicerides (TG) and oxLDL levels have been evaluated at baseline (T0), end-of-treatment (EOT) and after 12-weeks of follow-up (FU).
Results: A significant decrease of HOMA-IR occurred during therapy and remained stable during FU (Table). The baseline proportion of patients with HOMA-IR≥4, diagnostic for a pre-diabetic state, was 45.5% and significantly decreased after treatment to 32.5% (p=0.03). The decline of HOMA-IR during antiviral treatment was gender-related, since men experienced a marked reduction of IR both during treatment and FU while women had no changes. TC and LDL-C levels significantly increased during antiviral therapy and FU (Table). The proportion of pts with optimal TC (TC<200 mg/dL) and LDL-C (LDL-C<129 mg/dL) significantly decreased during the study period from 88.3% to 70% (p=0.0075) and from 89% to 76.2% (p=0.04), respectively. Notably also oxLDL levels increased during the study period (Table), while HDLC did not change and TG levels declined only during treatment.
Conclusion: The improvement of insulin resistance and the significant reduction of the proportion of pts with a pre-diabetic state suggest that DAA treatment might revert HCV related metabolic alterations and prevent the development of diabetes. The modulation of the metabolic changes observed during treatment according to gender is an interesting aspect of the interplay between virus and host and an area of future research. The rapid and significant increase in total, LDL and oxLDL cholesterol levels observed in pts with advanced liver disease treated with DAA might increase their cardiovascular risk, suggesting the potential benefit of statin co-administration during or immediately after DAA therapy.

Table: Mean change of total cholesterol, LDL cholesterol, triglycedrides, oxidized LDL cholesterol and HOMA-IR during and after DAA treatment of HCV					
Parameters (mean ± ds)	T0	EOT	p	FU3	p
Total Cholesterol (TC), mg/dL	155.56 ± 34.48	170.29 ± 33.09	<0.001	181.6 ± 40.71	0.002
LDL Cholesterol (LDL-C), mg/dL	82.36 ± 31.99	94.97 ± 25.02	<0.001	109.28 ± 31.4	<0.001
Triglycerides (TG), mg/dL	119.26 ± 64.08	100.24 ± 61.56	0.001	117.83 ± 133.87	0.129
HOMA-IR	4.46 ± 3.08	3.5 ± 2.07	<0.001	3.62 ± 1.95	0.259
Oxidized LDL Cholesterol (OxLDL), U/L N°=32	53.71 ± 19.74	61.17 ± 18.44	0.04	72.59 ± 20.63	0.002

576 INFLUENCE OF DAA THERAPY ON ALT LEVELS IN HCV- AND HIV/HCV-INFECTED PATIENTS (GECCO)

Stefan Mauss[1], Christoph Boesecke[2], Florian Berger[1], Patrick Ingiliz[3], Thomas Lutz[4], Knud Schewe[5], Malte Wehmeyer[6], Axel Baumgarten[3], Jürgen K Rockstroh[7], Stefan Christensen[8]
[1]Cntr for HIV and Hepatogastroenterology, Duesseldorf, Germany, [2]Univ Hosp Bonn, Bonn, Germany, [3]Cntr for Infectiology, Berlin, Germany, [4]Infektiologikum, Frankfurt, Germany, [5]dagnae e. V., Berlin, Germany, [6]I. Univ Hosp Hamburg–Eppendorf, Hamburg, Germany, [7]Bonn Univ Hosp, Bonn, Germany, [8]CIM Infectious Diseases, Münster, Germany

Background: The definition of normal ALT is under debate and currently not defined by the absence of pathological conditions, but rather by random selection of individuals considered healthy. In the case of chronic hepatitis C a relevant proportion of patients exhibit normal ALT levels before therapy. On the other hand in some patients ALT remains elevated despite eradication of HCV. The purpose of this study is to assess the effect of treating chronic hepatitis C with directly-acting agents (DAA) on ALT levels.
Methods: GECCO cohort is a multicenter cohort from 9 sites in Germany enrolling consecutively patients on DAA therapy. In this analysis all patients with documented ALT at baseline and sustained virologic response (SVR12) 12 weeks after end of therapy (EOT) were included. Normal ALT was defined < 35 U/l. For statistical analysis Fishers exact chi-square and Mann-Whitney U test were used.
Results: HIV coinfection was present in 266/1263 (21%) with 99% on cART, 766/1263 (61%) were male. Median age 53 years, BMI 24.5 kg/sqm, ALT 66 U/l. HCV genotype (GT) distribution: GT1 74%, GT2 3%, GT3 17%, GT4 6%. HCV RNA >6 Mio IU/ml 238/1263 (19%) HCV pretreatment 578/1263 (47%), liver cirrhosis 328/1263 (26%), Diabetes mellitus 78/1263 (6%), regular alcohol consumption 112/402 (28%), opiate substitution therapy (OST) for 227/1263 (18%). At baseline ALT was <35 U/L in 191/1263 (15%). The course of ALT in patients with low and high ALT is shown in table 1. At SVR12 186/1263 (15%) still had ALT ≥35 IU/ml. In univariate analysis neither high HCV RNA (p=0.6), HIV coinfection (p=0.8), Diabetes (p=0.2), regular alcohol use (p=0.12), or OST (p=0.8) were associated with elevated ALT. However, male sex (p<0.001), ≥60 years (p=0.038), BMI ≥30 kg/sqm (p<0.001), GT2 (p=0.013), baseline ALT ≥35 U/l (p<0.001), treatment experienced (p=0.017) and liver cirrhosis (p<0.001) were associated with elevated ALT. In multivariate analysis sex (p<0.001), BMI ≥30 (p<0.001), GT2 (p=0.026) and liver cirrhosis (p<0.001) remained statistically significant.
Conclusion: Successful DAA treatment in patients with normal ALT levels at baseline achieves considerable ALT reductions indicating an ongoing necroinflammation even in these patients. Elevated ALT at SVR12 was mainly correlated with conditions known to be associated with higher ALT. Being HIV-coinfected and being treated with antiretrovirals however was not associated with elevated ALT after SVR.

Table 1: ALT during DAA therapy (median and IQR)					
	baseline	therapy week 04	EOT	SVR12	SVR24
HCV ALT baseline <35 U/l	27 (23-31) n=153	16 (13-21) n=139	15 (12-20) n=140	14 (11-18) n=153	13 (10-18) n=111
HCV ALT baseline ≥35 U/l	76 (54-122) n=844	27 (19-37) n=814	24 (17-34) n=745	22 (17-31) n=844	21 (16-29) n=593
HIV-HCV ALT baseline <35 U/l	25 (19-31) n=37	19 (14-25) n=34	20 (15-29) n=25	18 (15-22) n=37	17 (14-22) n=25
HIV-HCV ALT baseline ≥35 U/l	74 (52-125) n=229	28 (22-39) n=215	27 (21-37) n=173	23 (18-31) n=229	22 (16-31) n=179

577 HIGH PREVALENCE OF HEPATITIS DELTA VIRUS AMONG CAMEROONIAN HBSAG-POSITIVE SPECIMENS

Mary Rodgers[1], Kelly Coller[1], Ka-Cheung Luk[1], Emily Butler[1], Jill Fuhrman[1], Elizabeth Krilich[2], Devin Barnaby[2], Nicaise Ndembi[3], Lazare Kaptue[4], **Gavin Cloherty**[1]
[1]Abbott Labs, Abbott Park, IL, [2]Franciscan Univ of Steubenville, Stuebenville, OH, [3]Inst for Human Virology Nigeria, Abuja, FCT, [4]Univ of Montagnes, Bangangté, Cameroon

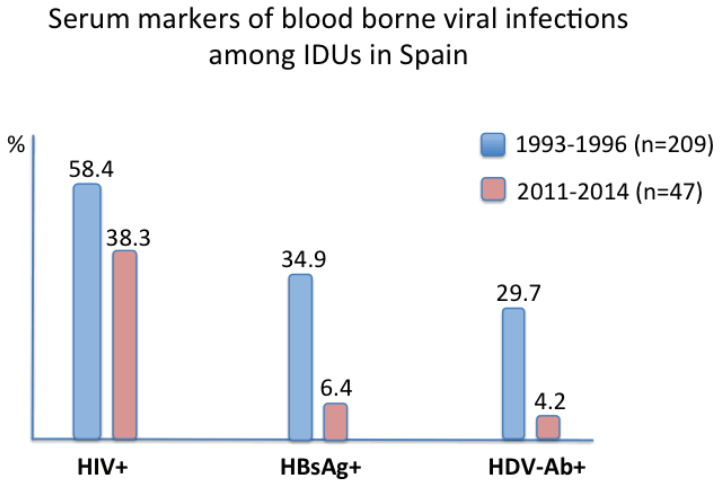
Background: Hepatitis Delta (HDV) is a defective RNA virus that requires Hepatitis B surface antigen (HBsAg) for productive infection. An estimated 15-20 million people are infected with HDV worldwide; however, limited data are available on the prevalence of this virus in sub-Saharan Africa where HIV infection rates are high. HDV/HBV/HIV co-

infection confers a greater risk for accelerated progression to liver disease and death. To determine the prevalence of HDV in HIV positive and negative populations in Cameroon, HDV antibodies and RNA were characterized in 1701 HBsAg positive specimens, of which 846 (49.7%) individuals were co-infected with HIV.
Methods: Plasma specimens were received from consenting subjects participating in surveillance studies in Cameroon collected over 8 years from 2007 – 2015. Samples were initially screened for antibodies (IgG) to HDV using a prototype HDV serology assay developed on the Abbott ARCHITECT. HDV reactive specimens with remaining volume were diluted 1:10 or 1:100 as necessary and screened using a prototype HDV RNA viral load assay with a calculated limit of detection of 5 IU/ml as calibrated by the HDV RNA WHO standard on the Abbott m2000 instrument. HDV RNA positive specimens with viral load >4.5 Log10 IU/ml were selected for complete genome Sanger sequencing of 3 overlapping regions, and a subset of specimens were selected for HIV or HBV sequencing for classification. All viral sequences were classified by phylogenetic analysis.
Results: HDV IgG antibodies were detected in 683 (40.2%) specimens, and a majority of samples exhibited evidence of chronic infection with HDV RNA detected in 68% (n=455) of the 669 tested samples with available volume. The rate of chronic HDV infection may be underestimated due to sample dilution during processing. The seropositive rate of HIV/HBV/HDV co-infection was 16.9% (288/1701), with 61.3% positive for HDV RNA. HDV/HBV/HIV co-infected specimens included HIV subtypes A, CRF02, CRF11, D, and G and HBV genotypes A and E. HDV genotypes 1, 6, and 7 were present in this population.
Conclusion: HDV seroprevalence is high in HBsAg positive Cameroon individuals (40.2%), indicating that a large portion of HBV patients in Cameroon are at elevated risk for severe hepatitis and death. Screening and diagnosis of HDV in HBV/HIV-1 carriers in Cameroon might identify individuals at increased risk for developing liver disease.

578 DECLINE AND CHANGING PROFILE OF HEPATITIS DELTA AMONG INJECTION DRUG USERS IN SPAIN

Antonio Aguilera[1], **Vincent Soriano**[2], Pablo Barreiro[2], Jose M. Peña[2], Rocio Trastoy[1], Jose J. Costa[1]
[1]Complexo Hospario Univ Santiago, Santiago, Spain, [2]La Paz Univ Hosp, Madrid, Spain

Background: Around 15 million people worldwide suffers from hepatitis delta, which is the most severe form of chronic viral hepatitis, often leading to cirrhosis and liver cancer. To date there is no effective antiviral treatment for hepatitis delta, although promising agents (i.e., myrcludex and lonafarnib) are being tested in clinical trials. Injection drug users (IDUs) are the largest HDV reservoir. The resurgence of intravenous drug use in North America and Europe may represent a new opportunity for HDV widespread.
Methods: We examined all consecutive active IDUs seen for the first time and enrolled in detoxification programs at two reference clinics in Spain during two different periods (1993-1996 and 2011-2014, respectively). Markers of HIV, HBV and HDV infection were tested in serum specimens.
Results: A total of 209 IDUs were examined in the first period (1993-1996). Mean age was 27 years-old. All had markers of past or current HBV infection. The rate of HIV-Ab, HBsAg and HDV-Ab was as follows: 122 (58.4%), 73 (34.9%) and 62 (29.7%), respectively. Serum HDV-Ab was recognized in 53.4% of HBsAg+ and 16.9% of HBsAg-neg patients (p<0.001). Positivity for HDV-Ab was associated with HIV infection regardless HBsAg status. A total of 47 active IDUs were tested in the second period (2011-2014). Anti-HDV was recognized in only two individuals (2.1%), both with positive HBsAg. Both were immigrants coming from HDV endemic countries.
Conclusion: Acute HBV-HDV co-infections and self-limited HDV infections were frequent in the nineties among IDUs in Spain, especially in HIV-positive individuals. In contrast, circulation of HDV has dramatically declined over the last two decades among active IDUs in Spain and is currently very rare, and concentrated in foreign immigrants. It may reflect the benefit of universal HBV vaccination as well as the success of needle exchange programs in Spain.



579 UNCONVENTIONAL T CELLS IN A PEG-INF-2A ADD-ON STRATEGY FOR SUPPRESSED HBV INFECTION

Camilla Tincati[1], **Elvira S. Cannizzo**[1], Francesca Binda[2], Paola Ronzi[2], Federico A. Cazzaniga[1], Antonella d'Arminio Monforte[1], Giulia Marchetti[1], Laura Milazzo[2]
[1]Univ of Milan, Milan, Italy, [2]Luigi Sacco Univ Hosp, Milan, Italy

Background: Eradication of chronic HBV (CHB) is rarely achieved with either nucleos(t)ide (NUC) analogues or pegylated interferon (Peg-IFN), yet encouraging results in terms of HBsAg decay and HBsAb seroconversion have emerged from small studies on the combined/sequential use of the two strategies. We hypothesized this may due to the adjuvant role of Peg-IFN during viral control and in particular to its influence on unconventional T-cells (iNKT, γδT) which bridge innate and adaptive responses. We therefore explored the effects of a Peg-IFN-2α add-on strategy to suppressive treatment with tenofovir (TDF) in CHB patients on the frequency and function of iNKT and γδT cells.
Methods: 30 CHB, TDF-treated subjects, with HBV suppression for at least 2 years were randomized (1:2) at baseline (W0) to either receive Peg-IFN-2α add-on therapy (Add-On; n=10) for 48 weeks (W48) or continue TDF alone (Nuc; n=20). In a subgroup of 24 CHB (10 Add-On; 14 Nuc) and 8 HBV-uninfected subjects we studied γδT and iNKT frequency and function (flow cytometry) at W0 and W12. Wilcoxon, Mann-Whitney and Kruskall-Wallis tests were used for statistics.
Results: Compared to controls, at W0, CHB subjects showed fewer iNKT (p=0.04), γδT (p=0.03) and Vδ2-expressing γδT populations (p=0.001) (Table). In contrast, no differences between groups were detected in cytokine-producing iNKT and γδT cells (Table). A greater HBsAg decay occurred in Add-On compared to Nuc at W12 (p=0.016) and W24 (intention-to-treat, p=0.01; on-treatment, p=0.001); HBsAg loss with HBsAb seroconversion was achieved in 2 Add-on and none Nuc. The addition of Peg-IFN-2α accounted for the decline in iNKT frequencies (p=0.0005) and expansion of cytokine-producing subsets (iNKT+IFN-γ+, p=0.03; iNKT+TNF-α+, p=0.006) (Table). A contraction of the γδT compartment was also observed (p=0.03), without modifications in cytokine expression (Table). No changes in iNKT and γδT cell surface and intracellular phenotype was detected in Nuc (Table).
Conclusion: We show that virally-suppressed CHB subjects, compared to uninfected controls, display lower unconventional T-cells with preserved functional capacity. Further, our findings of a selective increase in iNKT function vis-à-vis the conserved cytotoxic potential of γδT during a Peg-IFN add-on strategy push the boundaries of existing knowledge on the possible immune determinants of HBsAg decay in this context, suggesting a critical role of iNKT in the clinical efficacy of combined treatment for HBV.

580 INCREASED RATES OF HBV SEROCONVERSION UNDER LONG-TERM HBV ACTIVE THERAPY IN HBV/HIV

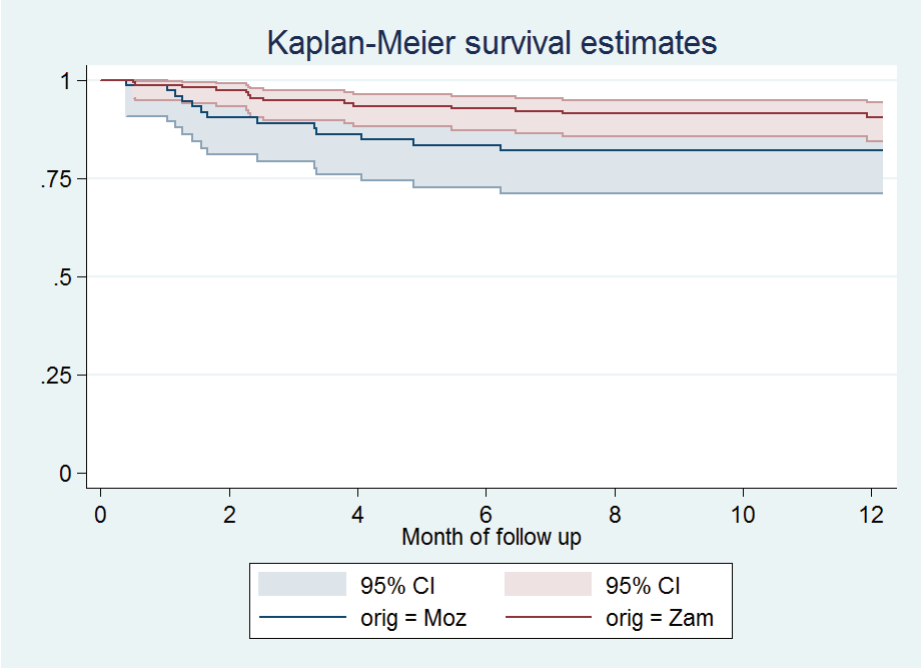
Christoph Boesecke[1], Fabian Busch[1], Clara Lehmann[2], Carolynne Schwarze-Zander[1], Jakob Malin[1], Joerg Janne Vehreschild[2], Jan-Christian Wasmuth[1], Gerd Fätkenheuer[2], Jürgen K. Rockstroh[1], for the Cologne Bonn Cohort
[1]Bonn Univ Hosp, Bonn, Germany, [2]Cologne Univ Hosp, Cologne, Germany

Background: Patients with HIV have a 6x higher rate of developing chronic hepatitis B following acute HBV infection. Immune reconstitution under successful ART however, may increase the likelihood of clearing HBV infection successfully after prolonged dual HIV/HBV active nucleoside therapy. Data on rates of HBsAg loss over time under HBV nucleos(t)ide therapy are sparse. Here we evaluate rates of HBV seroconversion under HBV active ART in a large German cohort with a median follow-up of at least 8 years.
Methods: Non-interventional retrospective cohort at 2 German academic HIV care centres assessing rates of HBV seroconversion defined as HBsAg loss in 95 HBV/HIV coinfected patients under HBV active (tenofovir (TDF) and/or lamivudine (3TC) containing) cART. Fisher's exact, chi-square and Mann-Whitney U test were used for statistical analysis.
Results: In total, 95 patients were included. 78% patients were male, median age was 40 years (IQR 34-45). 57% were of central European, 27% of African, 9% of Eastern, 5% of Southern European descent. Main routes of HIV transmission were MSM (43%), origin from high prevalence country (24%) and heterosexual intercourse (12%). CDC stage at HIV diagnosis was C3 in 25% followed by A2 (19%). 42.9% were ART-naïve when TDF and/or 3TC containing therapy was initiated (baseline). Median CD4 cell count at baseline was 270 (140-480). 54% were HBeAg positive at baseline. 95% were HBV PCR positive at baseline. 84% received TDF, 16% TDF and 3TC. 55% received a boosted protease inhibitor, 40% NNRTI and 5% an integrase inhibitor. Median follow-up was 107 months (76-144), median CD4 gain was 165 (3-315). Overall, HBV seroconversion (HBsAg loss) occurred in 15/95 (16%) patients. Median time to HBsAg loss was 35 months (18-49). There was no significant correlation between HBsAg loss and gender (p=0.562), age (p=0.677), country of origin (p=0.274), CDC stage (p=0.585), CD4 cell count (p=0.249), CD4 gain (p=0.7), HBeAg (p=0.712), receiving TDF or TDF/3TC (p=0.576) or ART class (p=0.582).
Conclusion: HBV seroconversion defined as HBsAg loss is occurring at a much higher rate in HBV HIV coinfected patients even after years on HBV active ART when compared to published seroconversion rates of 4.5% over 96 weeks from the extension phase III tenofovir trials in HBV monoinfected subjects. Positive predictors remain unclear to date but immunreconstitution under ART appears to allow better control of HBV infection.

581 MORTALITY OF HIV/HBV COINFECTED PATIENTS ON ART IN URBAN AND RURAL SOUTHERN AFRICA

Jonas Hector[1], Michael J. Vinikoor[2], Kalo Musukuma[2], Roma Chilengi[2], Laura Jefferys[3], Michael A. Hobbins[1], Mary-Ann Davies[4], Matthias Egger[5], Gilles Wandeler[5]
[1]SolidarMed, Luzern, Switzerland, [2]Cntr for Infectious Disease Rsr in Zambia, Lusake, Zambia, [3]SolidarMed, Pemba, Mozambique, [4]Univ of Cape Town, Cape Town, South Africa, [5]Univ of Bern, Bern, Switzerland

Background: Chronic hepatitis B virus (HBV) infection affects 10% of HIV+ people in sub-Saharan Africa (SSA) and is an important cause of liver disease in this population. Due to high rates of losses to follow-up (LTFU), precise mortality estimates among cohorts of patients on antiretroviral therapy (ART) in the region are scarce. We compared one-year mortality of HIV/HBV-coinfected patients on tenofovir-containing ART between rural and urban primary care clinics after systematic tracing of patients LTFU.
Methods: We enrolled HIV/HBV coinfected adults initiating ART at two urban clinics in Zambia and three rural clinics in Mozambique between May 2013 and July 2015. Quantitative real-time PCR for HBV viral load was performed using the COBAS Ampliprep/TaqMan System and HBV sequencing according to an in-house protocol. Medication possession ratio (MPR; proportion of follow-up days with ART possession) was used as a proxy for adherence. All patients LTFU (>3 months without a clinical visit) were traced by phone and home visits for ascertainment of vital status. Baseline characteristics were evaluated using Fisher`s exact test and Wilcoxon rank sum tests. Mortality rates and associated risk factors were assessed using multivariable Cox proportional hazards regression.
Results: We enrolled 263 HIV/HBV-coinfected patients in Mozambique and Zambia. Mozambican participants were more likely to be female (61% vs. 41%, p<0.01), to have a moderate-severe anaemia (16% vs. 6%, p=0.03) and had higher median ALT (31 UI/l vs. 23UI/l, p=0.04) and CD4 cell counts (232/µl vs. 208/µl, p=0.03) compared to Zambia. The predominant HBV genotype was A1 in Mozambique (68%) and E (50%) in Zambia. The proportion of patients with an HBV viral load > 20.000 UI/ml was similar across sites (52% vs 45%, p=0.10). Over the first year on ART, median MPR was lower in Mozambique compared to Zambia (62% vs. 100%, p<0.01). At 1 year, after the systematic tracing of patients LTFU, vital status was unknown in only one patient (1.3%) in Mozambique and 7 patients (3.8%) in Zambia. One-year mortality was 16 % in Mozambique and 8% in Zambia (p=0.06) (Fig.1). In adjusted analyses, low BMI, moderate/severe anaemia and male sex were independent risk factors for mortality. Mortality was similar by genotype and by baseline HBV VL.
Conclusion: Early mortality of HIV/HBV-coinfected individuals on ART is very high in SSA, especially in rural settings, where access to care and treatment adherence may be reduced.



582 EFFECTIVENESS OF HAV VACCINATION AMONG HIV-POSITIVE PATIENTS DURING AN HAV OUTBREAK

Kuan-Yin Lin[1], Szu-Min Hsieh[1], Hsin-Yun Sun[1], Yi-Chun Lo[2], Wang-Huei Sheng[1], Yu-Chung Chuang[1], Sung-Ching Pan[1], Chien-Ching Hung[1], Shan-Chwen Chang[1]
[1]Natl Taiwan Univ Hosp, Taipei, Taiwan, [2]Taiwan Cntrs for Disease Control, Taipei, Taiwan

Background: An unprecedented outbreak of acute hepatitis A virus (HAV) infection has been occurring among men who have sex with men (MSM) in Taiwan since June 2015, with more than 750 cases reported to the Taiwan Centers for Disease Control as of 23 September, 2016. We evaluated the effectiveness and serologic response of HAV vaccination in HIV-positive patients in this outbreak setting.
Methods: From June 2015 to September 2016, testing for HAV antibodies were prospectively performed for all HIV-positive patients and HAV-seronegative patients were advised to receive 2 doses of HAV vaccines (HAVRIX® or VAQTA®) at an interval of 6 months between the two doses. The primary endpoint of this study was serologic response 4 weeks after the last dose of vaccination and acquisition of acute HAV infection during the follow-up. The secondary endpoint was serologic response at week 48 of vaccination.
Results: During the study period, 1574 HAV-seronegative patients were included, with 94.5% being MSM and median CD4 count 568 cells/mm3. As of 23 September 2016, 1037 patients (65.9%) had received at least one dose of HAV vaccine and 537 (34.1%) declined to receive vaccine; 303 (19.3%) had completed the 2-dose vaccine series. The seroconversion rate at 4 weeks, weeks 5-8, weeks 9-16, and weeks 17-24 was 15.8% (65/411), 25.9% (42/162), 50.3% (86/171), and 50.4% (130/258), respectively. One month after the last dose, the seroconversion rate increased to 94.7%. The factors associated with seroconversion between the first and last doses of HAV vaccination were receiving VAQTA® (adjusted odds ratio [AOR], 2.3; 95% CI, 1.5-3.5), time to anti-HAV IgG testing (AOR, per 1-week increase, 1.1; 95% CI, 1.1-1.2) and previous HAV vaccination (AOR, 32.3; 95% CI, 11.9-87.7). With a total observation duration of 421.5 and 411.5 person-years of follow-up (PYFU), the incidence rate of acute HAV infection in patients without receiving HAV vaccine and those receiving at least 1 dose of HAV vaccine was 11.6 and 0.7 per 100 PYFU, respectively, resulting in vaccine effectiveness of 93.6%. The factors associated with acquisition of acute HAV infection included having not received HAV vaccine (adjusted hazard ratio [AHR], 33.3; 95% CI, 8.9-93.6) and recent syphilis (AHR, 4.7; 95% CI, 2.7-8.3).
Conclusion: Despite the delayed serologic response to HAV vaccination in HIV-positive MSM, the risk of acute HAV infection was significantly reduced by HAV vaccination during the outbreak setting.

583 ACTIVE HPGV-2 INFECTION IS RESTRICTED TO COCIRCULATING HCV INFECTION

Kelly Coller, Michael Berg, Matthew Frankel, Kenn Forberg, John Hackett, Gavin Cloherty, George Dawson
Abbott Labs, Abbott Park, IL, USA

Background: A second human Pegivirus (HPgV-2) was recently identified that is extensively associated with HCV infection. In contrast, the distantly related Pegivirus, GBV-C (HPgV-1) circulates in the general population, with a higher prevalence in HCV and HIV infected individuals. Although the clinical relevance of HPgV-2 infection is not understood, the virus appears to develop a chronic infection in 1% of HCV viremic individuals. We developed molecular and serologic tools to screen 4346 donor samples (volunteer donor, HCV-, HBV-, HIV-infected) for HPgV-2. All 24 strains identified have been isolated from active or resolved HCV infections.
Methods: Serologic assays were developed using two HPgV-2 proteins, NS4AB and E2 for high-throughput screening on the Abbott ARCHITECT. Additionally, a serologic test using the envelope glycoprotein E2 of HPgV-1 was developed for comparison. Samples reactive to either HPgV-2 antigen were screened for viral RNA using a multiplex qPCR assay with 2 targets in HPgV-2 and 1 target in HPgV-1 on the Abbott m2000 platform. HPgV-2 RNA positive samples were subjected to next generation sequencing for molecular characterization and phylogenetic analysis.
Results: Antibodies to HPgV-2 were infrequently found in all subject groups tested, with the highest prevalence in HCV co-infected (3.31%). This is in stark contrast to HPgV-1 infection where all groups screened had antibodies with the highest prevalence found among HCV and HIV groups (48.76% and 41.71 %). Active cases of HPgV-2 infection, with viral loads ranging from 2.2-6.6 log copies/ml, were found primarily in samples with HCV antibodies; one has been found in an acute case, and another in a resolved HCV infection. Similar to HCV, HPgV-2 viremia was strongly associated with the presence of HPgV-2 antibodies. This is in contrast to HPgV-1 where simultaneous detection of viral RNA and E2 antibodies is predominantly exclusive. Strains identified thus far share approximately 94% nucleotide identity to one another and cluster tightly in a deep clade most closely related to bat and rodent pegiviruses.
Conclusion: HPgV-2 infection occurs alongside HCV infection. Whether HPgV-2 is pathogenic on its own or exacerbates HCV-related disease will be addressed with future studies. Due to its low prevalence, high throughput diagnostic tools will facilitate global surveillance to further assess prevalence and the diversity present in this novel human virus.

584LB TDF TO PREVENT PERINATAL HEPATITIS B VIRUS TRANSMISSION: A RANDOMIZED TRIAL (ITAP)

Gonzague Jourdain[1], Nicole Ngo-Giang-Huong[1], Linda J. Harrison[2], Luc Decker[1], Camlin Tierney[2], Tim R. Cressey[3], Jullapong Achalapong[4], George K. Siberry[5], Noele Nelson[6], Nantasak Chotivanich[7]
[1]IRD, Chiang Mai, Thailand, [2]Harvard Univ, Boston, MA, USA, [3]Prog for HIV Prevention and Treatment, Chiang Mai, Thailand, [4]Chiangrai Prachanukroh Hospl, Chiang Rai, Thailand, [5]NIH, Bethesda, MD, USA, [6]CDC, Atlanta, GA, USA, [7]Chonburi Hospital, Chonburi, Thailand

Background: Pregnant women with high hepatitis B virus (HBV) DNA load still transmit to their infants despite infant HB immunoglobulin (HBIg) and HB vaccine.
Methods: This phase III, double-blind, clinical trial randomized pregnant women with HBV infection (HBsAg and HBeAg positive) to tenofovir DF (TDF) 300 mg once daily or matching placebo (1:1) from 28 weeks gestation through 2 months postpartum in 17 sites in Thailand. All infants received HBIg at birth, and vaccine at birth, 1, 2, 4 and 6 months of age. Main inclusion criteria were: age ≥18 years, confirmed ALT ≤60 IU/L, negative HIV and hepatitis C serology, creatinine clearance >50 mL/min, and no history of TDF treatment. Mothers and infants were followed until 12 months postpartum. The primary efficacy endpoint was detection of HBsAg confirmed by HBV DNA at 6 months of age. The target sample size was 156 evaluable mother/infant pairs per arm to detect a difference in HBV infected infants of 3% (TDF) vs. 12% (placebo) with 90% power accounting for one interim efficacy analysis, using a one-sided Fisher's exact test. Analyses are based on data through 6 months postpartum.
Results: From January 2013 to August 2015, 331 women (168 TDF, 163 placebo) were enrolled. Median age at enrollment was 26 years, gestational age (GA) 28.3 weeks, weight 61 kg, and HBV DNA load 8.0 $\log_{10}$ IU/mL. The 322 (97%) on-study deliveries (85 Cesarean, 26%) resulted in 323 live births (including 2 twin pairs) and 1 stillbirth (TDF arm). Median GA at delivery was 38.9 weeks. Median birth weight was 3,050 g (3,028 g TDF, 3,061 g placebo). There were 21 (7%) preterm newborns (8 TDF, 13 placebo). 322 (>99%) infants received HBV vaccine a median of 1.2 hrs. after birth and 320 (99%) HBIg a median of 1.3 hrs. after birth. In the primary complete case analysis at 6 months (table), 0/147 infants had HBV infection in the TDF arm vs. 3/147 (2.0%) in the placebo arm (p=0.12). One newborn with gross abnormalities (placebo arm) died soon after birth. Following study treatment discontinuation, 9 (6%) women experienced an ALT >300 IU/mL in the TDF arm vs. 5 (3%) in the placebo arm (two-sided p=0.29). The proportions of maternal and infant adverse events, and infant growth were similar between arms.
Conclusion: TDF resulted in a small non-significant reduction in perinatal HBV transmission beyond the low risk achieved with the recommended use of HBIg and HBV vaccine. It appeared safe for pregnant women and their infants and there was no evidence of impaired infant growth.

Efficacy and Safety Endpoints	TDF			Placebo			P-value
Categorical endpoints	N	Event	Percent (95% CI)	N	Event	Percent (95% CI)	Fisher's exact test
Infant: 6 month HBV Infection: Primary analysis	147	0	0.0 (0.0,2.5)	147	3	2.0 (0.4,5.8)	0.12
Infant: 6 month HBV Infection: Missing considered as infected	167	20	12.0 (7.5,17.9)	163	19	11.7 (7.2,17.6)	0.60
Infant: 6 month anti-HB antibodies ≥10IU/L	147	147	100.0 (97.5,100.0)	147	145	98.6 (95.2,99.8)	0.25
Women: Grade 3/4 adverse events or serious adverse events	168	41	24 (18,32)	163	44	27 (20,34)	0.62
Women: ALT >300 U/L after treatment discontinuation	154	9	5.8 (2.7,10.8)	157	5	3.2 (1.0,7.3)	0.29
Infants: Grade 3/4 adverse events or serious adverse events	161	43	27 (20,34)	160	38	24 (17,31)	0.61
Continuous Endpoints	N		Mean (SD)	N		Mean (SD)	Student's T-test
Women: Delivery HBV DNA (log_{10} IU/mL)	161		4.0 (1.6)	159		7.3 (1.7)	<0.001
Infant: 6 month WHO weight-for-age Z-score	148		-0.4 (1.1)	146		-0.2 (1.1)	0.09
Infant: 6 month WHO length-for-age Z-score	148		-0.6 (1.1)	146		-0.6 (0.9)	0.76

585 EFFECTS OF TREATMENT WITH MARAVIROC A CCR5 INHIBITOR ON HUMAN HEPATIC STELLATE CELLS

Salvatore Martini[1], Angelica Perna[1], Angela Lucariello[1], Margherita Macera[1], Maria Aurora Carleo[2], Germano Guerra[3], Vincenzo Esposito[2], Antonio De Luca[1], Nicola Coppola[1]
[1]Second Univ of Naples, Naples, Italy, [2]AORN dei Colli, Naples, Italy, [3]Univ of Molise, Campobasso, Italy

Background: After an acute liver damage, tissue regeneration repairs lesions with degradation of deposed fibrotic material, while mechanisms of tissue restoration are persistently activated following several repeated injuries, inducing deposition of extracellular matrix. (ECM). Factors responsible for ECM remodeling have been identified in a pathway involving a family of zinc-dependent enzyme matrix metalloproteinases (MMPs), together with tissue inhibitor of metalloproteinases (TIMPs). Recent experimental models suggested a role of CCR5 receptor in the genesis of liver fibrosis. We evaluated the effects of the treatment with the CCR5 inhibitor Maraviroc on LX-2, a human hepatic stellate cell line (HSC), derived from normal human stellate cells spontaneously immortalized.
Methods: LX-2 viability was determined using MTT [3-(4,5-dimethylthiazol-2- yl)-2,5-diphenyltetrazolium bromide]; the cells, pretreated with Maraviroc and TGF-β1, have been studied by Western blot assay to evaluate the expression of cyclin D1, p21, p53, collagen type I, -SMA, TGF-β1. The expression of MMP-2, MMP9, TIMP-1 and TIMP-2 were evaluated by RT-PCRs in correlation to GADPH expression to standardize differences in the quantity of cDNA used in the PCR reaction.
Results: Treatment with Maraviroc resulted in a block in S phase of LX-2 cells with increased expression levels of cyclin D1 and p21 while the expression of p53 was reduced. Treatment with Maraviroc was also able to block the accumulation of fibrillar collagens and extracellular matrix proteins (ECM), as demonstrated by the decrease of specific markers as Collagen type I, α-SMA and TGF-β1. In addition we observed a down regulation of both metalloproteins (MMP-2, MMP-9), used for the degradation of the extracellular matrix and their inhibitors (TIMP-1, TIMP-2).
Conclusion: The identification of a compound that may modulate the dynamic of liver fibrosis could be crucial in all chronic liver diseases. Maraviroc could play an important role because, in addition to its own anti-HIV activity, it could reduce the release of pro-inflammatory citokynes implicated in liver fibrogenesis, making this drug particularly recommended for antiretroviral regimens chosen to treat HIV/HCV coinfected patients.

586 CORRELATION OF BLOOD TRANSCRIPTOME WITH OUTCOME AFTER DAA TREATMENT FOR HCV INFECTION

Cody Orr[1], Paul Nietert[1], Shyam Kottilil[2], Gary Hardiman[1], **Eric G. Meissner**[1]
[1]Med Univ of South Carolina, Charleston, SC, USA, [2]Univ of Maryland, Baltimore, MD, USA

Background: Combination treatment with direct acting antivirals (DAA) results in a sustained virologic response (SVR) in most patients. For reasons that are poorly understood, some patients experience virologic relapse after treatment. The ability to predict relapse and identify biomarkers allowing shorter treatment would have practical implications in resource limited settings. We previously showed differences in hepatic expression of interferon-related genes that correlated with SVR in patients treated with sofosbuvir and ribavirin. Here, we hypothesized that whole blood gene expression would correlate with treatment outcome and suggest mechanisms of relapse.
Methods: We analyzed cryopreserved paired whole blood samples collected in PAXgene tubes before and at the end of treatment (prior to relapse) from 40 chronically infected HCV patients (n=26 SVR, n=14 relapse) treated with 24 weeks of sofosbuvir and ribavirin in the NIH SPARE trial (NCT01441180). mRNA was extracted using the PAXgene Blood miRNA Kit (Qiagen) with quality determined by Agilent Bioanalyzer (median RIN 7.2, range 5.3-8.5). Expression of 579 unique immune-related transcripts was determined using the Nanostring Human Immunology v2 Panel. Data were analyzed with non-parametric approaches (SPSS software). NSolver Advanced Analysis Software 3.0 was used for immune cell type profiling of gene expression results.
Results: Considering all 40 patients, expression of 251 of 579 genes changed significantly during treatment. Comparing SVR vs. relapse patients, differential expression was observed for 39 mRNAs pre-treatment, 27 mRNAs at the end-of-treatment, and 35 mRNAs over the course of treatment (post-pre). Intriguingly, genes involved in inhibition of host immunity had higher pre-treatment (CD244, CTLA4, SOCS1) and end-of-treatment (PD1, SOCS1) expression in relapsers. Immune cell type abundance based on transcriptional profiling suggested B-cell, CD4+ Th1-cell, and total, exhausted, and cytotoxic CD8+ T-cell frequencies decreased with treatment, while the neutrophil transcriptional profile increased, data that corresponded with changes in immune cell frequency determined by flow cytometry. Interestingly, there was a trend (p=0.08) towards higher transcriptional expression of an exhausted CD8+ T-lymphocyte profile at the end of treatment in relapsers.
Conclusion: Whole blood gene expression profiles differ by outcome for DAA treatment of HCV infection and suggest a relationship of cellular exhaustion with relapse.

587 DO MAIT CELLS IMPACT FIBROSIS IN HCV AND HIV/HCV COINFECTED PATIENTS?

Boris J. Beudeker[1], Gertine van Oord[1], Joop Arends[2], Julian Schulze zur Wiesch[3], Marieke van Heide - Mulder[1], Robert de Knegt[1], Annelies Verbon[1], Andre Boonstra[1], **Mark Claassen**[4]

[1]Erasmus Univ Med Cntr, Rotterdam, Netherlands, [2]Univ Med Cntr Utrecht, Utrecht, Netherlands, [3]Univ Med Cntr Hamburg-Eppendorf, Hamburg, Germany, [4]Rijnstate Hosp, Arnhem, Netherlands

Background: Mucosal-associated invariant T (MAIT) cells are important innate T cells with anti-microbial and immunoregulatory activity that have been recently shown to be depleted in blood of patients with HIV and HCV mono-infections. In this study, we assessed the impact of HIV, HCV and HCV/HIV co-infection on circulating and intrahepatic MAIT cells and correlations with liver fibrosis.
Methods: In this cross-sectional study, 9 healthy subjects, 9 HIV, 20 HCV and 22 HCV/HIV co-infected patients were included. Blood and liver fine needle aspirate biopsies (FNAB) were studied using flowcytometry for CD3+CD161+Vα7.2+ MAIT cell frequency, phenotype and function in HCV mono-infected and HCV/HIV co-infected patients without or with mild fibrosis (Metavir-score F0-F1) or severe fibrosis to cirrhosis (Metavir-score F3-F4).
Results: Circulating MAIT cells were decreased in blood of HCV, HIV and HCV/HIV patients without or with only mild liver fibrosis. In HCV/HIV co-infected individuals with F3-F4, the frequency of circulating MAIT cells was even further depleted, whereas their function was comparable to HCV/HIV co-infected patients with low or absent fibrosis. In contrast, in HCV mono-infected patients, MAIT cell frequencies were not related to fibrosis severity; however, MAIT cell function was impaired in mono-infected patients with more fibrosis. More advanced liver fibrosis in HCV or HCV/HIV-infected patients was not reflected by increased accumulation of MAIT cells in the affected liver.
Conclusion: Severe liver fibrosis is associated with dysfunctional MAIT cells in blood of HCV mono-infected patients, and lower MAIT frequencies in blood of HCV/HIV co-infected patients, without evidence for accumulation in the liver.

588 PATHOGENESIS OF HIV-INDUCED LIVER DISEASE IN DUAL IMMUNE AND LIVER HUMANIZED MICE

Raghubendra S. Dagur, Weimin Wang, Yan Cheng, Weizhe Li, Edward Makarov, Natalia Osna, Santhi Gorantla, Larisa Y. Poluektova
Univ of Nebraska, Omaha, NE, USA

Background: HIV-1 infection has a negative impact on liver function, and liver diseases have become a leading cause of mortality in infected patients. Mechanisms of liver damage remain unclear. In vitro cell culture experiments usually have limitation; moreover, collection of clinical data depends on multiple boundaries: time of infection, co-infections with hepatitis viruses, drugs of abuse, and treatment of patients. To overcome such limitations, we utilized chimeric mice dually reconstituted with human blood and liver.
Methods: TK-NOG (CIEA, Japan) males were simultaneously transplanted with human CD34+ hematopoietic stem cells (HSCs) and hepatocytes (Hep) at 6-8 weeks of age, intrasplenically. Levels of human liver and immune reconstitution were monitored by human albumin (Alb) in plasma (ELISA) and the presence of human immune cells in blood, spleen and liver tissues (FACS). At 5 months post-transplantation, mice were infected with HIV-1 and euthanized at 5 weeks post infection. Liver pathomorphology was assessed by staining for CK-18, apoptotic Hep (M30), αSMA (fibrosis), GFAP (stellate cells activation), human HLA-DR, CD4, CD8 infiltration, and HIV-1 p24 antigen. Infection was confirmed by detection of virus in plasma and HIV-gag mRNA expression in primary hepatocytes. Changes in liver infiltrating immune cells milieu were evaluated by comparison of the expression of TLR receptors, chemokines and their receptors, and acute and chronic inflammatory responses by RT-PCR array. To further dissect the mechanisms of Hep damage at cellular and functional levels, primary Hep cultures were exposed to HIV-1.
Results: HIV-infected mice showed a decline of human Alb concentration (42%,$p < 0.05$) and significant reduction in CK18+ Hep (50%,$p< 0.05$), compared to uninfected. The decrease in human albumin level was correlated with CD4+ cells in liver (R^2=0.72,$p < 0.05$) and increase in HIV-1 viral load in plasma (R^2=0.77, $p < 0.05$). In vitro and in vivo, HIV-1 caused apoptosis of Hep. In infected-liver tissues, up-regulation of TLR7(5.9 fold) > 9(4.1)>1(2.0)>3(1.9)> 4(1.5) and increased expression of chemokines involved in the formation of lymphoid aggregates (CCL7(3.3 fold), CCL23(2.8) and CCL21(2.6)), attraction of lymphocytes (CXCL10(15.9)) and neutrophils (CXCR1(3.6fold) and CXCR2(3.2)), as well as an elevation of IL23A (2.3), compared to uninfected were evident.
Conclusion: Dual reconstituted TK-NOG mice are a feasible platform to study in vivo HIV-mediated human liver damage and therapeutics development.

589 PERIPHERAL ENDOTHELIAL FUNCTION IS SUBOPTIMAL IN HCV-UNTREATED, HIV-SUPPRESSED ADULTS

Kara W. Chew[1], Eric Daar[2], Jordan E. Lake[3], Chrisandra L. Shufelt[4], Zhaoping Li[1], Diana Liao[1], Wilbert Jordan[5], C. Noel Bairey Merz[4], Judith S. Currier[1], Debika Bhattacharya[1]
[1]Univ of California Los Angeles, Los Angeles, CA, USA, [2]Los Angeles Biomed Rsr Inst at Harbor–UCLA Med Cntr, Torrance, CA, USA, [3]Univ Texas Houston, Houston, TX, USA, [4]Cedars-Sinai Med Cntr, Los Angeles, CA, USA, [5]Charles R. Drew Univ of Med and Sci, Los Angeles, CA, USA

Background: Hepatitis C virus (HCV) infection may increase risk of atherosclerotic disease. Endothelial dysfunction contributes to atherosclerosis, but endothelial function has not been characterized in HIV/HCV co-infection. We hypothesized that endothelial function would be abnormal in HIV/HCV-coinfected persons on suppressive antiretroviral therapy (ART).
Methods: We enrolled HIV/HCV-coinfected adults with HIV RNA <50 copies/mL, $CD4^+$ T cell count ≥200 cells/mm^3, HCV RNA ≥10,000 IU/mL, with no known cardiovascular disease, and measured endothelial function by peripheral arterial tonometry (PAT). Standardized conditions for PAT testing included: fasting and avoidance of vigorous exercise for 12 hours (h), nicotine held for 4h, caffeine/stimulants for 24h, select antihypertensive agents for 24-48h, and vaccines for 14 days. Endothelial dysfunction was defined as reactive hyperemia index (RHI) by PAT ≤1.67 and optimal endothelial function as RHI >2. Wilcoxon rank sum tests were conducted to compare RHI between groups. Multiple linear regression analysis was used to assess predictors of natural log-transformed RHI (lnRHI).
Results: Forty-three participants had RHI for analysis; 86% were male, 35% Black, and 40% Hispanic, with median age of 52 years. Median nadir and current $CD4^+$ T cell count were 149 and 502 cells/mm^3, respectively, median HCV RNA 6.16 log IU/mL, and waist circumference (measured at the level of the iliac crest) 97 cm. Thirty-five % reported current smoking, 9% current stimulant (cocaine or methamphetamine) use, 14% had dyslipidemia, 23% hypertension, 12% cirrhosis, and none had diabetes. Nine (21%) had RHI ≤1.67 and 25 (58%) had RHI <2.0. RHI was similar between those on abacavir (n=15) and those not (median RHI 1.94 vs 1.98, p=0.49), on a boosted HIV-1 protease inhibitor (n=12) vs not (1.98 vs 1.98), and with and without cirrhosis (1.90 vs 1.98, p=0.84). In multiple regression analysis, higher HCV viral load and current smoking were associated with worse lnRHI (see Table).
Conclusion: Peripheral endothelial function was suboptimal in the majority of participants in this cohort with untreated HCV and ART-treated, virologically suppressed HIV infection. Whereas degree of HCV viremia does not predict liver disease progression, it may contribute to endothelial dysfunction and cardiovascular morbidity in HIV/HCV-coinfected patients, even with HIV suppression.

590 LEUKOCYTE TELOMERE ATTRITION IS RAPID FOLLOWING HIV BUT NOT HCV SEROCONVERSION

Alejandro Gonzalez-Serna[1], Abhinav Ajaykumar[2], Izabelle Gadawski[2], M. Ángeles Muñoz-Fernández[3], Kanna Hayashi[1], M.-J. Milloy[1], P. Richard Harrigan[1], **Helene C. Cote**[2]
[1]BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada, [2]Univ of British Columbia, Vancouver, British Columbia, Canada, [3]General Univ Hosp Gregorio Marañon, Madrid, Spain

Background: Age-related diseases are more prevalent in persons living with HIV, suggesting accelerated aging. Both HIV and hepatitis C virus (HCV) infection have been associated with shorter leukocyte telomere length (TL). Whether this TL shortening occurs rapidly following HIV and/or HCV seroconversion or gradually over the chronic infection period is unclear.
Methods: In the retrospective study, PBMC TL was measured in 95 subjects enrolled in Vancouver Injection Drug Users Study (VIDUS)/ AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), who subsequently acquired HIV (n=51) or HCV (n=16). PBMCs were collected at two time points: a median of 3 months before and 9 months after seroconversion. Control participants who did not seroconvert (NS) for either virus (n=29) were analyzed at 2 random time points a median one year apart. TL was assayed via monochrome multiplex qPCR. Within-individual TL change between the two time points were compared for each group using the Wilcoxon signed rank test.

Results: Compared to pre-seroconversion, TL was significantly shorter (-13%) post-seroconversion in those who acquired HIV [Median 8.2 (6.9-10) vs 9.1 (7.7-11.1), p=0.025], but not among HCV seroconverters [8.4 (7.2-9.9) vs 8.5 (6.9-10), p=0.552] or control non-seroconverters [9.6 (8.8-11.2) vs 9.6 (8.7-11), p=0.353]. Among HCV seroconverters, 31% (5/16) were already HIV+ while 90% (46/51) of the HIV seroconverters were already HCV+. One subject seroconverted for both viruses.
Conclusion: The average PBMC TL shortening that occurs with HIV infection is detected within a year of HIV seroconverting. In contrast, the lack of a similarly rapid TL loss with HCV seroconversion suggests that the previously reported association between HCV and shorter TL may be primarily driven by longer term chronic infection. Together, these data suggest that HIV infection modulates cellular aging and immunosenescence very early in infection.

591 MULTIPLE-TEST SCREENING STRATEGIES IMPROVE BIOPSY-PROVEN HSIL-DETECTION IN HIV+ WOMEN

Dorothy J. Wiley[1], Elizabeth Chiao[2], Jeanette Lee[3], Ashish A. Deshmukh[4], Scott B. Cantor[5], Joel Palefsky[6], Elizabeth A. Stier[7]
[1]Univ of California Los Angeles, Los Angeles, CA, USA, [2]Baylor Coll of Med, Houston, TX, USA, [3]Univ of Arkansas for Med Scis, Little Rock, AR, USA, [4]Univ of Florida, Gainesville, FL, USA, [5]Univ of Texas MD Anderson Cancer Cntr, Houston, TX, USA, [6]Univ of California San Francisco, San Francisco, CA, USA, [7]Boston Univ, Boston, MA, USA
Background: Anal cancer disproportionately affect HIV-infected women. Biopsy-confirmed anal high-grade squamous intraepithelial lesion (aHSIL) is a precancer lesion. There is no consensus for providing aHSIL screening. Thus, we estimated test characteristics for a series of aHSIL-screening strategies.
Methods: In a cross-sectional study, anal Dacron-swab specimens for 200 HIV-infected women were tested for abnormal cytology (≥ ASC-US) & high-risk HPVs (hrHPVs) using both hrHPV-E6/E7-mRNA (E6/E7-mRNA) (GenProbe Corp, Marlborough, MA) & hrHPV-DNA (Qiagen Corp., Valencia, CA) assays. High-Resolution Anoscopy with biopsy evaluated tissue for high-grade squamous intraepithelial lesions (bHSIL), an anal cancer precursor, for all subjects. Sensitivity, specificity, positive and negative predictive value of one or more tests to predict bHSIL (test characteristics) were estimated for seven screening strategies (Table): 1) abnormal Dacron cytology, 2) E6/E7-mRNA+, 3) hrHPV-DNA+; 4) E6/E7-mRNA+ or hrHPV-DNA+, defined as in parallel testing, 5) abnormal cytology, then E6/E7-mRNA+, defined as in series, 6) abnormal cytology, then hrHPV-DNA+ (in series), & 7) E6/E7-mRNA+ then hrHPV-DNA+ (in series). Logistic regression analyses, adjusted for age, compared screening-positive vs. -negative results & were used to determine the benefit of adding hrHPV testing following a positive anal cytology result.
Results: Abnormal cytology (55%) & bHSIL (27%) were common. Performance characteristics are listed in Table 1 & show specificity alone is improved using any of the in series screening strategies (p<0.05). Conditional analyses suggest a positive effect of hrHPV-DNA+ or E6/E7-mRNA+ on bHSIL detection, given abnormal cytology: OR=3.04 (1.26, 7.34), OR=7.39 (2.72, 20.09), respectively.
Conclusion: Strategies that refer women with abnormal cytology and either positive E6/E7-mRNA or hrHPV-DNA test results to HRA improved anal cancer screening. Our findings suggest E6/E7-mRNA & hrHPV-DNA testing add value to detection of abnormal cytology in comparison to cytology testing alone. Larger studies are needed.

592 MULTITEST SCREENING STRATEGIES ADD VALUE FOR PREDICTING BIOPSY-PROVEN HSIL FOR MSM

Dorothy J. Wiley[1], Hilary K. Hsu[1], Matthew G. Moran[1], Jenny Brook[1], David Elashoff[1], Martha Ganser[1], Stephen Young[2], David Morris[3], Otoniel Martínez-Maza[1], Ronald T. Mitsuyasu[1]
[1]Univ of California Los Angeles, Los Angeles, CA, USA, [2]Tricore Reference Labs, Albuquerque, NM, USA, [3]Desert AIDS Proj, Palm Springs, CA, USA
Background: Biopsy-confirmed anal high-grade squamous intraepithelial lesion (bHSIL) is a precursor lesion for anal cancer (AC). AC disproportionately affects HIV-infected MSM. Multi-test screening strategies to assess the value of adding molecular & cytology assays may improve bHSIL screening.
Methods: A single-visit RCT evaluated two specimen collection protocols for 301 MSM: Dacron & nylon-flocked (NF) swabs. High-Resolution Anoscopy (HRA) & biopsy evaluated tissue for bHSIL. Dacron- & Nylon-Flocked (NF) cytology specimens were evaluated for atypia (≥ASC-US) & high-risk HPV-DNA (DNA). Dacron-cytology was also tested for hrHPV-E6/E7-mRNA (E6/E7). Receiver-Operator Curves (ROC), adjusted for swab order, age, & smoking, estimated accuracy (AUC) to predict bHSIL for combinations of abnormal cytology & E6/E7- & DNA-test positivity using logistic regression analysis for HIV-infected & uninfected men. Fold-change in AUC compared performance of screening strategies.
Results: Men were White (76%), HIV-infected (60%), 55 (+11) years of age, & 47% showed bHSIL. NF-cytology sampling improved accuracy for predicting bHSIL. When combined, NF-DNA & –cytology testing improved accuracy 5%, vs. NF-cytology (AUC=0.8 vs. 0.75, p=0.01) or NF-DNA testing alone (AUC=0.8 vs. 0.75, p=0.02). Paired Dacron-E6/E7 & NF-cytology testing improved accuracy 11% over cytology alone (AUC=0.83 vs. AUC=0.72; p<0.001). Together, Dacron-E6/E7 & NF-DNA screening improved accuracy 5% over DNA testing alone (AUC=0.8 vs. 0.75, p=0.007). Adding Dacron-E6/E7 to Dacron-cytology testing improved accuracy 11% for predicting bHSIL over Dacron-cytology alone (AUC=0.83 vs. 0.72, p<0.001), but was no more accurate than Dacron-E6/E7 alone (p=0.78). Paired Dacron-DNA & Dacron-E6/E7 testing improved accuracy 5% over Dacron-DNA alone (AUC=0.81 vs. AUC=0.76, p=0.02); however, Dacron-E6/E7 testing alone was as accurate as paired testing (AUC=0.80 vs. 0.81, p=0.65). Paired Dacron- cytology & Dacron-DNA testing did not improve accuracy over Dacron-cytology (p=0.06) or Dacron-DNA (p=0.97) testing alone. HIV-infected & –uninfected men showed small differences in accuracy across all strategies (Table). However, adding E6/E7 to NF- or Dacron cytology improved accuracy for predicting bHSIL 1.16-1.32-fold over cytology alone (Table).
Conclusion: For HIV-infected & –uninfected MSM, hrHPV-E6/E7-mRNA & -DNA testing adds value to cytology screening for predicting bHSIL over cytology alone. Larger studies are needed.

Table: Comparison of Test Accuracy for Eight Screening Strategies to Predict Anal Biopsy-Confirmed High-grade Squamous Intraepithelial Cancer (bHSIL) for 301 HIV-Infected and -Uninfected Gay, Bisexual and Other Men Who Have Sex With Men (MSM)

Testing Strategy: Sequence of Tests	Accuracy				Testing Strategy: Sequence of Tests	Accuracy			
	Fold-Improvement Adding Test 2	HIV-uninfected (AUC)	Fold-Improvement Adding Test 2	HIV-infected (AUC)		Fold-Improvement Adding Test 2	HIV-uninfected (AUC)	Fold-Improvement Adding Test 2	HIV-infected (AUC)
Dacron Swab Specimen Collection					Nylon Flocked Swab Specimen Collection				
Cytology Alone	1.10	0.65	1.08	0.68	Cytology Alone	1.15 ϒ	0.71	1.10 ϕ	0.68
Cytology + hrHPV-DNA		0.72		0.73	Cytology + hrHPV-DNA		0.81		0.74
hrHPV-DNA Alone	0.99	0.73	1.03	0.71	hrHPV-DNA Alone	1.09 ϕ	0.75	1.06	0.70
hrHPV-DNA + Cytology		0.72		0.73	hrHPV-DNA + Cytology		0.81		0.74
Cytology Alone	1.32 ϑ	0.62	1.17 ξ	0.67	Cytology Alone	1.18 ϑ	0.73	1.16 ξ	0.68
Cytology + hrHPV-E6/E7-mRNA		0.82		0.78	Cytology + hrHPV-E6/E7-mRNA*		0.87		0.79
hrHPV-E6/E7-mRNA Alone	1.02	0.80	1.01	0.78	hrHPV-E6/E7-mRNA* Alone	1.05	0.82	1.03	0.77
hrHPV-E6/E7-mRNA + Cytology		0.82		0.78	hrHPV-E6/E7-mRNA* + Cytology		0.82		0.79
hrHPV-DNA Alone	1.08	0.74	1.09	0.71	hrHPV-DNA Alone	1.09 ϕ	0.74	1.09 ϒ	0.70
hrHPV-DNA + hrHPV-E6/E7-mRNA		0.79		0.77	hrHPV-DNA + hrHPV-E6/E7-mRNA*		0.81		0.77
hrHPV-E6/E7-mRNA Alone	1.01	0.78	1.00	0.77	hrHPV-E6/E7-mRNA* Alone	1.05	0.77	1.00	0.77
hrHPV-E6/E7-mRNA + hrHPV-DNA		0.79		0.77	hrHPV-E6/E7-mRNA* + hrHPV-DNA		0.81		0.77

ϕ=0.05 ϒ=0.02, ϑ=0.01, ξ=0.003; *hrHPV-E6/E7-mRNA tests are collected using Dacron swab; False Discovery Rate = 9 observed vs. 1 expected

593 ANAL HIGH-RISK HPV ASSOCIATIONS WITH SERUM CYTOKINES/CHEMOKINES AND FREE TESTOSTERONE

Dorothy J. Wiley[1], Hilary K. Hsu[2], Sitram Vangala[3], David Elashoff[3], Xiang Lu[3], Todd Brown[4], Gysamber D'Souza[2], Elizabeth Breen[3], Stephen Young[3], Nancy Joste[1]
[1]Univ of California Los Angeles, Los Angeles, CA, USA, [2]The Johns Hopkins Univ, Baltimore, MD, USA, [3]Tricore Reference Labs, Albuquerque, NM, USA, [4]Univ of New Mexico Hlth Scis Cntr, Albuquerque, NM, USA

Background: Inflammatory cytokines and chemokines (biomarkers) prevent infection acquisition or promote clearance. Persistent Group/1-hrHPVs increase risk for anogenital invasive squamous cell carcinomas (SCC) and their precursor lesions, including anal cancers. Anal SCCs are emerging as important non-AIDS defining cancer among HIV-infected gay, bisexual and other men who have sex with men (MSM) and women. Associations between Group/1-hrHPV infections and biomarkers is unclear, especially within the context of HIV coinfection.

Methods: Anal-swab specimens for 691 men who have sex with men (MSM) from Multicenter AIDS Cohort Study were evaluated using cross-sectional analysis. Dacron-swab collected anal cytology specimens were tested for 37 HPVs using PCR and a sensitive linear blot-hybridization assay. Twenty-four inflammatory cytokines/chemokines and free testosterone (sFT) were measured in cryopreserved serum that was collected approximately 24 months before HPV testing. Stepwise logistic regression models selected biomarker candidates ($p<0.2$) for multivariate analyses. Final analyses compared odds of Group/1-hrHPVs (vs. not) associated with MIP-1β, IFN-γ, and sFT, adjusting for the effects of age, race, smoking, sex-partner number; HIV infection and, among the infected, (HIV) virus load and CD4-T-lymphocyte counts.

Results: The median age was 52 years, 79% were HIV-infected, and 62% tested positive for >1 Group/1-hrHPVs. Group/1-hrHPV-infection was associated with MIP-1B, CXCL13/BLC/BCA-1, IFN-γ cytokines/chemokines in bivariate analyses (p-values<0.05), but not associated with HIV-infection. IFN-γ measurements were substantially lower than population estimates reported using the same technology. Multivariable analysis showed the odds of Group/1-hrHPV infections decreased 1.3-fold with every log10 increase in serum MIP-1β ($p=0.01$) (Table). Similarly, each log10 increase in sFT increased the odds of detecting Group/1-hrHPVs 1.5-fold ($p=0.03$) (Table). Positive associations between IFN-γ and Group/1-hrHPVs were suggestive but may not be biologically meaningful (OR=1.4, $p=0.06$).

Conclusion: MIP-1β may protect against infection or promote clearance. sFT is positively associated with Group/1-hrHPV infections. More research is needed.

Table: Association between Cytokine and Chemokine Inflammatory Biomarkers and Serum Free Testosterone and Group 1, Strongly Carcinogenic, High-Risk Human Papillomaviruses among Male Multicenter AIDS Cohort Participants

Characteristic	Model 1*		Model 2*		Model 3**	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (years)	0.98 (0.96, 1.00)	0.057	0.98 (0.96, 1.00)	0.077	1 (0.97, 1.03)	0.9
Race						
White	1.48 (1.01, 2.17)	**0.047**	1.37 (0.92, 2.03)	**0.119**	1.37 (0.85, 2.20)	0.195
Non-White	1		1		1	
HIV Infection Characteristics		**<0.001**		**<0.001**		**<0.001**
HIV-uninfected	1		1		1	
HIV-infected						
Low HIV-viral Load	2.40 (1.51, 3.81)	**<0.001**	2.39 (1.50, 3.81)	**<0.001**	1.54 (0.89, 2.66)	**0.121**
HIV-viral Load, CD4-T-cell ≥500 cells/mm^3	2.33 (1.48, 3.67)	**<0.001**	2.42 (1.52, 3.83)	**<0.001**	1.82 (1.06, 3.15)	**0.031**
HIV-viral Load, CD4-T-cell <500 cells/mm^3	5.22 (3.09, 8.83)	**<0.001**	5.07 (2.97, 8.63)	**<0.001**	3.78 (2.04, 7.00)	**<0.001**
Number of Partners (Log Scale)	1.22 (1.08, 1.38)	**0.002**	1.22 (1.07, 1.38)	**0.002**	1.15 (0.99, 1.33)	**0.062**
Tobacco						
Never smoked	1		1		1	
Ever smoked	1.43 (1.02, 2.00)	**0.037**	1.41 (1.00, 1.98)	**0.048**	1.6 (1.07, 2.39)	**0.021**
IFN Gamma (Log_{10} Scale)	-		1.49 (0.99, 2.24)	**0.059**	1.58 (0.96, 2.62)	**0.074**
MIP-1 Beta (Log_{10} Scale)	-		0.75 (0.60, 0.94)	**0.014**	0.65 (0.49, 0.86)	**0.002**
Free Testosterone (Log_{10} Scale)	-		-		1.52 (1.05, 2.21)	**0.028**

* N=691 MSM **N=504 MSM

594 MULTIPLE HPV INFECTIONS AND ANAL PRECANCEROUS LESIONS IN HIV-INFECTED MEN

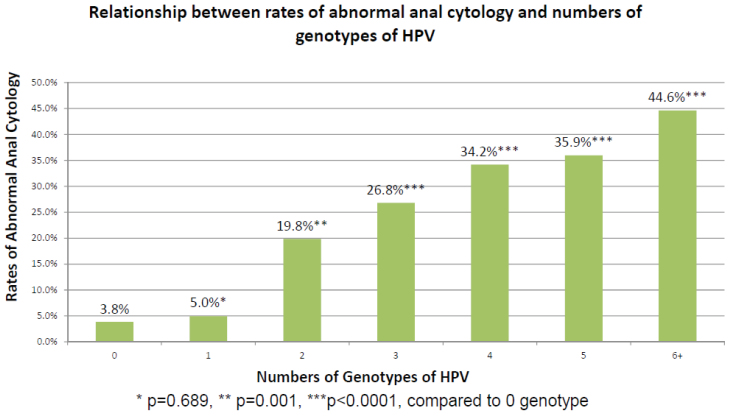
Shu-Hsing Cheng[1], Chien-Yu Cheng[1], Chi-Chao Wang[1], Fang-Yeh Chu[2], Yu-Mei Hsueh[3]
[1]Taoyuan General Hosp, Taoyuan, Taiwan, [2]Far Eastern Memorial Hosp, New Taipei, Taiwan, [3]Taipei Med Univ, Taipei, Taiwan

Background: Men who were infected with HIV are at increased risk of developing anal cancer. Though previous reports had showed multiple HPV infections were common among HIV-infected patients, whether multiple HPV types are associated with precancerous anal lesions was not explored.

Methods: Between March 2010 and June 2016, HIV-infected men who visited the outpatient clinics of Taoyuan General Hospital, Taiwan, had been enrolled. After informed consents obtained, the subjects inserted saline-wetted Dacron swabs approximately 5 cm beyond the anal verge. Rectal swabs were rinsed immediately in a vial containing PreservCyt solution (Cytyc, Marlborough, MA). Thin preparation Pap smears (ThinPrep; Hologic, Marlborough, MA) were interpreted according to the 2001 Bethesda System. HPV genotyping was performed by a reverse line blotting method (Linear Array HPV Genotyping Test; Roche Molecular System, Branchburg, NJ). Thirty-seven types of HPV were detected, including oncogenic types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; and non-oncogenic types, 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39, and CP6108.

Results: Totally 714 HIV-positive subjects were enrolled. Their mean ages were 30.7 years. Among them, 83.2% were men who have sex with men. There were 175 subjects (24.5%) had atypical squamous cells with undetermined significance (ASCUS) or higher grades (ASCUS+) in anal cytology, comprising 87 (49.7%) ASCUS, 73 (41.7%) low-grade squamous intraepithelial lesions (SIL), and 15 (8.6%) high-grade SIL (HSIL)/atypical squamous cells cannot exclude HSIL. Comparison between subjects who carried ASCUS+ and who did not revealed 97.7% vs. 81.4% had any type of HPV ($p < .0001$); and 94.8% vs. 63.6% had multiple HPV types ($p < .0001$). Among subjects who had 0, 1, 2, 3, 4, 5 and more than 5 types of HPV infection, frequencies of ASCUS+ (OR, 95% CI) were 3.8% , 5.0% (1.31, 0.43 – 5.04), 19.8% (6.24, 2.09 – 8.66), 26.8% (9.24, 3.09 – 27.65), 34.2% (24.22, 4.35 – 39.46), 35.9% (14.16, 4.61 – 43.50), and 44.6% (20.32, 7.11 – 58.10), respectively (p trend < .0001). Multivariate logistic regression analysis showed a significant association of ASCUS+ with numbers of HPV genotypes (OR 1.42; 95% CI 1.020 – 1.979, p =.037).

Conclusion: Subjects who have more than 5 types of HPVs have 20 times of risk to have anal ASCUS+. Multiple HPV infections in anal sites among HIV-infected patients deserved aggressive follow-up.



595 SCREENING FOR PRECANCEROUS ANAL LESIONS WITH P16/KI67 DUAL STAIN CYTOLOGY IN HIV

Sergio Serrano-Villar[1], Beatriz Hernández-Novoa[2], Amparo de Benito[1], Jorge Romero[3], Antonio Ocampo[4], Laura Pérez-Martínez[5], Mar Masia[6], Elena Sendagorta[7], Gonzalo Sanz[8], José Antonio Pérez-Molina[1]

[1]Hosp Univ Ramón y Cajal, Madrid, Spain, [2]Brystol-Myers-Squibb, Madrid, Spain, [3]Centro Sandoval, Madrid, Spain, [4]Hosp Xeral de Vigo, Vigo, Pontevedra, [5]Hosp San Pedro, Logroño, Spain, [6]Hosp General Univ de Elche, Elche, Spain, [7]Hosp Univ La Paz, Madrid, Spain, [8]Hosp Clínico San Carlos, Madrid, Spain

Background: Anal cancer is among the most prevalent neoplasias in HIV-infected MSM. Screening with anal citology results yields to high rates of false positive results and elevated burden of high-resolution anoscopies (HRA) with anal biopsies. High risk HPV up-regulate p16 expression and increase proliferation (Ki67 expression) in epithelial cells. We assessed the usefulness of P16/Ki-67 dual staining cytology for the diagnosis of precancerous anal lesions.

Methods: Prospective multi-center cohort study in 6 HIV clinics. Concomitant anal liquid cytology with p16/Ki-67 dual staining (CINtec® PLUS, Roche) and HRA with biopsy of acetowhite lugol-negative lesions was performed. We compared the diagnostic performance of an abnormal anal cytology (atypical squamous cells [ASC], LSIL or HSIL) and p16/Ki-67 dual positivity relative to HRA-guided biopsy. We calculated the independent predictive values of anal cytology and p16/Ki-67 positivity in multivariate logistic regression models adjusted by potential confounders.

Results: A total of 328 HIV-infected MSM underwent 386 full examinations. Mean age was 39±10 years, median nadir CD4 367 (258-510) cells/uL, 57% had detectable plasma HIV RNA and 30% reported unprotected anal sex in the prior 3 months. Sixty-three % of anal cytologies were abnormal: 24(6.2%) ASC, 143(37%) LSIL and 74(19.2%) HSIL. HSIL was histologically diagnosed in 80 subjects (24.1%), and 2 (0.6%) were diagnosed with anal cancer, in whom the cytology had showed LSIL and HSIL, respectively. An abnormal citology showed the following statistics for the diagnosis of biopsy proven HSIL: sensitivity 95.6% (CI95%, 91.2-99.9), specificity 58.8% (CI95%, 52.2-65.4), positive predictive value 39.8% (CI95%, 33.2-46.4), negative predictive value 95.8% (CI95%, 91.6-99.9). P16/Ki67 dual positivity was not associated with higher rates of biopsy-proven HSIL (Table 1). After adjustment by potential confounders (age, nadir CD4, detectable HIV RNA, tobacco use), an abnormal anal citology, but not a positive P16/Ki67 stain, was an independent predictor of HSIL (OR, 12.1; CI95% 3.5-41.3 and OR, 1.2; CI95% 0.6-2.5, respectively).

Conclusion: P16/Ki67 dual staining does not improve the diagnostic accuracy of anal cytology, which shows a high sensitivity yet poor specificity. Other approaches aimed at improving the diagnostic accuracy of current techniques for the diagnostic of precancerous anal lesions are warranted.

Table 1. Frequencies of dual P16/Ki67 positive stain in anal cytologies from HIV-infected MSM and diagnostic accuracy for biopsy-proven HSIL in abnormal cytologies.

	Histology				
Cytology	*Unsatisfactory*	*Negative*	*LSIL*	*HSIL*	*Total*
P16/Ki67 (-)	6 (85.7%)	77 (77%)	38 (61.3%)	40 (58.8%)	161 (67.9%)
P16/Ki67 (+)	1 (14.3%)	23(23%)	24 (38.7%)	28 (41.2%)	76 (32.1%)
Total	7 (100%)	100 (100%)	62 (100%)	68 (100%)	237 (100%)

**Between-group comparisons, p=NS. Dual P16/Ki67 was not obtained in 12/80 biopsy-proven HSIL.*

Dual P16/Ki67 positivity accuracy in anal cytology for the diagnosis of biopsy-proven HSIL diagnosis: sensitivity 42.3% (CI95%, 29.8.2-55.4), specificity 61.1% (CI95%, 50.8-71.4), positive predictive value 42.6% (CI95%, 29.8-55.4), negative predictive value 38.9% (CI95%, 28.6-49.2).

596 IMPACT OF ART COVERAGE AND SCREENING ON ANAL CANCER IN HIV+ MEN WHO HAVE SEX WITH MEN

Nello Blaser[1], Barbara Bertisch[1], Manuel Koller[1], Marcel Stoeckle[2], Matthias Cavassini[3], Roger Kouyos[4], Janne Estill[1], Matthias Egger[1], **Olivia Keiser**[1], for the Swiss HIV Cohort Study

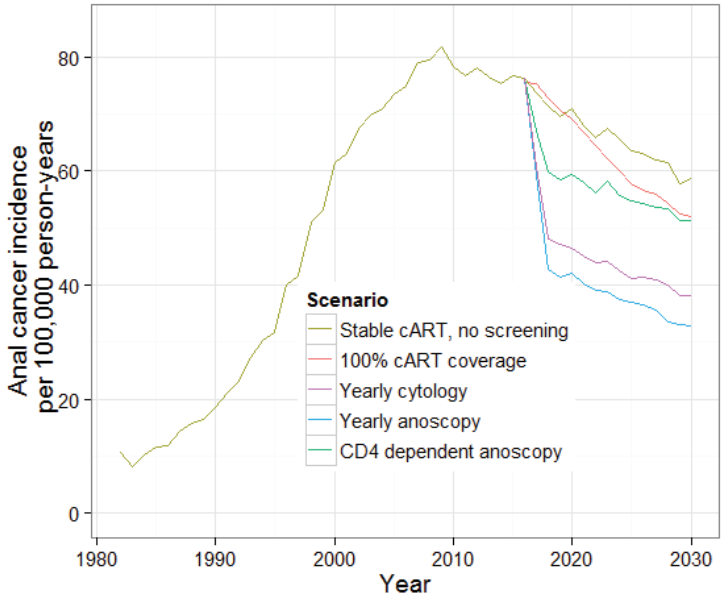
[1]Univ of Bern, Bern, Switzerland, [2]Univ Hosp Basel, Basel, Switzerland, [3]Univ of Lausanne, Lausanne, Switzerland, [4]Univ of Zurich, Zurich, Switzerland

Background: In HIV-positive men who have sex with men (MSM), the incidence of anal cancer is 60-190 times higher than in the general population. The incidence has been rising for many years, but has declined in recent years. In this population, where we assume that almost everybody had a history of contact with oncogenic Human Papillomaviruses (HPV), the most important risk factor for anal cancer is a low CD4 cell count. Little is known about the likely impact of increased antiretroviral therapy (ART) coverage and screening on anal cancer incidence.

Methods: We developed a mathematical model to estimate the incidence of anal cancer in HIV-positive MSM in Switzerland up to 2030. We considered two scenarios of future ART coverage: "stable" (same cART coverage between 2016 and 2030 as between 2010 and 2015 and no screening for AIN2/3) and "100% cART coverage" (all individuals diagnosed with HIV are on ART); and four screening scenarios: "no screening", "yearly cytology", "yearly anoscopy" and "CD4-dependent anoscopy" (people were screened with anoscopy five years after their CD4 cell count dropped to below 200 cells/µl). We parameterized the model with data from the Swiss HIV Cohort Study (SHCS) and the literature. We considered CD4 cell count trajectory the main predictor of anal cancer.

Results: The median nadir CD4 cell count of 6,411 MSM in the SHCS increased from 112 cells/µl in 1980-1999 to 394 cells/µl after 2010. Predicted cancer incidence increased to a maximum of 78.7/100,000 person-years in 2010 and has since stabilized. Model estimates up to 2014 are consistent with observed anal cancer incidence in the SHCS. By 2030, incidence will decrease to 58.9/100,000 person-years in the stable scenario, and to 52/100,000 in the 100% cART coverage scenario. Treating patients with electrocautery after yearly anoscopy decreased anal cancer incidence by 37.9%, after yearly cytology by 30.9% and after CD4-dependent anoscopy by 13% (Figure 1). To prevent one anal cancer case 3817 screening tests were needed in the yearly anoscopy strategy, 4684 in the yearly cytology strategy and 242 in the CD4-dependent strategy.

Conclusion: Yearly anoscopy leads to the most pronounced decrease in anal cancer incidence and CD4 dependent anoscopy results in most anal cancers prevented per screening test. Expanding ART will have only a modest effect.



597 PREVALENCE OF HPV TYPES COVERED BY CURRENT VACCINES IN HIV-INFECTED MEN, SUN STUDY

Pragna Patel[1], Tim Bush[1], Lois Conley[1], Elizabeth Unger[1], Teresa Darragh[2], Keith Henry[3], Gerome Escota[4], Joel Palefsky[2], John T. Brooks[1], Erna M. Kojic[5]
[1]CDC, Atlanta, GA, USA, [2]Univ of California San Francisco, San Francisco, CA, USA, [3]Hennepin County Med Cntr, Minneapolis, MN, USA, [4]Washington Univ, St. Louis, MO, USA, [5]Brown Univ, Providence, RI, USA

Background: High-risk anal HPV infection is prevalent among HIV-infected men; but the proportion infected with types covered by current HPV vaccines and association with abnormal cytology have not been well characterized.
Methods: The SUN Study was a prospective cohort study of HIV-infected patients receiving care at 7 HIV clinics in 4 US cities. Patients were enrolled from 2004 to 2006. At baseline, providers collected separate anal swabs for HPV detection and cytopathologic examination. We examined the prevalence of the 7 high-risk (HR)-HPV types covered by the nonavalent (9v) HPV vaccine (16, 18, 31, 33, 45, 52, and 58) and associated abnormal cytology (atypical squamous cells of undetermined significance or worse) to assess the impact of the 9v-HPV vaccine.
Results: The characteristics of men who have sex with men (MSM, n=403) and men who have sex with women (MSW, n= 96) were similar: median age 42 years, prescribed antiretroviral therapy (78% and 81% respectively), median CD4 cell count (454 cells/mm3 and 379 cells/mm3), CD4 counts >200 cells/mm3 (90% and 83%) and undetectable viral load (74% and 75%). The baseline prevalence of any 9vHR-HPV type in the anus among MSM and MSW was 74% and 32% and of any 5 types other than HPV 16 or 18 was 23% and 15%, respectively. Among MSM and MSW with prevalent 9vHR-HPV types, 63% and 44% had abnormal anal cytology, respectively. Among 368 MSM with adequate anal cytology, abnormal cytology was detected in 206 (56%) MSM and correlated with the presence of any 9vHR-HPV (relative risk [RR] = 1.8 95% CI: 1.3-2.3 $p < 0.001$) and with > 1 9v HR-HPV types (RR = 1.5, 95% CI: 1.3-1.9 $p < 0.001$). Among 87 MSW, abnormal anal cytology was detected in 17 (20%) and correlated with the presence of any 9vHR-HPV (RR = 5.3 95% CI: 2.1-13.6 $p < 0.001$) and with > 1 HR-HPV-9v types (RR = 5.4, 95% CI: 2.7-10.6, $p < 0.001$). Among MSM and MSW, sensitivity of anal 9vHR HPV detection for the presence of anal cytologic abnormalities was good (83 (78-88)% and 71 (44-90)%, respectively). Specificity was poor among MSM (38 (30-46)%) but good among MSW (79 (67-87)%).
Conclusion: In this contemporary cohort of HIV-infected men, the prevalence of 7 high risk HPV types in the nonavalent vaccine was high and correlated with the presence of cytologic abnormalities. Among MSW, HPV detection may be an initial screening step and the 9v-HPV vaccine may offer substantial prevention benefit.

598 EARLIER VERSUS DELAYED ANTIRETROVIRAL THERAPY INITIATION AND RISK OF CANCER

Michael J. Silverberg[1], Wendy Leyden[1], Haiqun Lin[2], Li Qin[2], Chad J. Achenbach[3], Gysamber D'Souza[4], Eric A. Engels[5], Charles Rabkin[5], Keri N. Althoff[4], Romain Neugebauer[1]
[1]Kaiser Permanente, Oakland, CA, USA, [2]Yale Univ, New Haven, CT, USA, [3]Northwestern Univ, Chicago, IL, USA, [4]Johns Hopkins Univ, Baltimore, MD, USA, [5]NCI, Rockville, MD, USA

Background: Cohort and trials evaluating mortality and AIDS events informed guidelines for immediate combination antiretroviral therapy (ART) for all HIV patients. Studies with extended follow-up are needed to evaluate effectiveness of earlier ART on rare events such as cancer.
Methods: Cohort study of ART-naïve, AIDS-free, HIV+ adults followed between 1996 and 2009 in the North American AIDS Cohort Collaboration on Research and Design. Subjects were followed from first CD4 of 350-500 cells/µl (baseline) until incident cancer, death, lost-to-follow-up or 2009. Cancers were confirmed by chart review or cancer registry linkage and grouped as: any cancer, virus-unrelated and virus-related non-AIDS-defining cancers (NADC), and AIDS-defining cancers (ADC) (defined in Table footnote). We compared cancer risk among individuals with earlier ART initiation (start ART within 6 months of baseline) with those who delayed ART initiation (no ART, or start ART after 6 months). We used marginal structural modeling with inverse probability weighting to account for time-dependent confounding and informative right-censoring (see variables in Table footnote). Primary results emulated an intention-to-treat randomized trial; we also emulated a per-protocol trial, by accounting for ART discontinuation.
Results: A total of 10,434 HIV-infected individuals contributed >44,000 person-years. Participants were 84% men, 46% white, 43% black, with mean age at baseline of 39 years. The most common cancers were: Kaposi sarcoma (n=67) and non-Hodgkin's lymphoma (n=66) among ADC (n=135); lung (n=45) and prostate cancer (n=40) among virus-unrelated NADC (n=198); and Hodgkin lymphoma (n=15), anal (n=13) and liver cancer (n=13) among virus-related NADC (n=45). Earlier ART constituted 27% of contributed person-time and delayed ART constituted 73% of person-time. Earlier ART initiators had higher median CD4 than late initiators (405 vs. 323 cells/µl). In adjusted intention-to-treat analysis (Table), earlier ART resulted in a 47% hazard reduction for any cancer (p=0.002), 42% reduction for virus-unrelated NADC (p=0.032) and 60% reduction for ADC (p=0.007). No reduction was observed for the smallest cancer group of virus-related NADC (p=0.91). Per-protocol results were similar, although somewhat attenuated (Table).
Conclusion: Results from this large North American HIV cohort suggest that the burden of certain cancer groups may be substantially reduced as more HIV providers and patients adopt ART guidelines for immediate initiation.

Table. Earlier versus delayed antiretroviral therapy initiation and risk of cancer

		Unadjusted[1]			Adjusted[1]		
Analysis/Cancer group[2]	n	HR	(95% CI)	P	HR	(95% CI)	P
(a) Intention-to-treat							
Any cancer	368	0.73	(0.57, 0.94)	0.015	0.53	(0.36, 0.79)	0.002
Virus-unrelated NADC	198	0.78	(0.56, 1.09)	0.14	0.58	(0.35, 0.95)	0.032
Virus-related NADC	45	0.92	(0.46, 1.82)	0.81	0.93	(0.31, 2.85)	0.91
ADC	135	0.59	(0.38, 0.93)	0.024	0.40	(0.20, 0.78)	0.007
(b) Per-protocol							
Any cancer	341	0.75	(0.57, 0.98)	0.035	0.62	(0.41, 0.94)	0.024
Virus-unrelated NADC	180	0.75	(0.52, 1.09)	0.14	0.66	(0.38, 1.13)	0.13
Virus-related NADC	42	1.01	(0.49, 2.08)	0.97	1.01	(0.29, 3.54)	0.99
ADC	128	0.65	(0.40, 1.04)	0.007	0.50	(0.25, 0.99)	0.047

ADC, AIDS-defining cancers; CI, confidence interval; HR, hazard ratio; NADC, non-AIDS-defining cancers

[1]From marginal structural modeling based on inverse probability weighting contrasting early versus late (reference) antiretroviral therapy initiation. Adjusted model accounts for weights for antiretroviral therapy initiation, and censoring due to death, loss-to-follow-up, and antiretroviral therapy discontinuation (per-protocol analysis only). Variables considered for weights included age, sex, cohort, entry year, AIDS, CD4 (updated), time since last CD4, race/ethnicity, HIV risk, smoking, hepatitis B and C, and months since entry

[2] Virus-related NADC included anal, liver, HPV-related oral/pharyngeal, penile, vaginal, vulvar cancers and Hodgkin lymphoma. ADC included Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer. Virus-unrelated NADC included all other cancers.

599 TIMING OF CART INITIATION INFLUENCES CANCER RISK AMONG WOMEN LIVING WITH HIV

Kate Salters[1], Monica Ye[2], Neora Pick[3], Angela Kaida[1], Sam Wiseman[4], Shahab Jabbari[2], Mark Hull[2], Jean A. Shoveller[2], Julio S. Montaner[2], Robert S. Hogg[2]
[1]Simon Fraser Univ, Burnaby, British Columbia, Canada, [2]BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada, [3]Oak Tree Clinic, Vancouver, British Columbia, Canada, [4]St. Paul's Hosp, Vancouver, British Columbia, Canada

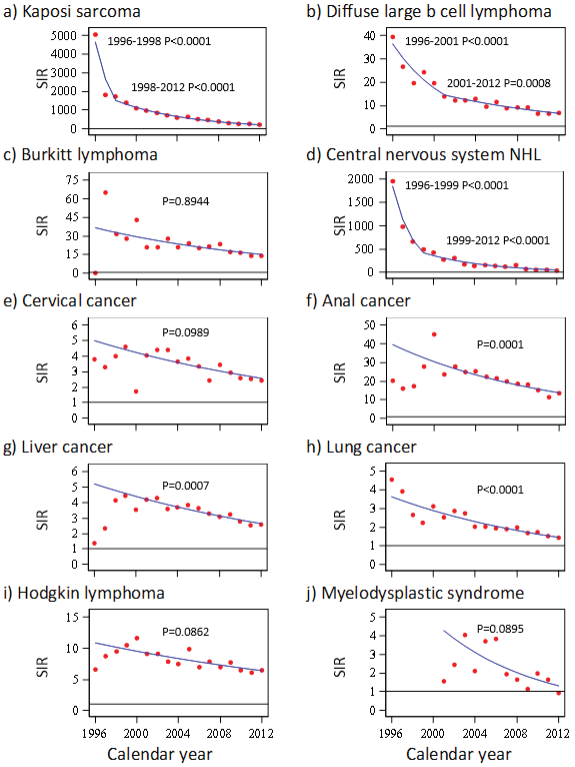
Background: Since the advent of combination antiretroviral therapy (cART), the incidence rate of AIDS-defining malignancies (ADM) in people living with HIV has declined, largely due to improved immune function. However, these trends are not gender-stratified and may obscure changes in cancer risk specific to women living with HIV (WLWH), in particular ADM such as cervical cancer, and non-ADM. We assessed the impact of early cART initiation on the incidence of all-type cancer, ADMs, and non-ADM among WLWH.
Methods: The Comparison of Outcomes and Service Utilization Trends (COAST) study is comprised of a retrospective, administrative database of people living with HIV, both on and off cART, in British Columbia, Canada between January 1996 and March 2013. Our analytic study population was restricted to women with HIV diagnosis and incident cancer cases after HIV diagnosis were identified by ICD-O codes. We conducted a Poisson regression to determine correlates of all-type cancer, ADM, and non-ADM diagnosis, and calculated the cancer incidence rate (per 1,000 person-years (PYs)) by CD4 cell count at cART initiation (≤200, 200-349 and ≥350 cells/mm3). We also calculated the attributable fraction of risk associated with CD4 cell count at cART initiation.
Results: Among 1,660 WLWH, 50 women were diagnosed with cancer after HIV diagnosis (31 ADM and 19 non-ADM). Earlier initiation of cART (≥350 cells/mm3) was associated with lower all-type cancer incidence (Relative Risk (RR): 0.33 [95% CI: 0.16, 0.70]) and non-ADM diagnosis (RR: 0.15 [95%CI: 0.03, 0.64]), but not ADM diagnosis, compared to cART initiation at CD4 of ≤200 cells/mm3. After adjusting for age at HIV diagnosis, the incidence of all-type cancer and non-ADM was 5.55 [95% CI: 3.89, 7.91] cases per 1,000 PY and 2.50 [95% CI: 1.47, 4.27] cases per 1,000 PY, respectively for those with CD4 cell count of ≤200 cells/mm3 compared to those with baseline CD4 of 350 cells/mm3. The attributable fraction of risk for all-type cancer incidence was 63.6% and 82.06% for non-ADM incidence for those with CD4 cell count of ≤200 cells/mm3 at cART initiation.
Conclusion: Early initiation of cART was protective against all-type cancer and non-ADM cancer among WLWH, however no additional benefit was observed for reducing incidence of ADM cancers. In the context of 'Treatment as Prevention', this study suggests there are significant oncological health benefits of early treatment initiation for WLWH.

600 CANCER RISK AMONG HIV-INFECTED PEOPLE IN THE US DURING THE MODERN TREATMENT ERA

Raul Ulises Hernandez-Ramirez[1], Meredith S. Shiels[2], Robert Dubrow[1], Eric A. Engels[2]
[1]Yale Univ, New Haven, CT, USA, [2]NCI, Rockville, MD, USA

Background: HIV-infected people have an elevated risk for many cancers, mainly AIDS-defining cancers (ADC) and virus-related non-ADC (VRNADC), but not for most virus-unrelated non-ADC (VUNADC). Although ADC risk declined substantially after the introduction of effective antiretroviral therapy (ART) in 1996, trends for other cancers have been less clear. We describe recent patterns of cancer risk among a cohort of 448,258 HIV-infected people from 9 US states (1996-2012).
Methods: We assembled this cohort using the HIV/AIDS Cancer Match Study, a population-based linkage of HIV and cancer registries. We calculated standardized incidence ratios (SIRs) to measure risk relative to the general population. For cancers with SIRs that were elevated and changing over time (based on unadjusted Poisson models), we further assessed calendar trends using piecewise models that adjusted for demographic characteristics.
Results: Between 1996-1999 and 2009-2012, the proportion of follow-up time among HIV-infected people 50+ years-old increased from 12% to 29%. Overall cancer risk was elevated (SIR 1.69, 95%CI 1.67-1.72; N=21,294 cases). SIRs were elevated (p<0.001) for ADC (14.0) and VRNADC (5.4) but not for VUNADC as a group (0.9). SIRs were elevated for each individual ADC (Kaposi sarcoma [KS, 498], non-Hodgkin lymphoma [NHL, 11.5], and cervix [3.2]), most VRNADC (oropharynx/tonsil [1.6], anus [19.1], vagina [3.6], vulva [9.4], penis [5.3], and liver [3.2]), and 10 other cancers, e.g., lung [2.0], larynx [2.1], scrotum [6.8], conjunctiva [5.6], and myelodysplastic syndrome [2.0]. Risk was not elevated for other common cancers, e.g., colorectum, breast, and prostate. SIRs for ADC, VRNADC, VUNADC, and some individual cancers decreased significantly across calendar periods. Among 10 cancers selected for detailed assessment, 6 cancers (KS, diffuse large B-cell lymphoma, central nervous system NHL, anus, liver, and lung) showed significantly decreasing SIRs across 1996-2012 (Fig. 1).
Conclusion: Risks of ADC, some VRNADC, and lung cancer have decreased over time but remain elevated in the most recent years. Risk is also elevated for some rare cancers but not for several common cancers. Further research is needed to determine the contributions of changes in demographic characteristics (e.g., aging), cancer risk factors, and improving effectiveness and wider use of ART to these SIR trends. Although SIRs did not increase for any cancer site over time, it is important to continue monitoring cancer risk in HIV-infected people.

Figure 1. Standardized incidence ratios for selected cancers in HIV-infected people, HACM Study 1996-2012



SIR, standardized incidence ratio; NHL, non-Hodgin lymphoma.
Dots depict observed SIRs and lines depict fitted crude trends characterized by Joinpoint. P value from model adjusted for age, sex/HIV-risk group, state, race/ethnicity, and attained follow-up.

601 CANCER INCIDENCE AMONG PERSONS ON MODERN SUPPRESSIVE ART, 2000–2012

Ann N. Burchell[1], Kate Salters[2], Oghenowede Eyawo[3], Joanne Lindsay[4], Jason Chia[5], Michelle Cotterchio[6], Mark Hull[3], Monica Ye[7], Janet M. Raboud[1], Robert S. Hogg[1]
[1]St. Michael's Hosp, Toronto, Ontario, Canada, [2]Simon Fraser Univ, Vancouver, British Columbia, Canada, [3]BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada, [4]St. Michael's Hosp, Toronto, Canada, [5]Cancer Care Ontario, Toronto, Canada, [6]Univ of Toronto, Toronto, Ontario, Canada

Background: International studies suggest that the incidence of some cancers is rising among people with HIV (PLHIV) due to longevity gains from combination antiretroviral therapy (cART) and longer exposures to carcinogens. We sought to quantify excess cancer risk among PLHIV who initiated modern cART in a setting with free and universal access to cART. We hypothesized that AIDS-defining malignancies (ADMs) decreased while non-AIDS-defining malignancies (NADMs) increased over time, most notably for cancers with established infectious causes.

Methods: We conducted a population-based cohort study of adults (≥ 19 years) living with and without HIV via record linkage between the BC Centre for Excellence in HIV/AIDS and Population Data BC in British Columbia (BC), Canada. The comparison sample of HIV-negative individuals was generated from a 10% random sample of the total BC population. For PLHIV, we included only those who initiated cART in 2000 and later. Incident primary cancer diagnoses were ascertained using ICD-O codes from 2000 to 2012 via record linkage with the BC Cancer Agency registry. Cancers were classified as: ADMs (Kaposi sarcoma; non-Hodgkin lymphoma; cervical cancer) vs NADMs (all others); and infectious (Kaposi's sarcoma, non-Hodgkin's lymphoma, cervical, anal, other genital, oropharyngeal, liver, stomach, and Hodgkin's lymphoma) vs non-infectious (all others). Using the 1991 Canadian population as the standard, we report age-adjusted incidence rates (aIR) per 1,000 person-years (PY) with 95% confidence intervals [CI] and incidence rate ratios (aIRR) comparing rates between PLHIV and HIV-negative individuals.

Results: A total of 4,320 PLHIV and 480,127 HIV-negative individuals were followed for 21,077 PY and 4,372,011 PY, respectively. New cancers were diagnosed among 195 HIV-positive and 21,538 HIV-negative residents. Combining all cancers across all years, there was 190% excess cancer among PLHIV (aIRR=2.9 [2.3, 3.4]). However, this varied by calendar period and cancer classification (Table).

Conclusion: Our findings confirm higher risk for ADMs and cancers with infectious causes among people with HIV, even among those who initiated modern suppressive ARV therapy and had few economic barriers to its access. Although rates declined over time, by 2008-12, ADMs remained 10 times more common and infectious cancers were 8 times more common, respectively, than in the general population.

Table. Age-standardized incidence rate (aIR, per 1000PY) of cancers among persons on modern cART and age-adjusted incidence rate ratio (aIRR) compared to an HIV-negative population sample, British Columbia, by calendar period

	2000-03		2004-07		2008-12	
	aIR [CI]	aIRR [CI]	aIR [CI]	aIRR [CI]	aIR [CI]	aIRR [CI]
All cancers	21.1 [11.4, 30.8]	6.6 [3.5, 9.6]	15.3 [10.4, 20.2]	4.7 [3.2, 6.2]	7.4 [5.3, 9.5]	1.8 [1.3, 2.4]
ADMs	18.4 [9.2, 27.7]	77.2 [38.2, 115]	11.2 [6.8, 15.7]	43.1 [26.3, 60.3]	2.9 [1.6, 4.2]	10.0 [5.4, 14.3]
NADMs	2.7 [0.0, 5.8]	0.90 [0.00, 1.9]	4.0 [1.8, 6.2]	1.3 [0.61, 2.0]	4.5 [2.9, 6.2]	1.2 [0.77, 1.7]
Infectious cancers	20.0 [10.4, 29.7]	51.2 [26.6, 76.1]	12.7 [8.2, 17.3]	30.0 [19.0, 40.3]	3.9 [2.5, 5.2]	8.1 [5.2, 10.9]
Non-infectious cancers	1.1 [0.0, 2.33]	0.38 [0.00, 0.83]	2.5 [0.74, 4.3]	0.89 [0.26, 1.5]	3.5 [1.9, 5.1]	1.00 [0.55, 1.4]

602 CANCER BURDEN AMONG HIV+ INDIVIDUALS ON ART IN MALAWI: A RECORD LINKAGE STUDY

Marie-Josephe Horner[1], Steady Chasimpha[2], Adrian Spoerri[3], Julia Bohlius[3], Hannock Tweya[4], Eddie Moffo Phiri[5], Sam Phiri[6], Kennedy Malisita[5], Charles Dzamalala[2], Satish Gopal[7]
[1]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Malawi Cancer Registry, Blantyre, Malawi, [3]Univ of Bern, Bern, Switzerland, [4]Lighthouse Trust Clinic, Lilongwe, Malawi, [5]Queen Elizabeth Hosp ART Clinic, Blantyre, Malawi, [6]Lighthouse Trust, Lilongwe, Malawi, [7]Univ of North Carolina Proj–Malawi, Lilongwe, Malawi

Background: With improved antiretroviral therapy (ART) access in Africa, epidemiologic data are needed to characterize evolving cancer burden in contemporary HIV+ populations. In Malawi, HIV prevalence is 11% and estimated ART coverage 67%. The Malawi HIV-Cancer Match Study aims to characterize incidence and timing of cancer among new ART users.

Methods: We used probabilistic record linkage to link cancer cases from the population-based national cancer registry with electronic medical records supporting ART delivery within the country's two largest HIV cohorts. The study period includes years of overlap between the national cancer registry and HIV cohorts from Lighthouse Trust in Lilongwe (2007-2010) and Queen Elizabeth Hospital in Blantyre (2000-2010). Poisson regression was used to estimate cancer incidence rates (IR) and incidence rate ratios (IRR) among naïve ART initiators, stratified by sex, age at ART start (<30, 30-40, ≥40 years), and CD4 count at ART start (<50, 50-250, ≥250 cells/μL).

Results: Preliminary results from Lighthouse Trust included 15,920 naïve ART initiators, with 57.8% women, mean age 34.4 years (SD 10.8), and median CD4 cell count of 47 cells/μL (IQR 14-173) at start of therapy. Among reasons for ART initiation, 56.6% patients started due to a WHO stage III/IV condition, and 41.1% due to CD4 <250 cells/μL, the Malawi treatment threshold during the study period. Of 3,499 cancers; 82.2% were prevalent at HIV cohort enrollment, and 624 incident cancers occurred subsequently over 53,115 person-years at risk after enrollment. The overall IR was 1199 per 100,000 person-years (95%CI: 1109, 1296). Kaposi sarcoma (KS) was by far the commonest cancer (93.5%), followed by cervical cancer (4.1%). Non-AIDS defining cancers represent an emerging burden (Figure). The overall rate of cancer was higher among patients with CD4 ≥250 compared to <50 cells/μL (IRR 19.6, 95%CI 15.5, 24.7), but did not significantly differ by sex or age.

Conclusion: Despite likely underascertainment, cancer burden remains high among ART users in Malawi, and is a common reason for entry into HIV care. Paradoxically, we found increased cancer risk among patients with higher CD4, perhaps due to reductions in competing risks. This suggests increasing cancer burden as earlier application of ART continues in Malawi and HIV+ populations age. Integrated KS and cervical cancer management within ART programs remains a critical component of HIV care in Malawi in the current era.

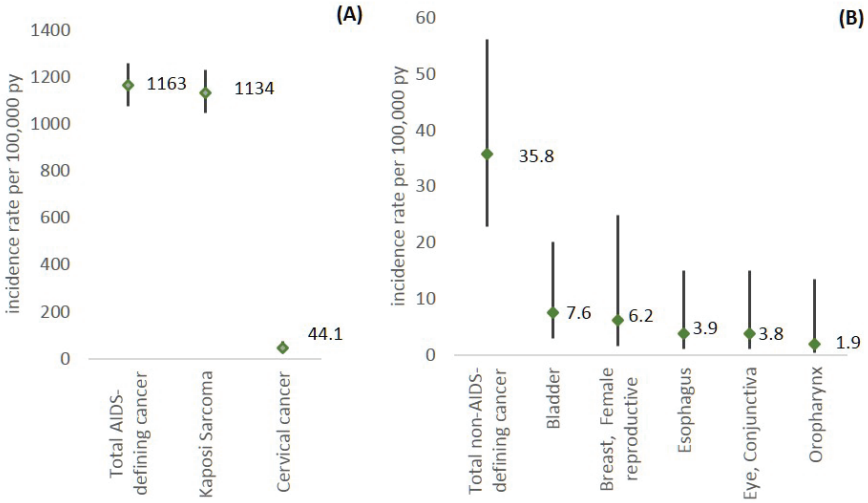


Figure. Cancer-specific incidence rates (95%CI) per 100,000 person-years, by AIDS-defining (A) and non-AIDS defining (B) cancer category. (Note: Non-Hodgkin lymphoma not reported in (A); liver and Hodgkin lymphoma not reported in (B) due to sparse data)

603 LYMPHOMA IN HIV-2–INFECTED PATIENTS IN CART ERA: A 15-PATIENT SINGLE-CENTER SERIES

Anne-Marie Ronchetti[1], Sophie Matheron[2], Lionel Galicier[1], Florence Damond[2], Nadia Mahjoub[1], Amel Besseghir[3], Veronique Meignin[1], Francois Simon[1], Eric Oksenhendler[1], **Laurence Gerard**[1]
[1]Saint Louis Hosp, Paris, France, [2]Bichat-Claude Bernard Hosp, Paris, [3]INSERM, Bordeaux, France

Background: In France HIV-2 infection represents 1.6% of all HIV infections. Despite difference in pathogeniciy and disease progression between HIV-2 and HIV-1 infection, similar patterns of opportunistic complications are reported at similar CD4 level. However, although lymphoma occurs in 4 to 5% of HIV-1 patients (pts) and is a major cause of mortality, this complication has been rarely reported in HIV-2-infected pts.
Methods: Patients were recruited from an ongoing prospective single-center cohort of HIV-lymphoma. Characteristic of HIV-2 pts were compared with HIV-1 pts included in the cohort >1996. Prevalence and incidence of HIV-2-lymphoma were evaluated from a national prospective multicentric French cohort of HIV-2 patients, including 1068 pts (ANRS-C05).
Results: Among the 949 pts included in the HIV-lymphoma cohort, 15 were HIV-2-infected (1.6%), close to the 2% prevalence of HIV-2 infection in our institution (60/3000). In the ANRS C05 cohort, the prevalence of lymphoma was 1.7% and the incidence 0.9/1000 PY. Compared to HIV-1 pts, HIV-2 pts were older and more pts were originated from West Africa (Table). At the time of lymphoma diagnosis, median CD4 cell count was similar in both groups, but more HIV-2 pts had an undetectable viral load. Clinical presentation of lymphoma was aggressive in both groups. Histologic subtype was HL in 18% of HIV-2 and 13% of HIV-1 pts. Among NHL, diffuse large B-cell lymphoma and Burkitt lymphoma were the most frequent histologic subtype in both groups. All but one HIV-2 pt received intent-to-treat chemotherapy, adapted to histologic subtype. Concomitant cART was maintained or introduced in all pts. Complete remission was achieved in 60% of HIV-2 and 73% of HIV-1 pts. The median overall survival (OS) was lower in HIV-2 pts (16 mths) compared to HIV-1 pts (12 yrs). The cause of death in HIV-2 pts was lymphoma (6) and treatment toxicity (4), no pt died from AIDS.
Conclusion: This is the first series of lymphoma in HIV-2 pts. The incidence was close to the incidence of HIV-1-lymphoma in France (0.8/1000 for NHL and 1.2/1000 PY for HL). HIV-2 pts developed lymphoma at the same CD4 level than HIV-1 pts, but a higher proportion of pts had controled HIV infection. Despite some differences in histological subtypes, clinical presentation of lymphoma was close to HIV-1. However, although all pts received adapted chemotherapy and concomitant cART, HIV-2-lymphoma displays an unexpected poor survival, with median OS of 16 mths.

Characteristics of pts at the time of lymphoma diagnosis	HIV-2 (n=15)	HIV-1 (n=934)
Epidemiologic		
Female, %	33	15
Age, median yrs	51	45
Originated from West Africa	86	2
HIV		
Duration of infection, median yrs	6.6	6.5
History of AIDS, %	20	35
CD4 cell count, median x10^6/L	209	244
Undetectable HIV RNA, %	67	42
On cART, %	53	66
Lymphoma		
Stage III/IV, %	73	77
Performans status > 2, %	53	38
EBV-associated tumor, %	25	30
HHV-8-associated tumor, %	0	16

604 EPSTEIN-BARR VIRUS DNA LOAD: A POSSIBLE PREDICTOR OF AIDS-RELATED LYMPHOMA

Simone H. Hijlkema, Jeroen J. van Kampen, David van de Vijver, Ineke van der Ende
Erasmus Univ Med Cntr, Rotterdam, Netherlands

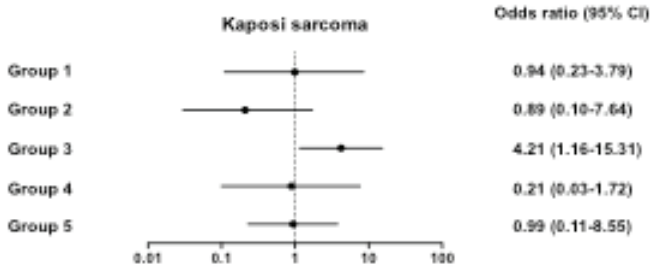
Background: After the introduction of combined antiretroviral therapy, lymphoma remains the main cause of AIDS-related death in HIV-infected adults. AIDS-related lymphoma is associated with Epstein-Barr virus (EBV). Patients with high EBV viral loads seem more at risk for developing AIDS-related lymphoma. The aim of this study was to investigate the relationship between the level of serum/plasma EBV DNA load and non-Hodgkin lymphoma.
Methods: We included HIV-positive patients with stored EBV DNA serum and plasma samples between January 2004 and October 2015 in an academic hospital in the Netherlands. We compared EBV DNA load between patients with and without non-Hodgkin lymphoma. To improve power of the study we randomly selected four controls for each case. EBV DNA was measured using a quantitative real-time Taqman PCR. The EBV DNA load was 10 log transformed.
Results: We identified 157 patients of whom 31 were diagnosed with non-Hodgkin lymphoma. Patients had a median age of 43, were predominantly male (80%) and the majority of the patients was born in Europe (56%). Patients had a median CD4 cell count of 100 cells/µl (interquartile range: 30; 265) and nadir CD4 cell count of 60cells/µl (interquartile range: 20; 176. Median HIV RNA load, after exclusion of patients with undetectable viral loads (n=47), was 100000 copies/ml (interquartile range: 7778; 160500). The geometric mean of the peak EBV DNA load measured before onset of non-Hodgkin lymphoma was 11614 IU/ml in the lymphoma group versus 242 IU/ml in the control group (P<0.001). There were 3 patients in the lymphoma group and 60 patients in the control group who had a peak EBV DNA load below 50 IU/ml. Patients with an EBV DNA load greater or equal to 50 IU/ml have an increased risk of developing non-Hodgkin lymphoma compared to patients with an EBV DNA load below 50 IU/ml (odds ratio 8.75; 95% confidence interval 2.53; 30.29).
Conclusion: This study showed that patients who developed non-Hodgkin lymphoma had higher EBV DNA loads prior to the disease compared to patients who did not develop non-Hodgkin lymphoma. In addition, patients of whom peak EBV viral loads were greater or equal to 50IU/ml had approximately a nine times increased risk of developing non-Hodgkin lymphoma. High blood EBV DNA load can be a potential predictive biomarker to detect non-Hodgkin lymphomas in an earlier stage.

605 THE IMMUNE ACTIVATION PROFILE LINKED TO KAPOSI SARCOMA IN HIV-1–POSITIVE ADULTS

Christina Psomas[1], Mehwish Younas[2], Jacques Reynes[1], Pierre Portales[3], Jean-François Eliaou[3], Pierre Corbeau[2]
[1]Univ Hosp of Montpellier, Montpellier, France, [2]Inst of Human Genetics, Montpellier, France, [3]Univ Hosp of Montpellier, Montpellier, France

Background: Kaposi sarcoma (KS), a vascular neoplasm, still remains a frequent cancer even in efficiently treated persons living with HIV with a satisfactory degree of immune restoration. Human herpes virus 8 is necessary, but not sufficient to cause KS. In in vitro and in animal models, inflammatory cytokines have been shown to induce KS lesion

formation. Moreover, the risk of developing KS is increased in the context of immune reconstitution inflammatory syndrome. These observations suggest that KS might be fueled by immune activation. To test this hypothesis we studied whether patients previously diagnosed for KS present with a particular immune activation phenotype.
Methods: The ACTIVIH study is a cross sectional study in which we analyzed 68 markers of immune, endothelial, and coagulation activation in 120 virologic responders, and have recently identified 5 different profiles of immune activation. We looked in the medical history of these patients for a relationship between past history of KS and immunological profile, using logistic regressions.
Results: The frequency of past history of KS (n = 11) was significantly elevated in one patient group (profile 3), as compared with the other groups (p = 0.03, Figure 1). Of note, the frequency of past history of other cancers was not increased in the same group of patients (odds ratio 0.52 [95% CI 0.11-2.46], p = 0.52). Patients who had developed KS, as compared with those who had not, were characterized by a low percentage of naïve (CD45RA+CD27+) CD4+ T cells (29.3±16.0 versus 40.3±16.5, p = 0.04), a tendency to a high percentage of CD4+ T cells expressing the inhibitory receptor PD-1 (32.8±14.5 versus 40.1±9.5, p = 0.06), and a high percentage of senescent (CD57+) NK cells (42.9±17.6 versus 57.6±15.0, p < 0.01).
Conclusion: Our data are compatible with the hypothesis that a particular type of chronic immune activation paves the way for KS. The marks of CD4+ T cell activation and NK senescence we unveiled in KS patients are consistent with (i) the previous report that the supernatants of activated T cells transform normal endothelial cells into KS cells, and (ii) the link between KS and immunosenescence. If our data are confirmed by a longitudinal study, the immune activation profiling of HIV patients, might help to identify those at risk to develop KS. Furthermore, deciphering which immune activation pathway(s) fuels the transformation of endothelial cells into KS cells might identify future therapeutic targets.



606 TREATMENT AND OUTCOMES OF NON–SMALL-CELL LUNG CANCER IN LATER ART-ERA HIV INFECTION

Keith M. Sigel[1], Kristina Crothers[2], Sheldon T. Brown[3], Cynthia L. Gibert[4], Matthew B. Goetz[5], Roger Bedimo[6], Roxanne Wadia[7], Maria Rodriguez-Barradas[8], Fatma Shebl[9], Lesley Park[10]
[1]Icahn Sch of Med at Mt Sinai, New York, NY, USA, [2]Univ of Washington, Seattle, WA, USA, [3]James J. Peters VA Med Cntr, Bronx, NY, USA, [4]Washington, DC, VA Med Cntr, Washington, DC, USA, [5]VA Greater Los Angeles Hlth Care System, Los Angeles, CA, USA, [6]VA North Texas Hlth Care Cntr, Dallas, TX, USA, [7]VA Connecticut Hlthcare System, West Haven, CT, USA, [8]Baylor Coll of Med, Houston, TX, USA, [9]Yale Univ, New Haven, CT, USA, [10]Stanford Med, Stanford, CA, USA

Background: Studies evaluating lung cancer outcomes in HIV+ persons have found worse survival which has been attributed to treatment disparities or more aggressive cancer behavior. We used population-based data to compare treatment trends and outcomes among HIV-infected (HIV+) and uninfected Veterans diagnosed with non-small cell lung cancer (NSCLC).
Methods: We linked the Veterans Aging Cohort Study with national Veterans Affairs cancer registry data to identify 1,456 (581 HIV+) cases of incident NSCLC diagnosed during 2002-2015. We collected data on the first course of lung cancer treatment including surgical approach, use of radiotherapy and chemotherapy. We used Kaplan-Meier methods to compare median overall survival (OS) by HIV status and Cox regression to evaluate predictors of OS in HIV+ NSCLC patients. We also restricted these analyses to lung cancer patients diagnosed in the later antiretroviral (ART)-era (2009-2015; n=344 HIV+).
Results: HIV+ NSCLC patients were younger than uninfected NSCLC patients (Table 1; p=0.01). Stage and histologic subtype did not differ by HIV status. HIV+ patients were equally likely to receive surgery (and did not differ in surgical approach) and radiotherapy as uninfected patients, but were less likely to be treated with chemotherapy (35% vs 45%; p<0.001), a difference that persisted when limiting to the later time period. Median OS was significantly worse for HIV+ patients than for uninfected patients (10 months vs 13 months; p<0.001) but in the later ART-era (2009-2015) there was no difference in OS (p=0.2). In the overall cohort, there was no difference in survival between stage I HIV+ and uninfected patients; and for early stage patients treated with surgical resection there was also no difference in cancer recurrence rates. Among HIV+ NSCLC patients who received stage-appropriate treatment older age, cancer stage, poorer viral suppression (>500 copies/ml) at cancer diagnosis, low CD4 (<200 cells/mm^3) and low CD4/CD8 ratio (<0.7) were all independently associated with worse survival (all p<0.05). Except for poorer viral suppression, these factors were all associated with worse OS when restricting the cohort to cancer cases diagnosed in the later ART-era.
Conclusion: In the late ART-era, we found that HIV+ NSCLC patients experienced cancer treatment disparities, but had outcomes that were similar compared to uninfected patients, and that several HIV biomarkers were independently predictive of outcomes in NSCLC patients.

607 ETIOLOGY OF HEPATOCELLULAR CARCINOMA IN WEST AFRICA: THE HIV CONTRIBUTION

Antoine Jaquet[1], Boris Tchounga[2], Aristophane tanon[2], Aklesso Bagny[3], Didier K. Ekouevi[4], Hamar A. Traore[5], Annie J. Sasco[1], Moussa Maiga[6], François Dabis[1], for the IeDEA West Africa Collaboration
[1]Univ de Bordeaux, Bordeaux, France, [2]CHU de Treichville, Abidjan, Cote d'Ivoire, [3]CHU Campus, Lomé, Togo, [4]Univ de Lomé, Lomé, Togo, [5]CHU du Point G, Bamako, Mali, [6]Hôpital Gabriel Touré, Bamako, Mali

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer in West Africa where Hepatitis B Virus (HBV) is endemic. However, limited information is available on other risk factors such as alcohol use, hepatitis C virus (HCV) and HIV infections.
Methods: A case-control study was conducted in referral hospitals of Abidjan (Cote d'Ivoire), Bamako (Mali) and Lome (Togo). Cases were matched with two controls on age, gender and participating site. All participants underwent a standardized abdominal ultrasound and a serum α-fetoprotein measurement. The diagnosis of HCC was based on the combination of one or more space-occupying ultrasound lesions suggestive of an HCC and a serum α-fetoprotein level ≥400 ng/ml. HIV, HBV and HCV serology tests were systematically performed. Alcohol use was assessed using the AUDIT questionnaire (a score >7 defined hazardous drinking). A conditional logistic regression model estimated the associations by the Odds Ratio (OR) with its 95% confidence interval (CI).
Results: A total of 160 HCC cases (Abidjan n=44, Lome n=40, Bamako n=76) and 320 controls were recruited. They were predominantly male (80.0%) and had a median age of 47 years (IQR 38 – 57). The prevalence figures of HBV, HCV and HIV infection were 9.7%, 4.7% and 2.8%, respectively in the control group; hazardous drinking was reported by 5% of them. In multivariate analysis, HBV, HCV and hazardous drinking were independently associated with HCC (table). Combining the effect of HBV and HIV infection in an additional model; HBV/HIV co-infected patients had an OR of 82.0 (CI 6.2-1 075.0) and HBV mono-infected had an OR of 59.9 (CI 19.6-182.6) (Ref: HBV/HIV-negative). Combining the effect of

HBV infection and alcohol, HBV-infected hazardous drinkers had an OR of 149.8 (CI 13.5-1 667.0) and HBV mono-infected an OR of 57.4 (CI 18.8-175.3) (ref: HBV-negative with no hazardous drinking).

Conclusion: No independent association was reported between HCC and HIV itself. However, HBV/HIV co-infected patients seemed to have a higher risk of HCC compared to HBV-infected patients supporting the deleterious effect of HIV on HBV infection that might facilitate the occurrence of HCC. Aside the independent association of alcohol use, HBV and HCV infections with HCC, a synergistic effect between alcohol use and HBV infection was identified. Timely preventive measures against HBV infection and hazardous drinking in West Africa might prevent a significant number of HCC, especially in those diagnosed with HIV.

Table. Factors associated with hepatocellular carcinoma in Abidjan, Bamako and Lome, the IeDEA West Africa collaboration, 2014-2015.

	Controls (n=320)	Cases (n=160)	Unadjusted analysis		Adjusted analysis†	
	n (%)	n (%)	OR (95% CI)	p	OR (95% CI)	p
Formal education				$<10^{-3}$		0.21
No	90 (28.1)	66 (41.2)	1		1	
Primary school	56 (17.5)	33 (20.6)	0.7 (0.4 – 1.2)		0.6 (0.2 – 1.6)	
Secondary and over	174 (54.4)	61 (38.2)	0.3 (0.2 – 0.6)		0.4 (0.2 – 1.1)	
Alcohol use*				$<10^{-4}$		0.04
No/moderate use	304 (95.0)	134 (83.7)	1		1	
Hazardous drinking	16 (5.0)	26 (16.3)	3.9 (2.0 – 7.8)		4.5 (1.1 – 18.5)	
HIV antibody test				0.37		0.89
Negative	311 (97.2)	153 (95.6)	1		1	
Positive	9 (2.8)	7 (4.4)	1.6 (0.6 – 4.5)		1.2 (0.1 – 10.4)	
HBs antigen test				$<10^{-4}$		$<10^{-4}$
Negative	289 (90.3)	48 (30.0)	1		1	
Positive	31 (9.7)	112 (70.0)	31.5 (13.8 – 71.8)		62.5 (20.5 – 190.7)	
HCV antibody test				$<10^{-4}$		$<10^{-4}$
Negative	305 (95.3)	116 (72.5)	1		1	
Positive	15(4.7)	44 (27.5)	12.5 (5.3 – 29.5)		35.9 (10.0 – 130.3)	

* Declared alcohol use during the past 12 months and scored using the AUDIT questionnaire (a score >7 defined hazardous drinking)
† Conditional logistic regression matched on age (+/- 2years), gender and participating referral hospital
Abbreviations: HCV Hepatitis C virus, OR Odd Ratio, CI Confidence Interval

608 THE EFFECT OF ART ON INFLAMMATION, COAGULATION, AND VASCULAR INJURY IN START

Jason Baker, Shweta Sharma, Birgit Grund, for the INSIGHT START (Strategic Timing of AntiRetroviral Treatment) Study Group
Univ of Minnesota, Minneapolis, MN, USA

Background: The INSIGHT START trial demonstrated that immediate (at CD4 >500cells/μL) versus deferred (to CD4 <350cells/μL or AIDS) antiretroviral therapy (ART) initiation led to reductions in AIDS and serious non-AIDS (SNA) events. ART decreases inflammation and coagulation, and we have previously demonstrated that IL-6 and D-dimer strongly predict risk for SNA events. We studied the effect of ART initiation on 7 biomarkers of inflammation, coagulation and vascular injury in START.

Methods: Biomarker levels (Table) were measured from stored plasma at baseline and month 8. Mean changes in biomarker levels from baseline to month 8 were compared between the immediate and deferred ART arms by intent-to-treat using ANCOVA models, adjusted for baseline levels. Predictors of biomarker changes in the immediate ART group (age, gender, race, CD4 cell counts, CD4:CD8 ratio, log10 HIV RNA, BMI, smoking) were evaluated in multiple regression models, and biomarker changes within the 1st and 4th quartiles were presented for 2 factors that were consistently associated with biomarker changes. In all models, biomarkers were analyzed on the log2 scale; mean changes were back-transformed and presented as percent change on the original scale.

Results: Of the 4,685 participants in START, 4487 (96%) consented to store plasma and 3890 participants (85%) had baseline and month 8 biomarkers. At month 8, 96% in the immediate and 9% in the deferred groups were using ART. Levels of IL-6, D-dimer, amyloid A, sICAM and sVCAM declined in the immediate group; differences between immediate and deferred ART at month 8 ranged from 12%-21% (each $p<0.001$; Table). Higher baseline viral load and lower CD4:CD8 ratios were significantly associated with steeper biomarker reductions following ART initiation for 6 and 5 of the 7 biomarkers, respectively (Table). To illustrate, the reduction in IL-6 for those in the lowest (<0.48) versus highest (>0.89) quartile of the CD4:CD8 ratio was 12.7% versus 2.7%, respectively ($p<0.001$ for association of CD4:CD8 with IL-6). No other clinical factors were consistent predictors of biomarker change in multivariate models.

Conclusion: In START, early ART initiation reduced biomarker levels of inflammation, coagulation and vascular injury. Those with higher HIV viral load and lower CD4:CD8 ratio tend to experience greater reductions in systemic inflammation and coagulation following ART initiation.

Table: The Effect of ART on Biomarker Levels in START (n=3890): % change from baseline to month 8, and, for immediate ART group, % change in the 1st and 4th quartiles of baseline CD4:CD8 ratio and HIV RNA.

Biomarkers	Baseline Median	% Change in biomarkers from baseline to Month 8								
		Imm.	Def.	Difference (Imm-Def) (p-value)	Immediate ART group, % change in 1st and 4th quartiles					
					CD4:CD8 Ratio			HIV RNA (cp/mL)		
					q1 (<0.48)	q4 (>0.89)	p-value*	q1 (<3K)	q4 (>40K)	p-value*
IL-6 (pg/mL)	1.39	-9.4	2.1	**-11.6** (<0.001)	-12.7	-2.7	**0.001**	-5.5	-19.3	**0.001**
D-dimer (µg/mL)	0.32	-12.6	6.5	**-19.1** (<0.001)	-18.3	-9.2	**0.02**	-3.7	-21.9	**<0.001**
hsCRP (mcg/mL)	1.73	6.4	8.9	-2.5 (0.51)	-5.8	13.3	**0.03**	15.1	-11.5	**0.03**
IL-27 (pg/mL)	243	-5.4	-1.6	-3.8 (0.11)	-10.6	-2.7	0.10	-1.0	-10.9	**0.03**
Serum Amyloid A (mg/L)	4.51	-12.4	2.3	**-14.6** (<0.001)	-17.5	-7.5	0.08	-8.5	-23.0	0.11
sICAM-1 (µg/mL)	548	-11.8	0.1	**-11.9** (<0.001)	-14.7	-8.4	**<0.001**	-5.6	-18.4	**<0.001**
sVCAM-1 (µg/mL)	727	-21.9	-0.5	**-21.4** (<0.001)	-26.1	-17.3	**<0.001**	-13.7	-29.3	**<0.001**

* p-values are for associations of the CD4:CD8 ratio and $\log_{10}$ HIV RNA (continuous variables) with changes in biomarkers in the immediate ART group, estimated in multiple regression models that also included age, gender, race, CD4 cell count, BMI, smoking.
hsCRP = high sensitivity C-reactive protein; IL = interleukin; sICAM = soluble intercellular adhesion molecule, sVCAM = soluble vascular cellular adhesion molecule.

609 PROTHROMBOTIC EFFECTS OF ABACAVIR IN AN IN VIVO MODEL

Isabel Andujar[1], Victor Collado-Diaz[2], Samuel Orden[1], Ainhoa Sanchez-Lopez[2], Maria Angeles Martinez-Cuesta[2], **Angeles Alvarez**[2], Juan V. Esplugues[2]
[1]FISABIO, Valencia, Spain, [2]Univ of Valencia, Valencia, Spain

Background: The controversy surrounding the association between Abacavir (ABC) and cardiovascular disease is fuelled by the lack of a convincing mechanism of action. ABC shares structural similarities with endogenous purines; i.e. ATP or ADP, signalling molecules capable of triggering prothrombotic/proinflammatory programmes. We have previously reported that ABC induces platelet-leukocyte-endothelial cell interactions through a mechanism involving interference with the purinergic system, specifically ATP-P2X7 receptors. The present study expands these concepts and assesses whether clinically relevant concentrations of ABC generate a pro-thrombotic environment in a validated animal model of thrombosis.

Methods: Male wild-type C57BL/6 and P2X7 homozygous knock-out mice (B6.129P2-P2rx7tm1Gab/J) were pretreated with ABC or TDF (2.5–7.5 µg/mL and 0.3 µg/mL intrascrotally 4h), or rofecoxib (0.1 mg/kg, i.p. 2h). In some cases mice were pre-treated (30 min) with ATP-P2X7 (A804598) or ATP-P2X2/3 (A317491) receptor antagonists. Arteries of the cremaster muscle were visualized with an intravascular microscope and their blood flow analyzed with a Doppler velocimeter. The endothelium-damaging agent Ferric chloride was superfused at a concentration (25 mM), which does not itself modify blood flow, but predisposes arterioles to thrombosis when additional vascular deleterious agents are present. Images were recorded until blood flow ceased, or for 8 min if no vessel occlusion occurred.

Results: ABC treatment did not affect blood flow in the absence of ferric chloride. However, treatment with ABC significantly accelerated vessel occlusion in a dose-dependent manner after superfusion of ferric chloride (Figure 1). Selective blockade of P2X7 receptors, but not of other purinergic receptors, reverted the pro-thrombotic effect of ABC. The pro-thrombotic effect of ABC was non-existent in P2rx7 KO mice. TDF had no effect, whereas inhibition of COX-2 with rofecoxib induced a level of thrombosis similar to that produced by the highest dose of ABC evaluated.

Conclusion: Exposure to ABC dose-dependently increases thrombus formation in vivo through interference with ATP-P2X7 receptors. These results suggest that ABC induces a pro-inflammatory vascular environment.

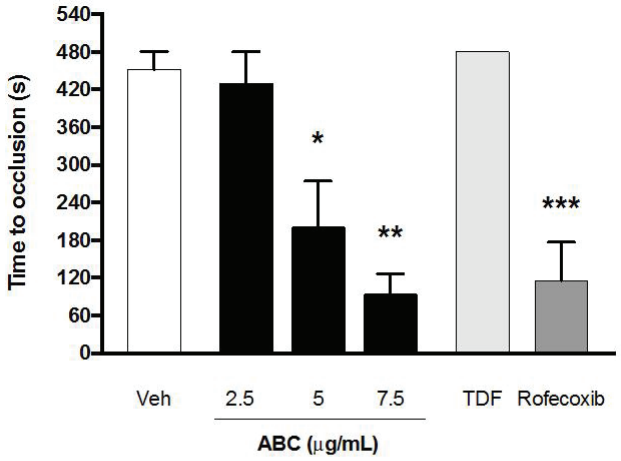


Figure 1. Thrombus formation induced by Abacavir in cremasteric arterioles of wild-type mice. Animals were treated (intrascrotally) with saline (vehicle, 4 h), abacavir (2.5 - 7.5 µg/mL, ABC, 4 h), tenofovir (0.3 µg/mL, TDF, 4 h), rofecoxib (0.1 mg/kg, 2 h, positive control). After mice surgery, a ferric chloride solution was superfused in the cremaster and time to occlusion of the arterioles was determined. Results are mean ± SEM, n≥5. *p<0.05 or **p<0.01 vs. corresponding value in vehicle-treated group (ANOVA followed by Newman-Keuls test).

610 A SWITCH TO RALTEGRAVIR DOES NOT LOWER PLATELET REACTIVITY IN HIV-INFECTED ADULTS

Wouter A. van der Heijden, Marjolein Bosch, Reinout van Crevel, Monique Keuter, André van der Ven, Quirijn de Mast
Radboud Univ Med Cntr, Nijmegen, Netherlands

Background: HIV infection is associated with platelet hyperreactivity and increased platelet-monocyte aggregation (PMA), which may contribute to the excess cardiovascular risk. In a cross-sectional study we recently showed that individuals using a raltegravir-based regimen have reduced platelet reactivity and PMA compared to other antiretroviral regimens. The aim of this study was to investigate whether switching a non-nucleoside reverse transcriptase inhibitor (NNRTI)- or protease inhibitor (PI)-based regimen to a raltegravir-based regimen reduces platelet reactivity and/or PMA.

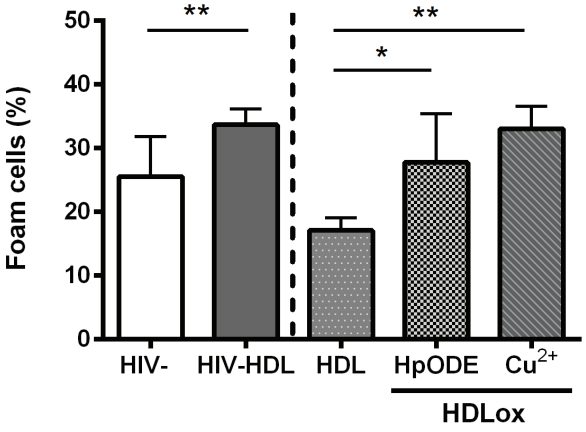
Methods: This study was designed as an investigator initiated, single-center, prospective randomized, open-label, blinded endpoint (PROBE) trial. We enrolled 40 adult HIV-infected individuals with undetectable (<40 copies/mL) viral load receiving a standard backbone of two NRTI's (either TDF/FTC or ABC/3TC) with either a NNRTI (EFV or RPV) or a boosted PI (DRV/r, ATZ/r or LPV/r). Participants were randomized (1:1) to continue the same ART regimen or to switch to raltegravir during 3 months. The primary outcome was the change (Δ) in platelet reactivity at 3 months. This was determined using a flow-cytometry based assay by measuring platelet expression of the platelet granule protein P-selectin

and the binding of fibrinogen to the activated αIIbβ3 integrin upon ex vivo stimulation of whole blood with three different platelet agonists (ADP, collagen-related-peptide and thrombin receptor activator peptide). Plasma markers of platelet activation (platelet factor-4, beta-thromboglobulin and P-selectin) and inflammation (high-sensitive C-reactive protein (hs-CRP) were also measured. Analysis was based on intention-to-treat using an unpaired t-test or Mann-Whitney test. Clinicaltrials.gov identifier: NCT02383355.
Results: The groups were well matched. Overall, 95% of participants were male with a median age of 48yrs, and a median CD4 count of 660 cells/μL. No Grade III-IV adverse events were recorded. At 3 months, the Δ platelet reactivity, to all three platelet agonists, were similar between the two groups. Neither PMA formation nor plasma levels of platelet factor-4, beta-thromboglobulin and soluble P-selectin were different between groups. In addition, plasma hsCRP did not differ between treatments at 3 months.
Conclusion: A switch to a raltegravir-based regimen in virally suppressed HIV-infected individuals reduces neither platelet reactivity nor platelet-monocyte aggregation.

611 DYSFUNCTIONAL HDL FROM HIV+ INDIVIDUALS PROMOTES FOAM-CELL FORMATION IN VITRO

Thomas A. Angelovich[1], Anna Hearps[1], Margaret D. Shi[1], Theodoros Kelesidis[2], Anthony Jaworowski[1]
[1]Burnet Inst, Melbourne, Australia, [2]Univ of California Los Angeles, Los Angeles, CA, USA

Background: Atherosclerotic cardiovascular disease (ACVD) is among the leading causes of non-AIDS-related comorbidity and mortality in HIV+ individuals on potent antiretroviral therapy (ART). High-density lipoprotein (HDL), an acceptor of lipid exported from monocytes/macrophage, is functionally altered in HIV+ individuals, possibly due to increased oxidation, which may lead to impaired cholesterol accepting abilities. However, the effect of HIV-1-related altered HDL function on the generation of lipid-laden macrophage associated with atherosclerotic disease progression known as foam cells is unclear.
Methods: The function of HDLs isolated from the plasma of HIV- (n=5) or HIV+ (n=10) individuals (HIV-HDL) was measured by two established independent cell free assays: assay A (measured lipid peroxidation and antioxidant function) and assay B (measured rate of apoA-I exchange). The foam cell forming ability of native HDL, HIV-HDL or commercial HDL oxidized in vitro (Cu2+ or 13(3)-HPODE; HDLox) was measured using an established in vitro model of monocyte transendothelial migration and foam cell formation where monocytes exposed to HDLs migrate across a TNF-activated endothelial monolayer into a collagen matrix. Following migration and culture, monocyte-derived foam cells were counted by microscopy.
Results: HIV+ individuals had a median age of 42 (range 35-46 years), median CD4 count 550 cells/mm3, viral load <50 copies/ml and were all on efavirenz/emtricitabine/tenofovir DF. All participants had low risk for CVD and no history of dyslipidemia or statin use. HIV-HDL had reduced antioxidant function and rate of apoA-I exchange, indicative of dysfunction, than native HDL from HIV- individuals (P<0.05 for both assays). Dysfunctional HIV-HDL promoted monocyte-derived foam cell formation more than HDLs isolated from matched HIV- individuals (33.0% vs 26.2% foam cells, respectively; P<0.01). In vitro HDLox gave similar results compared to unoxidised HDL (P<0.05 for both).
Conclusion: Dysfunctional HDLs isolated from HIV+ individuals on potent ART promote monocyte-derived foam cell formation in an in vitro model of atherosclerosis. Foam cell formation was enhanced when monocytes were exposed to artificially oxidised HDL, implicating a role for oxidised HDL in enhanced foam cell formation in HIV+ individuals. These data provide important mechanistic insight into the role of dysfunctional HDLs as possible drivers of increased atherosclerotic risk in this population.



612 HDL CHOLESTEROL EFFLUX CAPACITY IS INVERSELY RELATED TO CLASSICAL MONOCYTE NUMBER

Santhosh R. Mannem[1], **Dominic Chow**[1], Martin Playford Playford[2], Beau K. Nakamoto[1], Kalpana J. Kallianpur[1], Mary Margaret Byron[1], Brooks I. Mitchell[1], Cecilia Shikuma[1], Nehal N. Mehta[2]
[1]Univ of Hawaii, Honolulu, HI, USA, [2]Natl Heart, Lung and Blood Inst, Bethesda, MD, USA

Background: HIV represents a chronic inflammatory state with increased incidence of cardiovascular disease (CVD). Circulating monocytes are thought to play a role in CVD. High-density lipoprotein (HDL) cholesterol efflux capacity provides dynamic function of HDL and several studies showed that HDL cholesterol efflux capacity is correlated strongly with cardiovascular risk. Reverse HDL cholesterol transport from macrophages/monocytes may be inhibited by HIV which may contribute to increased CVD. Our current study evaluates the relationship between HDL cholesterol efflux capacity and monocyte subsets.
Methods: Longitudinal analysis performed on HIV participants on stable antiretroviral therapy > 3 months enrolled in the Hawaii Aging with HIV Cardiovascular Study. Baseline HDL cholesterol efflux capacity and monocyte subsets were measured and defined by differential expression of CD14 and CD16 determined monocyte subsets: classical (CD14++CD16-), intermediate (CD14++CD16+) and non-classical (CD14+/low CD16++) respectively. Simple and multivariable analyses to evaluate the relationship between HDL cholesterol efflux capacity and monocyte subsets were performed.
Results: Our study included 116 patients with median age of 50 years of which 86% are male with median CD4 count of 490 cells/mm3, and a majority with undetectable viral load (86%). The HDL cholesterol efflux capacity was negatively associated with classical monocyte number (beta -0.21, P=0.02) even after adjusting for traditional cardiovascular risk factors, demographics, HIV viral load and body mass index. There were no significant associations between HDL cholesterol efflux capacity and other monocyte subsets.
Conclusion: HDL cholesterol efflux capacity is inversely associated with classical monocyte number and may suggest an involvement in pro-inflammation and cardiovascular disease in HIV patients. Our findings might suggest that increasing or restoring HDL cholesterol functionality could be an attractive means to modulate monocyte subset distribution and influence monocyte subset counts in CVD.

613 EFFECT OF ART INITIATION ON MONOCYTE AND HDL FUNCTION

Jane A. O'Halloran[1], Theodoros Kelesidis[2], Luke O'Brien[1], Therese Herlihy[3], Louise Rainford[3], John Lambert[4], Gerard Sheehan[4], Niall Mahon[4], Leo Lawler[4], Patrick W. Mallon[3]
[1]Univ Coll Dublin, Dublin, Ireland, [2]Univ of California Los Angeles, Los Angeles, CA, USA, [3]Mater Misericordiae Univ Hosp, Dublin, Ireland

Background: Dysfunction of monocytes (MNC) and HDL despite potent ART may be a major contributor to cardiovascular disease (CVD) risk in HIV infection. HIV+ patients have HDL with reduced antioxidant function (high HDL redox activity; HRA) and impairment in ABCA1-mediated MNC cholesterol efflux (MCE). Limited data exists on the effect of ART initiation on HDL and MNC function. We examined the effect of ART initiation on MCE and HRA.
Methods: In a prospective cohort study we compared MCE and HRA in HIV+ subjects with low overall CVD risk pre and post ART initiation to HIV- controls matched for age, gender, ethnicity, smoking and viral hepatitis status. Subjects' monocytes were isolated from fasting whole blood using anti-CD14+ conjugated magnetic beads and loaded *in vitro* with human LDL cholesterol from health donors (HD). MNC intracellular (MIC) and extracellular (EC) cholesterol were then measured by fluorescence at fixed time points over 24 hours in the presence and absence of apoA1 from HD (ABCA1-mediated efflux). Higher EC:MIC ratios indicate greater MCE. HDL function was assessed using a HRA assay normalized to HDL amount and a pooled control from HD (nHRA, no units). Data are median [IQR] and non-parametric analyses used.
Results: One hundred subjects, 50 HIV+ (age 35 [29, 41] years, 80% male, 76% white, CD4+T cells 410 (268, 588) cells/mm3, log HIVRNA 4.01 (3.52, 4.78), Framingham 10yr CDV risk 1.8 [0.5, 6]%) and 50 HIV- controls (age 35 [30, 43] years, 78% male, 76% white, CVD risk 1.8 [0.9, 4.9]%) were recruited with repeat assessments on 20 HIV+ subjects 17 (13, 18) months post viral suppression with ART (CD4+T cells 627 (458, 836) cells/mm3). Although the untreated HIV+ group had unexpectedly higher MCE compared to controls (1.27 [1.06, 1.50] versus 1.13 [0.92, 1.35] p=0.05), ART was associated with further increased MCE compared to both untreated HIV+ (1.89 [1.55, 2.4], p<0.0001) and controls (p<0.0001). nHRA was higher in untreated HIV+ compared to controls (1.08 [0.86, 1.34] versus 0.84 [0.74, 0.96]; p<0.0001) and reduced with ART (0.84 [0.76, 0.99]; p<0.0001) to levels similar to controls (p=0.2)
Conclusion: This is the first study to explore the impact of ART on both MNC and HDL function. Untreated HIV is associated with both increased MNC cholesterol efflux and dysfunctional HDL. While ART initiation was associated with improvements in antioxidant HDL function, MNC cholesterol efflux remained increased. The impact of these changes on CVD progression remains to be determined.

614 CHOLESTEROL EFFLUX RESPONDS TO THE IMMUNE STATUS IN PROGRESSION OF HIV INFECTION

Olivia Tort[1], Roque Pastor[1], Felipe Garcia[2], Esteban Martinez[2], Montserrat Plana[2], Tuixent Escribà[1], Montserrat Cofán[1], Emma Fernández[2], Jose M. Gatell[2], **Mireia Arnedo**[1]
[1]IDIBAPS, Barcelona, Spain, [2]Hosp Clinic of Barcelona, Barcelona, Spain

Background: Cholesterol efflux capacity (CEC) is an emerging cell-based assay that successfully predicts cardiovascular events in the general population and could be used as a biomarker of atherosclerosis. Uncontrolled HIV infection is associated with impaired CEC, which can be everted with antiretroviral therapy. The potential influence of different immunological or virological HIV conditions on CEC may help to understand better the pathogenesis of atherosclerosis in HIV-infected patients. With this aim, we compared CEC, lipoprotein levels and immunological and inflammatory markers in HIV-infected patients at different stages of disease progression and HIV-exposed seronegative individuals.
Methods: In this cross-sectional study we assessed a cholesterol efflux capacity (CEC) assay to evaluate high density lipoprotein (HDL) functionality of ApoB-depleted plasma. CEC, plasma lipids, cholesterol, lipoproteins, viral load, inflammatory biomarkers (high-sensitive C-reactive protein (hsCRP) and Lipoprotein(a)), CD4-T and CD8-T cell counts were evaluated in four groups of patients: untreated HIV infected patients (UHIV; n=44), elite controllers (EC; n=8), HIV-exposed seronegative individuals (HESN; n=32) and healthy control individuals (HC; n=14).
Results: Among UHIV, those with CD4<450 presented the significant lowest CEC, HDL-C and ApoAI levels. EC showed similar HDL-C, ApoAI and CEC compared to HC. Among HIV-infected individuals (UHIV and EC), CEC positively correlated with current CD4+ T cell counts (Pearson r=0.58, p<0.0001) and inversely with current plasma HIV-1 RNA levels (Pearson r=-0.58, p<0.0001). However, HESN presented significantly higher CEC (0.78±0.14) than UHIV (0.65±0.17; p=0.0005), but lower than HC (0.90±0.13; p=0.009). hsCRP levels were higher in the groups of HIV-infected patients (UHIV and EC) compared to uninfected (HESN and HC; p=0.01). hsCRP partially and negatively correlated with CEC (Spearman r=-0.27; p=0.007). Lipoprotein(a) showed no significant differences between groups (p=0.47).
Conclusion: We found low CEC in HIV-infected patients associated with lower CD4, higher plasma HIV-1 RNA, and higher hsCRP. CEC was also lower in HESN as compared with HC. Our results suggest that inflammation or immune status secondary to HIV infection or exposition to HIV may influence HDL functionality.

615 LOWER RATES OF CVD PROCEDURES IN HIV-INFECTED PATIENTS WITH ACUTE CORONARY SYNDROME

Meredith Clement[1], Li Lin[2], Ann M. Navar[1], Nwora L. Okeke[1], Susanna Naggie[1], Pamela Douglas[1]
[1]Duke Univ, Durham, NC, USA, [2]Duke Clinical Rsr Inst, Durham, NC, USA

Background: Cardiovascular disease (CVD) is an increasing cause of morbidity and mortality in adults with HIV infection. HIV-infected patients have been shown to be less likely to receive treatment with procedures and surgery in the setting malignancy and orthopaedic disease. The degree to which disparities exist for CVD interventions is unknown.
Methods: We compared rates of cardiac catheterization and revascularization (including percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery) among HIV-infected and uninfected adults hospitalized with acute coronary syndrome (ACS) from 2009-2012. We used the National Inpatient Sample (NIS), a dataset that includes information on 8 million hospital discharges per year, for our analysis. ICD-9 codes were used to determine HIV diagnoses and to identify hospitalizations and procedures for ACS. Multivariable analysis adjusting for age, sex, race, income, hospitalization year, tobacco, alcohol, and substance use and comorbidities was used to compare procedure rates by HIV status, with appropriate weighting to account for the sampling design including stratification and hospital clustering in the NIS.
Results: Overall, the dataset included 1,091,759 ACS hospitalizations, 0.35% of which (n=3783) were in HIV-infected patients. HIV-infected patients were more often male (76.6% vs 57.9%), Black (44.4% vs 10.9%), and of lower income status (45.3% vs 30.2% in first quartile of income by zip code) compared to uninfected patients. Overall rates of cardiac catheterization and revascularization (PCI or CABG) were 53.3% and 37.4%, respectively. In multivariable regression, we found that HIV-infected patients were 1) less likely to undergo catheterization (OR 0.68, CI 0.62-0.73), 2) less likely to undergo revascularization with PCI or CABG (OR 0.80, CI 0.73-0.89), and 3) less likely to receive a drug eluting stent (OR 0.74, 0.63-0.86) when PCI was performed. There was no difference in time to catheterization between the two groups.
Conclusion: HIV-infected patients are less likely to receive standard catheterization and revascularization procedures after ACS presentation, suggesting disparities in access to care for these patients. In addition, the lower rates of CABG and PCI with DES may impact long-term outcomes for these patients, as these procedures are associated with less frequent need for repeat revascularization. Reasons for lower utilization of CVD procedures in HIV-infected patients warrants further investigation.

Table 1. Rates of CVD procedures for HIV-infected versus uninfected patients

		HIV+ (n=3783)	Other (n=1087976)	p-value	Adjusted Odds Ratio
		%	%		
ACS event-type	STEMI	19.9	18.3	0.01	
	NSTEMI	52.7	51.0	0.06	
	UA	27.8	31.0	0.0002	
Catheterization	Any	52.3	53.3	0.38	0.68 (0.62, 0.73)
	If yes, w/in 24 h- STEMI	83.4	82.8	0.75	0.87 (0.75, 1.00)
	If yes, w/in 48 h- NSTEMI	67.7	66.7	0.56	0.97 (0.84, 1.13)
Revascularization	Any (PCI or CABG)	35.6	37.4	0.08	0.80 (0.73, 0.89)
	PCI	30.1	29.2	0.31	0.87 (0.80, 0.95)
	If PCI, DES	64.0	73.0	<0.0001	0.74 (0.63, 0.86)
	CABG	5.8	8.4	<0.0001	0.79 (0.69, 0.91)
Outcomes	Mortality	7.5	6.9	0.12	1.60 (1.38, 1.86)
	Length of Stay, mean	6.5 days	5.5 days	<0.0001	0.57 (0.24, 0.90)

Variables included in the models were: age, sex, race/ethnicity, income, year of hospitalization, tobacco use, alcohol use, substance abuse and comorbidities including congestive heart failure, renal disease, malignancy, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, diabetes, and obesity. Abbreviations: STEMI: ST-elevation myocardial infarction, NSTEMI: non-ST-elevation myocardial infarction, UA: unstable angina, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, DES: drug eluting stent

616 EXERCISE, OXIDATIVE STRESS, AND FIBRINOLYTIC FUNCTION IN HIV-1 INFECTED ADULTS

Elizabeth Connick[1], Jared Greiner[2], Caitlin Dow[2], Kyle Diehl[2], Brian Stauffer[3], Christopher DeSouza[2]
[1]Univ of Arizona, Tucson, AZ, USA, [2]Univ of Colorado Boulder, Boulder, CO, USA, [3]Univ of Colorado Denver, Aurora, CO, USA

Background: The capacity of the endothelium to release tissue-type plasminogen activator (t-PA), the primary activator of the fibrinolytic system, is the primary endogenous defense mechanism against intravascular fibrin deposition and thrombosis. We have previously demonstrated that the ability of the endothelium to release t-PA is markedly blunted in HIV-1-infected adults. Moreover, this dysfunction is due, in large part, to oxidative stress. Regular aerobic exercise is an effective lifestyle intervention for improving cardiovascular health and reducing cardiovascular risk. We tested the hypothesis that: 1) regular aerobic exercise improves endothelial fibrinolytic capacity in HIV-1-seropositive adults; and 2) increased endothelial capacity to release t-PA is mediated by a reduction in oxidative stress.

Methods: Net endothelial release of t-PA was determined, in vivo, in response to intra-brachial infusions of bradykinin (BK: 125-500 ng/min) and sodium nitroprusside (SNP: 2.0-8.0 mcg/min). BK was selected to stimulate endothelial t-PA release due to its effectiveness at eliciting and local and rapid response. SNP was required to establish that any observed differences in t-PA release to BK were not due to increased blood flow related sheer stress. To determine the effects of oxidative stress on endothelial t-PA release, the BK and SNP dose response curves were repeated with a co-infusion of the antioxidant vitamin C (24 mg/min). 17 HIV-1-seropositive adults (age: 37±2 yr; 12M/5F) on stable antiretroviral therapy completed the home-based exercise intervention (walking ~4.9 d/wk, ~50 min/d @ ~71% of maximal heart rate).

Results: The capacity of the endothelium to release t-PA in response to BK was significantly higher after (from -1.4±0.9 to 89.4±11.6 ng/100 mL tissue/min) vs before (-1.4±0.7 to 48.1±6.5 ng/100 mL tissue/min) exercise training. Importantly, before exercise training the co-infusion of vitamin C significantly increased endothelial t-PA release in response to BK (-2.2±1.3 to 95.5±10.1 ng/100 mL tissue/min). However, after exercise training the co-infusion of vitamin C did not significantly increase endothelial t-PA release (-1.1±0.9 to 101.6±15.3 ng/100 mL tissue/min). There was no effect of exercise training on t-PA release to SNP.

Conclusion: In summary, habitual aerobic exercise improves endothelial fibrinolytic function in HIV-1-seropositive adults. This adaptation appears to be mediated by a reduction in oxidative stress.

617 VITAMIN D DEFICIENCY IMPAIRS THE BENEFICIAL EFFECTS OF STATIN IN TREATED HIV

Corrilynn O. Hileman[1], Vin Tangpricha[2], Abdus Sattar[1], Grace A. McComsey[1]
[1]Case Western Reserve Univ, Cleveland, OH, USA, [2]Emory Univ, Atlanta, GA, USA

Background: Vitamin D deficiency is common in HIV. Statins may increase vitamin D levels and it is unknown whether vitamin D status modifies the effect of statins on cardiovascular disease.

Methods: The SATURN-HIV study is a 96-week, randomized, placebo-controlled clinical trial designed to evaluate the effect of rosuvastatin 10 mg daily on immune activation and subclinical vascular disease in HIV-infected adults on antiretroviral therapy with fasting LDL ≤130 mg/dL and heightened immune activation (proportion of CD8+ T-cells that express CD38 and HLA-DR ≥19%) and/or inflammation (high sensitivity C-reactive protein ≥2 mg/L). In this secondary analysis, mixed effects linear modeling and ANOVA were used to assess the rosuvastatin effect on plasma 25-hydroxyvitamin D [25(OH)D] levels over time and to determine whether baseline vitamin D status modifies the effect of rosuvastatin on changes in markers of subclinical vascular disease, immune activation, inflammation, lipids and insulin resistance that differed between groups over the study. See Figure for specific outcomes tested.

Results: 147 adults were randomized (72 to rosuvastatin, 75 to placebo). Seventy-eight percent were men and 68% were African American. Mean age was 45 years. Mean current and nadir CD4+ T-cell counts were 640 and 200 cells/mm3, respectively, and known duration of HIV infection was 12 years. All participants were on ART by design (51% on protease inhibitor- and 49% on efavirenz-containing regimens) and 76% had HIV-1 RNA level <48 (range 20-600) copies/ml. Baseline 25(OH)D levels were similar (overall mean 18 ng/ml) with 65% of participants below 20 ng/ml. Changes in 25(OH)D at 96 weeks were small and not significant within- or between-groups. There were significant group by vitamin D status interactions for changes in LDL, proportion of CD14dimCD16+TF+ monocytes, lipoprotein-associated phospholipase A2 and common carotid artery intima media thickness at most time points including week 96. For each of these outcomes, the beneficial effects of rosuvastatin were either not apparent or attenuated in participants with vitamin D deficiency (25(OH)D levels <20 ng/ml) (see Figure).

Conclusion: While levels of 25(OH)D did not change with rosuvastatin, baseline vitamin D deficiency decreased the effectiveness of rosuvastatin. Vitamin D supplementation may be warranted for deficient patients initiating statin therapy.

618 EFFECT OF STATIN ON ARGININE METABOLITES IN TREATED HIV INFECTION

Sahera Dirajlal-Fargo[1], **Vanessa El Kamari**[2], Abdus Sattar[2], Nicholas Funderburg[3], W. H. Wilson Tang[4], Grace A. McComsey[2]
[1]Rainbow Babies and Children's Hosp–Case Western Sch of Med, Cleveland, OH, USA, [2]Case Western Reserve Univ, Cleveland, OH, USA, [3]Ohio State Univ, Columbus, OH, USA, [4]Cleveland Clinic, Cleveland, OH, USA

Background: Asymmetric dimethylarginine (ADMA), an arginine metabolite, is an endogenous inhibitor of nitric oxide and an independent risk factor of cardiovascular disease (CVD). Statins lower ADMA in HIV negative populations but it is unknown whether statins have similar effect in HIV+ populations, and whether such an effect could contribute to the favorable changes on carotid intima media thickness (cIMT). This analysis examines the relationship between statin, ADMA and cIMT.
Methods: This secondary analysis of SATURN-HIV trial, in which HIV+ adults on stable antiretroviral therapy (ART), with HIV-1 RNA< 1,000 copies/mL and LDL-cholesterol <130mg/dL were randomized to 10mg daily rosuvastatin or placebo. Arginine metabolites, including ADMA and global arginine availability ratio (GABR), and markers of inflammation were assessed at baseline and at 48 weeks, cIMT was measured at baseline, 48 and 96 weeks. Classical t-tests were used for comparison between groups. Spearman correlations were used to explore relationships between variables. Linear mixed-effect model was used to assess the interaction of ADMA and statin on cIMT.
Results: Overall, 79% were male, 68% African Americans, with median age of 46 years. In the statin arm, no significant change in ADMA levels was observed at 48 weeks (0.70%), whereas a significant increase (23.78%) was observed in the placebo group (Fig.1). Change in ADMA was significantly correlated with changes in intracellular cell adhesion molecule (p=0.02) and in T-cell activation markers (CD8+CD38+, p=0.05 and CD4+ CD38+ HLA-DR+, p<0.01). Moreover, a significant decrease in GABR (33.56%, p=0.03) was observed at 48 weeks in the statin arm, while no significant change was observed in the placebo arm (p=0.32). Elevated baseline ADMA (highest tertile) was independently associated with a 0.03mm increase in cIMT (p=0.03) after adjusting for statin and study duration. No interaction was seen between baseline ADMA and statin treatment on change in cIMT (p=0.20).
Conclusion: Daily rosuvastatin in HIV+ subjects on ART prevented the increase overtime in ADMA levels on ART. Elevated baseline levels of ADMA were associated with increases in cIMT. However, the favorable effect of rosuvastatin on cIMT was independent of the arginine pathway. Further studies are warranted to investigate the role of the arginine metabolites in HIV and specifically whether arginine supplementation could enhance the beneficial effects of statin in this population.

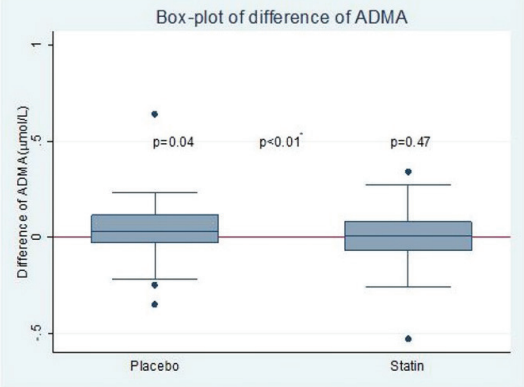


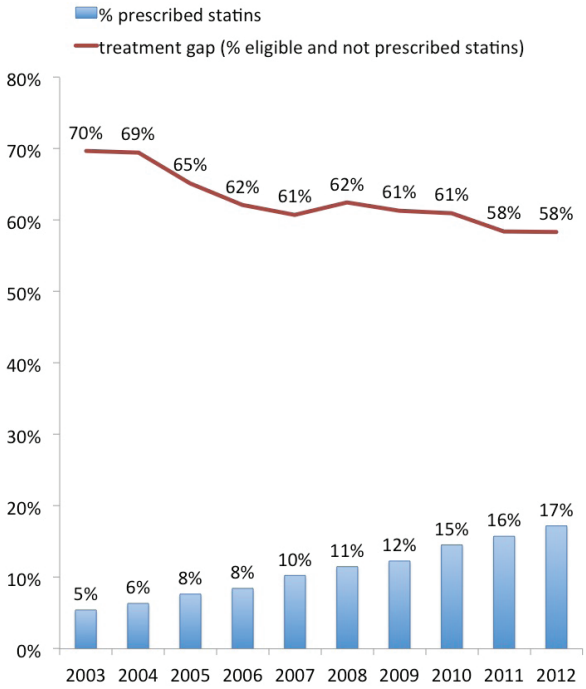
Figure 1: Box-plot of the difference of ADMA for Placebo and Statin group

619 THE LARGE GAP BETWEEN STATIN ELIGIBILITY AND PRESCRIPTION AMONG HIV+ IN NORTH AMERICA

Keri N. Althoff[1], Micheal A. Horberg[2], Joseph J. Eron[3], Stephen J. Gange[1], Heidi M. Crane[4], Amy Justice[5], Mari Kitahata[4], Joseph B. Margolick[1], Oghenowede Eyawo[6], Richard D. Moore[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]Univ of Washington, Seattle, WA, USA, [5]VA Connecticut Hlthcare System, West Haven, CT, USA, [6]BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada

Background: Those aging with HIV have a higher risk of cardiovascular disease (CVD) than uninfected adults. Statins are hypothesized to impact traditional CVD risk factors, such as low-density lipoprotein (LDL) cholesterol, and may impact HIV-specific mechanisms, such as inflammation and immune activation. The objective of this study was to estimate the statin treatment gap, defined as the proportion eligible but not prescribed statins among HIV-infected adults.
Methods: Data from 14 dynamic clinical cohorts in the North American AIDS Cohort Collaboration on Research and Design were used to estimate trends in statin prescription. The statin treatment gap was defined using the final Adult Treatment Panel III guidelines as ≤1 risk factors and LDL ≥190 mg/dL, or ≥2 risk factors with 10-year predicted Framingham Risk Score (FRS) 0-20% and LDL ≥130 mg/dL, or diabetes and FRS >20% and LDL ≥130 mg/dL. The treatment gap analysis was restricted to those who had measurements needed to determine statin eligibility. Log binomial models with generalized estimating equations for repeated measures and an ordinal variable for calendar time were used to estimate the p-value for trend.
Results: A total of 88,463 and 40,898 adults contributed to the estimation of the trends in statin prescription and the statin treatment gap, respectively. There were a greater proportion who were white and MSM in the gap compared with the prescription study populations (48% vs 39% p<.001 and 56% vs 49% p<.001, respectively). Over time, the proportion prescribed statins increased from 5% to 17% (p-trend<.001) (Figure 1). The statin treatment gap was large, but decreased from 70% to 58% (p-trend<.001). The gap was largest for males (72% to 59%), those with injection drug use HIV transmission risk (81% to 58%), and ever smokers (73% to 60%; all p-trend<.001). By age, the gap was largest and fluctuated among those <40 years with no clear trend (77% to 88% p-trend=.01). The decrease in the gap was similar among whites (72% to 57%) and blacks (71% to 58%), and larger in Hispanics (74% to 65%; all p-trend<.001).
Conclusion: The statin treatment gap was substantial from 2003 through 2012, prior to statin guideline changes in 2013. The gap may be underestimated due to the differences in the prescription and gap populations. Given the increased risk of CVD in HIV-infected adults, further narrowing the gap between statin eligibility and prescription may preserve the health of those aging with HIV.

Figure 1: The proportion of HIV-infected adults prescribed statins (n=88,463) and the statin treatment gap (n=40,898), 2003-2012, NA-ACCORD



620 FIRST AND RECURRENT VENOUS THROMBOSIS IN HIV PATIENTS OF THE DUTCH ATHENA COHORT

Casper Rokx[1], Jaime Borjas Howard[2], Colette Smit[3], Ferdinand Wit[3], Elise D Pieterman[1], Karina Meijer[2], Wouter Bierman[2], Vladimir Tichelaar[2], Bart Rijnders[1]
[1]Erasmus Univ Med Cntr, Rotterdam, Netherlands, [2]Univ Med Cntr Groningen, Groningen, Netherlands, [3]Stichting HIV Monitoring, Amsterdam, Netherlands

ased risk for first venous thrombotic events (VTE) compared to the general population. What causes this increased risk and whether HIV patients are also at increased risk for recurrent VTE is unclear. An assessment of VTE risk factors and a reliable recurrence estimate are essential to determine the optimal duration of anticoagulant therapy (ACT). We assessed the risk factors for a first VTE and evaluated VTE recurrence rates in HIV patients.

Methods: Observational study using data of the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. To identify VTE, we systematically reviewed charts of patients who initiated ACT in 2003-2014 in 12 participating centers, covering 70% of the Dutch HIV population. The sensitivity of this case finding strategy was confirmed by full chart review of all patients in 2 centers. We analyzed risk factors for first VTE (regardless of location) by time-updated Cox regression models. VTE recurrence after ACT withdrawal was analyzed in patients with a first VTE in proximal leg veins or pulmonary arteries only. VTE associated with estrogen use, pregnancy, surgery, cancer or trauma were considered provoked.

Results: 229 first VTE occurred in 14,386 HIV patients (80% males) during 97,556 person-years (py) of follow up (2.3 VTE/1000 py). Lower CD4 T-cell counts were independently associated with a higher first VTE risk in HIV patients and this association remained significant after adjustment for the high hospitalization rates in severely immunocompromised HIV patients (Table). HIV patients with >500 CD4 T-cells/mm3 had 1.3 VTE/1000 py while HIV patients with <200 CD4 T-cells/mm3 had 7.1 VTE/1000 py. 153 of 202 HIV patients with first VTE localized in proximal leg veins or pulmonary arteries withdrew ACT, including 108 with unprovoked VTE. VTE recurred in 31 HIV patients (57 VTE/1000 py; 95%CI: 39-79). Kaplan-Meier recurrence rates at 1, 2 and 5 years of follow up were 16%, 19%, and 28% following unprovoked first VTE and 5%, 9%, and 15% following provoked first VTE.

Conclusion: The increased risk for a first VTE in HIV patients was strongly driven by lower CD4 T-cell counts. VTE incidence in those with high CD4 T-cell counts approached the incidence in non-HIV patients. The VTE recurrence rate was high in patients with unprovoked first VTE and clustered in the first year after ACT withdrawal. Our results suggest that ACT withdrawal in HIV patients with unprovoked VTE and low CD4 T-cell counts should be cautiously considered.

621 PREVALENCE AND PROGNOSTIC IMPACT OF PULMONARY HYPERTENSION IN HIV-INFECTED ADULTS

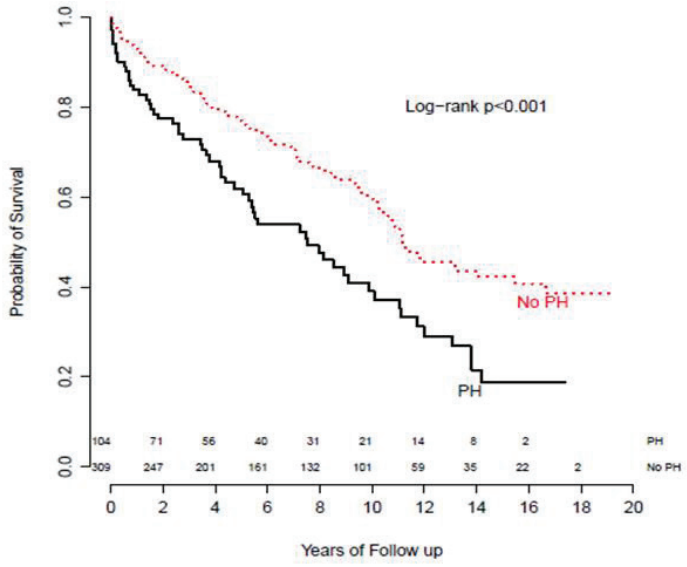
Courtney Zola, John R. Koethe, Meng Xu, Quinn S. Wells, Eric Farber-Eger, Evan L. Brittain
Vanderbilt Univ, Nashville, TN, USA,

Background: HIV- infected individuals are at increased risk for the development of pulmonary hypertension (PH). The prevalence of PH, risk factors associated with its development, and the prognostic impact in HIV infected individuals are poorly understood.

Methods: We used Vanderbilt's de-identified electronic medical record (the Synthetic Derivative) to identify HIV infected individuals defined using International Classification of Disease 9 or 10 codes. Demographic, clinical, and echocardiogram data were extracted. The first echocardiogram after documented HIV infection was used to determine PH status, defined as right ventricular systolic pressure (RVSP) ≥ 40mmHg. Vital status was determined using the Social Security Death Index.

Results: We identified 8,558 HIV infected adults, of whom 418 had echocardiograms with reported RVSP values. The prevalence of PH was 25% (105/418). The mean RVSP in individuals with PH was 55±17mmHg versus 28±6 in those without PH ($p < 0.001$). There were no significant differences in age, gender, race, or antiretroviral exposure by PH status. Individuals with PH had a higher prevalence of heart failure (HF) and chronic obstructive pulmonary disease (COPD), higher brain natriuretic peptide, and lower left ventricular ejection fraction (LVEF; all $p < 0.05$). PH was associated with increased risk of mortality (Figure; log rank $p < 0.001$). In Cox regression analysis, PH was independently associated with increased mortality in HIV infected individuals (HR 1.71, 95%CI 1.21-2.40) after adjusting for age, gender, race, HF, LVEF, COPD, and exposure to antiretroviral therapy (ART). Receipt of ART conferred a reduced risk of mortality that approached statistical significance (HR 0.76, 95%CI 0.55-1.04, $p=0.08$).

Conclusion: PH is common among HIV infected individuals referred for a clinical echocardiogram. The presence of PH is associated with increased mortality compared to those without PH, which persisted after adjusting for likely confounders. Further studies are warranted to identify the HIV populations at greatest risk for development of PH and explore the viral and immune mechanisms contributing to this condition

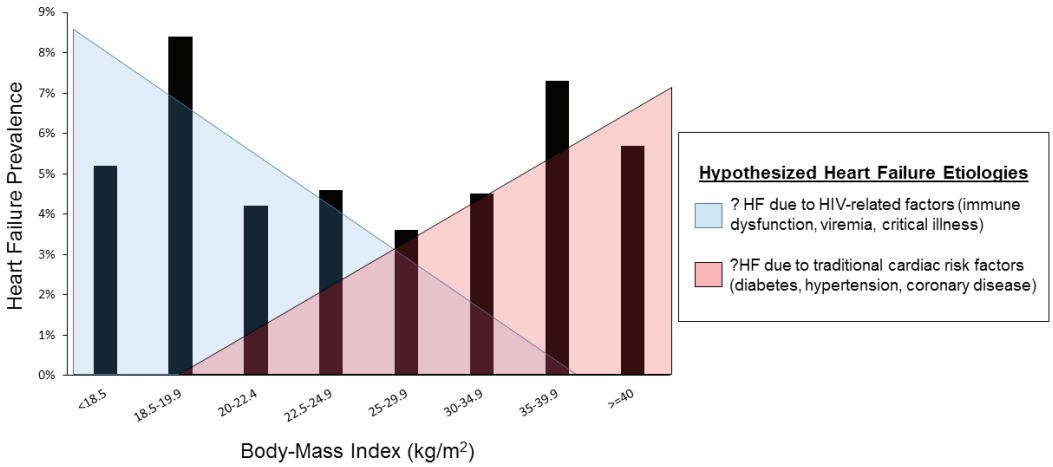


622 BODY-MASS INDEX AND ADJUDICATED HEART FAILURE IN A LARGE ELECTRONIC HIV COHORT

Matthew J. Feinstein, Alexandra B. Steverson, Anna Pawlowski, Daniel Schneider, Prasanth Nannapaneni, Sadiya S. Khan, Mercedes Carnethon, Chad J. Achenbach, Sanjiv J. Shah, Donald M Lloyd-Jones
Northwestern Univ, Chicago, IL, USA

Background: Heart failure (HF) is increasingly recognized as a cause of morbidity and mortality in HIV and may reflect a final common manifestation of diverse HIV-related pathologies. The association between body-mass index (BMI) and HF in HIV is unknown. Whereas some HIV-infected (HIV+) persons at low and low-normal BMI may be at risk for HF due to advanced HIV with associated wasting, obese HIV-infected persons may be at risk for HF due to traditional risk factors such as hypertension and diabetes. Our central hypothesis was that underweight and obese HIV+ persons would have significantly greater risks for HF than HIV+ persons with high-normal BMI.
Methods: Using an electronic data repository, we identified all HIV+ adults who received care at a large academic medical center between January 1, 2000 and June 1, 2016 and had complete demographic and anthropometric data. Baseline BMI was determined using the earliest available concurrent height and weight measurement for each participant. Possible HF events were identified using a broad screening protocol that incorporated physician diagnoses, biomarkers, and/or use of intravenous diuretics; HF events were then independently adjudicated by two physicians. Associations between BMI category at baseline and HF were assessed using multivariable logistic regression.
Results: Of the 5039 HIV+ patients included for analysis, 216 (4.3%) experienced HF. HF was most common among patients at BMI extremes and least common among mildly overweight patients (BMI 25-29.9 kg/m2) (Figure). After adjustment for demographics, cardiovascular risk factors, and HIV-related markers (nadir CD4 T cell count, HIV viral load, antiretroviral use, and protease inhibitor use), odds ratios (95% confidence interval) for HF for patients with baseline BMI <18.5, 18.5-19.9, 20-22.4, 22.5-24.9, 25-29.9 (referent), 30-34.9, 35-39.9, and >40 kg/m2 were 1.87 (0.75-4.70), 3.19 (1.67-6.11), 1.73 (1.01-2.95), 1.84 (1.15-2.93), 1, 1.39 (0.79-2.45), 1.96 (0.96-4.01), and 1.11 (0.51-2.45), respectively.
Conclusion: Heart failure is significantly more common among underweight and low-normal weight HIV+ patients and somewhat more common among obese HIV+ patients when compared with mildly overweight HIV+ patients. This "reverse J-shaped" association may reflect diverse pathophysiologies of HF in HIV, including chronic disease-related wasting for HIV+ patients with low-normal BMI versus traditional cardiovascular risk factor burden among obese HIV+ patients.

Figure. Heart Failure Prevalence among HIV-Infected Persons by Body-Mass Index



623 ASSOCIATION OF INFLAMMATION AND COAGULATION WITH CLINICAL RISK IN THE START TRIAL

Jason Baker, Shweta Sharma, Birgit Grund, for the INSIGHT START (Strategic Timing of AntiRetroviral Treatment) Study Group
Univ of Minnesota, Minneapolis, MN, USA

Background: The START trial demonstrated that immediate (at CD4 >500cells/μL) versus deferred (to CD4 <350 cells/μL) antiretroviral therapy (ART) reduced a composite outcome of AIDS, serious non-AIDS (SNA) events and death (N Eng J Med 2015). The SMART trial demonstrated that inflammation and coagulation biomarkers strongly predict risk for these events. We characterized associations for clinical event risk in START with inflammation, coagulation and vascular injury biomarkers.
Methods: Biomarkers (Table) were measured from stored plasma at baseline; levels analyzed on the log2 scale. Associations of biomarker levels with event risk were estimated with Cox regression, pooled across treatment groups. Homogeneity of the associations across treatment groups, age and gender was assessed. Models were adjusted for age, gender, and treatment group and stratified by region.
Results: Of the 4685 participants enrolled in START, baseline biomarker levels were available for 4299 (92%). Mean follow-up was 3.0 years. There were 129 primary events (AIDS, SNA or death); 57 AIDS or AIDS-death events (23 tuberculosis [TB]), 74 SNA or non-AIDS deaths, 50 cancer (AIDS or non-AIDS; 12 Kaposi sarcoma), and 24 CVD. Higher levels of IL-6 and D-dimer were associated with higher risk of AIDS and SNA events (HRs ranged 1.4-1.5 per doubling of biomarker) (Table); associations with AIDS were driven by TB (HRs 1.7-1.8, p<0.008). Higher IL-6 levels are associated with CVD. No biomarkers were associated with cancer risk. Associations of biomarkers with clinical event risk did not differ across immediate and deferred groups, except for sVCAM with AIDS or TB and sICAM with TB (positive associations only seen in deferred arm), and sICAM for SNA (non-significant association in both groups). Significant biomarker associations were consistent across age and gender, except for D-dimer with AIDS (stronger at lower age), and sICAM with TB (stronger at higher age).
Conclusion: Among a diverse global population of HIV+ persons with high CD4 counts, higher IL-6 and D-dimer levels had the strongest association with risk for SNA, AIDS, and their composite. These data, combined with prior biomarker work from INSIGHT trials, demonstrate that IL-6 and D-dimer consistently predict clinical risk across a broad spectrum of CD4 counts for those both ART naïve or treated. Randomized clinical trials are needed to evaluate whether lowering these biomarker levels decreases clinical risk.

Table: Hazard Ratios (HR) for Clinical Event Risk Associated with Two Fold Higher Biomarker Levels in START. Significant (p≤0.05) associations are in bolded.

	HR (95%CI)					
Biomarkers	**AIDS, SNA, or death**	**AIDS**	**SNA**	**Cancer (AIDS or SNA)**	**TB**	**CVD**
IL-6	**1.39** [1.16,1.66]**	**1.46** [1.13, 1.88]*	**1.41** [1.11, 1.79]*	0.94 [0.68, 1.30]	**1.79** [1.25, 2.58]**	**1.64** [1.09, 2.47]*
D-dimer	**1.41** [1.16, 1.72]**	**1.52** [1.14, 2.01]*	**1.37** [1.05, 1.78]*	1.07 [0.76, 1.52]	**1.72** [1.15, 2.57]*	1.31 [0.82, 2.08]
hsCRP	1.08 [0.98, 1.19]	1.15 [1.00, 1.32]	1.06 [0.93, 1.21]	0.94 [0.79, 1.11]	**1.26** [1.03, 1.54]*	1.09 [0.86, 1.38]
IL-27	1.01 [0.92, 1.12]	1.10 [0.95, 1.28]	0.97 [0.85, 1.10]	1.03 [0.89, 1.18]	1.12 [0.87, 1.45]	0.87 [0.70, 1.09]
Serum amyloid A	**1.13** [1.02, 1.25]*	**1.17** [1.01, 1.35]*	1.12 [0.98, 1.28]	1.02 [0.84, 1.22]	**1.27** [1.04, 1.56]*	1.19 [0.94, 1.51]
sICAM-1	1.23 [0.92, 1.65]	**1.66** [1.09, 2.52]*	1.05 [0.71, 1.55]	1.08 [0.67, 1.73]	**1.97** [1.04, 3.73]*	1.12 [0.54, 2.30]
sVCAM-1	1.13 [0.84, 1.52]	1.39 [0.90, 2.14]	0.98 [0.66, 1.45]	1.10 [0.67, 1.80]	1.50 [0.79, 2.85]	1.02 [0.50, 2.09]

*CI = confidence interval; CVD = cardiovascular disease; IL = interleukin; hsCRP = high sensitivity C-reactive protein; sICAM = soluble intercellular adhesion molecule; sVCAM = soluble vascular cellular adhesion molecule; TB = tuberculosis HRs were estimated in proportional hazards models, pooled across treatment groups, adjusted for age, gender, treatment group, stratified by geographic location. HRs are per doubling of biomarker(s), HRs for IL-6 & D-dimer score are per doubling of both IL-6 and D-dimer. *p < 0.05 ** p < 0.001*

624 HIV VIRAL BURDEN ASSOCIATED WITH SUBCLINICAL CORONARY ARTERY DISEASE IN HIV+ MEN

Sabina Haberlen[1], Ruibin Wang[1], Frank J. Palella[2], Lisa Jacobson[1], Todd Brown[1], Mallory Witt[3], Kathryn Berlacher[4], Matthew Budoff[5], Alison Abraham[1], Wendy Post[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Northwestern Univ, Chicago, IL, USA, [3]Los Angeles Biomed Rsr Inst at Harbor–UCLA Med Cntr, Torrance, CA, USA, [4]Univ of Pittsburgh, Pittsburgh, PA, USA, [5]Harbor–UCLA Med Cntr, Torrance, CA, USA

Background: Coronary artery disease (CAD) is more common in HIV-infected (HIV+) compared to HIV-uninfected (HIV-) men in the Multicenter AIDS Cohort Study (MACS). Cumulative HIV RNA burden and associated inflammation may contribute to CAD. We assessed the relative prognostic value of viral copy-years (VCY), a cumulative viral load (VL) metric, to other VL measures on presence of CAD.
Methods: MACS participants age 40-70 years without history of coronary revascularization were evaluated for subclinical CAD by cardiac CT angiography (CTA) from 2010-2013. Our sample included 223 HIV+ men with CTA measurements, a baseline VL measurement at or within 6 months prior to combination antiretroviral (cART) initiation, and subsequent VL measurements no more than 2 years apart. VCY since cART initiation was calculated using the trapezoidal rule to estimate the area under the curve between VL measurements. The association of VCY with subclinical CAD was compared to four alternative VL metrics since cART initiation: 1) peak VL, 2) baseline VL, 3) detectable VL (>50 copies/mL) at most recent measure before CTA (yes/no), and 4) any detectable VL within 5 years before CTA (yes/no). We used logistic regression to estimate odds ratios for two outcomes: coronary artery stenosis ≥50% (obstructive CAD) and non-calcified plaque. Models included age, race, MACS site, cohort, smoking status, ASCVD risk score, and nadir CD4+ T cell count. Model fit was assessed by the Akaike Information Criterion (AIC).
Results: Studied men were 42% non-white, median age 52 years, a median 10.4 years from cART initiation to CTA (IQR 7.7, 13.8). The prevalence of stenosis ≥50% and non-calcified plaque were 16% and 62%, respectively. With the exception of most recent VL, each VL exposure metric was statistically significantly (p <0.05) associated with coronary artery stenosis ≥50% (Table 1). Both each log10 increase in VCY and detectable VL during the previous 5 years were associated with more than a two-fold increased odds of coronary artery stenosis (OR 2.4 CI: 1.4,4.0 and OR 2.6, CI: 1.1,6.2, respectively). Regression using VCY demonstrated the best fit based on AIC. None of the VL measures were associated with non-calcified plaque presence.
Conclusion: Cumulative viral load was strongly associated with obstructive CAD in HIV+ men. Other metrics of viremia, particularly the widely used most recent VL measure, may underestimate the role of ongoing exposure to viral replication in the development of coronary artery disease in HIV+ individuals.

Table 1: Odds Ratios for Coronary Artery Stenosis ≥50% and Non-calcified Plaque Associated with Alternative Measures of HIV Viral Load Burden among 223 HIV-Infected Men in the Multicenter AIDS Cohort Study

	Coronary Artery Stenosis ≥50%			Non-calcified Plaque		
	Adjusted Odds Ratio	95% Confidence Interval	Akaike's Information Criterion	Adjusted Odds Ratio	95% Confidence Interval	Akaike's Information Criterion
Recent Detectable VL	1.6	[0.6,4.3]	191.1	1.1	[0.5,2.2]	294.2
5 Year Detectable VL	2.6*	[1.1,6.2]	187.0	1.0	[0.5,1.8]	294.2
Peak VL, copies/mL (log10)	1.4*	[1.1,1.9]	185.9	1.0	[0.8,1.3]	294.2
Pre-HAART VL, copies/mL (log10)	1.6*	[1.1,2.5]	186.1	0.7	[0.6,1.0]	290.4
Viremia copy-years (log10)	2.4**	[1.4,4.0]	179.9	0.9	[0.6,1.3]	293.8

Detectable VL (>50 copies/mL). Each odds ratio is from a separate regression model. Models are adjusted for age, race, MACS center, cohort recruitment, smoking status, ASCVD risk score and nadir CD4+ T cell count. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. A lower AIC indicates a better fit.

625 HIGHER CARNITINE LEVELS ARE ASSOCIATED WITH SUBSEQUENT MYOCARDIAL INFARCTIONS IN HIV

Arjun Sinha[1], Peter W. Hunt[1], Jeffrey N. Martin[1], Yifei Ma[1], Heidi M. Crane[2], Daniel Drozd[2], Peter Ganz[1], Stanley Hazen[3], **Priscilla Hsue**[1]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Univ of Washington, Seattle, WA, USA, [3]Cleveland Clinic, Cleveland, OH, USA

Background: HIV infection is associated with an increased risk of myocardial infarction (MI); however, the pathophysiology is incompletely understood. HIV alters the gut microbiome. Choline, carnitine, betaine, and trimethylamine N-oxide (TMAO), are small molecules that are metabolized or produced by the gut microbiome and TMAO is associated with MIs among adults without HIV. We have shown that carnitine and betaine are independently associated with carotid artery intima-media thickness in HIV-infected subjects, but TMAO and choline are not. We assessed the hypothesis that these gut microbiota-associated small molecules are independently predictive of MI in HIV-infected adults.
Methods: This was a nested case-control study of HIV-infected individuals with suppressed viral load (VL) on antiretroviral therapy (ART) within the US based 8-site CNICS network. The cases had adjudicated and confirmed Type 1 MI from 2001-2012. The controls were matched by incidence density sampling to each case by calendar time, age, gender, race, duration of VL suppression, and CD4 count. Plasma levels of TMAO, Betaine, Carnitine, and Choline were measured at Cleveland Clinic using stable isotope dilution liquid chromatography tandem mass spectrometry. Plasma samples for cases and controls were collected prior to the event date. Associations between the small molecules and MI were assessed using conditional logistic regression.
Results: There were 36 cases and 69 controls. The median age was 49 years (46, 58) and 77% were male. The median time of VL suppression was 3 months (1, 5) and the median CD4 count was 562 cells/mm3 (381, 809). The two groups had similar proportion of hypertension, T2DM, and active smoking. Cholesterol levels were similar as well but the cases had higher median triglycerides (184 mg/dL vs 146 mg/dL, p=0.05). After adjusting for triglycerides, elevated carnitine levels were strongly associated with MI (OR=4.95 for the top quartile (>33 μM) versus quartiles 1-3; (95% CI [1.29, 18.95], p=0.02, see Table). The other small molecules did not have a significant association with MI. Cholesterol and triglyceride levels as well as smoking were not associated with carnitine levels.
Conclusion: Carnitine is independently predictive of MI in treated and suppressed HIV-infected individuals and appears to be independent of TMAO. This finding suggests that the mechanism of atherosclerosis in HIV is distinct from uninfected individuals and unique interventions may be indicated in HIV to reduce CV risk.

Table: Association Between Small Molecules and MI After Multivariable Adjustment

Small Molecule	Odds Ratio, Quartile IV vs Quartiles I-III (95%CI)	P Value
Carnitine	4.95 (1.29, 18.95)	0.02
TMAO	0.90 (0.29, 2.75)	0.85
Choline	1.34 (0.46, 3.90)	0.59
Betaine	0.65 (0.16, 2.61)	0.54

626 VACS INDEX IS SUPERIOR TO NADIR CD4 COUNT FOR PREDICTING AMI AND MORTALITY

Christopher Rentsch[1], Janet Tate[1], Vincent C. Marconi[2], Matthew Budoff[3], Adeel A. Butt[4], Matthew Freiberg[5], Matthew Goetz[6], Maria Rodriguez-Barradas[7], David Rimland[8], Amy Justice[9]
[1]VA Connecticut Hlthcare System, West Haven, CT, USA, [2]Emory Univ, Atlanta, GA, USA, [3]Harbor–UCLA Med Cntr, Torrance, CA, USA, [4]Weill Cornell Med Coll, New York, NY, USA, [5]Vanderbilt Univ, Nashville, TN, USA, [6]VA Greater Los Angeles Hlth Care System, Los Angeles, CA, USA, [7]Baylor Coll of Med, Houston, TX, USA, [8]Atlanta VA Med Cntr, Decatur, GA, USA, [9]VA Connecticut Hlthcare System, West Haven, CT, USA

Background: After adjustment for cardiovascular risk factors and despite higher mortality, HIV remains independently associated with a higher risk of acute myocardial infarction (AMI). Among HIV+ patients, time-updated Veterans Aging Cohort Study (VACS) index is superior in predicting incident AMI and mortality over baseline, time-updated, and cumulative measures of HIV-1 RNA and CD4 count. Nadir CD4 count has also been shown to be independently associated with incident AMI after controlling for other cardiovascular risk factors. We compare the associations between nadir CD4 count and time-updated VACS Index on AMI incidence and all-cause mortality.
Methods: We included HIV+ patients starting combination antiretroviral therapy (cART) in VACS from 1996–2012. Patients were followed from cART initiation until AMI, death, last clinic visit or 9/30/2012. Primary outcomes were incident AMI (Medicaid, Medicare and Veterans Affairs ICD-9 codes) and all-cause mortality. For each outcome we fitted

adjusted proportional hazards models for nadir CD4 count and time-updated VACS Index, for each exposure separately and a combined model including both exposures to assess independent effects. The Akaike information criterion (AIC) was used to assess model fit (lower AIC = better model fit).
Results: 8,168 HIV+ (55,263 person-years) were analyzed with 196 incident AMIs and 1,711 deaths. Adjusting for known cardiovascular risk factors, nadir CD4 count predicted mortality, and time-updated VACS Index predicted both AMI and mortality. Nadir CD4 count <50 was associated with a HR of 0.69 (95% CI: 0.31-1.54) for AMI and a HR of 3.17 (95% CI: 2.09-4.81) for mortality. Time-updated VACS Index score of 55+ was associated with a HR of 3.36 (95% CI: 2.14-5.28) for AMI and a HR of 32.02 (95% CI: 26.40-38.85) for mortality. Time-updated VACS Index had the lowest AIC for both outcomes and was not substantively lower with addition of nadir CD4. After adjusting for time-updated VACS Index, nadir CD4 count <50 was no longer associated with mortality (HR 0.69, 95% CI: 0.45-1.05).
Conclusion: Time-updated VACS Index predicted both AMI and mortality and nadir CD4 count was predictive of mortality. When both were entered in a single model, nadir CD4 count was no longer predictive of either event. These findings suggest that current health determines risk more than prior history and that risk assessment can be improved by biomarkers of organ injury.

627 EPICARDIAL FAT, IMMUNE ACTIVATION, AND CORONARY PLAQUE AMONG HIV+ AND HIV- WOMEN

Suman Srinivasa[1], Michael Lu[1], Kathleen V. Fitch[1], Travis R. Hallett[1], Tricia H. Burdo[2], Janet Lo[1], Sara E. Looby[1], Udo Hoffmann[1], Steven K. Grinspoon[1], Markella V. Zanni[1]
[1]Massachusetts General Hosp, Boston, MA, USA, [2]Temple Univ, Philadelphia, PA, USA

Background: Mechanisms underlying the three-fold increased risk of myocardial infarction among HIV-infected vs. non-HIV-infected women remain unclear. HIV infection and/or treatment predisposes to deposition of ectopic fat, and ectopic fat depots are known to release immunomodulatory cytokines relevant to atherogenesis. No prior studies have explored the epicardial fat depot in relation to immune activation and subclinical coronary atherosclerotic plaque among HIV-infected and non-HIV-infected women.
Methods: 55 HIV-infected and 27 non-HIV-infected women without known cardiovascular disease who previously underwent coronary CT angiography (CCTA) and metabolic/immune phenotyping were included. Epicardial adipose tissue (EAT) volume was derived from CT and related to systemic markers of immune activation and arterial inflammation, in addition to extent and composition of subclinical coronary atherosclerotic plaque. ANOVA and the Kruskal-Wallis test were performed to investigate trends among groups stratified by HIV serostatus and high/low EAT (defined in reference to median EAT for each serostatus group).
Results: Asymptomatic HIV-infected women (mean age 47±8 years, duration HIV 15±6 years, duration ART 8±5 years, CD4+ count 599±299 cells/µl, undetectable VL 84%) and age-matched non-HIV-infected women with comparable BMI (28±5 vs. 29±5 kg/m2) had similar median volumes of EAT(54[41,79] vs. 65[41,78]mm3)(P>0.05). Markers of monocyte activation and arterial inflammation differed by [HIV serostatus/EAT volume] subgroup (sCD163 (P=0.004), sCD14 (P=0.03), CXCL10 (P=0.02), Lp-PLA2 (P=0.04)) and were highest among HIV-infected women with excess EAT as compared to HIV-infected women without excess EAT, non-HIV-infected women with excess EAT, and non-HIV-infected women without excess EAT. Notably, the percent of non-calcified coronary atherosclerotic plaque also differed by [HIV serostatus/EAT volume] subgroup (P<0.05) and was highest among HIV-infected women with excess EAT.
Conclusion: Among women with HIV, excess epicardial fat is associated with immune activation and arterial inflammation, as well as non-calcified subclinical coronary atherosclerotic plaque. Future treatment strategies aimed at reducing ectopic fat among HIV-infected women may have potential to dampen systemic immune activation and favorably influence plaque morphology.

628 DIVERGENT EFFECTS OF HIV AND SMOKING ON AORTIC INFLAMMATION

Chris T. Longenecker[1], Claire E. Sullivan[2], Justin T. Morrison[2], Corrilynn O. Hileman[1], David A. Zidar[1], Robert Gilkeson[1], James O'Donnell[1], Grace A. McComsey[1]
[1]Case Western Reserve Univ, Cleveland, OH, USA, [2]Univ Hosps of Cleveland Med Cntr, Cleveland, OH, USA

Background: The detrimental effects of smoking on cardiovascular disease (CVD) and mortality in patients with and without HIV may be mediated in part by systemic and tissue-specific inflammation.
Methods: We prospectively studied 55 HIV+ subjects on stable antiretroviral therapy and 19 age-matched HIV-uninfected controls without known CVD who underwent 18flurodeoxyglucose positron emission tomography (FDG-PET). Aortic target-to-background ratio (TBR) and spleen standardized uptake values (SUV) measured 2-hours post-FDG were the primary outcomes of interest. We used hierarchical linear and logistic regression to examine the association of HIV and smoking status with PET variables. We additionally explored relationships of PET variables with biomarkers of inflammation, monocyte activation, and coronary calcification after adjustment for HIV, smoking, and other traditional CVD risk factors.
Results: Overall, mean (SD) age was 48(11) years; 81% were male and 54% were current smokers [median 0.5 packs per day, 25 pack-years]. HIV+ and HIV-neg groups were well-matched for demographics and clinical variables (p>0.2) except HIV+ were more likely to be African American (73 vs. 47%) and to have hypertension (56 vs. 16%). For HIV+, median CD4+ was 690 cells/ml and 88% had HIV-1 RNA <20c/ml; 43% were on a protease inhibitor. In fully-adjusted models (see Figure), HIV was associated with 0.15 (95%CI 0.04-0.27; p=0.01) higher aortic TBR while current smoking was marginally associated with a lower TBR [-0.11 (95%CI -0.22 to 0.01); p=0.07]. Spleen SUV was not associated with either HIV or smoking in unadjusted or adjusted models. There was no evidence for an HIV*smoking interaction for aortic TBR or spleen SUV models (all p>0.1). In unadjusted models, spleen SUV was associated with presence of coronary calcification [OR per 1 standard deviation increase in SUV 1.7 (95%CI 1.0-2.9), p=0.047], but this was attenuated in fully adjusted models (p=0.15). Soluble CD163 was positively associated with spleen SUV in fully adjusted models (p=0.05), but not with aortic TBR (p=0.9).
Conclusion: To our knowledge, this is the largest sample of HIV+ subjects studied by PET/CT to date, allowing us to explore important relationships with traditional and non-traditional risk factors. As measured by aortic FDG uptake, HIV is associated with increased aortic inflammation independent of traditional risk factors. In contrast, current smoking is marginally associated with lower aortic inflammation.

629 CRP PREDICTS SUBCLINICAL CVD PROGRESSION IN HIV- BUT NOT HIV+ WOMEN

Caitlin A. Moran[1], Aswani Vunnava[1], Anandi N. Sheth[1], Christina Mehta[1], Phyllis Tien[2], Michael Plankey[3], Elizabeth T. Golub[4], Arshed Quyyumi[1], Robert C. Kaplan[5], Igho Ofotokun[1]
[1]Emory Univ, Atlanta, GA, USA, [2]Univ of California San Francisco, San Francsico, CA, USA, [3]Georgetown Univ, Washington, DC, USA, [4]The Johns Hopkins Univ, Baltimore, MD, USA, [5]Albert Einstein Coll of Med, Bronx, NY, USA

Background: HIV infection is associated with an increased risk of early cardiovascular disease (CVD), but identifying those with HIV who would benefit from targeted CVD risk modification remains challenging. Biomarkers including C-reactive protein (CRP) improve CVD event prediction in the general population, but their use in the HIV population is less clear. We assessed the association of CRP with subclinical CVD progression among women enrolled in the Women's Interagency HIV Study (WIHS).
Methods: Retrospective analysis of the WIHS cardiovascular substudy, in which B-mode carotid artery (CA) ultrasound was performed at baseline (BL) and at 1-3 follow-up visits from 2004-2013 to assess CA plaques and common carotid artery intima-media thickness (CIMT). High sensitivity (hs) CRP was measured previously from plasma obtained at BL. We used multivariable logistic and linear regression models stratified by HIV serostatus to determine the association of BL hsCRP with CA plaque and CIMT progression, defined as increases in plaque number and in CIMT between BL and final visits, adjusting for traditional CVD risk factors.
Results: 783 women [572 HIV(+), 211 HIV(-), 62% Black, 29% Hispanic, median age 41 (IQR 35-47) years] were followed for a median 6.6 (IQR 6.4-7.0) years. Among HIV(+) participants, median CD4 was 452 (IQR 288-658) cells/mm3 and 46% had HIV RNA <80 cop/mL at BL. BL median (IQR) 10-year Framingham risk score was 8 (3-12) in HIV(+) vs. 9 (3-13) in HIV(-), p=0.43). BL median (IQR) hsCRP was 2.2 (0.8-5.3) mg/L in HIV(+) and 3.2 (0.9-7.7) mg/L in HIV(-) women (p=0.005). Unadjusted CA plaque progression occurred in 65 (12%) vs. 15 (8%) of HIV(+) and HIV(-) women, respectively. Mean (SD) CIMT change was 25 (47) µm in HIV(+) women and 26 (62) µm in HIV(-) women. The adjusted odds of CA plaque progression in HIV(+) women were 0.99 (95%CI 0.77-1.28) per unit increase of hsCRP (p=0.94) and 3.74 (95%CI 1.34-10.24) in HIV(-) women (p=0.01). The adjusted mean difference in CIMT change per unit increase in hsCRP among HIV(+) women was 3.0 µm (95%CI -1.5-7.5, p=0.20) and 5.4 µm (95%CI 0.2-10.7, p=0.04) in HIV(-) women.

Conclusion: HsCRP was associated with progression of CA plaques and CIMT in HIV(-), but not HIV(+), women despite similar BL CVD risk, suggesting that the pathogenesis and therefore the biomarkers associated with subclinical CVD may be different in the setting of HIV infection. Additional studies of CVD pathogenesis in the HIV population are warranted to aid targeted CVD risk modification.

630 SERUM ST2 IS AN INDEPENDENT PREDICTOR OF ALL-CAUSE MORTALITY IN HIV-INFECTED PATIENTS

Rodolphe Thiébaut[1], Sophie Hue[2], Fabien LeMarec[1], Jean Daniel Lelievre[2], Michel Dupon[3], Emile Foucat[2], Isabelle Pellegrin[3], Christine Lacabaratz[2], Fabrice Bonnet[3], Yves Levy[2]
[1]INSERM, Bordeaux, France, [2]INSERM, Créteil, France, [3]CHU de Bordeaux, Bordeaux, France

Background: Soluble Suppression of Tumorigenicity 2 (sST2) is a decoy receptor of IL-33. The IL-33/ST2 axis is involved in several inflammatory and immune diseases. The predictive value of sST2 for death in HIV infection is unknown.

Methods: Patients enrolled in the ANRS CO3 Aquitaine Cohort, a prospective hospital-based cohort of HIV-1-infected patients, who had a plasma sample available in the bio-bank were systematically eligible. sST2 and sCD14 were measured using Luminex® multiplex bead-based technology (R&D Systems) and a Bio-Plex 200 instrument (BioRad). Mean coefficient of variation was <12% for sST2 and <14% for sCD14. A good correlation between ELISA and Luminex technology was observed. Predictive capacities of sST2, sCD14 and of the Veteran Aging Cohort Study (VACS) clinical score at baseline on overall mortality were compared using multivariable Cox proportional hazards models adjusted for sex, age, tobacco consumption, anemia, duration of viral load > 500 cp/mL, low glomerular filtration, history of diabetes or cancer and hepatitis B virus infection.

Results: During a median follow-up of 7.2 years (IQR: 6.0; 7.9), 93 deaths from all causes (incidence rate 9.9 per 1000 patient-years; 95% confidence interval 7.9; 11.9) were reported in 1,414 patients with median baseline CD4+ cell count of 742 cells/mm3 (inter-quartile range [IQR]: 545; 970). The median sST2 baseline concentration was 22.9 ng/mL (IQR: 17.7; 30.3) and was higher (30.8 ng/mL, IQR: 21.5; 42.1) in patients who died as compared to those who stayed alive (22.6 ng/mL; IQR: 17.5; 29.6) (p<10-4). An increased risk of death of 2% for a concentration 1.0 ng/mL higher of sST2 remained after adjustment for sCD14 and VACS score (adjusted hazard ratio: 1.02; p<10-4). Compared to those with <17.7 ng/mL (first quartile), patients with >30.3 ng/mL (fourth quartile) had a three-fold higher probability of dying during follow-up (HR=3.31, 95% CI [1.53; 7.15], p<10-3). The predictive capacity of sST2 was confirmed in a validation cohort (n=246, 15 deaths) with an improved area under the curve from 0.708 without sST2 to 0.724 with sST2.

Conclusion: sST2 is a new valuable biomarker to evaluate the risk of all-cause mortality in HIV disease. These results validate sST2/IL-33 as an emerging key pathway that could be involved in systemic disease including HIV infection.

631 A LOWER CD COUNT PREDICTS MOST CAUSES OF DEATH EXCEPT CARDIOVASCULAR DEATHS

Gisela Leierer[1], Armin Rieger[2], Brigitte Schmied[3], Mario Sarcletti[1], Maria Geit[4], Bernhard Haas[5], Ninon Taylor[6], Michaela Rappold[1], Bruno Ledergerber[7], **Robert Zangerle**[1]
[1]Med Univ of Innsbruck, Innsbruck, Austria, [2]Med Univ of Vienna, Vienna, Austria, [3]Otto-Wagner Hosp, Vienna, Austria, [4]Kepler Univ Hosp Linz, Linz, Austria, [5]General Hosp Graz South-West, Graz, Austria, [6]Paracelsus Med Univ, Salzburg, Austria, [7]Univ of Zurich, Zurich, Switzerland

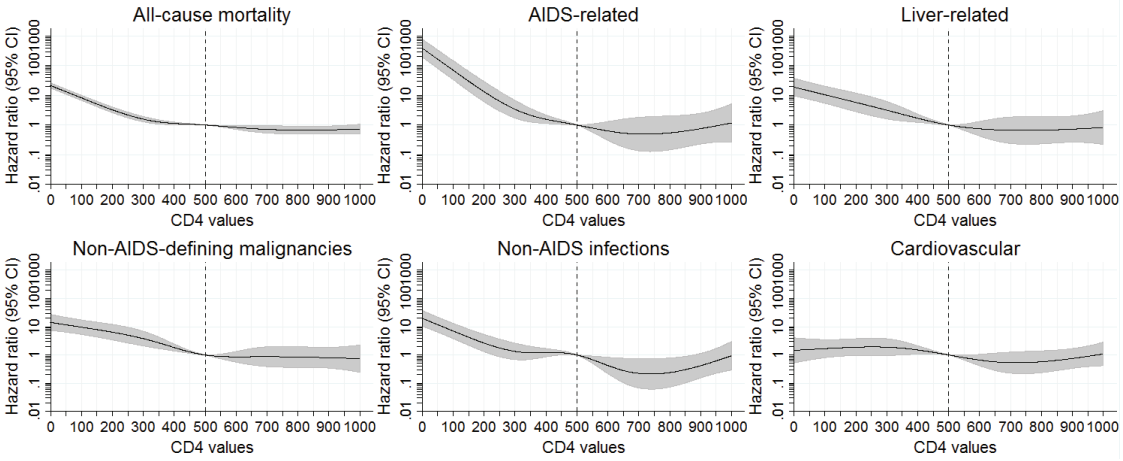
Background: To investigate changes in mortality rates and predictors of all-cause mortality as well as specific causes of death over time among HIV-positive individuals in the combination antiretroviral therapy (cART) era.

Methods: We analyzed all-cause as well as cause-specific mortality among the Austrian HIV Cohort Study between 1997 and 2014. Observation time was divided into five periods: period 1: 1997-2000; period 2: 2001-2004; period 3: 2005-2008; period 4: 2009-2011; and period 5: 2012-2014. Mortality rates are presented as deaths per 100 person-years (d/100py). Potential risk factors associated with all-cause mortality and specific causes of death were identified by using multivariable Cox proportional hazard models. Models were adjusted for time-updated CD4, age and cART, HIV transmission category, population size of residence area and country of birth. To assess potential nonlinear associations we fitted all CD4 counts per patient using restricted cubic splines with truncation at 1000 cells/mm^3. Vital status of patients was cross-checked with death registry data.

Results: Of 6852 patients (59,704 person-years of observation), 1192 died: 380 (31.9%) from AIDS-related diseases. All-cause mortality rates decreased continuously from 3.49 d/100py in period 1 to 1.40 d/100py in period 5. Death due to AIDS-related diseases, liver-related diseases and Non-AIDS infections declined, whereas cardiovascular diseases as cause of death remained stable (0.27 d/100py in period 1, 0.10 d/100py in period 2, 0.16 d/100py in period 3, 0.09 d/100py in period 4 and 0.14 d/100py in period 5, respectively) and deaths due to Non-AIDS-defining malignancies increased. Compared to latest CD4 counts of 500 cells/mm^3, lower CD4 counts conferred a higher risk of deaths due to AIDS-related diseases, liver-related diseases, Non-AIDS infections and Non-AIDS-defining malignancies, whereas no significant association was observed for cardiovascular mortality (Fig. 1). Results were similar in sensitivity analyses where observation time was divided into 2 periods: 1997-2004 and 2005-2014.

Conclusion: Since introduction of cART, risk of death decreased and causes of death changed. We do not find evidence that HIV-positive individuals with a low CD4 count are more likely to die from cardiovascular diseases.

Fig. 1: Associations of latest CD4 counts with all-cause mortality and specific causes of death.
Results from adjusted Cox regression models including all time periods.



632 ASSOCIATIONS BETWEEN HIV CONTROLLER STATUS AND SUBCLINICAL CAROTID ATHEROSCLEROSIS

Rebeccah McKibben[1], David B Hanna[2], Sabina Haberlen[3], Robert C Kaplan[2], Frank J Palella[4], Elizabeth T Golub[1], Peter Bacchetti[5], Ruth Greenblatt[5], Todd Brown[6], Wendy Post[1]
[1]Johns Hopkins Univ, Baltimore, MD, USA, [2]Albert Einstein Coll of Med, Bronx, NY, USA, [3]Johns Hopkins Bloomberg SPH, Baltimore, MD, USA, [4]Northwestern Univ, Chicago, IL, USA, [5]Univ of California, San Francisco, San Francisco, CA, USA, [6]Johns Hopkins Univ, Baltimore, MD, USA

Background: Heightened immune activation among HIV-infected persons may contribute to atherosclerosis. In the absence of antiretroviral therapy (ART), HIV controllers (HC) maintain viral suppression yet exhibit enhanced immune activation compared with HIV-uninfected (HIV-) and ART-treated HIV-infected (ART-HIV+) individuals. We compared the presence of subclinical carotid atherosclerosis among HIV controller populations with that among ART-HIV+ and HIV- participants of the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS). We hypothesized that HC would exhibit a greater prevalence of atherosclerosis compared to HIV- individuals.
Methods: B-mode carotid artery ultrasound was performed on MACS and WIHS participants. HC were defined as 1) viremic controllers (VC, HIV RNA ≤2,000 copies/mL for ≥2 years not on ART) or 2) long-term non-progressors (LTNP) (CD4+ T-cell counts ≥500 cells/μL for ≥5 years not on ART). Participants who ever satisfied the definition of HC were included in this category, even if they no longer met criteria when imaged. Prevalence of plaque was compared between HC, HIV+ (± detectable viremia) and HIV- individuals (reference) using Poisson regression with robust standard errors adjusting for age, race/ethnicity, income, education, center, alcohol use, smoking, BMI, diabetes, systolic blood pressure, total and HDL cholesterol, hypertensive and cholesterol medications.
Results: 3046 (2051 HIV+, 955 HIV-) men and women were studied, including 144 VC and 140 LTNP. Of the VC, 23% were EC and 45% also met the definition of LTNP. There was no statistically significant difference in the presence of carotid plaque between HIV controllers and HIV- individuals (VC prevalence ratio [PR] 0.97, 95% confidence interval [CI] 0.66-1.42; LTNP PR 1.06, CI 0.76-1.49), and a marginally statistically significant difference between HIV+ individuals without detectable viremia and HIV- individuals (PR 1.22, CI 0.998-1.48). In contrast, HIV+ individuals with detectable viremia more frequently had carotid plaque (PR 1.37, CI 1.06-1.79) compared to HIV- individuals.
Conclusion: The presence of subclinical carotid artery atherosclerosis among viremic controllers or LTNP was similar to that of HIV- individuals. However, HIV+ individuals with detectable viremia were substantially more likely to have carotid plaque. These results indicate that uncontrolled viremia likely plays an important role in development of atherosclerosis in HIV infection.

Table. Association between HIV controller status and presence of carotid artery lesion

	WIHS (N=1733)		MACS (N=1308)		WIHS + MACS (N=3041)	
	PR	95% CI	PR	95% CI	PR	95% CI
HIV-	1.00	Reference	1.00	Reference	1.00	Reference
Other HIV+, detectable	1.49	(0.96, 2.31)	1.23	(0.94, 1.62)	1.38	(1.11, 1.72)
Other HIV+, undetectable	1.16	(0.71, 1.88)	1.20	(0.97, 1.48)	1.22	(0.998, 1.48)
Viremic controller	0.47	(0.06, 3.53)	1.08	(0.74, 1.56)	0.97	(0.66, 1.42)
HIV-	1.00	Reference	1.00	Reference	1.00	Reference
Other HIV+, detectable	1.45	(0.94, 2.24)	1.24	(0.94, 1.63)	1.37	(1.10, 1.71)
Other HIV+, undetectable	1.11	(0.68, 1.81)	1.21	(0.98, 1.49)	1.21	(0.995, 1.48)
Long term non-progressor	1.02	(0.14, 7.39)	1.08	(0.77, 1.51)	1.06	(0.76, 1.49)

PR = prevalence ratio, CI = confidence interval. Controller includes elite/viremic controllers. Multivariable models are adjusted for age, race/ethnicity, smoking, income, education, center, alcohol use, BMI, diabetes, systolic blood pressure,, total and HDL-cholesterol, and medications for blood pressure and cholesterol.

633 ASSOCIATION BETWEEN CARDIOVASCULAR EVENTS AND HIV-SPECIFIC RISK FACTORS

Stefan Esser[1], Norbert H. Brockmeyer[2], Martin Hower[3], Volker Holzendorf[4], Christina Schulze[5], Marina Arendt[5], Till Neumann[6], Nico Reinsch[7], for the HIV HEART Study Group
[1]Univ Hosp Duisburg-Essen, Essen, Germany, [2]Ruhr-Univ Bochum, Bochum, Germany, [3]City Hosp Dortmund, Dortmund, Germany, [4]Univ Leipzig, Leipzig, Germany, [5]Univ Hosp Essen, Essen, Germany, [6]Cardiologic Outpatient Clinic Staubach, Bochum, Germany, [7]Alfried Krupp Hosp, Essen, Germany

Background: In the aging HIV-positive patients (HIV+) cardiovascular events (CVE) and strokes are more frequent than in the general population. Traditional risk scores underestimate the rates. The increased risk of HIV+ may be explained by effects of the HIV infection itself, antiretroviral treatment (ART), drug use, coinfections and vascular inflammation.
Methods: We investigated the effect of known cardiovascular risk factors (CRF) and HIV-specific risk factors (HRF) on CVE (Figure 1) in 1481 HIV+ outpatients of the prospective multicenter HIV HEART cohort study (HIVH) performed in the German Ruhr area since 2004. CVE were defined as a diagnosis of myocardial infarction, stroke, coronary heart disease, heart failure or death of any reason. CRF are smoking behavior, diabetes mellitus, arterial hypertension and age. Cox proportional hazard models were used to determine the effect of CRF and HSF on CVE. We calculated hazards ratios (HR) and corresponding 95% confidence intervals. As time to event we define the duration from study start to the first CVE or last contact.
Results: The mean age of the 1481 HIV+ at their last follow-up visit was 50.8±10.7 years (Y) and the mean duration of HIV-infection of 14.7±7.6 Y (84% male, 88% Caucasian, 51.8% MSM). 33% of the HIV+ had already AIDS in their medical history. Mean CD4-cell count was 639±306 cells/μl and the mean CD4/CD8 ratio 0.9±3.0. 84.9% of the 1428 ART-treated HIV+ had an HIV-RNA below the level of detection (<50 Copies (c)/ml). The mean duration of ART was 13.6±8.2 Y. Most HIV+ get two NRTIs combined with one NNRTI (35.2%), PI (35.8%) or INI (13.3%). Chronic HCV-coinfection was diagnosed in 161 (11%) HIV+. Mean Framingham risk score was 8.3±7.7 (diabetes 8.6%, current smoker 43.6%, arterial hypertension 30.4%). During a follow-up period of 6.9±3.0 Y 373 CVE in 215 HIV+ had been observed. HRF at Baseline (BL) which were independently associated with a shorter time to the first CVE, were AIDS (Adjusted HR 1.41 [1.06 to 1.89]; p=0.018), lower CD4/CD8 Ratio [decline of one unit] (HR 2.19 [1.18 to 4.03]; p=0.012) and detectable HIV-RNA [≥ 50 c/ml] (HR 1.49 [1.10 to 2.00]; p=0.009). Smoking at BL was the traditional CRF with the highest HR (3.20 [2.33 to 4.41]; p<0.001).
Conclusion: HIV specific factors, such as AIDS, CD4/CD8 ratio or detectable HIV RNA were independently associated with an increased cardiovascular risk but not the duration of ART. Traditional CRF maintained a major effect on CVE.

634 IMPAIRED ANTIVASCULAR CONTRACTION OF PERIVASCULAR ADIPOSE TISSUE IN HIV INDIVIDUALS

Dan Wang, Cheng Wang, Cuiwei Wang, Chenglong Liu, Jennifer Verbesey, Philena Sun, Seble Kassay, Mary Young, Christopher Wilcox, for the Hypertension, Kidney, and Vascular Research Center and DC Women's Interagency HIV Study
Georgetown Univ, Washington, DC, USA

Background: Perivascular adipose tissue (PVAT) exhibits anti-contractile capacity to regulate vascular tone, whereas reactive oxygen species (ROS) impair vascular function. But PVAT effects on microvessels in HIV are unexplored. We previously reported an enhanced vascular contraction in subcutaneous microvascular arterioles (SMAs) dissected from a gluteal skin biopsy in HIV infected individuals. We tested the hypothesis that HIV associated microvascular dysfunction, at least partially by augmented microvascular ROS and impaired PVAT anti-contractile function and signaling.
Methods: SMAs were prepared from HIV-infected (n=8) and matched HIV-uninfected young African American women (n=6) enrolled in the DC Women's Interagency HIV Study (DC-WIHS). HIV-infected participants were virally suppressed on HAART and had no identified other CVD risk factors. The concentration-contractile responses to U-46,619 and phenylephrine (PE) in PVAT-intact or denuded SMAs were recorded by a wire myograph. Microvascular cellular ROS generation (temp-9AC fluorescence) and mitochondria ROS (MitoSOX Red fluorescence) were quantitated by RatioMaster system. The ROS biomarkers (malondialdehyde, MDA) and adipokines were measured in adipose fat homogenate and/or plasma.
Results: HIV-infected participants had significantly increased (P<0.05) adipose MDA (15.1 ± 2.5 vs 10.9 ± 2.6 ng/mg protein) and adipose leptin (40 ± 9 vs 28 ± 7 ng/mg protein); and reduced adiponectin in plasma (14 ± 2 vs 23 ± 2 ng/ml and in PVAT (2.1 ± 0.3 vs 4.6 ± 1.3 ng/mg protein, p<0.05. U-46,619 induced contraction (199 ± 22 vs 131 ± 16%, P<0.05), endothelin-1 induced cellular ROS (Δ0.32 ± 0.05 vs 0.10 ± 0.02 fluoresce unit) and mitochondria ROS (Δ0.10 ± 0.04 vs 0.09 ± 0.04 fluoresce unit) were significantly increased in PVAT-denuded vessels from HIV-infected participants (p<0.05). PVAT significantly (p<0.05) reduced contraction response to U-46,619 in both groups, but the reduction (anti-contraction) of U46,619 response was smaller in the PVAT intact-vessel (47 ± 3 vs 68 ± 4%, P<0.05). The contraction and anti-contractile response to PE had no difference between HIV and control group.
Conclusion: HIV-infected individuals have increased intrinsic vascular effects of ROS leading to reduction of the beneficial microvascular PVAT signaling pathway on microvascular contractile reactivity. Therapeutic targets for vascular dysfunction in HIV should include ROS elimination and its extravascular actions on PVAT.

635LB NOVEL IMAGING STRATEGY SHOWS HIGH-LEVEL AORTIC CD206+ MACROPHAGE INFILTRATION IN HIV

Markella V. Zanni[1], **Mabel Toribio**[1], Moses Q. Wilks[1], Michael T. Lu[1], Tricia H. Burdo[2], Fred Cope[3], Udo Hoffmann[1], Kenneth C. Williams[4], Georges El-Fakhri[1], Steven K. Grinspoon[1]
[1]Massachusetts General Hosp, Boston, MA, USA, [2]Temple Univ, Philadelphia, PA, USA, [3]Navidea Biopharmaceuticals, Dublin, OH, USA, [4]Boston Coll, Chestnut Hill, MA, USA

Background: Systemic monocyte activation and arterial macrophage infiltration are thought to contribute to heightened cardiovascular disease (CVD) risk in HIV. Current in vivo investigative techniques including 18-F fluorodeoxyglucose (18F-FDG) uptake on positron emission tomography/computed tomography (PET/CT) do not allow for quantification of macrophage-specific arterial inflammation.
Methods: We performed a first-in-human investigation testing whether systemic administration of 99mTc-tilmanocept (which specifically binds CD206+ macrophages) would enable quantification of arterial macrophage infiltration. Our primary outcome measure, aortic 99mTc-tilmanocept uptake on SPECT/CT, was assessed among 6 HIV-infected subjects with subclinical atherosclerosis and 3 non-HIV-infected subjects with similar Framingham Risk Scores. The clinical significance of aortic 99mTc-tilmanocept uptake was established through relation to atherosclerotic plaque burden on computed tomography angiography (CTA) and to measures of systemic immune activation.
Results: 99mTc-tilmanocept uptake localized to three regions: kidney, liver, and aorta. High-level 99mTc-tilmanocept uptake (>/=5x uptake in muscle as a reference region representing non-specific tissue and blood pool uptake) was apparent across 20.4% of the aortic surface volume in HIV-infected subjects versus 4.3% in controls (P=0.009). Among all subjects, aortic high-level 99mTc-tilmanocept uptake related robustly to non-calcified plaque volume (r=0.78, P=0.01) and to circulating levels of soluble CD14 (ρ=0.72, P=0.03), CD14+CD16- monocytes (ρ=0.77, P=0.02), CD8+ T cell count (ρ=0.73, P=0.02), and CD8+PD1+ T cells (ρ=0.70, P=0.04). Ex vivo experiments on banked aortic tissue demonstrated increased CD206+ macrophage infiltration among HIV-infected subjects vs. controls (30.1±7.9 vs. 14.2±7.0 macrophages/mm2, P=0.0002) and significant tilmanocept co-localization with CD206+ macrophages. Figure 1.
Conclusion: Application of a novel macrophage-specific molecular imaging strategy highlights the high degree of aortic macrophage infiltration among HIV-infected subjects with low Framingham Risk Scores and shows that aortic macrophage infiltration relates strongly to CV risk parameters and select systemic immune parameters. Macrophage-specific imaging strategies may help elucidate immune mechanisms of macrophage-mediated end-organ damage in HIV and may identify HIV-infected patients at risk for such complications.

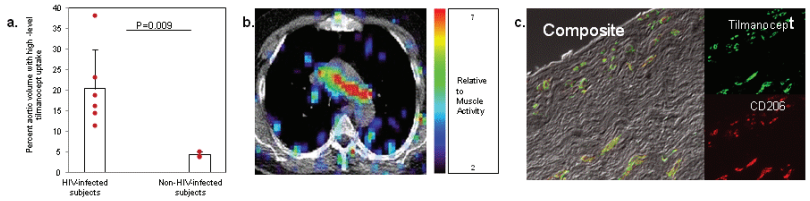


Figure: a. The percent aortic volume with high-level ^{99m}Tc-tilmanocept uptake was significantly increased among the HIV-infected subjects (N=6) compared to the non-HIV-infected subjects (N=3) (P=0.009). Results are mean ± SD. b. ^{99m}Tc –tilmanocept SPECT/CT of representative HIV-infected subject demonstrating high-level tilmanocept uptake in the aorta. Aortic volume with high-level ^{99m}Tc-tilmanocept uptake for this subject was 103,901mm^3 and the percent aortic volume was 38.1%. c. Double-label immunofluorescence using a CD206 antibody and tilmanocept-Alexa-488 revealed a high and similar degree of co-localization of tilmanocept and CD206 in sections from HIV-infected (N=10) and non-HIV-infected individuals (N=10) (89.1 ± 6.3 % vs. 86.3 ± 6.8 %, respectively). The percentage of CD206+ tilmanocept- macrophages and the percentage of CD206-tilmanocept+ macrophages in the HIV-infected individuals (N=10) vs. the non-HIV-infected subjects (N=10) were 7.8 ± 7.0% vs. 10.4 ± 6.2% and 3.1 ± 1.8% vs. 3.3 ± 2.1%, respectively. Results are mean ± SD.

636LB GUT MICROBIOTA, TRYPTOPHAN CATABOLISM AND ATHEROSCLEROSIS IN HIV INFECTION

Qibin Qi[1], Simin Hua[1], David B. Hanna[1], Clary Clish[2], Jason Lazar[3], Wendy Post[4], Kathryn Anastos[1], Robert Burk[1], Robert C. Kaplan[1]
[1]Albert Einstein Coll of Med, Bronx, NY, USA, [2]Broad Inst of MIT and Harvard, Cambridge, MA, USA, [3]SUNY Downstate Med Cntr, Brooklyn, NY, USA, [4]Johns Hopkins Univ, Baltimore, MD, USA

Background: Gut microbiota alteration and disturbed tryptophan catabolism have been observed in HIV infection. Yet, the relationship of tryptophan catabolism with HIV-related cardiovascular disease (CVD) risk remains unknown.
Methods: Plasma metabolomics profiling (including 155 soluble metabolites of known identity) was performed in 407 women (294 HIV+, 113 HIV-) in the Women's Interagency HIV Study (WIHS) and 339 men (229 HIV+, 110 HIV-) in the Multicenter AIDS Cohort Study who underwent repeated B-mode carotid artery ultrasound imaging in 2004 2013. We

examined associations of plasma tryptophan, kynurenic acid, a metabolite of tryptophan catabolism, and tryptophan-to-kynurenic acid (Kyn/Trp) ratio, a measure of tryptophan catabolism, with incident carotid plaque (focal intima-media thickness >1.5 mm) over 7 years (all participants without carotid plaque at baseline). High-resolution bacterial community profiling was performed in fecal samples in 49 WIHS women.

Results: Over 7 years, 114 participants developed incident carotid plaque. Plasma tryptophan was significantly associated with decreased risk of incident carotid plaque (RR 0.75 [95% CI 0.64-0.88] per SD), while kynurenic acid (RR 1.34 [1.08-1.65] per SD) and Kyn/Trp ratio (RR 1.41 [1.22-1.64] per SD), were significantly associated with increased risk of incident carotid plaque (Figure 1A), after correction for multiple testing on 155 metabolites. Plasma tryptophan was significantly lower (P<0.001), while Kyn/Trp ratio was significantly higher (P=0.01) in HIV+ vs. HIV- persons (Figure 1B). Of note, tryptophan and related metabolites correlated with HIV viral load and specific inflammation/immune activation markers (e.g., sCD14, T-cell activation surface markers) rather than global inflammation markers or traditional CVD risk factors (Figure 1C). In addition, we identified that gut microbes enriched in Proteobacteria phylum were significantly correlated with decreased plasma tryptophan and increased plasma kynurenic acid and Kyn/Trp ratio, after correction for multiple testing on 193 taxa.

Conclusion: Our data indicate that disturbed tryptophan catabolism and related metabolites, correlating with HIV infection parameters, specific inflammation/immune activation markers, and gut microbiota dysbiosis, may play a role in the progression of HIV-related atherosclerosis. Our study suggests a potential modifiable target for the prevention and intervention of CVD in people with HIV, though further investigations are needed.

637 INTEGRATING CARDIOVASCULAR DISEASE RISK-FACTOR SCREENING IN HIV SERVICES IN SWAZILAND

Miriam Rabkin[1], Anton M. Palma[1], Margaret L. McNairy[1], Samkelo Simelane[2], Averie B. Gachuhi[1], Raymond A. Bitchong[3], Harriet Nuwagaba-Biribonwoha[1], Pido Bongomin[2], Velephi Okello[4], Wafaa M. El-Sadr[1]

[1]ICAP at Columbia Univ, New York, NY, USA, [2]ICAP Swaziland, Mbabane, Swaziland, [3]Raleigh Fitkin Memorial Hosp, Manzini, Swaziland, [4]Swaziland Ministry of Hlth, Mbabane, Swaziland

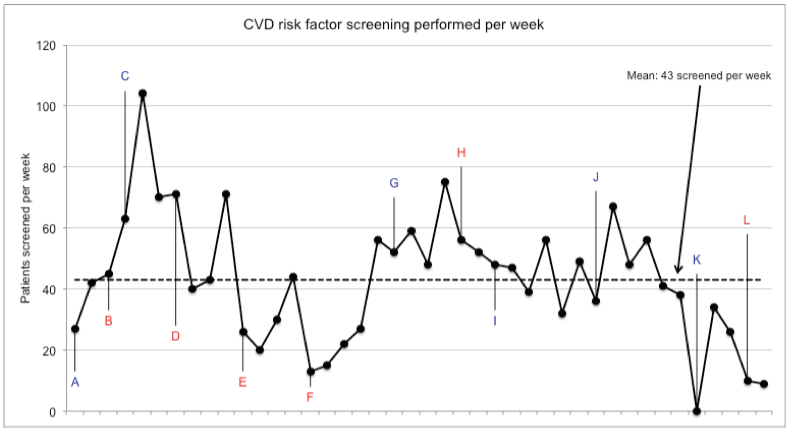
Background: Cardiovascular disease risk factors (CVDRF) are prevalent among people living with HIV (PLWH), yet routine screening for CVDRF in HIV programs in sub-Saharan Africa is uncommon. We assessed the feasibility and acceptability of CVDRF screening of adults on antiretroviral therapy (ART) at a large HIV clinic in Swaziland.

Methods: PLWH ≥40 years on ART were screened via blood pressure (BP) measurement, assessment of tobacco use, and point-of-care (POC) testing for HbA1c and total cholesterol (TC). Hypertension (HTN) was defined as SBP > 140 mmHg, DBP > 90 mmHg, and/or current use of anti-HTN medication. Diabetes mellitus (DM) was defined as HbA1c > 6.5% and/or current use of DM medication. High cholesterol (HC) was defined as TC > 6.2 mmol/L. WHO/ISH risk stratification was used to assess 10-yr CVD risk. Screened and unscreened patients (pts) were observed using external-observer continuous observation time-motion methodology. We compared total visit time and time spent on HIV services among screened/unscreened pts using Wilcoxon rank-sum tests. We tracked the number of pts screened per week and explanations for variation in screening volume using a run chart. A subset of screened pts participated in exit interviews.

Results: 1,826 ART pts were screened for CVDRF over a period of 42 weeks, of whom 1,063 (58%) were women. 532 (29%) had one CVDRF and 140 (8%) had ≥ 2 CVDRF. 407 pts (22%) had HTN, 167(9%) were smokers, 136 (7%) had HC, and 116 (6%) had DM. 36 pts (2%) had ≥ 10% 10-year CVD risk. Time-motion data from the visits of 172 pts (50 unscreened, 122 screened) showed that visit length for screened pts was significantly higher than for unscreened pts (median 15 min vs. 4 min, p <0.01) with no difference in the time spent providing HIV services (p = 0.57). The most time-consuming elements were POC testing (median 10 min, range 4-20) and BP measurement (median 2 min, range 0-3). On average, 43 pts were screened per week; screening volume varied markedly, and was limited by challenges related to staffing, space, systems, and supplies (Figure 1). 126 pts participated in exit interviews; all described the screening process as satisfactory and indicated that they would recommend it to others.

Conclusion: While screening for CVDRF added substantial time to visits, with implications for staffing and wait time, routine screening of PLWH for CVDRF was feasible and appreciated by pts. It was also high-yield, identifying CVDRF in 37% of PLWH screened.

Figure 1: Implementation of CVDRF Screening: Barriers and Facilitators



KEY: Timeline of screening activities and clinic events (Sept 2015 to June 2016)
Blue = issues related to space, supplies, and systems, Red = issues related to staffing

	Date (MM/DD)	Description
A	09/14	1st screening room opened
B	09/28	Additional nurses posted to RFM
C	10/5	2nd screening room opened
D	10/26	Kaposi's Sarcoma clinic opened; fewer nurses available
E	11/23	Baby clinic opened, off-site trainings occurred; fewer nurses available
F	12/21-12/31	Clinic short 4 nurses for the holidays
G	2/1	Study staff start helping with screening
H	2/22	Clinic nurses reduce screening due to presence of study staff
I	3/7	BP machine broke
J	4/18	Early morning screening and enrollment begins
K	5/30	POC test kit stock-out
L	6/20	No clinic nurses assigned to screening

638 COMPOSITE "HIV/ HYPERTENSION/ DIABETES CONTROL" OUTCOME IN SEARCH CHRONIC CARE MODEL

Dalsone Kwariisima[1], Jeanna Wallenta[2], James Ayieko[3], Florence Mwangwa[4], Asiphas Owaraganise[4], Tamara D. Clark[2], Edwin D. Charlebois[2], Maya L. Petersen[5], Diane V. Havlir[2], Moses R. Kamya[6]

[1]Makerere Univ Joint AIDS Prog, Kampala, Uganda, [2]Univ of California San Francisco, San Francisco, CA, USA, [3]Kenya Med Rsr Inst, Nairobi, Kenya, [4]Infectious Diseases Rsr Collab, Kampala, Uganda, [5]Univ of California Berkeley, Berkeley, CA, USA, [6]Makerere Univ Coll of Hlth Scis, Kampala, Uganda

Background: With the aging HIV population, health outcomes for HIV-infected adults need to be evaluated in a broader outcomes model that incorporates non-communicable diseases (NCD) such as hypertension (HTN) and diabetes (DM). We assessed prevalence and predictors of composite HIV, HTN and DM control in a multi-disease chronic care management delivery system used in the ongoing SEARCH HIV test and treat study (NCT01864603)

Methods: Population-based screening for HIV, HTN and DM was conducted in 10 rural Ugandan communities on 39,569 adults (≥15 years) attending multi-disease community health fairs. We examined outcomes in HIV+ adults with DM, HTN or both receiving care through an integrated HIV streamlined care model that included nurse triage, 3 month visits and patient centered care at a local government sponsored clinic. Disease "control" definitions were 1) HIV: RNA<500 copies/ml; 2) HTN: systolic< 40 mm Hg and diastolic<90 mm Hg; and, 3) DM: blood sugar < 12 mmol/L). We evaluated multivariate predictors of control over 3 years (missing=fail), adjusting for occupation, age, sex, baseline viral suppression, and mobility using logistic regression with robust standard errors.

Results: Of 193 HIV infected adults with a NCD, the majority were co−diagnosed with HTN only (178/193(92%)), 13(7%) had DM only and 2 (1%) had both HTN and DM. The median age of those with HIV and any NCD was 44 years (IQR: 38, 51) overall, 45 (IQR: 38, 52) among the 73 males and 44 (IQR: 37.5, 51) among the 120 females. After up to 3 years of follow up, 174/193 (90%) of persons had ever achieved HIV RNA suppression. However the composite endpoint of both HIV and HTN control was achieved in only 67% (114/178). In those adults with DM, 12/13 had blood sugar controlled and 69% (9/13) achieved both HIV and DM control. Among the 2 patients with both HTN and DM, all 3 diseases were controlled. Among adults with HIV and HTN, only mobility (defined as >1 month living outside of community in the past 12 months) was associated with a lower risk for composite control (OR: 0.35; 95% CI: 0.13, 0.98; p-value=0.046)

Conclusion: Using a composite endpoint, 69% (133/193) of adults had controlled HIV and NCD after 2 years, lagging behind HIV control only (90%) in this population receiving an integrated chronic care model. Composite endpoint should be used to assess progress in the future in integrated HIV/NCD care.

639 THE ART ADVANTAGE: HEALTHCARE UTILIZATION FOR DIABETES & HYPERTENSION IN SOUTH AFRICA

Jennifer Manne-Goehler[1], Livia Montana[2], Xavier Gomez-Olive[3], Guy Harling[4], Ryan Wagner[5], Alisha Wade[6], Julia K. Rohr[2], Stephen Tollman[7], Till Baernighausen[8], Thomas Gaziano[9]

[1]Beth Israel Deaconess Med Cntr, Boston, MA, USA, [2]Harvard Univ, Cambridge, MA, USA, [3]Tintswalo Hosp, Acornhoek, South Africa, [4]Harvard Univ, Boston, MA, USA, [5]Univ of the Witwatersrand, Acornhoek, South Africa, [6]MRC/Wits Rural Pub Hlth and Hlth Transitions Rsr Unit, Johannesburg, South Africa, [7]Univ of Witwatersrand, Johannesburg, South Africa, [8]Heidelberg Univ, Heidelberg, Germany, [9]Brigham and Women's Hosp, Boston, MA, USA

Background: There is a growing recognition that HIV-infected populations also face an increasing burden of diabetes and hypertension but limited understanding of the role that ART programs play in the delivery of services for these comorbid conditions. The aim of this study is to assess the relationship between ART and utilization of healthcare services for diabetes and hypertension.

Methods: The Health and Aging in Africa: Longitudinal Studies of INDEPTH Communities (HAALSI) Study is a cohort of 5,059 adults aged 40+ in Agincourt, rural South Africa. The study collects biomarker-based data on HIV (HIV antibody and viral load, biomarkers for exposure to lamivudine and emtricitabine), diabetes (point-of-care glucose) and hypertension (systolic and diastolic blood pressure), as well as self-reported data on healthcare utilization (self-reported testing, awareness, preventive counseling and treatment for diabetes and hypertension). We calculated differences in healthcare utilization by HIV and ART status, where ART use was defined exclusively by biomarker-based testing for ART exposure. We did multivariable logistic regressions to estimate the relationship between ART and measures of healthcare services for diabetes and hypertension, controlling for age, sex, body mass index (BMI), educational attainment and wealth quintile.

Results: The prevalence of diabetes and hypertension were as follows: HIV-negative 12.3% & 63.7%, HIV+/No ART 6.3% & 43.5%, HIV+/ART 7.8% & 38.7%. Compared to the HIV-negative population, mean age, BMI and systolic blood pressure were all lower in the HIV-positive population (all p<0.001), as was the percentage of participants with hypertension and diabetes (all p<0.001). Multivariable logistic regression showed that ART was significantly associated with greater odds of blood sugar measurement (aOR 1.27 95% CI 1.07-1.52), blood pressure measurement (aOR 1.26, 95% CI 1.03-1.53), and counseling regarding exercise (aOR 1.74, 95% CI 1.23-2.46). ART was also significantly associated with greater odds of awareness of hypertension diagnosis (aOR 1.49, 95% CI 1.11-2.02) and receipt of hypertension treatment (aOR 1.62, 95% CI 1.21-2.16).

Conclusion: The burden of diabetes and hypertension is substantial in Agincourt. HIV-positive patients who use ART are more likely to have received healthcare services for diabetes and hypertension. This apparent ART advantage needs to be confirmed in future studies but points to the potential of ART programs as a vehicle for strengthening health systems.

640 CARDIOVASCULAR RISK ASSESSMENT IN A SUB-SAHARAN AFRICA HIV CLINICAL COHORT

Mosepele Mosepele[1], Linda C. Hemphill[2], Tommy Palai[1], Isaac Nkele[3], Kara Bennett[4], Shahin Lockman[5], Virginia Triant[2]

[1]Univ of Botswana, Gaborone, Botswana, [2]Massachusetts General Hosp, Boston, MA, USA, [3]Botswana–Harvard AIDS Partnership, Gaborone, Botswana, [4]Bennett Statistical Consulting Inc, New York, NY, USA, [5]Harvard Univ, Boston, MA, USA

Background: HIV-infected patients are at increased risk for cardiovascular disease (CVD). However, risk prediction for CVD in HIV-infected persons has not been well-established in sub-Saharan Africa, which suffers from both the highest global burden of HIV and a rising rate of CVD.

Methods: HIV-infected adults between 30-50 years of age with documented virologic suppression were enrolled into a cross-sectional study in Gaborone, Botswana. All participants were screened for the following CVD risk factors (CVDRF): hypertension (current blood pressure) or use of anti-hypertensive treatment, weight, height, waist circumference, cigarette smoking, lipid profile, glycosylated hemoglobin. Bilateral carotid intima-media thickness (cIMT) was measured and 10-year predicted risk of cardiovascular disease was calculated using the 2013 Pooled Cohorts Equation (ASCVD). ASCVD ≥7.5% was considered elevated risk for CVD. Pearson's correlations assessed the association between CVDRF / HIV factors and cIMT. Agreement in classification of participants as high risk for CVD by cIMT (≥75th percentile) and ASCVD risk score (≥7.5%) was assessed using McNemar`s Test; additionally, the cut point for cIMT that corresponded with ASCVD≥7.5% was assessed using Youden's J statistic.

Results: Among 208 HIV-infected patients (Female: 55%, mean age 39 years), multiple traditional CVD risk factors correlated with cIMT. Among HIV factors, longer duration of HIV disease was associated with increased cIMT (r=0.14, p=0.04). A higher proportion of patients were classified as high risk by cIMT versus ASCVD (42.3% versus 14.1% identified as high risk, respectively; McNemar`s exact p-value <0.001). An ASCVD score of ≥ 7.5% was equivalent the 88th percentile of cIMT.

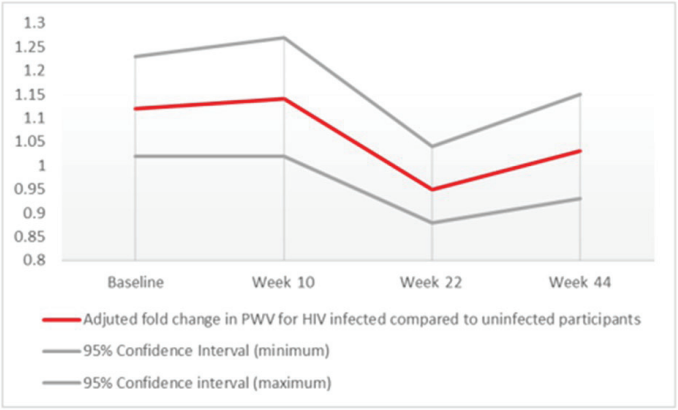
Conclusion: There was discordance in classification of high CVD risk when using the ASCVD risk score versus a cIMT threshold, with more patients classified as high risk using cIMT. More research is urgently needed to establish optimal CVD risk prediction strategies for HIV-infected patients in sub-Saharan Africa

641 HIV AND IMMUNE ACTIVATION ARE RISK FACTORS FOR ENDOTHELIAL DAMAGE IN ADULT MALAWIANS

Christine Kelly[1], Henry Mwandumba[2], Rob Heyderman[3], Raphael Kamng'ona[2], Mishek Chammudzi[2], Irene Sheha[2], Jane E. Mallewa[4], Sarah Walker[3], Nigel Klein[3], Saye Khoo[5]
[1]Univ Coll Dublin, Dublin, Ireland, [2]Malawi Liverpool Wellcome Clinical Rsr Prog, Blantyre, Malawi, [3]Univ Coll London, London, UK, [4]Univ of Malawi, Blantyre, Malawi, [5]Univ of Liverpool Inst of Translational Med, Liverpool, UK

Background: Mortality from cardiovascular disease (CVD) is predicted to surpass that of infectious disease in subSaharan-Africa (SSA) by 2030. HIV doubles the risk of CVD in high resource settings, but the contribution of HIV and immune activation to the risk of CVD in SSA is unknown.
Methods: HIV-1-infected adults with CD4<100 cells/ul were recruited 2 weeks following initiation of anti-retroviral therapy (ART) within the REALITY trial (NCT01825031), along with healthy HIV-uninfected adults and followed for 44-weeks. Acute infections (malaria, TB, cryptococcal meningitis, pneumonia, gastroenteritis) were recorded. Pulse wave velocity(PWV) was assessed using the Vicorder system. Flow cytometry identified T-cell activation(HLADR/CD38+), exhaustion(PD1+) and senescence(CD57+) in all participants, and circulating microparticles(CMPs) in 72 participants. Independent predictors of PWV were identified using linear regression with backwards elimination (exit p>0.1) of variables with univariable p<0.2 (spearman-rho or ranksum).
Results: 279 HIV-infected adults had similar median(IQR) age [36(31-43) vs 35(3-41) years, p=0.4], but lower systolic BP [120(108-128) vs 128(114-134)mmHg, p<0.01], BMI [20(18-21) vs 22(20-25)kg/m2, p<0.01] and proportion of women [122(44%) vs 66(60%), p<0.01] than 110 HIV uninfected adults. Following adjustment for confounders, HIV was associated with a 12%-increase in PWV (p<0.01) at baseline, which remained at week 10 (14%-increase, p=0.02) but resolved by week 24 (Figure 1). %CD4-PD1 and %CD8-PD1 were independently associated with PWV at baseline (fold change 2% and 3% per 10%increase, p=0.06 and 0.05 respectively). A decrease in %CD4-PD1 was associated with improvement in PWV by week 44 (rho 0.20, p=0.02). At baseline, median (IQR) CMPs were increased in HIV infection [5.1(2.0-18.0)x106 versus 0.4(0.2-6.0)x106, p<0.00001) and high versus low immune activation [4.0(2.3-5.6)x106 versus 0.3(0.1-0.5)x106, p<0.0001)] and were strongly related to PWV (rho 0.42, p<0.001). An acute infection during the study carried a 51% adjusted increase in %CD8 activated Tcells at week 44 (p=0.02) and an increase in PWV at week 44 of 0.80m/s [versus -0.10m/s (p=0.01)].
Conclusion: These results strongly implicate HIV and immune activation in increased endothelial damage during the first 12 weeks of ART therapy. Improvement in PWV on ART and cotrimoxazole is associated with decreases in immune activation. HIV and co-infections may present modifiable CVD risk factors in low resource SSA setting.

Figure 1: Adjusted fold change in PWV for HIV infected participants compared to uninfected



642 INCREASING PREVALENCE OF HYPERTENSION AMONG HIV-POSITIVE ADULTS IN SENEGAL, 1994–2015

Noelle A. Benzekri[1], Papa Salif Sow[2], **Moussa Seydi**[2], Stephen E. Hawes[1], Geoffrey Gottlieb[1]
[1]Univ of Washington, Seattle, WA, [2]CHU de Fann, Dakar, Senegal

Background: Non-communicable diseases, including hypertension, are increasingly recognized as important causes of morbidity and mortality among people living with HIV (PLHIV) in resource limited settings. However, the prevalence and correlates of hypertension among HIV-positive individuals in Senegal are not well understood. The goals of this study were to determine the prevalence of hypertension among PLHIV in Senegal and to identify factors contributing to hypertension among HIV-positive versus HIV-negative adults.
Methods: We conducted a retrospective study using data from individuals enrolled in previous studies in outpatient clinics in Senegal from 1994-2015. Blood pressure, height, and weight measurements taken during study visits were used for analysis. Hypertension (HTN) was defined as a systolic blood pressure ≥140 or a diastolic blood pressure ≥90. Data were analyzed using SPSS.
Results: Data from 2848 adults were included in this study, of whom 1687 were HIV-positive and 1161 were HIV-negative. The prevalence of HTN among HIV-positive individuals was 12%, vs. 18% among those who were HIV-negative (p<0.01). During 1994-1999 the prevalence of HTN among HIV-positive individuals was 11%, vs. 22% during 2010-2015 (p=0.03) and the odds of HTN increased with time (OR 2.4 from 2010-2015 vs. 1994-1999, p=0.02). Among HIV-negative individuals, the prevalence of HTN during 1994-1999 was 16%, vs. 32% during 2010-2015 (p<0.01) with an increase in the odds of HTN with time (OR 2.6 from 2010-2015 vs. 1994-1999, p=0.02). Risk factors for HTN among both HIV-positive and HIV-negative individuals included increasing age, increasing BMI, and obesity (HIV-positive OR for obesity 4.4, p<0.01; HIV-negative OR 5.4, p<0.01). HTN was not associated with sex, education, or alcohol use in either group. Smoking was associated with HTN among HIV-negative, but not HIV-positive individuals. Among HIV-positive individuals, WHO stage 1 or 2 (OR 2.8, p<0.01) and CD4 counts ≥200 (OR 2.0, p<0.01) were associated with increased risk of HTN; there was no association with ART.
Conclusion: This is the first study to document the increasing prevalence of hypertension among both HIV-positive and HIV-negative adults in Senegal, with an increase of 100% over the past 20 years. The strongest predictor of hypertension was obesity. Our findings highlight an urgent need for the integration of chronic disease management, including the prevention and treatment of hypertension and obesity, into HIV programs in Senegal.

643 MITOCHONDRIAL D-LOOP SNPS ASSOCIATED WITH AGE-RELATED COMORBIDITIES IN HIV PATIENTS

Rumi Minami, Soichiro Takahama, Yasunori Koga, Masahiro Yamamoto
Natl Hosp Org, Kyushu Med Cntr, Fukuoka, Japan

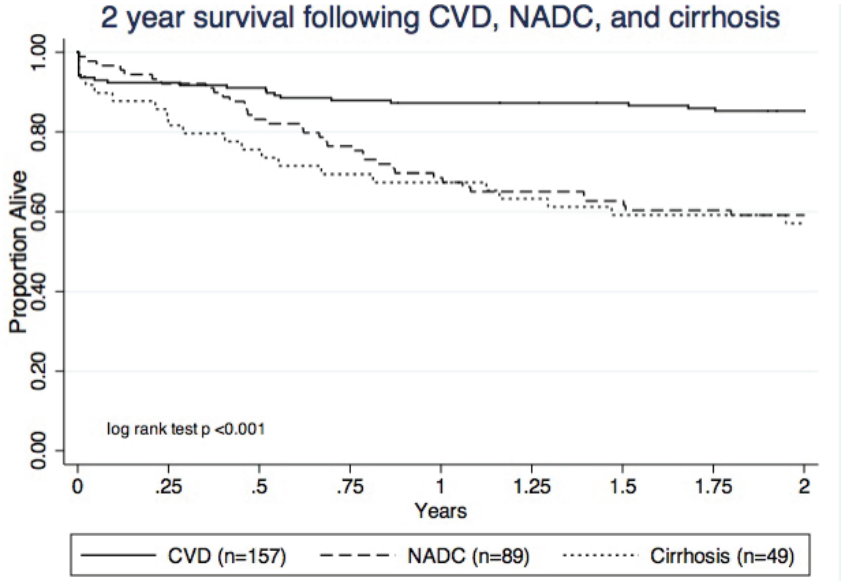
Background: HIV-1-infected patients age prematurely and develop certain age-related diseases. The mitochondrial displacement loop (mt D-loop) accumulates mutations and single nucleotide polymorphisms (SNPs), which are associated with some age-related diseases. In this study, we analyzed the numbers and variations of SNPs in the mtDNA D-loop of combination antiretroviral therapy (cART) treated HIV patients and uninfected healthy controls. We also determined which clinical parameters were associated with SNPs in mtDNA D-loop in HIV patients.

Methods: Three hundred and sixty-nine HIV patients on stable cART for > 6 months who achieved a viral load < 40 copies/ml, and 146 age-matched HIV-uninfected controls were enrolled. Peripheral blood mononuclear cells (PBMC) were obtained and a full sequence analysis of mtDNA D-loop was performed using direct sequencing. Linear regression analysis was used to analyze the factors associated with the numbers and variations of SNPs. We assessed several variables associated with HIV infection (CD4, HIV-RNA, HIV-DNA), cART (duration, regimen), and others (age, smoking, body mass index, hypertension). We also examined the relationship between SNPs and some age-related comorbidities. Variables found to be important in univariate analysis were multivariate model candidates.
Results: We evaluated 33 SNPs with a frequency > 2%. The numbers of SNPs were larger in HIV patients than controls, but this was not significant. In HIV patients, HIV-DNA (r=0.129, p=0.0129) and nucleoside reverse transcriptase inhibitor (NRTI) use (r=0.115, p=0.0269) were independent factors to determine the numbers of SNPs. As for individual SNPs, T152C, C16261T, T310C, and T199C were independently associated with decreased mtDNA copy numbers in PBMC (r=−0.125, p=0.0171), GFR decreasing (r=−0.146, p=0.0249), high mean-intima-media thickness (r=0.203, p=0.0155), and bone mineral density T-score (r=−0.211, p=0.0361), when adjusting the covariates of important variables. The frequency of these SNPs was higher in HIV patients than controls.
Conclusion: HIV-DNA and NRTI use were associated with the numbers of SNPs in the mtDNA D-loop, which was compatible with previous data showing that HIV-TAT and nucleotide analogues caused mitochondrial damage and mtDNA mutations. Furthermore, certain SNPs were linked with age-associated diseases. These findings suggest good virological control with decreased toxicity can help improve outcomes among HIV patients.

644 IMMUNOLOGIC AND VIROLOGIC MEASURES AND MORTALITY AFTER NCD IN HIV+ ADULTS

Jessica L. Castilho, Megan M. Turner, Bryan E. Shepherd, John R. Koethe, Sally S. Bebawy, Carmen E. Bofill, Stephen P. Raffanti, Timothy R. Sterling
Vanderbilt Univ, Nashville, TN, USA

Background: In the setting of virologic suppression, occurrence of non-communicable diseases (NCD) including cardiovascular disease (CVD), cirrhosis, and non-AIDS-defining cancers (NADCs) has been associated with circulating CD4 and CD8 counts in HIV-infected adults on antiretroviral therapy. However, the importance of CD4/CD8 ratio and risk of short-term mortality following NCD has not been established.
Methods: We used Cox proportional hazard models to assess the relationship between patient factors, immunologic (absolute CD4 count, nadir CD4, and CD4/CD8ratio) and virologic measures with mortality risk during the two years following incident CVD diagnosis (coronary artery disease, cerebrovascular disease, and peripheral vascular diseases), cirrhosis, or NADC diagnosis (excluding skin cancers) diagnoses among in a clinical cohort of HIV+ adults in Tennessee.
Results: Between 1998-2013, 295 HIV+ patients had an incident NCD and were included in this study: 157 with CVD, 89 with NADC, and 49 with cirrhosis. Among all patients, the median age at NCD was 48 years, 117 (40%) were non-white race, and 54 (18%) were women. There were 80 patients who died within two years of NCD event, including 23 after CVD, 36 after NADC, and 21 after cirrhosis (see Figure). In multivariable analysis (which also included age, anemia, CD4 count, CD4/CD8 ratio, and year), female sex (aHR = 1.88 [95% CI 1.10-3.23]), undetectable HIV-1 RNA (aHR = 0.46 [0.27-0.79]), and NADC or cirrhosis diagnosis (compared to CVD, aHR = 3.37 [1.191-5.4] and aHR = 2.72 [1.40-5.27], respectively) were significantly associated with mortality risk in the two years after NCD. Among patients with undetectable viral load (n=197), only NCD diagnosis (NADC vs. CVD) was statistically associated with mortality risk in bivariate analyses.
Conclusion: Virologic suppression, not CD4 or CD4/CD8 ratio, at the time of NCD diagnosis was associated with decreased risk of short-term mortality after CVD, NADC, and cirrhosis diagnosis. Female sex was also associated with increased risk of death in adjusted analyses. Detectable viral load may serve as a marker not only for HIV virologic activity but also social factors related to failure to achieve virologic suppression (such as adherence or other health-related behaviors) that increase risk of mortality after NCD. Further research is needed to understand disparities among HIV+ adults with NCDs for identification of those at high risk and development of interventions for poor outcomes following NCD diagnosis.



645 VITAMIN D METABOLITES AND MORTALITY RISK AMONG HAART-TREATED HIV-INFECTED MEN

Long Zhang[1], Todd Brown[1], Joseph B. Margolick[1], Sabina Haberlen[1], Mallory Witt[2], Frank J. Palella[3], Lawrence Kingsley[4], Andrew Hoofnagle[5], Lisa Jacobson[1], Alison Abraham[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Los Angeles Biomed Rsr Inst at Harbor–UCLA Med Cntr, Torrance, CA, USA, [3]Northwestern Univ, Chicago, IL, USA, [4]Univ of Pittsburgh, Pittsburgh, PA, USA, [5]Univ of Washington, Seattle, WA, USA

Background: Low serum 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D (1,25(OH)2D) levels are associated with increased all-cause mortality risk in the general population. However, little is known about these associations in HAART-treated HIV-infected individuals.
Methods: The MACS vitamin D ancillary study quantified 25(OH)D and 1,25(OH)2D levels from stored samples 1-3.5 years after HAART initiation from 1996-2013 in 641 HIV-infected men. Standardized 25(OH)D and 1,25(OH)2D levels were divided into quartiles, and the highest quartile was compared to lower three quartiles. Men contributed follow-up time from the date of the vitamin D metabolite measurement to death or to 31 March 2016. Cox proportional hazards models were used to evaluate the relationship between vitamin D levels and all-cause mortality or non-AIDS mortality risk with adjustment for covariates. The analysis was also stratified by plasma HIV viral load (VL) suppression status.

Results: Of the 641 men studied, 425 were VL suppressed and 261 were VL unsuppressed at baseline. 60% were white; 75% were former or current smokers; 8% were HCV-infected; 32% had hypertension. Median age, CD4+ T cell count, and VL of participants were 44 years (IQR: 39-50), 512 cells/μL (IQR: 344-695) and <50 copies/mL (IQR: <50-129), respectively. The median 25(OH)D was 22.2 ng/mL (IQR: 16.2-28.3) and that for 1,25(OH)2D was 46.4 pg/mL (IQR: 37.1-56.0). The median follow-up was 12 years (IQR: 8-16), with 96 deaths (15%) observed: 46 AIDS-related, 10 cardiovascular, 11 from cancer, and 29 from other diseases or unknown causes. All-cause mortality did not differ across quartiles of 25(OH)D. In contrast, those with high 1,25 (OH)2D at baseline had reduced all-cause mortality compared to those in the lower three quartiles of 1,25 (OH)2D among VL-suppressed men at baseline (HR=0.25, P=0.022), but not among VL-unsuppressed men (HR= 0.90, P=0.774; interaction P=0.050). High 1,25(OH)2D levels were marginally associated with decreased risk of non-AIDS mortality among VL suppressed men (HR= 0.16, P=0.078), but not among VL unsuppressed men (HR=0.25, P=0.204; interaction P=0.575).
Conclusion: High levels of $1,25(OH)_2D$, but not of the more commonly measured 25(OH)D, were associated with lower all-cause and non-AIDS-related mortality risk among virologically suppressed HIV-infected men. Further studies are needed to determine if $1,25(OH)_2D$ levels have utility as a prognostic indicator of mortality risk in this population.

Hazards Ratios of All-cause Mortality for Highest Quartile (Q4) versus Lower Three Quartiles (Q1-Q3) of Vitamin D Metabolite among HAART-Treated HIV-infected Men

			All-cause mortality			
			HIV-infected (N=641)	HIV-unsuppressed (N=216)	HIV-suppressed (N=425)	Interaction P-value
$1,25(OH)_2D$	Model 1	Q1-Q3	REF	REF	REF	
		Q4	**0.51 (0.29-0.90)**	0.75 (0.39-1.44)	**0.25 (0.08-0.82)**	
	Model 2	Q1-Q3	REF	REF	REF	
		Q4	**0.55 (0.31-0.97)**	0.90 (0.45-1.80)	**0.25 (0.08-0.81)**	0.050
25(OH)D	Model 1	Q1-Q3	REF	REF	REF	
		Q4	1.21 (0.78-1.89)	1.13 (0.63-2.00)	1.32 (0.65-2.67)	
	Model 2	Q1-Q3	REF	REF	REF	
		Q4	1.31 (0.83-2.07)	1.37 (0.75-2.49)	1.29 (0.73-2.68)	0.575

Model 1: no adjustment; model 2: adjusted for age, race, smoking, hypertension, HCV, CD4+ T cell count and log10 IL-6. HIV suppression was defined as <50 copies/mL. The threshold of highest quartile of standardized $1,25(OH)_2D$ is 56.0 pg/mL, and that for 25(OH)D is 28.3 ng/mL. **Bold** represents significant hazard ratios.

646 LONGITUDINAL HIV VIRAL TRAJECTORIES AND COMORBIDITIES IN THE WIHS

Seble Kassaye[1], Cuiwei Wang[2], Jeff Collmann[3], Tracey Wilson[4], Kathryn Anastos[5], Mardge H. Cohen[6], Ruth Greenblatt[7], Joel Milam[6], Stephen J. Gange[7], Michael Plankey[1]
[1]Georgetown Univ, Washington, DC, USA, [2]SUNY Downstate Med Cntr, Brooklyn, NY, USA, [3]Albert Einstein Coll of Med, Bronx, NY, USA, [4]John H.Stroger Jr. Hosp of Cook County, Chicago, IL, USA, [5]Univ of California San Francisco, San Francisco, CA, USA, [6]Univ of Southern California, Los Angeles, CA, USA, [7]The Johns Hopkins Univ, Baltimore, MD, USA

Background: Current HIV treatment goal is universal long-term viral suppression. We studied the association between longitudinal HIV viral trajectories (LHT) and HIV-related and unrelated comorbidities among women enrolled in the Women's Interagency HIV Study (WIHS).
Methods: Logistic trajectory modeling was performed to identify LHT among women enrolled in the WIHS to determine the probability of achieving HIV RNA <80 c/mL. The association between LHT and co-morbidities was determined using generalized linear models for repeated measures. Kaplan-Meyer survival analysis was conducted to explore the relationship between LHT and mortality (SASv9.2).
Results: 2,440 women contributed 56,209 visits from 1994-2015. The baseline median age was 36.4 years, 58.2% were African American, with a median CD4+ T lymphocyte count of 464/μL and median HIV RNA of 7000 c/mL. Three distinct LHT were identified: sustained viremia (N=1010); intermittently viremic (N=719), and; non-viremic (N=711). Cumulative years of viral suppression were 20 years (non-viremic), 13 years (intermittent-viremia), and 5 years (non-viremic) across groups. Mortality differed significantly among the 3 LHT: 37.6% (sustained viremia), 31.0% (intermittent viremia), and 14.8% (non-viremic) (p<0.0001). On multivariate analysis adjusted by race, age, CD4, depression with CESD ≥16, illicit drug use, alcohol use >7 drinks/wk, antiretroviral therapy, self-reported adherence, HIV risk category, enrollment site and death (yes or no), individuals with AIDS defining conditions and AIDS-associated cancers were more likely to have sustained viremia, but no significant association was identified between LHT and non-AIDS related malignancies. Compared to women with sustained viremia, women with viral suppression were more likely (HR 1.4, p=0.0072) to report risk factors for cardiovascular (CV) disease (hypertension, hyperlipidemia, diabetes), without concurrent increased incidence in CV disease outcomes (OR 1.1, P=0.4116).
Conclusion: Increasing cumulative duration of viral suppression was associated with lower mortality. However, we identified an unexpected increase in self-reported risk factors for CV disease among women with long-term viral suppression. Further analyses, continued follow up of participants, and CV risk and disease outcome ascertainment is critical to identify differences in CV disease risk and outcomes.

647 OXIDATIVE STRESS PREDICTS SERIOUS NON-AIDS EVENTS IN HIV-INFECTED PATIENTS

Mar Masia[1], Sergio Padilla[2], Marta Fernández[2], Xavier Barber[3], Santiago Moreno[4], Jose A. Iribarren[5], Joaquin Portilla[6], Alejandro Peña[7], Francesc Vidal[7], Félix Gutiérrez[2]
[1]Hosp General Univ de Elche, Elche, Spain, <[2]Univ Miguel Hernández, Elche, Spain, [3]Hosp Ramon y Cajal, Madrid, Spain, [4]Hosp Donostia, San Sebastián, Spain, [5]Hosp General Univ de Alicante, Alicante, Spain, [6]Hosp Univ San Cecilio, Granada, Spain, [7]Hosp Univ de Tarragona Joan XXIII, Tarragona, Spain

Background: Non-AIDS events have become major causes of morbidity and mortality in people living with HIV. Recognition of potentially modifiable mechanisms implicated in their pathogenesis might help improve outcomes of the patients. HIV infection has been associated with increased oxidative stress, but its relationship with the development of non-AIDS events has not been explored. We assessed the association between F2-isoprostanes and serious non-AIDS events, and whether they improve the predictive performance of inflammation and coagulation biomarkers.
Methods: Prospective cohort linked to a centralized BioBank where blood samples are archived at entry, and annually/biannually thereafter. The study population included all patients with available blood samples at the BioBank. Patients who had an incident serious non-AIDS event and a random group of patients with no events during the same period were selected. Measurement of F2-isoprostanes, highly-sensitive C-reactive protein (hsCRP), interleukin-6, D-dimer, sCD14, sCD40, sCD163 and neopterin levels was performed in successive plasma samples. Adjusted analyses controlled for age, sex, CD4 cell count, HIV RNA and HCV coinfection were carried out.
Results: Biomarkers were measured in 78 patients developing serious non-AIDS events or death, and 388 patients with no events. Adjusted levels of F2-isoprostanes, and also of hsCRP, interleukin-6, sCD14 and D-dimer were higher in patients who developed serious non-AIDS events, including or not non-AIDS deaths. The same results were observed when

only samples from patients with virological suppression were analyzed. The additive incorporation of each biomarker, ending with F2-isoprostanes, in an adjusted model was associated with a graded and significant increase in the quality of model fitting, and 95.27% sensitivity, 49.56% specificity and 0.86 accuracy to predict serious non-AIDS events.
Conclusion: Oxidative stress is associated with a higher risk of serious non-AIDS events, including non-AIDS deaths. This effect is independent and additive to biomarkers of inflammation, monocyte activation and coagulation. Our results suggest that oxidative stress should be included among mechanisms to deal with to improve outcomes of HIV-infected patients.

Adjusted model showing the association of the sequential addition of each biomarker with the occurrence of non-AIDS events, including and not including death

			All samples	
Outcome variable	**Model #**	**Variables included in Model***	**Deviance explained (%)**	***p* value**
Serious NAE	**1**	hsCRP	12.6	-
	2	Model#1, IL-6	14.7	0.035
	3	Model#2, D-Dimer	16.8	0.001
	4	Model#3,s-CD14	18.0	0.001
	5**	Model#4, F2-isoprostanes	18.8	0.003
Combined outcome: Serious NAE or Non-AIDS condition related-Death	**1**	hsCRP	5.3	-
	2	Model#1, IL-6	6.0	0.306
	3	Model#2, D-Dimer	6.8	0.006
	4	Model#3,s-CD14	7.5	0.021
	5***	Model#4, F2-isoprostanes	9.0	0.001

*All models also included sex, age at cohort entry, RNA-HIV viral load and CD4-T cell count closest to biomarker determination and hepatitis C virus coinfection. P value refers to the p value of ANOVA test for difference between nested models. ** Accuracy (95% CI) 0.86 (0.84-0.89); Sensitivity: 0.9527; Specificity: 0.4956; Positive predictive value: 0.8944; Negative predictive value: 0.7000. ***Accuracy (95% CI): 0.85 (0.82, 0.87); Sensitivity: 0.9796; Specificity: 0.1496; Positive predictive value: 0.8617; Negative predictive value: 0.5758
NAE, non-AIDS event; hsCRP, highly sensitive C-reactive protein; IL-6, interleukin-6

648 INFLAMMATION BIOMARKERS PREDICT CLINICAL TREATMENT FAILURE IN HIV-INFECTED ADULTS

Rupak Shivakoti[1], Nikhil Gupte[2], Sandy Pillay[3], Cynthia Riviere[4], Sandra W. Cardoso[5], Ashwin Balagopal[1], Richard Semba[1], Thomas Campbell[6], Amita Gupta[1], for the NWCS 319 and ACTG 5175 PEARLS Study Team
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]BJGMC Clinical Trials Unit, Pune, India, [3]Durban Univ of Tech, Durban, South Africa, [4]Les Cntrs GHESKIO, Port-Au-Prince, Haiti, [5]Inst Nacional de Infectologia (INI/Fiocruz), Rio de Janeiro, Brazil, [6]Univ of Colorado Denver, Aurora, CO, USA

Background: Single biomarkers have been assessed in antiretroviral (ART)-naïve HIV-infected adults in multiple studies. Results show that specific biomarkers of inflammation or micronutrient concentrations are associated with adverse treatment outcomes. However, many of these biomarkers are correlated with each other. The objective of this study was to conduct exploratory factor analysis (EFA), by representing correlated variables with a smaller set of potential underlying factors, and to assess the relationship of these extracted factors with HIV clinical treatment failure (CTF).
Methods: Within a multi-country randomized trial of ART efficacy (ACTG5175 PEARLS) among HIV-infected adults, we nested a case-control study (n=470; 236 cases, 234 controls) to identify underlying factors, based on 23 baseline (pre-ART) biomarkers of inflammation and micronutrient status, and determine their association with CTF. Cases were CTF, defined as incident WHO stage 3, 4 or death by 96 weeks of ART. Factors were extracted and Varimax rotation was for EFA. The factor scores were used in multivariable Cox proportional hazards models to determine the association of each factor with CTF.
Results: Based on EFA, the baseline biomarkers could be explained as linear combinations of three factors. Factor 1 ("carotenoids") had high loadings of α-carotene, β-carotene, β-cryptoxanthin, lutein and zeaxanthin. Factor 2 ("Other nutrients") had high loadings of selenium, vitamin B6, vitamin E and lycopene. Factor 3 ("inflammation") had high loadings of C-reactive protein (CRP), soluble CD14 (sCD14), Interleukin 18 (IL18) and ferritin). In multivariable models adjusting for gender, age, country, body mass index (BMI), CD4 count, viral load and TB status, there was an increased hazard of CTF (adjusted hazard ratio: 1.50, 95% CI: 1.22-1.84) per unit increase of "inflammation" factor score (factor 3 but not factor 1 or 2). Further adjusting for hemoglobin or albumin gave similar results.
Conclusion: In our analysis of various inflammatory and nutritional markers, two factors ("carotenoids" and "other nutrients") were extracted based on the grouping of nutritional markers while a third factor ("inflammation") was extracted based on the grouping of inflammatory markers. Only the "inflammation" factor was associated with CTF. Our results corroborate the significant role of inflammation in HIV outcomes while directing the focus on key markers of inflammation.

649 ART EFFECTS ON RENAL AND BONE HEALTH IN LIFELONG HIV SURVIVORS

Aviva Mattingly[1], Sara Jones[2], Aylin Unsal[1], Julia Purdy[3], James Reynolds[3], Jeffrey Kopp[4], Rohan Hazra[5], Colleen Hadigan[1]
[1]NIAID, Bethesda, MD, USA, [2]Liedos Biomed Rsr Inc, Frederick, MD, USA, [3]NIH, Bethesda, MD, USA, [4]NIDDK, Bethesda, MD, USA, [5]NICHD, Bethesda, MD, USA

Background: Antiretroviral therapy (ART) is associated with renal and bone toxicity, but little is known about the effects in adults exposed to ART from birth. Our goal was to evaluate renal function and bone health in adults with near lifelong HIV infection.
Methods: We conducted prospective, longitudinal cohort studies at the NIH of 65 adults infected with HIV early in life and 21 matched healthy controls. Detailed assessments included Dual-energy X-ray absorptiometry (DEXA) for bone mineral density (BMD). Cross sectional comparisons of controls vs. HIV adults at last follow-up were made using Wilcoxon rank-sum tests and chi-squared tests. Paired t-test was used for longitudinal comparison of baseline vs. last follow-up in a subset of 33 HIV subjects. Linear regression was used for associations between variables.
Results: Compared to controls, the HIV group had significantly higher albumin/creatinine (A/C) ratio, protein/creatinine (P/C) ratio, and anion gap. Also, NTX-telopeptides and osteocalcin were significantly elevated in HIV patients. The HIV group had lower whole body BMD and lower BMD Z-scores. Within the HIV group, lower GFR correlated with increased CD8 T-cells (r=-0.26, p=0.04). Years on tenofovir (TDF) correlated with higher anion gap (r=0.33, p=0.01) but did not correlate with any bone health parameters. However, longer duration of didanosine (DDI) and stavudine (D4T) use correlated with lower whole body BMD (DDI: r=-0.3, p=0.02 and D4T: r=-0.27, p=0.03) and lower BMD Z-scores (DDI: r=-0.29, p=0.03 and D4T: r=-0.29, p=0.02). Longitudinal analyses of patients revealed that a decline in GFR correlated with increasing years of TDF (r=-0.42, p=0.02) and increasing CD4 (r=-0.44, p=0.01) and CD8 T-cells (r=-0.41, p=0.02). BMD and bone markers tended to improve over time. At last follow up, AP Spine BMD (p=0.0001), whole body BMD (p<0.0001), and whole body BMD Z-scores (p=0.0014) increased vs. baseline. Osteocalcin (p=0.03) and NTX-telopeptides (p=0.03) significantly decreased in the HIV group over time.

Conclusion: Subclinical markers of renal dysfunction were increased in HIV adults, while microalbuminuria, proteinuria and low GFR were uncommon in both groups. Further, patients with lifelong HIV had abnormal bone density as they approached the age of peak bone mass, associated with DDI and D4T exposure. Despite evidence of dysfunctional bone formation relative to healthy controls, there was a tendency for improvement in markers of bone turnover and BMD with time.

	HIV+ (n=65)	Control (n=21)	P-value
Age (y)	23 (20, 27)	25 (22, 27)	0.11
Sex, male (n, %)	25 (39)	10 (48)	0.46
Race (n, %)			
Caucasian	24 (37)	11 (52)	0.54
African- American	33 (51)	9 (43)	
Other	8 (12)	1 (5)	
BMI (kg/m^2)	25 (22, 28)	25 (23, 29)	0.44
Bone Density			
Whole Body BMD (g/cm^2)	1.15 (1.08, 1.22)	1.21 (1.15, 1.28)	**0.008**
Whole Body Z-Score	-0.1 (-1, 0.7)	0.4 (-0.2, 1.6)	**0.01**
AP Spine BMD (g/cm^2)	1.03 (0.94, 1.14)	1.07 (0.97, 1.12)	0.41
AP Spine Z-Score	-0.5 (-1.3, 0.4)	-0.3 (-0.9, 0.3)	0.57
Markers of Renal Health			
GFR* (mL/min)	129 (116, 142)	118 (113, 128)	**0.02**
Proteinuria (n, %)	1 (2)	0 (0)	0.56
Microalbuminuria (n, %)	5 (9)	2 (10)	0.85
Serum Markers			
25-hydroxyvitamin D (ng/mL)	23 (16, 32)	21 (17, 34)	0.97
Alkaline Phosphatase (U/L)	76 (62, 93)	67 (51, 82)	**0.02**
Anion Gap (mEq/L)	10 (9, 13)	8 (7, 11)	**0.004**
Creatinine (mg/dL)	0.71 (0.64, 0.84)	0.78 (0.72, 0.95)	**0.03**
Osteocalcin (ng/mL)	30.1 (23.4, 39.6)	22.1 (16, 25.5)	**0.007**
Parathyroid Hormone (pg/mL)	40 (34.3, 53.4)	34.4 (29.6, 38.7)	**0.02**
Urine Markers			
Albumin/Creatinine Ratio (mg/g)	6.9 (4.6, 15.3)	4.6 (2.9, 6.4)	**0.006**
Protein/Creatinine Ratio (mg/mg)	0.13 (0.11, 0.17)	0.09 (0.08, 0.14)	**0.008**
NTX-Telopeptides (nmol/mm)	52 (34, 70)	33 (21, 57)	**0.03**

* GFR= Glomerular Filtration Rate

650 FACTORS ASSOCIATED WITH RAPID EGFR DECLINE IN PATIENTS RECEIVING TDF AND/OR ATV

Lisa Hamzah[1], Sophie Jose[2], Rachael Jones[3], Deborah Williams[4], David Chadwick[5], Andrew Phillips[2], Caroline Sabin[2], Frank Post[6]
[1]King's Coll Hosp, London, UK, [2]Univ Coll London, London, UK, [3]Chelsea and Westminster NHS Fndn Trust, London, UK, [4]Brighton and Sussex Univ Hosps, Brighton, UK, [5]South Tees Hosps NHS Fndn Trust, Middlesbrough, UK, [6]King's Coll Hosp NHS Fndn Trust, London, UK

Background: Rapid estimated glomerular filtration rate (eGFR) decline is a risk factor for cardiovascular events in diabetics and for mortality in the general population. In HIV-positive people, tenofovir (TDF) and atazanavir (ATV) have been associated with rapid eGFR decline. We analysed risk factors for, and mortality associated with, rapid eGFR decline in subjects receiving TDF and/or ATV.
Methods: Individuals in UK CHIC with a first episode of either TDF or ATV exposure since 1/1/2000 with ≥1 year exposure and ≥1 creatinine value (excluding first 3 months after TDF/ATV start) were considered for analysis. Despite overlap, periods of TDF and ATV exposure were analysed separately. eGFR slopes were generated for each group using mixed effects models adjusted for age, ethnicity and sex; individuals with rapid eGFR decline (>3mL/min/1.73m^2/year) were identified. Demographic and HIV factors associated with rapid eGFR decline for those on TDF and ATV were analysed using logistic regression, and factors associated with all-cause mortality using Poisson regression.
Results: 16172 individuals commenced TDF (mean age 38 years, 73% white, 79% male, mean eGFR at TDF start 82 mL/min/1.73m^2, 21% co-administered with ATV) and 4162 commenced ATV (mean age 37 years, 68% white, 72% male, mean eGFR at ATV start 80, 81% co-administered with TDF). Adjusted eGFR slopes (95% CI) for TDF and ATV were -0.26 (-0.33, -0.19) and -0.61 (-0.79, -0.43) respectively; 15.8% of those on TDF and 21.7% of those on ATV experienced rapid eGFR decline. In adjusted analyses, rapid eGFR decline was associated with black ethnicity, lower baseline eGFR and shorter TDF/ATV exposure (Table 1). In addition, younger age, AIDS and co-exposure to ATV/lopinavir (LPV) in the TDF group and female sex and TDF exposure in the ATV group were associated with rapid decline. During a mean (SD) follow up of 8.0 (4.8) years, 573 died. After adjustment for age, sex, ethnicity, nadir CD4, hepatitis status, baseline eGFR and ART regimen, rapid eGFR decline remained associated with all-cause mortality (aHR [95% CI] 1.56 [1.27, 1.92] and 1.83 [1.31, 2.56] for TDF and ATV respectively, p<0.001). Similar results were obtained when rapid eGFR decline was defined as >5 mL/min/1.73m^2/year.
Conclusion: Rapid eGFR decline was observed in a substantial proportion of those who received TDF or ATV and identified a subset of patients at increased risk of death. Black ethnicity, lower baseline eGFR, TDF/ATV and TDF/LPV co-exposure were associated with rapid eGFR decline.

Table 1: Factors associated with rapid decline (>3 ml/min/1.73m²/year) on TDF *or* ATV

		On TDF N=16,126				On ATV N=4,162			
		Crude OR [95% CI]	p-value	Adj. OR* [95% CI]	p-value	Crude OR [95% CI]	p-value	Adj. OR* [95% CI]	p-value
Age/5 year ↑		1.04 [1.01, 1.06]	0.001	**0.96 [0.93, 0.98]**	**<0.0001**	1.00 [0.97, 1.05]	0.8		
Sex	Male	1		1		1			
	Female	1.11 [1.00, 1.23]	0.04	1.07 [0.95, 1.22]	0.2	1.42 [1.21, 1.67]	<0.0001	**1.40 [1.14, 1.73]**	**0.002**
Ethnicity	White/other	1		1		1			
	Black	1.06 [0.96, 1.16]	0.2	**1.26 [1.12, 1.42]**	**<0.0001**	1.55 [1.27, 1.88]	<0.0001	**1.33 [1.04, 1.71]**	**0.03**
Prior ADI		1.22 [1.11, 1.34]	<0.0001	**1.15 [1.04, 1.28]**	**0.006**	1.06 [0.86, 1.30]	0.6		
Baseline eGFR /10ml/min ↑^		0.85 [0.83, 0.86]	<0.0001	**0.99 [0.98, 0.99]**	**<0.0001**	0.88 [0.84, 0.92]	<0.0001	**0.99 [0.98, 0.99]**	**<0.0001**
Time on TDF *or* ATV	1-2 years	1				1		1	
	2-3 years	1.26 [1.10, 1.44]	0.0007	**1.26 [1.09, 1.44]**	**0.0001**	1.07 [0.87, 1.31]	0.5	1.02 [0.83, 1.26]	0.8
	3-4 years	1.03 [0.89, 1.18]	0.7	0.94 [0.81, 1.08]	0.4	0.89 [0.69, 1.12]	0.3	0.79 [0.62, 1.01]	0.06
	4-5 years	0.77 [0.66, 0.88]	0.0004	**0.66 [0.57, 0.77]**	**<0.0001**	0.58 [0.44, 0.76]	0.0001	**0.51 [0.39, 0.68]**	**<0.0001**
	>5 years	0.49 [0.43, 0.55]	<0.0001	**0.36 [0.32 0.42]**	**<0.0001**	0.26 [0.20, 0.33]	<0.0001	**0.23 [0.18, 0.29]**	**<0.0001**
ART regime at TDF start	NNRTI	1							
	ATV/r	1.46 [1.29, 1.66]	<0.0001	**1.34 [1.18, 1.53]**	**<0.0001**	N/A			
	DRV/r	1.40 [1.19, 1.63]	<0.0001	1.12 [0.95, 1.31]	0.2	N/A			
	LPV/r	1.53 [1.34, 1.74]	<0.0001	**1.53 [1.34, 1.76]**	**<0.0001**	N/A			
	Other PI	1.24 [0.93, 1.64]	0.1	1.11 [0.83, 1.48]	0.3	N/A			
	Other	1.27 [1.08, 1.47]	0.004	1.16 [0.98, 1.37]	0.09	N/A			
ART regime at ATV start	TDF	N/A				1.29 [1.07, 1.54]	0.006	**1.34 [1.11, 1.62]**	**0.002**

*adjusted for age, sex, ethnicity, prior AIDS defining illness, time on TDF or ATV and ART regime at TDF or ATV start
Ethnicity included as an apriori confounder instead of HIV risk ^quadratic term best fits model

651 DISCONTINUATION OF DTG, EVG/C, AND RAL DUE TO TOXICITY IN A PROSPECTIVE COHORT

Josep M. Llibre[1], Anna Esteve[2], Jose M. Miro[3], Gracia Mateo[4], Adrià Curran[5], Daniel Podzamczer[6], Melchor Riera[7], Francesc Homar[8], Luis Force[9], for the PISCIS Cohort Study Group
[1]Univ Hosp Germans Trias, Barcelona, Spain, [2]Cntr d'Estudis Epidemiològics Sobre les ITS i Sida de Catalunya, Barcelona, Spain, [3]Univ of Barcelona, Barcelona, Spain, [4]Hosp Sant Pau, Barcelona, Spain, [5]Hosp Vall d'Hebró, Barcelona, Spain, [6]Hosp Univ de Bellvitge, Barcelona, Spain, [7]Hosp Univ Son Espases, Palma de Mallorca, Spain, [8]Hosp Son Llàtzer, Palma de Mallorca, Spain, [9]Hosp de Mataró, Mataró, Spain

Background: The rates of discontinuation (D/C) due to adverse events (AEs) of the integrase strand transfer inhibitors (INSTI) dolutegravir (DTG), raltegravir (RAL) and cobicistat-boosted elvitegravir (EVG/c) have been very low in randomized clinical trials. However, some real-life retrospective series have reported unexpectedly high rates of D/C due to AEs, particularly with DTG. We aimed to compare the D/C rates due to AEs of the three INSTI inhibitors in a prospective multicenter cohort.
Methods: The PISCIS Cohort is an ongoing observational study that includes about 21000 HIV-infected patients aged ≥16 years from 10 hospitals in Catalonia and 2 in the Balearic Islands (Spain). All subjects having started one of these 5 regimens including DTG with abacavir/lamivudine (ABC/3TC) or tenofovir fumarate/emtricitabine (TDF/FTC; regimens A and B, respectively), RAL with ABC/3TC (C) or TDF/FTC (D), or the co-formulation EVG/c/TDF/FTC (E) since July 2013 as their initial regimen or a switch with plasma HIV-1 RNA <50 c/mL were included. The incidence rate and 95% confidence interval [IR (95% CI)] of D/C due to toxicity is estimated as the ratio of the number of discontinuations by 100 patients/year of follow-up. Adjusted hazard ratios (aHR) and their 95% CI were obtained from multivariate Cox models, adjusted for gender, age, transmission group, origin, treatment-naïve and hepatitis B/C co-infection.
Results: Out of 13066 patients on follow-up at July 2016, 2096 subjects were included (90% naives), receiving regimens A (n=859), B (n=108), C (n=208), D (n=280) and E (n=641). Of them, 430 (stopped prematurely their regimen, due to AEs in 74. The corresponding IR (95%CI) for DTG, RAL and EVG/c were 5.1 (3.6-7.0), 3.0 (1.8-4.5), and 2.8 (1.7-4.1), respectively. Among those receiving DTG, the IR with ABC/3TC or TDF/FTC were 4.9 (3.3-6.9) and 6.3 (2.0-12.9), respectively, with no significant differences between them. The aHR of D/C due to AEs with DTG vs. RAL was 1.1 (0.6-2.1), DTG vs. EVG/c 1.6 (0.8-2.9), and EVG/c vs. RAL 0.8 (0.4-1.6).
Conclusion: In subjects starting an initial therapy or a switch regimen with an undetectable plasma HIV-1-RNA, there are no significant differences in the D/C rates due to AEs among those receiving DTG, RAL or EVG/c. For those receiving DTG, there are no significant differences between those receiving ABC/3TC or TDF/FTC. Marginal structural models adjusted for baseline and time-varying confounding variables will be run in further analysis.

652 IMPACT OF TENOFOVIR DIFUMARATE ON TELOMERE LENGTH OF AVIREMIC HIV-INFECTED PATIENTS

Rocio Montejano[1], Natalia Stella-Ascariz[1], Susana Monge[2], Jose I. Bernardino[1], Ignacio Pérez-Valero[1], Laura Pintado[3], Marisa Montes[1], Jesus Mingorance[1], Rosario Perona[3], Jose R. Arribas[1]
[1]Inst de Investigación Hosp Univ La Paz, Madrid, Spain, [2]Univ de Alcalá de Henares, Madrid, Spain, [3]Inst of Biomed Rsr "Alberto Sols," Madrid, Spain

Background: In vitro tenofovir is a potent inhibitor of human telomerase (J Inf Dis 2013; 207:1157, J Acquir Immune Defic Syndr 20 August 2016. doi:10.1097/QAI.0000000000001154). The in vivo relevance of this inhibition is unknown.
Methods: Cross sectional study of HIV-1 infected patients with suppressed virological replication (HIV-1 RNA < 50 copies/mL for > 1 year). Telomere length (TL) was measured in whole blood by monochrome quantitative multiplex PCR assay. All samples were run in triplicate. We performed a multivariate analysis to elucidate factors associated with TL and also evaluated the association between TL and the use of tenofovir difumarate (TDF) adjusted by significant confounders.
Results: 200 patients were included: 72% male, median age 49 IQR (45-54.5) years; median time on ART 14.9 years (10.28-17.92), on NRTIs 11.9 (9.01-16.16) years, and with virologic suppression 6.8 years (4.56-7.68); median current CD4 776 cells/µL (551-1037); 64% currently receiving triple therapy, 32.5% ritonavir-boosted protease inhibitor monotherapy and 3.5% other NRTI-sparing regimen. 103 patients had exposure to TDF (median time 8.5 years (3.88-10.37), 69.9% >5 years) and 97 were never exposed to TDF. In the univariate analysis (Figure 1) TL was not associated with duration of TDF exposure; compared to patients with <5 years of TDF-exposure, those with TDF-exposure for 5-10 years had 8.7% longer TL (p=0.060) and those with >10 years of exposure had 6.4% longer TL (p=0.189). In contrast, Caucasian race, older age, smoking, time with known HIV infection, time receiving ART and time on NRTI were significantly associated with shorter TL. In the multivariate analysis significant predictors of shorter TL were: older age ≥50 years (p=0.008), parental age at birth (p=0.038), Caucasian race (p=0.048) and longer time of known HIV infection (known infection for 10-20 years and ≥20 years compared with <10 years, p=0.003 and p=0.056 respectively). There was no association between TDF exposure and TL after adjusting for possible confounding factors (age, parental age at

birth, race and time of HIV infection). Total time receiving ART and duration of treatment with NRTIs were associated with shorter TL but these associations were explained by time of known HIV infection.

Conclusion: Our data do not suggest that telomerase activity inhibition caused by TDF in vitro, leads to telomere shortening in peripheral blood of HIV infected patients.

653 DARUNAVIR/R USE AND INCIDENT CHRONIC KIDNEY DISEASE IN HIV-POSITIVE PERSONS

Lene Ryom[1], Jens D. Lundgren[1], Peter Reiss[2], Ole Kirk[1], Matthew Law[3], Michael Ross[4], Philippe Morlat[5], Christoph A. Fux[6], Amanda Mocroft[7], for the D:A:D Study Group
[1]CHIP, Rigshosp, Copenhagen, Denmark, [2]Stichting HIV Monitoring and Academic Med Cntr Amsterdam, Amsterdam, Netherlands, [3]Kirby Inst, Sydney, Australia, [4]Mt Sinai Sch of Med, New York, NY, USA, [5]CHU Bordeaux, Bordeaux, France, [6]Clinic for Infectious Diseases and Hosp Hygiene, Kantonsspital Aarau, Aarau, Switzerland, [7]Univ Coll London, London, UK

Background: Prior studies have linked exposure to protease inhibitors (PIs) with excess risk of chronic kidney disease (CKD). Whether such safety signals remain for more contemporary PIs, such as darunavir (DRV/r), remains unclear.

Methods: D:A:D participants with >3 estimated glomerular filtration rate (eGFR) measurements, were followed from their first eGFR>60 mL/min/1.73m^2 after 1.1.2009 to the earliest of CKD (confirmed, >3 months apart, eGFR<60 mL/min/1.73m^2), last visit plus 6 months or 1.2.2015. Poisson regression was used to model associations between CKD and use of two contemporary PI's (ritonavir boosted atazanavir (ATV/r) and DRV/r), adjusting for demographics, other antiretroviral treatment, renal and HIV-related risk factors.

Results: Of 26,939 persons 1,209 developed CKD (incidence rate (IR) 8.6/1000 PYFU [95%CI 8.1-9.1]). 13.1% and 24.8% of the follow-up time (140,966 PYFU) was after starting DRV/r and ATV/r respectively. Median age at baseline was 44 (IQR 38-50) years, median CD4 count was 510 (IQR 370-700) cells/mm^3, and 28.8%, 35.9% and 35.3% were at low, medium and high 5-year CKD risk estimated by the D:A:D CKD risk score. While the CKD IR was low in individuals unexposed to DRV/r or ATV/r and increased with increasing exposure, after adjustment, only ATV/r (adjusted IR ratio (aIRR) 1.86 [1.58-2.20]), but not DRV/r (1.29 [0.94-1.77]) exposure remained significantly associated with CKD after >4 years (figure). Further multivariate analysis excluding those unexposed to DRV/r showed no statistically significant association between increasing DRV/r exposure and CKD (aIRR 1.21/5 years [0.83-1.75]). After exclusion of those unexposed to ATV/r the CKD rate significantly increased with increasing ATV/r exposure (aIRR 1.24/5 years [1.01-1.52]). The results were similar for individuals at low, medium or high estimated CKD risk (p>0.05, test for interaction). The rate of discontinuing ATV/r, but not DRV/r, was associated with lower eGFR levels (aIRR 1.74 [1.36–2.22] for ATV/r and 1.24 [0.83-1.86] for DRV/r at eGFR<70 vs. >90).

Conclusion: In a large heterogeneous cohort of contemporarily treated HIV-positive persons with six years median follow-up, DRV/r discontinuation was eGFR unrelated and more extended DRV/r use was not significantly associated with excess CKD risk, although a similar association as seen with ATV/r could not be ruled out. The previously reported association between gradually increasing risks of CKD with longer use of ATV/r remained.

654 HIV AS A RISK FACTOR OF AIRWAY OBSTRUCTIVE DISEASE

Alain Makinson[1], Sabrina Eymard-Duvernay[2], Céline Ribet[3], Lucie Marchand[4], Maurice Hayot[1], Gilles Pialoux[5], Jacques Reynes[6], Marie Zins[3], Vincent Le Moing[1], for the ANRS EP48 HIVCHEST Study Team
[1]Univ Hosp Montpellier, Montpellier, France, [2]INSERM, Montpellier, France, [3]INSERM, Villejuif, France, [4]France Recherche Nord et Sud Sida-HIV et Hépatites, Paris, France, [5]Tenon Hosp, Paris, France, [6]CHU de Montpellier, Montpellier, France

Background: We previously showed high prevalence of chronic obstructive pulmonary disease (COPD) in an all-smoking cohort of HIV-individuals. Whether COPD prevalence is higher in HIV-individuals than in the general population remains to be determined. The objective of this study was to compare the prevalence of airflow obstruction (AO) in HIV-individuals and in age and gender matched individuals from the general population, and to determine whether HIV-status was an independent factor of AO.

Methods: HIV-infected individuals were included in the ANRS EP48 HIV-CHEST study (NCT01207986), a multicentre, French, lung cancer screening study with chest CT. Each HIV-individual was randomly matched by age and gender with two individuals from a general population cohort CONSTANCES. All individuals were smokers ≥ 20 pack-years, possibly stopped within the previous 3 years, and aged ≥ 40 years. HIV-individuals also had a CD4 T-lymphocyte nadir count < 350/µL, and a last CD4 T-lymphocyte count > 100/µL. Both populations underwent spirometry without administration of a bronchodilator. The primary endpoint defining AO was the forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) ratio < 0.70 and a FEV1 measure <80 % of the theoretical value. A logistic regression model evaluated the association of AO with age, gender, HIV status, Body Mass Index, smoking (pack-years), and former smoking.

Results: 351 HIV-infected individuals were matched to 702 subjects (table); 68 (19%) of HIV-infected versus 60 (9%) of HIV-negative individuals had AO. In multivariate analysis, factors associated with AO were HIV (OR: 2.03, 95% CI (1.33-3.10)), age (per 10 years increase) (OR 1.68, 95% CI (1.23-2.29)), and smoking (per 5 pack-years increase) (OR: 1.10, 95% CI (1.02-1.19)). Adding HCV and history of cannabis inhalation in a sensitivity analysis slightly diminished the association between HIV and AO (OR: 1.71, 95% CI (1.08-2.72)).

Conclusion: Prevalence of AO was higher in HIV-smokers aged ≥ 40 years than in age and gender matched smokers from the general population. HIV was an independent risk factor for AO, even after further adjustment for HCV (a proxy for history of intravenous drug use), and cannabis inhalation. Smoking was associated with AO, underscoring the importance of smoking cessation programs. Finally, both high prevalence and increased risk of AO in HIV-individuals that smoke argue for early systematic diagnosis of AO with spirometry in HIV-smokers ≥ 40 years.

	HIV-negative individuals n=702	HIV-positive individuals n=351
Age (years), median (Q1-Q3)	50 (46-54)	50 (46-54)
Women, n (%)	122 (17%)	61 (17%)
BMI, median (Q1-Q3)	26 (23-28)	23 (20-25)
Smoking (pack-years), median (Q1-Q3)	28 (23-35)	30 (25-39)
Smoking cessation (< 3 years), n (%)	234 (33%)	30 (9%)
History of cannabis inhalation, n (%)	67 (10%)	125 (36%)
HCV, n (%)	13 (2%)	106 (30%)
T-CD4 lymphocyte level (cells/µl), median (Q1-Q3)	Not applicable	573 (395-767)
CD4 nadir level (cells/µl), median (Q1-Q3)	Not applicable	174 (75-259)
History of AIDS, n (%)	Not applicable	104 (30%)
Viral load < 50 copies/ml, n (%)	Not applicable	311 (89%)
History of intravenous drug use, n (%)	Not available	94 (27%)

655 CHRONIC HIV PULMONARY DISEASE (CHPD) IN NEVER-SMOKING HIV PATIENTS

Antonella Santoro[1], Riccardo Scaglioni[1], Giulia Besutti[1], Andrea Malagoli[1], Jonathon Leipsic[2], Janice Leung[2], Gabriella Orlando[1], Stefano Zona[1], Guido Ligabue[1], Giovanni Guaraldi[1]
[1]Univ of Modena and Reggio Emilia, Modena, Italy, [2]Univ of British Columbia, Vancouver, British Columbia, Canada

Background: The aim of this study was to characterize lung diseases by mean of: CT lung abnormalities, lung function and respiratory symptoms in never smoking HIV patients (pts) on antiretroviral therapy, not referred for acute pulmonary disease

Methods: Cross-sectional study of 329 HIV patients, never smoking (currently non-smoking and with a pack-year <1) who underwent chest and abdominal CT scans for the evaluation of Coronary Artery Calcium score (CACs) and for the assessment of subcutaneous and visceral adipose tissue (SAT and VAT). Epicardial adipose tissue (EAT) was calculated in a subset of 153 patients. CT Images were evaluated for pulmonary findings by 3 radiologists by consensus. Emphysema was classified by severity score (mild, moderate, severe) and by subtype (centrilobular, paraseptal, panlobular). Prevalence of respiratory symptoms was assessed with St. George Respiratory Questionnarie (SGRQ). Impairment was defined with Symptoms Score>15. COPD was defined by spirometry (forced expiratory volume in one second/forced vital capacity < 0.70); DLCO was considered reduced if <70% of predicted value. Univariable and multivariable logistic regression analyses were performed to identify factors independently associated with the presence of lung disease.

Results: Emphysema was found in 15.57% of pts (centrilobular 43%, Paraseptal 30%, panlobular 17%. Mild was 62%, Moderate 13%, Severe 25%). Bronchiolitis was found in 11.7% of pts, Bronchial Wall Thickening in 38.8%, Bronchiectasis in 14.8% and nodules >4mm in10%. Patients complained following respiratory symptoms: cough (22.4%) spit (14 %), loss of breath (16.8%) and whistles (8.4%). COPD was diagnosed in 1,2% of pts, DLCO reduction in 15%of pts. Table 1 shows demographic and clinical characteristics of patients with and without emphysema. Univariable analysis showed significant associations between the presence of emphysema and: age (p=0,001), Framingham risk score (p=0,01), Hypertension (p=0,012), CACs (p=0,012), diabetes (p=0,048), VAT (p=0,006) and EAT (p=0,004). In a multivariable model, significant predictors of emphysema severity were: age (OR=1.098) and EAT (OR=1.015).

Conclusion: We described a Chronic HIV Pulmonary Disease (CHPD) in never smoking HIV patients with emphysematous lung changes, respiratory symptoms and reduced CO diffusion capacity. Emphysema was independently associated with EAT, but not BMI or HIV-related variables underlying a common pathogenetic mechanism linking lung CT abnormalities and ectopic fat accumulation.

	Total	Emphysema=0 282 N, 85.7%	Emphysema=1 47 N, 14.3 %	P value
Age (mean; ±S.D.)	49.57 (8.89)	48.88 (8.59)	53.68 (9.62)	0
Male (n°;%)	243 (73.86%)	203 (71.99%)	40 (85.11%)	0.09
BMI (mean; ±S.D.)	24.64 (3.75)	24.48 (3.69)	25.6 (4.03)	**0.05**
Visceral Adipose Tissue (VAT)	127 (88-178.5)	124 (86-166)	155 (110.5-221)	**<0.01**
Epicardial Adipose Tissue (EAT)	76.4 (48.5-100.3)	69.7 (47-96.9)	102 (79.8-131)	**<0.01**
Calcium score (mean;±S.D.)	53.04 (244.91)	8.33 (32.95)	68.86 (282.76)	**<0.01**
Framingham(median;±I.Q.R.)	3 (1-7)	0 (0-1)	4 (2-8)	**<0.01**
COPD present	4 (1.22%))	3 (1.06%)	1 (2.13%)	1
DLCO reduction	10 (14,9%)	7 (66%)	3(33,3%)	1
CD4 cell count (mean; ±S.D.)	616.63 (242.71)	619.54 (245.17)	599.2 (229.21)	0.91
CD4 Nadir (mean; ±S.D.)	210 (100-300)	215.5 (108.25-300)	176 (79.5-307)	0.37
PCR(mean; ±S.D.)	0.92 (9.38)	1.02 (10.13)	0.27 (0.39)	0.19
White Blood Cell (mean; ±S.D.)	2825.18 (3168.35)	2693.59 (3127.38)	3547.32 (3331.95)	0.07

Table 1

656 THE INFLUENCE OF HIV INFECTION ON PULMONARY FUNCTION IN A RURAL AFRICAN POPULATION

Alinda Vos[1], Meri Varkila[1], Hugo Tempelman[2], Walter Devillé[2], Roos Barth[1], Diederick Grobbee[1], Roel Coutinho[1], Kerstin Klipstein-Grobusch[1], for the Ndlovu Research Group
[1]Univ Med Cntr Utrecht, Utrecht, Netherlands, [2]Ndlovu Care Group, Groblersdal, South Africa

Background: Epidemiological data about obstructive lung disease (OLD) in HIV from Sub-Saharan Africa (SSA) are scarce, and the association between HIV-infection and OLD in SSA remains unclear. This study aimed to investigate the prevalence of OLD in HIV infection, and to determine whether HIV infection affects pulmonary function in a South African population.

Methods: As part of the Ndlovu Cohort study across-sectional study was conducted in a rural area in Limpopo, South Africa. HIV-positive and HIV-negative participants, aged 18 years and older without known cardiovascular disease who attended a baseline or follow-up visit at the cohort site were invited to participate. A respiratory questionnaire and pre- and post-bronchodilator spirometry were performed. Airflow obstruction was defined as a forced expiratory volume in one second / forced vital capacity (FEV1/FVC) ratio less than the lower limit of normal. Prevalence of airflow obstruction in HIV-positive and HIV-negative individuals was calculated. Multiple regression analysis was used to investigate if HIV was independently associated with a decrease in FEV1 and FEV1/FVC, adjusted for age, sex, history of pneumonia or tuberculosis, ever smoking, occupational exposure (mining, dusty job, work with chemicals) and exposure to solid fuels.

Results: 201 consecutive participants were enrolled in the study from April to May 2016;84 were HIV-positive (82.1% on antiretroviral therapy). The median age (IQR) for the study population was 38 (29-51) years. 195 participants provided acceptable pre- and postbronchodilator spirometry. Both pre- and postbronchodilator FEV1 and FEV1/FVC-ratios were significantly lower in the HIV-positive group compared to the HIV-negative group (table 1). In sex and age adjusted analysis, the prevalence of airflow obstruction was significantly higher in the HIV-positive group (n=10, 12.2%) than the HIV-negative group (n=4, 3.5%), p-value 0.010. HIV was associated with a decrease in both FEV1 (B -0.148, p 0.048) and FEV1/FVC ratio (B -0.066, p 0.003) in multivariable regression analysis adjusted for respiratory risk factors and occupational exposure.

Conclusion: The prevalence of airflow obstruction was observed to be significantly higher in HIV-infection than in HIV-negative controls and HIV-infection was associated with a decrease in lung function measured by FEV1 and FEV1/FVC ratio.

Table 1: **Baseline characteristics and spirometry results**

	All	HIV-	HIV+
	N=201	*N=117*	*N=84*
Men	101 (50.3%)	76 (65.0%)	25 (29.8%)*
Smoking	94 (46.8%)	67 (57.3%)	27 (32.1%)
Electricity for cooking	177 (88.1%)	104 (88.9%)	73 (86.9%)
Mining work	20 (10.0%)	15 (12.8%)	5 (6.0%)
Dusty job ≥1 year	38 (18.9%)	26 (22.2%)	12 (14.3%)
Pneumonia	10 (5.0%)	2 (1.7%)	8 (9.5%)*
Pulmonary TB	35 (17.4%)	6 (5.1%)	29 (34.5%)*
Spirometry results	*N=195*	*N=113*	*N=82*
Post- FEV_1 (L)	2.943 (0.79)	2.987 (0.047)	2.800 (0.057)*
Post- FEV_1/FVC -ratio	0.84 (9.03)	0.85 (0.008)	0.82 (0.009)*
FEV_1/FVC < LLN	14 (7.2%)	4 (3.5%)	10 (12.2%)*
FEV_1/FVC < 0.70	9 (4.6%)	3 (2.7%)	6 (7.3%)

cART, combination antiretroviral thrapy; FEV_1 forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal. Data in n (%), mean (SD or SE) or median (IQR). Data have been adjusted for sex and age. *p<0.05

657 FACTORS ASSOCIATED WITH PULMONARY IMPAIRMENT IN HIV-INFECTED SOUTH AFRICAN ADULTS

Akshay Gupte[1], Michelle Wong[2], Reginah Msandiwa[3], Grace Barnes[1], Jonathan Golub[1], Richard Chaisson[1], Chris Hoffmann[1], Neil Martinson[3]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Univ of the Witwatersrand, Soweto, South Africa, [3]Perinatal HIV Rsr Unit, Soweto, South Africa

Background: HIV-infected individuals have increased risk of developing obstructive lung disease (OLD). While studies from developed countries report high viral load (VL), low CD4 counts, and anti-retroviral therapy (ART) to be associated with OLD, these findings may not be generalizable to populations with different socio-economic and epidemiological profiles.

Methods: We conducted a prospective cohort study in Soweto, South Africa from November 2008 to May 2011 to identify factors associated with OLD and lung function decline in 753 HIV-infected black African adults (>17 years). Spirometry without bronchodilators was performed according to ATS/ERS guidelines at enrollment and repeated annually thereafter. OLD was defined as FEV1/FVC<0.70. Logistic regression models were used to identify factors associated with OLD at enrollment. Excess annual declines in FEV1 and FVC were modelled as the product-term of follow-up time and exposures using random effects regression.

Results: Median (IQR) age was 36 (31-41) years and 15% were males. 30% ever-smoked; median (IQR) exposure of 3 (2-7) pack-years; and none reported exposure to biomass fuels or having worked in a mine. Median (IQR) CD4 count and VL at enrollment were 374 (263-527) cells/mm3 and 2690 (87-13486) copies/mL respectively, and 25% received ART. At enrollment, 734 (97%) participants underwent spirometry and 35 (5%) had spirometry-defined OLD (Table). Age (aOR=1.07 per year increase [95%CI 1.01-1.13], p=0.01), current smoking (aOR=4.05 [95%CI 1.33-12.36], p=0.01), and CRP (aOR=1.01 per unit increase [95%CI 1.00-1.03], p=0.03) were independently associated with OLD at enrollment; while CD4 count (aOR=1.03 per 100 cells/mm3 increase [95%CI 0.86-1.24], p=0.67), VL (aOR=0.76 per log increase [95%CI 0.49-1.19], p=0.23), ART (aOR=0.57 [95%CI 0.18-1.84], p=0.35) and history of TB/PCP (aOR=0.35 [95%CI 0.05-2.10], p=0.25) were not. Median (IQR) participant follow-up was 12 (6-24) months. History of TB was independently associated with greater declines in FEV1 (45 mL/year excess loss [95%CI 7-83], p=0.01) and FVC (64 mL/year excess loss [95%CI 18-110], p=0.006); while smoking, CD4, VL, ART and CRP were not.

Conclusion: Prevalent OLD was associated with older age, current smoking and higher CRP levels; but not CD4 count, VL and ART; in HIV-infected South African adults. Even modest smoking impairs lung function; better understanding of the long term effects of TB, smoking and inflammation on lung function in HIV-infected populations is urgently needed.

Table: Lung function and obstructive lung disease (OLD) by participant characteristics at enrollment

Characteristics	Full cohort N=753 n (%)	Females (N=636) FEV1 (L) mean (SD)	Females (N=636) FVC (L) mean (SD)	Females (N=636) OLD n (%)	Males (N=112) FEV1 (L) mean (SD)	Males (N=112) FVC (L) mean (SD)	Males (N=112) OLD n (%)
Age (years)							
19-30	118 (16)	2.80 (0.41)	3.31 (0.49)	3 (3)	3.40 (0.31)	4.38 (0.60)	0
30-40	418 (56)	2.63 (0.40)	3.17 (0.49)	9 (3)	3.44 (0.50)	4.35 (0.62)	6 (11)
40-50	177 (24)	2.36 (0.42)	2.89 (0.49)	6 (5)	3.06 (0.53)	3.91 (0.72)	5 (12)
≥50	35 (5)	2.01 (0.40)	2.65 (0.51)	5 (18)	2.80 (0.41)	3.79 (0.34)	1 (17)
p-value		***<0.001***	***<0.001***	***0.006***	***<0.001***	***<0.001***	0.84
Smoking status							
Never	514 (70)	2.57 (0.49)	3.10 (0.52)	16 (3)	3.20 (0.54)	3.98 (0.68)	0
Former	161 (22)	2.60 (0.44)	3.19 (0.49)	4 (4)	3.25 (0.51)	4.09 (0.67)	5 (8)
Current	64 (9)	2.55 (0.52)	3.12 (0.50)	3 (10)	3.29 (0.60)	4.33 (0.69)	7 (23)
p-value		0.88	0.37	0.16	0.83	0.11	***0.05***
CD4 count (cells/mm3)							
<250	146 (21)	2.53 (0.45)	3.08 (0.50)	6 (5)	3.15 (0.55)	3.98 (0.69)	3 (13)
250-500	354 (51)	2.57 (0.44)	3.09 (0.50)	9 (3)	3.32 (0.52)	4.20 (0.68)	4 (7)
≥500	195 (28)	2.60 (0.47)	3.15 (0.55)	7 (4)	3.16 (0.61)	4.17 (0.75)	4 (22)
p-value		0.28	0.27	0.57	0.87	0.22	0.16
Viral load (copies/ml)							
<50	155 (22)	2.45 (0.46)	2.97 (0.52)	9 (7)	3.08 (0.50)	4.02 (0.56)	2 (10)
50-400	76 (11)	2.64 (0.40)	3.19 (0.46)	2 (3)	3.34 (0.46)	4.35 (0.64)	2 (33)
400-10,000	248 (36)	2.62 (0.46)	3.16 (0.52)	6 (3)	3.34 (0.60)	4.20 (0.80)	2 (7)
≥10,000	215 (31)	2.57 (0.43)	3.11 (0.52)	5 (3)	3.28 (0.55)	4.15 (0.69)	5 (12)
p-value		***0.03***	0.07	0.28	0.29	0.75	0.33
ART							
Never	567 (75)	2.59 (0.44)	3.14 (0.51)	16 (3)	3.28 (0.55)	4.15 (0.70)	9 (11)
Recent (< 6 months)	155 (21)	2.49 (0.49)	3.00 (0.56)	7 (6)	3.12 (0.50)	4.07 (0.62)	3 (12)
Chronic (≥ 6 months)	29 (4)	2.71 (0.35)	3.28 (0.44)	0	3.76 (0.24)	4.70 (0.11)	0
p-value		0.54	0.52	0.42	0.94	0.60	1.00
H/o TB/PCP							
No	676 (90)	2.58 (0.45)	3.12 (0.52)	22 (4)	3.26 (0.53)	4.16 (0.69)	11 (11)
Yes	72 (10)	2.50 (0.40)	3.03 (0.49)	1 (2)	3.20 (0.65)	4.01 (0.57)	1 (10)
p-value		0.19	0.20	0.71	0.76	0.51	1.00
CRP (mg/L)							
<1	133 (19)	2.72 (0.41)	3.26 (0.47)	0	3.43 (0.73)	4.31 (0.83)	1 (5)
1-3	184 (26)	2.65 (0.43)	3.20 (0.52)	6 (4)	3.32 (0.41)	4.21 (0.55)	3 (13)
3-9	195 (28)	2.48 (0.46)	3.01 (0.54)	8 (5)	3.23 (0.53)	3.99 (0.62)	1 (5)
≥9	183 (26)	2.48 (0.43)	2.99 (0.47)	8 (5)	3.11 (0.49)	4.09 (0.74)	6 (20)
p-value		***<0.001***	***<0.001***	0.06	***0.02***	0.13	0.29

N – frequency; SD – standard deviation; FEV1(L) – forced expiratory volume in the first second expressed in liters; FVC(L) – forced vital capacity expressed in liters; OLD – obstructive lung disease defined as FEV1/FVC<0.70; ART – anti-retroviral therapy; H/o – self reported history; TB – tuberculosis; PCP – pneumocystis pneumonia; CRP – C-reactive protein

P-values reported for FEV1 and FVC comparisons are for trends across groups and considered significant at $\alpha \leq 0.05$

P-values reported for OLD comparisons are for Fishers exact test and considered significant at $\alpha \leq 0.05$

658 CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND MORTALITY IN HIV

Matthew Triplette[1], Sheldon T. Brown[2], Matthew B. Goetz[3], Joon W. Kim[4], Maria Rodriguez-Barradas[5], Guy W. Soo Hoo[3], Cherry Wongtrakool[6], Kathleen Akgün[7], Amy Justice[8], Kristina Crothers[1]

[1]Univ of Washington, Seattle, WA, USA, [2]James J. Peters VA Med Cntr, Bronx, NY, USA, [3]VA Greater Los Angeles Hlth Care System, Los Angeles, CA, USA, [4]James J. Peters VA Med Cntr, Bronx, NY, USA, [5]Baylor Coll of Med, Houston, TX, USA, [6]Emory Univ, Atlanta, GA, USA, [7]Yale Univ, New Haven, CT, USA, [8]VA Connecticut Hlthcare System, West Haven, CT, USA

Background: Aging HIV-infected (HIV+) individuals face an increased burden of multimorbidity, including chronic obstructive pulmonary disease (COPD), which is associated with frailty and decreased physical function in those with HIV. However, the impact of COPD on mortality in HIV+ patients is unclear. We determined the association between COPD, defined by pulmonary function tests (PFTs) and chest CT scans, with mortality using data from the Examinations in HIV Associated Lung Emphysema (EXHALE) study, a substudy of the Veterans Aging Cohort Study (VACS).

Methods: EXHALE enrolled 196 HIV+ and 165 uninfected smoking-matched subjects between 2009-2012. Subjects underwent baseline PFTs (spirometry and diffusing capacity [DLCO]) to define COPD and chest CT scans to define emphysema both by semi-quantitative (≤ or >10% lung involvement) and quantitative methods (% low attenuation areas), and were followed through 9/2015. We determined associations between PFT and CT markers of COPD and emphysema with mortality using multivariable Cox regression models, adjusting for smoking pack-years, demographics and the VACS Index, which predicts mortality and incorporates age, CD4 count, HIV RNA level, hepatitis C infection, and measures of organ dysfunction (hemoglobin, FIB-4, eGFR).

Results: The mortality rate was 2.9 per 100-person-years among HIV+ subjects compared to 1.6 per 100-person-years among uninfected (p=0.07). The median follow-up time was 64 months (IQR 47-73), and was similar by HIV status. In multivariable models, lower forced expiratory volume in 1 second (FEV1), DLCO, and radiographic emphysema were associated with increased mortality in HIV+ subjects (Table). HIV+ subjects with airflow obstruction consistent with COPD had 2.9 times the risk of death (HR 2.9 [95% CI 1.1-7.6]), compared to those without; those with >10% emphysema had 3.0 times the risk of death (HR 3.0 [95% CI 1.1-8.0]) compared to those with ≤10% emphysema. While these markers were not associated with mortality in the uninfected, formal tests of interaction between HIV status and these markers did not reach significance.

Conclusion: Markers of COPD were associated with greater mortality in HIV+ subjects, independent of the VACS Index. COPD may be an important contributor to mortality in HIV+ patients in the antiretroviral therapy era, and may have a different impact in HIV+ and uninfected patients. Further studies are needed to identify ways to improve outcomes of HIV+ patients with COPD and mitigate decline in pulmonary function.

Table. Hazard Ratios for Morality for Key Pulmonary Function and Chest CT Variables in HIV+ and Uninfected Subjects

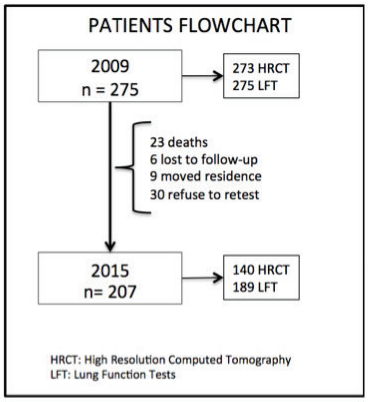
Variable	HIV+ (n=196 with 27 deaths)		Uninfected (n=165 with 13 deaths)	
	Unadjusted HR	Adjusted HR[a]	Unadjusted HR	Adjusted HR[a]
Airflow obstruction (FEV1/FVC<0.7)	**2.3 (1.1-5.2)**	**2.9 (1.1-7.6)**	1.2 (0.30-4.5)	0.68 (0.16-2.8)
Lower FEV1 %-predicted[b]	**1.4 (1.1-1.7)**	**1.4 (1.1-1.8)**	0.98 (0.70-1.4)	0.85 (0.59-1.2)
Lower FVC %-predicted[b]	**1.3 (1.0-1.6)**	1.0 (0.76-1.4)	1.1 (0.76-1.6)	0.94 (0.65-1.4)
Lower DLCO %-predicted[b]	**1.6 (1.2-2.2)**	**1.8 (1.2-2.7)**	1.4 (0.90-2.3)	1.2 (0.71-1.9)
Emphysema >10% severity	1.9 (0.86-4.2)	**3.0 (1.1-8.0)**	3.0 (0.83-11)	3.9 (0.88-17)
Higher % LAA on CT[c]	**1.3 (1.1-1.6)**	**1.4 (1.1-1.8)**	1.2 (0.71-2.0)	1.1 (0.64-2.0)

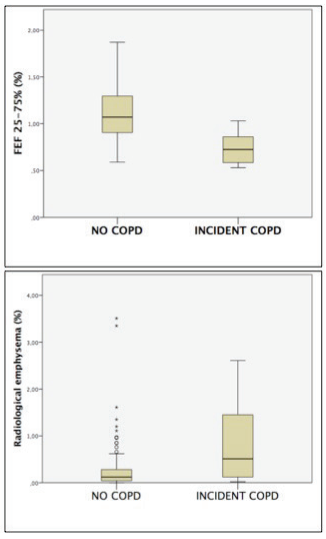
FEV1=forced expiratory volume in 1 second (post-bronchodilator); FVC=forced vital capacity (post-bronchodilator); DLCO=diffusion capacity (corrected for hemoglobin); LAA=low attenuation areas
[a] adjusted for age, sex, race/ethnicity, pack-years smoking and the VACS Index
[b] HR per 10-unit decrease
[c] HR per 5% increase

659 SPIROMETRIC AND RADIOLOGICAL PREDICTORS OF INCIDENT COPD IN A SPANISH COHORT

Francisco Fanjul, Gloria Sampériz, Javier Verdú, Helem Haydee Vilchez, Antoni Campins, Luisa Martin, María Peñaranda, Maria Angeles Ribas, María Leyes, Melchor Riera
Hosp Univ Son Espases, Palma de Mallorca, Spain

Background: Chronic Obstructive Pulmonary Disease (COPD) is a prevalent comorbidity in HIV-infected population. According to recent literature, up to 21% of HIV-infected individuals have obstructive ventilatory defects and more than 50% show reduced diffusing capacity. COPD may also progress more rapidly in HIV-infected population.
Methods: Prospective observational cohort study including 275 middle-aged (40-69 years) HIV-infected patients randomly selected from the population followed up in Hospital Son Espases. At the inclusion in the cohort in 2009 patients underwent: a) lung function tests (LFT) including spirometry, plethysmography, diffusion capacity measures and 6MWT. b) quantitative emphysema radiological estimation measured by High-Resolution Chest CT Scan. In 2015 patients who continued follow-up were offered to repeat these tests. Smoking, comorbidities and epidemiological data including socio demographic variables were registered.
Results: In 2009, 275 patients aged 48.5+-6.6 years were included. 60,7% of patients were active smokers, 17.2% had airway limitation (AL) in spirometry and 52% diffusion altered capacity. Radiological emphysema was observed in 10.5% of patients. Patient flow diagram is presented in Figure 1. At the end of follow-up, 25.4% of patients had COPD with 11% of incident cases. Radiological emphysema was observed in 25,73% of patients. Higher mortality was observed in patients with initial AL in spirometry (14,63% vs 8,1%) Possible predictors of incident COPD were compared in patients who underwent both spirometric tests and had shown no AL in the first one. Univariate analysis showed that active smoking (OR 24,88 CI95% 6,98-88,69, p<0,0001) abnormal forced expiratory flow 25-75% (50% vs 9,8%, OR 9,14, CI95%: 2.59-32.19, p<0.001) and radiological emphysema (OR 8.11, CI95% 2,36-27,78 p<0,001) were associated with higher risk of incident COPD. No differences were observed between groups in gender or age. In the multivariate analysis , only FEF 25-75% (p=0,009) and radiological emphysema (p=0,002) remained statistically significant.
Conclusion: 1.- COPD initial prevalence in our cohort was high and associated higher mortality. 2.- We hypothesize that both radiological emphysema and abnormal FEF25-75% values could be early markers of incipient airway limitation, preceding most traditional spirometric COPD criteria. They could help clinicians to diagnose those patients at COPD higher risk.





660 EFFECT OF HIV INFECTION ON ALPHA-1 ANTITRYPSIN FUNCTION: ROLE IN EMPHYSEMA?

Sarah E. Stephenson[1], **Engi F. Attia**[2], Carole L. Wilson[1], Cherry Wongtrakool[3], Kristina Crothers[2], Irina Petrache[4], Lynn M. Schnapp[1]
[1]Med Univ of South Carolina, Charleston, SC, USA, [2]Univ of Washington, Seattle, WA, USA, [3]Emory Univ, Atlanta, GA, USA, [4]Natl Jewish Hlth, Univ of Colorado, Denver, CO, USA

Background: Emphysema is one of the most common lung diseases in HIV+ patients and is characterized by reduced diffusing capacity for carbon monoxide (DLCO). Pathogenesis of HIV-associated emphysema remains unclear; however, the radiographic distribution with greater lower lobe involvement and earlier age at presentation in HIV+ patients are similar to patients with deficiency of alpha-1 antitrypsin (A1AT), a key elastase inhibitor in the lung. We hypothesized that HIV is associated with decreased A1AT activity and explored whether decreased A1AT activity is associated with reduced DLCO and radiographic emphysema.
Methods: The Examinations of HIV Associated Lung Emphysema (EXHALE) study enrolled 196 HIV+ and 165 HIV- smoking-matched subjects between 2009-2012. Subjects underwent pulmonary function tests, chest CT scans and phlebotomy; a subset (n=53) underwent research bronchoscopy. We analyzed plasma and bronchoalveolar lavage fluid (BALF) from 22 HIV+ and 31 HIV- patients. Differential cell counts and pro-inflammatory cytokines were measured in BALF. We measured A1AT levels in plasma and BALF by ELISA. In BALF, we assessed anti-elastase activity as an indicator of A1AT function and measured oxidized and polymerized A1AT by western blot. Differences in levels of markers were compared by HIV status and presence of lung disease, defined by DLCO <60% predicted or any radiographic emphysema on chest CT, using Wilcoxon rank sum tests.
Results: In the BALF of HIV+ patients, neutrophils and granulocyte colony stimulating factor (G-CSF), a chemoattractant for neutrophils, tended to be elevated compared to HIV- patients (Table). Total A1AT was increased in BALF, but not in plasma, of HIV+ compared to HIV- patients. Concurrently, we detected decreased anti-elastase activity by A1AT in BALF in HIV+ compared to HIV- patients, suggesting impaired A1AT function. We detected modifications of A1AT, including polymerized and oxidized forms, in HIV+ patients, which may account for decreased A1AT anti-elastase activity. BALF A1AT and elastase activity did not differ by DLCO or emphysema. However, those with lower lobe emphysema had greater median BALF A1AT (1105 [IQR 490-1162] vs 582 [205-1089]; p=0.08) and a trend for increased elastase activity (0.88 [0.52-0.96] vs 0.58 [0.21-0.88]; p=0.1).
Conclusion: These findings suggest that in the lungs of HIV+ patients, post-translational modifications of A1AT produce a functional deficiency of this critical elastase inhibitor, which may contribute to emphysema development.

Table. BALF and plasma levels* of select biomarkers by HIV status

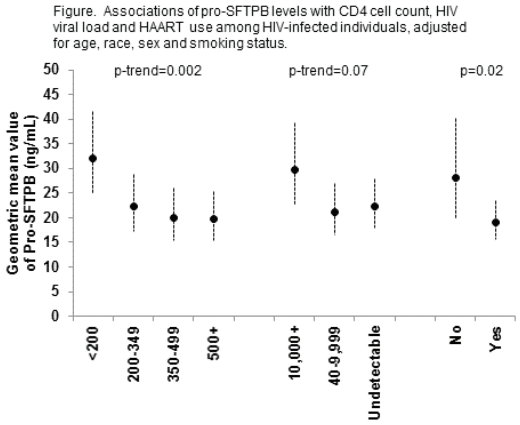
	HIV+ *n* = 22	HIV- *n* = 31	p-value
BALF A1AT (ng/mL)	1083 (490 – 1870)	523 (183 – 841)	0.02
BALF oxidized A1AT (ng/mL)	1958 (436 – 3642)	1091 (539 – 2245)	0.2
BALF polymerized A1AT (OD)	3.79 (2.00 – 4.16)	2.91 (1.63 – 6.61)	0.1
BALF elastase activity (OD)	0.85 (0.54 – 1.16)	0.54 (0.21 – 0.86)	0.01
BALF neutrophils (per 100 cells/field)	3 (1 – 10)	2 (1 – 3)	0.2
BALF G-CSF (pg/mL)	9.01 (7.31 – 17.2)	4.94 (3.25 – 9.06)	0.1
Plasma A1AT (mg/mL)	1.49 (1.22 – 1.68)	1.62 (1.43 – 1.90)	0.08

* Data reported as median (IQR)

661 HIV AND CIRCULATING LEVELS OF PRO-SURFACTANT PROTEIN B AND SURFACTANT PROTEIN D

Meredith S. Shiels[1], Gregory D. Kirk[2], M. Brad Drummond[3], Dilsher Dhillon[4], Samir Hanash[4], Ayumu Taguchi[4], Eric A. Engels[1]
[1]NCI, Rockville, MD, USA, [2]Johns Hopkins Univ, Baltimore, MD, USA, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]MD Anderson Cancer Cntr, Houston, TX, USA

Background: Lung cancer risk is elevated 2-3 times in people with HIV compared to the general population after controlling for smoking. It has been hypothesized that chronic pulmonary infections or inflammation may contribute to elevated risk. In a cohort of HIV-infected and uninfected adults, we evaluated serum levels of pro-surfactant protein B (pro-SFTPB) and surfactant protein D (SFTPD), two markers of lung inflammation and damage that are prospectively associated with lung cancer.
Methods: Circulating levels of pro-SFTPB and SFTPD were measured in the serum of 500 HIV-infected and 300 uninfected people enrolled in the Study of HIV Infection in the Etiology of Lung Disease. We estimated geometric mean surfactant protein levels by HIV status, adjusted for age, race, sex, and smoking status. Among HIV-infected individuals, we also assessed surfactant protein levels by CD4 cell counts, HIV RNA viral load and current HAART use.
Results: Pro-SFTPB levels were positively associated with increasing age, current smoking, cigarettes/day and chronic obstructive pulmonary disease while SFTPD levels were positively associated with current smoking and white race. Pro-SFTPB and SFTPD levels were weakly correlated (r=0.20). Pro-SFTPB levels were significantly higher among HIV-infected compared to HIV-uninfected participants (adjusted geometric mean: 19.7 vs. 16.7 ng/mL; p=0.03). Pro-SFTPB levels were higher among those with lower CD4 cell counts (geometric mean 32.1 vs. 19.7 ng/mL for CD4 <200 vs. ≥500 cells/mm3; p-trend=0.002), higher HIV RNA viral loads (29.8 vs. 22.3 ng/mL for <10,000 copies/mL vs. undetectable levels; p-trend=0.07), and among those not currently being treated with HAART (28.2 vs. 19.2 ng/mL for untreated vs. treated individuals; p=0.02; Figure). However, no difference in SFTPD levels was observed by HIV status (85.8 vs. 93.6 ng/mL; p=0.15) or across categories of CD4 cell count (p-trend=0.99), HIV RNA viral load (p-trend=0.76) or current HAART use (p=0.78).
Conclusion: In summary, HIV-infected people manifest elevated levels of pro-SFTPB, but not SFTPD, compared to uninfected people, independent of tobacco use. Pro-SFTPB levels are further increased in association with declining CD4 cell count, high HIV RNA viral load, and in the absence of HIV treatment. As pro-SFTPB is a predictor of lung cancer risk in the general population, these findings provide support for a role of pulmonary inflammation and lung damage in explaining the increased risk of lung cancer among HIV-infected people.

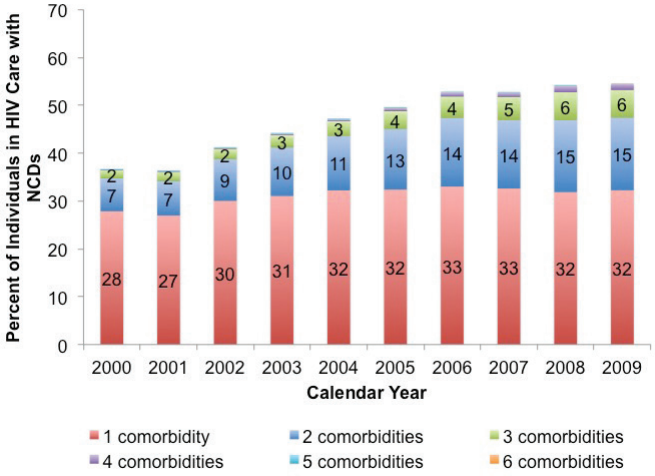


662 TREND IN MULTIMORBIDITY AMONG HIV+ ADULTS IN CLINICAL CARE IN THE US

Cherise Wong[1], Stephen J. Gange[1], Richard D. Moore[2], Amy Justice[3], Alison Abraham[4], Kelly Gebo[1], John Gill[5], Jeffrey N. Martin[4], Angel Mayor[5], Keri N. Althoff[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]VA Connecticut Hlthcare System, West Haven, CT, USA, [3]Univ of Calgary, Calgary, Canada, [4]Univ of California San Francisco, San Francisco, CA, USA, [5]Univ Central del Caribe, Bayamon, Puerto Rico

Background: With the increased life expectancy of ART-treated individuals living with HIV, chronic non-communicable diseases (NCD) are becoming increasingly common. Trends in NCD among HIV-infected adults in North America, particularly among the most heavily affected subgroups, have not been studied. These data are needed in order for providers, health care systems, and policy-makers to prepare for the long-term management of those with HIV.
Methods: Our study population included ART-exposed, HIV-infected adults (≥18) in US clinical care during 2000-2010 from the North American AIDS Cohort Collaboration on Research and Design. For this study, we had an interest in the prevalence of concurrent NCDs (multimorbidity), defined as having two or more of the following: hypertension, diabetes, chronic kidney disease, hypercholesterolemia, end-stage liver disease, and non-AIDS-related cancer. NCDs were time-updated and absorbent. Annual prevalence of multimorbidity was estimated among individuals who were in care (based upon having ≥1 CD4 measurement in the calendar year). Adjusted (aPR) prevalence ratios and 95% confidence intervals ([,]) for multimorbidity were estimated by Poisson regression with robust variance, using generalized estimating equations for repeated measures.
Results: Our analysis included n=22,969 adults; 79% male, 36% black, and median age at entry was 40 years (IQR: 34 - 46). The frequency of multimorbidity was 12% (for 2 conditions), 4% (for 3), and 0.9% (for >3). Between 2000-2010, multimorbidity prevalence increased from 8.2% to 22.4% (p-trend<0.001; Figure 1). Hypertension and hypercholesterolemia were the most common co-occurring conditions. Adjusting for age, sex, race, HIV risk, year, regimen, years of ART, AIDS, CD4 at ART start, viral suppression, and CD4, individuals residing in the South (aPR=1.55 [1.30,1.85]) and the West (aPR=1.33 [1.11,1.60]) relative to the Northeast were more likely to have multimorbidity. There was no difference by sex and blacks were less likely to have multimorbidity (compared to whites, aPR=0.86 [0.75,0.98]).
Conclusion: The prevalence of multimorbidity has increased among those living with HIV. As the HIV-infected population ages with effective HIV treatment, the prevention and treatment of NCDs will increasingly become a critical co-management need for this population that care providers, health care systems and policy-makers must adapt to.

Figure 1. Annual Prevalence of Non-Communicable Disease Burden Among Individuals Living with HIV in Clinical Care in the U.S. (n=22,969)



663 NON-AIDS ILLNESS BURDEN DIFFERS BY SEX, RACE, AND INSURANCE TYPE IN AGING HIV+ ADULTS

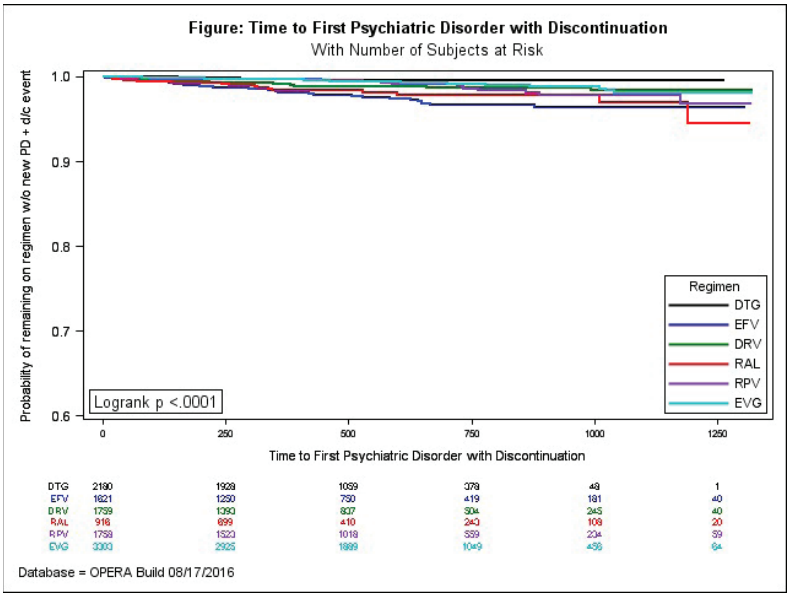
Frank J. Palella[1], Rachel Hart[2], Carl Armon[2], Ellen Tedaldi[3], Bienvenido Yangco[4], Richard Novak[5], Linda Battalora[6], Douglas Ward[7], Bonnie Dean[2], Kate Buchacz[8]
[1]Northwestern Univ, Chicago, IL, USA, [2]Cerner Corporation, Kansas City, MO, USA, [3]Temple Univ, Philadelphia, PA, USA, [4]Infectious Disease Rsr Inst, Tampa, FL, USA, [5]Univ of Illinois, Chicago, IL, USA, [6]Colorado Sch of Mines, Golden, CO, USA, [7]Dupont Circle Physicians Group, Washington, DC, USA, [8]CDC, Atlanta, GA, USA

Background: Understanding the epidemiology of non-AIDS chronic co-morbidities (NACM) among aging HIV-infected (HIV+) persons is essential to optimize clinical care, and to plan health screening strategies. We evaluated number and types of NACMs in large diverse population of HIV+ adults on ART.

Methods: We studied HIV Outpatient Study (HOPS) patients at 8 US HIV clinics, seen during 1/1/1997 to 6/30/2015, who were followed for a minimum of 5.0 years with ≥75% of observation time having viral load (VL) <200 copies/mL and on ART. In stratified analysis (by age at last observation:18-40, 41-50, 51-60, >61 years), we assessed number and types of NACMs documented in medical records anytime during HOPS observation and evaluated for differences in NACM prevalence and type by age group, sex, race, insurance type, HIV risk and HIV clinical factors. NACMs included were cardiovascular disease, cancer, hypertension, diabetes, dyslipidemia, arthritis, chronic HBV or HCV infection, anemia, and psychiatric illness.
Results: Of 1540 patients, there were 1247 (81%) men, 406 (26%) non-Hispanic black, 183 (12%) Hispanic/Latino, 846 (55%) with private insurance, 575 (37%) with public insurance, 939 (61%) men who have sex with men (MSM), 375 (24%) heterosexuals and 125 (8%) with injection drug use history. Patients numbered 180, 502, 560, and 298, respectively, in the age strata 18-40, 41-50, 51-60, >61 years, with HOPS observation of a median of 10.8 years (range: min-max = 5.0-18.5). Mean number of NACMs increased by age category; 1.8, 2.6, 3.5, 4.3, respectively, (P<0.001). Overall prevalence of all NACMs increased with older age categories (P<0.001) except HBV and HCV infection and psychiatric illness (Figure). Significant differences (all P< 0.05) in mean number of NACMs were apparent by sex (women > men, 3.5 vs 3.1), race (blacks > non-blacks, 3.4 vs 3.1), and by insurance status (public > private, 3.9 vs 2.6). These differences were especially apparent in older age groups (51-60 and > 61 years, 3.5 and 4.3 vs 2.3 for ≤ 50 years of age), and were driven primarily by differences in specific NACMs: anemia, HCV, and diabetes.
Conclusion: We observed age-related increase in prevalence of NACMs and polymorbidity, with disproportionate burden most apparent among older women, blacks, and the publicly insured. These groups should be targeted for screening and prevention strategies aimed at risk reduction and disease intervention.

664 PSYCHIATRIC DISORDERS OBSERVED IN HIV+ PATIENTS USING 6 COMMON THIRD AGENTS IN OPERA

Ricky Hsu[1], Jennifer Fusco[2], Cassidy Henegar[2], Felix Carpio[3], Karam Mounzer[4], Michael Wohlfeiler[5], Vani Vannappagari[6], Michael Aboud[7], Lloyd Curtis[8], Gregory Fusco[2]
[1]New York Univ, New York, NY, USA, [2]Epividian, Durham, NC, USA, [3]Altamed Hlth Services, Los Angeles, CA, USA, [4]Philadelphia FIGHT, Philadelphia, PA, USA, [5]AIDS Hlthcare Fndn, Los Angeles, CA, USA, [6]ViiV Hlthcare, Rsr Triangle Park, NC, USA, [7]ViiV Hlthcare, Brentford, UK, [8]GlaxoSmithKline, Uxbridge, UK
Background: Psychiatric disorders (PD) are reported frequently in people living with HIV and may be associated with specific antiretroviral (ARV) use. We sought to evaluate PD in patients (pts) taking dolutegravir (DTG)-containing regimens compared to five other widely prescribed ARVs in an observational database.
Methods: Pts prescribed DTG, efavirenz (EFV), raltegravir (RAL), darunavir (DRV), rilpivirine (RPV) or elvitegravir (EVG)-based regimens for the first time in the OPERA database between 1/1/2013 and 8/15/2015 were analyzed. Each was observed from the regimen start date until regimen discontinuation, loss to follow up, death, or data freeze (8/15/2016). Events were diagnoses of anxiety, depression, insomnia, or suicidality. PD diagnoses followed by 3rd agent discontinuation within 14 days were also evaluated. Time to each of these events was described. Pairwise comparisons were made using Pearson's chi-square or Fisher's exact tests; Kaplan-Meier curves were compared with log-rank tests.
Results: Out of 70,106 HIV+ pts in the OPERA database, 11,539 qualified for the analysis of DTG (18.9%), EFV (14.1%), RAL (7.9%), DRV (15.2%), RPV (15.2%) or EVG (28.6%)-containing regimens. History of PDs was common and not evenly distributed across groups (DTG 39.2%; EFV 23.8%, RAL 39.9%, DRV 34.0%, RPV 28.4%, EVG 30.8%). Pts prescribed DTG were significantly (p<.05) more likely to have a history of anxiety, depression, or insomnia than EFV, DRV, RPV, and EVG. History of suicidality did not differ across groups. In analyses including pts with history of PDs, pts prescribed RAL regimens experienced more PDs over follow up (21.0%) than DTG (17.6%) regimens. The other four regimens did not differ significantly from DTG (EFV 18.1%, DRV 18.2%, RPV 16.6%, EVG 19.3%). When pts with PD history were excluded, incidence of new PDs was less frequent and similar across regimens (DTG 12.8%, EFV 14.3%, RAL 14.4%, DRV 11.7%, RPV 12.8%, EVG 13.9%). Incidence of PD associated discontinuation was significantly less frequent in pts treated with DTG (0.3%) vs EFV (2.2%), RAL (1.7%), DRV (1.7%), RPV (1.0%), and EVG (0.8%). Time to PD with discontinuation was longer for pts prescribed DTG.(Figure)
Conclusion: In a large cohort of HIV+ patients in care, DTG use was not associated with an increased risk of PD despite a higher rate of pts with a history of PD prior to DTG treatment. Pts prescribed DTG were less likely than those prescribed five other ARVs to discontinue their ARV regimen due to PD.



665 FRAILTY HAS A STRONGER ASSOCIATION THAN NEUROCOGNITIVE IMPAIRMENT WITH POOR OUTCOMES

Kristine Erlandson[1], Mona Abdo[2], Kevin Robertson[3], Susan L. Koletar[4], Robert Kalayjian[5], Babafemi Taiwo[6], Frank J. Palella[6], Katherine Tassiopoulos[2], for the A5322 Study Team
[1]Univ of Colorado, Aurora, CO, USA, [2]Harvard Univ, Boston, USA, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]Ohio State Univ, Columbus, OH, USA, [5]MetroHlth Med Cntr, Cleveland, OH, USA, [6]Northwestern Univ, Chicago, IL, USA
Background: Frailty and neurocognitive impairment (NCI) are closely-related constructs of vulnerability in older adults. We previously found that NCI was one of the strongest predictors of frailty in HIV-infected adults; however, the overlap of frailty and NCI, and their impact on poor outcomes in HIV-infected persons is unknown.
Methods: Participants in a longitudinal, observational study of aging in HIV (A5322, HAILO) completed entry evaluations for: 1) frailty, defined as presence of ≥3 criteria of slow gait, weak grip, unintentional weight loss, exhaustion, and low physical activity and: 2) NCI, defined by ≥1 normalized z-score >2 SD below 0 or ≥2 z-scores >1 SD below 0 on Trailmaking A and B and the Wechsler Adult Intelligence Scale-Revised Digit Symbol tests. Outcomes of falls (any), disability (increase in number of limitations in independent

activities of daily living), or mortality were combined. Log binomial models estimated prevalence ratios (PR) for frailty/NCI and ≥1 outcome over 96 weeks. An a priori decision was made to adjust for age as well as variables with the strongest confounding effect.
Results: Of the 897 participants with follow-up data (94%) median age at entry was 51 (IQR 46-56) years, 19% were female, 49% Caucasian, median CD4 count was 620 (IQR 453, 821) cells/μL, and 95% had an HIV-1 RNA <200 copies/mL. The majority (80%) of participants had neither frailty nor NCI; 4% had frailty but no NCI, 14% had NCI without frailty, and 2% had frailty and NCI. Forty-one percent had ≥1 outcome: falls (20%), disability (12%), death (1%), falls + disability (6%), and falls + mortality, disability + mortality, or all 3 (<1% each). Outcomes occurred among 76% of those frail without NCI, 48% with NCI only, 88% with frailty + NCI and 36% without frailty/NCI. In models adjusted for age and education, frailty without NCI was associated with 2x the risk of poor outcome (PR 2.0; 95% CI 1.6, 2.4); a strong association was also seen with frailty + NCI (PR 1.8; 95% CI 1.4, 2.4). A weaker association was seen with NCI without frailty (PR 1.2; 95% CI 1.0, 1.5). Similar results were seen when adjusted for insurance status.
Conclusion: The presence of frailty, with or without NCI, was associated with a greater risk of falls, disability or death in HIV-infected adults than NCI alone. Although frailty and NCI may involve similar pathologic mechanisms, interventions targeted at reducing and reversing frailty may have greater impact on these outcomes than NCI-specific interventions.

666 FRAILTY STATUS AND RISK OF FALLS IN HIV-INFECTED OLDER ADULTS IN THE ACTG A5322 STUDY

Katherine Tassiopoulos[1], **Mona Abdo**[1], Susan L. Koletar[2], Frank J. Palella[3], Babafemi Taiwo[3], Kristine Erlandson[4], for the A5322 Study Team
[1]Harvard Univ, Boston, MA, USA, [2]Ohio State Univ, Columbus, OH, USA, [3]Northwestern Univ, Chicago, IL, USA, [4]Univ of Colorado, Aurora, CO, USA
Background: Falls are a significant risk factor for morbidity and mortality in the general population. Among HIV-infected individuals, frailty is common, but an understanding of the association between frailty and falls is limited.
Methods: AIDS Clinical Trials Group (ACTG) A5322 is a longitudinal cohort study that enrolled 1035 HIV-infected adults ≥40 years to examine the long-term effects of HIV and antiretroviral therapy on the occurrence of clinical events, physical and neurocognitive function, and inflammation and aging. Research visits take place every 6 months and include medical chart abstraction, medication review, physical exams, laboratory tests, repository specimen collection, questionnaires – including a falls interview, and neurocognitive assessments. Participants also complete a frailty assessment (4-meter walk, grip strength, and self-reported weight loss, exhaustion, and low physical activity). Participants meeting ≥3 of 5 criteria are considered frail, 1-2 criteria are pre-frail, and no criteria are non-frail. Multinomial logistic regression was used to assess the association between frailty status at entry and falls (single and recurrent [2+]) over the following year. The individual frailty components of grip and 4-meter walk were also examined.
Results: Of 967 individuals, 81% were male, 30% Black and 19% Hispanic. Median (IQR) age was 51 (46, 56) years. Most participants (92%) were virologically suppressed at entry, and median CD4 count was 618 (IQR 451, 821) cells/μL. Six percent were frail, 39% pre-frail, and 55% non-frail; 174 individuals (18%) had ≥ 1 fall, and 7% had 2+ falls. Among persons with 1 or more falls, 21% sought medical attention and 5% had ≥ 1 fracture. In multivariable models, pre-frail individuals were more likely than non-frail to experience 1 fall (OR=1.55; 95% CI=0.97-2.48) and 2+ falls (OR=3.78; 95% CI=1.86-7.69); this association was stronger for frail individuals (1 fall: OR=2.27; 95% CI=0.86-6.01; 2+ falls: OR=18.6; 95% CI=7.60-45.3). Weaker associations were seen with recurrent falls and slow 4-meter walk (OR=2.90; 95% CI=1.57-5.36) and weak grip (OR=3.86; 95% CI=2.25-6.63).
Conclusion: Aging HIV-infected pre-frail and frail individuals are at significantly increased risk of falls. Regular incorporation of frailty assessments or simple evaluations of 4-m walk or grip strength in the clinical setting may help identify older HIV-infected individuals at increased risk for falls and those who would benefit from falls prevention interventions.

667 PHYSICAL FUNCTION AND INFLAMMATION IN OLDER HIV-INFECTED MEN

Hillary McClintic[1], Matthew Freiberg[2], Stephen Crystal[3], David Leaf[4], Julie A. Womack[5], Karen Nieves-Lugo[6], Janet Tate[7], Kristina Crothers[8], Amy Justice[7], Krisann Oursler[9]
[1]Virginia Tech, Roanoke, VA, USA, [2]Vanderbilt Univ, Nashville, TN, USA, [3]Rutgers, The State Univ of New Jersey, New Brunswick, NJ, USA, [4]VA Greater Los Angeles Hlthcare System, Los Angeles, CA, USA, [5]VA Connecticut Hlthcare System, Branford, CT, USA, [6]The George Washington Univ, Washington, DC, USA, [7]VA Connecticut Hlthcare System, West Haven, CT, USA, [8]Univ of Washington, Seattle, WA, USA, [9]Salem VA Med Cntr, Salem, VA, USA
Background: Aging with HIV infection is often characterized by chronic inflammation, multimorbidity, and frailty distinguished in part by decreased physical function. However, the relationship among these factors is not well understood and varies by the measure of function. We previously found in older HIV+ that the six-minute walk distance (6-MWD) correlates with cardiopulmonary fitness and lung function and further, that the survey-based physical health composite score (PCS) predicts mortality independently of comorbidity. Our current objective is to better understand the relationship between physical function and inflammation by comparing the association of the 6-MWD and the PCS with a panel of biomarkers of inflammation.
Methods: This is a cross-sectional study of 177 HIV+ men enrolled in the Veterans Aging Cohort Study (VACS) without prior diagnosis of cardiovascular disease. The 6-MWD test was performed at least 48 hours from blood sampling for IL-6, hsCRP, TNFα, sTNFrI, and sTNFrII. The physical health composite score (PCS) was derived from SF-12 survey items with a higher number representing better function. The association of 6-MWD and PCS with log transformed level of biomarkers was determined by Spearman's correlation and age-adjusted linear regression models.
Results: The mean (SD) age was 54.5 (7.3) years and 80% were African American race. The mean (SD) 6-MWD was 499 (82) meters, which was 21% lower than age/gender predicted value. The median (IQR) PCS was 49.6 (39.9-54.7). There was a modest correlation between 6-MWD and PCS (ρ= 0.16, p=0.04). Both 6-MWD and PCS correlated with IL-6 and sTNFrI (Table). Only 6-MWD correlated with hsCRP. In age-adjusted linear regression models, the association of 6-MWD and hsCRP was the only relationship that remained significant. A log increase in hsCRP level was associated with a decrease of 16 meters in the 6-MWD with adjustment for age (β= -16.1, 95%CI (-25.4, -6.9)).
Conclusion: Decreased ambulatory function and poor self-reported function are associated with elevated levels of biomarkers of inflammation in HIV+ older men. Levels of hsCRP predicted 6-MWD but not PCS, independently of age. While limited in size, our study contributes to a growing literature suggesting that inflammatory processes may play a greater role among those aging with HIV. Further research with longitudinal assessments of objective and precise measures of physical function are warranted.

Correlation of 6-MWD and self-reported physical function with inflammation				
	6-MWD, m		Physical Composite Score (PCS)	
Biomarker (log)	Rho (ρ)	p-value	Rho (ρ)	p-value
IL-6	-0.19	.01	-0.18	.04
hsCRP	-0.30	<.01	-0.12	.17
sTNFrI	-0.19	<.01	-0.16	.04
sTNFrII	-0.03	.73	-0.16	.03
TNFα	-0.08	.27	0.04	.64

668 VACS INDEX AS A PREDICTOR FOR NON-AIDS DEFINING CONDITIONS IN A LONGITUDINAL COHORT

Brian K. Agan[1], Seung Hyun Won[1], Christina Schofield[2], Anuradha Ganesan[1], Margaret Glancey[1], Jason Okulicz[3], Edmund C. Tramont[4], Julie Pavlin[1], for the IDCRP HIV Working Group
[1]Uniformed Services Univ of the Hlth Scis, Bethesda, MD, USA, [2]Madigan Army Med Cntr, Takoma, WA, USA, [3]San Antonio Military Med Cntr, Fort Sam Houston, TX, USA, [4]NIAID, Bethesda, MD, USA

Background: The Veterans Aging Cohort Study (VACS) Index predicts all-cause mortality among HIV infected populations, as well as non-AIDS cardiovascular (CV) and neurocognitive diseases. The US Military HIV Natural History Study (NHS) is a longitudinal cohort of HIV infected military active duty and beneficiaries that collects detailed clinical information including medical diagnoses. We evaluated the VACS Index as a predictor of non-AIDS, as well as AIDS and mortality risk in the NHS.
Methods: We included all NHS subjects with HAART initiation (HI) from 1996 to 2014, who had all VACS Index variables, and at least one year of follow-up after HI. We evaluated the correlation of VACS Index with mortality, AIDS, and non-AIDS conditions (including cancer, CV, gastrointestinal, respiratory, endocrine, musculoskeletal, neurological and psychological diseases) individually, by group, and in aggregate. We calculated Harrell's concordance index at three time points (HI, 6 months after HI, and 1 year after HI). Harrell's c > 0.5 implies a prediction ability, increasing as the value approaches 1. Levels >0.7 are often considered evidence of good prediction.
Results: 2,091 participants (93.3% male, 44.7% African American, median age 32.7 years ([IQR 12.0 years]) met our inclusion criteria. The mean/median VACS Index scores at HI were 22.5/17.0, at 6 months 13.9/10.0 and at 1 year 13.4/10.0 [VACS Index can range from 0 to 164]. The Harrell's c index between the VACS Index and death or AIDS showed strong correlations at all three time-points (Table). For more severe non-AIDS illnesses such as cancer and CV disease, the correlation was not as strong. Earlier precursors of disease such as hypertension and hyperlipidemia were not correlated with the VACS index. The VACS Index also did not correlate highly with other diseases such as depression or asthma.
Conclusion: In this longitudinal cohort of young, healthy individuals, and a substantial number of African Americans, the VACS Index decreased after HAART initiation, as expected, and was strongly correlated with mortality and AIDS. For serious non-AIDS, such as a CV event or cancer, although not strongly correlated, the correlation trended positive; evaluation was limited by the number of endpoints. The VACS Index was not predictive of less serious non-AIDS diseases. In our HIV infected cohort, the VACS Index was a useful predictor of clinical outcomes with graded correlation along the spectrum of HIV related disease.

		Harrell's concordance index		
	# Events	At HAART Initiation (HI)	6 months after HI	1 year after HI
Death	187	0.73	0.78	0.79
AIDS	148	0.77	0.81	0.80
Cancer	103	0.60	0.64	0.63
Cardiovascular	145	0.63	0.64	0.65
Diabetes	114	0.55	0.53	0.52
Hyperlipidemia	730	0.50	0.48	0.47
Hypertension	353	0.49	0.48	0.47
Depression	254	0.51	0.49	0.48
Asthma	64	0.46	0.49	0.47
Total non-AIDS*	1234	0.51	0.49	0.49

*Individuals with one or more non-AIDS diagnoses.

669 AMERICAN GINSENG FOR THE TREATMENT OF HIV FATIGUE: A RANDOMIZED CLINICAL TRIAL

Adriana Andrade[1], Jeff Sloan[2], Chun-Su Yuan[3], Brent Bauer[2], Paul Novotny[2], Judith Rabkin[4], Jeffrey Hsu[1], Adrian Dobs[1], Todd Brown[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Mayo Clinic, Rochester, MN, USA, [3]Univ of Chicago Med, Chicago, IL, USA, [4]Columbia Univ, New York, NY, USA

Background: HIV-related fatigue is prevalent and linked to neurocognitive deficits, nonadherence, poor quality of life (QOL) and physical functioning, but targeted treatment for HIV fatigue is not available. Research suggests American ginseng (AG) may ameliorate cancer fatigue. We examined the safety and efficacy of AG for HIV-related fatigue.

Methods: We conducted a 6-week, double-blind, parallel-arm, placebo-controlled trial comparing encapsulated, standardized AG powdered root (≥5% total ginsenoside content confirmed yearly by HPLC) 1000 and 3000mg PO QD to placebo. HIV-infected adults, on stable ART, undetectable viral load (VL), with a Fatigue Severity Score (FSS) >=4.5, and without other illness associated with fatigue, received AG or placebo for 4 wks, and were observed until wk 6. Primary endpoint was change in FSS from baseline to wk 4. Secondary outcomes assessed other measures of fatigue (sleep quality, depression, and QOL (MOS HIV)). Changes were compared between groups using nonparametric Wilcoxon tests supplemented with repeated measures mixed models to adjust for age, gender, race, baseline insomnia and depression.
Results: Of the 120 planned subjects, 96 were enrolled (African-American race (91%) and male (54%) with a median age of 52.5 years and median CD4 count of 624 ul/mL); 32 were randomized to AG 1000mg, 31 to AG 3000mg, and 33 to placebo. FSS changes were not significantly different between either of the AG arms and placebo. Mean (SD) FSS decreases were: -24.7 (18.6) on AG 1000mg, -16.9 (15.0) on AG 3000mg, and -18.7 (17.4) on placebo (p=0.15 AG 1000mg vs placebo, p=0.73 AG 3000mg vs placebo). Self-reported assessment of having much or very much improvement in fatigue was not different between arms: 45% on AG 1000mg, 34% on AG 3000mg, and 39% on placebo. In a post-hoc analysis, combining the 2 AG arms confirmed that fatigue was no different than placebo in the primary endpoint, but AG showed modest improvements in fatigue on 3/4 subscales of Brief Fatigue Inventory (p = 0.01-0.03) and trends toward improvement in 4 of 10 subscales of the MOS HIV QOL questionnaire (p = 0.01-0.07) compared to placebo. Adverse events were not different between the study arms. Overall mean adherence was ≥96% for all study arms.
Conclusion: AG did not reduce fatigue compared to placebo with short-term administration to HIV-infected subjects with fatigue. The clinical significance of small improvements in the AG arms in some of the secondary endpoints relative to the large placebo effect is unclear.

670 APPLES—THE AUSTRALIAN POSITIVE & PEERS LONGEVITY EVALUATION STUDY

Kathy Petoumenos[1], Robin Huang[1], Jennifer Hoy[2], Mark Bloch[3], David J. Templeton[4], David Baker[5], Michelle Giles[6], Matthew Law[1], David A. Cooper[1]
[1]Kirby Inst, Sydney, Australia, [2]The Alfred Hosp and Monash Univ, Melbourne, Australia, [3]Holdsworth House Med Practice, Sydney, Australia, [4]RPA Sexual Hlth, Camperdown, Australia, [5]East Sydney Doctors, Darlinghurst, Australia, [6]Monash Hlth, Melbourne, Australia

Background: In Australia, 50% of HIV positive (HIV+) people are now aged over 50 years and are predominately men who have sex with men (MSM). MSM engage more in behaviours that may increase the risk of age-related comorbidities, including smoking, high alcohol consumption and recreational drug use. The objective of APPLES is to compare these comorbidities and risk factors in HIV+ MSM ≥55 years with an appropriate control group of HIV negative (HIV-) MSM.
Methods: A prospectively recruited cross-sectional sample of HIV+ and HIV- MSM >= 55 years. Detailed data collection at recruitment included clinic data, a self-completed health and lifestyle survey, and blood sample collection for biomarker assessment and storage. We report key demographic, laboratory markers, self-reported comorbidity, and biomarker results by HIV status. For selected comorbidities and biomarkers we also adjust HIV status a priori for age, smoking and body mass index (BMI).
Results: Over 16 months 228 HIV+ and 218 HIV- men were recruited. Median age was 63 years (IQR: 59-67). More HIV+ men reported ever having smoked (61% vs 39%), while HIV- men reported more current smoking (24% vs 19%) (p=0.029). Greater alcohol use was reported by HIV- men (p=0.002), and recreational drug use reported more often by HIV+ men (p<0.001). 98% of HIV+ men had a viral load below 200 copies/mL and all but three were currently on ART. Unadjusted rates for selected comorbidities, lipids and biomarkers by HIV status are shown in Table 1. Rates of diabetes (DM), heart disease (HD), thrombosis and neuropathy were elevated in HIV+ men (HIV+ vs HIV-:15% vs 9%, 20% vs 12%, 10% vs 4%, 22% vs 1% respectively). After adjustment, HIV+ men had significantly increased odds of DM (Adjusted Odds ratio (aOR): 2.03, p=0.030), thrombosis (aOR: 3.10, p=0.006), neuropathy (aOR: 36.8, P<0.001), and borderline increased odds for HD (aOR: 1.77, p=0.056). HIV+ men had significantly higher hsCRP and cystatin-C. There was no significant difference in IL6 or D-dimer (Table 1). After adjustment cystatin-C remained significantly elevated for HIV+ men (p<0.001) but not hsCRP (p=0.562).
Conclusion: HIV+ men have increased self-reported comorbidities and have higher risk for some comorbidities and biomarkers, even after adjustment for age, smoking and BMI. This study underscores the importance of an appropriate HIV- control group for more accurate evaluation of the risk and attribution of age-related comorbidities in HIV+ people.

TABLE 1: CRUDE RATES FOR SELECTED SELF-REPORTED COMORBIDITIES, LIPIDS AND BIOMARKERS

	HIV- n (%)	HIV+ n (%)	P-value		HIV- Med *(IQR)*	HIV+ Med *(IQR)*	P-value
Diabetes	17 (9%)	31 (15%)	0.065	IL6 (pg/mL)	2.27	2.37	0.149
Heart Disease	24 (12%)	42 (20%)	0.043		*(1.77-3.20)*	*(1.98-3.24)*	
Hypertension	86 (45%)	90 (44%)	0.841	hsCRP (µg/mL)	1.10	1.70	<0.001
Neuropathy	2 (1%)	47 (22%)	<0.001		*(0.60-2.00)*	*(0.80-3.40)*	
Thrombosis	8 (4%)	21 (10%)	0.022				
LDL ≥3.5 (mmol/L)	51 (24%)	33 (15%)	0.028	Cystatin-C (mg/dL)	0.86	0.95	<0.001
HDL <1.0 (mmol/L)	58 (27%)	69 (32%)	0.292		*(0.77-0.94)*	*(0.81-1.07)*	
Trigs ≥2.0 (mmol/L)	35 (17%)	80 (37%)	<0.001				
Tot Chol ≥5.5 (mmol/L)	58 (27%)	53 (27%)	0.523	D-dimer (µg/mL)	0.37	0.34	0.2773
Gluc (>7 fast/>11 non-fasting)	5 (2%)	12 (7%)	0.089		*(0.26-0.53)*	*(0.25-0.51)*	

671 PATIENTS' BELIEFS ABOUT THEIR HAART IN COMPARISON WITH THEIR CHRONIC COTREATMENTS

Susan Kamal[1], Olivier Bugnon[1], Matthias Cavassini[1], Marie-Paule Schneider[2], for the Swiss HIV Cohort Study
[1]Univ of Lausanne, Lausanne, Switzerland, [2]Univ of Geneva, Univ of Lausanne, Lausanne, Switzerland

Background: Thanks to the success of highly active antiretroviral therapy (HAART), HIV infected patients almost reach a normal life expectancy. This has resulted in an aging HIV population suffering from other chronic co-morbidities such as cardiovascular diseases, osteoporosis, and depression. Our hypothesis is that patients' perceptions and attitudes towards their HAART which is perceived as crucial to their survival differ from their beliefs about their co-treatments and this may have an impact on their medication adherence.
Methods: We used the Beliefs about Medicine Questionnaire (BMQ f©) to measure the perceptions of patients about their co-treatments and the BMQ-HAART© to measure their beliefs about their HAART from a representative sample (n=150) of patients enrolled in the Swiss HIV Cohort Study (SHCS) and followed at the Infectious Disease Service at the University Hospital in Lausanne, Switzerland. The BMQ-Specific comprises two sub-scores: Specific-Necessity and Specific-concerns. The sub-scores were standardized by dividing the score scale by the number of questions in the scale resulting in a range of responses between 1 (low) and 5 (high). Self-reported medication adherence was measured using the SHCS adherence questionnaire (SHCS-AQ). Socio-demographic variables were retrieved by reviewing the SHCS database.
Results: A response rate of 73% (109/150) was achieved. 105 (70%) patients were included in the analysis: median age was 56 (IQR: 51, 63) and 74 were male (70%). 87 patients (83%) were adherent to HAART and 75 (71%) were adherent to their co-treatments. The standardized mean (SD) responses of BMQ necessities sub-scores were 3.84 (0.41) and 2.79 (0.94) for HAART and co-treatments respectively (p < 0.0001). For concerns the standardized mean (SD) responses were 4.34 (0.97) for HAART and 4.06 (0.81) for co-treatments (p= 0.004). Co-treatment and HAART concerns increased as the number of co-treatments increased (p 0.03 and p 0.00003 respectively).
Conclusion: Patients had higher concerns and necessities for their HAART in comparison with their co-treatments which reflected in higher adherence to HAART suggesting that it could be important to focus on patient beliefs to improve adherence to co-treatments.

672 BIOMARKERS OF AGING IN HIV-POSITIVE INDIVIDUALS AND MATCHED CONTROLS

Davide De Francesco[1], Sebastian Oehlke[2], Alexander Bürkle[2], Ferdinand Wit[3], Claudio Franceschi[4], Neeltje A. Kootstra[5], Claude Libert[6], Peter Reiss[3], Caroline Sabin[1], for the CoMorBidity in Relation to Aids (COBRA) Collaboration

[1]Univ Coll London, London, UK, [2]Univ of Konstanz, Konstanz, Germany, [3]Stichting HIV Monitoring and Academic Med Cntr, Amsterdam, Netherlands, [4]Alma Mater Studiorum Univ di Bologna, Bologna, Italy, [5]Academic Med Cntr, Amsterdam, Netherlands, [6]VIB, Ghent, Belgium

Background: Despite successful combination antiretroviral therapy (cART), HIV+ve people have been suggested to experience signs of more rapid aging. We compared established aging biomarkers in HIV+ve people aged ≥45 years and demographically-comparable HIV-ve controls and identified factors associated with apparent age advancement in both groups.

Methods: The biological age of each individual was derived using a set of 10 biomarkers (5 of which were measured in mononuclear cells), identified through the EU FP7 MARK-AGE project. The difference between biological and chronological age ('age advancement') was assessed for significance in each group using paired t-tests, with associations between this age advancement and HIV status, lifestyle, viral (cytomegalovirus (CMV), hepatitis B (HBV) and C (HCV) viruses) and HIV parameters investigated using t-tests, Pearson's correlation coefficient and linear regression.

Results: Biomarkers were measured in 134 HIV+ve (median age: 56 yrs (range 45-82), 93% male, 88% white ethnicity, 86% MSM) and 79 HIV-ve (median age: 57 yrs (range 46-80), 92% male, 97% white ethnicity, 80% MSM) people. Biological age was significantly greater than chronological age by 13.2 and 5.5 yrs in the HIV+ve and HIV-ve groups, respectively ($p<0.0001$ for each, Table 1), with the apparent age advancement being significantly greater in HIV+ve than HIV-ve persons ($p<0.0001$). No significant associations were found between age advancement and lifestyle factors, but higher total and high avidity anti-CMV IgG antibody titer were both associated with an increased age advancement, independently of HIV-status ($p=0.03$ and $p=0.02$, respectively). In HIV+ve persons, a positive correlation was found between age advancement and time since HIV diagnosis ($r=0.17$, $p=0.05$), duration of cART ($r=0.17$, $p=0.05$) and time with a CD4 count <200 cells/μL ($r=0.19$, $p=0.03$). HIV+ve persons co-infected with HBV also showed a greater age advancement.

Conclusion: Our findings suggest that there is an apparent advancement in biological age in successfully treated HIV+ve people. Whilst this does not appear to be explained by differences in participant characteristics, and may reflect the effects of HIV on monocytes and lymphocytes, we cannot rule out the possibility that other unmeasured confounders may exist. Longitudinal follow-up will allow us to further investigate the causal nature of the association and whether it is likely to reflect a process of accentuated or accelerated aging.

Table 1: Association between age advancement and HIV and lifestyle factors

Variable	N	Mean (95% CI) Age advancement	Difference (95% CI) between groups	*p*-value
HIV-status				<0.0001
HIV-positive	134	13.20 (11.55,14.85)	7.64 (5.12, 10.15)	
HIV-negative	79	5.47 (3.75,7.19)		
Smoking status				0.34
Never smoked	66	9.35 (7.14, 11.55)	0	
Ex-smoker	87	10.06 (8.07, 12.04)	0.71 (-2.41, 3.83)	
Current smoker	60	11.81 (8.99, 14.64)	2.46 (-0.95, 5.88)	
Alcohol consumption				0.43
Never consumed	16	11.75 (8.17, 15.34)	0	
Previous consumption only	21	12.55 (8.69, 16.41)	0.6 (-5.57, 7.16)	
Current consumption	175	9.96 (8.45, 11.46)	-1.80 (-6.81, 3.21)	
Recreational drug use in past 6 months				0.90
Yes	118	10.06 (8.27, 11.85)	-0.51 (-4.29, 3.27)	
No	33	10.56 (7.28, 13.85)		
Chronic hepatitis B infection (**HIV+ve only**)				0.01
Yes	7	21.95 (10.53, 33.36)	9.14 (1.85, 16.43)	
No	124	12.80 (11.14, 14.46)		

673 LONGITUDINAL ASSOCIATION BETWEEN ALCOHOL USE AND INFLAMMATORY BIOMARKERS

Kaku So-Armah[1], Matthew Freiberg[2], Debbie Cheng[1], Gregory Patts[1], Russell Tracy[3], Margaret Doyle[3], Natalia Gnatienko[4], Kendall J. Bryant[5], Evgeny Krupitsky[6], Jeffrey H. Samet[1]

[1]Boston Univ, Boston, MA, USA, [2]Vanderbilt Univ, Nashville, TN, USA, [3]Univ of Vermont, Colchester, VT, USA, [4]Boston Med Cntr, Boston, MA, USA, [5]Natl Inst on Alcohol Abuse and Alcoholism, Bethesda, MD, USA, [6]St.Petersburg Pavlov State Med Univ, St. Petersburg, Russian Federation

Background: Biomarkers of inflammation (interleukin-6; IL-6), monocyte activation (soluble CD14; sCD14) and altered coagulation (D-dimer) predict mortality. Prior studies on the association of heavy drinking and these biomarkers in HIV populations report mixed results. Limitations of prior work include cross-sectional design and possible misclassification of alcohol use by relying solely on self-reported alcohol consumption. The objectives of the Russia Alcohol Research Collaboration on HIV/AIDS (ARCH) study were to evaluate 1) the association between heavy alcohol use (corroborated by phosphatidylethanol [PEth], an alcohol biomarker) and inflammatory biomarkers over time, and 2) the association between changes in alcohol use and changes in these biomarkers.

Methods: This study included 350 HIV-infected (HIV+) antiretroviral therapy naive Russians assessed at baseline, 12 and 24 months. Heavy drinking was defined as >14 drinks/week or 4 drinks/day (men), and >7 drinks/week or >3 drinks/day (women) by self-report (Timeline Followback) or PEth≥80 ng/mL. Linear mixed effects models were used to determine whether heavy drinking was longitudinally associated with IL-6, sCD14 and D-dimer adjusting for demographics, HIV factors, comorbid conditions, and zinc supplementation (Russia ARCH includes participants in a clinical trial administering zinc). Secondary analyses investigated the association between self-reported changes in average drinks/week and changes in IL-6, sCD14 and D-dimer over the past year.

Results: Baseline characteristics: male (71%), mean age 34 years, hepatitis C (87%), smoking (86%) and HIV viremia (mean (SD) log10(HIV RNA)=4(1) copies/mL). Self-reported inflammatory diseases of aging like diabetes (1%) were uncommon. Heavy drinking was common (77%) and associated with elevated IL-6, sCD14 and D-dimer in adjusted models over time (Table). Changes in drinks/week (categorized as: large or small decrease; or large or small increase) after 1 year were not significantly associated with changes in IL-6, sCD14 or D-dimer compared to those with no changes in drinks/week.

Conclusion: Among HIV+ adults, heavy alcohol use is independently associated with increased IL-6, sCD14 and D-dimer over time. However, changes in alcohol over 1 year do not appear to be associated with changes in the biomarkers. Since these biomarkers predict mortality, interventions to mitigate effects of heavy drinking on these immune processes merit consideration.

Model	Exposure	Interleukin-6		Soluble CD14		D-dimer	
		Ratio of means (95% CI)	P-value	Difference in means (95% CI)	P-value	Ratio of means (95% CI)	P-value
1	Not heavy drinker	1 (ref)	0.002	0 (ref)	0.009	1 (ref)	0.04
	Heavy drinker	1.35 (1.14, 1.61)		143.2 (40.1, 246.3)		1.19 (1.01, 1.40)	
2	Change in average drinks/week	Difference in means (95% CI)	Global P-value	Difference in means (95% CI)	Global P-value	Difference in means (95% CI)	Global P-value
	No change	0 (ref)	0.20	0 (ref)	0.62	0 (ref)	0.38
	Large decrease	0.99 (-1.11, 3.08)		93.5 (-137.1, 324.1)		-0.08 (-0.77, 0.61)	
	Small decrease	0.71(-1.33, 2.75)		42.6 (-182.0, 267.2)		0.12 (-0.55, 0.79)	
	Small increase	0.12 (-2.09, 2.34)		154.3 (-89.2, 397.8)		0.42 (-0.31, 1.14)	
	Large increase	-1.24 (-3.52, 1.04)		-2.5 (-253.8, 248.9)		-0.29 (-1.04, 0.46)	

All models adjusted for age, sex, duration since HIV diagnosis, HIV RNA, smoking, hepatitis C, illicit drug use, study time-point, and zinc supplementation.
Change in drinks/week: Large vs. small decrease/increase dichotomized at median among those who either decreased (median=-10.8) or increased (median=7.5). Between baseline and 12 months or 12 and 24 months, the following changes in drinks/week occurred: No change (N=64); large decrease (N=88); small decrease (N=89); small increase (N=56); large increase (N=57).

674 ASSOCIATION OF ANISOCYTOSIS WITH MARKERS OF INFLAMMATION AND IMMUNE EXHAUSTION IN HIV

Sadeer Al-Kindi, David A. Zidar, Grace A. McComsey, **Chris T. Longenecker**
Case Western Reserve Univ, Cleveland, OH, USA

Background: Treated HIV infection is associated with heightened inflammation, which can contribute to increased risk of cardiovascular disease (CVD). We have previously shown that anisocytosis, as measured by red cell distribution width (RDW), is independently associated with prevalent CVD in persons living with HIV (PLHIV). In this study, we sought to identify immune correlates of RDW in PLHIV on antiretroviral therapy.

Methods: We performed a cross-sectional and longitudinal analysis of 147 virally-suppressed PLHIV without severe anemia (hemoglobin >9g/dL) who participated in a randomized trial of statin therapy. All had LDL<130 mg/dL and evidence of heightened inflammation at baseline. A complete blood count and biomarkers of inflammation and immune activation/exhaustion were measured from peripheral blood at entry, 24, and 48 weeks. Associations with RDW were estimated using linear regression and linear mixed models.

Results: Median age (IQR) for the cohort at enrollment was 46 [40-53] years; 78% were male and 68% were African American. Median RDW for the cohort was 13.4 [12.9-14.0] and median hemoglobin was 14.3 [13.1-15.1] g/dL. Compared with the lowest RDW tertile, patients in the highest tertile were less likely to be male, more likely to be African American, have lower hemoglobin, lower mean corpuscular volume, and higher platelet counts (all p<0.05). At baseline, RDW weakly correlated with C-reactive protein (r=0.196), d-dimer (r=0.214), fibrinogen (r=0.192), interleukin-6 (r=0.257), CD4+DR+38+ T-cells (r=0.195), and CD4+PD1+ T-cells (r=0.227), all p<0.05. Only IL-6 and CD4+PD1+ T-cells remained associated after adjustment for clinical factors known to affect RDW in the general population (see Table). Over 48 weeks, RDW did not change and there was no significant statin effect (p=0.45). After adjustment for clinical parameters, a statistically borderline positive association between RDW and log CD4+PD1+ T-cells persisted across all time points (p=0.05).

Conclusion: Anisocytosis, as measured by RDW, is associated with interleukin-6 and CD4+PD1+ T-cells in treated HIV patients; however, only CD4+PD1+ T-cells are associated with RDW in longitudinal analyses. RDW may be a useful prognostic biomarker of cardiovascular risk that partially reflects chronic inflammation and immune exhaustion in PLHIV on antiretroviral therapy.

Table: Relationship of clinical variables and biomarkers of inflammation and immune activation to log-transformed red-cell distribution width. All biomarkers were non-normally distributed and log-transformed prior to analysis. * Age, sex, race, hemoglobin, smoking, and estimated glomerular filtration rate (eGFR) were forced into the adjusted model and candidate biomarkers were then selected using forward selection.

	Unadjusted		Adjusted*	
	Beta	p-value	Beta	p-value
Clinical Parameters				
Age	-0.073	0.942	0.032	0.722
Male	-0.218	**0.008**	0.038	0.699
African American	0.324	**<0.001**	0.245	**0.004**
Hemoglobin	-0.267	**0.001**	-0.172	0.081
Smoking	0.145	0.08	0.100	0.211
eGFR	0.120	0.149	0.044	0.640
Biomarkers				
C-Reactive Protein (Log)	0.185	**0.025**		
D-Dimer (Log)	0.191	**0.020**		
Fibrinogen (Log)	0.179	**0.030**		
IL-6 (Log)	0.236	**0.004**	0.253	**0.002**
%CD4+DR+38+ (Log)	0.203	**0.015**		
%CD4+PD1+ (Log)	0.223	**0.007**	0.232	**0.005**

675 GREATER ART ADHERENCE IS ASSOCIATED WITH LESS INFLAMMATION IN HIV-SUPPRESSED UGANDANS

Jose Castillo-Mancilla[1], Mary Morrow[2], Yap Boum[3], Jessica E. Haberer[4], Jeffrey N. Martin[5], David Bangsberg[6], Samantha MaWhinney[1], Nicholas Musinguzi[7], Peter W. Hunt[5], Mark J. Siedner[4]

[1]Univ of Colorado Denver, Aurora, CO, USA, [2]Colorado SPH, Aurora, CO, USA, [3]Epicentre, MSF, Mbarara, Uganda, [4]Massachusetts General Hosp, MA, USA, [5]Univ of California San Francisco, San Francisco, CA, USA, [6]MGH-Ragon Inst, Boston, MA, USA, [7]Mbarara Univ of Sci and Tech, Mbarara, Uganda

Background: Residual inflammation persists in individuals living with HIV who achieve viral suppression. Because higher levels of inflammation predict cardiovascular events and mortality, there is great interest in identifying interventions to reduce inflammation in this population. We aimed to determine if ART adherence, measured by electronic monitoring, has an inverse relationship with inflammation among individuals who achieve HIV viral suppression.

Methods: We enrolled adults living with HIV in Mbarara, Uganda, and measured interleukin-6 (IL-6), D-dimer, soluble (s)CD14, sCD163, kynurenine/tryptophan (K/T) ratio, and CD8+ T cell activation (HLA-DR+/CD38+ co-expression) at ART initiation and 6 months later. Adherence was measured with the Medication Event Monitoring System (MEMS) and calculated by averaging daily observed/prescribed device openings per participant over the 6-month period, capping daily adherence at 100%. We limited our analysis to participants who achieved viral suppression (<400 copies/ml) and had biomarker levels at baseline and the 6-month visit. We graphically depicted relationships between average adherence and the log-transformed inflammatory biomarkers at 6 months, and identified a linear relationship between them. We then fit linear regression models to estimate the relationship between adherence and biomarkers of inflammation after 6 months of ART, adjusting for baseline biomarker levels.

Results: Median (IQR) age was 35 (30, 40) years, and 196 (70%) of participants were women. Median (IQR) adherence was 88 (84, 98) percent. Most participants (61%) were taking zidovudine/lamivudine/nevirapine, or lamivudine/stavudine/nevirapine (28%). At baseline, median (IQR) CD4+ cell count was 134 (80, 198) cells/mm3 and 151 (54%) had an HIV viral load >100,000 copies/ml. Among those suppressed after 6 months of ART, each 10% increase in average adherence was associated with lower plasma levels of IL-6, D-dimer, K/T ratio and sCD14 (Table).

Conclusion: Among HIV-infected patients who achieved viral suppression during early ART in rural Uganda, higher adherence is associated with lower biomarkers of inflammation. ART adherence could have significant biological consequences beyond viral suppression, possibly driven by mitigating viral replication below clinically-available laboratory thresholds. Whether this association persists during chronic suppression, or if optimized ART adherence in virologically-suppressed individuals could reduce inflammation-related morbidity, remains unknown.

Table. Antiretroviral adherence and inflammatory biomarkers 6 months after treatment initiation.

Biomarker	Number of participants	Percent biomarker reduction 6 months after ART initiation for each 10% increase in adherence*	95% CI	*P*-value
IL-6	267	-13.34	(-19.31 to -6.93)	<0.001
D-dimer	271	-9.36	(-16.69 to -1.37)	0.023
K/T ratio	270	-3.10	(-6.07 to -0.04)	0.047
sCD14	267	-2.20	(-4.33 to -0.01)	0.049
% HLA+/CD38+ CD8+	199	-1.09**	(-2.22 to 0.05)	0.061
sCD163	267	-2.44	(-5.97 to 1.23)	0.190

* Estimates are adjusted for baseline levels of biomarkers.
** Absolute decrease in % HLA+/CD38+ CD8+ T cells per 10% increase in adherence.

676 IMMUNOLOGICAL EFFECTS OF SYNBIOTIC SUPPLEMENTATION IN ADVANCED HIV DISEASE

Sergio Serrano-Villar[1], Maria Lagarde[2], Jose I. Bernardino[3], Mariano Matarranz[2], Alfonso Cabello[4], Judit Villar[5], Jose Ramón Blanco[6], Otilia Bisbal[2], Alberto Díaz de Santiago[7], Vicente Estrada[8]

[1]Hosp Univ Ramón y Cajal, Madrid, Spain, [2]Hosp 12 de Octubre, Madrid, Spain, [3]Hosp Univ La Paz–IdiPAZ, Madrid, Spain, [4]Hosp Univ Fndn Jiménez Díaz, Madrid, Spain, [5]Hosp del Mar, Barcelona, Spain, [6]Hosp San Pedro, La Rioja, Spain, [7]Hosp Puerta de Hierro, Madrid, Spain, [8]Hosp Univ Clínico San Carlos, Madrid, Spain

Background: Late diagnosed HIV-infected subjects show impaired immunological recovery resulting in a greater risk of clinical progression. Gut bacteria metabolism appears to impact immune recovery in HIV-infected subjects, and while nutritional interventions with prebiotics and probiotics seem to exert immunological effects, the clinical implications in this key population remain unknown.

Methods: Pilot multicenter randomized placebo-controlled, double blind clinical trial in which 76 HIV-infected ART-naive subjects with <350 CD4 T cells/mm3 or AIDS were randomized (1:1) to either the synbiotic nutritional supplement PMT25441 or placebo for 48 weeks, each in combination with first-line ART. Primary outcomes were safety and immunological recovery. Secondary outcomes included changes in fecal microbiota structure and plasma inflammatory markers. We herein report an intention-to-treat analysis of the 24-week data on the primary outcome. We used linear mixed models with robust variance estimators and interaction terms to assess whether changes in longitudinal variables over time differed significantly between arms.

Results: 64 patients completed the follow-up, mean age 37±12 years, 78% MSM, CD4 T cells 225±110/mm3, CD4/CD8 ratio 0.26±0.19, 12% diagnosed with an AIDS-defining condition. All patients initiated triple ART (61% with integrase inhibitors) and 92.2% had HIV RNA <400 copies/ml at week 24. Baseline characteristics were balanced between arms. Overall, PMT25341 was well tolerated despite frequently reported bad taste, and non grade 3-4 adverse effects attributable to the intervention were identified. We did not detect statistically significant differences in CD4 T cells or CD4/CD8 ratio over the study period. For CD4 T cells, mean difference relative to placebo was -14 cells/mm3 (95%CI -87, 59) at week 4 and -19 (95%CI -103-63) at week 24, and for CD4/CD8 ratio 0.09 (95%CI -0.002, 0.18) at week 4 and 0.05 (95%CI -0.07, 0.17) at week 24.

Conclusion: While a positive effect on CD4 T counts has been observed in previous studies evaluating the impact of prebiotics and probiotics in ART-naive subjects, our data suggest that the clinical impact of nutritional strategies aimed at restoring the gut microbiota might be very limited in HIV-infected patients initiating ART at advanced disease.

677 BONE MICROARCHITECTURAL CHANGES AND FRACTURE-RISK PREDICTION IN HIV AND HCV

Roger Bedimo[1], Beverley Adams-Huet[2], John Poindexter[2], Irfan Farukhi[3], Rosinda Castanon[3], Geri Brown[3], Diana Turner[3], Teresa Moore[3], Pablo Tebas[4], Naim Maalouf[2]

[1]VA North Texas Hlth Care Cntr, Dallas, TX, [2]Univ of Texas Southwestern Med Cntr, Dallas, TX, [3]VA North Texas Hlthcare System, Dallas, TX, [4]Univ of Pennsylvania, Philadelphia, PA

Background: Both HIV and HCV infections are associated with an increased risk of osteoporotic fractures (OF). HIV/HCV co-infected subjects have a 3-fold increased fracture incidence compared to uninfected individuals, and have a greater risk than HIV or HCV mono-infected. Trabecular bone score (TBS) is a novel practical, non-invasive measurement of bone microarchitecture from dual x-ray absorptiometry (DXA) images. TBS is a proven OF predictor, even after adjusting for BMD, and is now included as an independent risk factor in the FRAX® algorithm for fracture risk prediction. Our goals were: 1) To evaluate if micro-architectural changes underlie the increased fracture risk in HIV/HCV and HCV infection 2) To evaluate the impact of impact of including TBS in FRAX score among HIV and HCV infected patients

Methods: We have measured BMD and TBS in our Dallas cohort of 450 veterans: 45 HIV/HCV, 151 HIV, 103 HCV and 151 uninfected. We conducted analysis of covariance comparing TBS between groups, controlling for age, race, BMI and smoking. We then calculated FRAX® scores in all participants, with BMD alone (FRAX-BMD) and with TBS included (FRAX-BMD-TBS).
Results: Both HIV and HCV were associated with lower total hip and femoral neck BMD (Table). Compared to controls, HCV and HIV/HCV subjects had significantly lower meanTBS scores (p=0.048 and 0.009, respectively). HIV/HCV also had lower TBS than HIV (p=0.02). Mean TBS scores were similar between HIV and controls (p=0.65) and between HCV and HIV/HCV (p=0.27) (Table). Compared to controls, HCV was associated with higher covariate-adjusted FRAX® scores (p=0.01), but HIV was not (p=0.36). The inclusion of TBS in the FRAX® calculator resulted in a significantly higher estimated absolute risk of major OF in HCV mono-infected and HIV/HCV co-infected, but not in HIV mono-infected (Table). The calculated absolute 10-year probability of fracture increased significantly when TBS was included in the HIV/HCV (+0.4; p=0.006) and HCV group (+0.3; p<0.0001) in HCV. It did not significantly change in the HIV group (-0.1; p=0.65).
Conclusion: Our results suggest that the increased OF risk among HCV-infected individuals may be mediated by altered bone micro-architecture as assessed by TBS. Using FRAX-BMD-TBS may provide a more accurate risk assessment of the real fracture risk in this population.

	Groups				ANCOVA p-value (adjusting for age, race, BMI, smoking)	
	A:HIV/HCV	B: HIV	C: HCV	D: Controls	HIV vs. non-HIV (A+B vs.C+D)	HCV vs. non-HCV (A+C vs. B+D)
Total Hip BMD*	0.92 (0.12)	0.99 (0.15)	1.02 (0.13)	1.06 (0.14)	0.0007	0.0008
Fem Neck BMD*	0.79 (0.13)	0.82 (0.15)	0.86 (0.14)	0.91 (0.15)	0.0001	0.005
L-Spine BMD*	1.01 (0.12)	1.07(0.18)	1.10 (0.17)	1.10 (0.17)	0.14	0.15
TBS	1.33 (0.10)	1.36 (0.12)	1.33 (0.12)	1.36 (0.11)	0.33	0.003
FRAX-BMD**	2.4 [1.6-4.2]	3.3 [1.8-6.7]	2.6 [1.8-4.4]	2.0 [1.4-3.2]	0.79	0.03
FRAX-BMD-TBS**	2.8† [1.7-4.5]	3.2 [1.9-6.6]	3.0†[2.0-4.8]	2.2†[1.4-3.9]	0.59	0.002

*mean (SD)
** median [IQR]

678 FRAX-TOOL FRACTURE-RISK COMPARISON: HAVE A LITTLE BACKBONE!

Linda Battalora[1], Carl Armon[2], Kate Buchacz[3], John Hammer[4], John Spear[1], John T. Brooks[3], Benjamin Young[5], Edgar T. Overton[6]
[1]Colorado Sch of Mines, Golden, CO, USA, [2]Cerner Corporation, Kansas City, MO, USA, [3]CDC, Atlanta, GA, USA, [4]Denver Infectious Disease Consultants, Denver, CO, USA, [5]APEX Family Med, Denver, CO, USA, [6]Univ of Alabama at Birmingham, Birmingham, AL, USA

Background: While osteoporosis, determined by dual energy X-ray absorptiometry (DXA), remains a key determinant for fragility fractures, the Fracture Risk Assessment (FRAX) tool incorporates several risk factors, including femoral neck (hip) BMD, to provide 10-year fracture probability (10YFP). Lumbar spine (L1-L4) BMD measurements often differ from hip BMD and are not included in the FRAX tool. A method exists that uses L1-L4 T-score to adjust FRAX tool results. We compared FRAX tool results using hip BMD "unadjusted FRAX" (uFRAX) and modified with L1-L4 T-scores "adjusted FRAX" (aFRAX).
Methods: We analyzed available DXA values of the left hip, L1-L4 T-scores and clinical data collected prospectively during 2004-2012 from two CDC-sponsored HIV cohorts. Osteoporosis of either site was defined as a T-score<-2.5. We calculated FRAX 10YFP of a major osteoporotic fracture (hip, spine, forearm, or shoulder) with both uFRAX and aFRAX tool results. Harrell's C-statistics and Cox proportional hazards analyses of factors associated with incident fracture were performed using both the uFRAX and aFRAX scores.
Results: Characteristics of 1000 persons included in the analysis were: median age 43 years (interquartile range [IQR] 36-49), 83% male, 67% non-Hispanic white, median CD4+ cell count [CD4] 461 cells/mm^3 (IQR 312-659). Among 86 patients with osteoporosis at either L1-L4 spine or hip, only 24 had osteoporosis at both. During 4056 person-years (py) of observation after DXA, we identified 84 incident fractures (20.7/1000py) including 22 major osteoporotic fractures (5.4/1000py). Fracture incidence increased when either the uFRAX or aFRAX score was≥3% (Figure). Of 84 fractures, 41 occurred among 291 persons (29%) with aFRAX score≥3%. Using the L1-L4 aFRAX tool had minimal effect on the estimate of fracture risk for the population. C-statistic values increased from 0.63 to 0.64 by including L1-L4 data. In multivariable Cox proportional hazards analyses with uFRAX, HCV co-infection (HCV) (Hazard Ratio [HR] 1.91, 95% confidence interval [CI] 1.15-3.19) and FRAX 10YFP≥3% (HR 2.32, CI 1.51-3.56); with aFRAX, HCV (HR 1.84, CI 1.10-3.07) and FRAX 10YFP≥3% (HR 2.59, CI 1.68-3.97); were associated with incident fracture.
Conclusion: In a large convenience sample of relatively young HIV-infected US adults, a FRAX 10YFP≥3%, and HCV were significantly associated with elevated risk of incident fracture. uFRAX and aFRAX tools had similar associations with incident fracture rates.

679 FRACTURE-RISK ESTIMATES IN HIV-POSITIVE AND -NEGATIVE SUBJECTS: DATA FROM HIV UPBEAT

Aoife G. Cotter[1], Dylan Shannon[1], Tara McGinty[1], Alan Macken[1], Eoin Kavanagh[2], Geraldine McCarthy[2], Jennifer J. Brady[2], Juliet Compston[3], Caroline Sabin[4], Patrick W. Mallon[1]
[1]Univ Coll Dublin, Dublin, Ireland, [2]Mater Misericordiae Univ Hosp, Dublin, Ireland, [3]Cambridge, Cambridge, UK, [5]Univ Coll London, London, UK

Background: Although low bone mineral density (BMD) and fractures are common in HIV it is unclear if currently available, general population-derived fracture risk prediction tools are valid in HIV. We aimed to determine if adding HIV as a secondary risk factor and/or markers of bone quality (BMD or trabecular bone score (TBS)) impacted fracture risk estimates using commonly used risk prediction tools.
Methods: Fracture risk (10-year major osteoporotic and hip fracture) was calculated using the Fracture Risk Assessment Tool (FRAX), Garvan and QFracture algorithms from baseline data, including falls history, in a prospective cohort study of HIV+ and HIV- subjects. From femoral neck (FN) dual xray absorptiometry (DXA) we derived TBS using iNsight software v2.2.1. FRAX and Garvan algorithms include BMD, Qfracture and Garvan incorporate falls history but Qfracture does not include BMD. FRAX permits inclusion of TBS and non-specific secondary risks (including HIV), while Garvan and Qfracture include disease-specific secondary risks (but not HIV). Using non-parametric analyses, we compared FRAX risk estimates between groups based on clinical risk alone, recalculated with HIV as a secondary risk and again after adding FN BMD and TBS. Results are median [IQR] unless specified.
Results: In 202 HIV+ (age 39 [33,46] yrs, 58% male, 40% African) compared to 263 HIV- subjects (age 42 [34,49] yrs, 44% male and 25% African), falls prevalence (past month) was similar (HIV+ 5.0% vs HIV- 6.5%, P=0.50) but BMD significantly lower in the HIV+ versus HIV- group (FN z-scores -0.3[-1.3, 0.6] vs 0.2[-0.5, 1.3] (P<0.0001)). Although there was no between group difference in FRAX risk derived from clinical factors, incorporating HIV as a secondary risk significantly increased risk estimates in the HIV+ group; major osteoporotic 0.9 [0.7, 1.9]% and hip fracture 0.1 [0.0, 0.5]%. After inclusion of BMD or BMD+TBS, FRAX risk estimates remained increased for major osteoporotic fracture but reduced for hip fracture (table 1). There were no significant between-group differences in major osteoporotic fracture risk using Garvan or Qfracture, although the HIV+ group had significantly greater Garvan hip fracture risk (table 1).
Conclusion: Although fracture risk using Garvan and Qfracture was similar between groups, adding HIV to FRAX significantly amended fracture risk, with the effect attenuated for hip fracture with addition of measures of bone quality. Further research is needed to validate these tools in HIV+ populations.

Table 1. Comparison of fracture risk estimates and absolute change in fracture risk estimates

	10-Year Probability of Fracture median (interquartile Range) %		
	HIV+ (n=263)	HIV- (n=203)	*P*
Major Osteoporotic Fracture Risk:			
(1) FRAX	2.9 (2.5, 5.3)	2.7 (2.4, 5.1)	0.40
FRAX + HIV as 2° risk	3.9 (3.3, 7.6)	2.7 (2.4, 5.1)	<0.0001
Absolute % Change in risk from (1)	*0.9 (0.7, 1.9)*	-	
FRAX + HIV as 2° risk + FN BMD [b]	3.5 (2.6, 6.1)	2.9 (2.5, 4.8)	0.01
Absolute % Change in risk from (1)	*0.2 (-0.5, 1.4)*	*0.1 (-0.3, 0.30)*	*0.01*
FRAX +HIV as 2° risk + FN BMD + TBS [c]	3.4 (2.5, 6.0)	2.9 (2.5, 4.8)	0.02
Absolute % Change in risk from (1)	*0.2 (-0.6, 1.4)*	*0.1 (-0.3, 0.3)*	*0.02*
QFracture	0.5 (0.4, 1.0)	0.5 (0.4, 1.0)	0.27
Garvan*	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.92
Hip Fracture Risk:			
(2) FRAX	0.2 (0.1, 0.6)	0.2 (0.1, 0.5)	0.10
FRAX + HIV as 2° risk [a]	0.4 (0.2, 1.1)	0.2 (0.1, 0.5)	<0.0001
Absolute % Change in risk from (2)	*0.1 (0.0, 0.5)*	-	
FRAX + HIV as 2° risk + FN BMD [b]	0.2 (0.0, 0.6)	0.1 (0.0, 0.3)	0.001
Absolute % Change in risk from (2)	*-0.1 (-0.2, 0.1)*	*-0.1 (-0.2, 0.0)*	*0.01*
FRAX + HIV as 2° risk + FN BMD + TBS [c]	0.2 (0.0, 0.6)	0.1 (0.0, 0.3)	0.001
Absolute % Change in risk from (2)	*0.1 (0.0, 0.5)*	*0.0 (0.0, 0.0)*	*<0.0001*
QFracture	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.99
*Garvan**	0.1 (0.0, 0.1)	0 (0.0, 0.1)	0.01

FRAX, WHO Fracture Risk Assessment Tool®; FN BMD, femoral neck bone mineral density; TBS, trabecular bone score. [a] HIV considered as a secondary risk factor in calculating estimates [b] FN BMD additionally included in calculating estimates [c] TBS additionally added after FN BMD in calculating estimates * % change in risk is absolute change in risk estimate from FRAX estimate without HIV as a secondary risk

680 SOCS-1/TRAF-6 UP-REGULATION IN BONE IMPAIRMENT IN HIV+ PATIENTS ON EFFECTIVE CART

Elvira S. Cannizzo, Federico A. Cazzaniga, Esther Merlini, Camilla Tincati, Lidia Gazzola, Nathalie Iannotti, Angelo Del Sole, Antonella d'Arminio Monforte, Giulia Marchetti
Univ of Milan, Milan, Italy

Background: Accelerated osteopenia/osteoporosis affects up to 30% HIV+ patients on virally-effective cART, yet the pathogenic molecular mechanism(s) remain poorly understood. Osteoclasts (OCs) from HIV transgenic rats express high levels of suppressor of cytokine signaling-1 (SOCS-1) and tumor necrosis factor receptor-associated factor-6 (TRAF-6), leading to increased osteoclastogenesis through IFN-g pathway inhibition. We investigated osteoclastogenesis and SOCS-1/TRAF-6 in OCs of HIV+cART+ patients with and without reduced bone mineral density (BMD).

Methods: We consecutively enrolled 50 HIV+ patients on virally-effective cART (HIV-RNA <40cp/ml) matched for viro-immunologic/demographic features (Fig1a): 16 with normal BMD (nBMD) by dual x-ray absorptiometry (osteopenia, Tscore -1/-2.5; osteoporosis, Tscore <-2.5), 34 with reduced BMD (rBMD, including osteopenic and osteoporotic patients) (Fig1a); 10 HIV-negative healthy controls (HIV-). Circulating OC precursors (OCPs; CD14+CD11b+CD51/61+) were studied by flow-cytometry. OCs were differentiated from peripheral blood-purified CD14+ supplemented with M-CFS and RANKL (8 days). OCs differentiation/maturation was evaluated by TRAP staining and dentin resorption. OC RANK, SOCS-1, TRAF6 expression were analyzed by Real-Time PCR and Western-Blot with and without IFN-γ stimulation (100 U,2 h). Kruskal-Wallis was used.

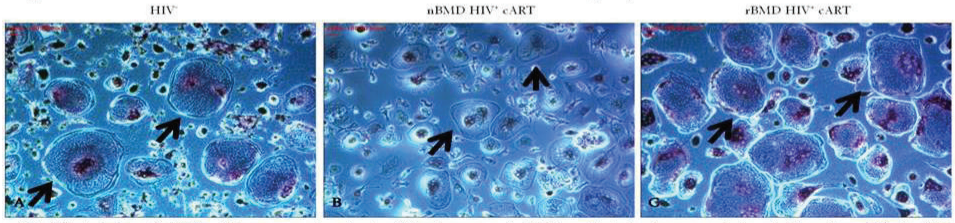
Results: HIV+rBMD presented significantly higher OCPs vs HIV+ nBMD (p=.029). CD14+ cultures from HIV+rBMD were enriched in large, multinucleated TRAP+OCs versus nBMD and HIV- (Fig.1b), as confirmed by TRAP quantification (p=.03; p=.04). Interestingly, despite equal RANK expression, OCs from HIV+rBMD expressed significantly higher SOCS-1 and TRAF-6: > 2.61, >1.62 fold vs HIV-, respectively, significantly higher than nBMD (p=0.027; p=0.05). IFN-γ challenge resulted in 1.2-fold decrease and 2.5-fold increase of SOCS-1 mRNA in HIV-OCs and HIV+OCs, respectively (p=0.04 for HIV+IFNy+ vs HIV-IFNy+).

Conclusion: HIV+rBMD patients show increased circulating OCPs and OCs ex-vivo differentiation, indicating heightened osteoclastogenesis in treated HIV+ osteopenic/osteoporotic patients. Relevantly, we show that OCs from HIV+rBMD express high SOCS-1/TRAF-6 levels, that are further upregulated upon IFN-γ challenge. Together, these findings identify deregulated SOCS-1/TRAF-6 as molecular pro-osteoclastogenesis pathway that might be sustained by abnormal interferon-mediated inflammation in successfully-treated HIV

Figure 1a. Characteristics of the Study Population

	nBMD (n=28)	rBMD (n=12)		p
Age, years(IQR)*	45 (38.5-48,5)	48 (43.5-50)		.667
CD4 count at time of analysis, cell/mmc, (IQR)*	545 (452-712)	567,5 (396-567)		.963
CD4 nadir, cell/mmc, (IQR)*	323(263-456)	177 (63-352)		.685
Ratio CD4/CD8, (IQR)*	1,5 (1-2)	2 (1-3,25)		.283
AIDS diagnosis, (yes)*	2	1		.985
cART duration, years (IQR)*	11,5 (5,75-16)	10 (6-14)		.485
Time since First HIV Ab+ test, years (IQR)*	14 (6-25)	12.5 (5.75-16.5)		.875
HIV-RNA Log cp/mL (IQR)*	<40	<40		1
cART type				
PI based (%)	8 (24,2)	2 (11,7)		.269
NNRTI based (%)	20 (60,6)	12 (70,5)		.596
Others (%)	5 (15)	3 (17,6)		.843
Tenofovir-including cART (%)	96	98		.945

Figure 1b. Generation and characterization of human osteoclasts (Ocs)



TRAP staining (pink) of human osteoclasts (black arrows) differentiated from peripheral blood purified CD 14⁺ cells and cultured for 8 days in the presence of MCSF (25 ng/ml) and RANKL (30 ng/ml). (A) HIV negative (HIV -) OCs (B) HIV positive (HIV+) cART-treated with normal BMD (nBMD) OCs (C) HIV positive cART-treated with reduced BMD (rBMD) OCs.

681 BONE DENSITY, MICROARCHITECTURE, AND BONE STRENGTH AFTER 1 YEAR OF TDF

Robert Güerri-Fernández[1], Hernando Knobel[1], Judit Villar[1], Alicia González-Mena[1], Ana Guelar[1], Ludovic Humbert[2], Elisabet Lerma-Chipirraz[1], Marta Trenchs-Rodríguez[3], Adolfo Díez-Pérez[1]

[1]Hosp del Mar, Barcelona, Spain, [2]Galgo Med, Inc, Barcelona, Spain, [3]CAP Passeig de Sant Joan, Barcelona, Spain

Background: Bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) measures the amount of mineral,but not other key aspects of bone strength such as bone microarchitecture or bone quality.Other techniques such as DXA-3D,Trabecular Bone Score (TBS)and in vivo microindentation directly measure cortical,trabecular microarchitecture and bone quality, respectively.These techniques provide a more comprehensive assessment of bone health in those situations where BMD is not fully capturing the decrease in bone strength,and thus,the risk of fracture.

Methods: Longitudinal study with HIV naïve patients starting TDF based ART.BMD (DXA-Hologic) was measured at lumbar spine and hip.Spine trabecular microarchitecture was measured by TBS (Medimaps inc).DXA-3D was measured by a 3D-software (Galgo Medical, Spain) on the hip DXA quantifying the volumetric BMD (vBMD),bone volume and cortical thickness distribution.Microindentation were measured using a Osteoprobe (Active-Life-Scientific,CA) at the anterior tibial face. Results are expressed as bone material strength index (BMSi) units. The BMD,TBS,BMSi and DXA-3D measurements at baseline and 1 year after treatment were compared using paired samples Student's t-test.

Results: Forty-nine HIV patients were included.Changes in DMO(g/cm^2)were: lumbar spine (0.976±0.024vs0.947±0.024;p<0.001;-2.8%),total hip(0.936±0.026 vs 0.930±0.025;p=0.56;-0.3%) and femoral neck (0.829±0.251vs0.802±0.023;p<0.001;-2.9%) at baseline and after 1 year of TDF treatment respectively.When analyzing DXA-3D a statistically significant decrease of the integral vBMD (-11.9 mg/cm3,-3.0%,p=0.001) and cortical vBMD (-4.0 mg/cm3,-0.4%,p=0.004) was observed at the femoral neck. The cortex at the neck was also significantly thinner after 1-year of treatment (-0.05 mm, -3.2%,p=0.006)with significantly significant difference for the trabecular vBMD.A significant reduction of TBS was observed (1.359±0.016vs1.322±0.01; p=0.0059; -2.5%).With microindentation,the BMSi was significantly higher (85.5±1.1 vs 88.5±1.2;p= 0.03; +3.8%),showing better bone strength after 1 year of treatment with TDF.

Conclusion: A decrease in trabecular and cortical microarchitecture at spine and hip was observed after 1 year of TDF therapy. However,tissue quality seemed to recover after 1 year of TDF,following the control of HIV infection.These techniques provide additional information to DXA about bone health in HIV patients.Due to its convenience and feasibility the role of them should be evaluated in future studies.

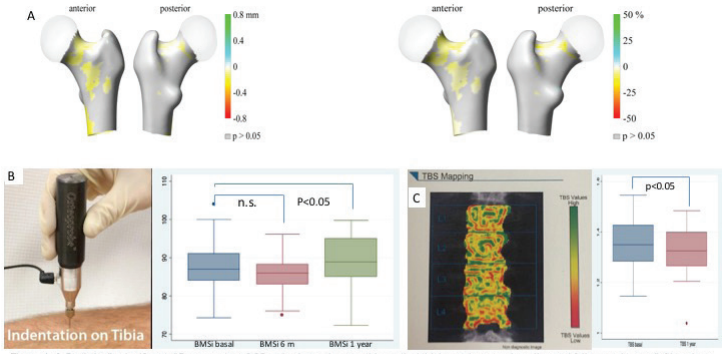


Figure 1: **A.**Statistically significant differences (p < 0.05, paired samples t-test) in cortical thickness between baseline and follow-up, in mm (left) and as a percentage (right). **B.**Microindentation on tibia for assessment of bone quality, comparative box-plot after 6 months and 1year of follow-up of TDF treatment. **C.**TBS results and comparative after 1 year of follow-up of TDF treatment.

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682 A RANDOMIZED TRIAL OF VITAMIN D3 (3000 VERSUS 1000 IU) IN HIV+ POSTMENOPAUSAL WOMEN

Michael T. Yin[1], Chengchen Zhang[1], Mariana Bucovsky[1], David Ferris[2], Susan Olender[1], Arindam Roy Choudhury[1], Anjali Sharma[3], Cosmina Zeana[4], Barry S. Zingman[5], Elizabeth Shane[1]
[1]Columbia Univ, New York, NY, USA, [2]Columbia Univ, New York, NY, USA, [3]Icahn Sch of Med at Mt Sinai, New York, NY, USA, [4]Albert Einstein Coll of Med, Bronx, NY, USA, [5]Bronx Lebanon Hosp Cntr, Bronx, NY, USA, [6]Montefiore Med Cntr, Bronx, NY, USA

Background: In HIV+ postmenopausal women, we observed an association between lower total 25-hydroxy vitamin D (25OHD) levels and greater bone loss at the distal radius. Since VitD supplementation improves musculoskeletal outcomes in older women, we compared the effects of Moderate (3000 IU) vs Low (1000 IU) VitD3 supplementation on bone mineral density (BMD) and bone turnover markers in HIV+ postmenopausal women on stable antiretroviral regimens
Methods: A 12-month prospective, randomized, double-blind, placebo-controlled study performed at a single center with the following outcomes: BMD measured by dual-energy X-ray absorptiometry (DXA); 25OHD, parathyroid hormone (PTH), and bone turnover markers (P1NP, a marker of bone formation and CTX, a marker of bone resorption). Regression analyses were used to test for associations between baseline 25OHD and percent change in BMD and bone turnover markers for each study arm.
Results: 83 participants were randomized (41 Moderate and 42 Low); 69 with 12-month DXA data were included in the primary intent-to-treat analysis. The study arms were well-balanced at baseline: median age 56 years; 55% African American, 45% Hispanic; median CD4 count 724 cells/mm3; median total 25OHD 19.7 ng/mL (49.3 nmol/L). Baseline BMI was lower in the Moderate VitD group (29±6 vs 32±6 kg/m2, p=0.02). Levels of total 25OHD were higher in the Moderate than Low VitD group at 6 months (33.1±10.3 vs 27.8±8.1 ng/ml, p=0.03) and 12 months (30.2±9.6 vs 24.3±7.6 ng/ml, p=0.007), but PTH levels did not differ between groups. In the Low VitD group, there was a significant decrease in BMD at the distal and ultradistal radius. However, percent change in BMD and bone turnover markers did not differ between Moderate and Low VitD groups after adjustment for baseline BMD and BMI (Table). In regression analyses, lower baseline 25OHD levels in the Moderate VitD group were associated with greater increase in BMD at the femoral neck (p=0.04) and ultra distal radius (p=0.045) at 12 months.
Conclusion: VitD supplementation at 3000 IU daily increased mean total 25OHD levels to > 30 ng/ml in HIV+ postmenopausal women, but did not result in increases in BMD or suppression of bone turnover markers compared with 1000 IU daily. This suggests that VitD repletion by itself does not adequately prevent bone loss in HIV+ postmenopausal women. Additional interventions are likely necessary to prevent or reverse bone loss in this population.

Table: Effect of Moderate vs Low Vitamin D Supplementation on Percent Change in BMD and Bone Turnover Markers (Adjusted For Baseline BMD and BMI)
*p<0.05 within-group change from baseline

	Low VitD (1000 IU)	Moderate VitD (3000 IU)	P Value
Lumbar spine BMD	0.07±0.7	-0.50±0.6	0.96
Total hip BMD	-0.41±0.5	-0.81±0.5	0.96
Femoral neck BMD	-1.36±0.7	-0.90±0.7	0.98
Distal radius BMD	-1.60±0.5*	-1.42±0.5*	0.10
Ultradistal radius BMD	-1.78±0.8*	-0.59±0.6	0.67
Pro-collagen type 1 N-terminal propeptide	-0.43±6.47	1.24±5.67	0.10
C-telopeptide	-8.96±7.95	-14.15±6.98*	0.97

683 SWITCHING FROM TDF TO TAF IN HIV-INFECTED ADULTS WITH LOW BMD: A POOLED ANALYSIS

Todd Brown[1], Michael T. Yin[2], Samir Gupta[3], Christine Katlama[4], Adriano Lazzarin[5], Kathy Melbourne[6], Calvin Cohen[6], YaPei Liu[6], Thai Nguyen-Cleary[6], Scott McCallister[6]
[1]The Johns Hopkin Univ, Baltimore, MD, USA, [2]Columbia Univ, New York, NY, USA, [3]Indiana Univ, Indianapolis, IN, USA, [4]Pierre and Marie Curie Univ, Paris, France, [5]Vita-Salute San Raffaele Univ, Milan, Italy, [6]Gilead Scis, Inc, Foster City, CA, USA

Background: Switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) may represent an important treatment strategy to improve bone health in HIV-infected individuals with low bone mineral density (BMD), but this has not been specifically investigated.
Methods: This analysis consisted of pooled data from two prospective Phase 3 studies (Studies 109 and 112) of HIV suppressed adults on a TDF-based regimen switching to elvitegravir, cobicistat, and emtricitabine (E/C/F) co-formulated with TAF. In adults with clinically significant low BMD by dual energy x-ray absorptiometry (T-score ≤ -2.0 at the lumbar spine, femoral neck, or total hip) at baseline (BL), we assessed percentage change in BMD and T-score at the lumbar spine and total hip and change in proportion with osteoporosis (T-score ≤ -2.5 at any site) at Weeks (W) 96. Logistic regression was used to determine BL predictors of a clinically significant improvement (≥ 5% increase) in lumbar spine and total hip BMD, adjusted for age, race, sex, and BL BMD.
Results: Of the 1117 enrolled who switched from TDF to TAF, 214 (19%) had clinically significant low BMD at BL (median age 46 years, 85% male, 63% White, 26% smokers) with 43% (93/214) osteoporosis. The BL median (interquartile range: Q1, Q3) T-score (lowest of any 3 sites) was -2.4 (-2.8, -2.2). At the spine, the median (Q1, Q3) % BMD change at W96 was 2.53% (0.22%, 5.31%) and T-score change was 0.19 (0.02, 0.42) (all p<0.001). At total hip, BMD change at W96 was 2.39% (0.72%, 4.18%) and T-score change was 0.14 (0.04, 0.24) (all p<0.001). Of the 86 with BL osteoporosis and W96 BMD data, 23% no longer met criteria for osteoporosis at W96. Of 214 with low BMD, 24% and 15% had a clinically significant BMD increase at the spine and total hip, respectively. In multivariable analysis, BL factors associated with clinically significant BMD increase at W96 were higher fraction excretion of phosphate (FEPO4 ≥ 10%) for the hip and higher BMI (≥30 kg/m2) and procollagen type 1 N-terminal propeptide (P1NP >1.85 log10 ng/mL) levels for spine.
Conclusion: HIV-infected individuals with clinically significant low BMD on a TDF-based regimen who switched to E/C/F/TAF experience a ~2.5% BMD increase over 96 weeks and a reversion from osteoporosis in approximately 1/4 of patients. Baseline urinary phosphate wasting and high bone turnover may identify TDF-treated HIV-infected patients with low BMD who may benefit the most from a switch to TAF.

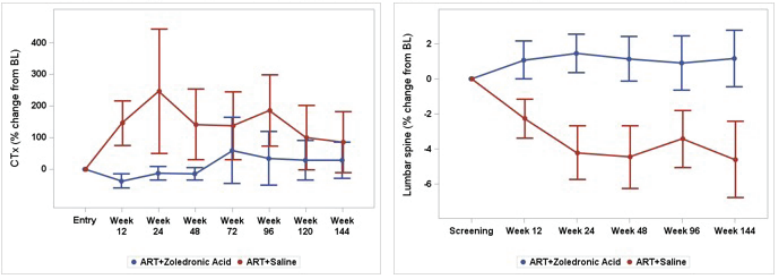
684 ANTIRETROVIRAL BONE LOSS IS DURABLY SUPPRESSED BY A DOSE OF ZOLEDRONIC ACID

Igho Ofotokun, Kehmia Titanji, Aswani Vunnava, Antonina Foster, Anandi N. Sheth, Cecile D. Lahiri, Jeffrey J. Lennox, Andrea Knezevic, Kirk A. Easley, M. N. Weitzmann
Emory Univ, Atlanta, GA, USA

Background: HIV infection and antiretroviral therapy (ART) are associated with bone loss leading to increased fracture rate in the HIV/AIDS population. Although the ART bone effects vary in magnitude, they appear to be universal to all regimen types and most intense in the first year of therapy, creating a window for prophylactic intervention. We previously showed that the long-acting antiresorptive zoledronic acid (ZOL) prevented ART bone effects through the first 48 weeks of therapy and here investigate whether these effects persisted.
Methods: We randomized 63 non-osteoporotic, viremic treatment-naïve adult HIV-infected subjects initiating ART to a ZOL (5mg) vs. placebo (PL) infusion in a double-blinded, placebo-controlled phase IIb clinical trial. Laboratory and safety measurements, plasma bone turnover markers, and bone mineral density (BMD) were performed at weeks 0, 12, 24, 48, 96, and 144. Repeated-measures analyses using mixed linear models were used to estimate and compare study endpoints.

Results: As shown in Figure 1, the ZOL arm had a 55% reduction in mean bone resorption (i.e., C-terminal telopeptide of collagen [CTx]) at 48 weeks relative to the placebo arm (CTx=0.120 ng/mL vs 0.268 ng/mL; p<0.001) and 62% lower at 96 weeks (n=41; 0.119 ng/mL vs 0.315 ng/mL; p=0.002). A 30% difference observed between the arms at 144 weeks was however not statistically significant (n=37; 0.137 ng/mL vs 0.195 ng/mL; p=0.13). A compensatory increase in osteocalcin (a marker of bone formation) was observed in the placebo arm but not in the ZOL arm. The ZOL arm had an 11% higher lumbar spine BMD at 48 weeks relative to the placebo arm (n=60; 1.30 g/cm2 vs 1.17 g/cm2; p<0.001) and remained 9-11% higher at 96 weeks (n=46) and 144 weeks (n=41, 1.31 g/cm2 vs 1.18 g/cm2; p <0.001; mean difference=0.13, 95% confidence interval 0.06, 0.21 g/cm2). Similar trends were observed in the hip and the femoral neck bones and ZOL did not result in long-term toxicities.
Conclusion: Our data suggest that ART enhanced bone resorption and BMD loss extend beyond the first 2 years of therapy and that a single dose of ZOL given at the time of therapy initiation durably blunt these effects at key fracture prone anatomical sites. These beneficial outcomes continued throughout the 3-year follow-up period. ZOL was well tolerated, preserved bone density, and ZOL or another similar intervention should be tested in a larger group of subjects.

Figure 1: Changes in C-terminal telopetide of collagen and Lumbar Spine BMD following ART



685LB HIGH DOSE VITAMIN D3 INCREASES SPINE BONE DENSITY IN HIV+ YOUTH ON TENOFOVIR (TDF)

Peter L. Havens[1], Charles Stephensen[2], Marta Van Loan[2], Brandy Rutledge[3], Bob Harris[3], Patricia M. Flynn[4], Catherine Gordon[5], Bill Kapogiannis[6], Kathleen Mulligan[7], for the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) 109 Study Team
[1]Med Coll of Wisconsin, Wauwatosa, WI, USA, [2]USDA, Davis, CA, USA, [3]Westat, Rockville, MD, USA, [4]St. Jude Children's Rsr Hosp, Memphis, TN, [5]Univ of Cincinnati, Cincinnati, OH, [6]NICHD, Bethesda, MD, USA, [7]Univ of California San Francisco, San Francisco, CA, USA

Background: Tenofovir disoproxil fumarate (TDF) decreases bone mineral density (BMD). Vitamin D (VITD) supplementation increases BMD in persons with VITD deficiency. We hypothesized that VITD administration would increase BMD in youth with HIV treated with TDF, independent of baseline VITD status.
Methods: Randomized double blind placebo controlled trial of directly observed oral VITD3 50,000 IU vs. placebo every 4 weeks for 48 weeks in youth, ages 16-24 years, HIV viral load <200 copies/mL, taking TDF-containing cART for ≥180 days. All participants (N=212) received a daily multivitamin containing VITD3 400 IU and calcium (Ca) 162 mg in addition to randomized VITD ('high dose group'; N=108) or placebo ('low dose group'; N=104). Primary outcome was change from baseline to week 48 in lumbar spine (L1-L4) BMD (LSBMD) measured by DXA. The study was designed for 90% power to detect a between-group difference in LSBMD percent change ≥1.8% at week 48. Completed June, 2016. Nonparametric testing was used to assess differences from baseline to week 48 and differences between VITD dose groups. Data presented as mean±standard deviation except LSBMD percent change is median (interquartile range).
Results: Age was 21.8±1.8 years; 84% were male and 74% black/African American. At baseline, VITD dose groups were similar in age, race/ethnicity, and Ca intake; low dose group had lower BMI, lower VITD intake and lower multivitamin use. Overall, baseline 25-hydroxyvitamin D (25-OHD) was 18.7±9.6 ng/mL. Prevalence of VITD deficiency (25-OHD <20 ng/mL) was 62%, with no randomized group differences. Daily multivitamin adherence was 48±24% and randomized study medication adherence was 96±8%. From baseline to week 48, LSBMD increased by 0.70% overall (P<0.001), increasing by 1.15% in the high dose group (P<0.001) and 0.09% in the low dose group (P=0.25), with no significant difference between groups (Table; P=0.12).). In the high dose group these changes occurred in participants with baseline 25-OHD < 20 ng/mL (1.17%; P=0.004) and with baseline 25-OHD ≥20 ng/mL (0.93%; P=0.03).There were no significant changes in hip or whole-body BMD.
Conclusion: For HIV-infected adolescents and young adults treated with TDF-containing cART, high dose, but not low dose, VITD3 supplementation administered every 4 weeks increased LSBMD through 48 weeks, independent of baseline VITD status.

VITD dose group	VITD intake at week 48 (IU/day)[1]	Serum 25-OHD at week 48 (mg/dL)[1]	Percent change in LSBMD baseline to week 48[2]		
			Overall	Baseline 25-OHD <20ng/mL	Baseline 25-OHD ≥20ng/mL
High	2019±261	36.8±7.8	1.15 (3.50); P<0.001	1.17 (3.72); P=0.004	0.93 (2.41); P=0.03
Low	300±165	20.8±8.5	0.09 (4.10); P=0.25		
P-value[3]	<0.001	<0.001	0.12		

[1]Mean±std.dev. [2]Median (interquartile range); P-value [3]Comparison high to low dose VITD group

686 PREVALENCE AND RISK FACTORS OF RENAL INJURY IN OPTION B+ DURING THE FIRST 6 MONTHS

Caroline Melhado, Jacob Phulusa, Mathius John, Allan Jumbe, Bryna Harrington, Bryan Mthiko, Mina C. Hosseinipour, for the S4 Team
Univ of North Carolina Proj–Malawi, Lilongwe, Malawi

Background: HIV-positive pregnant women in the Option B+ program are routinely initiated on Tenofovir/Lamivudine/Efavirenz (TDF/3TC/EFV) therapy without renal monitoring despite the potential for renal toxicity due to TDF. Physiological changes in kidney function during pregnancy might underestimate the prevalence of baseline kidney injury as measured by creatinine clearance (CrCl). We estimated the prevalence and risk factors for renal injury in the first 6 months of treatment to assess the need for monitoring renal function in the Option B+ population.

Methods: We analyzed data from newly diagnosed HIV-positive pregnant women initiating TDF/3TC/EFV. Participants were recruited at a government antenatal clinic in Lilongwe, Malawi as part of a prospective observational cohort study on Option B+. Renal function was assessed by measuring serum creatinine with estimation of CrCl via the Cockroft-Gault equation and proteinuria by urine dipstick at first visit, 3 and 6 months. Demographics and baseline laboratory evaluations were used for a multivariable logistic regression of a priori identified risk factors for six month renal injury.
Results: A total of 246 women were enrolled and 210 (85.4%) had evaluable data at 6 months (36 were lost to follow-up (17) or had no six month labs (19)). Participants had a median age of 30.0 years (IQR 27-35), a median BMI of 24.2 (IQR 22.4 -26.7), a median CD4 count of 356/uL (IQR 231-531) and a median hemoglobin of 11.1 g/dL (IQR 10.2-11.8). At enrollment 99.6% had a normal CrCl (>90ml/min), 13.9% had mild proteinuria (30-99 mg/dl) and 5.8% had moderate proteinuria (>100 mg/dl). Controlling for delivery status, the mean CrCl from enrollment to six months decreased by 42.4 ml/min (p <0.005, CI 36.4-49.0). Anemia, BMI, CD4 count and proteinuria were not significantly associated with a CrCl < 90 ml/min at six months.
Conclusion: The low baseline prevalence of kidney injury in HIV positive pregnant women in Option B+ supports the public health approach of rapid initiation of TDF-based therapy in absence of monitoring. While CrCl might be falsely elevated during pregnancy and decline substantially after delivery, the vast majority of women remained with normal kidney function at six months. No asymptomatic woman experienced treatment limiting renal toxicity. No risk factors for renal injury were identified. Clinical monitoring is likely sufficient to ensure safety in this population.

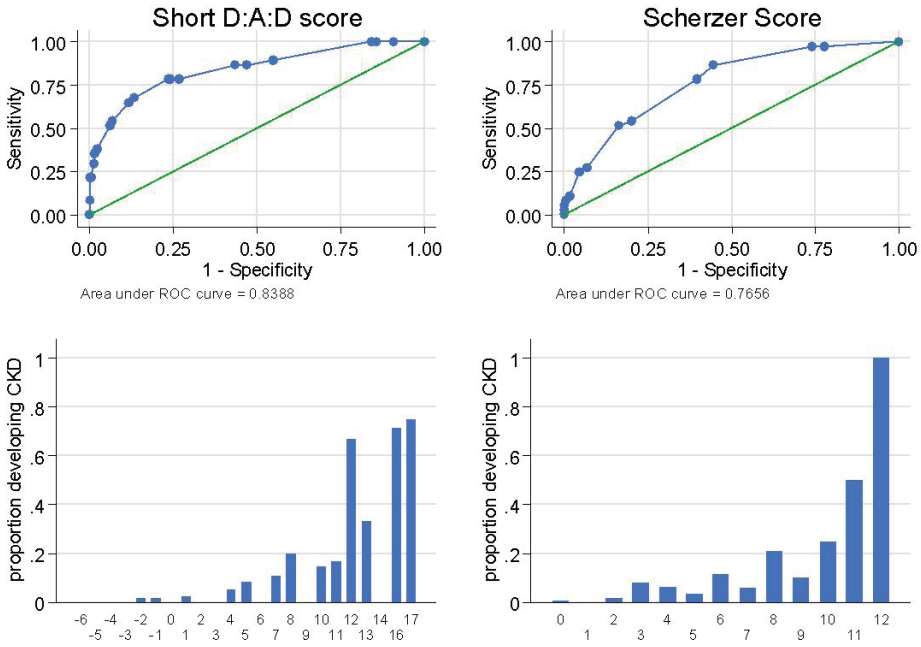
Table 1. **Changes in CrCl During First 6 Months of TDF-Based Option B+ Regimen**

Characteristic	Enrollment – Month 0	Month 3	Month 6
Total Participants	246	221	210
Normal CrCl (>90 ml/min) N (%)	245 (99.6%)	217 (98.1%)	184 (87.6%)
Moderately Reduced CrCl (60-90 ml/min) N (%)	1 (0.4%)	3 (1.3%)	24 (11.4%)
Low CrCl (<60 ml/min) N (%)	0 (0.0%)	1 (0.0%)	2 (1.0%)
Mean CrCl (ml/min)	164.9 ± 37.1	158.1 ± 42.1	122.2± 30.2
Mean Difference in CrCl (ml/min) From Month 0	N/A	-6.9 (p = 0.062, CI -14.1-0.3)	- 42.4 (p <0.005, CI -36.4 –[-49.0])
Range of CrCl (ml/min)	72.4-337.6	59.5 – 325.9	40.7 – 251.7
N (% Delivered of Enrollment Total)	0%	59 (24.0%)	205 (83.3%)
Mean CrCl (ml/min) of Post-Partum Participants (ml/min)	N/A	130 ± 35.3	118.7 ± 28.1

687 PREDICTORS OF CKD AND UTILITY OF RISK-PREDICTION SCORES IN HIV-POSITIVE INDIVIDUALS

Emily Woolnough[1], Jennifer Hoy[1], Allen Cheng[1], Rowan G. Walker[1], Anastasia Chrystostomou[1], Ian Woolley[1], Freya Langham[1], Michael Moso[1], Achini Weeraratne[2], Janine M. Trevillyan[1]
[1]*Alfred Hosp, Melbourne, Australia,* [2]*Monash Univ, Melbourne, Australia*

Background: Management of HIV-positive individuals with borderline estimated glomerular filtration rates (eGFR) is clinically challenging. This study aimed to identify factors associated with development of chronic kidney disease (CKD), and to validate existing risk prediction scores in individuals with eGFR >60ml/min at baseline.
Methods: This retrospective cohort study included HIV-positive individuals managed at The Alfred Hospital, Melbourne Australia, with a baseline visit between June 30 2008 and December 31 2009 (n=749). Data was collected from an HIV database and a manual review of electronic records. Individuals with an eGFR <60ml/min at baseline or <5 eGFR results were excluded. CKD was defined as ≥2 consecutive eGFR results <60ml/min sustained for 90 days. Linear regression models were constructed for change in eGFR over time and the lowest and highest terciles of slope were compared. The performance of CKD scores proposed by the D:A:D Study Group (PLoS Med 2015) and Scherzer et al. (AIDS 2014) were estimated by the area under the ROC curve.
Results: Participants were predominantly male (n=680, 91%) with a median age 46 (IQR 39, 53) years, time since HIV diagnosis 10 (4, 18) years, nadir CD4 count 153 (48, 261) cells/µL, and current CD4 count 484 (297, 691) cells/µL. 63.4% had an HIV viral load <50 copies/µL, with 87.3% currently on antiretroviral therapy (55.9% on tenofovir DF). At baseline the median eGFR was 106ml/min (95, 116). Thirty-seven (4.9%) developed new CKD, at a median 4.7 (2.2, 6.2) years. Factors associated with development of CKD were baseline eGFR 60-90 (vs eGFR 90-120: HR 11.7, 95% CI: 5.7, 24.2), diabetes (HR 4.9, 95% CI: 2.1, 11.1), proteinuria (HR 3.2, 95% CI: 1.7, 6.3), and age >60 years (vs age 35-49, HR: 6.3, 95% CI: 2.9, 13.7). Diabetes (OR 2.32, 95%CI 1.0, 5.5) and proteinuria (OR 1.66, 95%CI 1.1, 2.6) predicted a steeper slope of eGFR decline. Neither current nor cumulative tenofovir use was associated with progression to CKD (current TDF HR 0.69, 95% CI: 0.36, 1.33; cumulative TDF HR 0.88, 95% CI: 0.45, 1.7). Both the Short D:A:D and Scherzer scores were well calibrated but the Short D:A:D score had better discrimination (D:A:D AUROC 0.84, Scherzer AUROC 0.76, p=0.04).
Conclusion: Individuals with a lower baseline eGFR are at higher risk for CKD. Risk prediction tools may be useful in identifying those at greatest risk who may benefit from aggressive management of risk factors, specifically diabetes and proteinuria.



688 KIDNEY TRANSPLANT OUTCOMES IN HIV-POSITIVE AND HIV-NEGATIVE RECIPIENT PAIRS

Esther Gathogo[1], Frank Post[2]
[1]King's Coll London, London, UK, [2]King's Coll Hosp NHS Fndn Trust, London, UK

Background: HIV infection is a risk factor for end-stage kidney disease, and kidney transplantation has been successfully employed in HIV positive patients. Several studies have shown that HIV positive kidney transplant recipients are at increased risk of acute allograft rejection although the aetiology for this remains poorly defined. We examined allograft outcomes in HIV positive and HIV negative recipient pairs who each received a kidney from a deceased donor.

Methods: Data from a national cohort study of HIV positive kidney transplant recipients (2005-2013) were linked to the national kidney transplant registry (NHSBT). HIV sero-discordant recipients of deceased donor allografts during this period were identified. Donor characteristics and clinical outcomes in HIV+ and HIV- recipients were compared. Kaplan-Meier methods were used to estimate host/graft survival and cumulative incidence of allograft rejection. Logrank tests were used to compare survival and Cox-proportional hazard regression analysis to identify factors associated with acute graft rejection.

Results: Forty HIV sero-discordant kidney allograft recipient pairs were identified. HIV+ recipients were younger (43.5 vs. 52.0 years, p=0.009) and more often of black ethnicity (75% vs. 13%, p<0.001). Cold ischaemia time (15.0 vs. 14.8 hours, p=0.44), degree of HLA mismatch (1-2 mismatches: 43% vs. 48%, p=0.38) and incidence of delayed graft function (32% vs. 26%, p=0.51) were similar. HIV+ recipients were less likely to receive tacrolimus (49% vs. 86%, p=0.001) as part of their initial immunosuppressive regimen, and more likely to experience acute graft rejection in the first year post transplantation (45% vs. 35%, p=0.04). At 3 years, overall patient survival was similar (91% vs. 90%, p=0.93) but graft survival was less favourable (84% vs. 100%, p=0.02). HIV status, ethnicity and HLA mismatch were associated with acute graft rejection in univariable analysis. After adjustment, HIV status was no longer associated with allograft rejection (Table).

Conclusion: HIV positive kidney allograft recipients experienced higher rates of acute rejection than HIV negative recipients. However, adjustment for differences in recipient ethnicity and HLA mismatch attenuated the association between HIV infection and acute graft rejection.

Table: Factors associated with acute graft rejection in HIV positive and HIV negative recipient pairs

Characteristics		N=80			
		Univariable		Multivariable	
		HR (95% CI)	P	HR (95% CI)	P
Age at KT (per year older)		0.99 (0.96, 1.02)	0.61		
Ethnicity					
	Black	2.85 (1.30, 6.26)	**0.01**	2.00 (0.79, 5.04)	0.14
	Other	1		1	
HIV Status					
	Positive	2.24 (1.03, 4.86)	**0.04**	1.46 (0.60, 3.56)	0.40
	Negative	1		1	
Cold Ischaemia Time (per min increase)		0.999(0.999, 1.001)	0.89		
HLA mismatch					
	1-2	1	**0.05**	1	0.09
	3-4	2.41 (1.02, 5.72)		2.13 (0.88, 5.11)	
Initial Tacrolimus Use					
	Yes	0.64 (0.29, 1.40)	0.27		
	No	1			

689 PLANNED PRACTICE OF HIV POSITIVE-TO-POSITIVE TRANSPLANTS IN US TRANSPLANT CENTERS

Sarah Rasmussen, Mary Grace Bowring, Ashton Shaffer, Allan Massie, Aaron Tobian, Dorry Segev, Christine Durand
The Johns Hopkins Univ, Baltimore, MD, USA

Background: End-stage organ disease is increasing among HIV-positive (HIV+) individuals. Solid organ transplant outcomes among HIV+ recipients are excellent but there is a severe organ shortage. The HIV Organ Policy Equity (HOPE) Act of 2013 lifted the federal ban on using HIV+ organs for HIV+ recipients and allows HIV+-to-HIV+ transplants under research protocols. HIV+ organs are a novel source of organs for HIV+ recipients, but their use depends on transplant centers' knowledge, opinions and practice of these transplants, which is unknown.
Methods: From 01/2016-06/2016, we 209 identified US transplant centers that performed ≥1 adult organ transplant between 1/2014-6/2014. A transplant team member who could represent the center's practice of HIV+ transplantation was asked to respond. Contact information for 5 centers was unavailable. Relationships between responses and center characteristics from the Scientific Registry of Transplant Recipients were explored using Wilcoxon-Mann-Whitney tests.
Results: Overall response rate was 55.9% (114/204). Respondents were transplant surgeons (57.1%), infectious disease physicians (15.2%), hepatologists (7.6%), nephrologists (6.7%), pharmacists (6.7%) and other (6.7%). Nine centers (8.7%) thought HIV+-to-HIV+ transplants were still banned and 22 (21.4%) were unaware they are restricted to research. 50 (55.6%) centers plan to perform HIV+-to-HIV+ deceased donor transplants, 32 (64%) of which had read the research criteria. Sixty-six (72.5%) respondents believed donor to recipient HIV-superinfection is a moderate but manageable risk. Most respondents perceived risks of rejection (70.3%), and infections and hospitalizations (71.4%) as comparable to HIV negative-to-positive transplants but rated the risk of post-transplant HIV-associated nephropathy as unknown (30.8%) or higher (21.9%). Centers planning HIV+-to-HIV+ transplants had higher median transplant volume, HIV+ recipient volume, local HIV prevalence, and use of infectious-risk donor organs (Table 1). Seventy-nine (83.2%) respondents supported HIV+-to-HIV+ living donation.
Conclusion: Many transplant centers support and plan to perform HIV+-to-HIV+ transplants. Some centers are still unaware that HIV+-to-HIV+ transplantation is legal or restricted to research. There is substantial support for HIV+ living donor transplantation. Transplant center education is needed to implement HIV+-to-HIV+ transplantation which could alleviate the organ shortage and improve access to transplant among HIV+ and HIV- patients.

Table 1: Center level characteristics among centers planning and not planning HIV positive-to-positive transplants

	Planning N=50 55.6%	Not Planning N=40 44.4%	p-value
Annual transplant volume (Median (IQR))	80 (50-111)	40 (27-65)	**<0.01**
Volume of HIV+ recipients (Median (IQR))	4 (1-11)	0 (0-1)	**<0.01**
County HIV prevalence (per 100,000) (Median (IQR))	541 (281-1092)	321 (156-471)	**<0.01**
Proportion IRD organs (Median (IQR))	15.4% (12.2%-22.2%)	12.7% (8.5% - 16.3%)	**<0.01**

690 FOOD INSECURITY IS ASSOCIATED WITH POOR DIABETES CONTROL IN THE WIHS

Kartika Palar[1], Edward A. Frongillo[2], Tracey Wilson[3], Mardge Cohen[4], Eryka Wentz[5], Adaora Adimora[6], Daniel Merenstein[7], Janet M. Turan[8], Phyllis Tien[1], Sheri Weiser[1]
[1]Univ of California at San Francisco, San Francisco, CA, USA, [2]Univ of South Carolina, Columbia, SC, USA, [3]SUNY Downstate Med Cntr, Brooklyn, NY, USA, [4]Stroger Hosp, Chicago, IL, USA, [5]The Johns Hopkins Univ, Baltimore, MD, USA, [6]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [7]Georgetown Univ, Washington, DC, USA, [8]Univ of Alabama at Birmingham, Birmingham, AL, USA

Background: Food insecurity – or lack of access to sufficient quantity or quality of food – is associated with poor control of diabetes mellitus (DM) in the general United States (US) population. Women with HIV are at high risk for both food insecurity and type 2 DM, but no studies have examined the association between food insecurity and DM control among women or among people with HIV. We hypothesized that food insecurity would be associated with poor DM control, modified by HIV status.
Methods: We analyzed longitudinal data (2013-2016) from the Women's Interagency HIV Study (WIHS), a national study of US women with or at risk for HIV. We assessed associations between a validated measure of food insecurity and laboratory measures of DM control obtained via blood draw. Outcomes included a) fasting glucose (FG) (mg/dL) and optimal FG (70-130 mg/dL), to capture current DM control, and b) hemoglobin A1c (HbA1c) (%) and optimal HbA1c (<7%), to capture longer term DM control. We modeled the association between change in food insecurity and change in DM control using linear and logistic regression with random effects for continuous and dichotomous outcomes, respectively, controlling for age, race/ethnicity, income, health insurance, parity, and diabetes medication use. We also tested whether HIV status modified the association between food insecurity and DM control.
Results: The analysis included 495 women with DM (67% with HIV). Marginal, low, and very low food security affected 13.5%, 13.3%, and 11.5% of women, respectively. Mean FG was 138 mg/dL and mean HbA1c was 7.2%. Almost two-thirds had optimal FG (61%) and optimal HbA1c (65%). In adjusted models, very low food security was associated with 18.5 mg/dL higher FG ($p<0.01$) and 60% lower odds of optimal FG (AOR: 0.40; 95% CI 0.20, 0.83; $p<0.05$), compared to food security. Furthermore, very low food security was associated with 0.33 percentage points higher HbA1c ($p<0.01$) and 68% lower odds of optimal HbA1c (AOR: 0.32; 95% CI 0.13, 0.75; $p<0.01$), compared to food security. We found no effect modification by HIV status.
Conclusion: Food insecurity was longitudinally associated with multiple measures of poor DM control among women with or at risk for HIV. These results suggest food security should be addressed as part of optimal DM management for women, including in the context of HIV care. Future studies should test the impact of food security interventions on DM health among women with or at risk for HIV.

Table 1: Longitudinal association between food insecurity and diabetes control

	Glucose (mg/dL) β (SE)	Optimal glucose AOR (95% CI)	A1c (%) β (SE)	Optimal A1c AOR (95% CI)
Food Security				
High	Ref.	Ref.	Ref.	Ref.
Marginal	5.177	1.230	0.002	1.200
	(5.596)	(0.654 - 2.313)	(0.118)	(0.590 - 2.438)
Low	6.762	0.733	-0.067	1.115
	(6.891)	(0.354 - 1.518)	(0.143)	(0.498 - 2.498)
Very low	**18.457****	**0.402***	**0.330***	**0.317****
	(7.093)	**(0.195 - 0.829)**	**(0.156)**	**(0.134 - 0.750)**
Observations (person-visits)	927	927	1,087	1,087
Number of women	443	443	475	475

*** p<0.001, ** p<0.01, * p<0.05; All models controlled for the following covariates: age, race/ethnicity, income, health insurance status, parity, and diabetes medication use.

691 ADIPOSE MITOCHONDRIAL FUNCTION, ADIPONECTIN, AND INSULIN RESISTANCE IN ACTG A5224S

Todd Hulgan[1], Benjamin Ramsey[2], John R. Koethe[1], David C. Samuels[1], Mariana Gerschenson[3], Daniel Libutti[3], Grace A. McComsey[4], Paul E. Sax[5], Todd Brown[6], for the AIDS Clinical Trials Group Study A5224s Team
[1]Vanderbilt Univ, Nashville, TN, USA, [2]Univ of South Carolina, Greenville, SC, USA, [3]Univ. of Hawaii-Manoa, Honolulu, HI, USA, [4]Case Western Reserve Univ, Cleveland, OH, USA, [5]Brigham and Women's Hosp, Boston, MA, USA, [6]The Johns Hopkins Univ, Baltimore, MD, USA

Background: Some antiretroviral therapy (ART) and HIV itself confer a risk of metabolic effects which may be related to alterations in mitochondrial (mt) function and adipokine expression. ACTG study A5224s found that adipose mtDNA levels decreased in HIV+ persons starting ART, and electron transport chain complex I (CI) and IV (CIV) activity decreased in those starting tenofovir (vs. abacavir)-based regimens. A separate study found an association between a non-synonymous mtDNA mutation in CI (10398A>G encoding NADH dehydrogenase subunit 3) and decreased adiponectin on ART. We hypothesized that HIV+ persons with decreased adipocyte mt function on ART will have corresponding reductions in adiponectin and insulin sensitivity, and that these changes would be influenced by mtDNA mutation 10398G.
Methods: Analyses included A5224s data on adipose mtDNA levels, CI and CIV activity by immunoassay, visceral abdominal tissue (VAT) by CT scan, and fasting serum glucose at week 0 and 96 of ART. The 10398G mtDNA variant was available from GWAS data. Fasting insulin and adiponectin were measured from cryopreserved serum using multiplex bead array. Insulin resistance and β-cell function were estimated by HOMA-IR and HOMA-B, respectively. Spearman correlation and single-covariate linear regression were performed.
Results: 39 participants had week 0 and 96 adipose biopsies: median age was 39 years; body mass index (BMI) 25.7kg/m2; and adiponectin 7077ng/ml. Percent decreases in CIV activity and adiponectin over 96 weeks were correlated (Spearman rho 0.40; P=0.02; N=35). This association persisted after adjusting for age, sex, BMI, or VAT in separate regression analyses. Percent decrease in CIV activity correlated with increases in HOMA-IR (rho -0.44; P=0.01; N=33) and HOMA-B (rho -0.36; P=0.04; N=33). These relationships were less robust after adjusting as above (P=0.05-0.07). Among 12 non-Hispanic white participants, mtDNA 10398G was associated with change in adiponectin (P=0.048), but not HOMA; participants with the 10398G mutation had a median decrease in adiponectin over 96 weeks (-1552ng/mL) while those with 10398A had a median increase (+2555ng/mL). This difference remained statistically significant after adjusting for age, sex, BMI, or VAT.
Conclusion: These analyses suggest that decreased adipose mt CIV activity after ART initiation is related to changes in adiponectin and glucose homeostasis, and support prior findings that a common mtDNA mutation in CI influences adiponectin levels on ART.

692 PLASMINOGEN ACTIVATOR INHIBITOR-1 PREDICTS REDUCED INSULIN SENSITIVITY IN HIV

Kamonkiat Wirunsawanya[1], Dominic Chow[1], Loni Belyea[1], Cecilia Shikuma[1], Richard M Watanabe[2], Lindsay Kohorn[1], Bruce Shiramizu[1], Brooks Mitchell[1], Scott A. Souza[1], Lishomwa Ndhlovu[1]
[1]Univ of Hawaii, Honolulu, HI, USA, [2]Univ of Southern California, Los Angeles, CA, USA

Background: HIV-infected individuals despite long-term suppressive antiretroviral therapy (ART), remain at high risk for cardio-metabolic complications. None of studies have investigated plasma soluble biomarkers including plasminogen activator inhibitor type 1 (PAI-1) as a potential predictor of the development of insulin resistance (IR) in HIV. Here we assessed several soluble biomarkers to better document the development of IR among chronic HIV-infected adults on ART.
Methods: In a sub-cohort of HIV-infected individuals participating in the Hawaii Aging with HIV Cohort (≥40 years of age and on stable antiretroviral therapy for > 3 months) without diagnosis of DM at baseline and with availability of two year longitudinal data, we analyzed the correlation between various plasma biomarkers including TNF-α, VEGF, MCP-1, IL-8, IL-6, PAI-1, IFN-γ, CRP, SAA, MPO, MMP-9, sVCAM-1, sICAM-1, and sE-Selectin at baseline and whole body insulin sensitivity as measured by the Matsuda Index at baseline and at the two-year follow-up visit. Matsuda Index utilizes the mean plasma glucose and insulin concentration during a two-hour oral glucose tolerance test and provides a dynamic assessment of whole body insulin sensitivity rather than a static assessment such as homeostatic model assessment-2 (HOMA2) utilizing fasting glucose and insulin.
Results: 62 subjects: 90.3% male, median age 51 (Q1, Q3; 46,56) years, median glucose and insulin during OGTT 117.81(99.75,141.91) mg/dl and 53.77(38.58,71.44) mg/dl, median BMI 26.07 (24046, 27.81) kg/m2, median CD4 count 513 (362,713) cells/mm3, and 69% with HIV RNA<50 copies/mL. We found a negative correlation between PAI-1 and baseline Matsuda Index ($r = -.435$, $p = .001$) and a negative correlation with PAI-1 and Matsuda Index at two-year follow-up ($r = -.377$, $p = .005$). In a linear regression model that included age, total body fat mass percentage, serum amyloid A (SAA) and family history of diabetes mellitus, PAI-1 still remained associated with Matsuda Index at two-year follow-up ($r = -.409$, $p = .002$).
Conclusion: Plasminogen activator inhibitor type 1 (PAI-1), a key negative regulator of fibrinolysis, has been widely investigated to be a potential predictor of the development of IR and DM in non-HIV-infected individuals. Our results suggest that PAI-1 may be a particularly strong predictor of insulin resistance among chronically stable HIV-infected individuals, which is independent of age and body fat composition, 2 major traditional risk factors for IR.

Table: Multivariable linear regression of Matsuda Index at two-year follow-up

Model	Independent variable	Unstandardized Coefficients Beta	Standardized Coefficients Beta	Sig.
1	Age	-.116	-.278	.033
	Total body fat percentage	-.019	-.057	.679
	Log SAA	-.422	-.124	.358
	Log PAI-1	-4.960	-.375	.008
	Family history of DM	-.785	-.137	.276
2	Age	-.115	-.275	.033
	Log SAA	-.467	-.137	.292
	Log PAI-1	-5.200	-.393	.003
	Family history of DM	-.800	-.140	.263
3	Age	-.129	-.309	.015
	Log PAI-1	-5.422	-.409	.002

693 BODY MASS INDEX AND THE RISK OF SERIOUS NON-AIDS EVENTS: THE D:A:D STUDY

Amit C. Achhra[1], Caroline Sabin[2], Lene Ryom[3], Antonella d'Arminio Monforte[4], Stephane de Wit[5], Andrew Phillips[2], Christian Pradier[6], Jens D. Lundgren[7], Matthew Law[1], for the DAD Study Group
[1]Kirby Inst, Sydney, Australia, [2]Univ Coll London, London, UK, [3]CHIP, Copenhagen, Denmark, [4]Univ of Milan, Milan, Italy, [5]Univ Libre de Bruxelles, Brussels, Belgium, [6]Nice Univ Hosp, Nice, France, [7]Univ of Copenhagen, Copenhagen, Denmark

Background: Body mass index (BMI) (weight (kg)/ height(m2)) is a potentially modifiable risk factor for several serious non-AIDS events (SNAEs). However the relationship between BMI and SNAEs in HIV-positive individuals in not well understood.
Methods: We followed D:A:D study participants on antiretroviral therapy from their first BMI measurement to the first occurrence of a SNAE or 1/2/2014. The SNAEs of interest, all well-adjudicated, were cardiovascular disease (CVD- composite of myocardial infarction/stroke/invasive cardiovascular procedures); diabetes; non-AIDS-defining malignancies (NADM); BMI-associated cancers (composite of malignancies known to be associated with BMI in general population, including esophagus, pancreas, colon, rectum, breast, endometrium, kidney, thyroid and gallbladder); and all-cause mortality. BMI was time-updated and lagged by 1 year (i.e. there was at least 1 year time-gap between last BMI measurement and a SNAE, so as to minimize bias from reverse causation) and categorised at clinical cut-offs: 18.5, 23, 25, 27.5 and 30 kg/m2. Poisson regression models adjusted for key confounders for each SNAE were used.
Results: During 295,147 person-years of follow-up (PYFU) in 41,149 included individuals, incidence/1000 PYFU of outcomes were: CVD (n=1398): 4.8; diabetes (n=3025): 10.2; NADM (n=1143): 3.9; BMI-cancers (n=184): 0.6 and all-cause mortality (n=3025): 10.2. Participants were largely male (73%) with baseline mean age of 40 years and baseline median BMI of 23.3 (IQR: 21.2- 25.7). A majority of follow-up was in BMI categories of 18.5-23 (41%), 23-25 (22%) and 25-27.5 (17%). Overall, BMI showed a statistically significant J-shaped relationship with the risk of all outcomes except diabetes (Table). There was a higher risk of CVD, NADM, and all-cause mortality at BMI levels <18.5 and at 18.5-23 (especially for NADM and all-cause mortality), compared to the BMI at 23-25. High BMI (>30), compared to that at 23-25, was associated with the higher relative risk of CVD, diabetes, BMI-cancers and possibly all-cause mortality. For diabetes, there was a linear increase in risk with increasing BMI. Results were not sensitive to lagging latest BMI by 2 years (data not shown).
Conclusion: We found that the low BMI, even at the levels of 18-23 and after being lagged by 1 year, was associated with higher short-term risk of CVD, NADM and all-cause mortality in this population. High BMI (>30) was a risk factor for CVD, diabetes, NADM and BMI-cancers.

694 RANDOMIZED TRIAL OF BEHAVIORAL WEIGHT LOSS FOR HIV-INFECTED PATIENTS

Katie Becofsky[1], Edward J. Wing[2], Jeanne McCaffery[3], Matthew Boudreau[3], Rena R. Wing[3]
[1]Univ of Massachusetts Amherst, Amherst, MA, USA, [2]Brown Univ, Providence, RI, USA, [3]The Miriam Hosp, Providence, RI, USA

Background: Obesity is increasingly prevalent in HIV-infected patients and compounds their cardiovascular disease (CVD) risk. Behavioral weight loss programs are recommended for overweight and obese individuals, but have not been systematically studied in people living with HIV. We conducted the first randomized trial testing the efficacy of an empirically validated behavioral weight loss program in HIV-infected patients.
Methods: 40 overweight or obese HIV-infected patients (49.9± 8.8 years of age; BMI of 34.2±34.2), with an undetectable viral load and CD4 count >200 were randomly assigned to a fully-automated Internet-delivered behavioral Weight Loss program (WT LOSS) or Internet Education Control. The behavioral weight loss program includes 12 weekly video lessons, a platform to submit self-monitoring data, and automated feedback tailored to the individual. The primary outcome was weight loss over the 12-week program; secondary outcomes were health-related quality of life (HRQOL), use of weight control strategies, and CVD risk factors.
Results: 92% of participants completed the study. Average weight losses in intent-to-treat analyses were significantly greater for WT LOSS than Control (4.4 ± 5.4 kg vs 1.0±3.3 kg, p=.02). On average, participants viewed 7 lessons and submitted their data on 8 of the 12 weeks; both measures of adherence were strongly related to weight loss (r=.61 and .63, p<.01). Participants in WT LOSS reported greater increases in the use of weight control strategies than Controls; moreover, 59% of WT LOSS versus 21% of Controls reported improvements in HRQOL (p<.05). There were no significant differences between WT LOSS and Control on changes in CVD risk factors.
Conclusion: HIV-infected patients adhered to the behavioral weight loss program and, on average, lost 4.4 kg, which was similar to the outcomes previously reported using the same Internet program in non-HIV participants. HRQOL and use of healthy weight control strategies also improved. Thus, this population responded well to the program despite their low socioeconomic status (60% had income <$20,000), mental health comorbidities (67% had history of depression), and complex medical regimens (average 4.3 medications in addition to cART). This weight loss program is completely automated and can be easily disseminated. Further research on the efficacy of weight loss interventions for improving the health of HIV-infected patients is needed.

695 PREDICTORS OF SEVERE WEIGHT/BODY MASS INDEX GAIN FOLLOWING ANTIRETROVIRAL INITIATION

Priya Bhagwat[1], Igho Ofotokun[2], Grace A. McComsey[3], Todd Brown[4], Carlee Moser[5], Catherine A. Sugar[1], Judith S. Currier[1]
[1]Univ of California Los Angeles, Los Angeles, CA, USA, [2]Emory Univ, Atlanta, GA, USA, [3]Case Western Reserve Univ, Cleveland, OH, USA, [4]The Johns Hopkins Univ, Baltimore, MD, USA, [5]Harvard Univ, Boston, MA, USA

Background: Excessive weight gain following antiretroviral therapy (ART) is common and may predispose individuals to HIV-associated metabolic syndrome, sometimes leading to ART discontinuation and/or poor adherence. The objective of this study is to understand predictors of severe weight/body mass index (BMI) gain in individuals initiating ART.
Methods: This was a retrospective analysis of the ACTG A5257 study, where ART-naïve HIV-infected individuals were randomized to one of 3 regimens: atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), or raltegravir (RAL) each in combination with tenofovir disoproxil fumarate/emtricitabine. Severe weight/BMI gain outcomes over 96 weeks were defined two ways: (1) percent weight increase ≥ 10%; (2) an upward change in BMI category. Among those underweight at baseline, only those who were overweight or higher at follow-up were included in both outcomes. Logistic regression was used to examine the association between participant characteristics and severe weight/BMI gain.
Results: The study population (N=1,809) was 76% male, largely black non-Hispanic (41.9%) and white non-Hispanic (34.1%), with a mean baseline weight of 79 kg and BMI of 26 kg/m^2. Over 96 weeks, the average weight increased by 3.8 kg and BMI by 1.3 kg/m^2. Those with severe weight gain had a mean increase of 14.9 kg (N=373), and those with severe BMI gain had a mean increase of 4.4 kg/m^2 (N=361). The odds of severe weight gain were 1.55 times higher for black non-Hispanic compared to white non-Hispanic individuals (95% CI: 1.10 to 2.20; p=0.013). The odds of severe weight gain were 2.52 times higher for every 1 log (10-fold) higher in baseline HIV-1 RNA (95% CI: 2.00 to 3.16; p<0.0001), and 1.28 times higher for every 100 cell/mm^3 lower in baseline CD4+ count (95% CI: 1.18 to 1.39; p<0.0001). Results were similar for severe BMI. Results also suggested that treatment with protease inhibitors vs RAL may be protective against severe weight/BMI gain. The odds of severe weight gain were significantly lower for ATV/r vs RAL (OR: 0.72 [95% CI: 0.53 to 0.99]; p=0.043), while odds of severe BMI gain were significantly lower for DRV/r vs RAL (OR: 0.73 [95% CI: 0.53 to 0.99]; p=0.041).
Conclusion: Predictors of severe weight/BMI gain in this population included black race, higher baseline disease severity, and use of RAL. Understanding factors predisposing individuals to unhealthy weight gain may help better manage metabolic complications of HIV.

696 RALTEGRAVIR SWITCH AND BIOMARKERS OF LIVER STEATOSIS AND METABOLIC SYNDROME IN WOMEN

David Reynoso[1], Anoma Somasunderam[1], Maitreyee Nigalye[1], Judith S. Currier[2], Netanya S. Utay[1], **Jordan E. Lake**[3]
[1]Univ of Texas Med Branch at Galveston, Galveston, TX, USA, [2]Univ of California Los Angeles, Los Angeles, CA, USA, [3]Univ Texas Houston, Houston, TX, USA

Background: Persons with well-controlled HIV infection on antiretroviral therapy (ART) are at risk for metabolic syndrome (MetS) and fatty liver disease. Hepatic steatosis and fibrosis and MetS have been associated with changes in circulating levels of adiponectin, soluble ST2 (sST2, or IL-33R), chitinase 3-like 1 (Chi3L1, or YKL40), hyaluronic acid (HA), TIMP-1, lysyl oxidase-like-2 and TGF-β in non-HIV-infected populations and animal models. Protease (PI) and non-nucleotide reverse transcriptase inhibitors (NNRTI) may contribute to MetS and other comorbidities. The effect of switching from PI- or NNRTI-based regimens to raltegravir-based regimens on these biomarkers is unknown.
Methods: Plasma was obtained from a completed, prospective trial of 37 women with lipohypertrophy and well-controlled HIV infection on NNRTI- or PI-based regimens who were randomized to immediate vs delayed (24 weeks) switch to raltegravir. We quantified the above biomarkers by ELISA and Multiplex assays at baseline and 24 weeks after randomization. Wilcoxon signed-rank test evaluated within group changes. We investigated correlations among biomarkers and clinical covariates with nonparametric (Spearman) and parametric (linear regression) analyses. Associations were also evaluated by regression modeling.
Results: Participants had median age of 43 years, CD4 558 cells/mm3 and BMI 32 kg/m2; 35% met criteria for MetS. At baseline, higher adiponectin levels correlated with higher Chi3L1 levels (r=0.42, P=0.02), as did changes after 24 weeks (r=0.40, P=0.03). Baseline sST2 levels correlated with HA (r=0.52, P=0.003) and TIMP-1 levels (r=0.48, P=0.006); changes in sST2 correlated with changes in Chi3L1 (r=0.43, P=0.02) and adiponectin (r=0.40, P=0.03). Adiponectin and Chi3L1 levels decreased more in women switched to raltegravir immediately compared to those continuing NNRTI- or PI-based ART (Table). Other biomarkers did not change significantly. Adiponectin levels increased 10% per 1 mg/dL HDL increase. Adiponectin (1453 vs 3346 ng/ml, P=0.01) and sST2 (8473 vs 13206, P=0.02) were lower in participants with MetS vs without MetS. Adiponectin levels were also lower among women with higher subcutaneous adipose tissue volumes.
Conclusion: In women with HIV and lipohypertrophy, the hepatic steatosis/fibrosis marker Chi3L1 and the adipokine adiponectin decreased with switching to raltegravir. Whether switching from NNRTI/PI-based regimens to raltegravir would improve hepatic steatosis and dysmetabolism requires further study.

	Raltegravir (n=14)				NNRTI / PI (n=17)			
	Median (IQR)				Median (IQR)			
	Week 0	Week 24	Median of differences	p-value	Week 0	Week 24	Median of differences	p-value
HA (ng/ml)	48.7 (23.2, 81.7)	41.2 (26.2, 66.4)	-2.3	0.391	47.5 (28.8, 67.7)	36.1 (22.2, 63.1)	-2.2	0.5171
TGF-β1 (pg/ml)	31204 (13615, 37653)	22942 (11421, 36255)	-3561	0.391	31863 (21401, 42534)	27200 (15446, 39166)	-1258	0.3289
TGF-β2 (pg/ml)	1663 (1463, 1801)	1576 (1385, 1820)	-18	0.3575	1750 (1526, 1802)	1651 (1396, 1783)	-49	0.1202
TGF-β3 (pg/ml)	957 (408, 1140)	681 (456, 1040)	-61	0.1937	1000 (764.9, 1152)	892 (466.6, 1055)	-4.9	0.2435
sST2 (pg/ml)	12785 (8125, 15838)	10047 (7826, 12424)	-1202	0.104	9792 (7383, 13965)	10146 (8083, 11903)	354	0.8536
Chi3L1 (pg/ml)	40166 (22752, 54073)	23402 (22069, 39897)	-9747	**0.0266**	39026 (22539, 60770)	30105 (18705, 63513)	-5559	0.1324
TIMP-1 (pg/ml)	50588 (45517, 57075)	50407 (44823, 55746)	-354	0.7148	50746 (42257, 57211)	48543 (43086, 54250)	-1908	0.4586
LOXL2 (ng/ml)	0.11 (0, 3.4)	0 (0, 4.3)	0	0.8125	0 (0, 1.339)	0, (0, 1.1)	0	0.9375
Adiponectin (ng/ml)	2909 (1442, 5183)	1610 (935, 4217)	-872	**0.0166**	2093 (1041, 3232)	1802 (1003, 3455)	163	0.4874

697 CHANGES IN LIVER STEATOSIS AFTER SWITCHING EFAVIRENZ TO RALTEGRAVIR: THE STERAL STUDY

Juan Macías[1], Dolores Merino[2], Francisco Téllez[3], Federico Pulido[4], Juan González-Garcia[5], Manuel Márquez[6], Antonio Rivero[7], María Mancebo[1], Juan A. Pineda[1], for the RIS-HEP09
[1]Hosp Univ de Valme, Sevilla, Spain, [2]Complejo Hospario Univ de Huelva, Huelva, Spain, [3]Hosp Univ de Puerto Real, Cádiz, Spain, [4]Hosp 12 de Octubre, Madrid, Spain, [5]Hosp Univ La Paz, Madrid, Spain, [6]Hosp Virgen de la Victoria, Málaga, Spain, [7]Hosp Univ Reina Sofia, Cordoba, Spain

Background: Hepatic steatosis (HS) is a cause of liver disease. In addition, steatohepatitis can induce liver fibrosis and accelerate fibrosis progression associated with HCV. As a consequence, the effects of antiretroviral drugs less likely to induce increases in HS in HIV/HCV coinfection need to be investigated. Because of this, we aimed at comparing the impact of switching from efavirenz (EFV) plus two nucleoside analogs (nucs) to rategravir (RAL) plus two nucs versus continuing with EFV plus two nucs on HS among HIV/HCV-coinfected patients.
Methods: This was a phase IV, open-label, randomized clinical trial (ClinicalTrials.gov: NCT01900015). HIV-infected patients, with or without detectable plasma HCV RNA, on current EFV plus two nucs were randomized 1:1 to switch EFV to RAL (400 mg BID), maintaining nucs unchanged, or to continue with EFV plus two nucs. At baseline (BL), eligible patients should show controlled attenuation parameter (CAP) values ≥238 dB/m, i.e. significant HS. Changes in HS were measured using CAP at BL, 24 and 48 weeks of follow-up.
Results: In this interim analysis, 37 patients, 19 subjects randomized to RAL and 18 to EFV, have reached 48 weeks of follow-up. The proportion of men for RAL vs. EFV groups at BL were 90% vs. 83% (p=0.939). BL HCV RNA was detectable in 74% individuals switched to RAL vs. 67% subjects continuing on EFV (p=0.874). HIV viral load was undetectable at BL in 100% for the RAL group and 94% for the EFV group (p=0.515). The BL median (Q1-Q3) values for RAL vs. EFV group were: Age, 52 (45-55) vs. 48 (47-52) years (p=0.233); body mass index, 27 (23.9-29.5) vs. 25 (23.7-26.6) Kg/m2 (p=0.503); CD4 counts, 556 (342-856) vs. 582 (371-774) cells/mcL (p=0.684); HOMA, 2.4 (1.8-4) vs. 2.2 (1.8-5.4) (p=0.949); CAP, 273 (246-303) vs. 258 (247-287) dB/m (p=0.374); liver stiffness, 6.6 (5.3-10.9) vs. 6.7 (3.8-8.4) KPa (p=0.391). The median (Q1-Q3) of the difference in CAP values between baseline and 48 weeks (ΔCAP) was -20 (-67, 15) dB/m for the RAL group and 28.5 (-18.8, 47.8) dB/m for the EFV group (p=0.019). The proportion of patients with CAP <238 dB/m at 48 weeks was 9 (47%) for the RAL arm vs. 3 (17%) for the EFV arm (p=0.049).
Conclusion: After 48 weeks, HIV-infected individuals switching from EFV to RAL showed decreases in the degree of HS, as measured by CAP, compared with those continuing with EFV. In addition, the proportion of patients without significant HS after 48 weeks was greater for those who switched from EFV to RAL.

698 OBESITY IN ANTIRETROVIRAL-TREATED HIV-INFECTED ADULTS: PREDICTORS AND COMORBIDITIES

Anchalee Avihingsanon[1], Sivaporn Gatechompol[1], Opass Putcharoen[2], Jiratchaya Sophonphan[1], Supalak Phonphithak[1], Sasiwimol Ubolyam[1], Stephen J. Kerr[1], Kiat Ruxrungtham[2], Praphan Phanunphak[1], for the HIV-NAT 006
[1]HIV-NAT, Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [2]Chulalongkorn Univ, Bangkok, Thailand

Background: Obesity predisposes to cardiovascular disease, insulin resistance, and type 2 diabetes. At the same BMI as Caucasians, Asians have a higher percentage of visceral fat with proportionately higher obesity associated mortality. We therefore determined the prevalence, predictors and outcomes of obesity among 1412 HIV-infected patients on ART for a median of 11 years.
Methods: A prospective cohort study was conducted between July 1996-August 2016 in Bangkok, Thailand. Asian criteria of obesity were used as follows: underweight (<18.5 kg/m2), normal (18.5-22.9 kg/m2), overweight (23-24.9 kg/m2) and obese (>25 kg/m2). Liver fibrosis was assessed by Fibroscan; 10 year cardiovascular risk was assessed by Framingham score. A multivariate GEE was used to calculate Odds Ratios (OR) and 95% confidence intervals (95% CI) for factors associated with developing obesity, adjusting for variables significant in univariate analysis at P <0.1.
Results: The majority of participants (62.7%) were male. The prevalence of normal BMI, overweight and obesity at last visit was 49%, 22%, and 21%, respectively. Obesity increased from 12.9% before ART to 21.4% at last visit. Compared to normal BMI, the obese group had lower VL efficacy (<50 copies/mL) (87% vs 93%, p=0.03), higher diabetes mellitus (17% vs 7%, p=0.003), hypertension (43% vs 15%, p <0.001), advanced liver fibrosis (>9.5 KPa; 24% vs 5%, P<0.001), metabolic syndrome (54% vs 16%, p<0.001), dyslipidemia (76% vs 68%, P=0.005), central obesity (98% vs 24%, p<0.001), higher Framingham scores (9.9 vs 5.4, <0.001) and higher 10 year cardiovascular risk (21% vs 14%, p<0.001). In multivariate analysis, higher baseline BMI, ever smoked, triglycerides >150 mg/dL, HDL<40 mg/dL, Age >40 years, fasting glucose >100 mg/dL, baseline CD4< 350 cells/mm3, lipodystrophy, ever taking lopinavir/r or atazanavir and abnormal waist circumference were significantly associated with developing obesity (Table).
Conclusion: Obesity is highly prevalent among ART treated Thai patients and associated with higher rates of metabolic syndrome, cardiovascular risk and liver fibrosis. Relatively low VL efficacy in obesity requires further investigation. Traditional risk factors including older age, low baseline CD4, lipodystrophy and abnormal waist circumference were associated with developing of obesity. Given the strong relationships of obesity, chronic inflammation and high risk of cardiovascular disease, weight assessment and management programs should be a part of routine HIV care.

Covariate	Univariate			Multivariate		
	OR	95%CI	P	aOR	95%CI	P
At cohort entry						
Male vs female	1.15	0.95-1.39	0.14			
BMI ≥23 kg/m^2	33.13	24-45.75	<0.001	57.2	39.62-82.57	<0.001
Ever smoked	1.2	1.0-1.45	0.05	1.24	1.01-1.54	0.044
Ever consumed alcohol	0.9	0.79-1.04	0.16			
CDC class: A,B vs C	1.15	0.88-1.49	0.32			
Cholesterol > 200 mg/dL	1.33	1.04-1.72	0.03	0.98	0.72-1.35	0.924
Triglyceride > 150 mg/dL	2.29	1.79-2.94	<0.001	1.57	1.17-2.11	0.003
HDL < 40 mg/dL	1.88	1.48-2.38	<0.001	1.8	1.36-2.39	<0.001
Glucose > 100 mg/dL	2.19	1.43-3.36	<0.001	2.09	1.28-3.42	0.003
CD4 < 350 cell/mL	1.2	0.99-1.47	0.07	1.48	1.17-1.88	0.001
HIV-RNA >5 log	1.01	0.82-1.26	0.91			
PI exposed	0.85	0.7-1.03	0.09			
Lopinavir exposed	1.13	1.07-1.19	<0.001	1.08	1.01-1.15	0.03
Atazanavir exposed	1.39	1.31-1.47	<0.001	1.33	1.23-1.44	<0.001
Lipodystrophy	1.31	1.24-1.38	<0.001	1.11	1.03-1.2	0.005
Time updated						
Age > 40 years	1.50	1.44-1.56	<0.001	1.47	1.38-1.55	<0.001
Waist circumference abnormal vs normal	1.79	1.7-1.88	<0.001	2.15	2.02-2.3	<0.001

aOR = adjusted OR

699 WOMEN GAIN MORE WEIGHT THAN MEN FOLLOWING INITIATION OF ANTIRETROVIRAL THERAPY

Sara H. Bares[1], Laura M. Smeaton[2], Ai Xu[2], Catherine Godfrey[3], Grace A. McComsey[4]
[1]Univ of Nebraska, Omaha, NE, USA, [2]Harvard Univ, Cambridge, MA, USA, [3]DAIDS, NIAID, Bethesda, MD, USA, [4]Case Western Reserve Univ, Cleveland, OH, USA

Background: Obesity is prevalent among HIV-infected individuals on antiretroviral therapy (ART). Cross-sectional studies have suggested that HIV-infected women are more likely to be overweight or obese than men. Observational studies evaluating sex differences in body mass index (BMI) increases following ART initiation are conflicting. Three ACTG US-based randomized trials (A5142, A5202 and A5257) assessed changes in BMI over 96 weeks during 2005-2013 in treatment-naïve individuals initiating ART. We performed a pooled analysis of these studies to estimate whether BMI changes in the first 96 weeks following initiation of ART differed by sex at birth.

Methods: BMI data over 96 weeks following ART initiation were compared between 760 women and 3041 men in the three contributing clinical trials. Analysis excluded participants not starting ART and women who became pregnant. Multivariable linear regression estimated the relationship between sex and change in BMI from baseline to week 96.

Results: Women were older than men (mean 40.5 vs 37.7 years), and more likely to be black, non-Hispanic (58% vs 31%). Baseline CD4 count did not differ (mean 261 cells/mm3). Mean baseline BMI was higher in women vs men (28.4 vs 25.2 kg/m2), and fewer women were categorized as normal weight (32% vs 51%). After 96 weeks, women gained an average of 1.91 kg/m2 (95% CI 1.64, 2.19), men 1.39 kg/m2 (95% CI 1.30, 1.48); p for sex difference <.001; the sex difference persisted within each baseline BMI subgroup (see Table). After adjusting for baseline age, BMI, CD4 count, HIV-1 RNA, race/ethnicity, study and ART, mean BMI change for women was on average 0.63 kg/m2 (95% CI 0.41, 0.85) more than for men (p<.001). More women moved from normal to overweight/obese BMI category (40% of normal-weight women vs. 33% of normal-weight men). Statistical interactions were observed between sex and both baseline CD4 count and baseline HIV-1 RNA and suggest that for subgroups with higher viral load and lower CD4 at baseline, the estimated BMI changes in women are even larger than the average estimated difference.

Conclusion: In this pooled analysis, HIV-1 infected women experienced a significantly greater increase in BMI following ART initiation than men. These sex differences, even for women in the obese BMI category at baseline, suggest a problem of real clinical significance to women living with HIV. Future work will explore the impact of immune activation on these observations.

Mean Body Mass Index (BMI in kg/m2) change from ART initiation to week 96					
	n (%)	Women (n=760)	Men (n=3041)	Sex difference	p-value (t-test)
Overall Observed (i.e. unadjusted)					
	3801 (100%)	1.91	1.39	0.52	<0.001
Overall Model-based (i.e. adjusted)					
				0.63	<0.001
Observed By Pre-ART Initiation BMI Category					
Underweight (< 18.5)	126 (3%)	3.51	2.12	1.4	0.016
Normal (18.5 -< 25)	1802 (47%)	2.37	1.68	0.69	0.003
Overweight (25-< 30)	1230 (32%)	1.71	1.04	0.67	<0.001
Obese (≥ 30)	643 (17%)	1.41	0.99	0.43	<0.001

700 CT FAT DENSITY REFLECTS HISTOLOGIC FAT QUALITY IN ART-TREATED, HIV-1-INFECTED ADULTS

Jordan E. Lake[1], Carlee Moser[2], Liz Johnston[2], Clara Magyar[3], Scott D. Nelson[3], Kristine Erlandson[4], Todd Brown[5], Grace A. McComsey[6]
[1]Univ of Texas, Houston, TX, USA, [2]Harvard Univ, Boston, MA, USA, [3]Univ of California Los Angeles, Los Angeles, CA, [4]Univ of Colorado, Aurora, CO, USA, [5]The Johns Hopkins Univ, Baltimore, MD, USA, [6]Case Western Reserve Univ, Cleveland, OH, USA

Background: Adipose tissue (AT) quality and quantity may independently determine metabolic health. The gold standard for determining AT quality is measurement of adipocyte size on microscopic examination of biopsy specimens. Computed tomography (CT)-quantified AT density is believed to reflect adipocyte quality (lower density=larger, less differentiated, poor quality adipocytes); however, little human data exists to support this hypothesis. Using subcutaneous abdominal AT (SAT) biopsy specimens and L4-L5 single slice CT scans from a completed trial of antiretroviral therapy (ART) initiation, we previously demonstrated CT's ability to reflect biopsy-confirmed AT quality in treatment-naïve, HIV-1-infected adults. Significant changes in fat quality and quantity may occur on ART. As such, we explored whether CT density accurately reflects AT quality in ART-treated individuals.
Methods: AIDS Clinical Trials Group study A5224s participants were included in the analysis if they remained on their original ART regimen (ABC/3TC or TDF/FTC with either EFV or RTV/ATV) and had HIV-1 RNA <50 copies/mL, subcutaneous abdominal SAT biopsy and/or CT SAT or visceral AT (VAT) data at 96 weeks. Associations between SAT density (in Hounsfield Units, HU) and mean adipocyte area (in μm2) were assessed using Spearman's correlations, and linear regression models adjusted for clinical and demographic characteristics. Correlations between SAT and VAT density were also determined.
Results: Participants (n=30) were 89% were male and 67% white non-Hispanic. Median age was 41 years, body mass index 26.0 kg/m2 and CD4+ T lymphocyte count 219 cells/mm3. After 96 weeks of ART, median SAT density was -104 HU, VAT density -90 HU and adipocyte area 2759 μm2. Mean adipocyte area correlated with SAT density (r=-0.57, p=0.003), with some variation by ART regimen (Table). This relationship persisted in models adjusting for age, race, sex, CD4+ T lymphocyte count and SAT area. SAT and VAT density also correlated with each other (r=0.55, p=0.002).
Conclusion: CT SAT density correlates with biopsy-quantified subcutaneous adipocyte size and with VAT density in ART-treated, HIV-1 infected adults. CT may be a useful tool for non-invasive assessment of AT quality in both the SAT and VAT depots, although additional studies are needed to assess ART effects and relationships between CT density and clinical measures of AT function.

701 ASSOCIATION OF NAFLD WITH ADIPOKINE AND INFLAMMATORY MARKERS DIFFERS BY HIV STATUS

Jennifer Price[1], Ruibin Wang[2], Eric Seaberg[2], Matthew Budoff[3], Lawrence Kingsley[4], Frank J. Palella[5], Mallory Witt[6], Wendy Post[2], Chloe Thio[2]
[1]Univ California San Francisco, San Francisco, CA, USA, [2]The Johns Hopkins Univ, Baltimore, MD, USA, [3]Harbor–UCLA Med Cntr, Torrance, CA, USA, [4]Univ of Pittsburgh, Pittsburgh, PA, USA, [5]Northwestern Univ, Chicago, IL, USA, [6]Los Angeles Biomed Rsr Inst at Harbor–UCLA Med Cntr, Torrance, CA, USA

Background: Adipokines and serum markers of immune activation are implicated in the pathogenesis of nonalcoholic fatty liver disease (NAFLD) in HIV-infected (HIV+) persons. We evaluated associations between NAFLD and these markers in HIV+ and HIV-uninfected (HIV-) men in the Multicenter AIDS Cohort Study (MACS).
Methods: Non-contrast CT was used to assess fatty liver (liver/spleen Hounsfield units<1) and to measure abdominal visceral adipose tissue (VAT) volume in 552 MACS participants who drank <3 alcoholic drinks/day and who were not infected with hepatitis C or B viruses. We measured adipokine and inflammatory/immune activation marker levels at the time of CT. Multivariable logistic regression was used to assess associations of biomarkers and VAT with NAFLD and to evaluate potential interactions between HIV serostatus and biomarkers.
Results: The 348 HIV+ men (89% on HAART and 82% with undetectable HIV RNA) had significantly higher levels of sCD163, CRP, ICAM-I, and TNFαR2 and significantly lower levels of adiponectin and leptin than the 204 HIV- men. The 84 men (15%) with NAFLD (47 HIV+, 37 HIV-) were more likely to be non-Hispanic white, had higher median BMI, VAT, abdominal subcutaneous tissue, HOMA-IR, and triglyceride levels and had lower HDL levels than men without NAFLD. Among the HIV- men, in fully-adjusted models including VAT, we found a higher odds of NAFLD with increasing ICAM-1 (OR 4.81, p=0.004), CRP (OR 1.41, p=0.015), and TNFαR2 (OR 5.48, p=0.004) (Table). In contrast, among the HIV+ men, only higher adiponectin was independently protective against NAFLD in fully-adjusted models (OR 0.68, p=0.033). Moreover, we found a significant negative interaction between HIV serostatus and CRP (p=0.045) and TNFαR2 levels (p=0.005), indicating that these cytokines were associated with NAFLD only among HIV- men (see Table). In an analysis restricted to the HIV+, adjustment for HIV-related factors, including current and nadir CD4, HIV RNA, and current and cumulative HAART did not alter our findings.
Conclusion: Higher pro-inflammatory cytokine levels (ICAM-1, CRP and TNFαR2) were independently associated with NAFLD among HIV- men but not among HIV+ men, in whom lower levels of adiponectin (which is anti-inflammatory) were. These findings may indicate that among HIV+ persons, diminished levels of anti-inflammatory markers may be important in the pathogenesis of NAFLD than a higher inflammatory state.

Table. Association of adipokines and markers of immune activation with nonalcoholic fatty liver disease in entire study cohort and by HIV serostatus in fully adjusted model[1]

	Entire Cohort (N=552)		HIV+ (N=348)		HIV- (N=204)		P for interaction
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	
ICAM-1*	**2.71 (1.43-5.15)**	**0.002**	1.96 (0.93-4.15)	0.079	**4.81 (1.65-13.99)**	**0.004**	0.175
Adiponectin*	**0.67 (0.50-0.90)**	**0.008**	**0.68 (0.48-0.97)**	**0.033**	0.65 (0.39-1.10)	0.111	0.901
CRP*	1.15 (0.96-1.39)	0.125	0.99 (0.78-1.25)	0.933	**1.41 (1.07-1.87)**	**0.015**	**0.045**
IL-6*	1.20 (0.92-1.58)	0.184	1.05 (0.73-1.50)	0.811	1.46 (0.96-2.22)	0.075	0.221
TNFαRII*	1.53 (0.82-2.86)	0.179	0.82 (0.38-1.76)	0.616	**5.48 (1.73-17.35)**	**0.004**	**0.005**
sCD163†	1.00 (0.89-1.13)	0.941	0.89 (0.76-1.05)	0.174	1.19 (0.98-1.43)	0.073	**0.022**
Leptin* ≤13	**0.66 (0.46-0.95)**	**0.027**	**0.63 (0.40-1.00)**	**0.049**	0.71 (0.40-1.27)	0.249	
>13	1.40 (0.82-2.39)	0.218	1.37 (0.70-2.67)	0.361	1.45 (0.64-3.31)	0.375	0.896

Odds ratios for HIV+ and HIV- were calculated using logistic regression models with a biomarkers*HIV interaction term. P for interaction tested the significance of biomarker*HIV interaction term.
Abbreviations: OR, odds ratio; CI, confidence interval
*Per 2 times increase
†Per 100 ng/mL
[1]Adjusted for MACS site, age, race, abdominal visceral adipose tissue (VAT), homeostatic model assessment of insulin resistance (HOMA-IR), *PNPLA3* genotype and (entire study cohort only) HIV serostatus.

702 PREVALENCE AND RISK FACTORS FOR HEPATIC STEATOSIS IN HIV+ PERSONS

Jessie Torgersen[1], Kaku So-Armah[2], Matthew Freiberg[3], Matthew Budoff[4], Joseph Lim[5], Adeel Butt[6], Maria Rodriguez-Barradas[7], Amy Justice[8], Jay Kostman[9], Vincent Lo Re[1]
[1]Univ of Pennsylvania, Philadelphia, PA, USA, [2]Boston Univ, Boston, MA, USA, [3]Vanderbilt Univ, Nashville, TN, USA, [4]Harbor–UCLA Med Cntr, Torrance, CA, USA, [5]Yale Univ, New Haven, CT, USA, [6]Univ of Pittsburgh, Pittsburgh, PA, USA, [7]Baylor Coll of Med, Houston, TX, USA, [8]VA Connecticut Hlthcare System, West Haven, CT, USA, [9]Philadelphia FIGHT Community Hlth Cntrs, Philadelphia, PA, USA

Background: Hepatic steatosis is highly prevalent in Western countries, but its association with HIV infection is poorly defined. Factors associated with hepatic steatosis have not been completely examined in HIV. We compared the prevalence of hepatic steatosis between HIV+ and uninfected persons and evaluated risk factors for steatosis among persons with HIV.
Methods: We performed a cross-sectional study among 171 HIV+ and 97 uninfected patients with no prior cardiovascular disease diagnosis in the Veterans Aging Cohort Study. Using non-contrast abdominal computed tomography (CT), hepatic steatosis was defined by: 1) liver-to-spleen (L/S) attenuation ratio <1 (indicates hepatic steatosis affecting >5% of liver parenchyma), and 2) liver attenuation of <40 Hounsfield Units (HU; indicates steatosis affecting ≥30% of liver parenchyma). Logistic regression was used to determine adjusted odds ratios (ORs) of steatosis associated with HIV, controlling for body mass index (BMI), diabetes, and history of alcohol abuse. Among HIV+ persons, linear regression was performed to evaluate associations between risk factors of interest (nadir CD4 count, HIV viremia, hepatitis C virus [HCV] coinfection, and hepatic fibrosis by FIB-4) and severity of steatosis by liver attenuation (in HU), after adjustment for BMI, alcohol abuse, and diabetes.
Results: The overall prevalence of hepatic steatosis was similar between HIV+ and uninfected persons when defined by L/S attenuation ratio <1 (13 [7.6%] versus 8 [8.2%]; p=0.85); however, steatosis defined by liver attenuation <40 HU was less prevalent in HIV+ patients (13 [7.6%] versus 15 [15.5%]; p=0.04). After adjustment for BMI, diabetes, and alcohol abuse, HIV was not associated with hepatic steatosis (defined by L/S attenuation ratio <1) compared to uninfected individuals (OR, 1.00; 95% CI, 0.40-2.60). Among the HIV+ group, higher BMI (p=0.01), HCV coinfection (p=0.008), and higher FIB-4 (p<0.001), but not lower nadir CD4 count (p=0.14) or HIV viremia (p=0.87), were associated with greater severity of steatosis.
Conclusion: The prevalence of hepatic steatosis, defined by abdominal CT, was similar between HIV+ and uninfected persons, though the severity of steatosis was greater among uninfected persons. HCV coinfection, higher BMI, and more advanced hepatic fibrosis were associated with greater severity of steatosis in HIV+ persons. Future studies should compare the impact of steatosis on liver outcomes among HIV+ patients.

703 LIVER STEATOSIS AND FIBROSIS IN AT-RISK EUROPEAN HIV-MONOINFECTED PATIENTS

Maud Lemoine[1], Lambert Assoumou[2], **Patrick Ingiliz**[3], Pierre-Marie Girard[4], Stephane de Wit[5], Marc-Antoine Valantin[6], Anja Huefner[7], Jacqueline Capeau[8], Dominique Costagliola[9], Georg Behrens[10]
[1]Imperial Coll London, London, UK, [2]Inst Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France, [3]Cntr for Infectiology, Berlin, Germany, [4]Hôpital Saint-Antoine, Paris, France, [5]Univ Libre de Bruxelles, Brussels, Belgium, [6]AP–HP, Paris, France, [7]Universitätsklinikum Hamburg, Hamburg, Germany, [8]Univ Pierre & Marie Curie, Paris, France, [9]Medizinische Hochschule Hannover, Hannover, Germany

Background: Nonalcoholic fatty liver disease (NAFLD) has emerged as a new concern in HIV-infected patients. The ECHAM (European Cohort on HIV, Ageing and Metabolic liver disease) Study Group aimed to assess the prevalence of NAFLD and its complications i.e nonalcoholic steato-hepatitis (NASH), fibrosis and cirrhosis in at-risk HIV-monoinfected ART-treated individuals.
Methods: This cross-sectional study conducted in seven European centers enrolled HIV-infected individuals with persistently elevated transaminases (>1.5 ULN) and/or metabolic syndrome (MS), and/or lipodystrophy without other causes of liver disease (i.e HCV or HBV coinfections or excessive alcohol intake). All patients underwent complete non-invasive metabolic and liver assessments including hepatic MRI, Fibroscan®/CAP and Fibrotest®. A liver biopsy was indicated in case of suspected significant fibrosis (≥F2) based on Fibroscan® (>7kPa) and/or Fibrotest® (≥ 0.49).
Results: Between March 2014 and November 2015, 461 individuals were screened, 442 met the inclusion criteria and 402 had full liver assessment and were further analyzed. Patients were mainly males (85%) with a median age of 55 years (IQR 50-61). The median time since HIV diagnosis was 19 years (14-24), ART duration 16 years (12-19). Nadir of CD4 count was 184 (84 – 266)/mm3. HIV viral load was<50cp/mL in 97% of cases with a median CD4 count of 630/mm3 (510-832). Of the 402 patients, 269 (67%) had a MS and 218 (54%) insulin resistance defined by HOMA index ≥2.5. Median ALT, AST and GGT levels were 34 (24-50), 29 (23-37) and 48 (29-81) IU/L, respectively. Hepatic MRI identified 257 (64%) patients with significant steatosis defined by a fat fraction >5%. Using non-invasive markers of fibrosis, 140 (34%) were classified as suspected significant liver fibrosis including 12.5% with cirrhosis. However, the concordance between Fibroscan® and Fibrotest® for the diagnosis of fibrosis was poor (kappa coefficient 13%). Of 140 patients eligible for liver biopsy, 49 accepted the procedure; their demographic and clinical characteristics were similar to those who refused biopsy. Histological analysis reported steatosis in 76%, NASH in 43%, significant fibrosis (≥F2) in 30% and cirrhosis in 2 (4%) patients.
Conclusion: Nonalcoholic HIV-monoinfected patients on ART with metabolic disorders are at high risk of liver steatosis and fibrosis. However, non-invasive markers of fibrosis should be interpreted with caution in this population. (Study registered on clinicialtrial.org, NCT02093754)

704 CHANGES IN LIVER FIBROSIS AND STEATOSIS IN HIV MONOINFECTED PATIENTS OVER 24 MONTHS

Raphael Mohr, Christoph Boesecke, Carolynne Schwarze-Zander, Jan-Christian Wasmuth, Jonel Trebicka, Jürgen K. Rockstroh
Univ Hosp Bonn, Bonn, Germany

Background: While cross-sectional studies recently have identified factors associated with hepatic fibrosis and steatosis in HIV mono-infected patients, scare data are available on their evolution. The aim of this study was to assess the changes in liver stiffness and hepatic fat accumulation over time and to evaluate possible predictive factors for hepatic fibrosis and/or steatosis development.
Methods: 344 HIV mono-infected patients underwent annual transient elastography (TE) with simultaneous determination of the controlled attenuation parameter (CAP) over a period of 24 months. The associations between LS/HS changes and demographics, metabolic data, virologic factors and antiretroviral therapy were analyzed.
Results: The prevalence of significant liver fibrosis (TE > 7.1 kPa) did not change during the study, being 10% (median LS 5.2 kPa) at enrolment and 12% (median LS 5.4 kPa) after 24 months (p = 0.868). The only factor associated with an increase of LS was a lower CD4+ level (p = 0.037). Moreover, longer cART duration protected (HR, 0.777; 95% CI, 0.712-0.847), whereas persistent HIV viral replication promoted the development of significant liver fibrosis (HR 2.430; 95% CI, 1.095-5.396). At baseline 41% of the patients had significant steatosis (CAP > 238 dB/m) vs. 54% of the patients after 24 months (p = 0.023). Over the follow-up a significant increase in overall CAP values was observed (median CAP 226 dB/m vs. 244 dB/m; p = 0.002). Factors associated with increased CAP values were higher HbA1c levels (p = 0.015), higher BMI (p < 0.001), and higher triglycerides (p = 0.012). Longer cART-naïve periods were associated with less hepatic steatosis progression (HR 0.884; 95% CI, 0.832-0.940). Importantly, antiretroviral drugs had no impact on severity of steatosis and/or fibrosis.
Conclusion: Even though prevalence of liver fibrosis in HIV patients did not change over time, our data suggest that the HI virus might directly influence hepatic fibrosis and control of HIV replication blunts fibrosis. By contrast, prevalence of steatosis significantly increased during the follow-up of 24 months. Hepatic steatosis might be triggered by metabolic factors and should be a target of treatment in the future.

705 CO-TRIMOXAZOLE PROPHYLAXIS DECREASES TUBERCULOSIS RISK AMONG ASIAN PATIENTS WITH HIV

Wen-Wei Ku[1], Awachana Jiamsakul[2], Kedar Joshi[3], Mark Kristoffer Ungos Pasayan[4], Alvina Widhani[5], Romanee Chaiwarith[6], Sasisopin Kiertiburanakul[7], Kiat Ruxrungtham[8], Ly Penh Sun[9], Wingwai Wong[1]

[1]Taipei Veterans General Hosp, Taipei, Taiwan, [2]Kirby Inst, Sydney, Australia, [3]Inst of Infectious Diseases, Pune, India, [4]Rsr Inst for Trop Med, Manila, Philippines, [5]Cipto Mangunkusumo Hospital, Univ of Indonesia, Jakarta, Indonesia, [6]Rsr Inst for Hlth Scis, Chiang Mai Univ, Chiang Mai, Thailand, [7]Mahidol Univ, Bangkok, Thailand, [8]HIV-NAT, Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [9]Univ of Hlth Scis, Phnom Penh, Cambodia

Background: Co-trimoxazole (CTX) is recommended as prophylaxis against Pneumocystis jiroveci pneumonia, malaria and other serious bacterial infections in HIV-infected patients. Despite its in vitro activity against Mycobacterium tuberculosis, the effects of CTX preventive therapy (CPT) on tuberculosis (TB) remains unclear.

Methods: Adult patients enrolled in TREAT Asia HIV Observational Database (TAHOD) cohort who have initiated combination antiretroviral therapy (cART) were included. Factors associated with new TB diagnoses after cohort entry and survival after cART initiation were analysed using Cox regression, stratified by site. CTX and isoniazid initiated within 60 days prior to TB diagnosis were not regarded as routine prophylaxis.

Results: A total of 7355 patients from 12 countries in Asia were included in the study. There were 368 new cases of TB after cohort entry with an incidence rate of 0.99 per 100 person-years (/100pys). Multivariate analyses adjusted for viral load (VL), CD4 count, body mass index (BMI), and cART duration showed that CPT had a protective effect against the development of TB (HR 0.72, 95% CI: 0.56-0.93, p=0.011). Mortality after cART initiation was 0.85/100pys with a median follow-up time of 4.63 years. Predictors of survival included age (41-50 years, HR 1.49, 95% CI: 1.05-2.13, p = 0.027; and >50 years, HR 3.90, 95% CI: 2.70-5.62, p<0.001, compared to age ≤30 years), female sex (HR 0.70, 95% CI: 0.53-0.94, p=0.017), hepatitis C co-infection (HR 1.90, 95% CI: 1.33-2.72, p<0.001), TB diagnosis (HR 2.50, 95% CI: 1.73-3.63, p<0.001), HIV viral load (≥5000 copies/mL, HR 1.59, 95% CI: 1.09-2.34, p=0.017, compared to VL <400 copies/mL), CD4 count (51-100 cells/µL, HR 0.42, 95% CI: 0.29-0.62; 101-200 cells/µL, HR 0.19, 95% CI: 0.13-0.28; and >200 cells/µL, HR 0.06, 95% CI: 0.04-0.09, all p<0.001, compared to CD4 ≤50 cells/µL) and BMI (≥25 kg/m2, HR 0.40, 95% CI: 0.24-0.68, p=0.001, compared to BMI <25 kg/m2). Patients receiving CPT had improved survival; however, the effect was not statistically significant (HR 0.78, 95% CI: 0.58-1.03, p=0.081).

Conclusion: CPT had a protective effect against new TB infection in our Asian HIV cohort. The potential preventive effect of CTX against TB during periods of severe immunosuppression should be further explored.

Table: Factors associated with new TB diagnosis after cohort entry

	No. of TB	Rate	Univariate			Multivariate		
	diagnosis	(/100 pyr)	HR	95% CI	p-value	HR	95% CI	p-value
Total	368	0.99						
HIV viral load (copies/mL)					<0.01			<0.01
<400	76	0.3	1			1		
400-999	3	0.55	1.45	0.45, 4.63	0.534	1.02	0.32, 3.26	0.979
1000-4999	9	1.24	3.07	1.51, 6.26	0.002	**2.18**	**1.06, 4.48**	**0.034**
≥5000	100	2.93	5.35	3.77, 7.60	<0.001	**2.38**	**1.63, 3.47**	**<0.001**
CD4 (cells/uL)					<0.001			**<0.001**
≤50	78	9.91	1			1		
51-100	35	4.05	0.49	0.33, 0.74	0.001	**0.57**	**0.38, 0.86**	**0.007**
101-200	77	2.18	0.33	0.24, 0.46	<0.001	**0.42**	**0.30, 0.58**	**<0.001**
>200	158	0.5	0.09	0.06, 0.12	<0.001	**0.11**	**0.08, 0.15**	**<0.001**
BMI (kg/m²)								
<25	265	1.09	1			1		
≥25	27	0.46	0.39	0.26, 0.58	<0.001	**0.46**	**0.31, 0.69**	**<0.001**
cART duration					<0.001			**<0.001**
No treatment	53	3.2	1			1		
<6 months	84	5.43	1.72	1.15, 2.58	0.008	1.08	0.70, 1.66	0.727
6-12 months	29	1.45	0.54	0.32, 0.89	0.015	**0.47**	**0.28, 0.80**	**0.005**
>12 months	202	0.63	0.33	0.24, 0.46	<0.001	**0.40**	**0.28, 0.57**	**<0.001**
Co-trimoxazole use								
No	231	0.75	1			1		
Yes	137	2.13	1.71	1.36, 2.15	<0.001	**0.72**	**0.56, 0.93**	**0.011**
Isoniazid use								
No	353	0.98	1			1		
Yes	15	1.31	1.20	0.69, 2.08	0.520	1.12	0.64, 1.97	0.684

706 ISONIAZID PREVENTIVE THERAPY INITIATION, COMPLETION, & RETENTION IN CARE IN ETHIOPIA

Andrea Howard[1], Katharine Yuengling[1], Yael Hirsch-Moverman[1], Suzue Saito[1], Tsigereda Gadisa[2], Wafaa M. El-Sadr[1], Zenebe Melaku[3]

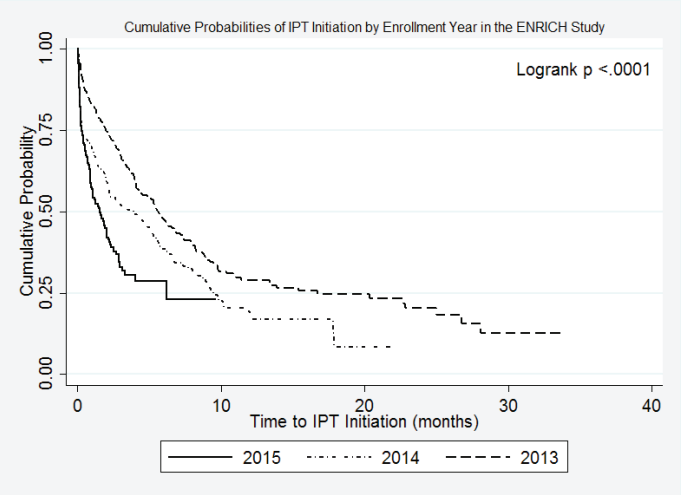
[1]ICAP at Columbia Univ, New York, NY, USA[2]ICAP at Columbia Univ, Maseru, Lesotho, [3]ICAP at Columbia Univ, Addis Ababa, Ethiopia

Background: Isoniazid preventive therapy (IPT) reduces risk of TB in people living with HIV (PLHIV); yet only 18% of PLHIV in Ethiopia received IPT in 2012. The ENRICH Study evaluated the effectiveness of a combination intervention package (CIP) to improve IPT initiation, adherence, completion and retention in care among PLHIV in Ethiopia.

Methods: Ten health centers were provided with IPT registers and site-randomized to receive CIP or standard of care (SOC). CIP included: nurse training and mentorship; IPT data review at multidisciplinary team meetings; patient transport reimbursement; and education and adherence support using interactive voice response messages and peer educators. Routine data were abstracted for newly-enrolled HIV+ patients >18 years. Interviewers administered monthly questionnaires to a subsample of patients initiating IPT to assess adherence based on 30-day recall. Generalized linear mixed models were applied to test for differences between study arms for IPT initiation, adherence, completion, and retention in care; frailty models were used to examine differences in time to IPT initiation.

Results: Among 883 patients enrolled in HIV care between 1/2013 and 11/2015 and eligible for IPT, mean age was 33.9±9.7 y; 57% were female; median (IQR) CD4 count among 756 patients with data was 247 (128-440). 60% (293/492) of CIP patients initiated IPT vs. 57% (222/391) of SOC patients (RR 1.05 95% CI 0.88-1.25). Time from enrollment to IPT

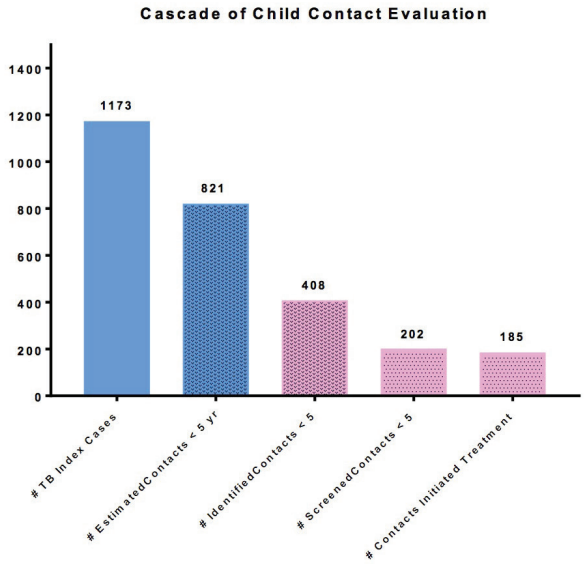
initiation was shorter for patients enrolled in 2014 and 2015 compared to those enrolled in 2013 (HR 1.42 95% CI 1.09-1.84 and HR 2.16 95% CI 1.67-2.80, respectively, p<0.0001) (Figure). IPT outcomes were available for 425/438 with sufficient follow-up time. IPT completion was achieved by 83% (200/240) in CIP vs. 80% (147/185) in SOC (RR 1.24 95% CI 0.79-1.95). Among IPT completers with ≥4 monthly questionnaires, 94% (240/256) reported on average ≥90% IPT adherence over 4-6 months of follow-up. Among 456 IPT initiators enrolled in care before 6/2015, 6 month retention was 87% (227/261) in CIP vs. 80% (155/195) in SOC (RR 1.09, 95% CI 0.89, 1.34). Among patients on concurrent IPT and ART for ≥4 months, 98% (204/208) reported on average ≥90% ART adherence over 4-6 months of follow-up.
Conclusion: High rates of IPT initiation, adherence and completion are achievable in HIV programmatic settings, even without additional enablers. Time to IPT initiation decreased over time. Retention in care and ART adherence were high in patients on concurrent IPT.



707 IPT COVERAGE IN NURSE-LED SCREENING OF CHILD TUBERCULOSIS CONTACTS

Nicole Salazar-Austin[1], Silvia Cohn[1], Grace Barnes[1], Molefi Tladi[2], Katlego Matlhaoleng[2], Neil Martinson[2], Richard Chaisson[1]
[1]*The Johns Hopkins Univ, Baltimore, MD, USA,* [2]*Perinatal HIV Rsr Unit, Soweto, South Africa*

Background: HIV and tuberculosis (TB) disproportionately affect women of reproductive age in sub-Saharan Africa, resulting in increased exposure of HIV-infected and HIV-exposed children to TB in their households. Isoniazid preventive therapy (IPT) is highly-effective at preventing TB disease in children <5 years and has long been recommended by the WHO, but a number of provider and patient challenges have hampered its implementation. To address barriers, the WHO recently recommended symptom-based screening in child TB contacts, as opposed to the traditional TST-based screening, thereby facilitating IPT initiation in child contacts.
Methods: We are conducting a cluster-randomized trial in 16 primary health clinics in the Matlosana sub-district of North West Province which are randomized to carry out child contact evaluations with either symptom-based screening or TST-based screening. We have introduced a standardized IPT file and child contact register to all 16 clinics including basic demographics and screening and treatment outcomes. TB nurses in decentralized clinics were given a baseline training on the use of the child contact file and register as well as training on the assigned screening mechanism. Feedback was provided to each TB nurse every 4-6 weeks for the first six months and then quarterly. Data was abstracted retrospectively from the index and child's file. The primary outcome is the percentage of children initiated on IPT or TB therapy. We report here the aggregate results from the training and rollout phase of the trial.
Results: During the training/rollout phase from October 1, 2015 through March 30, 2016, 1173 drug-susceptible TB index cases and 408 associated contacts <5 years were identified. Of these child contacts, 202 (50%) initiated screening and 185 (92%) initiated IPT. Contact tracing identified 0.35 contacts per case, vs. the expected 0.70 contacts per case determined in previous household-based studies in the Matlosana sub-district. Based on that expected number of contacts, we estimate 22% IPT coverage among child contacts exposed to TB in the Matlosana sub-district.
Conclusion: Clinic-based contact tracing tools under ascertain child contacts in this high-burden area. Once identified, nearly 50% of child contacts do not present to clinic for evaluation, but most children who are brought to clinic initiate IPT. Results of the randomized intervention will be determined once the second phase of the study is complete.



708 PROVISION OF IPT TO PEOPLE LIVING WITH HIV IN SWAZILAND: A RETROSPECTIVE COHORT STUDY

Munyaradzi Pasipamire[1], Batsabile Simelane[2], Kikanda Kindandi[3], Arnold Mafukidze[2], Marianne Calnan[2], Samson Haumba[2]
[1]Ministry of Hlth–Swaziland Natl AIDS Prog, Mbabane, Swaziland, [2]URC Swaziland, Mbabane, Swaziland, [3]Ministry of Hlth, Mbabane, Swaziland

Background: In 2010, the Swaziland AIDS Program (SNAP) scaled up provision of isoniazid preventive therapy (IPT) and targeted to initiate 50% of IPT eligible patients by 2015. However, national data show less than 10% IPT uptake. The low uptake is further coupled with challenges in reliable central reporting of the number of patients initiating isoniazid (INH). To estimate the uptake IPT, we evaluated the TB screening and INH provision cascade.
Methods: A retrospective cohort review of HIV positive patients aged ≥15 years was conducted from July to November 2015 at 11 purposively selected facilities. Patients who were seen between July and November 2014 were included. Patients who screened negative were assessed for IPT provision from time of screen until the date the client record was reviewed. TB diagnostic evaluation and IPT provision were assessed for those who screened positive and those who were evaluated negative respectively. IPT initiation among those completing anti-TB treatment were also assessed as recommended by the national guidelines. Cross validation with patient electronic records was also conducted. Proportions and logistic regression described and inferred findings respectively.
Results: There were 1760 clients seen at ART clinics during the period. There were 965 (55%) females, 791 (45%) males and 4 (0%) undocumented. TB screening was documented for 1710 (97%) patients with 1530 (76%) screening negative. Of these 100 (8%) were initiated on INH. Among those who screening positive (n=398), 219 (55%) had documented TB diagnostic evaluation and 61 (28%) evaluated negative for TB. Among those found to be TB negative, 6 (10%) were initiated on IPT. A total of 152 were diagnosed TB disease and were all started on anti-TB treatment. On completion of anti-Tb treatment, IPT was initiated on 24 (16%) patients. In the unadjusted model, age and history of TB diagnosis were significantly associated with the likelihood of being initiated IPT. There were no gender differences in the likelihood of initiating IPT. In the adjusted model (Table 1), those completing anti-TB treatment were 3.8 times more likely to be initiated IPT during the period compared to those who were not treated for TB [OR=3.7 (1.4- 10.4); p=0.01].
Conclusion: Initiation of INH among people living with HIV (PLHIV) was consistently low regardless of the eligibility points of interest. Eight percent among those screening negative for TB, 10% among those evaluated negative for TB and 16% among those who completed TB treatment.

Table 1: Factors associated with initiation of IPT among PLHIV

Variable	Univariate		Multiple	
	OR [95% CI]	P-value	OR [95% CI]	p-value
Sex				
Male	1 [---]		1 [---]	
Female	1.04 [0.73-1.48]	0.84	1.01 [0.43-2.35]	0.99
Prior TB treatment				
No	1 [---]		**1 [---]**	
Yes	3.67 [1.34- 10.05]	**0.01**	**3.78 [1.34- 10.40]**	**0.01**
Age (years)	1.03 [1.01- 1.04]	**<0.01**	1.02 [0.99- 1.07]	0.18

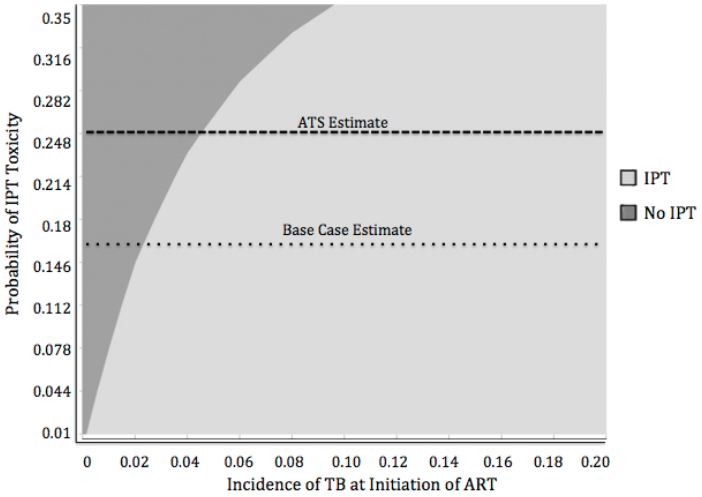
709 DOES THE BENEFIT OF IPT FOR PERSONS WITH HIV WHO CONSUME ALCOHOL OUTWEIGH THE RISK?

J. Morgan Freiman[1], Winnie Muyindike[2], Karen Jacobson[3], C. Robert Horsburgh[3], Jerrold Ellner[1], Judith Hahn[4], Benjamin Linas[3]
[1]Boston Med Cntr, Boston, MA, USA, [2]Mbarara Univ of Sci and Tech, Mbarara, Uganda, [3]Boston Univ, Boston, MA, USA, [4]Univ of California San Francisco, San Francisco, CA, USA

Background: Isoniazid preventive therapy (IPT) reduces mortality among people living with HIV (PLHIV)[1-4]. The World Health Organization recommends IPT for all PLHIV without symptoms of active TB, however, regular alcohol use is listed as a contraindication where transaminase monitoring is not routinely available[5]. This may exclude 18-35% of PLHIV in Uganda who report alcohol use despite their increased TB risk[6-9]. We postulate that the benefit of 6 months of IPT at the initiation of anti-retroviral therapy (ART) for PLHIV in Uganda who consume alcohol is greater than the risk of toxicity.
Methods: We developed a Markov model to compare the risks and benefits of ART alone to ART with 6 months IPT for PLHIV in Uganda who regularly consume alcohol. IPT provided one-year without TB risk, 6 months therapy with 6 months of extended benefit. Outcomes included grade 3 or 4 non-fatal toxicity, fatal toxicity, life expectancy,

cumulative TB cases and TB death. We selected base case parameters to replicate data for Uganda or sub-Saharan Africa. TB incidence varied from 6.6/100py in the first 3 months of ART to 1.2/100py after 3 years[10]. IPT toxicity was informed by the rate of grade 3 and 4 adverse events in the TEMPRANO trial[4]. For sensitivity analyses, we applied the risk ratio derived from increased toxicities reported in drinkers in Botswana[11] as well as that reported in the American Thoracic Society (ATS) guidelines[12].
Results: Life expectancy increased from 32.95 years with ART alone to 33.12 years with ART + IPT. IPT reduced the cumulative risk of TB by 16% and TB death by 1%, though toxicity developed in 15.2% and fatal toxicity in 0.8%. IPT provided longer life expectancy unless toxicity was > 23.3%. In a two-way sensitivity analysis of the probability of IPT toxicity and the incidence of TB at ART initiation, the base case favored IPT when TB incidence was >2%, whereas the ATS estimate favored IPT if incidence was > 4% (Figure 1).
Conclusion: In this simulation model, the risk-benefit profile of IPT among Ugandan PLHIV who regularly consume alcohol favors IPT. IPT extends life expectancy and reduces the cumulative incidence of TB and TB death compared to ART alone. However, IPT results in a drug-related mortality of 8 deaths per 1,000 people. Better data on IPT toxicity and TB incidence among PLHIV who drink could inform strategies that withhold IPT from those at the highest risk and increase the safety profile.

Figure 1. Two-way sensitivity analysis depicting the probability of isoniazid preventive therapy (IPT) toxicity and tuberculosis (TB) incidence at the initiation of antiretroviral therapy (ART). The dotted line indicates the estimated IPT toxicity derived for the base case scenario, while the dashed line indicates the IPT toxicity estimated using ATS guidelines.



710 HEPATOTOXICITY DURING IPT AND ART IN SEVERELY IMMUNOSUPPRESSED PEOPLE

McNeil Ngongondo[1], Sachiko Miyahara[2], Michael D. Hughes[2], Xin Sun[2], Amita Gupta[3], Johnstone Kumwenda[4], Thiago S. Torres[5], Gregory Bisson[6], Mina C. Hosseinipour[1], for the Adult AIDS Clinical Trials Group A5274 (REMEMBER) Study Team
[1]UNC Proj-Malawi, Lilongwe, Malawi, [2]Harvard Univ, Boston, MA, USA, [3]The Johns Hopkins Univ, Baltimore, MD, USA, [4]Coll of Med-Johns Hopkins Rsr Proj, Blantyre, Malawi, [5]Inst Nacional de Infectologia (INI-Fiocruz), Rio de Janeiro, Brazil, [6]Univ of Pennsylvania, Philadelphia, PA, USA
Background: Tuberculosis (TB) is a major cause of illness and death in people living with HIV (PLHIV). The World Health Organization recommends combining isoniazid preventive therapy (IPT) and antiretroviral therapy (ART) to prevent TB. Due to potential increased hepatotoxicity in PLHIV with severe immunosuppression that are on IPT and ART, we evaluated its occurrence in this group.
Methods: We conducted a secondary analysis of A5274— a randomized clinical trial that enrolled ART naïve PLHIV from 10 resource limited countries. We restricted analysis to one arm of the trial where participants started IPT for 24 weeks within 7 days of ART. Eligible participants were ≥13 years; had CD4 counts <50 cells/μL and did not have active TB. Participants with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 times upper limit of normal (ULN) were also eligible. Hepatotoxicity was defined as grade 3 (5.1–10.0 x ULN) or grade 4 (> 10.0 x ULN) AST or ALT or a diagnosis of hepatitis following initiation of IPT and ART. Raised pretreatment AST/ALT was defined as AST and/or ALT elevations at ≥1.25x ULN and <2.5xULN at study entry. Logistic regression was used to identify baseline risk factors for hepatotoxicity. Kaplan-Meier method was used to estimate the time to hepatotoxicity.
Results: Among 426 participants— 53% male, median age 35 years, median CD4 count 19 cells/μL—31 (7.3%) developed hepatotoxicity. Twenty of these participants discontinued IPT; four of these later restarted and 11 participants did not discontinue IPT. Two participants with hepatotoxicity died from TB; one died from hairy cell leukemia. In multivariate analysis conducted on 410 participants without missing data, the significant risk factors for hepatotoxicity were raised pretreatment AST (OR 3.6, 95% CI 1.7-7.7) and positive HBsAg at baseline (OR 4.7, 95% CI 1.7-12.9). Participants who had both of these conditions at baseline (N=5/11) had a higher risk (OR 19.9, 95% CI 5.3-74.3) and earlier onset of hepatotoxicity than participants who had none of these conditions (N=12/298) (Figure 1A and 1B).
Conclusion: The incidence of hepatotoxicity during IPT and ART was high in this population. Severely immunosuppressed PLHIV with raised pretreatment AST/ALT or positive HBsAg at baseline should have targeted closer monitoring for hepatotoxicity. They should be considered for alternative TB preventive regimens such as use of intermittent rifapentine plus isoniazid or rifampicin plus isoniazid which are less hepatotoxic.

711 THE SENSITIVITY OF QUANTIFERON-TB GOLD PLUS IS NOT AFFECTED BY HIV STATUS

L. Telisinghe[1], M. Amofa-Sekyi[2], K. Maluzi[2], D. Kaluba-Milimo[2], M. Cheeba-Lengwe[2], K. Chiwele[2], B. Kosloff[2], S. Floyd[3], S. L. Bailey[3], H. Ayles[4]
[1]Univ of Bristol, Bristol, UK, [2]Zambart, Lusaka, Zambia, [3]London Sch of Hygiene and Trop Med, London, UK, [4]London Sch of Hygiene and Trop Med, Lusaka, Zambia
Background: Interferon gamma release assays (IGRA) and tuberculin skin tests (TST) have poor sensitivity for latent TB infection (LTBI) among people living with HIV/AIDS (PLHIV). By combining CD4 and CD8 mediated immune responses, the new IGRA, QuantiFERON®-TB Gold Plus (QFT®-Plus; QIAGEN), may perform better among PLHIV. We investigated QFT®-Plus sensitivity for active TB (used as a surrogate for LTBI) in a Zambian TB clinic.
Methods: Consecutive smear or Xpert MTB/RIF positive adult (≥18years) pulmonary TB patients were recruited between 06/2015-03/2016. Venous blood was tested with QFT®-Plus. All participants were tested for HIV. Using logistic regression, factors associated with positive QFT®-Plus results were explored. Due to the small number of negative/indeterminate results, individual factors were adjusted for age alone.
Results: Among N=108 patients (median age 32 [interquartile range 27-38] years; 73% male and 63% HIV-positive), there were 90 QFT®-Plus positive, 11 negative and seven indeterminate results; sensitivity 83% (95% confidence interval [CI] 75-90%). There was no difference in sensitivity by HIV-status (HIV-positive 85% [95%CI 75-93%; n=68] and HIV-negative 80% [95%CI 64-91%; n=40]; p=0.59). Among PLHIV, sensitivity was lower when CD4 counts were <100cells/μl (50% [95%CI 16-84%]; n=8) compared with

≥100cells/µl (89% [95%CI 75-96%]; n=44) (p=0.02). In models adjusted for age, CD4 count <100cells/µl (odds ratio [OR] 0.15 [95%CI 0.02-0.96]; p=0.05), and, body mass index <18.5Kg/m2 (OR 0.27 [95%CI 0.08-0.91]; p=0.02), were associated with decreased odds of positive QFT®-Plus results. A study conducted at the same clinic in 2007 using the same methods estimated QuantiFERON®-TB Gold In-Tube (QGIT; QIAGEN) and TST sensitivity in a similar population, allowing QFT®-Plus, QGIT and TST sensitivity to be summarised. The overall QFT®-Plus sensitivity was similar to QGIT and TST, with comparable sensitivities among HIV-uninfected patients (Table). However, QFT®-Plus sensitivity was higher among PLHIV, when compared with QGIT and TST. While point estimates suggest QFT®-Plus sensitivity maybe higher than QGIT sensitivity in PLHIV with CD4 counts <100cell/µl, the small numbers in the stratum with wide CIs preclude any firm conclusions.
Conclusion: Overall QFT®-Plus sensitivity is similar to QGIT and TST, but in contrast to these, sensitivity is not affected by HIV-status. QFT®-Plus improves LTBI diagnosis among PLHIV with implications for the management of LTBI in this population.

712 LOOP-MEDIATED ISOTHERMAL AMPLIFICATION ASSAY TO DIAGNOSE TUBERCULOSIS IN RURAL UGANDA

Lydia Nakiyingi[1], Prossy Nakanwagi[2], Tifu Agaba[1], Mark Mugenyi[3], Frank Mubiru[1], Moses L. Joloba[4], Yukari C. Manabe[5]
[1]Infectious Diseases Inst, Kampala, Uganda, [2]Baylor Coll of Med Children's Fndn, Kampala, Uganda, [3]Kiboga Hosp, Kiboga, Uganda, [4]Makerere Univ, Kampala, Uganda, [5]The Johns Hopkins Univ, Baltimore, MD, USA

Background: In resource-limited settings, smear microscopy for tuberculosis (TB) diagnosis lacks sensitivity especially in HIV co-infection, resulting in undiagnosed TB and high mortality. Various molecular tests have been developed to improve TB diagnosis. The loop-mediated isothermal amplification assay (TB-LAMP test) can be staged with minimal infrastructure and is rapid, low cost and detection is with the naked eye. We assessed feasibility and accuracy of Eiken TB-LAMP test in the diagnosis of TB in a high prevalence TB/HIV rural setting in Uganda.
Methods: From October 2013-February 2014, TB-LAMP was carried out on sputum specimens from presumptive TB adults at a district hospital and two low-level health centers in Kiboga district where smear microscopy is the available routine diagnostic option and power cutoffs are frequent. TB LAMP was performed by a technician who had no prior experience in the technology, after a week of training; a simple room without bio-safety cabinet was used. MTB sputum cultures were used as reference standard.
Results: Of the 233 presumptive TB (126 at hospital; 107 at low-level health centers); 113 (48.5%) were HIV-infected; 55% male; median age 40(IQR 30-53). Compared to MTB culture, overall sensitivity and specificity of TB-LAMP were 55.4% (95 CI 44.1-66.3) and 98.0% (95 CI 94.3-99.6) respectively. In hospital setting, TB LAMP sensitivity and specificity were 62.2% (95 CI 44.8-77.5) and 97.8% (95 CI 92.1-99.7) respectively, while in low-level health centers, sensitivity and specificity were 50% (95 CI 34.9-65.1) and 98.4% (95 CI 91.2-100) respectively. Among HIV-infected participants, TB LAMP overall sensitivity and specificity were 52.3% (95 CI 36.7-67.5%) and 97.1% (95 CI 89.9-99.6) respectively compared to MTB culture. Similar accuracy indices among HIV-infected individuals were observed on stratification by setting. A summary of TB LAMP accuracy indices stratified by setting, determined using various reference standards are shown in the uploaded table.
Conclusion: In this high HIV prevalence rural setting, TB LAMP performs better than conventional smear microscopy in the diagnosis of MTB in both hospital and low-level health facilities, as well as among HIV-infected individuals. TB LAMP can easily be performed following a short training period and in the absence of sophisticated infrastructure and expertise. We recommend use of TB-LAMP test in the diagnosis of TB in rural resource-limited settings including low-level health facilities.

713 THE DIAGNOSIS OF EXTRAPULMONARY TUBERCULOSIS BY GENEXPERT MTB/RIF ASSAY IN ETHIOPIA

Mulualem Tadesse, Dossegnaw Aragaw, Alemayehu Bekele
Jimma Univ, Jimma, Ethiopia

Background: Extrapulmonary tuberculosis (EPTB) is the most common causes of death in HIV infected patients in Ethiopia. However, the diagnosis of EPTB remains challenging. World Health Organization has endorsed GeneXpert MTB/RIF for diagnosis of pulmonary TB. However, on Xpert MTB/RIF utility in EPTB, few studies have been carried out, most of these were from low-TB-burden countries, and none were from Ethiopia. We assessed the clinical utility of the Xpert MTB/RIF for the diagnosis EPTB patients in Ethiopia.
Methods: A total of 421 adult patients (>18 years) presenting to the Jimma University Specialized Hospital with suspected EPTB were included. Extrapulmonary specimens were collected from each patient on the basis of clinical criteria. Samples were divided into three portions, one for smear microscopy, second for MGIT960 culture system and third for Xpert MTB/RIF test. The diagnostic accuracy of Xpert MTB/RIF was computed using culture (MGIT 960) as the reference standard.
Results: In total, 421 extrapulmonary specimens (253 lymph node aspirate, 98 pleural fluid, 42 peritoneal fluids, 18 cerebrospinal fluids, 5 pericardial fluids, and 5 urine) were tested. Overall, 212 (50.4%) were culture-positive. Smear microscopy was positive in 112(26.6%) of 421 specimens tested. The Xpert MTB/RIF assay overall detected 214 (50.8%) of 421 samples as positive. The combined sensitivity and specificity of Xpert MTB/RIF were calculated to be 90.6% and 93.1% respectively when compared to culture. The sensitivities among the specimen types differed markedly for Xpert MTB/RIF. The highest sensitivity was documented for lymph node aspirates (93.3%) and moderate sensitivity for cerebrospinal fluids (75%), whereas the sensitivity of Xpert MTB/RIF was lowest (50%) for pleural fluids. In 13 culture-negative and 9 culture-contaminated cases, Xpert MTB/RIF remained positive. The combined sensitivity of Xpert MTB/RIF (90.6%) relative to culture was significantly higher than the sensitivity of smear microscopy (48.6%). Rifampicin resistance was detected in 6.5% of positive cases by Xpert MTB/RIF.
Conclusion: The specificity of Xpert MTB/RIF was very high across different sample types, highlighting its utility as a rule-in test for EPTB diagnosis. Xpert MTB/RIF is likely to be of greatest utility when testing lymph node aspirates and cerebrospinal fluid. In addition, Xpert MTB/RIF offered a rapid diagnosis and results would be available on the same day, avoiding loss of patients and treatment delay.

714 EXTRAPULMONARY TB AT ART PROGRAMS IN LOWER-INCOME COUNTRIES: DIAGNOSTICS AND OUTCOMES

Kathrin Zürcher[1], Marie Ballif[1], Sasisopin Kiertiburanakul[2], Marcel Yotebieng[3], Beatriz Grinsztejn[4], Denna Michael[5], Henri Chenal[6], Matthias Egger[1], April C. Pettit[7], Lukas Fenner[1]
[1]Inst of Social and Preventive Med, Univ of Bern, Bern, Switzerland, [2]Mahidol Univ, Bangkok, Thailand, [3]The Ohio State Univ, Columbus, OH, USA, [4]Inst Nacional de Infectologia (INI-Fiocruz), Rio de Janeiro, Brazil, [5]Natl Inst for Med Rsr, Kisesa HDSS, Mwanza, Tanzania, United Republic of, [6]CIRBA, Abidjan, Côte d'Ivoire, [7]Vanderbilt Univ, Nashville, TN, USA

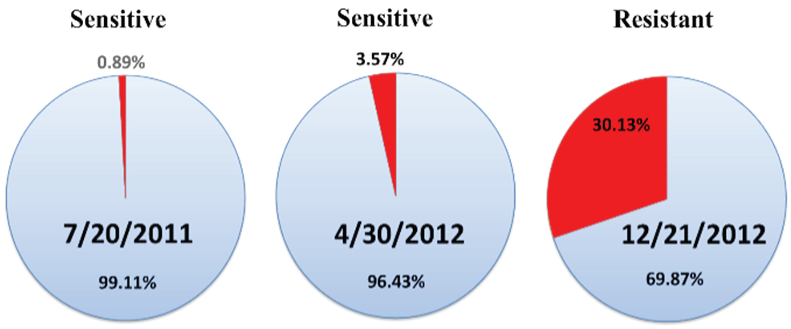
Background: Extrapulmonary tuberculosis (EPTB) is difficult to confirm bacteriologically and requires specific diagnostic capacities. We studied diagnostic modalities and clinical outcomes of EPTB compared to pulmonary tuberculosis (PTB) among HIV-positive adults.
Methods: We collected patient data from HIV/TB co-infected adults (≥16 years) from antiretroviral (ART) programs participating in the IeDEA network in Africa, Asia/Pacific and Central/South America between 2012 and 2014. We categorized TB as PTB (dominant site) and EPTB only. We used multivariable logistic regression to assess association of 1) clinical factors with EPTB and 2) EPTB with clinical outcomes, adjusted for age, sex, history of TB, CD4 cell counts, considering sites heterogeneity.
Results: We analysed 2,751 HIV/TB co-infected adults. The median age was 38 years (interquartile range [IQR] 32-45); 1,129 (41%) were female. Of these, 2,103 (76%) had PTB and 648 (24%) EPTB only (Table). At TB treatment start, patients with EPTB had lower median CD4 cell counts compared to PTB (105 vs. 118 cells/µl). Among EPTB patients, the most frequently involved organs were lymph nodes (25%), pleura (15%), abdomen (11%), and meninges (7%, Table). Available diagnostic tests were less frequently used in EPTB compared to PTB patients (58% vs. 80%), whereas in all other cases diagnosis was made based on clinical symptoms. Among EPTB patients, smear microscopy was the most commonly used diagnostic test (49%), followed by culture (13%), and Xpert (3%). Bacteriologic confirmation (culture, smear, Xpert, other molecular tests) was obtained in 837 (40%) of PTB, but only in 103 (16%) of EPTB cases; with the highest proportions of confirmed cases in lymph nodes (30%), meninges (19%), abdomen (14%), joint/bones (11%), pleura (13%), and others (13%). Among patients with CD4 <50 cells/µL, the risk of EPTB was significantly higher than PTB (adjusted odd ratio [aOR] 1.3, 95% confidence interval [CI] 1.1-1.6). EPTB overall was not associated with higher mortality compared to PTB (aOR 1.0, 95% CI 0.7-1.6), but meningitis was (aOR 2.1, 95% CI 1.3-3.3). Successful outcomes (cured/treatment completed) were as frequent among EPTB compared to PTB cases (aOR 1.1, 95% CI 0.8-1.3).

Conclusion: Diagnosis of EPTB at ART programs in lower income countries was mainly based on clinical symptoms. Strengthening of diagnostic services is needed to improve clinical management of EPTB, particularly in patients with low CD4 cell counts and severe forms.

715LB LOW-LEVEL M. TB GENOTYPIC HETERORESISTANCE PREDICTS PHENOTYPIC DRUG RESISTANCE

John Z. Metcalfe[1], Elizabeth Streicher[2], Christopher Allender[3], Darrin Lemmer[3], Rebecca Colman[4], Grant Theron[2], Rob Warren[2], David M. Engelthaler[3]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Stellenbosch Univ, Tygerberg, South Africa, [3]Translational Genomics Rsr Inst, Flagstaff, AZ, USA, [4]Univ of California San Diego, San Diego, CA, USA

Background: Tuberculosis (TB) accounts for one in three deaths among persons living with HIV, and multidrug-resistant TB (MDR-TB) imposes major human and programmatic costs. Resistance to fluoroquinolones (FQ) and second-line injectable (SLI) medicines, the backbone of most MDR-TB regimens, occurs during treatment in up to 15% of patients. Yet, little attention has been given to the evolutionary events occurring before development of phenotypic resistance. We hypothesized that high-resolution quantification of "micro-heteroresistance" (resistant subpopulations <5% of the total M. tuberculosis (M.tb) population, beneath the threshold of current commercial molecular TB assays) would predict later acquisition of full FQ and SLI resistance.
Methods: Next-generation sequencing (NGS) was performed on 145 serial MGIT 960 isolates obtained from 19 patients with MDR-TB acquiring additional resistance over 3-78 months in South Africa, 2008-2015. Single Molecule-Overlapping Reads (SMOR) is a targeted NGS approach able to reduce sequencing error by orders of magnitude, from ~1% for a high GC content organism to an M.tb–specific resolution of ~0.01%. We used SMOR to monitor proportions of single-nucleotide polymorphisms (SNPs) at specific loci within three gene regions corresponding to FQ (gyrA) and SLI (rrs, eis) resistance. Phenotypic resistance was defined by Middlebrook 7H11 indirect proportion method with WHO-recommended critical concentrations.
Results: At each serial time point, 1-10 resistance-conferring mutations were transiently detected in each target region in the same sputum specimen, though a single mutant ultimately became dominant in the majority (95%) of cases corresponding to acquisition of phenotypic resistance. Based on an average sequencing depth of 55,000X, 139 (39%) and 90 (25%) of 355 total SNPs detected within the target regions occurred at frequencies below 5% and 1%, respectively. Micro-heteroresistance (<5%) to FQs (gyrA) and SLIs (rrs, eis) was detected among 26% (5/19) and 42% (8/19) of patients, respectively, a median of 6 months prior to sputum sample collection for which phenotypic resistance was ultimately confirmed (Figure).
Conclusion: Small, previously undetectable M.tb subpopulations may be early precursors to phenotypic resistance. Detection and monitoring of micro-heteroresistance with tabletop NGS platforms could transform clinical management through early individualized treatment regimens and prompt reassessment of ineffective treatments.



Sample Date	Resist	Amino-glycoside Phenotype	*rrs* SNP (% resistant)
10/1/2008	MDR	S	none
11/19/2008	MDR	S	none
1/19/2010	MDR	S	none
7/20/2011	MDR	S	1401G (0.89%)
4/30/2012	Pre-XDR	S	1401G (3.57%)
12/21/2012	XDR	R	1401G (30.13%)

Figure. Representative drug resistance acquisition demonstrating early micro-heteroresistance followed by phenotypic aminoglycoside resistance in a single patient. Phenotypic DST is noted above each pie chart, with resistant fraction in dark red.

716LB HUMAN AND MOUSE HEMATOPOIETIC STEM CELLS ARE A DEPOT FOR DORMANT M. TUBERCULOSIS

Julia Tornack[1], Stephen Reece[1], **Wolfgang Bauer**[2], Alexis Vogelzang[1], Silke Bandermann[1], Ulrike Zedler[1], Georg Stingl[2], Stefan Kaufmann[1], Fritz Melchers[1]
[1]Max Planck Inst for Infection Bio, Berlin, Germany, [2]Med Univ of Vienna, Vienna, Austria

Background: An estimated third of the world's population is latently infected with Mycobacterium tuberculosis (Mtb), with no clinical signs of tuberculosis (TB), but lifelong risk of reactivation to active disease. The niches of persisting bacteria during latent TB infection remain unclear. We tested the hypothesis that in LTBI Mtb bacteria acquire a non-replicating state inside resting, long-term repopulating pluripotent hematopoietic stem cells (LT-pHSCs)
Methods: qPCR was used on peripheral blood pHSC isolated from patients with LTBI to detect Mtb sequences MPB64 and IS6110. qPCR and CFU assays were also used to detect Mtb sequences in different organs as well as pHSC in a mouse model of latent TB infection. Cytospins were used to visualise Mtb in pHSC. RT-PCR was used to detect the expression of Mtb dormancy genes in human and mouse pHSC. Intratracheal administration of Mtb-infected pHSCs was employed to demonstrate reactivation of TB in mice.
Results: We detect Mtb DNA in peripheral blood selectively in long-term repopulating pluripotent hematopoietic stem cells (LT-pHSCs) as well as in mesenchymal stem cells from latently infected human donors. In mice infected with low numbers of Mtb, that do not develop active disease we, again, find LT-pHSCs selectively infected with Mtb. In human and mouse LT-pHSCs Mtb are stressed or dormant, non-replicating bacteria. Intratracheal injection of Mtb-infected human and mouse LT-pHSCs into immune-deficient mice resuscitates Mtb to replicating bacteria within the lung, accompanied by signs of active infection.
Conclusion: We conclude that LT-pHSCs, together with MSCs of Mtb-infected humans and mice serve as a hitherto unappreciated quiescent cellular depot for Mtb during latent TB infection.

717 RISK FACTORS FOR DEATH IN ADVANCED HIV-INFECTED ADULTS IN AN EMPIRIC TB THERAPY TRIAL

Gregory Bisson[1], Ritesh Ramchandani[2], Sachiko Miyahara[2], Xin Sun[2], Jing Bao[3], Amita Gupta[4], Mina C. Hosseinipour[5], Johnstone Kumwenda[6], for the Adult AIDS Clinical Trials Group A5274 (REMEMBER) Study Team
[1]Univ of Pennsylvania, Philadelphia, PA, USA, [2]Harvard Univ, Boston, MA, USA, [3]NIH, Bethesda, MD, USA, [4]Johns Hopkins Univ, Baltimore, MD, USA, [5]Univ of North Carolina Proj–Malawi, Lilongwe, Malawi, [6]Malawi Coll of Med–Johns Hopkins Univ Rsr Proj, Blantyre, Malawi

Background: Many HIV-infected individuals present for care with advanced HIV disease. These patients are at high risk of death after antiretroviral therapy (ART) initiation, but risk factors for death in those with advanced HIV are unclear. We used data from a trial of empiric TB therapy to evaluate pre-ART risk factors for early mortality and to test the hypothesis that decreased early CD4 count response to ART is associated with mortality between weeks 4 and 48.

Methods: We used data from a multi-site randomized trial in HIV-infected adults initiating ART with CD4 counts <50 cells/mm3 to evaluate risk factors for death within 48 weeks after ART initiation. Cox proportional hazards models were fit to evaluate characteristics present at baseline and at 4 weeks after ART initiation, including the week 4 CD4 cell response and new opportunistic infections (OIs).
Results: Of 850 enrolled, the median pre-ART CD4 count was 18 cells/mm^3. Of 837 included in the baseline analysis, 66 died. Baseline risk factors for death included lymphadenopathy, marginally lower CD4 count, lower albumin, and lower hemoglobin (Table). Among 746 with complete data at week 4, the median change in CD4 count and viral load from week 0 to 4 for those who died (n=43) vs. survivors were 26 vs. 56 cells/mm^3 and -2.7 vs. -2.7 log $_{10}$ copies/mL, respectively (Table). Each 20 unit lower 4-week change in CD4 count was associated with a 25% increased risk of post week-4 mortality (adj. HR 1.25, 1.06-1.47). OIs newly detected by week 4 also increased risk of post week-4 mortality (adj. HR 2.76, 1.11-6.88).
Conclusion: Sub-optimal immunologic response and newly diagnosed OIs during the first month of ART are associated with death in the first year after ART initiation. Strategies to detect OIs and improve early immune response warrant further investigation.

Table: Baseline Characteristics and Early Mortality in Advanced HIV-infected Adults on Antiretroviral Therapy

		Death by Week 48			
Characteristic		Yes (N=66)	No (N=771)	Adjusted HR (95% CI)[1,2]	N (no. events)
Hemoglobin (g/dL)	Median (IQR)	10.6 (8.8, 11.8)	11.3 (10.1, 12.6)	1.33 (1.17-1.51)	837 (66)
Absolute CD4 count	Median (IQR)	14.5 (7.0, 19.0)	19 (9, 33)	1.46 (1.20-1.78)[5]	837 (66)
log 10 HIV-1 RNA/mL	Median (IQR)	5.4 (4.9, 5.9)	5.3 (4.9, 5.7)	0.86 (0.60-1.24)	837 (66)
Sex, Female	N (%)	30 (45%)	361 (47%)	1.02 (0.61-1.72)	837 (66)
Albumin (g/L)	Median (IQR)	33.0 (28.0, 36.7)	37.0 (32.1, 41.0)	1.08 (1.03-1.13)	834 (66)
Enlarged axillary/cervical lymph nodes	N (%)	11 (17%)	67 (9%)	2.15 (1.11-4.17)	829 (64)
Any diagnosed WHO stage 3 or 4 condition	N (%)	29 (44%)	287 (37%)	1.05 (0.63-1.73)	837 (66)
Post-Baseline Assessments[4]		**Yes (N=43)**	**No (N=703)**		
Change in CD4 Count from Week 0 to Week 4	Median (IQR)	26 (3, 43)	56 (22, 96)	1.25 (1.06-1.47)[5]	746 (43)
Change in log 10 HIV-1 RNA from Week 0 to Week 4	Median (IQR)	-2.7 (-3.1, -0.4)	-2.7 (-3.0, -2.4)	0.50 (0.35-0.74)	746 (43)
New WHO Stage 3 or 4 Conditions by Week 4 (Yes)	N (%)	6 (14.0%)	37 (5.3%)	2.76 (1.11-6.88)	746 (43)

1 Hazard ratios for continuous variables are given per unit *decrease*, unless otherwise noted
2 Hazard ratios adjusted for age, sex, BMI (categorical), hemoglobin, CD4 count, and log 10 HIV-1 RNA/mL
3 Hazard ratio is per 10 unit decrease
4 Post-baseline variables adjusted for all covariates in footnote 2, and all post-baseline variables in table
5 Hazard ratio is per 20 unit decrease

718 DOES TIME TO ART INITIATION IMPACT EARLY RESPONSES TO DR-TB TREATMENT?

Erika K. Mohr[1], Johnny Daniels[1], Odelia Muller[1], Bongani Chabalala[1], Jennifer Hughes[1], Virginia de Azevedo[2], Amir Shroufi[3], Sarah Jane Steele[3], Gabriella Ferlazzo[3], Laura Trivino Duran[1]
[1]MSF, Khayelitsha, Cape Town, South Africa, [2]City of Cape Town Dept of Hlth, Cape Town, South Africa, [3]MSF, Cape Town, South Africa
Background: Morbidity and mortality among RR-TB patients co-infected with HIV can be reduced by anti-retroviral treatment (ART). There is limited evidence on the best time to initiate ART following RR-TB treatment initiation.
Methods: We conducted a retrospective analysis of pulmonary RR-TB patients, co-infected with HIV who initiated treatment in Khayelitsha, South Africa, January 2014-December 2015. Culture conversion at 6-months was stratified by time of ART initiation and chi squared tests and logistic regression analyses were conducted to ascertain statistically significant differences.
Results: Of 375 patients initiated treatment for pulmonary RR-TB, 286 (76.3%) were HIV-infected; 240 were culture-positive at treatment initiation, had available laboratory information and included. Nearly half of the patients (112, 46.7%) initiated ART before RR-TB treatment; these patients were on ART for a median time of 8.4 (IQR 1.6-28.2) before RR-TB treatment. Twenty (8.3%) patients never initiated ART. Among patients who initiated ART following RR-TB treatment (108, 45.0%) median time to ART initiation was 3.9 weeks (IQR 2.4-5.2); 21 (8.8%), 70 (29.2%) and 17 (7.1%) patients initiated ART within <=2 weeks, 2-8 weeks or >8 weeks (median 14.7 weeks (IQR 12.6-24.0)), respectively. Mortality within 6-months was significantly higher among those that never initiated ART (8/20, 40.0%) compared to those that ever initiated ART (24/196, 12.2%) (OR 5.4, 95% CI 2.0-14.7, p=0.001). Among patients still alive at 6-months, there were no significant differences in the proportions of patients with culture conversion if ART was initiated after RR-TB treatment (p=0.90). Additionally, those who never initiated ART had 4.3 times the odds (95% CI 1.3-14.2, p=0.016) of being culture positive at 6-months (7/12, 58.3%) compared to those who ever initiated ART (48/196, 24.5%); overall, 26.4% (55/208) of patients remained culture positive at 6-months.
Conclusion: Despite universal access to ART in South Africa, some RR-TB patients never receive ART increasing their risk of early mobility and mortality. Clinical factors impacting time to culture conversion among those who initiate ART following RR-TB treatment need to be investigated in more detail. Over ¼ of the cohort was still culture positive following 6-months of RR-TB treatment; there is an urgent need for improved RR-TB regimens, additionally ART initiation among RR-TB patients should be prioritized.

719 HIV-RELATED TB TREATMENT INTERMITTENCY IN THE CONTINUATION PHASE AND MORTALITY

Brenda Crabtree-Ramírez[1], Cathy Jenkins[2], Bryan E. Shepherd[2], Karu Jayathilake[2], Valdilea Veloso[3], Eduardo Gotuzzo[4], Claudia P. Cortes[5], Denis Padgett[6], Catherine McGowan[2], Timothy R. Sterling[2]
[1]Inst Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico, Mexico, [2]Vanderbilt Univ, Nashville, TN, USA, [3]Oswaldo Cruz Fndn–Fiocruz, Rio de Janeiro, Brazil, [4]Univ Peruana Cayetano Heredia, Lima, Peru, [5]Univ of Chile, Santiago, Chile, [6]Hosp Seguro Social, Tegucigalpa, Honduras
Background: The 2016 ATS/CDC/IDSA tuberculosis (TB) treatment guidelines recommend daily TB treatment in both the intensive and continuation phases of treatment in HIV-infected persons to decrease the risk of relapse and acquired drug resistance. However, guidelines vary across regions and countries, and treatment is given 7, 5, 3, or 2 days/week. The effect of TB treatment intermittency in the continuation phase on mortality in HIV-infected persons is unknown; we are unaware of clinical trials addressing this issue.
Methods: An observational cohort study was performed of HIV-infected adults treated for TB with standard therapy (2-month initiation phase of daily isoniazid, rifampin, pyrazinamide ± ethambutol) and continuation phase of isoniazid and rifampin, administered concomitantly with antiretroviral therapy (ART) at participating Caribbean, Central and South America network for HIV epidemiology (CCASAnet) sites (Argentina, Brazil, Chile, Honduras, Mexico, Peru) between 2000-2013. Known CD4 at TB diagnosis and timing of ART and TB treatment were also inclusion criteria. Kaplan-Meier and Cox proportional hazards methods compared time to death between groups.
Results: 527 TB/HIV patients met inclusion criteria: 245 (46%) received TB treatment 7 days/week, 16 (3%) 5 days/week, 84 (16%) 3 days/week, and 182 (35%) 2 days/week in the continuation phase. Intermittency varied by site: 182 / 261 (70%) of patients receiving continuation phase treatment 5-7 days/week were from Brazil, and 209 / 266 (79%) receiving treatment 2-3 days/week were from Peru. The crude risk of death was lower among those receiving treatment 5-7 vs. 2-3 days/week (P<0.001) (Figure). After adjusting

for age, sex, CD4, ART use at TB diagnosis, and site of TB disease (pulmonary vs. extrapulmonary), mortality risk tended to be lower for those treated 5-7 days/week (HR 0.62, 95%CI 0.38, 1.04; P=0.07). However, after also stratifying by clinic site, there was no protective effect (HR 1.60, 95%CI 0.64-4.00; P=0.31).
Conclusion: TB treatment 5-7 days/week appeared to be associated with decreased risk of death compared to TB treatment 2-3 days/week in the continuation phase. However, although variation in TB treatment intermittency by country permitted this comparison, the results could have been driven by other differences between clinic sites. Prospective randomized trials are needed to more clearly assess optimum TB treatment frequency during the continuation phase in TB/HIV populations.

720 IMPACT OF INH ADHERENCE ON TB INCIDENCE AND MORTALITY BY WEEK 96 IN ACTG 5274 TRIAL

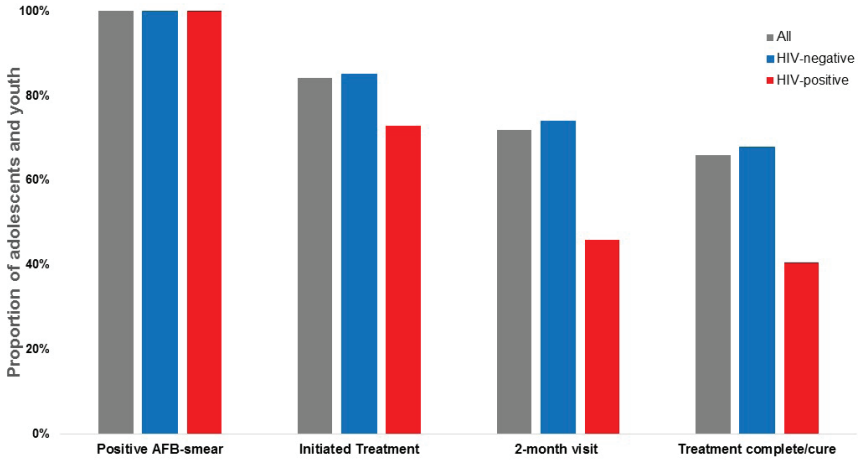
Amita Gupta[1], Xin Sun[2], Sachiko Miyahara[2], Mitch Matoga[3], Deborah Langat[4], Cynthia Riviere[5], Gregory Bisson[6], Johnstone Kumwenda[7], Mina C. Hosseinipour[3], for the ACTG A5274/REMEMBER Study Team
[1]Johns Hopkins Univ, Baltimore, MD, USA, [2]Harvard Univ, Boston, MA, USA, [3]Univ of North Carolina Proj–Malawi, Lilongwe, Malawi, [4]KEMRI/Walter Reed Proj, Kericho, Kenya, [5]Les Cntrs GHESKIO, Port-Au-Prince, Haiti, [6]Univ of Pennsylvania, Philadelphia, PA, USA, [7]Malawi Coll of Med–Johns Hopkins Univ Rsr Proj, Blantyre, Malawi
Background: TB is a major cause of morbidity and mortality in low- and middle-income countries despite the use of antiretroviral therapy (ART). The A5274/REMEMBER trial team previously reported that a strategy of Empiric 4-drug TB therapy +ART provided no additional benefit in reducing mortality within 24 weeks after ART initiation compared to INH preventive therapy (IPT)+ART. We now present the 96 weeks results.
Methods: In this multi-country randomized clinical trial, HIV-infected individuals with CD4<50 cells/mm3 were screened using a TB symptom screen, locally available diagnostics, and GeneXpert when available. Randomization was stratified by CD4 (<25 vs. ≥25 cells/mm3) and poor prognostic factors (BMI<18.5, HGB<8 g/dL, and recent hospitalization). To evaluate the effects of the intervention on longer-term outcomes, Kaplan-Meier estimates of the probabilities of death and confirmed/probable TB by week 96 were compared using a Z-test. In addition, Cox proportional hazards models were used to evaluate the association between TB medication adherence through week 24 (assessed via ACTG adherence questionnaire) and death or TB by week 96.TB adherence was defined as the number of visits with 100% adherence divided by the number of visits with available adherence assessments over all visit weeks up to week 24.
Results: Of 850 enrolled, 53% were male, 90% black, median age 36 years, and median baseline CD4 18 cells/mm3. At week 96, there was no statistical difference in mortality between the Empiric and IPT arms (10.1% vs. 10.5%, respectively); absolute risk difference 0.4% (95% CI: -3.8%, 4.6%; p=0.86). At week 96, the Empiric arm had more TB compared to the IPT arm (6.1% vs. 2.7%, respectively); absolute risk difference -3.4% (95% CI:-6.2%, -0.6%; p=0.02; unchanged in competing risk analysis). The hazard of death was 23% and 20% lower per 10% increase in the proportion of 100% adherence in the Empiric and IPT arms, respectively (p<0.01). Adherence had no effect on TB in the Empiric arm (p=0.44). However, hazard of TB was 17% lower per 10% increase in the proportion of 100% IPT adherence (p=0.03).
Conclusion: In this population of participants with advanced HIV, adherence to both empiric TB therapy and IPT was associated with improved survival. Adherence to IPT was associated with reduced risk of developing TB, but adherence to empiric TB therapy was not. Supporting IPT+ART initiation and adherence are critical to preventing the high TB incidence and mortality observed in those with advanced HIV.

721 WITHDRAWN

722 OUTCOMES ACROSS THE TUBERCULOSIS TREATMENT CASCADE AMONG ADOLESCENTS IN HAITI

Lindsey Reif[1], Rachel Bertrand[2], Eric Kutscher[3], Vanessa Rivera[3], Pierrot Julma[2], Serena Koenig[4], Jean W. Pape[3], Daniel Fitzgerald[3], Margaret McNairy[3]
[1]Columbia Univ, New York, NY, USA, [2]GHESKIO, Port-au-Prince, Haiti, [3]Weill Cornell Med, New York, NY, USA, [4]Harvard Univ, Boston, MA, USA
Background: Limited data are available on tuberculosis (TB) treatment outcomes among adolescents, especially among HIV co-infected adolescents. We describe the TB treatment cascade including diagnosis, treatment initiation, retention in care and treatment outcomes among adolescents with smear-positive disease, stratified by HIV status at the GHESKIO clinic in Port-au-Prince, Haiti.
Methods: Adolescents and youth ages 10-24 who were diagnosed with smear-positive TB and tested for HIV at the GHESKIO TB clinic between January 2011 and October 2014 were included. Outcomes across the treatment cascade were stratified by HIV status including: 1) diagnosis of smear-positive TB, 2) treatment initiation, 3) retention at 2 months, and 4) treatment completion/cure. Cure was defined as having no positive smear at 2, 5, and 6 month tests. Treatment abandonment was defined as no clinic visit after 5 months of diagnosis, and treatment failure was defined as a smear-positive test after 5 months of treatment. Death was ascertained from medical records. Differences were assessed by Chi-square test.
Results: A total of 1,005 individuals were diagnosed with TB, of whom 41% were female, median age 20 (IQR 18-23), and 64% lived in a slum-area of Port-au-Prince. Seventy-four (7%) were HIV-positive at the time of TB diagnosis, with a median CD4 cell count of 332 cells/mL (IQR 194-558) at enrollment. Outcomes at each step in the cascade comparing HIV-positive vs. HIV-negative participants include: 73% versus 85% started treatment (p =.006), 46% versus 74% were retained at 2 months (p<.001), and 41% versus 68% completed treatment/cured (p=.002) (Figure 1). Treatment abandonment was associated with being HIV-positive (p<.001). There was no significant difference among HIV-positive and HIV-negative adolescents in treatment failure (0% versus 1%) or death (4% versus 1%). Among 846 patients who started treatment, 791 (79%) started the same day as diagnosis. Participants who started treatment the same day as diagnosis were more likely to have a treatment complete/cure outcome (p <.001).
Conclusion: HIV-positive adolescents and youth are at increased risk for poor TB treatment outcomes and are in urgent need of interventions to strengthen retention and adherence. The greatest loss from the adolescent TB treatment cascade occurred between diagnosis and treatment initiation. Interventions including same-day TB treatment initiation can improve the proportion of adolescents with positive outcomes.

Figure 1. TB Treatment Cascade Among Adolescents and Youth Ages 10-24 in Haiti



All N(%)	1,005 (100%)	846 (84%)	722 (72%)	662 (66%)
HIV-Negative	931 (100%)	792 (85%)	688 (74%)	632 (68%)
HIV-Positive	74 (100%)	54 (73%)	34 (46%)	30 (41%)

723LB WITHDRAWN

724LB EFFICACY OF BEDAQUILINE, PRETOMANID, MOXIFLOXACIN & PZA (BPAMZ) AGAINST DS- & MDR-TB

Rodney Dawson[1], **Kendra Harris**[2], Almari Conradie[2], Divan Burger[3], Stephen Murray[4], Carl Mendel[2], Mel Spigelman[2]
[1]Univ of Cape Town, Mowbray, South Africa, [2]Global Alliance for TB Drug Development, New York, NY, USA, [3]QuintilesIMS, Bloemfontein, South Africa, [4]Mallinckrodt Pharmaceuticals, Bedminster, NJ, USA

Background: New anti-tuberculosis (TB) regimens are needed to treat drug sensitive (DS) and multi-drug resistant (MDR) TB. NC-005 is an ongoing Phase 2b open-label, partly randomized trial investigating the bactericidal activity of combinations of bedaquiline (Bloading dose/tiw or B200mg), pretomanid (Pa200mg), moxifloxacin (M400mg) and pyrazinamide (Z1500mg) in the first 8 weeks of treatment of DS-TB or MDR-TB.

Methods: Newly diagnosed patients with DS or MDR, smear positive pulmonary TB were enrolled. DS-TB patients were randomized to receive either $B_{\text{loading dose/tiw}}$PaZ, B_{200mg}PaZ or HRZE. MDR-TB patients received B_{200mg}PaMZ (BPaMZ). The primary outcome was bactericidal activity measured by the rate of change in time to sputum culture positivity (TTP) over 8 weeks of treatment. Upon treatment completion, all patients were referred to the local community TB clinic for treatment according to National TB Guidelines, and were scheduled to attend regular follow-up visits for 24 months. Safety was assessed by monitoring the incidence and severity of treatment emergent adverse events (TEAEs).

Results: Between 23 October 2014 and 6 May 2016, 180 subjects with DS-TB and 60 subjects with MDR-TB were enrolled at ten sites in South Africa, Tanzania and Uganda. 218 subjects completed treatment and were followed through the Day 140 follow-up visit. Among all treatment arms, BPaMZ showed the highest bactericidal activity as assessed by TTP for Days 0-56 (5.302, 95% BCI [4.518-6.157]), followed by that of B_{200mg}PaZ (5.223, 95% BCI [4.526;5.947]), $B_{\text{loading dose/t.i.w}}$PaZ (4.906, 95% BCI [4.274; 5.585]) and HRZE (4.016, 95% BCI [3.520; 4.499]). The differences in bactericidal activity of BPaMZ, B_{200mg}PaZ and $B_{\text{loading dose/t.i.w}}$PaZ treatment arms versus HRZE were statistically significant. While 81.7% of patients had at least one TEAE, only 5 patients (2.1%) had a serious drug-related TEAE (2 in $B_{\text{loading dose/t.i.w}}$PaZ, 2 in BPaMZ, and 1 in HRZE). Long-term safety follow-up out to 24 months post-treatment completion is ongoing.

Conclusion: The BPaMZ regimen in MDR-TB patients resulted in the highest level of bactericidal activity among all treatment arms. The BPaZ regimen was well tolerated and showed significantly higher bactericidal activity in DS-TB patients compared to HRZE. BPaZ and BPaMZ represent promising, simplified regimens to treat both DS-TB and MDR-TB.

725 TUBERCULOSIS IN SOUTH AFRICA IS MORE CONCENTRATED BY RACE THAN POVERTY

Eran Bendavid, Lea Prince, Douglas K. Owens, Jeremy D. Goldhaber-Fiebert, Jason R. Andrews
Stanford Univ, Stanford, CA, USA

Background: Partly fueled by the HIV epidemic, the prevalence and incidence of tuberculosis (TB) is higher in South Africa than any other country. It is known that the burden of TB is not evenly distributed, but the relative importance of race, socioeconomic status (SES), place of residence, and community SES in driving disparities in TB risk is not understood.

Methods: We analyze data from the South Africa General Household Survey (2002–2014, n=1.2 million) to characterize the risk of TB. Respondents who indicated they had "TB or severe cough with blood" in the prior month were analyzed as prevalent cases (HIV status was not reliably reported). We use logistic regressions to predict risk of TB by household SES, race, community SES (median SES of all households in a primary sampling unit), place of residence, gender, age, and year and province fixed effects. SES is based on a household level factor analysis of floor and roof materials, toilet type, and primary cooking fuel. We included community SES given the putative importance of local environments in the transmission of TB.

Results: Between 2002 and 2014, the overall prevalence of TB was 570 per 100,000 people, increasing from 590 in 2002 to 900 in 2009, before declining again through 2014. TB prevalence ranged from 770 per 100,000 in the lowest SES households to 350 in the highest. Black South Africans had the highest TB prevalence (630), followed by Coloured populations (440), and White/Asian/other (100). In the fully adjusted models, race was a consistently strong predictor of TB across SES categories. Adjusted prevalence of TB among Blacks in the highest SES households was > 4 times that of Whites/Asian/others in lowest SES households (430 and 100 per 100,000, respectively). Household SES was a bigger driver of TB prevalence than community SES or the type of place of residence – urban formal, urban informal, or rural/tribal. Specifically, the wealthiest households in the poorest communities had less than half the risk of TB than the poorest households in the wealthiest communities (predicted prevalence of 250 and 540, respectively).

Conclusion: Both race and poverty predict TB risk, but Black and Coloured individuals across socioeconomic classes suffer much higher rates of TB than the even poorest whites or Asians/Indians. Household impoverishment is more closely associated with the likelihood of TB than community SES. Interventions for TB should address the striking disparities in burden of TB associated with race and poverty.

726 HIGH TB INFECTION RATE IN CHILDREN & YOUNG ADULTS IN RURAL UGANDA IN THE SEARCH TRIAL

Carina Marquez[1], Atukunda Mucunguzi[2], Gabriel Chamie[1], Dalsone Kwariisima[3], Theodore Ruel[1], Laura B. Balzer[4], Tamara D. Clark[1], Edwin D. Charlebois[1], Maya L. Petersen[5], Diane V. Havlir[1]

[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Infectious Diseases Rsr Collab, Kampala, Uganda, [3]Makerere Univ Joint AIDS Prog, Kampala, Uganda, [4]Harvard Univ, Boston, MA, USA, [5]Univ of California Berkeley, Berkeley, CA, USA

Background: To end TB, age-specific prevention strategies are needed; however, data on TB risk factors in rural East African children and young adults are limited. We estimated TB transmission and characterized predictors of TB infection in children and young adults in rural Uganda.

Methods: In the SEARCH Study (NCT:01864603) we performed a tuberculin skin test (TST) survey, from 2015-2016, in a sample of residents ≥5 years in 8 rural communities in Eastern Uganda. Households were randomly sampled, and enriched for those with an HIV-infected adult. TB infection was defined as a positive TST, an induration ≥10mm for HIV-uninfected persons and ≥5mm for HIV infected persons. The annual risk of TB infection (ARTI) was calculated as 1-(1-prevlance)^(1/mean age +0.5). Risk factors for prevalent TB infection in children (5-14 years) and young adults (15-24 years) were assessed using multivariable logistic regression. All models were adjusted for community, BCG vaccination, and living in a household with an HIV-infected adult.

Results: 2,093 children and 953 young adults completed a TST. In this sample, the ARTI among 5-24 years olds was 1.2%; the prevalence of TB infection was 9% among children and 23% among young adults, and the prevalence of HIV was 1.2% in children and 1.9% in young adults. Predictors of TST positivity in children were age (aOR:1.1, 95%CI:1.0-1.2), household contact with TB (aOR:2.7, 95%CI:1.3-5.4), lowest wealth quintile (aOR:1.7; 95%CI:1.1-2.6) and a trend towards an association with living away from home for school (aOR:1.7, p=0.11). Among mother and child dyads that both had TSTs placed, maternal TB infection predicted TB infection in children (aOR:2.0, 95%CI:1.3-3.2). Predictors of TB infection in young adults were age (aOR:1.1, 95%CI:1.1-1.2), household contact with TB (aOR:4.0, 95% CI:1.5-10.7), and being a student (aOR:1.6, 95%CI:1.1-2.2). 5% of 5-24 year olds with a positive TST had a known household TB contact. HIV infection, mother's HIV status, and living in a household with an HIV-infected adult, were not associated with TB infection in children or young adults.

Conclusion: Our data suggest TB transmission is high in rural Uganda, and nearly a quarter of young adults in our sample are already infected with TB. Only 5% of 5-24 year olds with TB infection had a known household contact, suggesting undiagnosed household contacts or community and school-based contacts drive ongoing TB infections in children and young adults.

727 THE HIV-ASSOCIATED BURDEN OF RECURRENT TB DISEASE IN CAPE TOWN, SOUTH AFRICA

Sabine Hermans[1], Nesbert Zinyakatira[2], Judy Caldwell[3], Frank Cobelens[4], Andrew Boulle[2], Robin Wood[2]

[1]Amsterdam Inst for Global Hlth and Development, Amsterdam, Netherlands, [2]Univ of Cape Town, Cape Town, South Africa, [3]City Hlth, Cape Town, South Africa, [4]Univ of Amsterdam, Amsterdam Zuidoost, Netherlands

Background: Retreatment tuberculosis (TB) disease is common in high-prevalence settings such as Cape Town. We recently estimated that one third of TB patients go on to develop another episode of disease and risk of recurrence increases with every subsequent episode. The impact of HIV on this burden of disease is unclear. We determined the rates of recurrent TB stratified by HIV status as well as the HIV-associated population attributable risk fraction (PAF) over a period of 12 years.

Methods: All recorded TB episodes in the Cape Town metropolitan area between 2003-2015 were linked to individuals by deterministic linkage of personal identifiers. We created a virtual cohort of individuals who had their first episode notified in Cape Town (excluding those who were reported to have had TB treatment before, but whose first episode was not identified by the matching algorithm). We estimated the rate of recurrent TB disease stratified by HIV status and by the number of previous episodes. In case of HIV seroconversion between episodes we split the accrued person-time in half. We calculated the rate ratio of recurrent TB disease associated with HIV which we utilized to calculate the PAF of HIV infection in recurrent TB disease.

Results: A total of 287,003 TB episodes were included which represented 245,495 individuals; 16% had two or more episodes of TB. Rates of recurrent TB increased by subsequent episode (Figure 1). HIV-positive rates were higher than HIV-negative rates until episode 5: the rate ratio of recurrent TB disease associated with HIV decreased by subsequent episode: from 1.65 at the second episode to 0.86 at the sixth. The proportion of retreatment disease attributable to HIV in this population increased by subsequent episode: from 42% to 48% in the second to the sixth episode, respectively. Figure 1. Rates of recurrent TB by number of episodes, stratified by HIV status at start of current episode (with 95% confidence intervals).

Conclusion: We found a very high rate of TB disease recurrence in both HIV-negative and HIV-positive TB patients, with less than half of retreatment TB attributable to HIV. These findings suggest that the HIV epidemic does not explain the high burden of retreatment TB in Cape Town, and therefore that high antiretroviral coverage will not be sufficient to curb it. It is more likely explained by a high annual risk of TB infection in combination with an increased risk of infection or progression to disease associated with previous TB treatment.

728 HIV TESTING UPTAKE AMONG HOUSEHOLD CONTACTS OF MDR-TB INDEX CASES IN 8 COUNTRIES

Valarie S. Opollo[1], Xingye Wu[2], Richard Lando[3], Susan Swindells[4], Amita Gupta[5], Anneke Hesseling[6], Rodney Dawson[7], Michael D. Hughes[8], N. Sarita Shah[8], for the A5300/I2003 Study Team

[1]Kenya Med Rsr Inst, Kisumu, Nyanza, Kenya, [2]Harvard Univ, Boston, MA, USA, [3]Kenya Med Rsr Inst, Kisumu, Kenya, [4]Univ of Nebraska, Omaha, NE, USA, [5]The Johns Hopkins Univ, Baltimore, MD, USA, [6]Stellenbosch Univ, Tygerberg, South Africa, [7]Univ of Cape Town, Mowbray, South Africa, [8]CDC, Atlanta, GA, USA

Background: HIV co-infection rates among MDR-TB cases vary globally, and are associated with higher morbidity and mortality. Household contacts (HHC) of MDR-TB/HIV co-infected cases are at high risk for both HIV and TB infection. However, uptake of HIV testing among HHC is understudied. As part of a cross-sectional feasibility study for a randomized trial of preventive therapy for HHC of MDR-TB index cases (IC), we evaluated factors associated with HIV test uptake among HHC.

Methods: Adult IC with at least one HHC were eligible. A HHC was defined as living in the same dwelling and sharing housekeeping arrangements with an IC in the 6 months before the IC started MDR-TB treatment. All adult and child HHC were offered HIV testing if never tested or last tested HIV-negative >1year prior to study entry. HIV testing was done using standardized algorithms. Logistic regression for clustered data was used to evaluate associations.

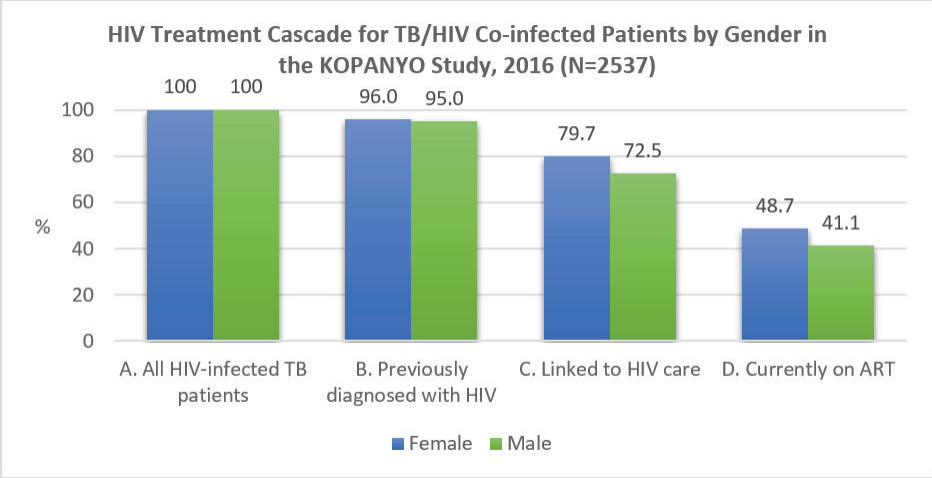
Results: From 10/2015–5/2016, 1007 HHC of 284 IC were enrolled from 16 sites in 8 countries (Botswana-1 Brazil-1, Haiti-1, India-2, Kenya-1, Peru-2, South Africa-7 and Thailand-1). Among the 284 IC, 102 (36%) were HIV-infected, 156 (55%) were HIV-uninfected, and 26 (9%) had unknown status. HIV status was known for 225 (22%) HHC: 39 (4%) were HIV-positive, 186 (18%) were HIV-negative. HIV testing was offered to 770 (98%) of the 782 remaining HHC, of whom 545 (71%) agreed to testing; 535 (98%) were tested, and 26 (5%) were HIV-positive. Testing uptake varied by site (median 86%; p<0.001); 4 sites had 100% uptake, but 5 sites had <50% uptake. Uptake was 74% for females versus 67% for males, and was lower in children 2–4y (51%), 5–12y (56%) and 13–17y (63%), compared to <2y (77%) and adults >18y (78%). Of the 225 HHC who declined testing, 119 (53%) gave a reason; common reasons were perception of low risk (23%), not wanting repeat testing (9%), not ready (5%), not enough time (3%), fear of disclosure (3%). The proportion of HHC of HIV-infected IC versus HIV-uninfected IC agreeing to HIV testing was similar (68% versus 67%, P=0.87), but the proportion testing positive differed (8% versus 2%, P=0.008). Of the 225 HHC who declined testing, 71 (32%) were contacts to an HIV-infected IC.

Conclusion: HIV testing uptake varied considerably among sites and was lower in children and adolescents compared to infants and adults. Addressing participant perceptions of HIV risk may increase HIV test uptake, with particular emphasis among HHC of HIV-positive IC given their higher risk of HIV infection.

729 HIV CONTINUUM AND EXPEDITED TB DIAGNOSIS IN TB/HIV COINFECTED PATIENTS IN BOTSWANA

Diane Gu[1], Sanghyuk S Shin[1], Chawangwa Modongo[2], Cynthia Caiphus[3], Othusitse Fane[2], Matsiri Ogopotse[2], Mbatshi Dima[2], Nicola M Zetola[4]
[1]Univ of California Los Angeles, Los Angeles, CA, USA, [2]Botswana–UPenn Partnership, Gaborone, Botswana, [3]Princess Marina Hosp, Gaborone, Botswana, [4]Univ of Pennsylvania, Gaborone, Botswana

Background: Linkage to HIV care has the potential to shorten the time from symptom onset to tuberculosis (TB) diagnosis. This study describes the HIV treatment cascade among TB/HIV co-infected patients and the impact of prior engagement in HIV care over the timeliness of TB diagnosis.
Methods: A cross-sectional study was conducted among new TB patients in Botswana from September 2012 through March 2016. We defined four stages of the HIV treatment cascade as: 1) all TB/HIV co-infected patients; 2) previously known HIV status prior to TB; 3) linked to HIV care (defined as having any CD4 count or receiving antiretroviral therapy); 4) currently on ART. Patients who were diagnosed with TB within 30 days of symptom onset were considered as having received expedited TB diagnosis. We used chi-square statistics to compare proportions of patients receiving expedited TB diagnosis across various stages of HIV care continuum vs. HIV-uninfected TB patients.
Results: Of 4,375 TB patients included in the analyses, 2,537 (58.0%) were co-infected with HIV. Of those, 2,422 (95.5%) had known HIV diagnosis prior to their TB diagnosis. Seventy-six percent (1,928/2,537) of patients were already linked to HIV care, and 44.8 % (1,136/2,537) were on ART at the time of TB diagnosis. Women were more likely than men to have been linked to HIV care (79.7% vs. 72.5%, respectively; P<0.001) and to have been on ART (48.7% vs. 41.1%, respectively; P<0.001). Overall, expedited TB diagnosis was reported in 53.1% of HIV-uninfected patients, 55.1% of HIV-positive TB patients, 55.2% of those with previously known HIV diagnosis, 54.6% of those linked to HIV care, and 55.4% of those on ART. No statistically significant differences were found when each HIV care group was compared to the HIV-uninfected group.
Conclusion: While most TB/HIV co-infected patients were previously diagnosed, only 76% were linked to HIV care and less than half were on ART at the time of TB diagnosis. While it is clear that linkage to HIV care and ART use positively impact clinical and public health TB outcomes, we found no evidence of a difference in expedited TB diagnosis between stages of the HIV care continuum. Public health efforts are needed to improve linkage to HIV care and reduce TB diagnostic delays among TB/HIV co-infected patients in Botswana.



730 IMPROVEMENT OF HIV/TB CARE: TIME-SERIES ANALYSIS OF HEALTH-FACILITY DATA

Nehaben Ramanlal[1], Dulce Bila[1], Orvalho Augusto[2], Nello Macuacua[1], Victorino Chavane[1], Leonel Zevo[1], Chadreque Muluana[3], Esmeralda Karajeanes[1], Paula Vaz[1]
[1]Fundação Ariel Glaser Contra o Sida Pediatrico, Maputo, Mozambique, [2] Univ Eduardo Mondlane, Maputo, Mozambique, [3]Direcção Provincial de Saude de Maputo, Maputo Provincia, Mozambique

Background: Tuberculosis (TB) is the most common opportunistic infection in Human Immunodeficiency Virus 1 (HIV-1) infected individuals. TB/HIV co-infection makes diagnosis, treatment and presentation of TB a challenge resulting in high mortality from TB in HIV-infected population. In 2012, the Ministry of Health of Mozambique strategically adopted a one-stop model of care, aiming to increase TB screening and treatment for HIV infected patients. Here we evaluate the effect of this strategy on access and retention to TB and HIV services at health facility (HF) level in Maputo province.
Methods: HF offering HIV and TB care services before 2012 and after 2013 are included. Indicators per HF were computed from an electronic patient track system (ePTS). Interrupted time series (ITS) analysis of HF level indicators was conducted. Time segments included before July 2012 (PRE:segment 1), the 12 months between PRE and POST (segment 3) and after June 2013 (POST: Segment 3) and Generalized estimating equation (GEE) linear and logistic regressions with robust standard errors were used to estimate per indicator the change on the level and the slope from PRE to POST.
Results: In total 24 HF were included in the analysis (N=3; Urban and N=21; Rural). Of these, one provided secondary level of care. The odds of TB screening increased significantly from end of segment 1 to beginning of segment 3 (OR: 4.10; 95%CI 2.41 - 6.99) and from a monthly odds-ratio of 1.06 to 1.12 respectively. Conversely, the mean time to ART initiation decreased from 180 days at the end of period 1 to 108 days at beginning of period 3 (relative decrease: 40%; 95%CI 32-47%) (Figure 1) and from monthly mean decrease of 2% to 5%. By July 2015, the mean time to ART initiation was less than 1 month. The odds to access to cothrimoxazole prophylaxis within 3 months of registration increased from end of period 1 to end of period 3 (OR: 2.21; 95% CI 1.75 – 2.81). Overall, no significant changes were observed in retention at 12 months, however it has improved from 77% to 88% among adolescents
Conclusion: Our results suggest benefit of this model of care for co-infected patients. Of note is the reduced time to ART initiation to less than 30 days coupled to improved access to cothrimoxazole prophylaxis. These two factors together with improved screening may significantly contribute to a reduction in mortality and morbidity associated to TB/HIV co-infection.

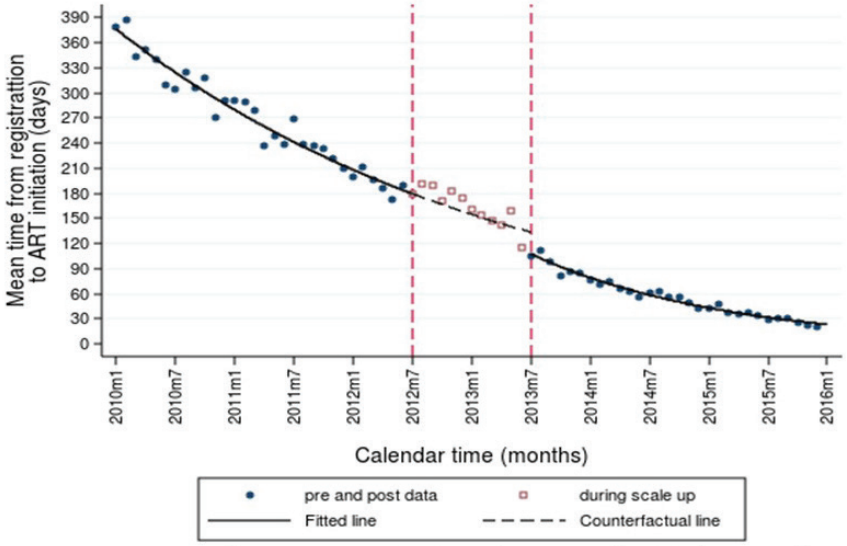


Figure 1. Time in days to ART initiation Pre (Segment 1), Pos adoption of one-stop-Model (Segment 3) of TB/HIV care.

731 INTEGRASE INHIBITORS ARE AN INDEPENDENT RISK FACTOR FOR IRIS: AN ATHENA COHORT STUDY

Ingeborg Wijting[1], Casper Rokx[1], Ferdinand Wit[2], Anneloes Postma[1], Andy Hoepelman[3], Ineke van der Ende[1], Peter Reiss[2], Bart Rijnders[1]
[1]Erasmus Univ Med Cntr, Rotterdam, Netherlands, [2]Stichting HIV Monitoring, Amsterdam, Netherlands, [3]Univ Med Cntr Utrecht, Utrecht, Netherlands

Background: Integrase inhibitors(II) are associated with an accelerated HIV-RNA decline and enhanced CD4 recovery. In late-presenters, these factors are associated with the immune reconstitution inflammatory syndrome (IRIS), a pathological immune reaction against antigens of opportunistic infections (OI). Whether the use of II containing cART is a risk factor for IRIS is unknown as phase-III trials of licensed II included few late presenters.
Methods: Observational study within the ATHENA cohort. Case finding by full chart review was done in all treatment-naïve patients initiating cART from 2009 onwards who were at increased risk for IRIS: those with CD4 ≤200cells/mm3, who were diagnosed with PCP, toxoplasmosis, Kaposi's sarcoma, CMV disease, cryptococcosis, mycobacterial disease or PML and/or initiated corticosteroids ≤12months after cART-initiation and/or died ≤12months after cART-initiation. 2 definitions of IRIS were used: IRIS criteria by French (=French IRIS) and IRIS diagnosed by the treating physician(=clinical IRIS). Patient charts were reviewed for both definitions using a standardized CRF. The 2 primary outcomes were French IRIS and combined clinical or French IRIS. Cox regression was used to compare the risk of IRIS in II and non-II users, while controlling for potential confounders. Patients were censored when switching from INI to non-INI or vice versa.
Results: 369 of 3250 patients initiating first-line cART fulfilled in- and exclusion criteria for chart review with a mean viral load and CD4 count of 275423c/ml and 38cells/mm3. Most prevalent OI were PCP (N=172), Candidiasis (N=143), Mycobacterial infections (N=51) and Kaposi's sarcoma (N=38). Any form of IRIS was observed in 26/69 (38%) of II-users compared to 47/300 (16%) in the non-II users (OR 3.2, 95%CI 1.8-5.8) (Table). Cox regression showed that use of II was independently associated with French as well as any form of IRIS (HR 2.6, 95%CI 1.3-5.1, p=0.004 and HR 2.6, 95%CI 1.6-4.4, p=0.0001).
Conclusion: Patients diagnosed with an OI and a CD4-count ≤200cells/mm3 initiating II-based cART had a more than doubled incidence of IRIS. If confirmed in future studies, initiating II-based cART in late-presenters with OI may have to be revisited, especially in resource limited-settings.

Table 1. Incidences of different types of IRIS in INI- and non-INI-containing first line cART-regimens in late-presenters.

	INI (N=69)	n-INI (N=300)	Total (N=369)
Type IRIS			
French IRIS, N(%)	13 (19)	27 (9)	40 (11)
Clinical IRIS, N(%)	13 (19)	20 (7)	33 (9)
Total, N (%)	26 (38)	47 (16)	73 (20)

Abbreviations: IRIS, Immune Reconstitution Inflammatory Syndrome; INI, INtegrase Inhibitor; n-INI, non-INtegrase Inhibitor.

732 INITIATION OF ART BASED ON INTEGRASE INHIBITORS INCREASES THE RISK OF IRIS

Marine Dutertre[1], **Lise Cuzin**[2], Pascal Puglièse[3], Veronique Joly[4], Marc-Antoine Valantin[5], Laurent Cotte[6], Thomas Huleux[7], Pierre Delobel[2], Guillaume Martin-Blondel[1], for the Dat'AIDS
[1]Toulouse Univ Hosp, Toulouse, France, [2]CHU Toulouse, Toulouse, France, [3]CHU de Nice, Nice, France, [4]Bichat Hosp, Paris, France, [5]AP–HP, Paris, France, [6]Hospices Civils de Lyon, Lyon, France, [7]Cntr Hosp de Tourcoing, Tourcoing, France

Background: Immunocompromised HIV-infected patients frequently initiate ART based on integrase inhibitors (INSTI). Together with a low CD4 T cell count and a high likelihood of opportunistic infection, the sharp control of viral replication associated with INSTI-based ART might synergize the risk of immune reconstitution inflammatory syndrome (IRIS). Our aim was to determine the incidence of IRIS in exposed patients who initiated ART with or without INSTI as a third agent.

Methods: We selected from the Dat'AIDS cohort patients with a CD4 T cell count < 200/mm3 starting from 01/01/2010 to 01/01/2015 ART based on 2 NRTIs associated with a bPI, a NNRTI or an INSTI, and admitted to hospital within 6 months. IRIS events were defined as symptoms consistent with an infectious or inflammatory condition associated with a drop of > 2 log10 copies/mL of HIV viral load, not explained by a newly acquired infection, the expected clinical course of a previous infection, or side-effects. Three physicians blinded to the ART regimen evaluated files and determined the classification by consensus. Characteristics associated with IRIS were analyzed in uni-and multivariate analysis.
Results: The study population included 2287 patients from 15 centers in France. Median age was 45 years (IQ25-75 37-53), and 63% were men. The third agent was bPI in 65%, NNTI in 12%, and INSTI in 12%. At ART initiation, the median HIV viral load and CD4 T cell count were 5.2 log10 copies/mL (4,8-5,7) and 83/mm3 (31-146). IRIS occurred in 41 patients (1.8%) and was associated with tuberculosis (12 cases), atypical mycobacteria (10), JC virus (6), CMV (5), HHV-8 (4), Toxoplasma (2), Cryptococcus (1) and HBV (1). Patients receiving INSTI-based ART did not differ from those without INSTI regarding pre-ART HIV viral load and CD4 T cell count (table). IRIS occurred in 12/398 (3%) patients receiving INSTI-based ART, compared to 29/1889 (1.5%) patients without INSTI (OR 1.99 (1.1-3.5), p=0.04). Repartition of opportunistic infections did not differ according to ART regimen.
Conclusion: Starting ART based on INSTI in exposed patients is associated with a higher risk of IRIS. The homogenous repartition of opportunistic infections among regimen groups argued against a bias of indication linked to mycobacterial infection and co-medication used, although we cannot preclude it formally. While effective control of HIV replication is key, initiation of ART not based on INSTI might be wise in selected patients at high risk of IRIS, deserving further studies.

733 INFLAMMASOMES PLAY A MAJOR ROLE IN TB IRIS PATHOGENESIS

Denise C. Hsu[1], Daniel Sturdevant[2], Eleanor Wilson[1], Virginia Sheikh[1], Ornella Sortino[3], Silvia Lage[1], Timothy G. Myers[1], Stephen Porcella[2], Irini Sereti[1]
[1]NIAID, Bethesda, MD, USA, [2]NIAID, Hamilton, MT, USA, [3]Leidos Biomed Rsr Inc, Frederick, MD, USA
Background: Tuberculosis (TB) immune reconstitution inflammatory syndrome (IRIS) affects 20% of patients with TB and HIV after antiretroviral therapy (ART) initiation. It is associated with significant morbidity and its pathogenesis is still not fully elucidated. We identified differentially expressed RNA transcripts between TB/HIV co-infected patients with and without IRIS.
Methods: Subjects in this cohort study (NCT01611402) were TB/HIV co-infected and had been on TB treatment and ART. Blood was collected in PAXgene tubes at the time of TB-IRIS or, for those without IRIS, at 8-12 weeks after ART initiation, then cryopreserved. RNA was extracted and hybridized on the Affymetrix GeneChip® Human Gene 2.0 ST array. The chip was then stained and scanned. Expression of transcripts was compared using ANOVA with multiple test correction using Benjamini–Hochberg false discovery rate method. Ingenuity Pathway Analysis (IPA) was used to identify canonical pathways and upstream regulators.
Results: Patients with (n=6), and without (n=10) TB-IRIS were enrolled. Patient characteristics are listed in Table 1. Patients with TB-IRIS had higher plasma HIV viral load (p=0.01), C-reactive protein (p=0.02) and absolute neutrophil count (p<0.001) and lower hemoglobin (p<0.001). Using p<0.05 as cut off, compared with patients with no IRIS, patients with IRIS had 355 differentially expressed transcripts, of which 167 had ≥ ±2 fold difference (148 up and 19 down regulated). IPA showed that innate antigen recognition signaling pathways including inflammasome (p=4.27e-6), TREM1 (p=2.70e-5) and Toll-Like Receptor signaling (p=4.13e-5) were the top over-represented pathways in TB IRIS. Upstream regulator analysis predicted Transglutaminase 2 (activated, z-score 2.8, p=9.06e-6), interferon-Y (activated, z-score 2.3, p=1.22e-4) and interferon regulatory factor 4 (inhibited, z-score -2.0, p=1.63e-4) to be potential upstream regulators of the aforementioned pathways and that the activation of these pathways would lead to an increase in caspase 1 breakdown of pro-interleukin (IL) 1b to IL-1b, resulting in a pro-inflammatory response.
Conclusion: Using RNA microarray analysis, transcripts of innate antigen recognition and signaling pathways were over expressed and likely play a crucial role in TB-IRIS. The use of agents that block inflammasome and IL-1b signaling in recalcitrant TB-IRIS merit further investigation.

	IRIS	No IRIS	P Value
Number of patients	6	10	
Male, n (%)	2 (33.3%)	6 (60%)	0.30
Age, median (IQR)	35.5 (32.3-43.8)	37.5 (35.8-43.5)	0.44
Black race, n (%)	5 (83.3%)	6 (60%)	0.59
Days on TB Treatment, median (IQR)	50.5 (41.5-65.75)	104 (63.5-139.5)	0.08
Days on antiretroviral therapy, median (IQR)	9.0 (6.5-31.5)	60.5 (56.3-65)	0.002
CD4+ T-cell count at study entry, cells/μL, median (IQR)	138 (65.8-228)	107 (60.3-238)	0.78
HIV viral load at study entry, log_{10} copies/mL, median (IQR)	3.4 (3.0-4.0)	1.7 (1.6-2.0)	0.01
CRP, mg/dL, median (IQR)	71.5 (25.9-169.5)	1.8 (1.1-8.8)	0.02
Hemoglobin, g/dL, median (IQR)	9.0 (8.5-9.4)	12.5 (11.5-13.4)	<0.001
Absolute neutrophil count, x 10^3/μL, median (IQR)	4.1 (3.2-9.4)	1.8 (1.2-2.6)	<0.001

734 THE DIABETES-TUBERCULOSIS COMORBIDITY AMONG PERSONS WITH HIV

Monica Sane Schepisi[1], Jalal Miah[2], Anna Kaluzhenina[3], Katerina Manika Manika[4], Emanuele Pontali[5], Monica Rios Prego[6], María Nieves Altet Altet[7], Diana Sanchez Mellado Sanchez Mellado[8], **Enrico Girardi**[1], for the TB NET
[1]Natl Inst for Infectious Diseases L. Spallanzani, Rome, Italy, [2]Newham Univ Hosp Barts NHS Trust, London, UK, [3]Volgograd State Med Univ, Volgograd, Russian Federation, [4]Aristotle Univ of Thessaloniki, Thessaloniki, Greece, [5]Galliera Hosp, Genova, Italy, [6]EComplexo Hospario Univ de Pontevedra, Pontevedra, Spain, [7]Unidad de Prevención y Control de la TB de Barcelona, Barcelona, Spain, [8]IIS-Fundacion Jimenez Diaz, UAM, Madrid, Spain
Background: Both HIV and Diabetes mellitus (DM) increase the risk of developing Tuberculosis (TB). While many studies addressed the relationship between HIV infection the risk of DM, the relationship between HIV infection and the co-morbidity tuberculosis-diabetes is still poorly explored.
Methods: We performed a retrospective study on 2395 adult patients consecutively diagnosed with TB in 7 European clinical centres (in Italy, Greece, Spain, Russia); patients included in this analysis had either a diagnosis of DM or sufficient clinical or laboratory information to define the presence or to exclude DM. Two distinct multivariable models were fitted to analyze: 1. the association between HIV and the co-morbidity tuberculosis-diabetes among all patients with TB, and 2. the effect of DM on clinical and radiological presentation of TB among HIV TB patients.
Results: Of the patients enrolled 292 (12.2%) were infected with HIV. HIV-TB co-infected compared to TB only patients were younger, more likely to be male, to be autochthonous and to have other co-morbidities. The overall prevalence of diabetes among the 2395 TB patients was 7.7%. DM prevalence amongst TB only patients and amongst TB-HIV co-infected patients were respectively 7.8% (164/2103) and 7.2% (21/292). After adjustment for potential confounders –age, gender, country of birth- there was no evidence of a significant association between HIV infection and the DM. Amongst 292 TB-HIV co-infected patients, DM was associated with cavities and night sweating, after adjustment for last CD4+ cell count, HAART, gender and age (table). Other presenting symptoms –persisting cough, weight loss, haemoptysis, fever- and clinical variables explored -TB site, sputum smear and sputum culture- were not significantly associated with DM.
Conclusion: DM may play among persons with HIV a role in TB occurrence and presentation similar to that documented in non-HIV infected persons. Increasing prevalence of diabetes among persons with HIV linked to the aging of this population may foster a recrudescence of HIV-associated TB.

735 RISK PROFILES IN MONOINFECTED TB PATIENTS AND THOSE COINFECTED WITH HCV AND/OR HIV

David Roth[1], James Johnston[1], Jason Wong[1], Mel Krajden[1], Zahid A. Butt[2], Nabin Shrestha[1], Mark Gilbert[1], Victoria Cook[1], Naveed Z. Janjua[1]
[1]BC Cntr for Disease Control, Vancouver, British Columbia, Canada, [2]Univ of British Columbia, Vancouver, British Columbia, Canada

Background: Acquisition risk factors for Hepatitis C Virus (HCV), HIV and tuberculosis (TB) are often shared or may differ between populations. Groups with different infection combinations may represent subpopulations with unique demographic and risk characteristics. Understanding the shared and differing risk factors between populations is key to developing targeted prevention strategies.
Methods: We used diagnostic testing, co-infection and risk factor data for active TB cases diagnosed in BC between 1990-2013 in the BC-Hepatitis Testers Cohort (BCHTC). The BCHTC includes ~1.5 million individuals tested for HCV or HIV, or reported as a case of HCV, HIV, HBV, or TB. This cohort is linked with medical visits, hospitalizations, prescription drugs, cancers and deaths. Demographic and acquisition risks were compared between: 1) TB mono infected, 2) TB/HIV coinfected, 3) TB/HCV coinfected, and 4) tri-infected (TB/HIV/HCV). Coinfection is defined over the clients' lifespan, and is not necessarily concurrent in time.
Results: A total of 5927 (90.0%) individuals were identified with TB only, 144 (2.2%) with TB/HIV, 294 (4.5%) with TB/HCV, and 222 (3.4%) with TB/HIV/HCV. TB mono infected cases were mostly foreign-born (FB) (73.5%) with low injection drug use (IDU) (3.2%), alcohol use (10.1%), and mental illness (12.4%). TB/HIV cases were evenly distributed between Canadian born (CB) (47.9%) and FB (47.9%), and showed moderate IDU (22.2%), alcohol use (27.8%), and mental illness (29.2%). In contrast, those with TB/HCV or TB/HIV/HCV infection were mostly CB (74.5% and 88.3%, respectively), with high proportions of IDU (TB/HCV: 45.2%, TB/HIV/HCV: 86.5%) and alcohol use (TB/HCV: 59.5%, TB/HIV/HCV: 64.4%). Mental illness was more common in the TB/HIV/HCV (58.1%) than in TB/HCV (33.0%). Approximately 20.3% of TB only cases belonged to the lowest quintile of the social deprivation index, compared to 45.8% of TB/HIV, 48.6% of TB/HCV, and 60.4% of TB/HIV/HCV.
Conclusion: Populations with TB only differ from those coinfected with HCV and/or HIV. Findings confirm a commonality of social disparities, mental illnesses and substance use across those with coinfections, especially in those with HCV. The TB/HIV/HCV population is particularly socially deprived with a greater proportion of comorbidities. For those TB/HIV/HCV, low threshold support services such as harm reduction and mental health interventions may help control both TB transmission and underlying co-morbid conditions.

736 PROBLEM DRUG USE PREDICTS HIGHER HIV PREVALENCE IN UK TUBERCULOSIS CASES, 2010–2014

Joanne R. Winter[1], Helen R. Stagg[1], Colette J. Smith[1], Maeve K. Lalor[2], Alison E. Brown[2], H. L. Thomas[2], Valerie Delpech[2], Ibrahim Abubakar[1]
[1]Univ Coll London, London, UK, [2]Pub Hlth England, London, UK

Background: HIV co-infection in tuberculosis (TB) patients is associated with poorer outcomes; including higher rates of recurrence, adverse events, treatment interruption or non-completion, and death. Black African ethnicity and being born in sub-Saharan Africa are known predictors of HIV co-infection.
Methods: We identified adults aged ≥15 years diagnosed with TB from 2010-2014 in England, Wales and Northern Ireland from national TB surveillance data. HIV status was determined by record linkage to national HIV surveillance data. We calculated the proportion of TB cases diagnosed with HIV and used logistic regression to identify associations between social risk factors (problem drug use, alcohol misuse, imprisonment, homelessness and index of multiple deprivation [IMD] score) and HIV co-infection.
Results: 30,064 adults diagnosed with TB were included, 931 (3.1%) were co-infected with HIV. The median age at TB diagnosis was 37 years (inter-quartile range 28-53). Among all TB cases, 4,756 (16.0%) were of black African ethnicity and 14,605 (48.6%) were of Indian/Pakistani/Bangladeshi ethnicity. 6,754 (22.5%) were UK-born and 3,467 (11.5%) were born in countries with high (>1%) HIV prevalence. Among all TB cases, 780 (2.6%) had a history of problem drug use, 855 (2.8%) alcohol misuse, 723 (2.4%) homelessness, and 772 (2.6%) incarceration. 6,298 TB cases (20.1%) were in the lowest IMD decile. In univariable analyses, increased odds of HIV co-infection were associated with drug use (odds ratio [OR] 2.31, 95% confidence interval 1.73-3.08), homelessness (OR 2.51, 1.88-3.35) and imprisonment (OR 1.55, 1.10-2.18), whilst increasing IMD decile was associated with lower odds of co-infection (OR 0.96 per decile increase, 0.93-0.99). Alcohol misuse was not significantly associated with HIV co-infection. In a multivariable model adjusted for age, sex, ethnicity, country of birth and year of diagnosis, drug use remained associated with HIV co-infection (OR 2.44, 1.71-3.49).
Conclusion: Problem drug use was associated with a higher prevalence of HIV among TB cases. Greater focus on screening and preventive activities for both TB and HIV may reduce the prevalence of HIV co-infection and improve outcomes for TB patients.

Univariable and multivariable odds ratios from logistic regression of social risk factors associated with HIV co-infection in tuberculosis cases diagnosed in England, Wales and Northern Ireland between 2010 and 2014

Social risk factor		TB cases *n* (% of total)	HIV co-infection *n* (row %)	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Problem drug use†	No	29,284 (97.4)	879 (3.0)	1	<0.001	1	<0.001
	Yes	780 (2.6)	52 (6.7)	2.31 (1.73 - 3.08)		2.44 (1.71 - 3.49)	
Alcohol misuse≠	No	29,209 (97.2)	897 (3.1)	1	0.148	-	
	Yes	855 (2.8)	34 (4.0)	1.31 (0.92 - 1.85)		-	
Homelessness†	No	29,341 (97.6)	879 (3.0)	1	<0.001	1	0.063
	Yes	723 (2.4)	52 (7.2)	2.51 (1.88 - 3.35)		1.38 (0.99 - 1.93)	
Imprisonment†	No	29,292 (97.4)	895 (3.1)	1	0.017	1	0.089
	Yes	772 (2.6)	36 (4.7)	1.55 (1.10 - 2.18)		0.71 (0.47 - 1.07)	
IMD score decile*							
for each unit increase		30,064	931 (3.1)	0.96 (0.93 - 0.99)	<0.001	0.99 (0.96 - 1.02)	0.626

†Prior or current. ≠Only includes patients whose ability to self-administer TB treatment is affected by alcohol misuse. ***IMD**: index of multiple deprivation decile, where 1 = most deprived and 10 = least deprived. **CI**: confidence interval, **OR**: odds ratio. The multivariable model (30,064 TB cases) included IMD score decile and prior or current drug use, homelessness and imprisonment, and was adjusted for year of TB diagnosis, sex, age at TB diagnosis, ethnicity, and HIV prevalence in country of birth.

737 OPPORTUNISTIC INFECTIONS AMONG US HIV-INFECTED ADULTS IN CARE, 2009–2014

Alejandro Pérez, John Weiser, Heather Bradley
CDC, Atlanta, GA, USA

Background: Despite improvements in antiretroviral therapy and rates of viral suppression, opportunistic infections (OIs) remain an important source of morbidity and mortality among people living with HIV. National estimates of the prevalence of OIs and trends over time among HIV-infected persons in care are limited. Addressing these gaps in data may help highlight OIs of special concern as well as guide clinical care.
Methods: We analyzed 2009–2014 medical record data from the Medical Monitoring Project (MMP), a surveillance system that uses an annual cross-sectional survey to produce estimates of the characteristics of HIV-infected adults receiving medical care in the US We reviewed medical record data for evidence of a diagnosis within the past 12 months of any of the stage-3-defining OIs according to CDC's HIV case definition. We estimated the weighted prevalence of diagnosis of any OI by year and assessed temporal change using linear regression. We further estimated the weighted prevalence of individual OIs combining the data over six years, reporting estimates where the coefficient of variation was less than 30%. Data were weighted for unequal selection probabilities and non-response.

Results: Overall, 7.0% (95% confidence interval [CI]: 6.1–8.0) of patients had at least one OI diagnosis documented in their medical record within the past 12 months. OI prevalence decreased from 8.0% (CI: 6.3–9.8) in 2009 to 6.0% (CI: 5.3–6.8) in 2014 (βtrend = -0.006; Ptrend = 0.03). Overall prevalence of individual OIs was as follows: wasting syndrome due to HIV, 1.4% (CI: 1.1–1.7); Pneumocystis pneumonia (PCP), 1.2% (CI: 0.9–1.6); candidiasis of bronchi, trachea, esophagus, or lungs, 1.1% (CI 0.9–1.3); herpes simplex (chronic ulcers greater than one month's duration or bronchitis, pneumonitis, or esophagitis), 0.8% (CI: 0.4–1.2); and Kaposi's sarcoma, 0.7% (CI: 0.6–0.8).
Conclusion: The overall prevalence of OIs among adults in HIV care decreased over time in the United States by 0.6% per year on average from 2009 to 2014. Specific OIs with the highest observed prevalence were found to be wasting syndrome, Pneumocystis pneumonia, candidiasis, herpes simplex, and Kaposi's sarcoma.

738 SIGNIFICANT HIGHER CMV-REACTIVATION IN PJP PATIENTS WITH ADJUNCTIVE CORTICOSTEROIDS

Gundolf Schuettfort, Sarah Tomasini, H.-R. Brodt, Philipp De Leuw, Siri Goepel, Gerrit Kann, Annette E. Haberl, Eva Herrmann, Timo Wolf, Christoph Stephan
Univ Hosp Frankfurt, Frankfurt, Germany

Background: Although the incidence of Pneumocystis jiroveci pneumonia (PJP) has declined with the widespread use of PJP prophylaxis and ART, PJP still remains the most common AIDS-defining infection in people living with HIV (PLWHIV) in western countries. The adjunctive administration of corticosteroids in severely ill patients with PJP has been recommended since the 1990`s and results in a significant reduction in overall mortality. Current recommendations are based on studies from the pre-HAART era. In addition, there is growing evidence that in these severely ill patients the rate of CMV infection and reactivation has been considerably underestimated. Data on reactivation of CMV and resulting complications in PLWHIV with PJP receiving adjunctive corticosteroids are still lacking. In order to assess the impact of adjunctive corticosteroids on the incidence of CMV reactivation in PLWHIV with PJP we conducted a retrospective cohort study with patients from the HIV-Center Frankfurt.
Methods: All patients from the Frankfurt HIV Cohort diagnosed with PJP between January 2005 and December 2013 were analyzed in this retrospective study. The primary endpoint was the incidence of CMV-reactivation in PJP-patients with vs. without adjunctive corticosteroids. CMV-reactivation was defined as presence of CMV-specific immunoglobulin G antibodies in combination with a positive CMV-PCR > 5000 copies/ml. Statistics were done with nonparametric tests using a significance level of alpha=5%.
Results: A total of 160 HIV-positive patients (20.3% female) were included in the analysis, 76.6% ART- naïve and 23.4% treatment-experienced. All 160 patients received Trimethoprim-sulfamethoxazole as PJP treatment.111 patients (69.3%) received adjunctive corticosteroids. The baseline characteristics of the study population are shown in table 1. With respect to potential confounders the rate of CMV reactivation was significantly higher in patients receiving adjunctive corticosteroids (65.7% vs. 34.7%; p = 0.0005; ODDS-Ratio = 3.48 ; CI = 1.171– 7.084).
Conclusion: Our data indicate an independent correlation between the administration of adjunctive corticosteroids and CMV-reactivation in HIV-positive PJP-patients. CMV-reactivation had no impact on mortality, most likely because 94% of these patients received specific CMV-treatment. Thus it is mandatory to be aware of a potential higher risk of CMV-reactivation and the resulting complications in HIV-positive patients receiving adjunctive corticosteroids for PJP treatment.

739 HIV COINFECTION HAS A SIGNIFICANT IMPACT ON TRANSCRIPTIONAL RESPONSE TO TUBERCULOSIS

Hanif Esmail[1], Rachel Lai[2], Christine Graham[2], Anne O'Garra[2], Robert Wilkinson[3]
[1]Univ of Oxford, Oxford, UK, [2]The Francis Crick Inst, London, UK, [3]Imperial Coll London, London, UK

Background: Active tuberculosis (TB) and HIV-1 infection both induce characteristic whole blood transcriptional responses but how these interact in co-infection is poorly understood. We aimed to characterize the transcriptional interaction between HIV and TB in order to gain insight into the biology of HIV-associated TB and to consider how the utility of proposed transcriptional biomarkers for active TB may be affected in persons co-infected with HIV-1.
Methods: Adult residents in Khayelitsha (a township of Cape Town) that were HIV un-infected, with (n=14) and without (n=15) active TB; HIV-1 infected and anti-retroviral therapy (ART) naïve, with (n=15) and without (n=40) active TB and HIV-1 infected established on ART without active TB (n=8) were recruited and had blood drawn into Tempus tubes for RNA preservation. All groups of HIV-1 infected participants were matched for CD4 count. Transcript abundance was determined by microarray and then a modular analysis was conducted to evaluate transcript abundance in 38 previously validated modules (groups of co-regulated transcripts, with biological function inferred from unbiased literature review). HIV uninfected participants without active TB were used as controls. Benjamini-Hochberg method was used to control for multiple comparisons.
Results: In comparison to the controls, those with HIV-1 infection only (ART naïve, median CD4=496/mm3) had significantly higher transcript abundance particularly in modules relating to interferon (3 modules, p≤0.0002) and cell cycle (2 modules, p≤0.006), which normalized in those taking ART, who had no significant differences to controls. HIV uninfected persons with active TB only, had significantly higher transcript abundance in modules relating to interferon (3 modules, p≤0.004), inflammation (4 modules, p≤0.01) and neutrophils (p=0.0019). In co-infected participants, transcript abundance in the interferon modules in comparison to controls was greater than in TB or HIV alone (3 modules, p<0.0001) but was lower in inflammation modules where transcript abundance was not significantly different to controls.
Conclusion: Modular analysis of the whole blood transcriptome shows that HIV associated TB in comparison to TB in HIV uninfected persons, results in increased transcript abundance in interferon modules but a reduction in transcripts relating to inflammation. This also suggests that biomarkers that detect TB in HIV uninfected persons may have different performance characteristics in HIV infected persons.

740 PREVALENCE OF ADVANCED HIV DISEASE AND CRYPTOCOCCAL INFECTION IN GABORONE, BOTSWANA

Kwana Lechiile[1], Hannah K. Mitchell[1], Fredah Mulenga[2], Irene Goercke[3], Martin S. Azama[2], Mooketsi Molefi[3], Tshepo B. Leeme[1], Mark W. Tenforde[4], Madisa Mine[5], Joseph N. Jarvis[6]
[1]Botswana–UPenn Partnership, Gaborone, Botswana, [2]Ministry of Hlth, Gaborone, Botswana, [3]Univ of Botswana, Gaborone, Botswana, [4]Univ of Washington, Seattle, WA, USA, [5]Natl Hlth Lab, Gaborone, Botswana, [6]US CDC, Gaborone, Botswana

Background: Botswana has one of the leading HIV-treatment programs in sub-Saharan Africa and is close to meeting the UNAIDS 90-90-90 targets. However, the incidence of opportunistic infections such as cryptococcal meningitis remains high. We performed a study to describe the CD4 count distribution of all patients receiving HIV care in the public sector in the greater Gaborone area, determine the prevalence of advanced disease (CD4<200 cells/μL), and to explore the utility of cryptococcal antigen (CrAg) screening.
Methods: From January 2014 to January 2016, CD4 data were collected from all patients attending antiretroviral therapy (ART) clinics in greater Gaborone and the referral hospital. Residual EDTA blood specimens from patients with CD4 counts ≤100 cells/μl were routinely screened for CrAg from January 2015 using the IMMY CrAg® Lateral Flow Assay. Basic demographic data were collected. CrAg results were communicated to the responsible clinicians along with provision of a standardized treatment algorithm.
Results: 140,793 CD4 counts were performed from 32,879 individuals; median age was 37 years and 65% (21,294) were female. The median CD4 count was 469 cells/μl (IQR 329-635); 24% (7,962/32,879) had nadir CD4 counts ≤200 cells/μl, and 11% (3,655/32,879) ≤100 cells/μl. Men were significantly more likely to have a nadir CD4 <200 cells/μl (OR 2.0, 95%CI 1.9-2.1). Two thousand samples from 1,622 individuals were screened for CrAg; 5.6% (91/1622) of individuals were CrAg positive. The median age of the 1,622 individuals screened was 37 years (IQR 32-44) and 49.6% (805) were female. CrAg positivity was associated with lower CD4 count (median CD4 32 cells/μl vs 56 cells/μl, p<0.001) and male sex (7.0% CrAg positive vs 4.2% p=0.016). 9.3% (151) of patients were hospitalized at the time of CrAg testing, and the remainder were outpatients. 4.4% (64/1471) of outpatients and 17.9% (27/151) of inpatients were CrAg positive.
Conclusion: There are still a substantial number of individuals with advanced immune suppression in the ART program in Gaborone, and the prevalence of cryptococcal infection in this group is high. Cryptococcal antigen screening would be a worthwhile and feasible intervention in this setting. Almost one in five inpatients with CD4 <100 cells/μL had cryptococcal infection, and screening should be routine in this group. Further work is needed to better understand why individuals, often men, are still presenting with low CD counts despite widespread access to HIV testing and ART.

741 CRYPTOCOCCAL ANTIGEN SCREENING AMONG PATIENTS WITH ADVANCED HIV INFECTION IN VIETNAM

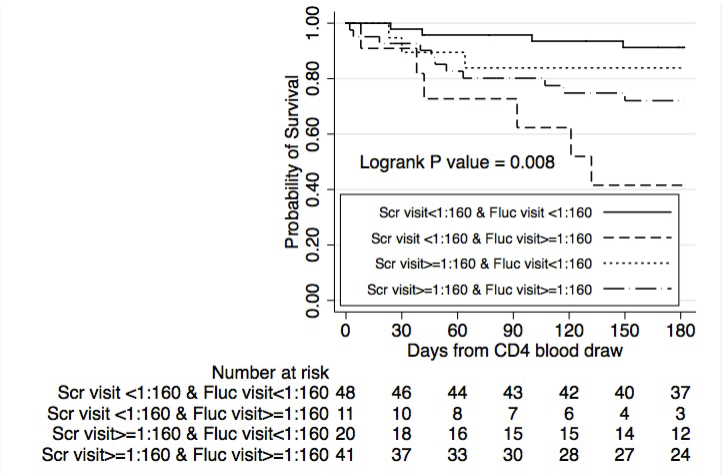
Dat Q. Vu[1], Kinh V. Nguyen[2], Dung T. Nguyen[2], Moses Bateganya[3], Sheryl Lyss[3], Anh T. Ho[4], Jonathan Kaplan[3], Presented by Hanzhu Qian, for the CRICS Team
[1]Hanoi Med Univ, Hanoi, Vietnam, [2]Natl Hosp for Trop Diseases, Hanoi, Vietnam, [3]CDC, Atlanta, GA, USA, [4]CDC, Hanoi, Vietnam

Background: South and Southeast Asia have the second highest burden of cryptococcal meningitis (CM) among people living with HIV after sub-Saharan Africa. The World Health Organization (WHO) recommends that countries consider cryptococcal antigen (CrAg) screening and fluconazole treatment of asymptomatic patients with advanced HIV to prevent cryptococcal disease, based on CrAg prevalence. We present preliminary data on the baseline prevalence of CrAg and other opportunistic infections in Vietnam to inform wider implementation of CrAg screening and other strategies to reduce mortality among patients with advanced HIV disease.
Methods: At 22 HIV outpatient clinics in Vietnam, we implemented a reflex CrAg screening program using lateral flow assay for newly presenting, antiretroviral therapy (ART)-naive patients with CD4 count ≤100 cells/μL. Those testing CrAg-positive were treated with high-dose fluconazole according to WHO's and national guidelines. We enrolled consenting patients for study follow-up, calculated CrAg prevalence, and summarized baseline prevalence of other opportunistic infections.
Results: Between August 2015 and June 2016, 723 (40.5%) of 1,787 ART-naive patients across 22 participating OPCs had CD4 count ≤100 cells/μL. Among these patients, we enrolled 642 (89%). In the current interim analysis, we use data from 587 (91.4%) patients whose baseline data were fully documented in our database by the end of June 2016. 150 (25.6%) patients were female. Median age was 35 years (interquartile range (IQR), 31-41). Median CD4 count at enrollment was 25 (IQR, 11-56). Common opportunistic infections documented at baseline included tuberculosis (31%), oral candidiasis (15.5%)and Pneumocystis pneumonia (5.3%). Among 17 (2.9%) CrAg-positive patients, 16 had no meningitis symptoms and were treated with high-dose fluconazole. One patient was diagnosed with CM and was treated according to the national guidelines.
Conclusion: Late presentation for HIV care was common, highlighting gaps in identifying people early and connecting them to effective treatment for optimal outcomes. CrAg prevalence was relatively low (2.9%) but other opportunistic infections such as tuberculosis, oral candidiasis and pneumocystis pneumonia were common. Longitudinal follow-up will help to evaluate the feasibility and cost of implementing CrAg screening and to assess survival among patients with advanced HIV infection in Vietnam.

742 CHANGES IN CRAG TITERS AMONG ASYMPTOMATIC HIV-POSITIVE PATIENTS

Agnes Kiragga[1], Francis Kakooza[1], Bozena M. Morawski[2], Elizabeth Nalintya[1], Radha Rajasingham[2], David Boulware[2], David Meya[3], Yukari C. Manabe[4]
[1]Infectious Diseases Inst, Kampala, Uganda, [2]Univ of Minnesota, Minneapolis, MN, USA, [3]Makerere Univ, Kampala, Uganda, [4]The Johns Hopkins Univ, Baltimore, MD, USA

Background: In resource-limited settings, 5-9% of HIV-infected persons with <100 CD4 cells/μL have asymptomatic cryptococcal antigenemia. Cryptococcal antigen (CrAg) titers >=1:160 are associated with poor outcomes despite high-dose fluconazole. Delays while patients are waiting for CrAg results may impact CrAg titers and patient outcomes. We sought to understand the rate of change in titers and correlate these with patient outcomes.
Methods: Asymptomatic, ART-naïve, HIV+ patients, >14 years, with CD4<100 cells/ μL received a lab-based reflexive plasma CrAg test with titers as part of an operational implementation study. Serum CrAg titers were repeated when positive participants returned for enrolment, receipt of fluconazole and ART initiation. We analyzed rate of change in log2 titers per day, and the correlation between CrAg titer change and outcomes.
Results: Out of 152 CrAg positive patients, 120 with titers at screening and fluconazole initiation visits were included: 53(44.2%) men, median age 32(Interquartile range (IQR):27,40) years, median CD4 count 26 cells/uL (IQR: 9,56). Median time between screening and fluconazole initiation visits was 5 days (IQR: 2,8). At screening 59(49%) had a titer <1:160, of which 11(19%) experienced an increase to >=1:160 at enrolment. Similarly, 61(51%) had titer >=1:160 at screening, and of these 41 (64%) had titers remain >1:160. Among patients with screening titers <1:160, the mean (SD) rate of change in (log2) CrAg titers/day was 0.11(±0.54). Log2 titers performed at fluconazole initiation were more predictive and associated with higher risk of death than titers performed at fluconazole initiation adjusted Hazard Ratio (aHR) (1.36 (95% CI: 1.15,1.60) compared to screening titers aHR 0.94(95% CI: 0.83, 1.06), with adjusting for baseline CD4 counts. Compared to participants with titers persistently <1:160, higher risk of death occurred in those with screening titers <1:160 which increased to >=1:160 at fluconazole initiation (aHR 9.58 (95%CI 2.69, 34.14) or persistently high titers >=1:160 at both time points (aHR 3.55 (95%CI 1.13,11.15)) (Figure 1).
Conclusion: Asymptomatic cryptococcal antigenemia with baseline titer >=1:160 or titers rising about that threshold is associated with increased risk of death at 6 months despite high dose fluconazole treatment and suggests that CrAg titers when starting preemptive antifungal therapy may guide the need for enhanced preemptive treatment.



743 HIGH PREVALENCE OF CNS DISSEMINATION WITH ASYMPTOMATIC CRYPTOCOCCAL ANTIGENEMIA

Azure T. Makadzange[1], Admire Hlupeni[2], Kathryn F. Boyd[3], Takudzwa Chagumaira[2], Christine Ross[4], Snigdha Vallabhaneni[4], Shirish Balachandra[4], Moses Bateganya[4], Chiratidzo E. Ndhlovu[2]
[1]Massachusetts General Hosp, Cambridge, MA, USA, [2]Univ of Zimbabwe, Harare, Zimbabwe, [3]Infectious Disease Rsr Lab, Harare, Zimbabwe, [5]CDC, Atlanta, GA, USA

Background: Screening for serum cryptococcal antigenemia (sCrAg) in advanced HIV is WHO recommended but with limited evidence to guide management of asymptomatic sCrAg+ individuals. We implemented a sCrAg screening program and estimated the prevalence of sCrAg antigenemia, central nervous system (CNS) dissemination, and mortality.
Methods: HIV-infected individuals with CD4 counts ≤100cells/μl were enrolled at 20 outpatient clinics in Harare from April 2015–June 2016 and screened for sCrAg using a lateral flow assay. Participants were excluded for symptoms of meningitis or recent diagnosis of cryptococcal meningitis (CM). Lumbar puncture (LP) was offered to sCrAg+ participants; those with CNS disease were hospitalized and received Amphotericin B with high dose fluconazole; sCrAg+ participants who declined LP and CSF CrAg- participants received

high dose fluconazole. All sCrAg- and sCrAg+ participants were initiated on ART or switched from a failing regimen within a week or 4-weeks of enrollment respectively. Crude mortality rates were determined, cause of death was ascertained by review of medical records and/or family report. Hospitalization costs were obtained. All participants have completed 10-weeks of follow-up, follow-up to 12-months is ongoing.
Results: We screened 1598 and enrolled 1334 asymptomatic participants; 132 were sCrAg+ (9.9%), 67 sCrAg+ (50.8%) participants agreed to an LP and CNS disease was confirmed in 13 (19.4%). All-cause mortality to date was 8.9% (n=119) and mortality among the sCrAg+ and sCrAg- groups was 17.4% and 8.0%, respectively (p=0.0003). Among those with LP, mortality in the CSF CrAg+ and CSF CrAg- was 30.8% and 13% respectively (p=0.12). Mortality was similar in those who accepted (16.4%) and those who declined LP (18.1%, p=0.79). Hospitalization costs for CSF CrAg+ participants ranged from US$650–950. Death occurred in a health care setting in 88 (74%) participants, cause of death was unknown in 53 (44.5%). A documented diagnosis or clinical suspicion of TB infection was present in 44 (35.3%) and CM in 9 (7.6%) participants who died.
Conclusion: A positive sCrAg is associated with increased mortality. The prevalence of CNS dissemination among asymptomatic sCrAg+ individuals is high. However, due to the suggested comparable mortality and high management costs, the impact of LP in resource limited settings needs further study with risk stratification to determine patients most likely to benefit from evaluation for CNS disease and hospital-based management.

744 SERTRALINE AND HIGH-DOSE FLUCONAZOLE TREATMENT OF CRYPTOCOCCAL MENINGITIS IN TANZANIA

Katende Andrew[1], Gladys Mbwanji[1], Diana Faini[1], Aneth Kalinjuma[1], Katherine Hullsiek[2], Josh Rhein[2], Maja Weisser[1], David Meya[3], David Boulware[2], Emilio Letang[1]
[1]Ifakara Hlth Inst, Morogoro, Tanzania, United Republic of, [2]Univ of Minnesota, Minneapolis, MN, USA, [3]Infectious Disease Inst, Kampala, Uganda
Background: Cryptococcus neoformans is the leading cause of adult meningitis in sub-Saharan Africa. First-line antifungals are largely unavailable in this region. Sertraline has fungicidal activity against Cryptococcus, has synergy with fluconazole, and has shown promising results as an adjuvant for the treatment of cryptococcal meningitis.
Methods: We prospectively enrolled 42 HIV-infected adults with cryptococcal meningitis at a regional referral hospital in the rural Kilombero district, Tanzania from October 2014 to September 2016. Participants received induction treatment with either: A) sertraline 400mg/day and fluconazole 1200mg/day for two weeks (n=28); or B) same regimen plus amphotericin B deoxycholate for 5 days (n=14). The consolidation phase for all participants consisted of sertraline 200mg/day and fluconazole 800mg/day for 12 weeks. Lumbar punctures were performed on day 1, 3, 7, 10 and 14. The primary outcome was early fungicidal activity (EFA) in cerebrospinal fluid (CSF) over the first 2 weeks calculated by linear regression. Secondary outcomes were 2 and 10-weeks survival.
Results: The CSF Cryptococcus clearance EFA rate was 0.25 log10 CFU/day (95%CI: 0.12-0.39) with fluconazole plus sertraline and 0.44 log10 CFU/day (95%CI: 0.31-0.57) with amphotericin (5 days), fluconazole, and sertraline, (p=0.04). With fluconazole plus sertraline, 2 and 10-week survival were 64% (18/28) and 25% (7/28), respectively. With amphotericin, fluconazole, and sertraline, 2 and 10-week survival were 93% (13/14) and 36% (5/14), respectively. Severe hypokalemia (<2.5 mEq/L) occurred in 21% (3/14) of participants treated with amphotericin.
Conclusion: Sertraline with fluconazole improved two-week CSF fungal clearance rate and clinical outcome as compared with fluconazole monotherapy (EFA=0.18) or short course amphotericin (EFA=0.30) in previously published data. Adding short course amphotericin B increased CSF clearance, reduced early mortality, and was safely implementable in this resource-limited setting. Further efforts are needed to improve outpatient survival in rural Africa.

745 MORTALITY DUE TO HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS IN BOTSWANA IN THE ART ERA

Tshepo B. Leeme[1], Raju K. Patel[1], Caitlin Azzo[2], Nametso Lekwape[1], Katlego Tsholo[1], Ephraim Tawanana[3], Mooketsi Molefi[4], Margaret Mokomane[3], Mark W. Tenforde[5], Joe N. Jarvis[6]
[1]Botswana–UPenn Partnership, Gaborone, Botswana, [2]Univ of Pennsylvania, Philadelphia, USA, [3]Botswana Ministry of Hlth, Gaborone, Botswana, [4]Univ of Botswana, Gaborone, Botswana, [5]Univ of Washington, Seattle, WA, USA, [6]US CDC, Gaborone, Botswana
Background: Cryptococcal meningitis (CM) is a leading cause of death in HIV-infected individuals in Africa. Case fatality rates of 20-35% with amphotericin-B based treatment have been reported in clinical trials conducted in Africa. These are not representative of standard medical care. We evaluated CM outcomes in a routine care setting utilizing centralized electronic medical records and robust civil registration data unique in Africa.
Methods: All laboratory-confirmed cases of CM at Princess Marina Hospital, Gaborone, from January 2012 to December 2014 were included in the study. Standard treatment for CM was amphotericin B 1mg/kg plus fluconazole 800mg for 14 days. Paper and electronic records were interrogated to retrieve demographic and clinical data and in-hospital mortality. Linkage with the National death registry allowed out of hospital deaths to be captured. The primary endpoint was mortality at 1 year.
Results: During the study period there were 283 episodes of CM among 236 individuals (199 patients had a single episode, 37 patients had multiple episodes). 69% of patients were male and the median age was 36 (IQR 32-42) years. 80% of patients had a known HIV diagnosis prior to presentation with CM, and 51% were already on ART. At the time of death registry linkage in December 2015 vital status was available for 92% (216/236) of patients. Median duration of follow-up in the remaining 20 patients was 25 (IQR 16-153) days. Overall documented mortality was 62% (146/236), and was 68% (146/216) in those with complete data. Two-week mortality, 10-week mortality, and 1-year mortality were 26% (60/233), 50% (112/224), and 65% (142/219). In a sensitivity analysis assuming all those lost to follow-up had died, this increased to 27% (63/236), 53% (124/236), and 67% (159/236). Abnormal mental status at presentation (HR 1.63, 95%CI 1.1-2.5), low CD4 counts (HR 0.84 per 50 cells/µl increase, 95%CI 0.73-0.99), and CSF white cell counts <20 cells/µl (HR 1.42, 95%CI 1.1-2.0) were associated with poor long-term survival.
Conclusion: Long-term outcomes in patients with HIV-associated CM are extremely poor, with only 35% of patients surviving to one year even with amphotericin B based therapy and universal ART access in one of the best-resourced health-care services in Africa. Novel strategies are urgently needed for prevention of new cases and effective management of patients with cryptococcal meningitis.

746 CSF IMMUNE RESPONSES ASSOCIATED WITH DEPRESSION FOLLOWING CRYPTOCOCCAL MENINGITIS

Sarah Lofgren[1], Kathy Huppler Hullsiek[1], Bozena M. Morawski[1], Josh Rhein[1], David Meya[2], Mahsa Abassi[1], Noeline Nakasujja[3], Abdu Musubire[3], David Boulware[1], for the Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis (ASTRO-CM)
[1]Univ of Minnesota, Minneapolis, MN, USA, [2]Infectious Disease Inst, Kampala, Uganda, [3]Makarere Univ, Kampala, Uganda
Background: Depression is common after AIDS-related central nervous system infections. Immunologic factors are involved in the development of depression, but few studies have evaluated CSF immune profiles.
Methods: We assessed risk factors for depression, defined by a Center for Epidemiological Studies-Depression (CES-D) score of >=16, among those with cryptococcal meningitis enrolled in two clinical trials in Kampala, Uganda from 2010-2014. We compared clinical factors and 19 CSF cytokines/chemokines (pg/mL) at screening with development and progression of depression at 4 and 12 weeks using descriptive statistics and t-tests.
Results: 186 participants with cryptococcal meningitis were screened for depression at 4 and/or 12 weeks. At 4 weeks, 75% of 146 were depressed versus 36% of 163 at 12 weeks. We grouped the 123 screened at both time points into those never depressed and those depressed at one/both time points. CSF opening pressure >25cm H20 was non-significantly higher in those never depressed (81% vs 57%, p=0.06), and closing pressure was significantly higher in those never depressed (11 vs 9cm H20, p=.04). CSF macrophage activation marker sCD14 was significantly higher in those never depressed (median 634 vs 202 ng/mL, p=.045). CSF cytokines TNFa (14 vs 6 pg/mL; p=.06), IL-4 (1.9 vs 0.9; p=.06), and MCP1 (748 vs 315; p=.06) all trended towards significantly higher in those never depressed. CSF WBC and quantitative cultures did not differ between groups (P=.94; P=.29, respectively). We further separated groups into those never depressed, those who were depressed but improved, and those who worsened. Opening pressure >25cm was least frequent in the group that improved (81% vs. 47% vs, 88%, respectively; p=.03). Closing pressure was also lower in those who resolved their depression by 12 weeks (11 vs 8.8 vs 10.5cm, respectively; p=.03).

Conclusion: Half of those with cryptococcal meningitis who were depressed at 4 weeks had resolved their depression by 12 weeks. Intracranial pressure was highest in the groups of those never depressed and those who worsened between 4 and 12 weeks. It is possible the elevated pressure of those never depressed had appropriate inflammation, with elevated intracranial pressure while those who worsened had dysfunctional inflammation, which raised intracranial pressure and potential risk for depression. Depression was possibly associated with lower levels of CSF inflammation of the innate immune system: sCD14, TNFa, and MCP1 (CCL2) as well as Th2 IL-4 response.

747 CLINICAL PERFORMANCE OF THE MP1P IMMUNOASSAY FOR RAPID DIAGNOSIS OF TALAROMYCOSIS

Thu T. Nguyen[1], Jasper F. Chan[2], Hien T. Ha[1], Nguyen Le Nhu Tung[3], Jeremy Day[1], Chau V. Nguyen[3], Guy Thwaites[1], Patrick C. Woo[2], Kwok-Yung Yuen[2], Thuy Le[1]
[1]Oxford Univ Clinical Rsr Unit, Ho Chi Minh, Vietnam, [2]Univ of Hong Kong, Hong Kong, [3]Hosp for Trop Diseases, Ho Chi Minh City, Vietnam, Ho Chi Minh, Vietnam

Background: The gold standard to confirm Talaromyces marneffei infection (previously penicilliosis) is culture which can take up to 2 weeks. Diagnostic delay is associated with high mortality. Antigen detecting immunoassays offer rapid, specific and sensitive results, and have transformed management of other mycoses such as cryptococcosis. We describe the performance of the Mp1p immunoassay in a cohort of HIV-infected patients with talaromycosis and matched controls.

Methods: We evaluated the performance of a novel monoclonal antibody-based immunoassay against Mp1p – an abundant mannoprotein in T. marneffei's cell wall. We used plasma samples from a case-control study: HIV-infected patients with culture-confirmed talaromycosis (N = 284 cases) and HIV-infected patients with other opportunistic infections (N = 332 controls) in Ho Chi Minh City between 2010 and 2015. Controls were matched to cases by age, sex, and CD4 count or WHO disease staging. We describe quantitative antigen dynamics over 90 days for 60 patients on treatment.

Results: The median CD4 count was 18 cells/mm3 (IQR: 4-22) in cases and 52 cells/mm3 (IQR: 11-56) in control patients. Amongst cases, blood culture (automated Bactec system) was positive in 200 (70%) patients. The other 84 patients had positive culture from skin lesions or lymph nodes. Common opportunistic infections in control patients included cryptococcal meningitis (N=83), oral or esophageal candidiasis (N=47), tuberculosis (N=46), bacterial pneumonia (N=33), PCP (N=22) toxoplasmosis (N=22), and bacterial sepsis (N=21). Based on an optical density cut-off value generated by a receiver operating characteristic curve (ROC) of 0.208, the sensitivity, specificity, positive predicted value, and negative predicted value of the assay were 89.8%, 92.6%, 91.1%, and 91.5%, respectively. Quantitative antigen testing for 60 patients showed that 90% of patients had cleared antigenemia by 3 months. The rates of antigenemia clearance were similar for patients treated with amphotericin B or itraconazole as induction therapy (P=0.079, Student t-test).

Conclusion: The Mp1p immunoassay provides an accurate test for differentiating talaromycosis from other HIV-associated opportunistic infections with sensitivity higher than blood culture, thus allows antifungal therapy to begin sooner, and has the potential to reduce talaromycosis mortality.

748 PREDICTING THE RISK OF DEATH IN HIV-ASSOCIATED TALAROMYCES MARNEFFEI INFECTION

Thanh T. Nguyen[1], Thu T. Nguyen[1], Nguyen Le Nhu Tung[2], Jeremy Day[1], Cecilia Shikuma[3], Chau V. Nguyen[2], Guy Thwaites[1], Thuy Le[1]
[1]Oxford Univ, Ho Chi Minh City, Vietnam, [2]Hosp for Trop Diseases, Ho Chi Minh City, Vietnam, [3]Univ of Hawaii, Honolulu, HI, USA

Background: Disseminated Talaromyces marneffei infection (formerly termed penicilliosis) is the third most common microbiologically confirmed opportunistic infection in Southeast Asia with mortality of up to 30% despite antifungal therapy. There are no clinical algorithms to predict treatment outcomes.

Methods: We performed logistic regression and developed a simple risk prediction model for HIV-associated talaromycosis using data from a retrospective cohort 2004-2009 (N=513) and a case-control study 2010-2011 (N=36) at the Hospital for Tropical Diseases in Ho Chi Minh City, Vietnam. Poor outcome was defined as death or worsening clinical status at hospital discharge. Covariables used in the model included age, sex, history of injection drug use, comorbidities, and clinical and laboratory characteristics. Based on the coefficients of predictors, a simple prognostic score was developed to estimate the risk of death. Single Conditional Mean Imputation was used for missing values of AST (22% missing) and creatinine (10% missing), and bootstrapping was used for internal validation of the final model.

Results: 549 patients with microbiology-confirmed HIV-associated talaromycosis were included in the analaysis. Poor outcome was observed in 175/549 patients (31.9%). In the univariate logistic regression analysis, hepatomegaly and splenomegaly were protective factors. Shorter duration of illness, higher respiratory rates, dyspnea, AIDS-associated central nervous system (CNS) disease, platelet counts <50,000 cells/mL, AST >300 U/L, ALT >150 U/L, creatinine >110 µmol/L, and bacterial septicemia were predictors of poor outcome. In the multivariate logistic regression analysis, shorter days of illness (OR=1.22, 95% CI: 1.12-1.20, P=0.019), higher respiratory rates (OR=3.03, 95% CI: 2.08-4.41, P<0.001), CNS diseases (OR=18.91, 95% CI: 6.74–53.07, P<0.001), AST >300 U/L (OR=2.27, 95% CI: 1.22-4.21, P=0.009), and creatinine >110 µmol/L (OR=3.24, 95% CI: 1.82 – 5.74, P<0.001) were independent predictors of poor oucome. The prognostic scores ranged from -2 to +52, corresponding to a mortality risk of 0% to 100%. The internal validation showed acceptable discrimination (AUC=0.68) and calibration slope (1.00). The Brier score was 0.14.

Conclusion: We developed a simple scoring system that can predict the risk of death in patients with HIV-associated talaromycosis based on routinely measured characteristics on admission. The scoring system will be externally validated using other cohorts in the region.

749 HOW WELL DO NEUROLOGIC SYMPTOMS IDENTIFY HIV-INFECTED INDIVIDUALS WITH NEUROSYPHILIS?

Arielle P. Davis[1], Joshua Stern[2], Shelia Dunaway[1], Lauren Tantalo[1], Sharon Sahi[1], Abigail Crooks[1], Claire Stevens[1], Sarah Holte[3], Christina Marra[1]
[1]Harborview Med Cntr, Seattle, WA, USA, [2]Univ of Washington, Seattle, WA, USA, [3]FRCHC, Seattle, USA

Background: Current CDC guidelines recommend lumbar puncture in syphilis patients with signs or symptoms of neurologic disease.

Methods: As part of a study of cerebrospinal fluid (CSF) abnormalities in syphilis, 410 HIV-infected individuals with untreated syphilis underwent lumbar puncture and a structured history that assessed the presence of new: headache, stiff neck, photophobia, vision loss, ocular inflammation, hearing loss, sensory loss, or gait incoordination. Severity was graded from 0 (absent) to 3 (severe). A symptom was considered present if it was graded as ≥2 in severity. Neurosyphilis was defined as a reactive CSF-VDRL. Association between categorical variables was assessed by chi-square or fisher exact test and by logistic regression. P-values <0.05 were considered significant. Diagnostic specificity and sensitivity were calculated using standard formulae.

Results: Participants were mostly white (73.4%) men (99.5%) with early syphilis (70.2%). Median RPR titer was 1:64 (IQR 1:16-1:256). Symptom frequency was: headache (18.5%), stiff neck (3.9%), photophobia (4.0%), vision loss (13.5%), ocular inflammation (4.4%), hearing loss (5.9%), sensory loss (0.7%) and gait incoordination (0.2%). CSF-VDRL was reactive in 69 (16.8%). Headache, stiff neck, photophobia and gait incoordination were not more common in those with a reactive CSF-VDRL. However, compared to those without each individual symptom, the odds of a reactive CSF-VDRL were significantly higher in those with vision loss (6.77 [95% CI 3.60-12.70], P<0.001) or hearing loss (3.28 [1.36-7.92], P=0.008); and bordered on significantly higher for those with ocular inflammation (2.58 [0.93-7.13], P=0.07) and sensory loss (10.03 [0.90-112.19], P=0.06). Taking into account serum RPR titer and antiretroviral use, the odds of a reactive CSF-VDRL remained significantly higher in those with vision or hearing loss. While the specificity of these 4 symptoms for neurosyphilis was high, the sensitivity was low (Table).

Conclusion: In HIV-infected individuals with syphilis, new headache, stiff neck, photophobia and gait incoordination were not more common in those with neurosyphilis, while vision or hearing loss, ocular inflammation and sensory loss were. While the latter 4 symptoms had high specificity, they were very insensitive. Lack of neurologic symptoms in HIV-infected patients with syphilis should not reassure clinicians that their patients do not have neurosyphilis.

750 TREATMENT OF NEUROSYPHILIS: IV PENICILLIN G VS IM PROCAINE PENICILLIN/ORAL PROBENECID

Shelia Dunaway[1], Claire Maxwell[2], Lauren Tantalo[1], Sharon Sahi[1], Arielle P. Davis[1], Claire Stevens[1], Abigail Crooks[1], Christina Marra[1]
[1]Harborview Med Cntr, Seattle, WA, USA, [2]Univ of Washington, Seattle, WA, USA

Background: The CDC recommends IV aqueous penicillin G (PenG) for 10-14 days to treat neurosyphilis (NS). IM aqueous procaine penicillin (APPG) plus oral probenecid is considered an alternative treatment that might be considered if compliance can be assured. APPG is preferable to PenG in some instances due to lower cost and greater convenience. We compare these 2 therapies for neurosyphilis.

Methods: Between April 2003 and May 2015, 150 individuals were enrolled in a study of cerebrospinal fluid (CSF) abnormalities in syphilis and were treated with PenG or APPG regimens for NS. They underwent follow-up CSF examinations and blood draws 3, 6, and 12 months after treatment. Relationships between categorical variables were determined by Chi square or Fisher exact test. Hazard ratios (HR) for normalization of CSF white blood cells (WBCs) (decline to <20/ul), CSF protein (decline to <50/mg/dl) and CSF-VDRL or serum RPR reactivity (4-fold decline or reversion to nonreactive) were determined using Cox regression.

Results: Both groups were well matched; most were HIV-infected Caucasian men in their early 40s. More patients treated with APPG had early stage syphilis (71% vs 47%, p=0.01) and more were treated for uncomplicated syphilis within 90 days of study entry (43% vs 19%, p=0.01). There were no differences in pre-treatment serum RPR titer, CSF WBCs, CSF-VDRL reactivity, or proportion with symptomatic NS. More patients treated with PenG had elevated CSF protein (p=0.07). Normalization of all 4 measures did not differ in the 2 treatment groups, or in HIV-infected, or in those treated for uncomplicated syphilis before entry. CSF protein normalized more slowly in those with higher pre-treatment CSF concentration [HR=0.2, p <0.001]. CSF-VDRL normalized more slowly in late syphilis [HR=0.5, p <0.01] but normalized faster in symptomatic NS [HR=1.7, p <0.05]. Serum RPR normalized faster in those with higher pre-treatment titers [HR=2.3, p < 0.001] and in those with symptomatic NS [HR=1.5, p <0.05] and more slowly in late stage syphilis [HR=0.4, p <0.001]. Multivariate analysis, taking into account stage and previous treatment in addition to other significant univariate variables, revealed no relationship between normalization of any measure and treatment regimen.

Conclusion: We did not see a difference in treatment response between NS patients treated with PenG or APPG. Although treatment was not randomized, we continued to see no difference in response even after taking into account pre-treatment differences.

751 STOPPING SECONDARY TE PROPHYLAXIS IN SUPPRESSED PATIENTS WITH CD4 100-200 IS NOT SAFE

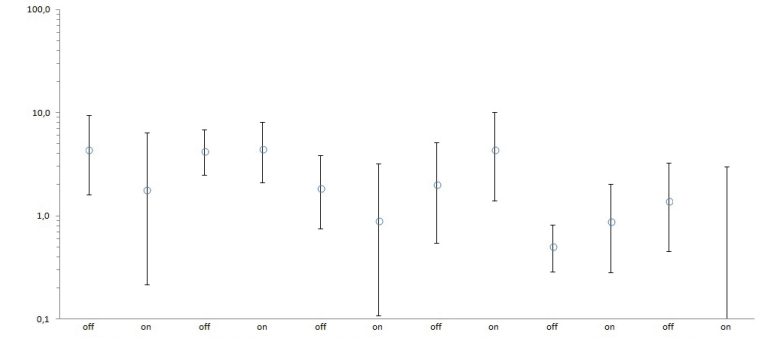
Jose M Miro, for the Opportunistic Infection Team of the COHERE in EuroCoord
IDIBAPS, Barcelona, Spain

Background: Current guidelines recommend that secondary Toxoplasma gondii prophylaxis can be safely discontinued in HIV-infected patients with suppressed viremia on antiretroviral therapy (ART) and a CD4 cell count >200 cells/mm3. Whether such a policy can be extended to patients with CD4 cell counts between 100-200 cells/mm3 is unknown.

Methods: The Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) included data from 10 European cohorts on 1151 HIV-infected patients who developed a toxoplasmic encephalitis (TE) and started ART after 1997. TE was diagnosed on the basis of the 1993 CDC case definition. A relapse was defined as a new TE episode after 4 months of the initial TE. Patient follow-up began at the date of the first TE and ended at the time of first TE relapse, last visit, or death, whichever occurred first. Incidence rates of TE relapses were calculated after stratification by current use of prophylaxis, current CD4 cell count, and current viral load (VL). Multivariate Poisson regression models were used to model incidence rate ratios (IRRs) of TE.

Results: There were 79 TE relapses during 6,030 person-years of follow-up (PYFU). The incidence of TE relapses stratified by current CD4 cell count, detectable or undetectable VL, and use of prophylaxis is shown in the figure. Among patients who had a current CD4 cell count of 100-200 cells/mm3 and an undetectable VL (<400 copies/mL), incidence of TE was 0.9 episodes per 100 PYFU (95% CI, 0.11-3.2; 2 episodes during 224 PYFU) in those receiving T. gondii prophylaxis and 1.9 relapses per 100 PYFU (95% CI, 0.75-3.8; 7 episodes during 376 PYFU), in those who stopped prophylaxis (P=0.349). Among virologically suppressed patients on ART without secondary T. gondii prophylaxis, the incidence of TE in patients with CD4 100-200 was significantly higher than that seen in patients with CD4>200 cells/mm3 (0.5 (95% CI, 0.3-0.8) episodes per 100 PYFU; P=0.002). Doubling CD4 cell count/mm3 (IRR, 0.77; 95% CI, 0.68–0.87; P<.001) was the only TE relapse predictor; whereas detectable VL (IRR, 1.64; 95% CI, 0.92–2.93; P=0.092) and prophylaxis (IRR, 1.00; 95% CI, 0.61–1.64; P=.998) were not predictors.

Conclusion: In suppressed HIV-infected adult patients, secondary prophylaxis against TE can be safely discontinued in patients with CD4 cell counts >200 cells/mm3. Conversely, secondary TE prophylaxis should not be stopped in virologically suppressed patients with CD4 counts of 100-200 cells/mm3



Current CD4/VL and use of *T.gondii* prophylaxis

752 ASYMTOMATIC INFECTION IN AN HIV COHORT: LEISHMANIASIS OUTBREAK IN FUENLABRADA, SPAIN

Alicia Castro[1], Eugenia Carrillo[2], **Juan V. San Martin**[1], Laura Botana[2], Laura Molina[1], Laura Fernandez[2], Belen Matia[1], Carmen Sanchez[2], Jose Manuel Ruiz-Giardin[1], Javier Moreno[2]
[1]Hosp Univ de Fuenlabrada, Fuenlabrada, Madrid, Spain, [2]Inst de Salud Carlos III, Majadahonda, Spain

Background: The largest leishmaniasis outbreak in Europe was declared since June 2009 in Fuenlabrada (Madrid, Spain). Our aim was to estimate the prevalence of asymptomatic Leishmania infection in the HIV cohort of Fuenlabrada, in this high exposure setting, and analyze the risk factors for the development of visceral leishmaniasis.

Methods: A representative sample of the Fuenlabrada's HIV cohort was selected for exposure test to Leishmania. An infected patient was defined as a positive result in, at least, one of following blood tests for Leishmania: PCR, serology (ELISA or IFAT) or SLA (stimulation to Leishmania antigen) lymphoproliferative test as marker of cellular immunity. Infected vs not infected patients, and visceral leishmaniasis vs asymptomatic infected patients, were analyzed with statistical tests looking for risk factors. This work has been

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Results: 583 patients of the Fuenlabrada's HIV cohort were followed since 1st June 2004 to 31th December 2015. 135 representative patients were selected for exposure test to Leishmania, including 12 symptomatic patients (10 visceral and 2 cutaneous). 19 (15.4%) of the 123 asymptomatic patients fulfilled the definition for Leishmania infection, none of them became symptomatic during the study period. Total prevalence of the cohort was estimated 17.5%. Multivariate analysis was performed in infected vs not infected patients and find association to the "distance to Bosquesur park", considered the focus of the outbreak, 1082 meters media distance to the park in infected vs 1719 meters not infected (ANOVA p=0.02). Multivariate analysis performed between patients who developed visceral leishmaniasis vs asymptomatic patients showed association to illness development only for patients with "negative SLA test with positive PCR or serology" (p<0,001, OR not calculable) and "less than 100 CD4 during outbreak period" (p=0,001, OR not calculable).
Conclusion: In the TARGA era, 15.4% of our HIV cohort has been infected by Leishmania, but are asymptomatic. Negative SLA test with positive PCR or serology, reflects the absence of specific immune response to Leishmania, and is therefore an independent risk factor for visceral leishmaniasis

753 DOSING FOR TWO: PLACENTAL TRANSFER OF DARUNAVIR AND SIMULATION OF FETAL EXPOSURE

Stein Schalkwijk, Aaron O. Buaben, Angela Colbers, David M. Burger, Rick Greupink, Frans G. Russel
Radboud Univ Med Cntr, Nijmegen, Netherlands

Background: Fetal antiretroviral exposure is usually derived from the cord-to-maternal (ctm) concentration ratio. This static parameter does not provide information on the pharmacokinetics in utero, limiting the assessment of a fetal exposure-effect relationship. Pregnancy physiologically-based pharmacokinetic (p-PBPK) modeling could provide a solution, although incorporation of placental antiretroviral transfer remains challenging. Here, we aimed to incorporate placental transfer into a p-PBPK model to simulate fetal exposure of darunavir at term.
Methods: An existing and validated p-PBPK model of maternal darunavir/ritonavir exposure was coded in Berkeley Madonna to allow expansion with a feto-placental unit and include bidirectional placental transport of darunavir, at term. In order to parameterize the model, we determined maternal-to-fetal (mtf) and fetal-to-maternal (ftm) darunavir/ritonavir placental clearance with an ex vivo human cotyledon perfusion model. Simulated maternal PK profiles were compared with observed clinical data to verify the validity of the maternal model aspect. Next, population fetal PK profiles were simulated for different darunavir/ritonavir dosing regimens. These profiles were compared with available cord blood concentrations in vivo.
Results: An average (±SD) mtf cotyledon clearance of 0.91±0.11 mL/min and ftm of 1.6±0.3 mL/min was determined (n=6 perfusions). Scaled placental transfer was included into a feto-placental unit and integrated in the p-PBPK model. For darunavir 600/100mg twice a day, the simulated fetal plasma C_{max}, C_{trough}, T_{max} and $T_{1/2}$ were; 1.1 mg/L, 0.57 mg/L, 3 hours, and 21 hours, respectively. This indicates that the fetal population C_{trough} is higher than the protein-adjusted EC_{90} for wild type virus (0.20 mg/L) and around the EC_{90} for resistance virus (0.55 mg/L). The simulated ftm plasma concentration ratio (range) over a dosing interval was 0.30 (0.16 - 0.37), compared to a median (range) ratio for observed darunavir ctm plasma ratio of 0.18 (0 - 0.82).
Conclusion: A p-PBPK model for maternal darunavir exposure was extended with a feto-placental unit. The simulated fetal darunavir plasma concentrations were in the range of observed cord blood concentrations. This advanced model provides a valuable tool in assessing the implications of new dosing regimens, optimizing the safety of maternal pharmacotherapy, and optimizing fetal antiretroviral treatment.

754 SUBSTANTIALLY LOWER RILPIVIRINE PLASMA CONCENTRATIONS DURING PREGNANCY

Angela Colbers[1], **Stein Schalkwijk**[1], Deborah Konopnicki[2], Andrea Gingelmaier[3], John Lambert[4], Ineke van der Ende[5], José Moltó[6], David M. Burger[1], for the PANNA network
[1]Radboud Univ Med Cntr, Nijmegen, Netherlands, [2]Saint-Pierre Univ Hosp, Brussels, Belgium, [3]Klinikum der Univ München, München, Germany, [4]Mater Misericordiae Univ Hosp Dublin, Dublin, Ireland, [5]Erasmus Univ Med Cntr, Rotterdam, Netherlands, [6]Fundació Lluita Contra la Sida, Badalona, Spain

Background: During pregnancy adequate antiretroviral exposure is important to prevent treatment failure, resistance and mother-to-child transmission (MTCT). However, pregnancy-related physiological changes may result in decreased antiretroviral exposure. Limited data is available on the pharmacokinetics (PK) of rilpivirine (RPV) during pregnancy. We aimed to study the PK of RPV during pregnancy, including placental transfer.
Methods: An open-label, multi-centre phase IV study in HIV-1-infected pregnant women recruited in HIV treatment centers in Europe (PANNA Network). Patients treated with RPV 25mg once daily during pregnancy had intensive steady-state 24-hour PK profiles in the third trimester and postpartum. RPV was taken with food. When feasible, cord blood and matching maternal blood samples were taken at delivery to asses placental transfer. RPV plasma concentrations were determined with a validated LC-MS method. The proposed minimum effective concentration of RPV was 0.04 mg/L (based on ECHO/THRIVE PK data).
Results: Fifteen patients (10 black, 2 white, 2 Asian and 1 other) with a median (range) age of 30 (19-36) years were included in the analysis. Median (range) gestational age at delivery was 40 weeks (38-42); birth weight was 3480 (2770-4470) gr. Approaching delivery all patients had a VL <50 cps/mL. No children were HIV-infected, no birth defects were reported. 15 PK curves during 3rd trimester and postpartum were available. Geometric Mean Ratios (90% confidence interval) of PK parameters third trimester/postpartum were: 0.53 (0.45-0.63) for AUC0-24; 0.63 (0.54-0.74) for Cmax; and 0.46 (0.37-0.56) for C0h. Two out of 15 patients had a sub-therapeutic C0h in the third trimester, no sub-therapeutic levels were observed postpartum. The median (range, n=5) ratio of cord blood/maternal plasma RPV concentrations was 0.5 (0.35-0.81).
Conclusion: In this study exposure to RPV was about 50% lower in the third trimester of pregnancy, however, in this limited number of patients, maternal VL was suppressed close to delivery and no MTCT took place. It is important that RPV is taken with a meal during pregnancy and we would advice TDM in the third trimester to avoid sub-therapeutic exposure.

755 ELVITEGRAVIR/COBICISTAT PHARMACOKINETICS IN PREGNANCY AND POSTPARTUM

Brookie Best[1], Edmund Capparelli[1], Alice Stek[2], Edward Acosta[3], Elizabeth Smith[4], Nahida Chakhtoura[5], Jiajia Wang[6], Adriane Hernandez[7], Mark Mirochnick[8], for the IMPAACT P1026s Protocol Team
[1]Univ of California San Diego, La Jolla, CA, USA, [2]Univ of Southern California, Los Angeles, CA, USA, [3]Univ of Alabama at Birmingham, Birmingham, AL, USA, [4]DAIDS, NIAID, Rockville, MD, USA, [5]NICHD, Bethesda, MD, USA, [6]Harvard Univ, Boston, MA, USA, [7]Frontier Sci & Tech Rsr, Amherst, NY, USA, [8]Boston Med Cntr, Boston, MA, USA

Background: Elvitegravir (EVG), an integrase strand transfer inhibitor, is significantly metabolized by CYP3A and UGT 1A1/3, and must be administered with a pharmacokinetic (PK) booster. It has not been studied in pregnant women or infants. This study described EVG/cobicistat (COBI) exposure during pregnancy compared to postpartum and in infant washout samples after delivery.
Methods: IMPAACT protocol P1026s is an ongoing, nonrandomized, open-label, parallel-group, multi-center, international and domestic, phase-IV prospective study of antiretroviral PK in HIV-infected pregnant women. Intensive steady-state 24 hour PK profiles of EVG/COBI following 150/150 mg once-daily dosing were performed during the 2nd trimester (2T), 3rd trimester (3T) and 6-12 weeks postpartum (PP). Infant EVG washout samples were collected if birth weight > 1000 grams and there were no severe malformations or medical conditions. EVG/COBI were measured by validated LC-MS/MS with a quantitation limit of 10 ng/mL. A two-tailed Wilcoxon signed rank test ($\alpha = 0.10$) was employed for paired within-subject comparison.
Results: Twenty-nine subjects from the US were enrolled – 19 black, 3 white, 6 Hispanic, 1 Asian/Pacific Islander with a median age of 29 years at 3T (range 19 – 48). EVG/COBI PK data were available for 16, 20 and 15 women in 2T, 3T and PP, respectively. EVG exposure was lower and clearance was higher in the 2T and 3T compared to PP (Table 1). COBI exposure was lower and clearance higher in the 2T and 3T compared to postpartum, significantly for 3T. Washout EVG/COBI PK data were available for 18 infants; EVG elimination half-life was 7.4 hours (range 4.3 - 13); COBI was undetectable in all infant samples. Viral load at delivery was < 50 copies/mL for 14 of 19 women (74%). Median infant gestational

age at birth was 38.8 weeks. Congenital anomalies were reported in 2 infants. Twenty of 26 infants were HIV-negative based on best available data, and 6 are indeterminate or pending thus far.
Conclusion: EVG/COBI exposure are substantially lower in pregnancy compared to postpartum. Infant EVG elimination half-life was similar to postpartum maternal subjects and historical non-pregnant adult controls. More PK, safety and outcome data in pregnant women are needed before EVG/COBI can be recommended for use during pregnancy.

756 PROTEASE-INHIBITOR–BASED CART IS ASSOCIATED WITH HIGH ESTRADIOL LEVELS IN PREGNANCY

Kayode Balogun[1], Monica Guzman[1], Eszter Papp[1], Mona Loutfy[2], Mark Yudin[3], Jay MacGillivray[4], Kellie Murphy[5], Sharon Walmsley[6], Michael Silverman[7], Lena Serghides[1]
[1]Univ Hlth Network, Toronto, Ontario, Canada, [2]Women's Coll Rsr Inst, Toronto, Ontario, Canada, [3]St. Michael's Hosp, Toronto, Ontario, Canada, [4]Mt Sinai Hosp, Toronto, Ontario, Canada, [5]Univ of Toronto, Toronto, Ontario, Canada, [6]Univ of Western Ontario, London, Ontario, Canada
Background: Over 1.5 million HIV-infected (HIV+) women become pregnant annually. Most of these women access combination antiretroviral therapy (cART) for their own health and to prevent perinatal transmission of HIV. Studies have linked protease inhibitor (PI)-based cART to adverse birth outcomes. Endocrine dysfunction is common among HIV+ individuals, and altered levels of estradiol (E2) have been reported in patients on cART. However, no data exist on the effect of cART on E2 in the context of pregnancy. Our objective was to investigate the effect of PI-based cART on E2, and to investigate the association between E2 and adverse birth outcomes in HIV+ pregnant women.
Methods: A multi-centre prospective cohort study of 96 pregnant women was conducted between 2010 and 2015 in Toronto, Canada. Plasma samples were collected from HIV+ pregnant women on PI-based regimens (n=46), PI-sparing regimens (n=8), and matched controls (n=42) at 3 different gestational time points defined as early (12-18 weeks), mid (24-28 weeks), and late (34-38 weeks). Maternal and cord plasma samples were also collected at delivery. Plasma levels of E2, sex hormone binding globulin (SHBG), and the E2 precursor dehydroepiandrosterone sulfate (DHEAS) were measured by ELISA. Associations between birth weight and hormone levels were assessed by Spearman correlation.
Results: Birth weight centile was lower in the HIV+ group compared to controls [median 25 IQR (9.5-55.9) vs. 53.5 (30.75-70.75), p=0.0008]. There was a significant increase in E2 levels from mid to late gestation in HIV+ women on PI-based regimens, but not in women on PI-sparing regimens or HIV-uninfected controls. E2 levels in the cord were significantly higher in the PI-cART group compared to controls [median 23.9 ng/mL IQR (16.36-36.40) vs. 15.68 (12.19-21.21, p=0.0018], as were DHEAS levels and the E2/SHBG index. There was a positive correlation between cord E2 and DHEAS levels in the PI-cART group (r=0.47; p=0.0013). Cord E2 levels correlated inversely with birth weight centile in the PI-cART exposed women (r= -0.41; p=0.007), but not in controls or non-PI-cART exposed women.
Conclusion: Our data suggest that PI-cART use in pregnancy may be associated with higher than normal levels of E2, perhaps stimulated by increased production of DHEAS. An association between high cord E2 levels and fetal growth restriction was observed in PI-cART exposed pregnant women.

757 RALTEGRAVIR PHARMACOKINETICS AND SAFETY IN HIV-1 EXPOSED NEONATES: DOSE-FINDING STUDY

Diana F. Clarke[1], Edward Acosta[2], Anne Chain[3], Mae Cababasay[4], Jiajia Wang[5], Hedy Teppler[6], Elizabeth Smith[7], Rohan Hazra[8], Mark Mirochnick[9], for the IMPAACT P1110 Protocol Team
[1]Boston Med Cntr, Boston, MA, USA, [2]Univ of Alabama at Birmingham, Birmingham, AL, USA, [3]Merck Rsr Labs, Rahway, NJ, USA, [4]Harvard Univ, Boston, MA, USA, [5]Merck Rsr Labs, North Wales, PA, USA, [6]DAIDS, NIAID, Rockville, MD, USA, [7]NICHD, Bethesda, MD, USA, [8]Boston Univ, Boston, MA, USA
Background: Raltegravir (RAL) has potential for use as prophylaxis of perinatal transmission and early intensive treatment of neonates with HIV infection. Safety and pharmacokinetics (PK) of RAL was studied to determine the appropriate dose of RAL oral granules for suspension during the first 6 weeks of life.
Methods: IMPAACT P1110 is a phase I multicenter trial enrolling full-term HIV-1 exposed neonates at high risk of acquiring HIV-1-infection, with or without in utero RAL exposure. Study design included two cohorts: cohort 1 infants received 2 single RAL doses 1 week apart; cohort 2 infants received daily RAL dosing for first 6 weeks of life. PK data from Cohort 1 (previously reported) and from older infants and children were combined in a population PK model and simulations were used to select this daily RAL dosing regimen for evaluation in RAL naïve infants in Cohort 2: 1.5 mg/kg daily starting within 48 hours of life through day 7; 3 mg/kg twice daily on days 8-28 of life; 6 mg/kg twice daily after 4 weeks of age. Four plasma samples were collected after the initial dose and on the 3 mg/kg dose between 15-18 days of life; sparse sampling was obtained when doses were changed. Samples were analyzed for RAL concentrations using a validated HPLC-MS-MS method. AUC was estimated using the trapezoidal method. Protocol exposure targets for each subject are AUC24 12-40mg*h/L, AUC12 6-20 mg*h/L, C12 or C24 > 33ng/mL. Safety was assessed based on clinical and laboratory evaluations.
Results: Twenty-six RAL-naïve infants were enrolled in Cohort 2. Evaluable PK results and 6 week safety data are available for 25 infants. After the first dose of 1.5 mg/kg, geometric mean (GM) RAL AUC24 was 38.2 mg*h/L and C24 was 948 ng/mL. On 3 mg/kg twice daily the GM RAL AUC12 was 14.3 mg*h/L and Cl2 estimated to be 176.1 ng/mL. There were no safety concerns associated with daily RAL administration through 6 weeks of life.
Conclusion: Daily RAL was safe and well tolerated during the first 6 weeks' of life. All GM protocol exposure targets were met. In some infants AUC24 following the initial dose was slightly above target range but this was considered acceptable given the rapid increase in RAL metabolism over the first week of life. The PK targets and the safety guidelines have been met for RAL-unexposed infants in cohort 2 using the specified dosing regimen.

Raltegravir Dose (Time of sampling)	Pharmacokinetic Parameter	Geometric mean (range)	# Infants who Met PK Exposure Target
Initial dose: 1.5 mg/kg QD (within 48 hours of life)	AUC_{24}	38.2 mg*h/L (18.6-78.3)	Above range: 11 Within range: 13 Below range: 0
	C_{24}	948 ng/mL (191-2789)	Above target: 25 Below target: 0
Increased dose: 3.0 mg/kg BID (Day 15-18 of life)	AUC_{12}	14.3 mg*h/L (4.7-28.8)	Above range: 7 Within range: 15 Below range: 1
	C_{12}	176 ng/mL (11-957)	Above target: 22 Below target: 1

PK exposure targets: AUC_{24}: 12-40 mg*h/L; AUC_{12}: 6-20 mg*h/L; C_{24} or C_{12} >33 ng/mL

758 PHARMACOKINETICS OF NEVIRAPINE PROPHYLAXIS IN HIV-EXPOSED LOW BIRTH WEIGHT INFANTS

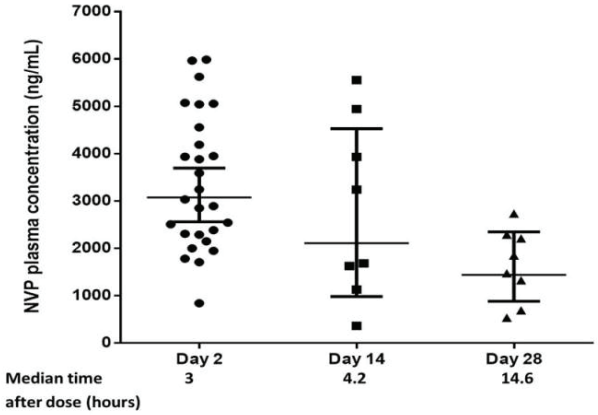
Adrie Bekker[1], Avy Violari[2], Mae Cababasay[3], Jiajia Wang[3], Lubbe Wiesner[4], Edmund Capparelli[5], Mark Cotton[1], Firdose Nakwa[2], Mark Mirochnick[6], for the IMPAACT P1106 Team
[1]Stellenbosch Univ, Cape Town, South Africa, [2]Univ of Witwatersrand, Johannesburg, South Africa, [3]Harvard Univ, Boston, MA, USA, [4]Univ of Cape Town, Cape Town, South Africa, [5]Univ of California San Diego, La Jolla, CA, USA, [6]Boston Med Cntr, Boston, MA, USA
Background: There are limited data on nevirapine (NVP) pharmacokinetics (PK) and safety in low birth weight (LBW) infants (< 2500g).

Methods: IMPAACT P1106 is a Phase IV study on PK and safety in LBW infants receiving antiretroviral and tuberculosis medicines as part of their clinical care in two South African sites. Arm 1 focused on NVP for HIV-1 prophylaxis. Infants were stratified by birth weight (<1400 g, 1400 - <1800 g, and 1800 - <2500g). NVP was dosed at 2 mg/kg once daily (birth to 14 days of age), followed by 4 mg/kg once daily. Infant characteristics, PK samples and safety data were collected at study entry (day 7-14 of age) and at 4, 6, 10, 16 and 24 weeks of age. An adverse event (AE) was classified as expected (associated with prematurity) or unexpected. Plasma samples were assayed for NVP by LC-MS with lower limit of detection of 0.02 µg/ml. The NVP trough target was > 0.1 µg/ml.
Results: Forty LBW infants, mean birth weight of 1675 g (range 950-2460 g) and mean gestational age of 33 weeks (range 28-40 weeks) were enrolled. NVP trough concentrations were available for 27 infants (94 observations) with mean weight of 2147 g (range 965 – 6050 g) and mean postmenstrual age of 37 weeks (range 29 – 56 weeks) at time of PK sampling. Mean NVP trough concentration across all visits was 1.87 µg/mL (range < 0.02 - 10.69 µg/mL). NVP trough concentrations were < 0.1 µg/ml in 6/94 (6%) observations. Below target samples were all from later visits (median postmenstrual age 44 weeks; median weight of 3903 grams) on infants already discharged to home and receiving NVP from caregiver. At the initial visit, lower gestational age was associated with higher NVP concentration. Across all visits, NVP trough concentrations were inversely related (p=0.001) to infant postnatal age (see figure). Three infants died; 2 from sudden unexpected death and 1 from confirmed septicemia. Ten infants had Grade 3/4 unexpected AEs, most common being pneumonia (n=4). Nine infants had Grade 3/4 expected AEs, most common being presumed or confirmed sepsis (n=6). All AEs were assessed as unrelated to NVP.
Conclusion: In premature infants, the NVP dosing regimen studied was safe and achieved trough concentrations above the 0.1 µg/mL prophylaxis target. NVP concentration at the initial visit increased with decreasing gestational age and subsequent concentrations decreased with increasing postnatal age. No treatment related adverse events were observed.

759 SAFETY OF 6-WEEK TRIPLE ANTIRETROVIRAL PROPHYLAXIS IN HIGH-RISK HIV-EXPOSED INFANTS

Suvaporn Anugulruengkitt[1], Piyarat Suntarattiwong[2], Pradthana Ounchanum[3], Ussanee Srirompotong[4], Watsamon Jantarabenjakul[1], Jiratchaya Sophonphan[5], Tim R. Cressey[6], Chitsanu Pancharoen[1], Thanyawee Puthanakit[7], for the CIPHER_AEPEP Study Team
[1]Chulalongkorn Univ, Bangkok, Thailand, [2]Queen Sirikit Natl Inst of Child Hlth, Bangkok, Thailand, [3]Chiang Rai Prachanukroh Hosp, Chiang Rai, Thailand, [4]Khon Kaen Hosp, Khon Kaen, Thailand, [5]HIV Netherlands Australia Thailand Rsr Collab, Thai Red Cross AIDS Rsr, Bangkok, Thailand, [6]Prog for HIV Prevention and Treatment, Chiang Mai, Thailand, [7]Chulalongkorn Univ, Bangkok, Thailand

Background: Triple-drug antiretroviral prophylaxis of zidovudine (AZT)/lamivudine (3TC)/nevirapine (NVP) for high risk HIV-exposed neonates is recommended within the Thai national program. However, there are limited data about the safety and drug concentration achieved with this regimen initiated at birth.
Methods: Prospective cohort of infants born from HIV-infected pregnant women in 4 clinical sites in Thailand. Neonates with high risk of HIV transmission (mother has HIV RNA >50 copies/mL prior to delivery or received ART <12 weeks) received AZT and 3TC twice daily, plus NVP (4 mg/kg/dose) once daily, for 6 weeks. As a control group, neonates with standard risk of HIV transmission who received 4-weeks of AZT were also enrolled. Blood for complete blood count, aspatate transaminase (AST), alanine transaminase (ALT) were drawn at birth, aged 1, 2 and 4 month. Adverse events were graded according to DAIDS toxicity table 2014. Sparse plasma NVP concentrations were collected at week 1, 2 and 4 and assayed by a validated liquid chromatography-triple quadrupole mass spectrometry assay. Target NVP plasma trough concentration for prophylaxis was >100 ng/mL.
Results: From October 2015 to August 2016, 94 infants were enrolled. 31 neonates received triple ARV prophylaxis and 63 infants received AZT only. Overall, median (IQR) gestational age and birth weight were 38 (37-39) weeks and 2.8 (2.5-3.2) kg, respectively. Maternal ART during pregnancy were 39 (42%) TDF/3TC/EFV, 13 (14%) AZT/3TC/LPV/r, 11 (12%) TDF/3TC/LPV/r and 28 (30%) others. Median (IQR) infant hemoglobin at week 1 and 4 were 16.3 (15.3-18.1) and 10.4 (9.3-11.7) g/dL with no significant difference between the groups. There was no difference in adverse event rates between triple and AZT prophylaxis; all grade anemia (43.6% vs 39.9%), grade 3-4 anemia (3.2% vs 3.1%), all grade neutropenia (3.2% vs 3.0%), grade 3-4 neutropenia (1.1% vs 0.3%), elevated AST (1.1% vs. 1.5%), and elevated ALT (3.2 vs. 4.0%). No infants were diagnosed HIV-infected at age 4 months. NVP concentrations were available from 18 infants: geometric mean (%CV) plasma NVP concentrations were 3075 (67), 2109 (92) and 1438 (72) ng/mL at weeks 1, 2 and 4, respectively (Figure 1). All infants maintained nevirapine concentrations >100 ng/mL during the first 4 weeks.
Conclusion: Triple ART infant prophylaxis with 6-weeks of AZT/3TC/NVP in high risk HIV-exposed infants appears to be safe with high NVP concentrations being rapidly achieved and maintained during the first 4 weeks of life.



760 SAFETY & PHARMACOKINETICS OF THE MONOCLONAL ANTIBODY, VRC01, IN HIV-EXPOSED NEWBORNS

Coleen K. Cunningham[1], Elizabeth J. McFarland[2], Edmund V. Capparelli[3], Petronella Muresan[4], Charlotte Perlowski[5], Megan Valentine[5], Elizabeth Smith[6], John R. Mascola[7], Barney S. Graham[7], for the IMPAACT P1112 Team
[1]Duke Univ, Durham, NC, USA, [2]Univ of Colorado, Aurora, CO, USA, [3]Univ of California San Diego, La Jolla, CA, USA, [4]Harvard Univ, Boston, MA, USA, [5]FHI360, Durham, NC, USA, [6]DAIDS, NIAID, Rockville, MD, USA, [7]Vaccine Rsr Cntr, NIAID, Bethesda, MD, USA

Background: Despite advances in the use of antiretroviral therapy (ART) to prevent mother to child HIV transmission (MCTC), children still become infected for a variety of reasons. A long acting monoclonal antibody might provide a strategy to further prevent transmission.
Methods: This is an ongoing, prospective, open label, dose escalating study of a HIV neutralizing, monoclonal antibody, VRC01, administered as a single 20 or 40 mg/kg subcutaneous (SC) dose within 72 hours of birth to infants at increased risk of HIV transmission. Healthy infants and their mothers receive ART as indicated to prevent MTCT. Infants complete safety assessments over 4 hours immediately after dosing and then have safety and pharmacokinetic (PK) measures at 24 hours, days 3, 7, 14, 28, weeks 8, 16 and 24. A non-compartmental PK analysis is used except for CL./F and Vss/F which are estimated using a 2-compartment model. Target VRC01 level is 50 mcg/mL on day 28.

Results: Both dose groups are fully accrued (13 each) from 10 sites in the continental US, Puerto Rico, and South Africa. Approximately half enrollees are male (56%) and black (52%). VRC01 was administered soon after birth, at a mean age of 1.8 (SD 1.0) days. Most infants (12/13) in the lower dose group received a single injection (average volume 0.6 mL) while 12/13 infants in the higher dose group received two injections (average volume 0.7 mL). Safety data are available for 25/26 subjects and PK data through day 28 for the lower dose are available for 12/13 (one child was under-dosed and excluded from PK analysis). Overall, VRC01 was well tolerated with no attributable serious systemic reactions. Local reactions were common, occurring in six (46%) and nine (75%) infants in the low and high dose groups, respectively. None of the local reactions were serious and 100% and 90% in the 20 and 40 mg dose groups, respectively, resolved within four hours of injection. Pain at the injection site was reported in only two infants, both grade 1. The PK measures for 12 infants in the 20 mg/kg group are shown in the table.
Conclusion: These preliminary results indicate that VRC01 administered to neonates via the SC route is safe and well tolerated. The PK for the lower dose demonstrate circulating antibody through day 28 of life close to but below the target in 9/12 (75%). The half-life of VRC01 would support monthly injections for infants at ongoing risk of HIV infection through breastfeeding.

Pharmacokinetic·measure¤	MEAN¤	STD·DEV¤	MEDIAN¤	MIN¤	MAX¤
Day·28·VRC01·level·(mcg/mL)¤	40.2¤	15.2.¤	39.2¤	16.7¤	75.6¤
Maximum·concentration·(mcg/mL)¤	234.7¤	43.5¤	233.3¤	153.6¤	333.0¤
CL/F·(L/d/kg;·apparent·clearance)¤	0.0049¤	0.0013¤	0.0049¤	0.0033¤	0.0067¤
Vss/F·(L/kg;·apparent·volume·of·distribution)¤	0.16¤	0.01¤	0.15¤	0.14¤	0.16¤
Serum·half-life·(d)¤	19.0¤	5.1¤	19.6¤	10.4¤	28.6¤
Time·at·maximum·concentration·(d)¤	2.4¤	1.89¤	1.6¤	0.9¤	6.11¤

761 MOTHER-TO-CHILD TRANSMISSION OF HIV IN KENYA: A MULTIYEAR NATIONAL EVALUATION

Lucy Ng'ang'a[1], Christine J. McGrath[2], Agnes Langat[1], Jillian Pintye[3], Mary Schmitz[1], Abraham Katana[1], Rose Wafula[4], John Kinuthia[5], Grace John-Stewart[3], Kevin De Cock[1]
[1]US CDC, Nairobi, Kenya, [2]Univ of Texas Med Branch, Galveston, TX, USA, [3]Univ of Washington, Seattle, WA, USA, [4]Natl AIDS and STD Control Prog, Ministry of Hlth, Nairobi, Kenya, [5]Kenyatta Natl Hosp, Nairobi, Kenya

Background: With the efforts toward elimination of mother to child transmission (EMTCT), the number of infants with HIV has declined sharply. However, EMTCT programs need to be monitored to identify gaps and design interventions to further reduce MTCT. This study determined MTCT at 6 weeks, 9 and 18 months, and cofactors for MTCT in a multi-year, nationwide registry-based survey in Kenya.
Methods: We conducted a retrospective chart review of HIV Exposed Infants (HEI) enrolled in 62 randomly selected facilities in Kenya between 2011-2013. MTCT was defined as infant positive DNA PCR test. Cohort analysis included infants with PCR result at <3 months of age followed to last known visit. Cox regression determined correlates of MTCT. Estimates were weighted to account for survey design.
Results: Overall, 8773 HEI were identified of whom 6034 (87.5%) had PCR results at <3 months and were included in the analysis. At 9 months, 75.4% of HEI remained in care and 57.1% at 18 months. By 18 months, 39.5% were lost, 0.9% reported dead, and 2.5% had transferred care. Overall MTCT was 2.7% at 6 weeks, 3.8% at 9 months, and 5.5% at 18 months (Table 1). From 2011 to 2013, 6 week MTCT declined from 3.5% to 2.8%; 9 month MTCT from 4.8% to 3.8%; and 18 month MTCT from 7.4% to 5.2%. Overall, 73.1% of HEI-mother pairs received maternal and infant ARVs, 10.6% maternal ARVs only, 8.7% infant ARVs only, and 7.7% no ARVs. Most women (68.6%) received HAART, 13.5% received short course prophylaxis (AZT+NVP+3TC), 1.5% single dose NVP (sdNVP) and 16.4% no ARVs. Among infants, 72.3% received NVP for 6 weeks during breastfeeding, 4.1% NVP+AZT+3TC for 7 days, 5.3% sdNVP only, and 18.3% no ARVs. MTCT was associated with older infant age (months) at enrollment (HR=1.02, 95% CI 1.00-1.04). Compared to complete PMTCT (maternal and infant ARVs), no maternal or infant ARVs, maternal ARVs only, and infant ARVs only were associated with increased MTCT [HR=7.4 (4.6-11.9), HR=2.3 (1.4-3.9), HR=2.0 (1.2-3.2), respectively]. MTCT was highest in women receiving short course prophylaxis and sdNVP compared to HAART [HR=2.5 (1.7-3.7) and HR=2.6 (1.0-6.5), respectively].
Conclusion: Despite decreases from 2011-2013, MTCT remains high underscoring the benefit of early HEI enrollment and need for rapid expansion of HAART to all HIV-infected women irrespective of immune status. The high loss to follow-up at 18 months underscores the need for better strategies to improve retention and the implementation of interventions to track and retain HEI in care.

Table 1. Infant HIV transmission combined and by year among HIV exposed infants with known PCR result at <3 months of age (n=6034), 2011-2013

	Weighted % (95% CI)				
	Overall	2011	2012	2013	P-value
6 weeks	2.7 (2.1-3.5)	3.5 (2.4-4.9)	1.8 (1.4-2.3)	2.8 (1.8-4.2)	.014
9 months	3.8 (2.8-5.0)	4.8 (3.5-6.7)	2.6 (1.9-3.6)	3.8 (2.2-6.5)	.065
18 months	5.5 (4.0-7.5)	7.4 (5.0-10.7)	4.0 (2.8-5.7)	5.2 (3.0-8.8)	.048

762 MISSED OPPORTUNITIES FOR REPEAT HIV TESTING AND EARLY ART INITIATION IN PREGNANCY

Anna Joy Rogers[1], Eliud Akama[2], Elly Weke[3], Justin Blackburn[1], George Owino[4], Elizabeth A. Bukusi[3], Patrick Oyaro[2], Zachary A. Kwena[2], Craig Cohen[5], Janet M. Turan[1]
[1]Univ of Alabama at Birmingham, Birmingham, AL, USA, [2]Kenya Med Rsr Inst, Kisumu, Kenya, [3]Kenya Med Rsr Inst, Nairobi, Kenya, [4]Kenya Med Rsr Inst, Rongo, Kenya, [5]Univ of California San Francisco, San Francisco, CA, USA

Background: It is estimated that a third of all mother-to-child transmission (MTCT) of HIV occurs among women with incident infection during pregnancy, making repeat HIV testing during the late antenatal period a crucial time to identify and initiate treatment for women who acquire HIV infection. International recommendations, adopted as part of the Kenya HIV Testing Services guidelines, suggest that pregnant women in generalized epidemic settings be offered retesting three months after an initial negative HIV test early in pregnancy.
Methods: Longitudinal analyses were conducted in a sample of 2164 women attending antenatal care (ANC) at a rural district hospital in Migori County, Kenya. Data were abstracted from registers for all women who attended ANC from the years 2011 to 2014.
Results: The majority of women (1954/2164, 90.2%) presented for their first ANC visit early enough (≤ 28 weeks gestation) to later be eligible for retesting, but several missed opportunities were noted including: (a) 310 (15.8%) women never returned to ANC and thus were considered to have an unknown HIV status at delivery; of the 495 women who returned to ANC when eligible, (b) only 132 (36.6%) were retested and (c) 126 (25.5%) failed to be retested even though eligible at two or more visits. On retest, two women tested

HIV-positive, suggesting a seroconversion rate of 1.5% from early to late pregnancy. Although most women came early in pregnancy and a quarter had at least 4 ANC visits, 59.7% of all women had unknown HIV status at delivery. For a minority of women (210/2164, 9.8%) who presented later (>28 weeks gestation) for their first ANC visit, retesting is not standard protocol. However, among them 8 (3.8%) tested HIV-positive, possibly constituting a missed opportunity for early antiretroviral therapy (ART) initiation.
Conclusion: Missed opportunities for repeat HIV testing and early ART initiation among pregnant women may contribute to continuing high rates of MTCT in Kenya and similar settings in sub-Saharan Africa, particularly in light of current recommendations that all pregnant women who test HIV-positive be started immediately on ART. Extrapolating the seroconversion rate to all women who missed a retest would suggest that potential cases of MTCT are slipping through the cracks. Contributors to missed opportunities include patient factors, such as not returning to ANC after testing negative for HIV early in pregnancy, and health system factors, such as a failing to retest eligible women.

763 LOW HIV INCIDENCE IN SOUTH AFRICAN PREGNANT WOMEN RECEIVING A PREVENTION INTERVENTION

Geoffrey Fatti[1], **Ashraf Grimwood**[1], Bon Egbujie[1], Eula Mothibi[1], Najma Shaikh[1], Debra Jackson[2], Brian Eley[3]
[1]Kheth'Impilo, Cape Town, South Africa, [2]UNICEF, New York, NY, USA, [3]Univ of Cape Town, Cape Town, South Africa

Background: Young Southern African women have the highest HIV incidence globally. Pregnancy doubles the risk of HIV acquisition, and maternal HIV acquisition contributes significantly to the Sub-Saharan paediatric HIV burden. HIV pre-exposure prophylaxis is currently contraindicated during pregnancy and breastfeeding in South Africa. Little evidence of combination HIV prevention interventions during pregnancy and lactation are available globally. We measured HIV incidence amongst pregnant and postpartum women receiving a community-based combination HIV prevention intervention in a high HIV incidence setting in South Africa.
Methods: A cohort study including HIV-uninfected pregnant women was performed. Lay community-based health workers provided sexual health counselling and performed three-monthly home and clinic-based individual and couples HIV testing and counselling (HTC) until 18 months postpartum. Male partners were referred for medical circumcision, sexually transmitted infections and HIV treatment as appropriate. Kaplan-Meier analyses and Cox's regression were used to estimate HIV incidence and factors associated with HIV acquisition.
Results: A total of 1356 women were included with median age of 22.5 years (IQR: 19.4-27.0) and median gestational age at presentation of 16 weeks (IQR: 12-16). Included women received 5289 HIV tests. Eleven new HIV infections were detected over 828.3 person-years (PY) of follow up, with HIV incidence being 1.33 infections/100 PY (95% CI: 0.74-2.40). The antenatal HIV incidence rate was 1.49 infections/100 PY (95% CI: 0.64 to 2.93) and the postnatal HIV incidence rate was 1.03 infections/100 PY (95% CI: 0.33-3.19). Women within known serodiscordant couples, adjusted hazard ratio (aHR)=32.7 (95% CI: 3.8-282.2), and women with newly diagnosed HIV-infected partners, aHR=126.4 (95% CI: 33.8-472.2) had substantially increased HIV acquisition. Women with circumcised partners had a reduced risk of incident HIV infection, aHR=0.22 (95% CI: 0.03-1.86).
Conclusion: Previous regional studies have measured maternal HIV incidence between 4.8 infections/100 PY to 16.8 infections/100 PY, thus HIV incidence in this study was 73%-86% lower than previous studies. Community-based combination HIV prevention interventions show promise in reducing high maternal HIV incidence. Expanded roll-out of home-based couples HTC and initiating pre-exposure prophylaxis for pregnant women within serodiscordant couples should be considered in Southern Africa.

764 HIV INCIDENCE, CASCADE, AND TESTING AMONG MOTHERS IN WESTERN KENYA

Alliance Nikuze[1], Stephen Wanjala[2], Jihane Ben-Farhat[1], Willis Omwoyo[3], Laura Oyiengo[4], Elisabeth Szumilin[5], Leon Salumu[5], Alexandra Vandenbulcke[5], Valarie S. Opollo[6], **David Maman**[7]
[1]Epicentre, Paris, France, [2]MSF, Nairobi, Kenya, [3]Ministry of Hlth, Homa Bay, Kenya, [4]Natl AIDS/STI Control Prog, Nairobi, Kenya, [5]MSF France, Paris, France, [6]Kenya Med Rsr Inst, Kisumu, Kenya, [7]Epicentre, Cape Town, South Africa

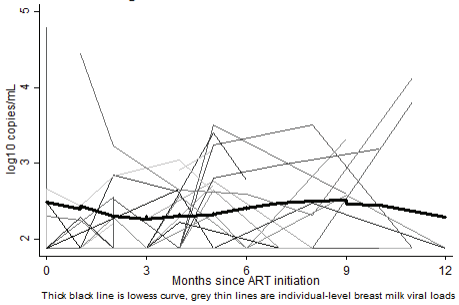
Background: There are limited evaluations of prevention of mother to child HIV transmission (PMTCT) programs, particularly testing coverage in pregnant women, since the implementation of option B+ in sub-Saharan Africa. The Impact of Expanded Screening Strategies (IESS) study aimed at reconstructing the PMTCT cascade in Ndhiwa sub-county
Methods: Through a cross-sectional facility-based survey at expanded programs of immunization (EPI) and maternity, mother-infant pairs were enrolled in the study from February 2016 July 2016. The questionnaires collected information on participants' background, reproduction, pregnancy, HIV/AIDS, ART coverage and survival. From thirty three health facilities providing ART services in the sub-county, 26 were selected due to their geographical coverage. All HIV-positive mothers and children had their VL measured, regardless of their ART status. Population viral load suppression is defined the proportion of HIV-positive women with a VL<1,000 cp/mL
Results: A total of 3,585 women were enrolled: 1925 at EPI 6 weeks, 1116 from EPI 9 months and 544 from maternity. Overall median age was 23 [IQR 19-29]. At ANC, testing coverage was high with 96.5% (95%CI 95.9-97.1) women testing during their last pregnancy but systematic retesting was very low with 38.1% (95%CI 36.4-40.0) of all women tested at least twice during ANC. Among 882 HIV-positive women (HIV prevalence: 24.7%; 95%CI 23.3-26.1), 513 were already diagnosed prior to the beginning of their last pregnancy, 336 were diagnosed during their last pregnancy and 33 (higher in EPI 6 weeks than 9months 23 vs. 6) were undiagnosed at the time of the survey. Overall HIV Incidence was 4.1 new cases per100PY (95%CI 2.9-5.7). HIV incidence varies with age from 3.1 among those <19 years to 4.7 and 5.9 new cases per 100py at 20-24 and 25-29 years. It then decreased at 3.3 new cases for those age 30 years or more. The different steps of the cascade were as follow: 96.3% were diagnosed, (95%CI 94.8-97.3), 92.4% (95%CI 90.5-94.9) were on ART and 78.1% (95%CI 75.0-80.8) were suppressed (VL<1,000 cp/mL)
Conclusion: High level of coverage and viral suppression were achieved among mothers following the implementation of option B+. Nevertheless, systematic retesting throughout pregnancy and breastfeeding needs to be reinforced as HIV incidence remained extremely high

765 DETECTION OF HIV IN BREAST MILK AMONG PREGNANT/POSTPARTUM WOMEN WITH RECENT HIV

Alison L. Drake[1], John Kinuthia[2], Daniel Matemo[2], Barbra A. Richardson[1], Sandy Emery[3], Vrasha Chohan[1], Julie Overbaugh[3], Grace John-Stewart[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Kenyatta Natl Hosp, Nairobi, Kenya, [3]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA

Background: Incident HIV infection during pregnancy/postpartum substantially increases mother-to-child HIV transmission (MTCT) risk due to high maternal HIV viral load (VL). Breast milk VL among women with recent infection has not been well characterized, and could contribute to postnatal MTCT. We prospectively measured breast milk and plasma VL among pregnant/postpartum women with recent HIV infection.
Methods: Pregnant/postpartum women in Western Kenya with recent HIV infection (documented negative ≤3 months prior) were identified and prospectively followed. Women who started antiretroviral therapy (ART) <40 days after HIV diagnosis with ≥1 breast milk sample were included in the analysis. VL lower limit of detection was 1.87 and 2.17 log10 copies/mL for breast milk and plasma samples collected serially, respectively. Generalized estimating equations with a logit link were used to determine the relationship between plasma VL and duration of ART on detection of HIV in breast milk.
Results: Among 25 women with recent infection, 14 were diagnosed in pregnancy and 11 postpartum. Median age was 21 years (interquartile range [IQR]:19-26) and time to ART initiation was 13 days (IQR 8-19). A total of 133 breast milk samples were tested for HIV, with a median of 6 (IQR 3-8) assays/woman. Median baseline plasma VL was 5.56 log10 copies/mL (IQR: 4.98-5.70). HIV was detected in the first breast milk sample collected from 5 (36%) women diagnosed during pregnancy and 6 (55%) diagnosed postpartum; breast milk VL ranges in both groups were similar (2.30-4.80 and 2.36-4.44 log10 copies/mL, respectively). Most (88%) women had HIV detected in ≥1 breast milk sample; individual-level breast milk VL over time are shown in Figure 1. Plasma VL and months since ART were not associated with detection of HIV in breast milk (Odds Ratio [OR] 1.15 per 1 log increase, 95% Confidence Interval [CI]:0.81-1.63) and OR 0.98, 95% CI:0.88-1.09; respectively). Two infants acquired HIV, at 2 weeks (mother diagnosed in pregnancy) and 6 months (mother/infant concurrently diagnosed). Breast milk VL for the mother who transmitted at 6 months was 4.4 log10 copies/mL at the time of diagnosis.
Conclusion: Among recently infected pregnant/postpartum women, HIV was detected in breast milk soon after infection and often concurrent with diagnosis. Breast milk HIV was detected among all women, even among women who initiated ART in pregnancy. Early identification and treatment of incident maternal HIV infections is critical to prevent MTCT.

Figure 1. Breast milk HIV RNA levels



766 UPTAKE AND RETENTION IN CARE OF PREGNANT WOMEN STARTING OPTION B+ IN MAPUTO

Esmeralda Karajeanes[1], Dulce Bila[1], Orvalho Augusto[2], Maria Lain[1], Basilio Muianga[1], Chadreque Muluana[3], Nello Macuacua[1], Victorino Chavane[1], Paula Vaz[1]
[1]Fundação Ariel Glaser Contra o Sida Pediatrico, Maputo, Mozambique, [2]Univ Eduardo Mondlane, Maputo, Mozambique, [3]Direcção Provincial de Saude de Maputo, Maputo Provincia, Mozambique

Background: Following the 2013 World Health Organization recommendation (WHO), Mozambique introduced the option B+ strategy to prevent mother to child transmission (PMTCT) of the human immunodeficiency virus (HIV). In Mozambique retention in care is still a challenge and undermines every effort made to control the epidemic. We compared attrition (defaulting from treatment or death) rates and retention in care of pregnant women (PW) initiating antiretroviral therapy (ART) on Option B+ with non-pregnant women of childbearing age initiating ART, followed at health facilities (HF) supported by Ariel Glaser Foundation in Maputo, Mozambique.
Methods: A cohort analysis was carried out on data from the electronic ART patient tracking system. Anonymous data from women who initiated ART between January 2014 and June 2015 was extracted. Descriptive statistics and Kaplan-Meier estimates were used to estimate retention. Cox proportional hazards regression was used to estimate the hazard-rate of attrition with robust cluster adjusted standard errors. Adjusting variables included HF's patient volume, WHO staging, prophylactic cothrimoxazole (CTZ), CD4 count, age at ART initiation, education and marital status.
Results: A total of 22079 women from 34 sites were included: 8316 were pregnant on B+ and 13763 non-pregnant. At ART initiation, PW were younger than non-pregnant women (mean age 26.8 Vs. 32.4, P<0.001) and with less advanced disease (WHO I/II) (95.2% Vs 75.4%, P<0.0001). In both groups, women were more likely to be single, have primary education and be on TDF/3TC/EFV regimen. Lower cumulative retention was observed in B+ PW at 12 and 24 months (71.5 and 59.1 vs. 83.9 and 74.0, P < 0.001). Incidence of attrition was more likely to occur in the first 6 months with higher rate for B+ women (25.9/100 PY; 95% CI: 20.1 - 31.6 vs. 13.3/100 PY; 95% CI:10.1 - 16.5) (Figure 1). PW had higher risk of attrition (adjusted HR:1.65; 95% CI: 1.44–1.88); other risk factors included lower age (15-19) and illiteracy.
Conclusion: The results from this study suggest that the benefits of ART to prevent MTCT through implementation of option B+ can be undermined by low retention rates in pregnant women on B+. Programmatic strategies should be implemented in order to improve retention in HIV positive pregnant women with particular emphasis to young girls.

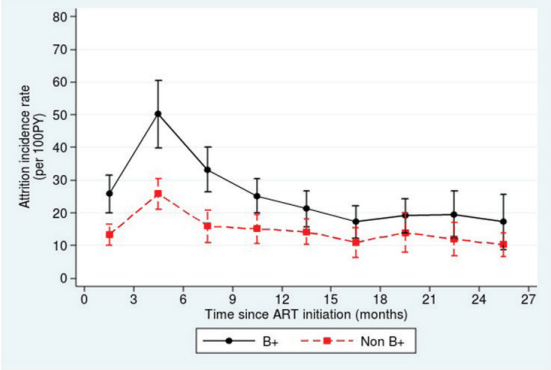


Figure 1: Cumulative incidence of attrition in B+ pregnant women, and non-pregnant women initiating ART.

767 STRATEGIES FOR VIRAL-LOAD MONITORING DURING PREGNANCY IN RESOURCE-LIMITED SETTINGS

Maia Lesosky[1], Elaine J. Abrams[2], Nei-Yuan M. Hsiao[3], Landon Myer[1], for the Maternal Child Health - Antiretroviral Therapy (MCH-ART) Study
[1]Univ of Cape Town, Cape Town, South Africa, [2]Columbia Univ, New York, NY, USA, [3]NHLS, Cape Town, South Africa

Background: Viral load (VL) monitoring is critical for effective antiretroviral therapy (ART). Pregnant women have unique monitoring needs due to MTCT risks and significant concerns about inadequate adherence, but there are few systematic insights into strategies for VL monitoring during pregnancy in resource-limited settings.
Methods: We developed a multi-compartment Monte Carlo simulation of VL trajectories during gestation and postpartum, parameterised using South African data from the Maternal & Child Health-Antiretroviral Therapy (MCH-ART) study. The model allows variable distributions of: pre-ART VL, gestation at ART start, time to viral suppression (VS), gestation at delivery and loss of VS over time. We simulated a cohort of 10,000 women starting ART in pregnancy followed through delivery and evaluated the performance of VL monitoring schedules with testing at different times and frequencies (including point-of-care [POC] testing with same-day results) to predict VL>1000 cps/mL as a threshold for possible interventions at delivery/postnatally.
Results: The model was parameterised with median (IQR) pre-ART log10 VL of 4.0 (3.3, 4.7), median gestation at ART start 20 weeks (16, 26), and 29% of individuals cumulatively experiencing VL>1000 cps/mL after VS by 6m postpartum. Four key findings emerge from applying different monitoring schemes to the simulated data: (i) if monitoring in pregnancy is based on current guidelines for non-pregnant adults with a first VL after 6m on ART, only 22% of women would be tested in pregnancy and 91% of all viraemia

would go undetected; (ii) if VL results can be available instantly (per POC) VL monitoring will capture 100% of viraemia but otherwise VL testing at any time point appears poorly predictive of raised VL occurring beyond 4 weeks in the future; (iii) the best-performing antenatal monitoring schedule (with 1 test at 36w gestation) predicts 77% of VL>1000 cps/mL at delivery but only 86% of women would be tested at this time due to preterm deliveries; (iv) the addition of pre-ART VL measures allows prediction of an additional 3-5% of all elevated VL.

Conclusion: This simulation suggests that pregnant women warrant VL monitoring approaches different from non-pregnant adults. Simple VL monitoring guidelines can be used to predict approximately three-quarters of all elevated VL at delivery, but effective implementation would require rapid turnaround times. POC testing may be important to detect larger proportions of viraemic women on ART for intervention.

768 VIRAL SUPPRESSION AMONG HIV+ PREGNANT WOMEN ENTERING ANTENATAL CARE ON ART IN UGANDA

Catherine A. Koss[1], Paul Natureeba[2], Deborah Cohan[1], Teddy Ochieng[2], Theodore Ruel[1], Miriam Nakalembe[3], Tamara D. Clark[1], Edwin D. Charlebois[1], Moses R. Kamya[3], Diane V. Havlir[1]

[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Makerere Univ–Univ of California San Francisco Rsr Collab, Kampala, Uganda, [3]Makerere Univ Coll of Hlth Scis, Kampala, Uganda

Background: As access to testing and treatment expands throughout Africa, an increasing number of HIV+ pregnant women are presenting for antenatal care already on ART. However, little is known about rates of viral suppression (VS) in this population throughout pregnancy, as many settings still lack routine viral load (VL) monitoring.

Methods: We evaluated VS among HIV+ pregnant women who enrolled in a study (NCT02282293) of HIV and malaria in rural Uganda between 12-28 weeks gestation. Participants had previously received care at area clinics per national guidelines without VL monitoring. At enrollment, women were ART-naïve or receiving NNRTIs; those on nevirapine (NVP) were switched to efavirenz (EFV). VL was tested at enrollment, 8 weeks after enrollment, delivery, and additionally as clinically indicated. Those with confirmed virologic failure (≥2 VL >1000 c/ml after >90 days on ART) were switched to protease inhibitors (PI). We assessed the prevalence of VS (HIV-1 RNA ≤400 c/ml) and used logistic regression to examine factors associated with VS at enrollment and delivery.

Results: From 12/2014-10/2015, 200 pregnant women entered the study: median age 31 years (IQR 25-35); median gravidity 4 (IQR 3-6); median CD4 503 cells/mm^3 (IQR 372-638); median years since HIV diagnosis 3.1 (IQR 0.7-6.4); 19.5% diagnosed with HIV in current pregnancy. At enrollment, among 161 (80.5%) participants already on ART (125 on EFV, 36 on NVP) for a median of 2 years (IQR 0.5-4.2), VS was 79.5%; among 135 who had been on ART for >90 days prior to enrollment, VS was 84.4%. In a multivariate model including ART regimen, VS at enrollment was associated with time on ART (aOR 1.41 per additional year, 95% CI 1.08-1.85, p=0.01) and older age (aOR 2.23 per 10 years, 95% CI 1.05-4.75, p=0.04). At delivery, 187/200 (93.5%) had VS and EFV vs. PI was associated with VS (aOR 16.3, 95% CI 3.9-67.9, p<0.01). Of 135 women with VS at enrollment, 98.5% maintained VS at delivery. Of 21 participants with unsuppressed VL at enrollment despite >90 days on ART, 17 (80.9%) achieved VL<1000 at delivery with switch to PI (N=11) and adherence counseling.

Conclusion: The majority of HIV+ women already on ART at entry into antenatal care had previously achieved and were able to sustain viral suppression during pregnancy. However, 15% of women already on ART for >90 days were not suppressed, and VL monitoring in these asymptomatic women triggered enhanced adherence counseling or ART switch, leading to 81% percent achieving VL<1000 at delivery.

769 MEASURES OF ENGAGEMENT IN ROUTINE HIV CARE TO PREDICT ELEVATED VIRAL LOAD ON ART

Tamsin Phillips[1], Allison Zerbe[2], Agnes Ronan[1], Nei-Yuan M. Hsiao[3], Greg Petro[1], James A. McIntyre[4], Andrew Boulle[1], Elaine J. Abrams[2], Landon Myer[1], for the Maternal Child Health - Antiretroviral Therapy (MCH-ART) Study

[1]Univ of Cape Town, Cape Town, South Africa, [2]ICAP at Columbia Univ, New York, NY, USA, [3]Natl Hlth Lab Service, Cape Town, South Africa, [4]Anova Hlth Inst, Johannesburg, South Africa

Background: Engagement in HIV care is a precursor to effective antiretroviral therapy (ART) use and viral suppression (VS). Engagement in care is commonly used as an outcome in ART implementation science and health service evaluation, yet associations between measures of engagement and their ability to predict viral load (VL) and VS have not been examined.

Methods: We followed a cohort of women initiating ART in pregnancy at a primary care clinic in Cape Town, South Africa, with regular study visits for up to 24 months (including VL measures [Abbott RealTime HIV-1] and self-reported engagement in HIV care [SR], taken separately from routine services). On completion of the study, we retrospectively assessed engagement in HIV care using different forms of routinely-collected medical records, including: (i) HIV-related laboratory testing, (ii) pharmacy dispensing of ART, and (iii) records of HIV/ART clinical visits. Analyses examined the agreement of different engagement measures expressed as kappa statistics. We also assessed the ability of each engagement measure (and an aggregate measure of engagement in any of laboratory, pharmacy and/or clinical service) to predict VS <50 and <1000 copies/mL at 12-18 months on ART, based on VL measured in the cohort study.

Results: Of 471 women included, 441 women (94%) had any evidence of engagement in care at 12-18 months on ART, including 65%, 62%, 59% and 87% with evidence from laboratory testing, pharmacy dispensing, clinical visits and SR, respectively. Agreement between laboratory, pharmacy and clinical visit sources was good (kappa 0.58) but agreement of these with SR was very low (kappa -0.04). Among 411 women with study VL available at 12-18 months on ART, 66% and 74% of women had VS <50 and <1000 copies/mL, respectively. Laboratory, pharmacy and clinical data sources had >75% sensitivity in predicting VS<50 and <1000 copies/mL, and the aggregate measure was 95% and 90% sensitive, respectively (Table). Specificities were more variable, with varying engagement in HIV care among women with raised VLs. The sensitivity of SR was high but specificity very poor.

Conclusion: This analysis provides novel evidence that routinely-collected medical records measuring engagement in HIV care are a strong predictor of VS on ART. While the utility of each measure of engagement requires careful consideration in different health systems, these results suggest that routine engagement measures can be robust outcomes for ART programme evaluations and implementation science.

Table: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to predict viral suppression (VS) <50 and <1000 copies/ml using different measures of engagement in care (n=411)

Source	VS<50 n=272	VS≥50 n=139	Sensitivity	Specificity	PPV	NPV
Any engagement[§]	258 (95)	71 (51)	95%	49%	78%	83%
Pharmacy	231 (85)	45 (32)	85%	68%	84%	70%
Laboratory	219 (81)	61 (44)	81%	56%	78%	60%
Clinical visit	225 (83)	39 (28)	83%	72%	85%	68%
Any self-report	269 (99)	126 (91)	99%	9%	68%	81%
Source	**VS<1000 n=304**	**VS≥1000 n=107**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Any engagement[§]	274 (90)	55 (51)	90%	49%	83%	63%
Pharmacy	240 (79)	36 (34)	79%	66%	87%	53%
Laboratory	235 (77)	45 (42)	77%	58%	84%	47%
Clinical visit	234 (77)	30 (28)	77%	72%	89%	52%
Any self-report	300 (99)	95 (89)	99%	11%	76%	75%

[§]Includes evidence of engagement in pharmacy, laboratory or clinical services

770 SELF-REPORT AND DRY BLOOD SPOTS AS MARKERS OF ANTIRETROVIAL ADHERENCE IN PREGNANCY

Maria L. Alcaide[1], Shandir Ramlagan[2], Violeta Rodriguez[1], Ryan Cook[3], Karl Peltzer[2], Stephen Weiss[1], Deborah Jones[1]
[1]Univ of Miami, Miami, USA, [2]HIV/AIDS, STIs, and TB Rsr Prog, Pretoria, South Africa, [3]Univ of California Los Angeles, Los Angeles, CA, USA

Background: Adherence to antiretroviral (ARV) therapy is essential for Prevention of Mother to Child Transmission (PMTCT). In South Africa (SA), PMTCT first line antiretroviral (ARV) regimens are TDF + 3TC (or FTC) + EFV. While self-report is widely used to assess adherence to ARVs, it may be over-reported. This study compared two self-report adherence scales with detection of ARV in dried blood spots (DBS) among HIV infected (HIV+) pregnant women in SA.
Methods: N = 392 HIV+ pregnant women receiving ARVs completed two self-reported adherence measures [Visual Analog Scale (VAS), AIDS Clinical Trials Group Adherence] and underwent a blood collection for DBS ARV testing at week 32 of pregnancy. Self-report adherence was coded as adherent if no missed doses were reported. DBS adherence was defined as 3 drugs detected (TDF + 3TC + EFV) or TDF + EFV detected. An area under the receiver operating characteristic curve (AUROC) analysis was conducted to examine the performance of the VAS and the ACTG scales in identifying participants as adherent, using DBS as the gold standard. Kappa statistics (κ), accuracy, sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated.
Results: DBS ARV detection was as follows: adherent = 74% ; Non-adherent = 26%. The proportion of participants identified as adherent by self-report were 86% (VAS) and 80% (ACTG). VAS relative to DBS: AUROC = 0.543 (VAS performed poorly in predicting adherence by DBS); κ = 0.101, (slight intermeasure agreement between the VAS and the DBS); accuracy = 0.719 [95% CI 0.67, 0.76]; sensitivity = 0.907 [95% CI 0.87, 0.94]; specificity = 0.178 [95% CI 0.11, 0.27]; PPV = 0.761 [95% CI 0.71, 0.80], and NPV = 0.400 [95% CI 0.26, 0.56]. ACTG relative to DBS: AUROC = 0.538, (ACTG performed poorly in predicting adherence by DBS); κ = 0.081 (poor intermeasure agreement between the ACTG and the DBS); accuracy = 0.673 [95% CI 0.63, 0.72]; sensitivity = 0.818 [95% CI 0.77, 0.86]; specificity = 0.257 [95% CI 0.18, 0.35]; PPV = 0.760 [95% CI 0.71, 0.81]; and NPV 0.329 [95% CI 0.23, 0.44].
Conclusion: Detectable levels of ARV were suboptimal in this population, indicating high risk of perinatal HIV infection and ARV resistance. Programs to strengthen ARV adherence among HIV+ pregnant women in rural SA are needed. Validation of self-reported ARV adherence among pregnant HIV+ women in SA are warranted to support PMTCT goals. Funded by NIH (R01HD078187 and P30AI073961).

771 UNINTENDED PREGNANCY PREDICTS SUBSEQUENT RAISED VIRAL LOAD IN THE POSTNATAL PERIOD

Kirsty Brittain[1], Tamsin Phillips[1], Allison Zerbe[2], Agnes Ronan[1], Greg Petro[1], Nei-Yuan M. Hsiao[3], James A. McIntyre[4], Elaine J. Abrams[5], Landon Myer[1], for the Maternal Child Health - Antiretroviral Therapy (MCH-ART) Study
[1]Univ of Cape Town, Cape Town, South Africa, [2]Columbia Univ, New York, NY, USA, [3]NHLS, Cape Town, South Africa, [4]Anova Hlth Inst, Johannesburg, South Africa, [5]ICAP at Columbia Univ, New York, NY, USA

Background: Unintended pregnancies are common in HIV-infected women in resource-limited settings and are a source of ongoing MTCT. Meanwhile non-adherence and raised viral load (VL) on ART occur frequently during the postpartum period, but the determinants of these are poorly understood. We investigated whether raised VL on ART is more common postpartum in women who had an unplanned pregnancy.
Methods: Working in a public sector clinic in Cape Town, South Africa, we followed consecutive HIV-infected women initiating ART from their 1st antenatal care (ANC) visit up to 18 months postpartum. Pregnancy intentions were measured at the 1st ANC visit with the London Measure of Unplanned Pregnancy (α=0.87); analyses categorised pregnancies as planned, ambivalent or unplanned. Viral load (VL) testing (Abbott RealTime HIV-1) was conducted at 3-6 monthly intervals postpartum along with standardised assessments of depression, alcohol use and intimate partner violence (IPV). In analysis, Poisson models examined the associations between pregnancy planning and elevated VL≥1000 copies/mL.
Results: A total of 358 women (mean age, 29 years) were followed for a median of 18 months postpartum. At 1st ANC visit, planned, ambivalent and unplanned pregnancy was reported by 20%, 21% and 59%, respectively. Overall, 115 women (32%) experienced one or more VL≥1000 copies/mL postpartum, with elevated VL occurring more frequently at each time point in the postpartum period in women reporting ambivalence or an unplanned pregnancy (Figure). Compared to women reporting a planned pregnancy, those reporting ambivalence (risk ratio [RR]: 1.90; 95% CI: 1.05-3.42) or unplanned pregnancy (RR: 2.05; 95% CI: 1.21-3.46) were more likely to experience elevated VL≥1000. These associations persisted after adjustment for demographic characteristics and were independent of depression, alcohol use and IPV. Neither breastfeeding duration nor MTCT varied significantly by pregnancy planning. Based on the most conservative adjusted estimates, we calculate that up to 30% of elevated VL in women on ART postpartum may be associated with unplanned pregnancy in this setting.
Conclusion: These novel data suggest that elevated VL postpartum occurs more frequently in women with unplanned pregnancies. This underscores the need to incorporate pregnancy planning into routine care for HIV-infected women, and to recognise that postpartum women who did not intend their pregnancies may require specific attention from counselling and support interventions.

772 SUBSEQUENT PREGNANCY OUTCOMES IN WOMEN DURING FOLLOW-UP IN PROMISE 1077HS

Jose H. Pilotto[1], Sean Brummel[2], Risa M. Hoffman[3], Paula Britto[2], Gaerolwe Masheto[4], Linda Aurpibul[5], Nahida Chakhtoura[6], Karin Klingman[7], Judith S. Currier[3], for the 1077HS Team
[1]Fiocruz, Rio de Janeiro, Brazil, [2]Harvard Univ, Boston, MA, USA, [3]Univ of California Los Angeles, Los Angeles, CA, USA, [4]Harvard Univ, Gaberone, Botswana, [5]Chiang Mai Univ, Chiang Mai, Thailand, [6]NICHD, Bethesda, MD, USA, [7]DAIDS, NIAID, Bethesda, MD, USA

Background: Rates of adverse pregnancy outcomes for women who conceive on antiretroviral therapy (ART) may be increased, but data are conflicting.
Methods: In PROMISE 1077HS, asymptomatic HIV+, non-breastfeeding women with pre-ART CD4 cell count ≥400 cells/mm^3 who started ART during pregnancy were randomized up to 42 days after delivery to continue (cART) or discontinue ART (dART). LPV/RTV with TDF/FTC or ZDV/3TC was the preferred study regimen. Sixty sites in Argentina, Botswana, Brazil, China, Haiti, Peru, Thailand and the US participated between 12/2011-11/2014. Women randomized to dART were recommended to restart if a subsequent pregnancy occurred or for clinical indications. This analysis includes outcomes for all subsequent pregnancies that occurred prior to offering all women ART in 7/2015. We compared subsequent pregnancy outcomes among women in the cART versus dART arm using Fisher's exact test (post hoc analysis).
Results: Subsequent pregnancies occurred in 277/1652 (17%) women (cART: 144/827, dART: 133/825). A pregnancy outcome was recorded for 266 women with median age 27.4 years (IQR 23.7, 31.1) at pregnancy diagnosis, and median CD4 688 cells/mm^3 (IQR 529, 867) recorded at 2 months prior to pregnancy diagnosis. Two hundred (75%) live births were included, 40 (15%) spontaneous abortions (<20 weeks gestation), 18 (7%) induced abortions (<20 weeks gestation) and 8 (3%) stillbirths (≥20 weeks gestation). At 12 weeks prior to pregnancy diagnosis, 86% (120/140) in the cART group were on a boosted/non-boosted PI regimen versus 6% (8/140) NNRTI. In the dART arm, 19/126 (15%) restarted ART prior to pregnancy diagnosis: 74% (14/19) were on a PI regimen versus 26% (5/19) NNRTI. After pregnancy diagnosis (first regimen during pregnancy), there was frequent use of PIs in the cART arm (89% (124/140) PI versus 7% (10/140) NNRTI) and among those restarting ART in the dART arm (53% (67/126) PI versus 27% (34/126) NNRTI). Spontaneous abortions were more common in the cART arm (cART: 19.3% (27/140), dART: 10.3% (13/126); p=0.06), as were stillbirths (cART: 4.3% (6/140), dART: 1.6% (2/126); p=0.29). When stillbirths and spontaneous abortions were combined, there was a statistically significant higher rate in the cART arm (cART: 23.6% (33/140), dART: 11.9% (15/126); p=0.02).
Conclusion: Women randomized to continue ART after their index pregnancy who subsequently conceived were more likely to have spontaneous abortion or stillbirth compared to women randomized to stop ART.

773 HIV AND RISK OF POSTPARTUM INFECTION, COMPLICATIONS, AND MORTALITY IN RURAL UGANDA

Lisa Bebell[1], Joseph Ngonzi[2], Mark J. Siedner[3], Winnie Muyindike[4], Bosco M. Bwana[2], Laura E. Riley[1], Yap Boum[5], David Bangsberg[6], Ingrid V. Bassett[1]
[1]Massachusetts General Hosp, Boston, MA, USA, [2]Mbarara Univ of Sci and Tech, Mbarara, Uganda, [3]Epicentre, MSF, Mbarara, Uganda, [4]MGH-Ragon Inst, Boston, MA, USA

Background: HIV infection may increase the risk of postpartum infection and infection-related mortality; yet there are insufficient data on epidemiology, microbiology, and risks factors in resource-limited settings. We hypothesized that postpartum infection incidence and attributable mortality in Mbarara, Uganda would be significantly higher in HIV-infected than HIV-uninfected women.
Methods: We performed a prospective cohort study of 4,231 women presenting to a regional referral hospital in 2015 for delivery or postpartum care. We collected vital signs after delivery, and performed microbiologic evaluation of febrile and hypothermic women. All febrile, hypothermic, and a subset of 1,708 randomly selected normothermic women were followed with postpartum phone interviews completed at 6 weeks. The primary outcome of interest was incident in-hospital postpartum infection. Secondary outcomes included in-hospital complications (mortality, re-operation, ICU transfer, need for imaging, blood transfusion, wound infection) and 6-week all-cause mortality. We analyzed risk of mortality and complications using Chi squared analysis. We performed univariable and multivariable logistic regression analyses to identify correlates of postpartum infection, with a particular focus on HIV infection.
Results: Mean age was 25.2 years and 481 participants (12%) were HIV-1 infected, with a median CD4+ T-cell count of 487 (IQR 338, 698) cells/mm3. Approximately 90% of HIV-infected women (193/215 selected for in-depth survey) were on ART. While hospitalized, 4.8% (205/4231) of the total cohort were febrile or hypothermic, of whom 174 (85%) had blood and urine samples collected. The most common causes of fever were postpartum endometritis (76/193, 39%), urinary tract infection (25/174, 14%), bloodstream infection (5/174, 3%) and malaria (5/174, 3%). Cumulative incidence of postpartum infection was 2.0% and did not differ by HIV status (AOR 1.4, P=0.49, Table 1). However, significantly more HIV-infected women than HIV-uninfected women (4.4% versus 1.2%, P=0.001) developed an in-hospital postpartum complication. Maternal mortality incidence was 0.11% (2/1768) in-hospital and rose to 0.26% (4/1526) by 6 weeks postpartum, without differences by HIV serostatus (P=0.71 and 0.24, respectively).
Conclusion: For women in rural Uganda with high rates of ART coverage, HIV infection was associated with increased risk of postpartum complications, but not with in-hospital postpartum infection, in-hospital or 6-week all-cause mortality.

Table 1. Univariable and multivariable logistic regression analysis of risk factors associated with postpartum infection.

	Univariable		*Multivariable*	
Characteristic	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Cesarean delivery	7.7 (3.9-15.1)	<0.001	3.9 (1.5-10.3)	0.006
Number of days in hospital	1.3 (1.2-1.4)	<0.001	1.2 (1.1-1.3)	0.001
Attended antenatal clinic ≥4 times	0.7 (0.41-1.2)	0.20	0.4 (0.2-0.9)	0.02
Referred from another facility	2.3 (1.4-4.0)	0.002	1.1 (0.6-3.3)	0.75
Number of hours in labor	1.0 (1.0-1.0)	0.26	1.0 (1.0-1.0)	0.66
Number of vaginal exams in labor	1.0 (1.0-1.1)	0.97	0.9 (0.8-1.1)	0.24
Age	0.9 (0.8-0.9)	<0.001	0.9 (0.9-1.0)	0.08
Residence in Mbarara	0.7 (0.4-1.1)	0.08	0.8 (0.5-1.5)	0.52
Formal employment	0.6 (0.4-1.0)	0.04	0.7 (0.4-1.2)	0.20
Multiparity	0.3 (0.2-0.5)	<0.001	0.5 (0.3-1.0)	0.06
HIV infection	***1.0 (0.5-2.1)***	***0.91***	***1.4 (0.6-3.3)***	***0.49***

774 CMV VIREMIA IN HIV-POSITIVE AND -NEGATIVE PREGNANT WOMEN IN BOTSWANA

Natasha O. Moraka[1], Maryanne R. Ibrahim[2], Sikhulile Moyo[1], Prisca Thami[1], Gloria Mayondi[1], Christiana Smith[3], Adriana Weinberg[4], Rosemary Musonda[1], Simani Gaseitsiwe[1], Shahin Lockman[5]
[1]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [2]Doris Duke Intl Clinical Rsr Fellowship, Los Angeles, CA, [3]Univ of Colorado, Denver, CO, USA, [4]Univ of Colorado, Aurora, CO, USA, [5]Harvard Univ, Boston, MA, USA

Background: Despite the success of PMTCT in Botswana, HIV-exposed uninfected (HEU) infants are more than twice as likely to die than HIV-unexposed infants. In Botswana, 26% of pregnant women are HIV infected, 96% of whom are CMV sero-positive. We studied the prevalence of CMV viremia in HIV-infected vs. HIV-uninfected women. We also explored the relationship between detectable maternal CMV viremia and adverse pregnancy outcomes, as well as morbidity and mortality in both HEU and HIV-unexposed children.
Methods: We enrolled (during or within 1 week of pregnancy) and followed (for 2 years postpartum) 443 HIV-infected and 451 HIV-uninfected mothers and their 453 HEU / 457 HIV-unexposed live-born infants in a prospective observational study in Botswana ("Tshipidi"). Maternal plasma samples from 295 HIV-positive and 51 HIV-negative women were randomly selected. CMV DNA was quantified from plasma samples obtained at enrollment using the Roche COBAS® AmpliPrep/COBAS® TaqMan® CMV Test (threshold of detection = 50 copies/mL).
Results: Median maternal baseline age and CD4 were 27.6 years (Q1, Q3: 23, 33) and 422 (Q1, Q3: 307,570), respectively. A total of 315 (91.2%) samples were successfully amplified, with 14.0% (95%CI 10.1- 17.8) positive for CMV DNA. Only 1(0.3%) participants had a quantifiable (>150 copies/mL) CMV DNA with the Roche TaqMan assay. There was a trend towards higher CMV detection among HIV-infected vs. HIV-uninfected mothers (15.4% vs. 6.1%, respectively; p=0.080). Among HIV-infected women, the presence of detectable CMV DNA was not associated with the composite adverse pregnancy outcome (preterm delivery or small for gestational age, OR = 1.46; 95%CI 0.77 – 2.78); and was not associated with the composite outcome of child hospitalisation and/or death by 24 months (HR = 1.40; 95% CI 0.72 – 2.69).
Conclusion: Very few HIV-infected and –uninfected women had detectable CMV DNA. CMV viremia was not associated with any pregnancy and infant outcomes in this small sample.

775 PREGNANCIES IN WOMEN WHO ACQUIRED HIV PERINATALLY

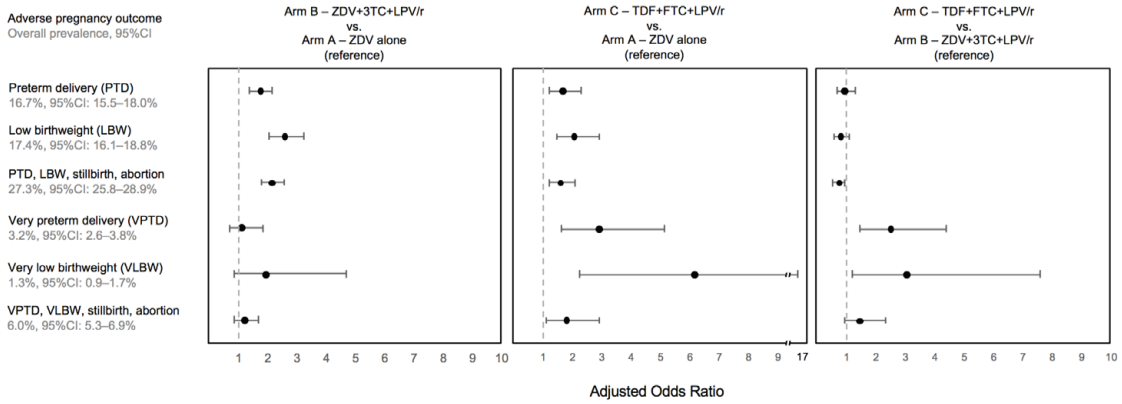
Mira Hleyhel[1], Catherine Dollfus[2], Roland Tubiana[3], Christine Rouzioux[4], Pierre Frange[4], Stephane Blanche[4], Jérôme Le Chenadec[1], Albert Faye[5], Laurent Mandelbrot[6], **Josiane Warszawski**[1]
[1]INSERM, Le Kremlin-Bicetre, France, [2]Trousseau Hosp, Paris, France, [3]Pitié-Salpétrière Hosp, Paris, France, [4]Necker Hosp, Paris, France, [5]Univ Paris Diderot, Paris, France, [6]Univ Paris Diderot, Colombes, France

Background: Pregnancies in women perinatally infected with HIV (PHIV) are increasing in frequency. We investigated whether perinatal HIV acquisition was associated with differences in care management, a higher risk of obstetric complications, uncontrolled viral load near delivery, and adverse neonatal outcomes.

Methods: Between 2006 and 2014, of the 2201 pregnant women aged 18-30 years enrolled in the National French Perinatal Cohort (ANRS-EPF-C01), 508 were primiparous and aware of their HIV-positive status before conception: 46 PHIV and 462 non-PHIV. We compared the risk of uncontrolled viral load (>50 cp/mL), obstetric complications (pre-eclampsia, diabetes, prematurity), and adverse neonatal outcomes (stillbirth, low birthweight) between these two groups.
Results: Among primiparous women under the age of 30 years, the proportion of PHIV women increased from 4.1 % to 17.7 % (p<0.001) over the study period. At the time of this first pregnancy, PHIV and non-PHIV women had similar living conditions, with about half not living with a partner, 40% being jobless, and less than 10% having psychoactive substance abuse. PHIV women were significantly more likely to have been born in France (73.9% vs 15.9%, p<0.001), and to be on combined antiretroviral treatment at the time of conception (71.7% vs. 54.1%; p=0.02). In women on treatment at conception, the proportion of uncontrolled viral load (VL) was higher for the PHIV than for the non-PHIV group during the first trimester (44.8% vs. 21.4%; p=0.007), as well as at delivery (26.7% vs. 10.6%; p=0.03). For those born outside France, virological failure at delivery remained more frequent in PHIV women, even after adjusting for initial VL (adjusted odds ratio: 8.3; 95% CI: 1.6-42.8; p=0.01). The prevalences of obstetric complications and neonatal outcomes were very similar in the two groups. No case of MTCT occurred in the PHIV group (upper CI =0.1%), versus three cases (0.7%; CI: 0.1-1.9) in the non-PHIV group.
Conclusion: Pregnancy and neonatal outcomes were similar in PHIV and non-PHIV women. However, despite similarities in marital and employment status, uncontrolled viral load was more frequent at conception and delivery in pregnant PHIV women, possibly due to difficulties in maintaining treatment adherence for long periods since childhood. Strategies needed to support adherence to treatment in PHIV women of childbearing age should be reinforced during all the course of pregnancy.

776 ANTENATAL ANTIRETROVIRAL THERAPY AND ADVERSE BIRTH OUTCOMES: THE PROMISE TRIAL

Benjamin H. Chi[1], Mona Farhad[2], Maxensia Owor[3], Tsungai Chipato[4], Min Qin[2], Sufia Dadabhia[5], Devasena Gnanashanmugam[6], Nahida Chakhtoura[7], Mary Glenn Fowler[5], Jeffrey S. Stringer[1]
[1]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Harvard Univ, Boston, MA, USA, [3]Makerere Univ–Johns Hopkins Univ Rsr Collab, Kampala, Uganda, [4]Univ of Zimbabwe, Harare, Zimbabwe, [5]The Johns Hopkins Univ, Baltimore, MD, USA, [6]DAIDS, NIAID, Rockville, MD, USA, [7]NICHD, Bethesda, MD, USA
Background: The PROMISE trial found that antiretroviral therapy (ART) in pregnancy reduced mother-to-child transmission, but also increased the frequency of several adverse birth outcomes (ABOs) compared to antenatal zidovudine alone.
Methods: PROMISE randomized HIV-infected women ≥14 weeks gestation and not in labor to receive 1 of 3 antenatal regimens: ZDV only (Arm A), ZDV+3TC+LPV/r (Arm B), or TDF+FTC+LPV/r (Arm C). In the early versions of the protocol, women could be randomized only to Arms A and B unless they tested HBsAg+; in version 3.0, women were randomized with equal probability into all 3 arms. We studied the association between antiretroviral regimen and ABOs: delivery <37 weeks (PTD); infant birthweight <2500g (LBW); composite of PTD, LBW, stillbirth (SB), and spontaneous abortion (AB); delivery <34 weeks (VPTD); infant birthweight <1500 g (VLBW); and composite of VPTD, VLBW, SB, and AB. Gestational age at delivery was estimated primarily by Ballard score. We adjusted for baseline factors (maternal age, BMI, HIV viral load, CD4, alcohol use, country, gestational age at entry) and obstetrical complications across all multivariable models. If there were zero counts in specific strata, the variable as a whole was not included in the model. In primary analysis, we included data from all participants; in sensitivity analysis, we restricted data to only those enrolled in version 3.0.
Results: 3423 women who enrolled and delivered in PROMISE were allocated to Arm A (n=1507), Arm B (n=1497), or Arm C (n=419). When we considered outcomes with PTD and/or LBW, women on ZDV+3TC+LPV/r (Arm B) and TDF+FTC+LPV/r (Arm C) each had higher risk for ABO compared to ZDV alone (Arm A). When analysis was restricted to severe outcomes (i.e., VPTD, VLBW), the risk associated with Arm C remained elevated. In head-to-head comparisons between the two ART regimens, Arm C had a higher risk of severe ABO such as VPTD (AOR: 2.55, 95%CI:1.46-4.44) and VLBW (AOR: 3.06, 95%CI:1.23-7.59). Findings remained consistent with protocol version 3.0 data alone.
Conclusion: LPV/r-containing ART was associated with a significantly elevated risk of ABO after adjustment for multiple obstetrical and clinical factors. For severe outcomes, this risk was higher among women on TDF-FTC compared to ZDV-3TC. Further study is needed to determine whether this is an independent effect of TDF-FTC, a result of drug-drug interactions with LPV/r, or due to other factors.



777 RISK FACTORS FOR LOW BIRTH WEIGHT AND PRETERM DELIVERY IN THE PROMISE TRIAL

Dorothy Sebikari[1], Min Qin[2], Maxensia Owor[1], Jeffrey S. Stringer[3], Mona Farhad[2], Nahida Chakhtoura[4], Benjamin H. Chi[3], Karin Klingman[5], Gerhard Theron[6], Mary Glenn Fowler[7]
[1]Makerere Univ–Johns Hopkins Univ Rsr Collab, Kampala, Uganda, [2]Harvard Univ, Boston, MA, USA, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]NICHD, Bethesda, MD, USA, [5]DAIDS, NIAID, Bethesda, MD, USA, [6]Stellenbosch Univ, Cape Town, South Africa, [7]The Johns Hopkins Univ, Baltimore, MD, USA
Background: Although antiretroviral therapy (ART) in pregnancy can reduce vertical HIV transmission to <1%, it may also increase the risk of low birth weight (< 2500g, LBW) and preterm delivery (<37 weeks, PTD), conditions that confer significant morbidity and mortality to newborns in resource-limited settings. In the multi-site PROMISE trial, we previously reported an increased risk of LBW and PTD among women initiating protease inhibitor (PI)-based ART during pregnancy, when compared to ZDV alone. We further describe obstetrical and clinical risk factors for LBW and PTD among study participants.
Methods: Within the antepartum component of PROMISE, we assessed baseline clinical and obstetrical risk factors associated with LBW and PTD. Risk factors with p-value <0.15 in univariate logistic regression were included in multivariate backward logistic regression models. We also adjusted for treatment arm, gestational age (GA) at entry, and country.
Results: Birth outcomes were available for 3423 HIV-infected women delivering between 4/2011-11/2014 across 14 sites in Africa and Asia. Among the 3333 women delivering at least one live born infant, median maternal age at enrollment was 26 years (IQR 22–30); 661 (20%) were primiparous, and 110 (3.3%) reported at least one prior PTD. Median birth weight was 2900g (IQR 2600–3200); and 558 (17%) infants weighed <2500 g. Median GA at birth was 39 weeks (IQR 38–40); 557 (17%, 95%CI: 16.1%-18.9%) were born prior to 37 weeks. In univariate analyses, clinical factors including maternal age 18-<21 year and entry RNA ≥20,000 copies were significant for PTD but not LBW; however, maternal age 18-<21 dropped out in the backward logistic model. In the final multivariate models, adjusted for country and GA at entry, obstetrical risk factors for LBW and/or PTD included

BMI, multiple gestation, prior PTD, pregnancy or chronic hypertension, IUGR, placental abruption, preterm labor, oligohydramnios, PROM, and antenatal ART were significant risk factors (table).

Conclusion: Besides receipt of antenatal PI-based ART, a number of obstetrical risk factors contributed to LBW and PTD for HIV-infected pregnant women in PROMISE. Along with optimization of ART regimens, public health interventions are needed to address modifiable obstetrical risk factors, including education of pregnant women and clinicians on early warning signs and management of pregnancy-associated complications.

778 DO HIV+ WOMEN ON PROTEASE INHIBITORS DELIVER PRETERM? FINDINGS FROM A UK STUDY

Graziella Favarato, Claire Townsend, Heather Bailey, Claire Thorne, for the UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC)
Univ Coll London, London, UK

Background: HIV-infected women on ritonavir-boosted protease inhibitor (PI/r) based ART regimens in pregnancy may be at higher risk of preterm delivery (PTD, <37weeks gestation) but evidence is inconsistent.

Methods: We analyzed national surveillance data on HIV-infected women delivering a live-born singleton in the UK and Ireland between 2007 and 2015, who received antenatal ART. We excluded women who switched ART regimen in pregnancy; for women with repeat pregnancies we retained the most recent one. We compared PTD risk in pregnant women on NNRTI+2NRTI regimens, LPV/r+2NRTI regimens and other-PI/r+2NRTI regimens using multivariable logistic regression models. Analyses were adjusted for calendar year, maternal age, intravenous drug use (IDU) history, ART at conception and first antenatal CD4 count. After excluding women with a history of IDU we explored whether the association between regimen in pregnancy and PTD was modified by first antenatal CD4 count and consequently, stratified analyses by CD4 count (≤350cells/µl vs >350cells/µl).

Results: Analyses included 1889 pregnant women on NNRTI+2NRTI, 2368 on LPV/r+2NRTI and 1816 on other PI/r+2NRTI; 10.4% and 3.8% of women delivered at <37weeks and <34weeks respectively. Overall, 3090 (50.9%) women conceived on ART; 105 (1.7%) women had an IDU history. Compared to women on NNRTI regimens women on LPV/r containing regimens were at higher risk of PTD (aOR 1.48, 95%CI 1.16, 1.88) but not those on other PI/r-based regimens (aOR 1.13 95%CI 0.89, 1.43). Increased PTD risk was also associated with first antenatal CD4≤350cells/µL (aOR 1.25 95%CI 1.03, 1.50), IDU history (aOR 1.80 95%CI 1.06, 3.07) and older age (>36years vs <28years) (aOR 1.30 95%CI 1.00, 1.67). After stratifying by first antenatal CD4 count (P interaction=0.0048), increased PTD risk in women on LPV/r compared to women on NNRTI was observed in those with CD4>350cells/µL but not in those with a lower CD4 count (see Table). In women with CD4≤350cells/µl conception on ART increased PTD risk whilst risk decreased with calendar year; no increased PTD risk in women on LPV/r (or other PI/r-based regimens) compared to women on NNRTI was observed.

Conclusion: In this national UK study pregnant women on LPV/r-based regimens but not on other PI/r-based regimens were at higher risk of PTD compared to pregnant women on NNRTI-based regimens but the association was only apparent in women with a higher CD4 count.

Factors associated with pre-term deliveries stratified by first antenatal CD4 count

		CD4≤350cells/µl (N=1829)			CD4 >350cells/µl (N=3839)		
		N	% PTD	aOR* (95%CI)	N	% PTD	aOR* (95%CI)
Regimen in pregnancy	NNRTI-+2NRTI	530	10.6	1.00	1246	8.0	1.00
	LPV/r+2NRTI	769	12.2	1.35 (0.92, 2.00)	1419	11.4	1.53(1.11, 2.11)
	Other PI/r+2NRTI	530	11.1	1.29 (0.86, 1.93)	1174	8.1	1.03(0.76, 1.40)
Maternal age	<28 years	476	11.1	1.00	895	8.2	1.00
	28-32 years	487	10.9	0.97 (0.65, 1.46)	926	10.6	1.37 (1.00, 1.89)
	32-36 years	455	10.3	0.90 (0.59, 1.38)	1047	8.1	1.06 (0.76, 1.49)
	>36 years	411	13.6	1.23 (0.81, 1.85)	971	10.3	1.42 (1.02, 1.98)
ART at conception	No	1193	10.5	1.00	1584	10.0	1.00
	Yes	636	13.2	1.50 (1.07, 2.09)	2255	8.8	1.01 (0.77, 1.32)
Calendar year	per 1 year increment	-	-	0.93 (0.87, 1.00)	-	-	1.00 (0.95, 1.05)

*Odds ratio all mutually adjusted – women with a history of IDU excluded

779 TDF/FTC IN PREGNANCY SHOWS NO INCREASE IN ADVERSE INFANT BIRTH OUTCOMES IN US COHORTS

Kathryn Rough[1], George R. Seage[1], Paige L. Williams[1], Sonia Hernandez-Diaz[1], Yanling Huo[1], Ellen G. Chadwick[2], Risa M. Hoffman[3], Emily Barr[4], David E. Shapiro[1], Kunjal Patel[1]
[1]Harvard Univ, Boston, MA, USA, [2]Ann & Robert H. Lurie Children's Hosp of Chicago, Chicago, IL, USA, [3]Univ of California Los Angeles, Los Angeles, CA, USA, [4]Children's Hosp Colorado, Aurora, CO, USA

Background: In the PROMISE (Promoting Maternal and Infant Survival Everywhere) trial, infants of women randomized to tenofovir, emtricitabine, lopinivir/ritonavir (TDF/FTC/LPV/r) had higher risk of very premature birth, very low birth weight, and death compared to those randomized to zidovudine, lamivudine, lopinavir/ritonavir (ZDV/3TC/LPV/r).

Methods: Data from two large prospective US-based cohort studies (the Surveillance Monitoring for ART Toxicities cohort and the International Maternal Pediatric Adolescent AIDS Clinical Trial Network P1025 study), were used to compare risk of adverse infant birth outcomes among women exposed to ZDV/3TC/LPV/r, TDF/FTC/LPV/r, and the more frequently used TDF/FTC with atazanavir and ritonavir (ATV/r). Exposure classification was based on first regimen used during pregnancy. We evaluated the risk of preterm birth (<37 weeks), very preterm birth (<34 weeks), low birth weight (<2,500 g), very low birth weight (<1,500 g), adverse event (preterm, low birth weight, fetal loss, or 14-day mortality) and serious adverse event (very preterm, very low birth weight, fetal loss, or 14-day mortality). Risk ratios (RR) with 95% confidence intervals (CI) were estimated using log binomial models. When number of outcomes was sufficient (preterm, low birth weight, adverse event), models were adjusted for confounding.

Results: Among 4,646 enrolled infants, 128 (2.8%) had mothers who received TDF/FTC/LPV/r, 539 (11.6%) had mothers who received TDF/FTC/ATV/r, and 954 (20.5%) had mothers who received ZDV/3TC/LPV/r. The overall prevalence of adverse birth outcomes was 18.8% for preterm birth, 4.5% for very preterm birth, 17.3% for low birth weight, and 1.9% for very low birth weight. In crude and adjusted comparisons, there was no statistically significant difference between TDF/FTC/LPV/r and ZDV/3TC/LPV/r for any outcome (Table), although TDF/FTC/ATV/r appeared slightly protective for preterm birth, low birth weight, and any adverse event.

Conclusion: Among pregnant women with HIV in the US, use of TDF/FTC/LPV/r was not associated with increased risk of adverse infant birth outcomes when compared to ZDV/3TC/LPV/r or TDF/FTC/ATV/r. Our findings support the use of TDF/FTC/ATV/r during pregnancy, as it appears to carry similar or slightly less risk of preterm birth, low birth weight, and adverse events than ZDV/3TC/LPV/r.

Table. Risk ratios (RR) and 95% confidence intervals (CI) for pregnancy outcomes based on comparison of first antiretroviral regimen during pregnancy

	TDF/FTC/LPV/r vs ZDV/3TC/LPV/r		TDF/FTC/ATV/r vs ZDV/3TC/LPV/r		TDF/FTC/LPV/r vs TDF/FTC/ATV/r	
	Crude RR (95% CI)	Adjusted RR (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Preterm birth	1.10 (0.77, 1.58)	0.95 (0.66, 1.39)	0.83 (0.65, 1.04)	0.76 (0.59, 0.99)	1.33 (0.91, 1.96)	1.23 (0.84, 1.82)
Very preterm birth	0.85 (0.19, 2.11)		1.04 (0.65, 1.68)		0.82 (0.32, 2.08)	
Low birth weight	1.27 (0.90, 1.78)	1.08 (0.76, 1.54)	0.86 (0.68, 1.09)	0.83 (0.64, 1.09)	1.47 (1.02, 2.13)	1.40 (0.97, 2.03)
Very low birth weight	0.41 (0.06, 3.06)		0.97 (0.45, 2.10)		0.42 (0.05, 3.27)	
Adverse event	1.03 (0.77, 1.39)	0.90 (0.66, 1.23)	0.87 (0.72, 1.05)	0.83 (0.67, 1.02)	1.18 (0.86, 1.62)	1.11 (0.81, 1.52)
Serious adverse event	1.01 (0.47, 2.17)		0.96 (0.61, 1.51)		1.04 (0.47, 2.34)	

780 MITOCHONDRIAL DNA CONTENT IN HIV-EXPOSED UNINFECTED INFANTS IN CAMEROON

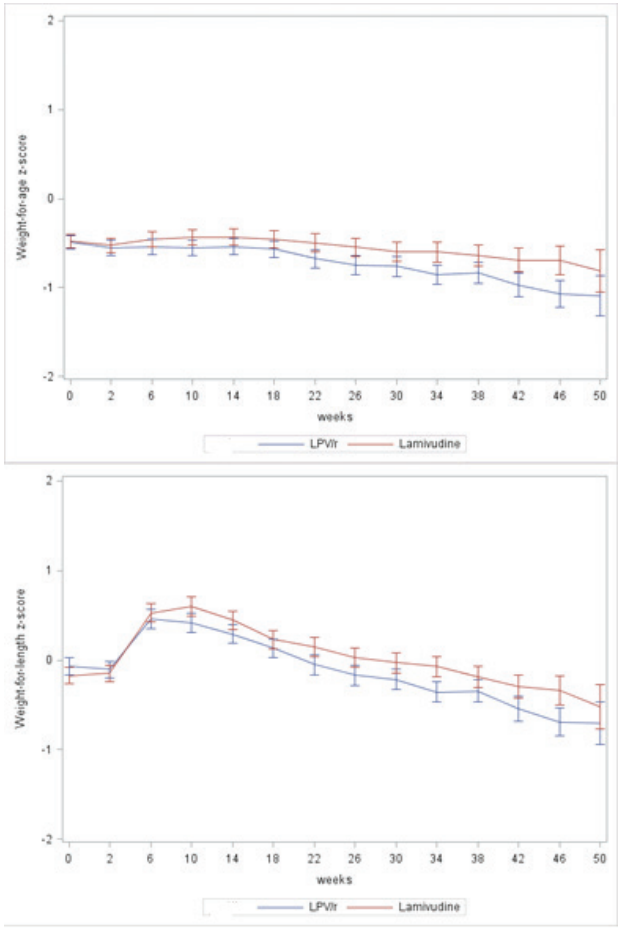
Jennifer Jao[1], Kathleen M. Powis[2], Brian Kirmse[3], Chunli Yu[1], Fanny Epie[4], Elaine J. Abrams[5], Derek LeRoith[1], Mitchell Geffner[6], Irwin J. Kurland[7], Helene C. Cote[8]
[1]Icahn Sch of Med at Mt Sinai, New York, NY, USA, [2]Massachusetts General Hosp, Boston, MA, USA, [3]Univ of Mississippi, Jackson, MS, USA, [4]Cameroon Baptist Convention Hlth Services, Bamenda, Cameroon, [5]Columbia Univ, New York, NY, USA, [6]Univ of Southern California, Los Angeles, CA, USA, [7]Albert Einstein Coll of Med, Bronx, NY, USA, [8]Univ of British Columbia, Vancouver, Canada

Background: In utero HIV/antiretroviral (ARV) exposure has been associated with mitochondrial dysfunction. Few studies have evaluated mitochondrial DNA (mtDNA) content in HIV-exposed uninfected (HEU) infants in Africa or the relationship between mtDNA levels and pathways of intermediary metabolism.
Methods: We quantified dried blood spot mtDNA content (ratio of mtDNA:nuclear DNA) by quantitative PCR at 6 weeks of life in HEU and HIV-unexposed uninfected (HUU) infants in Cameroon from 2011-2014. Infants were in utero HIV/ARV and postnatally exposed to either zidovudine (HEU-A) or nevirapine (HEU-N) or HUU. Acylcarnitines (ACs) and branch-chain amino acids (BCAAs), biomarkers of intermediary metabolism occurring in mitochondriae, were measured via tandem mass spectrometry. We used principal component analysis (PCA) to consolidate the ACs and BCAAs into 7 uncorrelated principal components (PC). Linear regression models were fit to assess the association of in utero/postnatal HIV/ARV exposure and infant mtDNA while adjusting for confounders and PCA-derived AC/BCAA component scores.
Results: Of 366 singletons, 38 were HEU-A, 118 HEU-N, and 210 HUU infants. Mothers of HEU-A and HEU-N were older than those of HUU infants (median age 30 vs. 30 vs. 28 years respectively, p=<0.01). Amongst HEU infants, 15 (10%) were exposed to no ARVs, 33 (21%) to AZT monotherapy, and 108 (69%) to combination ARV therapy in utero. Of the latter, all but two were exposed to a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen. The in utero ARV exposures did not differ significantly between HEU-A and HEU-N infants. Mean mtDNA content was lowest in HEU-A infants (140 vs. 160 in HEU-N vs. 174 in HUU, p<0.01). After adjusting for confounders, HEU-A infants remained at increased risk for lower mtDNA content (ß:-4.92, p=0.03 for HEU-A vs. HUU; ß:-1.60, p=0.29 for HEU-N vs. HUU). Furthermore, PC1 (composed of long chain ACs C14, C16, C16:1, C18, C18:1, C18:2, C0) was associated with lower (ß:-2.29, p<0.01) and PC3 (composed of short chain and BCAA-related ACs C2, C3, C4, C4-OH, C5-OH, C3-DC, C4-DC, C5-DC, C8:1) with higher (ß:2.37, p=0.02) mtDNA content.
Conclusion: Compared to HUU infants, HEU infants receiving postnatal AZT appear to be at increased risk for lower mtDNA content at 6 weeks of life. Moreover, mtDNA content in HEU infants may be associated with altered mitochondrial fuel utilization. Further studies are needed to assess the longterm significance of these findings.

781 LOPINAVIR/RITONAVIR INITIATED AT 7 DAYS OF LIFE IMPAIRS INFANT GROWTH

Nicolas Nagot[1], Thorkild Tylleskär[2], Chipepo Kankasa[3], Nicolas MEDA[4], James Tumwine[5], Mandisa Singata[6], Marianne Periès[1], Philippe Van de Perre[1], Stephane Blanche[7], for the ANRS 12174 Trial Group
[1]INSERM, Montpellier, France, [2]Univ of Bergen, Bergen, Norway, [3]Univ Teaching Hosp, Lusaka, Zambia, [4]Cntr MURAZ, Bobo-Doulasso, Burkina Faso, [5]Univ of Makerere, Kampala, Uganda, [6]Univ of Fort Hare, East London, South Africa, [7]Necker Hosp, Paris, France

Background: Lopinavir/ritonavir (LPV/r) remains a key drug for therapy of pediatric HIV and proved efficacious as an infant prophylaxis in the ANRS 12274 trial. However, reports of growth retardation in LPV/r vs. Nevirapine based combinations in HIV-infected children prompt the need to assess whether this drug could impact infant growth during the first year of life.
Methods: In the ANRS 12174 trial, implemented in 4 African countries, 1273 HIV-uninfected breastfed children born from HIV-infected mothers were randomized at 7 days for either lamivudine or LPV/r until the end of breastfeeding (max 50 weeks) as pre-exposure prophylaxis. Each month, weight and height were measured using standardized high-quality assessments. For these analyses, children were censored when they stopped the study drugs or when they became infected with HIV (N=19). Z-scores were calculated and compared between arms using the least mean squares method at 26 and 50 weeks, linear mixed models and spline regression models.
Results: Overall, 1266 children were included in the analyses, who accumulated 12443 visits. While the length for age score was not different between arms, the weight for age (WHA) score was consistently lower in the LPV/r arm than in the 3TC arm: difference of -0.18 (95%CI: -0.30;-0.5, p=0.006) at 26 weeks, and of -0.24 (95%CI : -0.44 ;-0.05, p=0.02) at 50 weeks. The weight for height (WHZ) score was similarly lower in the LPV/r arm, with differences of -0.22 (95%CI: -0.34;-0.09, p<0.001) at 26 weeks, and of -0.25 (95%CI: -0.46 ;-0.03, p=0.02) at 50 weeks. For both WHA and WHZ, the reduction over time was confirmed by linear mixed model (p=0.02 and p<0.001, respectively), while spline regression models suggest that this reduction occurs early and remain constant thereafter (p=0.02 with knot at 118 days for WHA, and p<0.001 with knot at 44 days for WHZ). Interestingly, the impact of LPV/r was much higher in girls than in boys, and in Burkina Faso and Uganda than in Zambia and South Africa.
Conclusion: This large randomized trial comparing LPV/r vs. 3TC administration in exposed-uninfected children provided a unique opportunity to evaluate the impact of LPV/r on growth. LPV/r initiated at 7 days of life induced a lower weight gain among HIV-uninfected children. These findings have implications for the early treatment of HIV-infected children and for further choice of prophylactic regimen.



782 GROWTH OUTCOMES OF HIV-EXPOSED UNINFECTED CHILDREN BY BIRTH PERIOD IN MALAWI

Malango T. Msukwa[1], Andreas Haas[2], Lyson Tenthani[1], Cristina B. Hofer[2], Janne Estill[2], Frank M. Chimbwandira[3], Adrian Spoerri[2], Joep J. van Oosterhout[4], Olivia Keiser[2], for the Umoyo Study Group

[1]Univ of Bern, Lilongwe, Malawi, [2]Univ of Bern, Bern, Switzerland, [3]Ministry of Hlth, Lilongwe 3, Malawi, [4]Dignitas Intl, Zomba, Malawi

Background: There is concern that in-utero ARV exposure may impair the development of HIV exposed uninfected children. We compared weight-for-age-z-scores up to two years of life of HIV exposed uninfected children who were retained in care and born either in the pre-Option B+, transition or Option B+ periods.

Methods: This was a retrospective cohort analysis of routine data on HIV exposed-uninfected children born between October 2009 and December 2014 from 21 health facilities in Malawi. We included all HIV exposed children with known sex, baseline weight, with at least one follow-up weight measurement and one valid HIV test result. We excluded children with either a positive HIV-1 DNA test result or a positive HIV antibody test that was taken ≥12 months after birth. We used linear mixed effects models to assess weight-for-age-z-scores until 24 months of age according to the child's birth period. We defined birth period as pre-Option B+ if born before September 2011, transition if born between September 2011 and May 2012 and Option B+ if born after May 2012.

Results: We included 6,993 children (median follow-up duration 15.0 months; IQR 8.5 - 21.5 months); 12.1% were born in the pre-Option B+ period, 20.7% in the transition period and 67.3% in the Option B+ period. There were no significant differences in birth weight ($p = 0.377$) and sex ($p = 0.833$) among children born in the three birth periods. Children born during the Option B+ period experienced faster longitudinal growth than those born in the pre-Option B+ period (adjusted β 0.29 [95% CI 0.20; 0.38], $p < 0.0001$). Lower weight-for-age z-scores over time were independently associated with low birth weight and non-exposure of the baby to prophylaxis ARVs at birth, but not with mother exposure to ART during pregnancy or triple combination ART during labour.

Conclusion: After the introduction of Option B+ more intensive exposure to ARV's during pregnancy did not affect birth weight and the growth rate of HIV exposed uninfected children improved, possibly due to effects related to improved health of the mothers.

783 GROWTH IN INFANTS EXPOSED TO EFV AND TDF THROUGH BREASTMILK: MALAWI PMTCT OPTION B+

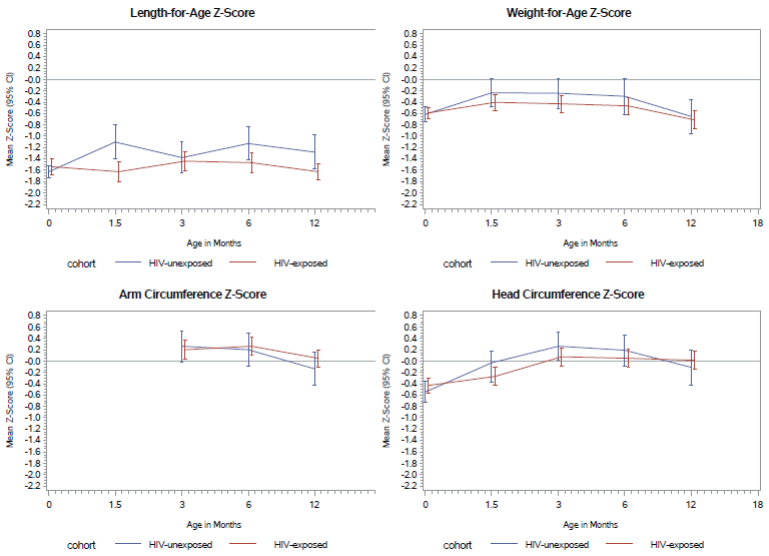
Atupele P. Kapito-Tembo[1], Austin Wesevich[2], Andy Bauleni[1], Mina C. Hosseinipour[2], Dennis Ongubo[2], Queen Dube[3], Amanda Corbett[4], Don Mathanga[1], Victor Mwapasa[1], Sam Phiri[5]

[1]Univ of Malawi, Blantyre, Malawi, [2]Univ of North Carolina Proj–Malawi, Lilongwe, Malawi, [3]Ministry of Hlth Queen Elizabeth Central Hosp, Blantyre, Malawi, [4]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [5]Lighthouse Trust, Lilongwe, Malawi

Background: Pregnant and breastfeeding women in Option B+ program in Malawi receive lifelong antiretroviral drugs (ARVs) containing efavirenz (EFV), tenofovir (TDF) and lamivudine. HIV-infected children on therapeutic doses of these drugs have experienced growth, renal, and bone metabolism adverse effects. Effects of long-term exposure to low doses of these drugs through breastmilk in HIV-exposed infants are unclear.

Methods: A prospective cohort of HIV-exposed breastfeeding infants of HIV-positive mothers on ARVs and control group of HIV-unexposed breastfeeding infants of HIV-negative mothers were recruited in 2:1 ratio and followed from birth through 12 months. Preterm infants were excluded. Length, weight, mid-upper-arm-circumference (MUAC) and head-circumference (HC) were assessed at birth, 6-weeks, 3, 6, and 12 months. Creatinine, alkaline-phosphatase and phosphorus were assessed at 3, 6, and 12 months. Anthropometric

z-scores were calculated using the WHO Child Growth Standards Anthro 2011 software version 3.2.2. Means and 95% confidence intervals of the z-scores were calculated. For biochemistry laboratory tests, Division of AIDS 2014 toxicity tables version 2 were used, with grades 1, 2, 3, and 4 defining mild, moderate, severe, and life-threatening events.
Results: Of the total 260 HIV-exposed breastfeeding infants with EFV and TDF exposure in breastmilk and 125 HIV-unexposed breastfeeding infants enrolled at birth, 87% and 99%; 83% and 62%; 79% and 59%; 74% and 51% completed 6 weeks, 3, 6, and 12 months visits respectively. There were no significant differences in the mean z-scores for length-for-age, weight-for-age, MUAC-for-age and HC-for-age between the two groups except at 6 weeks for length-for-age (refer to figure). There was no report of bone fracture occurrence. Of 677 and 688 creatinine and alkaline-phosphatase measurements, 2.5% and 2.6% reached toxicity levels respectively, however, there were no significant differences between the two groups at all visits.
Conclusion: Among infants of HIV-infected mothers on lifelong ARVs, long-term exposure to EFV and TDF through breastfeeding does not appear to result in growth, renal, or bone adverse outcomes. These data support the safety of breastfeeding of HIV-exposed children at 12 months in the context of PMTCT Option B+.



784 PREDICTORS OF NEURODEVELOPMENT IN CHILDREN OF HIV-INFECTED AND -UNINFECTED WOMEN

Jean Leidner[1], Paige L. Williams[2], Gloria Mayondi[3], Penny Holding[4], Adam Cassidy[5], Joseph Makhema[3], Chipo Petlo[6], Charlotte Mdluli[3], Shahin Lockman[2], Betsy Kammerer[5]
[1]Goodtables Consulting, Oklahoma, OK, USA, [2]Harvard Univ, Boston, MA, USA, [3]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [4]Independent Consultant, Nairobi, Kenya, [5]Boston Children's Hosp, Boston, MA, USA, [6]Ministry of Hlth, Botswana, Gaborone, Botswana

Background: We previously found equivalent neurodevelopmental scores in HIV-exposed, uninfected (HEU) and HIV-unexposed (HU) 24 month-old children in Botswana. Yet, the impact of other maternal, socio-economic, and infant birth characteristics on neurodevelopment remains unclear. We examined the association between these factors and neurodevelopmental scores in HEU and HU children at 24 months of age.
Methods: We enrolled HIV-infected and HIV-uninfected mothers (during pregnancy or within 1 week postpartum) and their babies in the prospective observational "Tshipidi" study in 2 sites in Botswana (1 urban and 1 rural) from May 2010 -July 2012. Live born infants and their mothers were followed for 24 months, with data on socio-demographic, health, and psychosocial characteristics collected at baseline and periodically during follow-up. Assessment of neurodevelopmental outcomes at 24 months of age included the Bayley Scales of Infant and Toddler Development III The Bayley contained 3 domains: Cognitive, Motor (Fine and Gross), and Language (Expressive and Receptive); each of these was modified for cultural appropriateness, and scored and analyzed separately.
Results: Among the 910 (453 HEU, 457 HU) infants enrolled, 670 (313 HEU, 357 HU) had one or more valid Bayley scores prior to 30 months of age, 90% of whom attempted the entire assessment. In univariate analyses, mean scores were associated with multiple predictors. Low birth weight (LBW), being male, younger maternal age, less maternal education, lack of indoor plumbing and a stove, food insecurity, and maternal tobacco use and depression were associated with worse scores. All factors remained significant after multivariable adjustment, except food insecurity and maternal depression. The relationship between higher maternal education and better scores was particularly strong among HEU children. These education-related increases in mean Cognitive and Expressive and Receptive Language scores were reflected by effect sizes of 0.26, 0.50, and 0.26, respectively ($p<0.05$). This relationship was not seen in HU children. Multivariable adjustment attenuated the effect of socio-economics in both exposure groups.
Conclusion: Multiple maternal, child and home environment factors impact development in both HIV exposed and unexposed children in Botswana. These data provide guidance in choosing support services for both mothers and children, particularly HEUs, to promote the child's cognitive, motor, and language development.

Adjusted Multivariable Effect Sizes at p<0.05 for ND outcomes

		Bayley Domain				
		Cognitive	Fine Motor	Gross Motor	Expressive Language	Receptive Language
HEU children only						
Maternal social and psychological factors	Higher maternal education level	0.26			0.50	0.26
	Maternal tobacco use		-0.56			
Infant birth factors	Male sex vs. female	-0.28	-0.24			
	Low birth weight			-0.32		
	Prematurity (<37 weeks)			-0.45		
HU children only						
Maternal social and psychological factors	Urban clinic site (vs. rural)					0.30
	Older maternal age at enrollment	0.17				
Socio-economic factors	No indoor toilet		-0.24			
	Home electricity					0.26
Infant birth factors	Male sex vs. female		-0.36		-0.24	
	Low birth weight	-0.56		-0.55		

785 B-CELL SUBSETS PROFILE AND VACCINE RESPONSE IN HIV-EXPOSED UNINFECTED (HEU) CHILDREN

Laurence Raymond Marchand[1], Catherine Gravel[1], Armelle Le Campion[2], Marc Boucher[2], Normand Lapointe[2], Valerie Lamarre[2], Fatima Kakkar[2], Helene C. Cote[3], Hugo Soudeyns[1], for the CIHR Team on Cellular Aging and HIV Comorbidities in Women and Children (CARMA)
[1]CHU Sainte Justine, Montreal, Canada, [2]Univ of Montreal, Montreal, Canada, [3]Univ of British Columbia, Vancouver, Canada

Background: HEU children present with a higher incidence of morbidity and mortality in early life. There is evidence that some HEU children exhibit immunologic abnormalities involving the B cell compartment that could be related to in utero and/or perinatal exposure to HIV and/or combination antiretroviral therapy (cART). Here, longitudinal profiling of B cell subsets, naïve-memory differentiation, and vaccine responses was performed during the 1st year of life in HEU children.
Methods: HEU children (n=60) from the CMIS Cohort were stratified based on whether maternal HIV-1 viral load (VL) throughout pregnancy was detectable or not (≥40 vs. <40 copies/ml). All received cART (AZT/3TC) from 12h after birth until week 6. Blood mononuclear cells were isolated at birth (cord blood), 6, and 12 months of age. CD19 B cell subsets (naïve; transitional T1 and T2/T3; classical memory; activated memory; atypical memory; plasmablasts) were characterized by flow cytometry based on the expression of CD10, CD20, CD21, CD27 and IgM. Vaccine responses were tested with fluorescent tetanus toxoid C fragment (TTCF) oligomers.
Results: At birth, HEU infants born to mothers whose VL in pregnancy was ≥40 copies/ml had or tended to have a lower frequency of transitional T1 B cells (p=0.042) and a higher frequency of plasmablasts (p=0.066). At 12 months of age, they showed a higher frequencies of naïve B cells (p=0.012) and transitional T2/T3 B cells (p=0.016) and they had higher levels of non-class switched B cells in classical memory (p=0.022), activated memory (p=0.009) and atypical memory (p=0.057) subsets compared to HEU born to mothers with VL <40 copies/ml. No significant differences were noted in the frequency of any TTCF-specific B cell subsets between the 2 groups.
Conclusion: Our results suggest an early maturation of the B cell compartment in infants born to mothers with detectable VL in pregnancy, with delayed development of antigen-experienced B cells and disturbances in class switching at 12 months of age. These differences in distribution of B cell subsets are analogous to those recently reported in HIV-infected children, compatible with effects induced by HIV exposure. Reassuringly, the presence of equal levels of TTCF-specific B cells in HEU children from both groups suggests and vaccine efficacy in the context of differential exposure to maternal viral load.

786 INFLAMMATORY RESPONSES ASSOCIATED WITH CMV AND MATERNAL HIV IN ZIMBABWEAN INFANTS

Ceri Evans[1], Bernard Chasekwa[2], Sandra Rukobo[2], Margaret Ghova[2], Kuda Mutasa[2], Robert Ntozini[2], Jean Humphrey[2], Andrew Prendergast[1]
[1]Queen Mary Univ of London, London, UK, [2]Zvitambo Inst for Maternal and Child Hlth Rsr, Harare, Zimbabwe

Background: Previously identified abnormalities in HIV-exposed uninfected (HEU) infants include elevated immune activation. The causes are uncertain, but may be related to maternal HIV viremia, maternal immunosuppression, or increased acquisition of infections such as cytomegalovirus (CMV). We compared the effect of HIV exposure and CMV acquisition on infant inflammatory responses.
Methods: Mother-infant pairs were recruited at birth to the ZVITAMBO trial before the availability of antiretroviral therapy in Zimbabwe. CMV and C-reactive protein (CRP) were measured at 6 weeks of age in cryopreserved plasma using real-time PCR and ELISA, respectively.
Results: 231 HEU infants and 100 HIV-unexposed infants were included. HEU and HIV-unexposed infants had a similarly high prevalence of CMV acquisition at 6 weeks of age (83.1% vs. 74.0%, respectively; P=0.13), but HEU infants had significantly higher CMV viral loads (P=0.005). HEU infants had higher CRP concentrations than HIV-unexposed infants at 6 weeks (median 0.43mg/L vs. 0.20mg/L; P<0.0001). There was no significant association between CRP and CMV DNAemia in HIV-unexposed infants. By contrast, in HEU infants, CMV DNAemia was associated with increased CRP; this association persisted after adjusting for maternal CD4 count, but was no longer present after adjusting for maternal HIV viral load. There were no associations between CMV viral load and infant CRP, maternal HIV viral load or maternal CD4 count (all P>0.05).
Conclusion: CMV acquisition was high in Zimbabwean infants irrespective of HIV exposure status. However, HEU infants had higher CMV viral loads which may suggest a failure to control viral infections. Compared to HIV-unexposed infants, HEU infants had more inflammation by 6 weeks of age. CMV DNAemia was associated with elevated CRP in HEU infants but not in HIV-exposed infants; this association appeared to be driven by more advanced disease in the mothers of CMV+ compared to CMV- HEU infants. In HEU infants, maternal HIV viremia had a greater influence on infant inflammation than maternal immunosuppression, highlighting the importance of rapid HIV viral load suppression in pregnant women to improve outcomes even in uninfected infants.

787 MATERNAL ART ASSOCIATED WITH IMPROVED PROTECTIVE TRANSPLACENTAL ANTIBODY TRANSFER

Scott Dryden-Peterson[1], Elize de Bruyn[2], Gloria Mayondi[3], Betsy Kammerer[4], Jean Leidner[5], Roger L. Shapiro[6], Haruna Jibril[7], Shabir Madhi[2], Shahin Lockman[6]
[1]Brigham and Women's Hosp, Boston, MA, USA, [2]Respiratory and Meningeal Pathogens Rsr Unit, Soweto, South Africa, [3]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [4]Boston Children's Hosp, Boston, MA, USA, [5]Goodtables Consulting, Norman, OK, USA, [6]Harvard Univ, Boston, MA, USA, [7]Botswana Ministry of Hlth, Gaborone, Botswana

Background: Transplacental transfer of pathogen-specific IgG antibodies is deficient in HIV-exposed uninfected (HEU) infants and may contribute to observed 2 to 5-fold increase in early infant mortality. We sought to determine whether maternal ART improves this deficit.
Methods: We utilized paired mother-infant serum specimens drawn within 7 days of birth from an observational study of HIV-infected pregnant women during transition from Option A to Option B+ in Botswana. Levels of IgG specific to pertussis, diphtheria, and tetanus toxoids, hepatitis B surface antigen, and capsular polysaccharides of H. influenzae type b and 13 types of S. pneumoniae (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) were measured by multiplex immune assay. Multivariable linear and Poisson models included adjustment for maternal CD4, age, and socioeconomic factors.
Results: Of 439 enrolled mothers receiving either zidovudine or ART in pregnancy, specimens were analyzable from 157 mother-infant pairs (49 ART-exposed) and an additional 34 infants (16 ART-exposed). There were no significant differences in specimen availability by ART exposure (p=0.60). Mothers received median of 2.4 months of zidovudine (IQR 2.0 to 2.8 months) or 22.3 months of ART (IQR 3.3 to 47.3 months) prior to delivery. CD4 cell count was higher for women receiving zidovudine than ART- median 448 and 421 cells/μL, respectively (p=0.023). Maternal ART was not associated with higher pathogen-specific IgG titers in maternal sera. However, in adjusted analyses, maternal ART was associated with 53% (95%CI 30 to 75%, p<0.001) improvement in the placental transfer ratio (infant/maternal pathogen-specific IgG titer) and 35% (95%CI 15 to 67%, p=0.016) increase in infant pathogen-specific IgG concentrations compared with zidovudine. The effect of ART placental transfer was similar in mothers initiating ART prior to or during pregnancy (p=0.35 for interaction). In adjusted individual IgG analyses, ART was associated with improved placental transfer for all antibodies except H. influenzae type b (Figure). Maternal ART had a greater effect on transplacental transfer of antibodies to S. pneumoniae types (61% increase, p=0.003 for interaction).
Conclusion: Maternal ART, whether started during or prior to pregnancy, is associated with improved transplacental transfer and higher concentrations of pathogen-specific antibodies in HEU infants. In addition to reduction in HIV transmission risk, maternal ART may enhance humoral immunity of vulnerable HEU infants.

788 EVALUATION OF MATERNAL AND INFANT HIV POINT-OF-CARE DIAGNOSTICS AT BIRTH IN TANZANIA

Issa Sabi[1], Hellen Mahiga[1], Jimson Mgaya[1], Otto Geisenberger[2], John France[3], Michael Hoelscher[2], **Arne Kroidl**[2]
[1]NIMR–Mbeya Med Rsr Cntr (MMRC), Mbeya, Tanzania, [2]Univ of Munich, Munich, Germany, [3]Mbeya Referral Hosp, Mbeya, Tanzania

Background: Point-of-Care (PoC) HIV testing for early infant diagnostics (EID) enables nurse-based, decentralized testing with the potential to replace centralized laboratory EID procedures which are complicated by linkage. Additionally, PoC maternal viral load (VL) monitoring around delivery can immediately identify high VL as a risk factor for mother-to-child transmission. In our study we investigated the operational feasibility and accuracy of a novel PoC technology for EID and maternal VL monitoring in primary obstetric health centers in Mbeya, Tanzania.
Methods: In this prospective cohort study we included HIV-infected pregnant women and their exposed infants during delivery. Maternal plasma HIV-RNA monitoring was performed by quantitative HIV PoC testing (Cepheid Xpert HIV-1 Quant) during delivery. Nurse based qualitative HIV EID PoC testing (Cepheid Xpert HIV-1 Qual) was performed at birth, and after 1, 2, 3 and 6 weeks postpartum. Maternal viral loads and positive EID PoC test results were confirmed from plasma and infants dry blood spots (DBS) using the Roche COBAS TaqMan system. HIV negativity in infants was confirmed from DBS at the last study visit.
Results: Between July 2015 and August 2016, 600 mother-child pairs were included, and 15 (2.5%) infants were diagnosed HIV positive. Of those 11 (73%) were diagnosed at birth suggesting intra-uterine infection, and 4 were either detected at week 1, 2 or 3 suggesting peripartal transmission. The Xpert HIV-1 Qual PoC test correctly identified all HIV infected and non-infected infants (no false positive or negative test results). In mothers we found a good agreement between the quantitative Xpert HIV-1 Quant PoC test and the TaqMan plasma HIV-RNA, however, the Xpert HIV-1 Quant HIV-RNA results indicated slightly higher viral loads as compared to the TaqMan with a mean difference of 0.34 log10 (range -0.46 to 1.14). PoC test procedures were well accepted by nurses/midwives and mothers.
Conclusion: We could demonstrate an excellent Xpert HIV-1 PoC test performance and operational feasibility for EID at birth up to week 6 and maternal viral load monitoring at delivery. Both tests have the potential to facilitate rapid infant antiretroviral treatment initiation or use of enhanced postnatal infant prophylaxis.

789 EVALUATION OF THE CEPHEID HIV-1 QUAL POINT-OF-CARE TEST FOR HIV DIAGNOSIS AT BIRTH

Maryanne R. Ibrahim[1], Sikhulile Moyo[2], Terence Mohammed[3], Kenneth Maswabi[2], Gbolahan Ajibola[2], Rebecca Gelman[2], Chloe Auletta-Young[1], Shahin Lockman[1], Joseph Makhema[2], Roger L. Shapiro[1]
[1]Doris Duke Intl Clinical Rsr Fellowship, Los Angeles, CA, USA, [2]Botswana Harvard AIDs Rsr Inst Partnership, Gaborone, Botswana, [2]Dana–Farber Cancer Inst, Boston, MA, USA

Background: HIV point-of-care (POC) testing may facilitate early infant diagnosis, but the accuracy of POC testing in the first week of life and in the setting of antiretroviral prophylaxis for the prevention of mother-to-child HIV transmission (MTCT) is unknown. This study aimed to evaluate the sensitivity and specificity of the Cepheid Xpert® HIV-1 Qual POC test compared with the Roche Taqman HIV DNA PCR platform to diagnose infant HIV infection in the first 96 hours of life.
Methods: As part of an early infant treatment study, infants < 96 hours of life were screened for HIV at 5 hospital maternity wards in Botswana. Infants received post-exposure antiretroviral prophylaxis (PEP) with single-dose nevirapine and zidovudine, and most mothers received 3-drug antiretroviral therapy in pregnancy and at delivery. Dried blot spot screening samples were initially tested using the Roche Taqman HIV DNA PCR platform. To evaluate sensitivity of POC testing, remaining dried blood spots from the PCR-positive screening samples were tested using the Cepheid Xpert® HIV-1 Qual test. Seventy-five HIV-exposed, PCR negative infants were also selected for testing by Cepheid to evaluate POC assay specificity. The study was powered to have a lower 95% confidence limit of 82% sensitivity with 15 true-positive samples.
Results: Fourteen of 15 PCR positive samples tested positive by Cepheid POC, yielding a sensitivity of 93.3% (95% CI: 68.1 – 99.8%). Among the 15 PCR positive infants, baseline viral load ranged from <40 copies/ml to >10,000,000 copies/ml, with a median of 2,403 copies/ml (Table 1). Twelve (80%) of the 15 infants were exposed to maternal 3-drug antiretroviral therapy near delivery, and all but one received PEP prior to screening. The HIV RNA for the infant with false negative POC testing was 1661 copies/mL. Of note, two infants with low HIV RNA (< 40 copies/mL and 272 copies/ml) were correctly identified as HIV positive by Cepheid POC. All of the 75 PCR-negative samples tested negative by Cepheid POC, yielding a specificity of 100% (95% CI: 96.1 –100%).
Conclusion: Our study demonstrates high sensitivity and specificity for the Cepheid POC assay in the first week of life despite low median infant HIV RNA and extensive PEP. The Cepheid POC testing platform may be a useful approach for adding early infant HIV diagnosis in Botswana.

790 TARGETED HIV SCREENING AT BIRTH CAN IDENTIFY THE MAJORITY OF IN UTERO TRANSMISSIONS

Maryanne R. Ibrahim[1], Kenneth Maswabi[2], Gbolahan Ajibola[2], Sikhulile Moyo[2], Michael D. Hughes[3], Chloe Auletta-Young[3], Daniel R. Kuritzkes[4], Mathias Lichterfeld[5], Joseph Makhema[2], Roger L. Shapiro[3]
[1]Doris Duke Intl Clinical Rsr Fellowship, Los Angeles, CA, USA, [2]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [3]Harvard Univ, Boston, MA, USA, [4]Brigham and Women's Hosp, Boston, MA, USA, [5]Massachusetts General Hosp, Boston, MA, USA

Background: Botswana tests for in utero and intrapartum mother-to-child HIV transmission (MTCT) by infant HIV PCR at age 6 weeks. Limitations to this strategy include early mortality, loss-to-follow-up, and delayed treatment initiation for infected infants. In 2015, the Botswana-Harvard Partnership launched the Early Infant Treatment Study to identify HIV-infected infants at birth and offer immediate antiretroviral therapy. To determine the feasibility of targeted birth testing for infants at high-risk of HIV infection, we evaluated risk factors for in utero MTCT that were identifiable at delivery.

Methods: HIV-exposed infants were screened at 5 hospital maternity wards by trained research assistants in the Gaborone and Francistown regions of Botswana. Screened infants met the following inclusion criteria: mother/guardian ≥ 18 years of age, gestational age at birth ≥ 35 weeks, birth weight ≥ 2000 grams, age < 96 hours, and eligible for antiretroviral treatment (ART) through the Botswana government program. Consenting mothers were assessed for MTCT risk factors by their obstetric card or verbally. Risk factors included < 8 weeks ART in pregnancy, last CD4 known to be <250 cells/mm^3, last HIV RNA known to be > 400 copies/mL, poor maternal ART adherence, lack of maternal zidovudine in labor, or lack of infant post-exposure prophylaxis. Infants underwent heel stick and 3-5 dried blood spots were collected for testing by Roche Cobas Ampliprep/Cobas Taqman HIV-1 qualitative PCR.
Results: In the first year of the study (April 2015 to April 2016), 4086 HIV-exposed infants were delivered at the screening maternities, of whom 3541 (87%) had not been discharged, 2580 (63%) were eligible, and 2303 (56%) agreed to be screened for HIV. Of the 2303 infants screened, 369 (16%) were identified as high-risk for HIV infection. In total, 12 (0.5%) of the 2303 infants were identified as HIV positive at birth. All 12 positive infants were identified as high risk at the time of screening, and all were identifiable as high risk by either < 8 weeks of maternal ART in pregnancy (75%) or lack of maternal HIV suppression at last test (25%) (Table 1).
Conclusion: In utero MTCT occurred only among infants identified as high risk at the time of delivery, using information available from the mother or her obstetric record. Birth testing that targets high risk infants is likely to identify the large majority of in utero HIV transmissions, and allows early ART initiation for these infants.

791 IMPACT OF BIRTH PCR ON RETENTION IN CARE OF HIV-EXPOSED INFANTS IN PRIMARY CARE

Aurelie Nelson[1], Laura Trivino Duran[1], Tali Cassidy[1], Gilles van Cutsem[2], Sarah Jane Steele[2], Mark Cotton[3], Janet Giddy[4], Jean Maritz[3]
[1]MSF, Khayelitsha, South Africa, [2]MSF, Cape Town, South Africa, [3]Stellenbosch Univ, Cape Town, South Africa, [4]KESS, Cape Town, South Africa
Background: The World Health Organization (WHO) recently recommended birth testing for all HIV-exposed infants (July 2016). Birth polymerase chain reaction (PCR) in this population was introduced in June 2015 in South Africa. There is an increased interest in point of care (POC) technology for birth testing to improve immediate retention in care and early treatment initiation. However, there is little data on the impact of either birth PCR or POC technology on longer term retention in care. We describe the impact of birth PCR (including POC) on retention in care at 6-10 weeks.
Methods: We compared the completion of routine 6-10 weeks testing (range:5-15 weeks) for three groups of HIV-exposed infants with varying risk of HIV transmission born in a primary care clinic, Khayelitsha, South Africa : a) historical control group born between August 2013 and March 2014 (n=321), without birth HIV testing; b) prospective group born between November 2014 and July 2015, (n=336) with a birth PCR done in a central laboratory (Roche CAP/CTM assays); c) prospective group born between August 2015 and April 2016 (n=321), tested with POC Alere Q birth PCR. Infants of the two latter groups received extra counselling, by a nurse employed for this study, on further routine infant testing. Return for PCR at 6-10 weeks of age was determined using a national laboratory database. Tracing (phone calls and home visits) was done for groups b and c. For the purposes of this analysis, those who returned only after tracing were not classified as completing 6-10 weeks PCR to improve comparability between the three groups. Summary statistics and relative risks were calculated in STATA.
Results: For the group without birth PCR, 197 (62%) returned for 6-10 weeks PCR at a median of 46 (IQR 43-50) days. For the group with birth PCR in central laboratory, 339 (78.1%) returned for the 6-10 weeks PCR at a median of 44 (IQR 42-47) days. For the group tested by birth POC, 241 (75%) returned for 6-10 weeks PCR at a median of 45 (IQR 43-50) days. Overall, the two groups with birth PCRs were more likely to return than the historical controls (RR: 1.3 [95% CI:1.07-1.5])
Conclusion: Birth PCR did not negatively impact return for further testing at 6-10 weeks. Limitations to this study include using a historical control. The extra counseling the two latter groups received could have also influenced positively their return for further infant's testing.

792 IMPACT OF EXPANDED SCREENING AND POC ON INFANT DIAGNOSIS AND ART INITIATION

Alliance Nikuze[1], Stephen Wanjala[2], Jihane Ben-Farhat[1], Willis Omwoyo[3], Laura Oyiengo[4], Elisabeth Szumilin[5], Leon Salumu[5], Alexandra Vandenbulcke[5], Valarie S. Opollo[6], **David Maman**[7]
[1]Epicentre, Paris, France, [2]MSF, Nairobi, Kenya, [3]Ministry of Hlth, Homa bay, Kenya, [4]Natl AIDS/STI Control Prog, Nairobi, Kenya, [5]MSF France, Paris, France, [6]Kenya Med Rsr Inst, Kisumu, Nyanza, [7]Epicentre, Cape Town, South Africa
Background: High HIV incidence among young women during pregnancy and breastfeeding periods necessitate systematic retesting. Furthermore, long turnaround time of early infant diagnosis can delay ART initiation in children. We assessed the impact of expanded women/child HIV testing outside PMTCT coupled to the introduction of near Point of Care early infant diagnosis devices on children diagnosis and ART initiation
Methods: A cross-sectional facility-based survey recruited mother-infant pairs seeking expanded programs of immunization (EPI), maternity, in and outpatient department services between February and July 2016, in 26 selected facilities of Ndhiwa sub-county, Kenya. Infants aged 0 (at birth), between 2 to 10 weeks and 8 to 10 months were eligible and if exposed to HIV, tested for HIV using GenXpert and Roche. The questionnaires collected information on participants' background, ANC attendance, and HIV/AIDS, including ART coverage. All HIV-positive mothers and children had their VL measured, regardless of their ART status
Results: A total of 3,970 mother/infant pairs were enrolled. Mothers had a median age of 23 years [IQR 19-29] and an overall prevalence of 24.9% (95%CI 23.5-26.4). Out of 909 exposed infants, 34 were HIV-positive (MTCT rate 3.5%; 95%CI 2.5-4.9). Of them, 9 had a mother who never initiated ART (MTCT 13.2%), 14 had a mother who initiated during the last trimester or after delivery (MTCT 8.2%) and 10 had a mother on ART initiated before the last trimester with a VL>1,000 cp/mL (MTCT 5.9%). Among HIV-positive women who initiated ART before the last trimester and had a VL<1,000 cp/mL, only 3 infants were HIV-positive (MTCT 0.5%). Out of 34 HIV-infected infants identified during the survey, 28 were undiagnosed. Of them, 12 (42.2%) had initiated treatment less than 1 month after the first test and 19(67.8%) less than three months after the first test
Conclusion: Expanding mother and infant screening outside PMTCT and introducing POC can help rapidly diagnosing and initiating HIV-positive infants. We found a MTCT rate of 3.5% mostly because of late/non initiation of ART or virological failure among mothers. As option B+ seems necessary but insufficient to eradicate MTCT in high incidence settings, more investment in improving infant diagnosis are needed

793 DELAYED HIV DNA PCR DETECTION AMONG INFANTS WHO RECEIVED COMBINATION ART PROPHYLAXIS

Thanyawee Puthanakit[1], Archawin Rojanawiwat[2], Tanawan Samleerat[3], Hansa Thaisri[2], Jiratchaya Sophonphan[4], Sarawut Boonsuk[5], Sumet Ongwandee[5], Varunee Jinarat[2], for the Thailand ACC Program
[1]Chulalongkorn Univ, Bangkok, Thailand, [2]Ministry of Pub Hlth, Nonthaburi, Thailand, [3]Chiang Mai Univ, Chiang Mai, Thailand, [4]HIV Netherlands Australia Thailand Rsr Collab,Thai Red Cross AIDS Rsr, Bangkok, Thailand, [5]Ministry of Pub Hlth, Nonthaburi, Thailand
Background: Early infant diagnosis (EID) for HIV-exposed infants is performed by DNA PCR assays. In utero transmission can be detected by HIV DNA PCR at birth, while peri-partum transmission is detected during the first 6 months of life. Triple drug antiretroviral regimens may be associated with delayed HIV DNA PCR detection, and this was assessed in the Thai National PMTCT program.
Methods: Retrospective chart reviews of HIV-infected infants reported in the "National Active Case Management Network to promote early ART initiation" (ACC), were conducted. According to the Thai national guidelines 2014; infants with high risk of vertical transmission (mother received ART< 4 weeks during pregnancy or has HIV RNA viral load > 50 copies/ml near time delivery) receive zidovudine(AZT)/lamivudine(3TC)/nevirapine(NVP) for 6 weeks and testing for HIV DNA PCR at birth,1,2 and 4 months, while infants with a standard risk of vertical transmission receive AZT for 4 weeks and HIV DNA PCR testing at 1, and 2-4 months. Infants who had their first or second HIV DNA PCR at age > 2 or > 4 month were excluded from the analysis. HIV DNA PCR was performed by either real time PCR or conventional assays on samples collected as dried blood spot (DBS;18-50 uL) or whole blood (WB;200 ul). The limit of detection of the assays is 1 copy/reaction. HIV DNA PCR tests were performed by the national EID network including 16 laboratories.

Results: From August 2014 to August 2016, 95 HIV-infected infants were diagnosed with HIV (73 high –risk and 22 standard-risk). Samples at birth (all DBS) from 37 neonates in the high-risk group were obtained, of which 17 were positive. The sensitivity of the DBS test was 46% (95% CI 29-63). Among the remaining 78 infants, the time to first positive HIV DNA PCR is shown in table 1. Thirty-three infants in high-risk group (59%) were HIV DNA PCR positive at the first sample, compared to 21 standard risk infants(95%) (p=0.001). Among high-risk infants, 12(21%) were initially HIV DNA PCR positive by the 2nd sample by 2 month of age, and 11(20%) by samples collected between 2-6 month of age.
Conclusion: Combination antiretroviral neonatal prophylaxis regimen may delay the time to HIV DNA detection. False negative HIV DNA PCR testing was observed in about 40% of high-risk HIV-infected infants tested at one month and 20% at two months. Therefore, to exclude HIV-infection in infants on triple antiretroviral prophylaxis, negative HIV DNA PCR should be documented when infants are at least 4 months of age.

Table 1. Time to first HIV DNA PCR positive among HIV-exposed infant receiving neonatal prophylaxis

	High-risk group receiving combination ART (N=56)			Standard-risk group received AZT (N=22)		
	Median age (days)	Number positive	Cumulative	Median age (days)	Number positive	Cumulative
Positive on first sample at 1-2 month	38 days	33	59% (45-72)	34 days	21	95% (77-100)
Positive on 2nd sample at 2 month	61 days	12	80% (68-90)	Not done		
Positive on additional samples at 2-6 month	123 days	11	100%	133 day	1	100%

794 HIV VIRAL-LOAD TRENDS WITHIN SOUTH AFRICA'S EARLY INFANT DIAGNOSIS PROGRAM, 2010–2015

Ahmad Haeri Mazanderani[1], Faith Moyo[1], Tendesayi Kufa-Chakezha[1], Gayle G. Sherman[2]
[1]NCID, Johannesburg, South Africa, [2]Univ of the Witwatersrand, Johannesburg, South Africa

Background: Within South Africa's PMTCT program, maternal antiretroviral therapy has evolved from WHO Option A in 2010, to Option B in 2013 and Option B+ in 2015, with daily infant nevirapine prophylaxis for at least 6-weeks duration remaining standard of care since 2010. The impact of antiretroviral prophylaxis on infant viraemia and the clinical implications thereof are unclear. We describe confirmatory viral load results within South Africa's early infant diagnosis program from 2010–2015.
Methods: HIV PCR and viral load test data from 2010–2015 were extracted from the South African National Health Laboratory Service's central data repository of all registered test-sets within the public health sector. HIV PCR and viral load results were linked by a patient linking-algorithm using probabilistic matching of patient demographics. All infants with a positive HIV PCR result and a subsequent HIV viral load result taken ≤6months of age were included. Simple linear regression and logistic regression were used to describe viral load trends.
Results: Amongst 5602 infants, 5386 (96.0%) had a quantified baseline viral load result and 216 (4.0%) had a result less than the quantifiable limit of the assay used (lower limit of quantification ranged from 20 to 150 RNA cps/ml). Median age at first PCR was 49 days (IQR: 43-81) and at baseline viral load was 88 days (IQR: 66-116). The median baseline viral load between 2010 and 2015 decreased from 6.3 Log10 (IQR: 5.7-6.8) to 5.8 Log10 (IQR: 4.8-6.4) (p<0.001), with the proportion of infants who had a baseline viral load <4 Log10 increasing from 1.9% to 34.6% (p<0.001). Adjusting for year of PCR testing, younger age at testing was associated with a lower viral load result, regression coefficient 0.09 [95% CI 0.07-0.12; p<0.001]. Amongst 155 infants with a less than quantifiable baseline viral load who had follow up testing there were 77 (49.7%) infants who were confirmed as being HIV infected, 69 (89.6%) of whom had their baseline viral load tested at <3months of age.
Conclusion: Between 2010–2015, alongside the introduction of improved maternal prophylaxis, younger age and later year of testing were associated with a significantly lower baseline HIV viral load. These results support findings that antiretroviral prophylaxis may be associated with loss of detectability using virological assays amongst some infants, thereby preventing confirmation of HIV infection early in life.

Table 1. Baseline HIV viral load results (copies/ml) by year and age range

Age	Median VL Log10 (IQR) by Year of Testing						
	2010	2011	2012	2013	2014	2015	Total
<1 mo	6.41 (6.02-6.80) n=2	5.00 (3.56-6.45) n=2	6.71 (5.32-6.86) n=7	5.67 (3.63-6.94) n=23	4.81 (3.44-6.05) n=61	4.65 (3.49-5.76) n=147	4.81 (3.52-6.00) n=242
1-<2 mo	6.53 (4.95-6.71) n=9	6.16 (5.51-6.57) n=30	6.05 (5.44-6.70) n=76	6.08 (5.40-6.61) n=237	5.89 (5.16-6.37) n=276	5.68 (4.69-6.31) n=177	5.94 (5.18-6.47) n=805
2-<3 mo	6.30 (5.78-6.72) n=50	6.01 (5.54-6.56) n=131	6.26 (5.55-6.73) n=223	6.17 (5.58-6.71) n=478	6.09 (5.46-6.65) n=654	5.94 (5.30-6.50) n=317	6.10 (5.49-6.64) n=1853
3-<4 mo	6.15 (5.52-6.72) n=46	6.08 (5.35-6.55) n=107	6.39 (5.70-6.95) n=165	6.28 (5.50-6.77) n=341	6.16 (5.31-6.79) n=412	5.95 (5.07-6.57) n=259	6.19 (5.34-6.76) n=1330
4-<5 mo	6.44 (5.83-6.79) n=38	6.11 (5.62-6.74) n=86	6.42 (5.65-6.88) n=118	6.20 (5.48-6.77) n=216	6.11 (5.38-6.82) n=240	6.04 (5.01-6.61) n=139	6.20 (5.44-6.79) n=837
5-≤6 mo	6.20 (6.56-6.89) n=20	6.28 (5.82-6.95) n=35	6.29 (5.53-6.94) n=45	6.13 (5.17-6.72) n=70	5.98 (5.03-6.49) n=88	5.90 (4.99-6.31) n=61	6.09 (5.27-6.72) n=319
Total	6.26 (5.65-6.76) n=165	6.11 (5.51-6.02) n=391	6.30 (5.57-6.85) n=634	6.18 (5.50-6.73) n=1365	6.05 (5.29-6.67) n=1731	5.80 (4.83-6.44) n=1100	6.09 (5.33-6.67) n=5386

VL=viral load; n=number of infants; mo=months IQR=interquartile range

795 DETECTION OF INDUCIBLE HIV IN CHILDREN ON ART DESPITE LOW HIV-1 DNA

Shalena Naidoo[1], Michele Sobolewski[2], Taylor Buckley[2], Joshua C. Cyktor[2], Melissa Tosiano[2], Mary Grace K. Katusiime[3], Gert U. van Zyl[3], Mark Cotton[1], Richard Glashoff[1], John Mellors[3]
[1]Stellenbosch Univ, Cape Town, South Africa, [2]Univ of Pittsburgh, Pittsburgh, PA, USA, [3]Stellenbosch Univ, Parow, South Africa

Background: Early ART initiation in infants reduces the number of HIV infected cells and may delay viral rebound after ART interruption. It is unknown whether the few HIV infected cells that persist on long-term ART harbor proviruses capable of virion production. This study was undertaken to evaluate how often HIV is inducible from CD4+ T lymphocytes in early ART treated children.
Methods: Stored PBMC samples were analyzed from Post-CHER participants who began ART at <1 year of age and sustained suppression of viremia through to time of sampling at age 7-8. Total HIV-1 DNA in PBMC was quantified by qPCR targeting a conserved region in integrase. Total inducible virus recovery (TVR) assays were performed on purified CD4+ T cells stimulated with PMA and ionomycin for 7 days. Virus outgrowth assays (VOA) were also performed with purified CD4+ T cells, activated with phytohemagglutinin and co-cultured for 28 days with irradiated HIV-1 negative feeder cells and CD8-depleted blasts. Depending on CD4+ T cell recovery, replicas of 1x10[6] CD4+ T cells were seeded for both assays. Supernatants were collected on day 8 for the TVR assay and days 7, 14, 21 and 28 for VOA. HIV-1 RNA was measured in cell culture supernatants using a quantitative HIV-1 PCR assay targeting integrase (iSCA) with single-copy sensitivity. VOA supernatants were also assayed for p24 antigen by EIA.
Results: Samples from 10 children (6 females, 4 males) were studied (median ART initiation age: 6 months) after 7-8 years of viremia suppression. Five participants had pre-ART HIV RNA >750,000 copies/ml and 5 had a median pre-ART HIV RNA of 635,000 copies/ml. The median CD4 percentage at the age of 7-8 years was 39%. Median cell associated HIV-1 DNA was 38 copies per million cells (range: 4.5-186). Two of 10 children had inducible HIV-1 RNA by TVR assay detected by iSCA at 2267 and 24 copies/ml, respectively. All VOA supernatants collected were negative for p24 antigen, but 4 participants had detectable HIV-1 RNA at day 21 (range: 9-697 copies/ml). No-RT controls excluded HIV-1 DNA contamination.
Conclusion: Children initiated on ART early did not have infectious virus that could be readily isolated in viral outgrowth assays. However, inducible virion production was detected in 4 of 10 children using a highly sensitive HIV-1 RNA assay. This assay may be a sensitive biomarker for virion production in latent HIV reservoirs from children from whom only small sample volumes are feasible.

796 HIV RESERVOIR SIZE IS NOT INCREASED BY SHORT ART INTERRUPTION IN KENYAN INFANTS

Mark D. Pankau[1], Dalton Wamalwa[2], Sarah Benki-Nugent[3], Agnes Langat[4], Ken Tapia[3], Elizabeth Maleche-Obimbo[5], Julie Overbaugh[1], Grace John-Stewart[3], Dara Lehman[1]
[1]FRCHC, Seattle, WA, USA, [2]Univ of Nairobi, Nairobi, Kenya, [3]Univ of Washington, Seattle, WA, USA, [4]US CDC, Nairobi, Kenya, [5]Kenyatta Natl Hosp, Nairobi, Kenya

Background: ART initiation during primary HIV infection limits the size of the latent reservoir. Interventions following early antiretroviral treatment (ART) are currently being tested to optimize post-treatment control. Evaluating these approaches will require treatment interruption, which may lead to viral rebound and an increased latent reservoir size, decreasing the benefits of early ART. Here we assess the impact of short ART interruption on HIV reservoir size in a cohort of early ART treated infants.
Methods: The Optimizing Pediatric HIV-1 Treatment study (NCT00428116) was a randomized trial comparing outcomes of Kenyan infants randomized to treatment interruption or continued therapy after ART for 24 months. Infants with CD4 >25% and normal growth characteristics were eligible for randomization. In the ART interruption arm, treatment was resumed if CD4 fell below 25%. Infants who suppressed virus levels during the first 24 months of ART, with at most 1 viral blip >1000c/mL after initial viral suppression, were included in this sub study. Infant reservoir size was quantified by ddPCR for total HIV DNA using cross-subtype pol primers at 24 months post ART initiation, and again 18 months later, following randomization to treatment interruption (n=7) or continued ART (n=7). Change in HIV DNA reservoir size was compared by Wilcoxon Rank sum test in infants with and without treatment interruption.
Results: Among 14 infants evaluated, median age at ART initiation was 4.8 months and age at randomization was 28.9 months. Infants randomized to continued ART had a median of 168 copies of HIV DNA/1e6 PBMCs (IQR: 100-235) at 24 months after ART initiation and a median of 50 copies of HIV DNA/1e6 PBMCs (IQR: 24-173) 18 months later. Infants randomized to treatment interruption had a median of 90 copies of HIV DNA/1e6 PBMCs (IQR: 54-485) at 24 months after ART initiation and 184 (IQR:92-280) copies HIV DNA/1e6 PBMCs 18 months after ART interruption. When HIV DNA for each infant was compared between 24 months after ART initiation and 18 months later, the median HIV DNA fold change in infants who continued ART was 0.23 (IQR: 0.15-0.51), while the median HIV DNA fold change in infants undergoing a median of 106 days of treatment interruption was 1.04 (IQR: 0.71-1.6) (p=0.073).
Conclusion: Our data suggest that while the latent reservoir decayed during continuous ART, short treatment interruption did not cause a large increase in the size of the latent reservoir.

797 HIV SUBTYPE D IS ASSOCIATED WITH INCREASED LATENT RESERVOIR SIZE IN CHILDREN

Leila B. Giron[1], Jane Achan[2], Paul Bangirana[3], Moses R. Kamya[3], Diane V. Havlir[4], Joseph K. Wong[4], Theodore Ruel[4], Satish K. Pillai[5]
[1]Fed Univ of Sao Paulo/Blood Systems Rsr Inst, Sao Paulo, Brazil, [2]Disease Control and Elimination Theme, Med Rsr Unit, Fajara, Gambia, [3]Makerere Univ, Kampala, Uganda, [4]Univ of San Francisco, San Francisco, USA, [5]Blood Systems Rsr Inst/UCSF, San Francisco, CA, USA

Background: Antiretroviral therapy (ART) has dramatically improved the survival of children with HIV infection. However, ART does not achieve viral eradication, due to the presence of integrated provirus in resting CD4+ T lymphocytes. This population of potentially long-lived, persistently-infected cells, often called the latent HIV reservoir, is the barrier to achieving HIV eradication. Although HIV subtype has been associated with virulence, replication capacity, and cognitive impairment in infected individuals, it is unclear if HIV subtype influences the size of the latent HIV reservoir in children on ART.
Methods: Peripheral blood mononuclear cell (PBMC) samples were collected from HIV-infected children enrolled in PROMOTE-pediatrics (NCT00978068) trial, in which children were randomized to receive either lopinavir or NNRTI-based ART. Samples were collected ~ 500 days after ART start. HIV-subtype was determined by population sequencing of the pol HIV DNA region, followed by application of the REGA and Recombinant Identification Program algorithms. Surrogates of HIV reservoir size (levels of total cell-associated HIV DNA and RNA) were measured using quantitative real time PCR. We compared reservoir size between subtype A and subtype D HIV-infected, ART-suppressed children using Mann-Whitney tests.
Results: The subtype distribution of 126 samples was: A:78, D:27, C:4, A1D:2; subtype indeterminate: 15. There was no difference in treatment assignment between subtypes. Among the 105 with subtype A or D, the mean age at time of sampling was 7.3 years, mean duration of ART was 566 days, and there were no differences in CD4+ count; 21 had detectable plasma HIV RNA at the time of sampling and were excluded. Subtype D-infected children had significantly higher levels of total HIV DNA (mean 390 copies/106cells) compared to subtype A-infected children (mean 291 copies/106cells; p=0.03). No difference was observed in cell-associated HIV RNA between the two groups. HIV RNA/DNA ratio (transcriptional ratio) approached statistical significance with higher mean in subtype A-infected children (mean 1.1) as compared to subtype D-infected children (mean 0.7; p=0.09).
Conclusion: Children infected with HIV subtype D had increased latent HIV reservoir size compared to subtype A. These observations suggest that subtype associated genetic variation may impact HIV persistence, and should be carefully considered in future studies targeting the latent reservoir of HIV in children.

798 B-CELL RESPONSES IN EARLY TREATED LONG TERM VIRAL SUPPRESSED SERONEG HIV+ CHILDREN

Paolo Palma[1], Paola Zangari[1], Nicola Cotugno[2], Eleni Nastouli[3], Laura McCoy[4], Salvatore Rocca[2], Bridget Ferns[3], Savita Pahwa[5], Paolo Rossi[1], for the EPIICAL Consortium
[1]Children's Hosp Bambino Gesù, Rome, Italy, [2]Univ of Rome Tor Vergata, Rome, Italy, [3]Univ Coll London Hosps NHS Trust, London, UK, [4]Univ Coll London, London, UK, [5]Univ of Miami, Miami, FL, USA

Background: The paucity of HIV specific immune responses in early treated HIV-infected (treated within 6 months of age; ET) children could represent an important limitation in the perspective of immune therapeutic studies. In ET, the failure to develop an immune response is attributed to the lack of Ag stimulation, possibly indicating shrinking HIV reservoirs. Analysis of HIV Ab can provide important insight in order to characterize host–immune profiles associated to HIV remission which appears to be associated with different serological profiles. Our aim was to further dissect B-cell responses in ET with different HIV Ab profiles and relate those to the predicted size of the HIV-reservoir (Total HIV-DNA).
Methods: Ab responses in 15 ET under stable viral control (undetectable at least 4 years) against 9 HIV proteins (gp120, gp160, gp 41, p24, p17, p51, p45, p39, p31) were analysed by Chemiluminescent Microparticle Immuno-Assay (CMIA),Western Blot (WB), ELISA to 4 different Env proteins (UG37 gp14, CN54 gp120, BX08 gp140, Bal.26 gp120) and Neutralization Activity. B-cell Fluorospot was performed to simultaneously detect IgM and IgG responses to gp120, gp160, gp41, p24, p66. Total HIV-DNA was quantified at the same time points for all patients using an in house assay.
Results: Five out of 15 ET were seronegative (SNP) for all HIV-Ags tested by CMIA, WB and ELISA assays. No statistical difference in terms of age at the time of viral control (<1year in both), or timing of ART initiation was observed between SNP and seropositive patients (SPP). Among SPP 4 patients presented NA vs 2 different pseudoviruses (Bal.26 clade B and 96ZM965.01 clade C). Secondary ELISA vs the pseudoviruses showed any IgM anti-HIV activity in these 4 patients. Total HIV-DNA was markedly reduced in SNP (median=27 cp/106 PBMCs) compared to SPP (median=239 cps per million PBMCs) (p=0.008). To further investigate the in-vitro ability of SNP to develop cellular responses for p24, gp41, gp120, gp160 and RT we performed B cell Fluorospot to simultaneously detect IgM and IgG secreting cells. A predominant IgM response to HIV-Ags (gp41 (p=0.04), p24 (p=0.01) and p17(0.02) was observed in the SNP compared to age matched SPP.
Conclusion: SNP present lower total HIV-DNA compared to SPP. The predominant IgM Ab response to HIV Ags, shown in SNP, is suggestive of a B-cell primary response with low/absent neutralizing activity in case of viral rebound. These patients will most likely require immunotherapy to mount an effective immune response.

799 RAPID RESTORATION OF EFFECTIVE ANTI-HIV CD4+ T-CELL ACTIVITY IN ART-TREATED CHILDREN

Emily Adland[1], Luisa Mori[2], Leana Laker[2], Alice Swordy[2], Anna Csala[1], Masahiko Mori[1], Philippa C. Matthews[3], Pieter Jooste[2], Philip J. Goulder[1]
[1]Univ of Oxford, Oxford, UK, [2]Kimberley Hosp Complex, Kimberley, South Africa, [3]Oxford Univ Hosps NGS Trust, John Radcliffe Hosp, Oxford, UK

Background: The successes of strategies to prevent mother-to-child transmission (pMTCT) of HIV and to implement antiretroviral therapy (ART) in sub-Saharan Africa have brought about new challenges. In particular, HIV-infected children facing a lifetime of ART dependence frequently run up against major problems of non-adherence, especially moving into adolescence. Alternative strategies to a lifetime of ART are needed, especially for HIV-infected children. We here investigate the impact of ART on recovery of HIV-specific T-cell immune function in HIV-infected children, that would set the stage for future immune-based therapies designed to facilitate cure.
Methods: We studied functional patterns of HIV-specific T-cell responses in a total of 58 treatment naïve children and 84 ART treated children with chronic HIV-1 C-clade infection from Kimberley, South Africa. A whole blood ICS assay was used to determine intracellular responses to HIV antigen stimulation based on expression of IL-2, IFNγ, MIP1β and TNFα.
Results: In ART-naïve children, a high absolute CD4 count was strongly correlated with a predominant IL-2 Gag-specific CD4+ T-cell response and with CD4+ and CD8+ T-cell polyfunctionality. Viral load in the same children was directly correlated with the magnitude of the CD4+ IFN-γ Gag-specific response and inversely related to IL-2, TNFα and MIP1β responses. In ART-treated children, a similar and consistent binary pattern emerged. Unsuppressed, viraemic children maintained predominantly IFN-γ responses, whereas those with suppression of viraemia, even for 12 months only, showed strong IL-2 responses. In ART-treated children, duration of viral suppression was associated with increasing polyfunctionality on CD4+ but not CD8+ T-cells, and with decreasing expression levels of immune activation and inhibitory receptors.
Conclusion: These findings support previous studies indicating that CD4 T-cell function is central to the maintenance of normal CD4 T-cell counts and non-pathogenesis in paediatric infection but that CD8+ T-cells play a less clear role. These studies highlight the fact that even short duration suppression of viral replication by ART in paediatric infection is associated with highly polyfunctional HIV-specific CD4 T-cell activity, characterized by strong IL-2 responses. These data support the notion that ART can bring about rapid immune recovery in paediatric infection, and can provide a setting in which immunotherapies around HIV cure such as CTL vaccination could be optimally effective.

800 PD-1+ MEMORY CD4 T CELLS, PROLIFERATIVE CAPACITY, AND INFLAMMATION IN HIV+ CHILDREN

Julia Foldi[1], Lina Kozhaya[1], Max Kilberg[1], Mussa Mwamzuka[2], Fatma Marshed[2], Aabid Ahmed[2], William Borkowsky[1], Derya Unutmaz[1], **Alka Khaitan**[1]
[1]New York Univ, New York, NY, USA, [2]Bomu Hosp, Mombasa, Kenya

Background: During HIV infection loss of HIV-specific proliferative capacity and cytokine production defines T cell exhaustion. PD-1 is a negative immune modulator that marks exhausted CD8 T cells in HIV, but its function on CD4 T cells remains unclear. We examined PD-1+ CD4 T cells in HIV+ children, their association with HIV disease progression, and their functional capacity.
Methods: In a Kenyan cohort of 82 perinatally-infected HIV+ children, comprising 41 untreated (ART-) and 41 on antiretroviral therapy (ART+), and 36 HIV uninfected-unexposed controls between 5-18 years old, we evaluated peripheral blood samples by flow cytometry to identify these markers: CD3, CD4, CD8, PD-1, CD45RO, CD27, CD38, HLA-DR, and Ki67. For proliferation experiments, PD-1+ and PD-1- memory CD4 T cells sorted from healthy adults or total PBMCs from HIV+ children were labeled then stimulated with OKT3 (TCR stimulus) or gag peptide pools for 7 days and analyzed by flow cytometry. Cytokines were identified by staining for IFNγ, IL-17A and IL-2 after PMA/Ionomycin activation. Statistical analysis was performed on GraphPad Prism with Mann-Whitney, Spearman's correlation, and linear regression analyses.
Results: Both ART- and ART+ children have significantly higher PD-1+ memory CD4 T cell percentages compared to HIV- controls (ART- p<0.0001; ART+ p=0.004). Increased PD-1+ CD4 T cells correlate with HIV disease progression, measured by viral load (p=0.04), %CD4 (p=0.0001), and CD4:CD8 ratios (p<0.0001). Moreover, PD-1+ CD4 T cells associate with markers of immune activation, CD38+HLA-DR+ CD4 (p<0.0001) and CD8 (p=0.009) and Ki67+ CD4 T cells (p=0.003). PD-1+ CD4 T cells demonstrate low proliferative capacity compared to PD-1- populations (median: PD-1+ 35%; PD-1- 81%; p=0.003) yet increased production of Th1 (p<0.05) and Th17 (p=0.007) cytokines. In HIV+ children, increased PD-1+ CD4 T cell levels predict lower proliferative capacity in response to OKT3 (p=0.009; R2=0.65), with a similar trend after HIV-specific stimulus. Finally, in HIV+ children, PD-1+ CD4 T cells produce significantly more IFNγ (p<0.0001) and IL-17A (p=0.003) compared to PD-1- cells and correlate with higher IFNγ (p-0.04) and lower IL-2 (p=0.008) cytokine levels.
Conclusion: HIV+ children have markedly elevated PD-1+ memory CD4 T cells that correlate with advancing disease. This population exhibits weak proliferative capacity yet enhanced production of inflammatory cytokines. Future studies are necessary for potential immune-checkpoint therapies in HIV.

801 MICROBIAL TRANSLOCATION DOES NOT DRIVE IMMUNE ACTIVATION IN UGANDAN CHILDREN WITH HIV

Felicity Fitzgerald[1], Edouard Lhomme[2], Kathryn Harris[3], Julia Kenny[1], Ronan Doyle[4], Cissy Kityo[5], Sarah Walker[4], Rodolphe Thiébaut[2], Nigel Klein[4], for the CHAPAS-3 Trial Team
[1]Univ Coll London Great Ormond Street Inst of Child Hlth, London, UK, [2]INSERM, Bordeaux, France, [3]Great Ormond Street NHS Fndn Trust, London, UK, [4]Univ Coll London, London, UK, [5]Joint Clinical Rsr Cntr, Kampala, Uganda

Background: Immune activation (IA), potentially driven by microbial translocation (MT), is linked to increased morbidity despite ART in HIV. We investigated MT as a driver of IA in HIV-infected African children

Methods: ART-naïve and ART-experienced children were recruited to a Ugandan site of the CHAPAS-3 Trial (ISRCTN69078957), with HIV-uninfected age-matched controls from the same communities. HIV-infected children were followed up for 96 weeks including viral load & CD4%. 19 markers (cellular and humoral) of IA, inflammation, vascular injury & disordered thrombogenesis were measured. Intestinal fatty acid binding protein (I-FABP) was used to quantify gut damage. MT was assessed using a panel of specific bacterial polymerase chain reactions (PCRs), broad-range 16S rDNA PCR & next generation sequencing (NGS)(Illumina method). Cluster analysis of IA & MT markers was performed in R.
Results: 249 children were included: 120 ART naïve & 22 ART experienced (median(IQR) age 2.8(1.7-4.0) & 6.5(5.9-9.2) years; median baseline CD4% 20(14-24) & 34(31-39) respectively) & 107 age-matched HIV-uninfected controls. Immune recovery was good (ART-naïve: median(IQR) CD4% change 17(12-22)) & viral load suppression <100 copies/ml at 96 weeks was 76%(ART-naïve) and 91%(ART-experienced). IA decreased over time on ART: median CD4+HLA-DR+CD38+ decreased from 7% to 2% at 96 weeks($p<0.0001$). Cluster analysis at Week 96 identified 4 clusters(Table 1): the first(n=105, 65% HIV+ virally suppressed, 32% HIV-) was characterized by low levels of IA(CD4+HLA-DR+CD38+<7%; CD8+HLA-DR+CD38+<18%); the second(n=120) by high CD4 percentage, P-selectin and thrombomodulin; the third(n=11) by high levels of DR+ and Ki-67+; & the fourth(n=13) by unsuppressed HIV(50%), high Interleukin-6 and Tumour Necrosis Factor-α. Specific and broad-range PCRs for bacterial DNA were negative/ very low in all groups, and across all clusters. At baseline using NGS, very low levels of microbial DNA were found in both HIV infected groups, including Staphylococcus aureus, Enterobacteriaceae, Veillonellae & Clostridiales. Levels of microbial DNA did not differ between clusters except Enterobacteriaceae(higher in clusters 1 & 3 compared to cluster 2 & 4($p<0.01$)).
Conclusion: IA decreased over time on ART, with clustering of IA markers indicating different IA patterns by HIV/ART status and viral load suppression. Levels of bacterial DNA were low regardless of HIV/ART/IA status or duration of ART. MT does not appear to be a significant driver of IA in this setting.

Table 1. Characteristics of the clustering and distribution of microbial translocation markers among children from a Ugandan site of CHAPAS 3 trial.

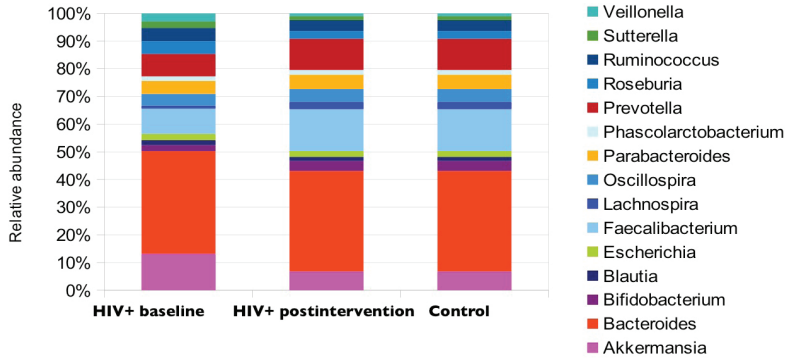
Characteristics	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-value
N (%)	105 (42)	120 (48)	11 (4)	13 (5)	
ART at baseline					0.0036
ART naive	57 (54)	50 (42)	6 (55)	7 (54)	
ART experienced	14 (13)	5 (4)	0 (0)	3 (23)	
HIV negative	34 (32)	65 (54)	5 (45)	3 (23)	
Virally suppressed at W96 (<100 copies/ml)					<0.0001
Yes	65 (62)	32 (27)	3 (27)	3 (23)	
No	6 (6)	14 (12)	3 (27)	6 (46)	
HIV negative	34 (32)	65 (54)	5 (45)	3 (23)	
Viral load missing	0 (0)	9 (8)	0 (0)	1 (8)	
I-FABP pg/ml*	176 (139)	187 (191)	158 (72)	192 (115)	0.93
16S rDNA **	48 (46)	61 (51)	6 (55)	6 (46)	0.86
Bifidobacterium spp. **	0 (0)	0 (0)	0 (0)	0 (0)	-
*Staphylococcus aureus***	3 (4)	5 (10)	0 (0)	0 (0)	0.58
*Streptococcus pyogenes***	0 (0)	0 (0)	1 (9)	0 (0)	0.05
*Fusobacterium spp.***	1 (1)	1 (1)	1 (9)	0 (0)	0.21
*Enterobacteriaceae***	47 (45)	30 (26)	5 (45)	1 (8)	0.006
Staphylococcus spp. **	0 (0)	0 (0)	0 (0)	0 (0)	-
*Lactobacillus spp.***	1 (1)	1 (1)	0 (0)	0 (0)	0.54

*I-FABP: Intestinal fatty acid binding protein, mean (standard deviation)
**Number of samples testing positive using PCR. Sensitivities from 0.5-500 colony forming unit (CFU) equivalents when compared with standard of known CFUs depending on assay.

802 TARGETING IMMUNOACTIVATION IN HIV+ CHILDREN BY MODIFICATION OF THE GUT MICROBIOTA

Talía Sainz[1], Nuria Jiménez-Hernández[2], Laura Diaz[3], Sergio Serrano-Villar[4], Maria José Mellado[1], Luis Prieto[5], Jose Tomas Ramos[6], M. Ángeles Muñoz-Fernández[3], María José Gosalbes[2], Maria Luisa Navarro[3]
[1]Hosp La Paz Inst for Hlth Rsr, Madrid, Spain, [2]FISABIO–Salud Pública, Valencia, Spain, [3]Gregorio Maranon Hosp, Madrid, Spain, [4]Hosp Univ Ramón y Cajal, Madrid, Spain, [5]Hosp de Getafe, Madrid, Spain, [6]Hosp Clínico San Carlos, Madrid, Spain

Background: Dysbiosis of the microbial gut appears to contribute chronic bacterial translocation and systemic inflammation in HIV-infected adults on antiretroviral therapy (ART). We aimed to modulate the intestinal microbiota of vertically HIV-infected children using a nutritional supplement, and to assess the impact on immunoactivation.
Methods: Pilot, double blind, randomized placebo-controlled trial including HIV-infected children receiving a symbiotic nutritional supplement. DNA was extracted at baseline and after a 4-week intervention from stool samples and 16S rRNA gene amplicons were pyrosequenced. Activated (CD38+HLADR+), senescent (CD57+CD28-), regulatory (CD4+/FoxP3+) and naive (CCR7+/CD45RA+)/memory T-cell subsets were determined using flow cytometry and analyzed using Wilcoxon matched pairs test. Uninfected siblings were recruited as controls for characterization of the microbiota in HIV-infected children.
Results: Twenty-two vertically HIV-infected children were recruited and compared to 11 controls. Mean age was 11.4±3.4 years and 8 (32%) were males. All were on ART and had HIV RNA<50/ml. At baseline, their microbiota showed reduced alpha diversity compared to controls (P=0.042) and distinct composition at the genus level (Unifrac distances, Adonis P=0.042). After the intervention, changes in overall microbiota structure between cases and controls were non-significant, and a significant increase of the butyrate producers Faecalibacterium and Butyricicoccus was documented. No significant changes in total CD4 counts or CD4/CD8 ratio was observed after intervention. Changes in the frequency of activated, senescent, regulatory and/or naive/memory T cells were all non-significant.
Conclusion: In this pilot study we observed that vertical HIV infection alters the fecal microbiota structure in children. A short symbiotic nutritional intervention increased the abundance of butyrate producing bacteria, generally indicative of a healthy gut-microbiota homeostasis although did not elicit detectable effects in peripheral T cell markers. The potential anti-inflammatory effect of targeting the microbiota early in life in HIV disease deserves further investigation.



803 B- AND T-CELL SUBSETS AND IMMUNOGENICITY OF ROTAVIRUS VACCINE IN PHIV & PHEU INFANTS

Adriana Weinberg[1], Jane Lindsey[2], Ronald Bosch[2], Deborah Persaud[3], Paul Sato[4], Barbara Heckman[5], Kelly Richardson[1], Amanda Zadzilka[6], Margaret Nelson[7], Myron Levin[1]
[1]Univ of Colorado, Aurora, CO, USA, [2]Harvard Univ, Boston, MA, USA, [3]The Johns Hopkins Univ, Baltimore, MD, USA, [4]DAIDS, NIAID, Bethesda, MD, USA, [5]Data Mgmt Cntr, Amherst, NY, USA, [6]Frontier Sci and Tech Rsr Fndn, Amherst, NY, USA, [7]Merck & Co, Inc, Upper Gwynedd, PA, USA

Background: IMPAACT P1072 was a double-blind placebo-controlled study of safety and immunogenicity of pentavalent rotavirus vaccine (RV5) in perinatally HIV-infected (PHIV) and exposed uninfected (PHEU) infants. This secondary analysis reports associations of HIV status and RV5 with B and T cell subsets and correlations of subsets with RV5 antibody responses.

Methods: 89 infants (23 PHIV/19 PHEU vaccine- and 24 PHIV/ 23 PHEU placebo-recipients) had activated (act), inflammatory (inflam) and regulatory (reg) B/T cells and B cell differentiation measured before vaccination, 3wks post-dose 1 (PD1), and 2wks PD3. Immunogenicity was measured by anti-RV5 IgA and anti-G1-4 and P IgG. Spearman correlations ($|\rho| \geq 0.2$) were used to identify associations. Area under the curve (AUC) was calculated for markers (log10 scale) using predicted values from mixed random effects models.

Results: At entry: PHIV had median HIV viral load (VL) of 33,500 c/mL and 28% CD4+ cells, and 89% had initiated cART. PHEU and PHIV did not differ significantly ($p>0.05$) in B/T cell subset distribution. In PHIV, VL positively correlated with act CD8+CD38+HLADR+%, CD19+IL21r+%, CD19+BAFFr+% and immature CD19+CD10+%; cART duration negatively correlated with inflam CD4+/CD8+CD17+%. In PHIV and PHEU, CD4+% and counts positively correlated with reg CD8+CD25+FOXP3+%. Among lymphocyte subsets, reg CD4+/CD8+/CD19+IL10+% and CD4+/CD8+/CD19+TGFb+% in general positively correlated with inflam CD4+/CD8+IL17+%; and act CD4+/CD8+CD38+HLADR+% positively correlated with immature CD19+CD10+%. Vaccination and HIV status were not significantly associated with differential changes in B/T cell subsets except for reg CD4+IL10+%, which increased in PHIV vaccinees and decreased in PHEU and PHIV placebo recipients. IgA and/or IgG responses to RV5 positively correlated with CD4+% and/or counts and with reg CD4+/CD8+CD25+FOXP3+%; but negatively correlated with reg CD4+IL10+%, CD4+TGFb+% and inflam CD4+IL17+% (Figure).

Conclusion: We did not find reg, inflam or act B/T-cell differences between PHEU and PHIV. Higher inflam, IL10+ and TGFb+ Tregs were associated with lower responses to RV5, while CD25+FOXP3+ Tregs were associated with higher responses. IL10+ and TGFb+ B/Tregs were associated with higher Tinflam, while CD25+FOXP3+ Tregs were associated with higher CD4+ cells. This is the 1st demonstration that phenotypically distinct Tregs differ in the way they associate with immune responses to vaccination and Tinflam or Tact.

804 IMMUNOLOGICAL RESPONSE AFTER A BOOSTER DOSE OF HBV VACCINE IN HIV-INFECTED YOUTH

Vania Giacomet[1], Daria Trabattoni[2], Pilar Nannini[2], Michela Masetti[2], Federica Forlanini[2], Mario Clerici[3], Gian Vincenzo Zuccotti[4]
[1]L. Sacco Hosp, Milan, Italy, [2]Univ of Milan, Milan, Italy, [3]Univ of Milan, Segrate, Milan, Italy, [4]Ospedale dei Bambini V. Buzzi, Milan, Italy

Background: Three doses of vaccine against HBV induce the production of protective antibody (Ab) levels (>10 IU/mL) in 95-100 % of healthy children but in only 23-56% of HIV-infected children. Ab titer elicited by vaccination decreases over time in both populations with a faster slope observed in HIV+. This decline protection against HBV is known to last almost three decades after vaccination in immunocompetent children, these data are limited in HIV+ children

Methods: 53 HIV+ patients (aged 8-25 years old) in whom HBV vaccination according the Italian schedule did not elicit the generation of protective Ab titers were enrolled in the study at Paediatric Infectious Diseases Unit, L. Sacco Hospital, University of Milan. All patients had undergone ART for at least 1 year; HIV viral load was undetectable in all of them, median CD4+ count 718 mm3. All patients received a booster dose of HBV vaccine (HBVAXPRO 10 micrograms i.m.). HBV-specific Ab titer, viral load and CD4 + were measured in all subjects at baseline (T0), at 1 (T1), 6 (T6) and 12 (T12) months after the booster dose. In a subgroup of 16 patients HBV-specific cell mediated immune (CMI) responses were evaluated at baseline and at T6.

Results: The booster HBV vaccine dose resulted in a seroconversion rate (anti-HBs ≥ 10 IU/mL) in 51% of patients at T1, 57% at T6 and 49% at T12; seroconversion rate was significantly correlated with CD4+T lymphocyte counts at T0 and to CD4 nadir ($p<0.05$). HIV viral load was undetectable at each time. CMI responses were evaluated in 11 responders (HBsAb >10 IU/mL) and 5 non-responders (HBsAb <10 IU/mL). Upregulation of HBV-specific CMI compared to baseline values was observed at T6 in responders alone. Memory ($p= 0.007$), Effector Memory ($p= 0.003$), TNFα- ($p= 0.041$), IFNγ- ($p= 0.004$), and granzyme-secreting CD8+ T cells ($p= 0.003$), Central Memory ($p= 0.005$) and IL2-secreting CD4+ T cells ($p= 0.015$) were significantly increased in responders compared to baseline values. Activated CD8+CD38+CD45RO+ T cells ($p= 0.004$) were significantly reduced as well at T6 in these individuals. No significant differences were observed when T0 and T6 data were compared in non responders.

Conclusion: In HIV+ patients no responding to the standard HBV immunization protocol, seroconversion induced by a booster dose of vaccine (Ab titers <10 IU/mL) correlates with the development of T cell immunological memory. Alternate immunization schedules should be designed for those individuals who don't respond even to a booster dose of vaccine

805 HPV4 VACCINE IMMUNOGENICITY/EFFECTIVENESS IN PERINATALLY HIV-INFECTED (PHIV) YOUTH

Anna-Barbara Moscicki[1], Brad Karalius[2], Katherine Tassiopoulos[2], Denise Jacobson[2], Kunjal Patel[2], Murli U. Purswani[3], George R. Seage[2], Tzy-Jyun Yao[2]
[1]Univ of California Los Angeles, Los Angeles, CA, USA, [2]Harvard Univ, Boston, MA, USA, [3]Bronx Lebanon Hosp, Bronx, NY, USA

Background: HIV-infected persons are at high risk of HPV-associated cancers. Efficacy of HPV vaccine may be suboptimal in PHIV children who have lower rates of protection from other vaccines. We sought to compare HPV antibodies and effectiveness between HPV-vaccinated PHIV and perinatally HIV-exposed uninfected (PHEU) youth.

Methods: PHIV and PHEU youth from PHACS who had ever received ≥1 dose of the HPV4 vaccine and had available repository sera drawn ≥20 days following last dose were included. Antibodies to HPV 6, 11, 16 & 18 were measured at Merck laboratories on the most-recent sample. We compared seroconversion and geometric mean titer (GMT) between PHIV and PHEU by number of HPV vaccine doses received, after correcting for age at 1st and time since last dose. We used general linear models to identify factors associated

with lower GMT in PHIV. Medical records were reviewed for diagnosis of abnormal cytology (≥ASCUS; AC) and genital warts (GW). Incidence rates (IR) per 100 person-years were calculated for AC/GW among sexually active girls. There were too few cases in boys (n=1) to study.
Results: For 303 PHIV and 116 PHEU youth, mean (SD) age at 1st dose was 13.4 (2.7) and 12.4 (2.1) years; mean years from last dose to specimen was 3.1 (1.6) and 2.8 (1.4), respectively. PHIV were less likely to seroconvert than PHEU after 1 dose for HPV 11 (83% vs 95%), 16 (88% vs 99%) and 18 (62% vs 87%) ($p<0.01$); lower seroconversion for PHIV was also observed for 2 and 3+ doses ($p\geq0.05$). Significant differences in GMT were seen for 1 and 2 but not 3+ doses for HPV 11, 16 & 18 in youth vaccinated at the target age of ≤13 years (Figure). This was also true for all ages. In multivariable models for vaccinated PHIV (≥1 dose), higher HIV RNA and older age at 1st dose were associated with lower GMT for all 4 HPV types. For those vaccinated prior to sexual debut, the IR (95% CI) for AC/GW was 10.1 (5.8-16.5) in PHIV and 0.0 (0-5.9) in PHEU girls. There was no difference in IR in PHIV girls vaccinated prior versus after sexual debut.
Conclusion: Vaccine effectiveness was much lower in PHIV girls than expected. Lower GMT for HPV 16/18, or presence of non-vaccine types, may partly explain this. Alternatively, mother-to-infant HPV transmission may have occurred as HIV-infected mothers have high rates of HPV shedding from genital/oral fluids. Studies are needed to assess HPV type infections. HPV vaccine trials in infants should be considered to optimize protection in PHIV.

806 DOLUTEGRAVIR PHARMACOKINETICS, SAFETY AND EFFICACY IN HIV+ CHILDREN 2 TO <6 YEARS OLD

Theodore Ruel[1], Edward Acosta[2], Rajendra P. Singh[3], Carmelita Alvero[4], Kathleen George[5], Stephanie Popson[6], Cindy Vavro[7], Rohan Hazra[8], Andrew Wiznia[9], for the P1093 Team
[1]Univ of California, San Francisco, San Francisco, CA, USA, [2]Univ of Alabama at Birmingham, Birmingham, AL, USA, [3]GlaxoSmithKline, King of Prussia, PA, USA, [4]Harvard Univ, Boston, MA, USA, [5]FHI 360, Durham, NC, USA, [6]Frontier Sci & Tech Rsr Fndn, Inc., Amherst, NY, USA, [7]ViiV HIthcare, Rsr Triangle Park, NC, USA, [8]NICHD, Bethesda, MD, USA, [9]Albert Einstein Coll of Med, Bronx, NY, USA

Background: There is an urgent need for new drugs to treat HIV-1 infected children globally. Dolutegravir (DTG; S/GSK1349572) is a first-line agent for the treatment of HIV-1 infected adults due to its potency, high barrier to resistance, and tolerability; it promises a similar role in children. IMPAACT P1093 is an ongoing phase 1/2 open-label pharmacokinetic (PK) and dose finding study of DTG in age-defined pediatric cohorts (4 weeks to <18 years of age). Pediatric doses that provide DTG exposure comparable to that observed from 50 mg once daily in adults with acceptable safety and tolerability will be selected for each age cohort.
Methods: Children ≥2 and <6 years old received DTG granules-in-suspension at doses of ~0.8 mg/kg once daily. At enrollment, DTG was either started as monotherapy or added to a stable-failing regimen. Intensive PK evaluations were completed after oral administration of weight-based dose between days 5-10; background regimen was then optimized. Safety, tolerability, and plasma HIV RNA levels were assessed at 4 weeks. Based on adult data, target individual exposures were AUC24h range of 37-67 mg*hour/L (primary) and C24h range of 0.77-2.26 mg/L (secondary).
Results: Ten children (5 female) with median (range) age 4 years (2-5), and weight 14.6kg (9.9-17.1) were studied. Median baseline (BL) CD4+ cell % and HIV-1 RNA levels were 28.0 (IQR: 22.0, 31.4) and 4.8 log10(c/mL) (IQR:4.7-5.3), respectively. Mean (range) DTG dose was 0.87 mg/kg (0.58 to 1.06). DTG demonstrated moderate intersubject PK variability. The geometric mean (CV%) AUC24h and C24h were 44.7 (36%) mg*hour/L and 0.51 (68%) mg/L, respectively. HIV-1 RNA levels were < 400 c/mL in 8/10 and < 50 c/ml in 6/10 after 4 weeks of treatment, with median (range) change from BL of -3.1 log10(c/mL) (-3.4 to -2.1). DTG was well tolerated with no Grade 3 or Grade 4 AEs and no discontinuations due to AEs.
Conclusion: DTG granules-in-suspension administered at ~0.8 mg/kg once daily in this cohort of children ≥2 to <6 years old achieved the target AUC24h; C24h was below the target but above the pharmacodynamic threshold reported in adults. DTG was virologically potent and well tolerated through week 4. These novel data will form the basis for dosing of DTG as dispersible tablets to be studied in this and younger age cohorts.

807 PHARMACOKINETICS OF RILPIVIRINE AFTER SWITCHING FROM EFAVIRENZ IN ADOLESCENTS

Watsamon Jantarabenjakul[1], Narukjaporn Thammajaruk[2], Torsak Bunupuradah[2], Jiratchaya Sophonphan[2], Tim R. Cressey[3], Angela Colbers[4], David M. Burger[4], Wanatpreeya Phongsamart[5], Thanyawee Puthanakit[1], Chitsanu Pancharoen[1]
[1]Chulalongkorn Univ, Bangkok, Thailand, [2]HIV Netherlands Australia Thailand Rsr Collab,Thai Red Cross AIDS Rsr, Bangkok, Thailand, [3]Prog for HIV Prevention and Treatment, Chiang Mai, Thailand, [4]Radboud Univ, Nijmegen, Netherlands, [5]Mahidol Univ, Bangkok, Thailand

Background: Rilpivirine (RPV) has become a recommended non-nucleoside reverse transcriptase inhibitor (NNRTI), replacing efavirenz (EFV) due to fewer CNS effects. RPV pharmacokinetics (PK) data are limited among HIV-infected adolescents, particularly after switching from EFV, which potentially reduces rilpivirine exposure due to fading CYP3A inducing capacity. This study aims to describe the pharmacokinetic profile of RPV after switching from EFV in HIV-infected adolescents.
Methods: HIV-infected adolescents aged 12-18 years, weighing ≥ 25 kilograms, treated with EFV-based antiretroviral therapy for ≥ 3 months and HIV RNA (VL) < 50 copies/mL were switched from EFV to RPV. RPV 25 mg was taken once daily with a meal. At week 4, a PK profile was determined at 0 (pre-dose), 1, 2, 4, 5, 6, 9, 12 and 24 hours following an observed intake of RPV with a standardized meal (525 kcal). RPV concentrations were measured using a validated liquid chromatography-mass spectrometry (LC-MS) method (lower limit of quantification (LLQ) 4 ng/mL). RPV PK parameters were calculated using a non-compartmental method (Winnonlin 6.3) and compared with published data (the PAINT and pooled ECHO/THRIVE PK substudies). The target RPV C24h was > 40 ng/mL. EFV plasma concentrations were measured at weeks 0 and 4 (LLQ 100 ng/mL). VL was measured at weeks 12 and 24. Adherence was determined by pill count.
Results: From January to June 2016, 20 adolescents were enrolled; 12 adolescents were male. Median age and weight (range) were 15.7 years (13.8-18.9) and 49 kilograms (31-93) respectively. Median baseline CD4 count (range) was 726 cells/mm3 (236 - 1145). Pre-switching regimens were TDF/3TC/EFV (90%) and AZT/3TC/EFV (10%). 16 adolescents had adherence of > 95% at their PK visit. The PK parameters of RPV are shown in Table 1. All values from the present study are comparable with the PAINT and ECHO/THRIVE sub-studies. Four adolescents (20%) had RPV C24h < 40 ng/mL, of which two reported poor adherence < 95%. Mean (SD) EFV plasma concentrations at week 0 was 2030 ng/ml (1037) which median (range) post-dose were 14 hours (2-16), but none had detectable levels at week 4. All evaluable adolescents had undetectable VLs (< 50 copies/ml) at weeks 12 and 24.
Conclusion: HIV-infected adolescents switching from EFV to RPV had adequate RPV pharmacokinetic profiles and there was no virological failure detected at 24 weeks following switching.

Table 1. Steady-state RPV pharmacokinetic profiles in adolescents of this study compared to data from naïve adolescents (PAINT substudy) and adults (pooled ECHO/THRIVES substudy).

Pharmacokinetic parameter of Rilpivirine*	This study Adolescents switched from EFV (n=20)	PAINT study Treatment naïve adolescents (n=23)	P-value**	Pooled ECHO/THRIVE Treatment naïve adults (n=44)	P-value**
AUC_{24h}, ng.h/L	2041 (745)	1872 (717)	0.45	2005 (970)	0.88
C_{24h}, ng/L	69 (29)	81 (40)	0.28	67.7 (39)	0.90
C_{max}, ng/L	143 (65)	109 (38)	0.04	134 (72)	0.65
T_{max}, hours	5 (0-9)	5 (2-9)	-	4 (1-12)	-

*Data shown are: mean (SD), except T_{max} as median (range)
** P-value was compared by an independent two sample T-test

808 NEVIRAPINE PK, VIROLOGICAL OUTCOME, AND AES IN AFRICAN CHILDREN ON PAEDIATRIC FDCS

Andrzej Bienczak[1], Paolo Denti[1], Adrian Cook[2], Lubbe Wiesner[1], Diana Gibb[2], David M. Burger[3], Sarah Walker[2], Helen Mcilleron[1], for the CHAPAS-3 Study Team
[1]Univ of Cape Town, Cape Town, South Africa, [2]Univ Coll London, London, UK, [3]Radboud Univ Med Cntr, Nijmegen, Netherlands

Background: Nevirapine is the only non-nucleoside reverse transcriptase inhibitor currently available as a paediatric fixed-dose combination tablet and is widely used in African children. Nonetheless, the number of investigations into pharmacokinetic determinants of virological suppression is limited and the predictive power of the current therapeutic range has not been evaluated in this population, limiting treatment optimisation.
Methods: We analysed data from 219 initially antiretroviral treatment (ART)-naïve African children (aged 0.3–13 years) from the CHAPAS-3 study treated with nevirapine, lamivudine, and either abacavir, stavudine, or zidovudine, and followed up to 144 weeks. Pharmacokinetic non-linear mixed effects model derived nevirapine trough concentrations (Cmin) and other factors were tested for associations with viral load (VL) >100 copies/mL and transaminase increases >grade 1 using proportional hazard and logistic models. Nevirapine Cmin most predictive of non-suppression and transaminase elevations was sought using likelihood profiling.
Results: Pre-ART VL, adherence and nevirapine Cmin were associated with VL non-suppression (hazard-ratio [HR]=2.08 [95% CI: 1.50-2.90, p<0.001] for 10-fold higher pre-ART VL, HR=0.78 [95% CI: 0.68–0.90, p<0.001] for 10% improvement in adherence and HR=0.94 [95% CI: 0.90-0.99, p=0.014] for a 1mg/L increase in nevirapine Cmin). There were additional effects of pre-ART CD4% and clinical site. The risk of virological suppression increased approximately linearly as Cmin decreased and there was no clear Cmin threshold predictive of virological non-suppression. Transient transaminase elevations >grade 1 were associated with high Cmin (>12.4 mg/L), HR=5.18 (95%CI 1.95–13.80, p<0.001).
Conclusion: Higher nevirapine concentrations were associated with significantly better virological outcomes but a meaningful cut-off predictive of increased risk of VL non-suppression could not be identified, possibly due to the effects of the ART companion drugs. Adverse events were rare. Although we detected an association between nevirapine Cmin >12.4 mg/L and transient transaminase elevations, this finding is unlikely to be clinically significant . Treatment initiation at lower VL and higher CD4%, increased adherence, and maintaining average Cmin higher than the current target, could have a positive effect on virological suppression in African children treated with nevirapine.

809 AN EASY-TO-USE PAEDIATRIC DOSING TOOL: ONE MG/KG DOSE DOES NOT FIT ALL

Paolo Denti[1], Nandita Sugandhi[2], Tim R. Cressey[3], Mark Mirochnick[4], Edmund V. Capparelli[5], Martina Penazzato[6], for the Paediatric ARV Working Group
[1]Univ of Cape Town, Cape Town, South Africa, [2]Clinton Hlth Access Initiative, New York, NY, USA, [3]Prog for HIV Prevention and Treatment, Chiang Mai, Thailand, [4]Boston Med Cntr, Boston, MA, USA, [5]Univ of California San Diego, La Jolla, CA, USA, [6]WHO, Geneva, Switzerland

Background: When designing safe and effective dosing regimens for children, the first assumption is to aim for drug exposures similar to those observed in successfully treated adults. Therefore, correctly scaling pharmacokinetics (PK) to children is a key first step. While several factors may contribute to difference in PK between children and adults, body size alone explains most of the changes down to children of 3 years of age. Allometric scaling describes the nonlinear effect of body size on PK parameters. This nonlinearity explains why using the same mg/kg dose in children and adults is incorrect, and causes under-dosing. Allometric scaling is widely used in PK modelling, but it is not uncommon for "first guess" paediatric dosing regimens to still incorrectly use constant mg/kg dosing. This is arguably due to the lack of accessibility of PK modelling results to clinicians. The objective of this work is to bridge this gap by proposing an intuitive and easy-to-use tool to assist researchers not conversant in PK modelling to design and evaluate paediatric dosing regimens.
Methods: The tool was designed using Microsoft Excel - chosen for its ubiquitousness and familiarity amongst clinicians - with easy steps to follow and results displayed in graphical form. The tool uses allometric scaling to adjust for the effect of body size on clearance and compares the expected exposure in terms of area under the concentration-time curve (AUC). Analysis of multiple drugs in a fixed-dose combination is possible, defining the separate amounts for each component and different tolerance ranges for the target exposure. Standard dosing weight-bands can be used, or boundaries can be customised to explore alternative approaches.
Results: The implementation of the tool has been validated by assessing current paediatric dosing regimens. The outputs produced are closely in line with results from PK modelling and generally coherent with those obtained in confirmatory clinical trials. In particular, the doses predicted using the tool are more accurate than those obtained with the constant mg/kg approach.
Conclusion: The purpose of the tool is to assist in the design of clinical trials for dosing in paediatrics, and is meant as a first step, not a substitute to confirmatory studies. The use of this tool (and thus allometric scaling) for study design would represent a significant step ahead from the constant mg/kg paradigm, possibly leading to improvements in the efficacy of paediatric dosing trials.

810 SERTRALINE PHARMACOKINETICS IN HIV-INFECTED ON ARV AND UNINFECTED YOUTH

Nathan Hanan[1], Mary Paul[2], Yanling Huo[3], Edmund Capparelli[1], Suad Kapetanovic[4], J. L. Ariansen[5], Elizabeth Smith[6], Pim Brouwers[4], Brookie Best , for the IMPAACT P1080 Protocol Team
[1]Univ of California San Diego, La Jolla, CA, USA, [2]Baylor Coll of Med, Houston, TX, USA, [3]Harvard Univ, Boston, MA, USA, [4]NIMH, Rockville, MD, USA, [5]FHI 360, Durham, NC, USA, [6]NIAID, Rockville, MD, USA

Background: Sertraline (SRT) is a selective serotonin reuptake inhibitor eliminated by hepatic metabolism by cytochrome P450 (CYP) enzymes: 2B6, 2D6, 2C9, 2C19 and 3A4, glucuronyl transferases, and monoamine oxidase A & B. SRT is often titrated to effectiveness. Due to comorbidities and interactions, the appropriate starting dose and titration range may require adjustment in pediatrics. This is the first report of SRT pharmacokinetics (PK) in HIV-1 infected and uninfected youth.
Methods: IMPAACT P1080 is a multicenter pilot PK study of psychiatric medications prescribed in youth. Eligible participants were treated with and stable on SRT, >6 to <25 years old, and: 1) HIV-uninfected (HIV(-)), 2) HIV-1 infected on a ritonavir-boosted protease inhibitor (PI/r), or 3) HIV-1 infected on efavirenz (EFV). Target enrollment was 45

total participants (15 per cohort). Six PK samples were collected per participant: pre-dose, 2, 4, 6, 12 and 24-hours post-dose. A validated LC-MS/MS method quantified SRT and its metabolite N-desmethylsertraline (D-SRT) in plasma. CYP2D6 activity was assessed by urinary dextromethorphan/dextrorphan (DXMO/DXO) ratio using LC-MS/MS. Noncompartmental methods estimated PK parameters, and HIV(-) and PI/r cohorts were compared by the Wilcoxon rank-sum test, two-sided with significance set to $p<0.05$. Due to low accrual, the EFV group was not included in statistical comparisons of PK parameters.

Results: Final results included 31 participants who completed PK visits (16 HIV(-), 12 PI/r, and 3 EFV). The median (range) values for weight, age, and dose were 69.5 (31.5-118.2) kg, 21.8 (9.1-24.7) years, and 75 (12.5-150) mg once daily. SRT exposure was highest for HIV(-) and lowest for EFV cohort. AUC_{0-24}, C_0 and C_{min} were significantly higher in HIV(-) compared to PI/r (Table 1). Oral clearance (dose-independent) did not differ significantly between cohorts ($p = 0.44$), whereas the DXMO/DXO ratio was significantly higher in HIV(-) compared to PI/r cohorts ($p = 0.01$). Two HIV(-) participants were CYP2D6 poor metabolizers (ln(DXMO/DXO) of > -0.5).

Conclusion: HIV(-) cohort had the highest SRT exposure compared to HIV-infected cohorts. Differences between SRT exposure in HIV(-) and PI/r participants appear modest; whether alterations in SRT dose titration ranges for PI/r participants are needed is not clear. Although greater in magnitude, the potential impact of EFV on SRT needs further investigation due to limited numbers of EFV participants.

811 SUBOPTIMAL COTRIMOXAZOLE PROPHYLACTIC CONCENTRATIONS IN CHILDREN

Claire Pressiat[1], Véronique Mea-Assande[2], Caroline Yonaba[3], Jean-Marc Treluyer[4], Désiré Lucien Dahourou[5], Madeleine Amorissani-Folquet[6], Stephane Blanche[7], Valeriane Leroy[8], Déborah Hirt[9], for the MONOD Study Group

[1]Paris Descartes Univ, Paris, France, [2]PACCI Prog, Abidjan, Cote d'Ivoire, [3]CHU Yalgado Ouédraogo, Ouagadougou, Burkina Faso, [4]Paris Cntr Hosp Group, Paris, France, [5]Cntr de Rsr Intl Pour la Santé, Ouagadougou, Burkina Faso, [6]CHU of Cocody, Abidjan, Cote d'Ivoire, [7]Necker Hosp, Paris, France, [8]INSERM, Toulouse, France, [9]Paris Cntr Hosp Group, Paris, France

Background: Cotrimoxazole (sulfamethoxazole (SMX) - trimethoprim (TMP)) is recommended to prevent opportunistic infections in HIV-infected children. Despite the overwhelming use of this medication, few pharmacokinetics (PK) data are available in children. We analyzed the concentrations of cotrimoxazole in a large population of West-African HIV-infected children, to identify factors influencing the PK and to evaluate the prophylactic doses recommended by the World Health Organization (WHO) during childhood.

Methods: HIV-infected children aged from 6 months to 2 years were enrolled in a therapeutic cohort, in Burkina Faso and Ivory Coast, offering a combined lopinavir-based antiretroviral therapy with cotrimoxazole prophylaxis (WHO recommended dose: syrup, 200/40 mg of SMX/TMP once daily). Patient's data, including demographic and clinical variables (age, sex, body weight, time of administration and time of sampling), were collected prospectively from inclusion (at ART initiation) and monthly visits until 25 months. Pharmacokinetic samples were taken during the initial treatment cohort at the month 6 (M6), M19 and M25 visits. For each visit, one or two samples per child were measured. Plasma concentrations were analyzed using a nonlinear mixed effects modeling, with NONMEM software. Estimated individual PK parameters were used to calculate individual exposures and simulate exposure for different administration schemes.

Results: Overall, 136 children (median age [range]): 1.9 years [0.7-4], median weight [range]: 9.5 kg [6-16.3]) were included. Data on a total of 482 plasma concentrations were collected (mean [range]: 3.5 [1-7] per child). Allometry effect significantly improved SMX and TMP pharmacokinetics description, suggesting the appropriateness of a dose/kg regimen. Simulations of the WHO recommended doses resulted in significantly lower SMX and TMP exposures in children from 10 to 15 kg compared to adults, potentially leading to reduce effectiveness of cotrimoxazole. Simulated regimens of 30 – 8 mg/kg for SMX-TMP in the 5 to 10 kg group and 25 – 6 mg/kg for SMX-TMP in the 10 to 15 kg group seems to be the more appropriate doses.

Conclusion: While prevalence of opportunistic infections remains high in this context, we observed lower exposures to cotrimoxazole in children than in adults. We suggest revising the current WHO recommendations of cotrimoxazole prophylaxis dosing in HIV-infected children and propose an adapted dose per kg scheme.

812 DOLUTEGRAVIR-BASED CART IN VERTICALLY HIV-1–INFECTED ADOLESCENTS, REAL-WORLD SETTING

Coralie Briand[1], Catherine Dollfus[2], Marion Caseris[3], Elie Kantor[4], Veronique Avettand-Fenoel[1], Diane Descamps[4], Veronique Schneider[5], Marie-Dominique Tabone[2], Stephane Blanche[1], **Pierre Frange**[1]

[1]Necker Hosp, Paris, France, [2]Trousseau Hosp, Paris, France, [3]Robert Debre Hosp, Paris, France, [4]Bichat Hosp, Paris, France, [5]Tenon Hosp, Paris, France

Background: Attaining long-term good therapeutic adherence and viral suppression remains a challenge in perinatally-infected adolescents. Dolutegravir (DTG)-based cART are now approved for use in HIV+ adolescents aged ≥12 years in many countries worldwide. However, published data about efficacy of DTG in this population with high risk of virological failure (VF) are scarce. This multicenter study provides the first data about safety and efficacy of DTG in adolescents in real-life setting.

Methods: Clinical and biological data from 50 adolescents, who initiated DTG-based cART between January 2014 and December 2015, were retrospectively analyzed. The primary endpoint was the proportion of patients who reached virological suppression (i.e. plasma viral load (PVL) <50 copies/mL obtained ≤ 3 months after DTG initiation) for viremic patients, and remained controlled until the last follow-up visit for all patients. The secondary endpoint was safety.

Results: At baseline, 17/50 adolescents were virologically suppressed. DTG-based HAART maintained virological success in 14/17 patients (82%). The 3 remaining adolescents experienced transient viral rebound, before reaching PVL <50 copies/mL again, without requiring cART change. Thirty-three viremic adolescents were enrolled; all but one were ART-experienced. Sustained virological success was obtained in 19/33 subjects (58%). Three additional adolescents with initial VF reached undetectable PVL at the end of follow-up with reinforced measures to improve adherence. Overall, sustained virological success and undetectable PVL at the last visit were obtained in 66% and 78% of patients, respectively. Compared to patients with virological success, subjects with VF were more often born in Sub-Saharan African countries (94% vs 52%; p=0.004), and had more frequently detectable viremia under ART during the 6 months prior to DTG initiation (82% vs 58%; p=0.03). Gender, age and characteristics of the DTG-based cART (number of pills/day, dosing frequency, cumulative GSS) were similar in the 2 groups. DTG was well tolerated; only 1 patient stopped treatment for severe drug-related side effect (dizziness, sleep disturbance). No emergence of resistance mutation was observed in patients with VF.

Conclusion: DTG was safe and provided good virological efficacy. Because of its high genetic barrier to resistance and small pill burden, DTG could be especially useful in ART-experienced adolescents with high risk of poor treatment adherence.

813 LONG-TERM EFFECTS OF WEEKENDS OFF ART IN HIV-1–INFECTED YOUNG PEOPLE ON EFV+2NRTI

Anna Turkova, for the BREATHER (PENTA 16) Trial Group

Univ Coll London, London, UK

Background: HIV-1 infected young people (YP) facing lifelong antiretroviral therapy (ART) liked short cycle therapy (SCT) with weekends off ART, as demonstrated in the BREATHER trial, showing SCT was non-inferior to continuous ART (CT) over 48 weeks, with similar resistance and safety profiles. Follow-up was extended to minimum 144 weeks, maintaining original randomisation.

Methods: BREATHER was a randomised, open-label, non-inferiority trial. YP (8-24yrs) on first-line efavirenz (EFV) +2NRTIs with HIV-RNA (VL) <50c/ml for >12 months were randomised to SCT (5-day on; 2-days off ART) or CT with 12-weekly VL monitoring. Kaplan-Meier methods were used to estimate the proportion with confirmed VL≥50c/ml by arm and differences between arms (12% non-inferiority margin) adjusted for region and age.

Results: 194/199 YP consented to long term follow-up (97 SCT, 97 CT). Median [IQR] follow-up was 184 [161-216] weeks; 93% were followed for ≥144 weeks. Over 144 weeks, 15 SCT vs 13 CT had confirmed VL≥50c/ml (difference 1.9%, 90%CI −6.6, 10.4; figure); results were similar in a per-protocol analysis (difference 0.9%, −7.8, 9.6). In total, 27 (28%, 95%CI 19, 37) SCT patients had returned to CT by 144 weeks. Of the 15 SCT with confirmed VL≥50c/ml, 1 resumed CT prior to rebound, the remaining 14 resumed CT on rebound; 13/14 resuppressed, 10 on the same regimen (2 later rebounded) and 3 with a switch to second-line. A further 12 SCT had restarted CT by 144 weeks: 4 for 3 unconfirmed VL≥50c/

ml (blips), 3 for patient preference, 4 for discontinuing EFV (3 toxicity, 1 other), 1 for poor clinic attendance. Of the 13 CT with confirmed VL≥50c/ml, 7/13 resuppressed, 5 without a treatment switch and 2 with a switch to second-line. Over 144 weeks, 3 SCT vs 6 CT switched to second-line for viral failure (p=0.50); and 3 had new CDC B events (2 SCT, 1 CT). There were no significant differences between SCT and CT in grade 3/4 AEs (21 vs 20; p=1.00) or ART-related AEs (10 vs 17; p=0.48). Reports of missed ART in the week before a clinic visit (excluding days off in SCT) were similar in SCT and CT (6.6% v 7.8%, p=0.86).
Conclusion: Sustainable non-inferiority of VL suppression in YP on EFV-based first line ART was demonstrated for SCT vs CT over almost 3yrs with >70% SCT patients remaining on the strategy; most YP experiencing viral rebound on SCT resuppressed on the same regimen on return to CT. SCT is a viable option for adherent HIV-1 infected YP on EFV-based first-line ART with 3-monthly VL monitoring.

814 COST-EFFECTIVENESS OF PREEMPTIVE SWITCH TO EFAVIRENZ (EFV) IN HIV-INFECTED CHILDREN

Sophie Desmonde[1], Simone C. Frank[2], Ashraf Coovadia[3], Désiré Lucien Dahourou[4], Elaine J. Abrams[5], Rochelle P. Walensky[2], Kenneth Freedberg[2], Louise Kuhn[6], Valeriane Leroy[7], Andrea L. Ciaranello[2]
[1]Univ of Bordeaux, Bordeaux, France, [2]Massachusetts General Hosp, Boston, MA, USA, [3]Empilweni Service and Rsr Unit, Johannesburg, South Africa, [4]Cntr de Rsr Intl Pour la Santé, Ouagadougou, Burkina Faso, [5]ICAP at Columbia Univ, New York, NY, USA, [6]Columbia Univ, New York, NY, USA, [7]INSERM, Toulouse, France
Background: Pre-emptive switching to EFV for HIV-infected children suppressed on lopinavir/ritonavir (LPV/r) can simplify ART while preserving LPV/r for second-line treatment. The South African NEVEREST3 trial found this switch strategy to be non-inferior to remaining on LPV/r. The MONOD ANRS 12206 trial in Côte d'Ivoire showed similar 6-month outcomes, although limited by low event rates. We evaluated the cost-effectiveness of a preemptive switch to EFV.
Methods: We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-Pediatric model to simulate South African children suppressed on LPV/r. The base case used NEVEREST3 data to examine 3 strategies: 1) Switch: switch to EFV-based ART (initial 24-week RNA suppression [<1000c/ml]: 98%; virologic failure (VF) after 24-week suppression: 0.15%/month), followed by return to 2nd-line LPV/r at observed VF; 2) WHO guidelines: Remain on LPV/r (VF after initial suppression: 0.22%/month), with switch to 2nd-line NNRTIs at observed VF; and 3) LPV/r only: Remain on LPV/r (VF after initial suppression: 0.22%/month) with no 2nd-line regimen, reflecting practice in many settings. We projected life expectancy (LE) and HIV-related healthcare costs. Sensitivity analyses varied all key clinical and cost parameters. A secondary analysis used data from MONOD, which also reported EFV 24-week suppression of 98%, but higher monthly VF after initial suppression for EFV (0.72%) than for LPV/r (0.34%).
Results: With NEVEREST3 data, the switch strategy led to the longest projected LE (21.38y) and lowest projected lifetime cost ($32,720; Table). Results were not affected by plausible variations in ART or healthcare costs, loss to follow-up rates, or age at time of LPV/r initiation or ART switch (unless this affected virologic outcomes on ART). Results were modestly sensitive to initial suppression rates: if 24 week RNA<1000c/ml was <90% for children switching to EFV (base-case value:98%), WHO guidelines was preferred. Results were most sensitive to risk of VF after initial suppression. This risk for children switching to EFV needed to be equal to or lower than that for children remaining on LPV/r for the switch strategy to remain the most effective and cost-saving. With MONOD data, for example, the WHO guidelines strategy maximized LE (20.21y) and minimized cost ($33,570; Table).
Conclusion: For children similar to NEVEREST3 participants and suppressed on LPV/r-based ART, pre-emptive switching to EFV can improve clinical outcomes and be cost-saving.

Table: Model-projected results

	Model-projected results		
	Life expectancy (years, discounted)	Lifetime costs (USD, discounted)	Cost-effectiveness
South African children suppressed on LPV/r (NEVEREST3 data)			
Switch to EFV	21.38	32,720	--
Stay on LPV/r with 2nd line NNRTI (WHO guidelines)	21.12	34,230	More expensive, less effective
Stay on LPV/r, no 2nd line ART (LPV/r only)	20.11	46,140	More expensive, less effective
South African children suppressed on LPV/r (MONOD data)			
Stay on LPV/r with 2nd line NNRTI (WHO guidelines)	20.21	33,570	
Switch to EFV	19.68	37,333	More expensive, less effective
Stay on LPV/r, no 2nd line ART (LPV/r only)	19.03	44,259	More expensive, less effective

* Strategies listed in order of ascending costs.
USD: United States dollars; LPV/r: lopinavir/ritonavir; ART: antiretroviral therapy; EFV: efavirenz; WHO: World Health Organization.

815 PREDICTORS OF SWITCH TO SECOND-LINE ART IN HIV-POSITIVE CHILDREN: A GLOBAL ANALYSIS

Kara K. Wools-Kaloustian[1], Colette J. Smith[2], Ruth Goodall[2], Intira J. Collins[2], Elaine J. Abrams[3], Mary-Ann Davies[4], Mary Paul[5], Jorge Pinto[6], Russell B. Van Dyke[7], for the CIPHER Durability of First Line Project Team
[1]Indiana Univ, Indianapolis, IN, USA, [2]Univ Coll London, London, UK, [3]ICAP at Columbia Univ, New York, NY, USA, [4]Univ of Cape Town, Cape Town, South Africa, [5]Baylor Coll of Med, Houston, TX, USA, [6]Univ Fed de Minas Gerais, Belo Horizonte, Brazil, [7]Tulane Univ, Metairie, LA, USA
Background: Data on durability of first-line antiretroviral therapy (ART) in children across settings are needed to understand key factors associated with, as well as appropriateness of, switch to second-line ART.
Methods: Data were pooled from 12 cohort networks within CIPHER. Children aged <18-years initiating combination ART (≥2 nucleoside reverse-transcriptase inhibitors [NRTI] plus non-NRTI [NNRTI] or boosted protease inhibitor [PI]) were included. Switch to second-line was defined as: (i) change of ≥1 NRTI plus either change in drug class (NNRTI to PI or vice versa) or PI change; (ii) change from single to dual PI; or (iii) addition of a new drug class. Factors associated with time to switch were explored using proportional hazards regression models with death and loss to follow-up (LTFU) as competing risks in (a) everyone, and (b) cohorts with routine CD4 monitoring. The effect of WHO immunological status for age was explored in model (b).
Results: Of 93,213 children included, 22% were from Southern Africa (South Africa, Lesotho, Botswana), 68% from the rest of sub-Saharan Africa and 10% from other regions. At ART start, median [IQR] age was 3.9 [1.6, 6.9] yrs; CD4% 15% [10, 22%], 89% and 11% initiated NNRTI- and PI-based ART respectively. Median duration of follow-up from ART start was 27 [9, 54] mo; 1% died, 25% LTFU and 20% transferred out. Overall, 3979 (4.3%) switched to second-line at a median of 35 [19, 57] mo after ART start. At switch, median CD4% (n=2892) was 20% [11, 28%] and 12% (n=2287) had VL<400 copies/mL. The cumulative incidence of switch at 3 yrs after ART start was 1.4% (95% CI 1.3, 1.6%) in low- to 7.0% (6.6, 7.4%) in upper/upper-middle-income countries. In model (a) males, children who initiated ART at older ages, started an NNRTI-based regimen, were in settings with routine CD4 and VL monitoring and higher income countries had a significantly shorter time to switch (p<0.0001, Table). In model (b) (n=32,989), severe immunodeficiency at ART start was also associated with shorter time to switch (p<0.0001).

Conclusion: Children followed by clinical or CD4-only monitoring had significantly longer time to switch to second-line as compared to routine or targeted VL monitoring. This likely represents delayed or under recognition of treatment failure, which has significant potential to impact their long term outcomes. The scale up of VL monitoring is likely to increase detection of treatment failure and demand for second-line ART.

816 FREQUENT FAILURE AFTER SECOND-LINE ART IN HIV-POSITIVE CHILDREN FROM LATIN AMERICA

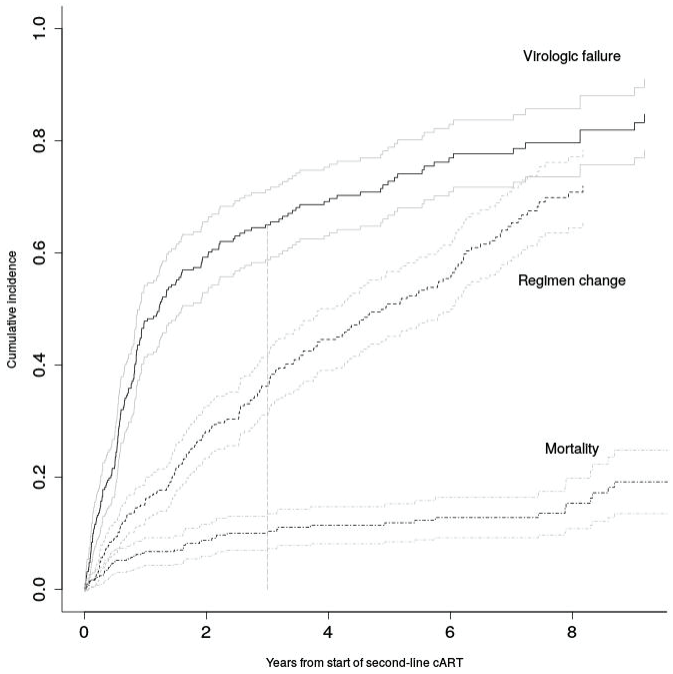
Bryan E. Shepherd[1], Cathy Jenkins[1], Regina Succi[2], Daisy Machado[2], Jorge Pinto[3], Vanessa Rouzier[4], Marco Luque[5], Sten Vermund[1], **Catherine McGowan**[1], for the Caribbean, Central and South America Network for HIV epidemiology (CCASAnet) *[1]Vanderbilt Univ, Nashville, TN, USA, [2]Univ Fed de Sao Paulo, São Paulo, Brazil, [3]Univ Fed de Minas Gerais, Belo Horizonte, Brazil, [4]Les Cntrs GHESKIO, Port-au-Prince, Haiti, [5]Hosp Escuela Univ, Tegucigalpa, Honduras*

Background: Latin America's diverse population has varying, often limited access to newer antiretrovirals. Data on pediatric second-line ART outcomes and their predictors are needed to guide design of optimal interventions.

Methods: HIV-positive ART-naïve children age ≤18, starting cART ($cART_1$) from 1999-2007 at 5 sites in Argentina, Brazil, Haiti, and Honduras, and changing to second-line cART ($cART_2$). Outcomes: $cART_2$ changes (≥2 agent change, outside-class substitution, or discontinuation); virologic failure on $cART_2$; all-cause mortality. Cumulative incidences were modeled with death as competing risk for non-mortality outcomes. Cox regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) adjusting for sex, mode of infection, age, CD4, AIDS, year at $cART_2$, change in CD4 and time from $cART_1$ to $cART_2$, $cART_2$ start reason, $cART_2$ class, and site. Haiti was not included in failure analyses.

Results: Of 1489 children, 413 (28%) started $cART_2$; most were perinatally-infected (93%), 52% were female, and 38% had AIDS at $cART_1$ start. Median ages were 5.1 (interquartile range [IQR] 1.8-10.1) and 9.2 (IQR 5.4-14.2) years and CD4s were 426 (IQR 139-878) and 456 (IQR 133-916) cells/μL at $cART_1$ and $cART_2$ starts, respectively. Median year of $cART_2$ start was 2007 (IQR 2005-2011). Most (56%) received protease inhibitor-based $cART_2$. On $cART_2$, median follow-up was 4.7 years (IQR 1.9-7.8), 202 (49%) changed regimens, 53 (13%) died, and 80 (19%) were lost to follow-up. Among 251 children with viral loads (VL), cumulative incidence of failure at 3 years after $cART_2$ start was 0.65 (CI=0.58-0.71, Figure). Older age at $cART_2$ start (HR=1.06 per year; CI=1.01-1.10) and failure as reason for starting $cART_2$ (HR=2.14; CI=1.24-3.71) increased risk of changing $cART_2$. Children with AIDS at $cART_1$ start had higher risk of $cART_2$ failure (HR=2.24; CI=1.22-4.13), though those starting $cART_2$ in later years had decreased risk (HR=0.84 per year; CI=0.73-0.97).

Conclusion: We observed high rates of switching from $cART_2$ in varied Latin American settings; 65% of children with VL data experienced treatment failure by 3 years. Interventions targeting adolescents and improved access to once-daily cART regimens are needed to improve outcomes in this population.



817LB HIV-INFECTED CHILDREN WITH SEVERE ACUTE MALNUTRITION: EARLY VS DELAYED ART INITIATION

Moherndran Archary[1], Benn Sartorius[1], Philip La Russa[2], thobekile sibaya[1], Micheal Healy[2], Raziya Bobat[1]
[1]Univ of KwaZulu-Natal, Durban, South Africa, [2]Columbia Univ, New York, NY, USA

Background: Delays in prompt HIV diagnosis and ART initiation in children from low and middle-income countries, frequently results in malnutrition at initial presentation. Despite ART initiation, HIV positive children with malnutrition have a higher mortality and delayed immune recovery. The optimal timing of ART initiation in children with malnutrition has not been established

Methods: Eighty-two HIV infected children with severe acute malnutrition (SAM) admitted to King Edward VIII Hospital between July 2012 and December 2015 were enrolled. Patients were randomized to initiate ART within 14 days from admission (Early arm) or delay ART initiation until nutritional recovery and more than 14 days from admission (Delayed arm). All patients received a standardized treatment and feeding protocol and were evaluated at 4, 8, 12, 24 and 48 weeks.

Results: The average age of the patients at baseline was 23·3 months (SD 27·9, range 1.6–129 months). The mean time from admission to ART initiation was 5·6 days (SD 4·4) in the early arm and 23 days (SD 5·8) in the delayed arm (p<0·001). There was no significant difference in mortality (p=0·621), virologic response (p=0·527) and anthropometric response (p= 0·566) between the two groups at 48 weeks. However the rates of change in CD4, viral load (figure 1), WAZ and HAZ scores occurred earlier and favored the delayed arm.

Conclusion: HIV–infected children admitted with SAM and initiated on ART demonstrated significant improvements in CD4 counts and anthropometric parameters, together with significant viral load reduction compared to baseline. In this randomized controlled trial comparing early versus delayed ART initiation in HIV infected children admitted with SAM, although the differences in CD4 count, viral suppression and anthropometric response at 48 weeks was not significant, the rates of change in CD4, viral load, WAZ and HAZ

scores occurred earlier and favored the delayed arm. Based on the results of this study, we recommend that ART initiation in children with SAM should be delayed for at least two weeks after starting nutritional rehabilitation.

818 TREATMENT OUTCOMES OF KAPOSI SARCOMA IN HIV-1–INFECTED CHILDREN IN MOZAMBIQUE

Faizana Amodo[1], Yolanda Cachomba[2], Dalila Rego[1], Orvalho Augusto[2], Dulce Bila[3], Paula Vaz[3]
[1]Hosp Central de Maputo, Maputo, Mozambique, [2]Univ Eduardo Mondlane, Maputo, Mozambique, [3]Fundação Ariel Glaser Contra o Sida Pediatrico, Maputo, Mozambique

Background: Kaposi Sarcoma (KS) in HIV-1-infected children is not uncommon in sub-Saharan Africa and the outcomes are influenced by the disease stage and respective treatment. Antiretroviral treatment (ART) is now widely accessible but chemotherapy is restricted to a few tertiary centers. Here we present a retrospective of 12 years 'outcomes of KS in children attending a reference public hospital in Maputo, Mozambique.
Methods: Children aged 0-14 years presenting with KS and HIV-1 infection were consecutively recruited, between December 2003 and December 2015, at Maputo Central Hospital. They received ART following WHO recommendations and chemotherapy either Paclitaxel or a combination of Adriamycin, Bleomycin, Vincristine (ABV). Descriptive statistics and survival analysis with competing risks (death, full remission and partial remission) are presented. Follow up ends at event occurrence or censor at 24 months.
Results: About 64 children started chemotherapy, with median age 9 years (IQR, 6 - 12) and male to female ratio of 1.7:1. Overall, the median follow-up time was 17 months. At 18th month of follow up, 28 (44%) were alive, 15 (23%) in full remission, 12 (19%) dead, 5 (8%) in partial remission and 4 (6%) lost-to-follow-up. All children were on ART, mostly on a regimen based on 2NRTI+1NNRTi 61 (95%). The incidence of full remission was 8 times higher on ABV chemotherapy when compared to Paclitaxel (p=0.002) (Figure 1). Grade III and IV toxicity was only observed in Paclitaxel users.
Conclusion: The present results suggest the superior benefit of ABV use in co-infected KS-HIV-1 children and the importance of early diagnosis of KS. In fact, our results show that despite the use of ABV, if children with KS are diagnosed late the poor the outcome observed.

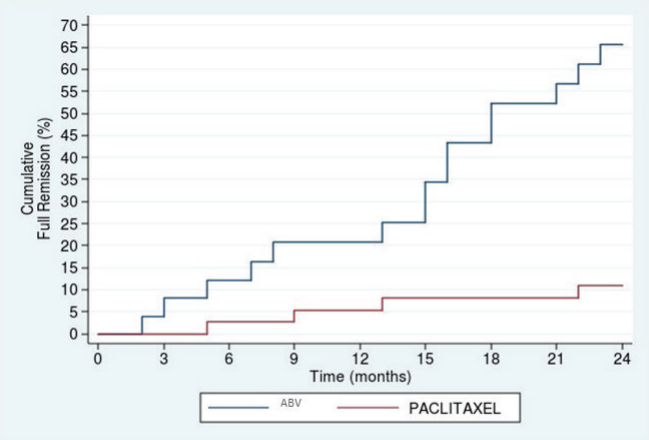


Figure1: Competing risk adjusted cumulative incidence of complete remission associated to ABV and PACLITAXEL therapy (p-value < 0.001).

819 DURABLE GAINS IN BONE MASS AMONG SOUTH AFRICAN CHILDREN SWITCHING TO EFAVIRENZ

Stephen M. Arpadi[1], Stephanie Shiau[1], Renate Strehlau[2], Faeezah Patel[2], Ndileka Mbete[2], Louise Kuhn[1], Ashraf Coovadia[2], Michael T. Yin[1]
[1]Columbia Univ, New York, NY, USA, [2]Empilweni Service and Rsr Unit, Johannesburg, South Africa

Background: We previously reported in our cohort study of pre-pubertal perinatally HIV-infected children that after 2 years, bone mineral content (BMC) Z-score of the whole body (WB) and lumbar spine (LS) was higher in children who switched to an efavirenz (EFV)-based antiretroviral therapy regimen from a ritonavir-boosted lopinavir (LPV/r)-based regimen in comparison to those who remained on a LPV/r-based regimen (-0.68 vs -1.20, p<0.01 and 0.01 vs -0.45, p<0.01, respectively). Now, we assess whether improvements in bone accrual are durable after an additional 1 year follow-up.
Methods: The CHANGES Bone Study follows HIV-infected children who participated in a randomized trial in Johannesburg, South Africa of pre-emptive switching to EFV (N=106) compared to remaining on LPV/r (N=113) for those initially suppressed on LPV/r. WB and LS BMC were assessed by DXA at baseline and 12 months (mean 2.1 and 3.1 years after ART switch, respectively). BMC Z-scores adjusted for sex, age, and height were generated using reference norms from the Bone Mineral Density in Childhood Study. We compared LPV/r and EFV groups by intent-to-treat.
Results: A total of 214 children (97%) completed both study visits, including 103 in the EFV group and 111 in the LPV/r group. The mean age was 7.4 years (SD 1.2). Similar to baseline, the WB and LS BMC Z-score at 12 months was significantly higher in those switched to EFV compared to those remaining on LPV/r (-0.77 vs. -1.26, p<0.01 and -0.07 vs. -0.53, p<0.01, respectively). The change in BMC Z-score from baseline to 12 months was not different between those switching to EFV and those remaining on LPV/r at the WB (-0.10 vs. -0.07, p=0.63) or LS (-0.08 vs. -0.08, p=0.99). However, WB and LS BMC Z-scores for both groups declined slightly relative to reference norms. At both baseline and 12 months, differences between the EFV and LPV/r groups were greater in the girls than the boys (Table 1).
Conclusion: Bone mass remains higher in pre-pubertal perinatally-infected children 3 years after switch to EFV in comparison to children remaining on LPV/r. Differences between groups are greater in girls than boys. Rate of change in BMC did not differ between groups during the last year of observation, suggesting that benefits of switching to EFV for bone may be greatest close to the switch. These findings provide additional rationale for switching children with sustained viral suppression receiving first line regimen with LPV/r
to EFV.

Table 1

Measurement	Timepoint	Boys			Girls		
		EFV (N=54)	LPV/r (N=53)	P	EFV (N=52)	LPV/r (N=60)	P
Whole body BMC Z-score	Baseline	-0.67 (0.76)	-1.02 (0.84)	0.03	-0.69 (0.76)	-1.37 (0.77)	<0.01
	12 Months	-0.68 (0.73)	-1.07 (0.78)	<0.01	-0.86 (0.77)	-1.43 (0.78)	<0.01
Lumbar spine BMC Z-score	Baseline	-0.01 (0.83)	-0.23 (0.72)	0.15	0.03 (0.85)	-0.64 (0.98)	<0.01
	12 Months	-0.14 (0.87)	-0.40 (0.79)	0.11	-0.004 (0.84)	-0.64 (0.99)	<0.01

820 EFFECTS OF CALCIUM AND VITAMIN D SUPPLEMENTATION ON BONE HEALTH IN HIV-INFECTED YOUTH

Tavitiya Sudjaritruk[1], Linda Aurpibul[1], Torsak Bunupuradah[2], Suparat Kanjanavanit[3], Tawalchaya Chotecharoentanan[1], Sineenart Taejaroenkul[1], Pradthana Ounchanum[4], Piyarat Suntarattiwong[5], Thanyawee Puthanakit[6], for the CAL-D Study Group

[1]Chiang Mai Univ, Chiang Mai, Thailand, [2]HIV Netherlands Australia Thailand Rsr Collab (HIV-NAT), [3]Nakornping Hosp, Chiang Mai, Thailand, [4]Chiang Rai Prachanukroh Hosp, Chiang Rai, Thailand, [5]Queen Sirikit Natl Inst of Child Hlth, Bangkok, Thailand, [6]Chulalongkorn Univ, Bangkok, Thailand

Background: Adverse bone health is an important complication in people living with HIV. Calcium and vitamin D (Ca/VitD) supplementation have demonstrated beneficial impacts on bone health. This study aimed to evaluate effects of Ca/VitD supplementation on bone metabolism and bone mineral density (BMD) in HIV-infected Thai youth.

Methods: An ongoing, multicenter, 48-week, randomized, open-label trial has been conducted. Perinatally HIV-infected adolescents (10-20 years) with viral suppression (HIV RNA<400 copies/ml) were randomized to receive calcium (1.2 g/day) and high-dose vitamin D (3200 IU/day) (high-dose group) or calcium (1.2 g/day) and normal-dose vitamin D (400 IU/day) (normal-dose group) for 48 weeks. BMD (primary outcome) was assessed at baseline and 48 weeks. Bone metabolism-related markers (secondary outcomes), including serum 25-hydroxyvitamin D (25OHD), intact parathyroid hormone (iPTH), alkaline phosphatase (ALP), and bone turnover markers (C-terminal cross-linked telopeptide of type I collagen [CTX; bone resorption marker], and procollagen type I amino-terminal propeptide [PINP; bone formation marker]) were measured at baseline, 24 and 48 weeks. Preliminary intention-to-treat analyses were conducted at 24 weeks using Wilcoxon rank sum and signed rank tests. Models stratified by baseline BMD (Z-score≤-2 vs. >-2) were also performed.

Results: From April 2015 to April 2016, 166 adolescents (83 each group) were enrolled. The population was 48% male; 35% receiving protease inhibitor-based cART. Median age was 16 years; CD4 count 711 cells/mm3. Median baseline BMD Z-score was -1.5; 67 (40%) had Z-score ≤-2. Overall adherence to Ca/VitD supplementation was 85%. At baseline, the study groups were well-balanced. At 24 weeks, serum 25OHD levels were increased (P<0.001), whereas iPTH, ALP, CTX, and PINP were declined (P<0.001) in both treatment groups. There was no difference in all bone metabolism markers observed between high- versus normal-dose vitamin D group (P>0.05) (Table1). Models stratified by baseline BMD yielded similar results. Two subjects (high-dose group) discontinued due to toxicities (acne; constipation).

Conclusion: Ca/VitD supplementation for 24 weeks increased serum 25OHD, decreased iPTH levels and re-established bone turnover dysregulation among adolescents in our cohort. Supplementation with high-dose vitamin D did not show difference in bone metabolism outcomes compared to normal-dose. Evaluation of the impact of Ca/VitD supplementation on bone mineral density is underway.

Table 1. Bone metabolism-related biochemical markers among perinatally HIV-infected Thai adolescents who received calcium and vitamin D supplementation

Parameters	Treatment groups	Baseline*	Week 24*	*P-value*†
25OHD, ng/ml	High-dose	28 (21 – 36)	35 (27 – 45)‡	0.18
	Normal-dose	25 (20 – 30)	31 (25 – 36)‡	
iPTH, pg/ml	High-dose	41 (33 – 54)	32 (27 – 41)‡	0.06
	Normal-dose	43 (35 – 58)	33 (25 – 47)‡	
ALP, U/l	High-dose	163 (109 – 263)	126 (90 – 220)‡	0.28
	Normal-dose	195 (137 – 283)	131 (102 – 212)‡	
CTX, ng/l	High-dose	1,270 (820 – 2,040)	910 (600 – 1,630)‡	0.11
	Normal-dose	1,390 (950 – 2,050)	1,020 (640 – 1,440)‡	
PINP, µg/l	High-dose	312 (145 – 592)	212 (124 – 498)‡	0.57
	Normal-dose	337 (177 – 625)	283 (119 – 443)‡	

*Data presented as median (interquartile range).
†*P*-values evaluate the difference in changes from baseline to week 24 between two treatment groups.
‡Indicates within-group difference from baseline to week 24 is a statistically significant (*P* <0.001).

821 METABOLIC PROFILES OF ADULTS VERTICALLY INFECTED WITH HIV AND THE GENERAL POPULATION

Elise Arrivé[1], **Jean-Paul Viard**[2], Elisa Arezes[3], Feriel Ayat[3], Benoit Salanave[4], Sophie Matheron[5], Véronique Reliquet[6], Corinne Vigouroux[7], Josiane Warszawski[3], for the ANRS CO19 COVERTE Study Group

[1]Univ of Bordeaux, Bordeaux, France, [2]Hôtel-Dieu de Paris, Paris, France, [3]INSERM, Le Kremlin-Bicêtre, France, [4]Equipe de Surveillance et d'Epidémiologie Nutritionnelle/Agence Natl de Santé Publique, Bobigny, France, [5]Bichat-Claude Bernard Hosp, Paris, France, [6]CHU Hôtel Dieu, Nantes, France, [7]INSERM, Paris, France

Background: Cardiometabolic risk is poorly documented for the first generation of young adults living with HIV since childhood and exposed to synergic risk factors, including antiretroviral drugs (ARV), lipodystrophy and HIV itself. We compared the metabolic profiles of these young adults and the general population of the same age in France.

Methods: We used two French national studies: (1) COVERTE (ANRS-CO19), a cohort of 18- to 30-year-old patients infected with HIV since childhood, and (2) ENNS, a national cross-sectional population-based household nutrition survey. Body mass index, blood pressure, waist circumference, fasting glucose, triglycerides, HDL-, LDL- and total cholesterol were determined in both studies. Metabolic abnormalities were categorized according to the Joint Interim Statement definition of metabolic syndrome (2009). Their prevalences were

compared, in COVERTE and ENNS, separately for men and women, with directed standardization for overweight and educational level, and logistic regression to estimate odds ratios (ORs) and their 95% confidence intervals (CI) adjusted for educational level, overweight and alcohol consumption.
Results: Most of the 269 HIV-infected patients included in COVERTE (47% male) had been on combined ARV therapy (40% including a protease inhibitor) for a mean of 19 years. Viral load remained detectable in 32%, but median CD4 count was 550 cells/mL. These subjects were compared with 245 young adults from ENNS (42% male). Tobacco use was similar in the two populations. After standardization, the prevalence of metabolic syndrome was 13.2% (CI: 7.1-19.2) in HIV-infected men versus 10.6% (CI: 1.5-19.7) in the general population. The corresponding prevalences in women were 9.8% (CI: 5.1-14.6) and 1.7% (CI: 0-4.1). HIV-infected men were more likely to have high triglyceride levels (OR 4.97; CI: 1.02-24.22) though less likely to be overweight (OR 0.23; 0.08-0.65) or have hyperglycemia (OR 0.25; CI: 0.07-0.86) than men from the general population. HIV-infected women were more likely to have a large waist circumference (OR: 3.47; CI: 1.14-10.55), low HDL-cholesterol levels (OR 2.68; CI: 1.30-5.50) and less likely to have high total cholesterol levels (OR 0.31; 0.14-0.66).
Conclusion: Young adults infected with HIV since childhood had no excess of behavioral risk factors, but were more likely to have dyslipidemia and metabolic syndrome than the general population, justifying close monitoring for cardiometabolic diseases.

822 EFFECTS OF VITAMIN D SUPPLEMENTATION ON CAROTID INTIMA-MEDIA THICKNESS IN HIV+ YOUTH

Allison R. Eckard[1], Paolo Raggi[2], Mary Ann O'Riordan[3], Julia C. Rosebush[4], Danielle Labbato[3], Ann Chahroudi[4], Joshua H. Ruff[4], Chris T. Longenecker[3], Vin Tangpricha[4], Grace A. McComsey[3]
[1]Med Univ of South Carolina, Charleston, SC, USA, [2]Mazankowski Alberta Heart Inst, Edmonton, Canada, [3]Case Western Reserve Univ, Cleveland, OH, USA, [4]Emory Univ, Atlanta, GA, USA
Background: HIV+ youth are at an increased risk of cardiovascular disease (CVD). Vitamin D deficiency is associated with CVD risk in HIV, but it is not known whether supplementation could affect this risk.
Methods: This is a 24-month randomized, active-control, double-blind trial comparing 2 different monthly vitamin D3 doses [60,000 (medium) or 120,000 (high) IU/month] vs. control of 18,000 IU/month in 8-26 year old HIV+ youth on ART with baseline 25-hydroxyvitamin D (25(OH)D) ≤30 ng/mL & HIV-1 RNA <1000 copies/mL. Carotid IMT was measured at baseline & 24 months. Comparisons of changes in IMT were made between the HIV+ control arm vs. combined supplementation arms (medium+high) & within these groups using appropriate two-sample tests. A matched healthy uninfected group was enrolled in a similarly-designed parallel study for comparison.
Results: We enrolled 102 HIV+ subjects: 64% men, 89% black, median age of 20 years. HIV & ART duration were 8 & 3 years, respectively with a CD4 count of 652 cells/mm^3. Baseline 25(OH)D was similar between groups (controls: 17 (11, 21) vs. supplementation group: 18 (14, 22) ng/mL; P=0.49) and increased to 32 (25, 38) and 41 (31, 46) ng/mL in the control and supplementation (medium+high) dose groups at 24 months, respectively (within & between groups P<0.001). Baseline bulb (0.65 vs. 0.63 mm, P=0.13) and common carotid artery (CCA) IMT (0.69 vs. 0.56 mm, P=0.81) were similar between groups. Over 24 months, bulb & CCA IMT decreased only in the control arm (Figure 1), with changes in bulb IMT being significantly different than supplementation arm at 24 months (P=0.02). Overall, changes in bulb IMT were significantly correlated with changes in 25(OH)D (R=0.43, P=0.001). In multivariable regression models, larger increases in 25(OH)D were associated with greater IMT increases. In contrast to the findings in HIV+ subjects, among the healthy uninfected group (N=88), there were no differences in changes in IMT between the control vs. supplementation arms and no significant correlations between changes in 25(OH)D and changes in IMT.
Conclusion: A modest vitamin D3 dose of 18,000 IU/month given over 24 months resulted in significant decreases in carotid IMT compared to high monthly doses of 60,000 or 120,000 IU. These results suggest a potential for a less optimal effect of high-dose vitamin D supplementation in this population, an effect that was not seen in the parallel HIV-uninfected study. On-going analyses are underway to better understand these surprising findings.

823 DOES PREMATURE VASCULAR STIFFNESS SLOWLY IMPROVE FOLLOWING EARLY ART?DATA FROM CHER

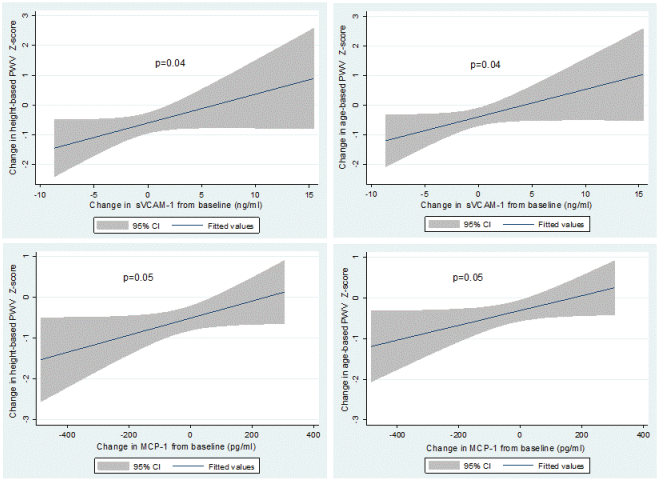
Steve Innes[1], Mark Cotton[1], Kennedy N. Otwombe[2], Barbara Laughton[1], Sara H Browne[3]
[1]Stellenbosch Univ, Cape Town, South Africa, [2]Univ of the Witwatersrand, Johannesburg, South Africa, [3]Univ of California San Diego, San Diego, CA, USA
Background: ➢ Cross-sectional data suggests increased prevalence of vascular disease in HIV+ children on antiretroviral therapy (ART) after adjusting for traditional atherosclerosis risk factors, typically associated with advanced HIV disease and ART, particularly lopinavir/ritonavir (LPVr) ➢ Thus far, pediatric studies have focused on children initiating ART much later than 3 months of age ➢ Whether very early ART will prevent HIV-related premature vascular disease is unknown ➢ Aorto-femoral pulse wave velocity (PWV) is a sophisticated and sensitive measure of elevated arterial wall stiffness, typically due to atherosclerosis or subclinical arteritis ➢ Reduced arterial wall elasticity leads to faster propagation of the arterial pulse wave ➢ PWV elevations strongly predict subsequent cardiovascular events in asymptomatic adults
Methods: ➢ Baseline and 1-year follow-up PWV measurements were performed in perinatally-HIV-infected primary-school-age children who initiated LPVr + zidovudine + lamivudine very early in infancy with minimal HIV disease and normal CD4 counts in a well-resourced trial setting (CHER); and in HIV-uninfected controls (HIV-exposed uninfected, HEU, and HIV-unexposed, HU) from the same communities and socio-economic background ➢ Changes in raw PWV, height-based PWV Z-score (PWVZ-ht) and age-based PWV Z-score (PWVZ-age) were compared by ANOVA followed by pairwise T-test, and adjusted, using multivariable regression, for body mass index, fasted glucose, total and low density lipoprotein cholesterol, triglycerides and serum cotinine
Results: ➢ 84 HIV+ (median age 7.7 [IQR: 7.6-8.5] years) who initiated ART at median 9 (7–12) weeks of age, with cumulative time on ART of median 7.1 (6.7–7.5) years and normal CD4 counts ➢ 51 uninfected (31 HEU; 20 HU) of median age 8.5 (IQR: 7.8-8.7) years, with similar anthropometric Z-scores between groups(p>0.10) ➢ Baseline PWV metrics in both HIV+ and HEU were higher than HU and this difference persisted in HIV+ after adjustment (p≤0.04 for all). (HEU could not be adjusted due to limited n) ➢ At follow-up, both PWVZ-ht and PWVZ-age had improved in HIV+ and HEU (p≤0.03) (see figure 1), whereas HU remained unchanged. This difference did not persist after adjustment, however the power of the adjustment was restricted by limited n
Conclusion: ➢ Suggests that, in children who initiated ART very early in life, PWV abnormalities gradually improve with accumulating time on ART ➢ Interestingly, early-onset PWV elevations in HEU also appear to wane with time

824 SVCAM AND MCP-1 INVOLVED IN PREMATURE ARTERIAL-WALL STIFFNESS IN PREPUBERTAL CHILDREN

Steve Innes[1], Richard Glashoff[1], Shalena Naidoo[1], Kennedy N. Otwombe[2], Barbara Laughton[1], Maile Karris[3], Mark Cotton[1], Sara H Browne[3]
[1]Stellenbosch Univ, Cape Town, South Africa, [2]Univ of the Witwatersrand, Johannesburg, South Africa, [3]Univ of California San Diego, San Diego, CA
Background: ➢ Cross-sectional evidence strongly suggests increased prevalence of vascular disease in HIV+ children on antiretroviral therapy (ART) after adjusting for traditional atherosclerosis risk factors. ➢ Soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1) and monocyte chemoattractant protein-1 (MCP-1) predict incident vascular events in adults. ➢ Whether these chemokines indicate clinically-detectable vascular disease in children is unknown. ➢ Aorto-femoral pulse wave velocity (PWV) is a sophisticated and sensitive measure of elevated arterial wall stiffness, typically due to atherosclerosis or subclinical arteritis. ➢ Reduced arterial wall elasticity leads to faster propagation of the arterial pulse wave. ➢ Early PWV elevations strongly predict subsequent cardiovascular events in asymptomatic adults.
Methods: ➢ Baseline and 1-year follow-up measurements of serum sVCAM-1, sICAM-1 and MCP-1 (by Luminex Multiplex® assays), and PWV (using Vicorder® device) in HIV+ primary-school-age children who initiated lopinavir/ritonavir + zidovudine + lamivudine very early in infancy with minimal HIV disease and normal CD4 counts in a well-resourced trial setting (CHER); and in HIV-uninfected controls (HIV-exposed uninfected, HEU, and HIV-unexposed, HU) from the same communities and socio-economic background. ➢ To avoid post-hoc analysis bias and the multiple comparisons problem, the choice of biomarkers and adjustment factors was set a priori. ➢ Changes in sVCAM-1, sICAM-1 and MCP-1 were compared with changes in raw PWV, height-based PWV Z-scores (PWVZ-ht) and age-based PWV Z-scores (PWVZ-age) by multivariable linear regression adjusting for body mass index, fasted glucose, total and low density lipoprotein cholesterol, triglycerides and serum cotinine.

Results: ➢ 135 children were assessed (median age 7.8; IQR 7.6–8.5 years): 84 HIV+ who initiated ART at median 9 (IQR: 7–12) weeks of age; and 51 uninfected (31 HEU + 20 HU) with similar anthrometric Z-scores between groups (p>0.10). ➢ Change in sVCAM-1 and MCP-1, but not sICAM-1, correlated with changes in PWVZ-ht and PWVZ-age in both univariate and adjusted analyses (p<0.05 for all)(see figure 1)
Conclusion: ➢ Consistent correlation of sVCAM-1 and MCP-1 with vascular stiffness may indicate the mechanism of premature vascular disease in HIV-affected children. ➢ As overt vascular events are delayed for many years, these chemokines may be useful as early surrogate endpoint biomarkers in prospective research

Figure 1: Longitudinal change in sVCAM-1 and MCP-1 predict incident changes in pulse wave velocity (PWV), a sophisticated measure of arterial wall stiffness



Stated p-values are adjusted for the following confounders, which were fixed *a priori*: body mass index, fasted glucose, total and LDL cholesterol, triglycerides and serum cotinine (measures tobacco smoke exposure over past 48-72 hours)

825 VASCULAR HEALTH AND CEREBRAL BLOOD FLOW IN PERINATALLY HIV-INFECTED CHILDREN

Charlotte Blokhuis[1], Sophie Cohen[1], Henriëtte J. Scherpbier[1], Henk-Jan M. Mutsaerts[2], Joost C. Meijers[3], Neeltje A. Kootstra[2], Peter Reiss[4], Ferdinand Wit[4], Charlotte E. Teunissen[5], Dasja Pajkrt[1]
[1]Emma Children's Hosp/Academic Med Cntr, Amsterdam, Netherlands, [2]Academic Med Cntr, Amsterdam, Netherlands, [3]Sanquin Rsr, Amsterdam, Netherlands, [4]Stichting HIV Monitoring and Academic Med Cntr, Amsterdam, Netherlands, [5]VU Univ Med Cntr, Amsterdam, Netherlands

Background: Despite effective virological suppression with cART, children perinatally infected with HIV show neuropsychological dysfunctioning with underlying macro- and microstructural brain injury. The potential role of vascular comorbidity and cerebral blood flow (CBF) in these deficits is unclear. This study aimed to assess whether CBF and vascular disease biomarkers were associated with cerebral and cognitive deficits in HIV-infected children.
Methods: This cross-sectional study included 36 cART-treated perinatally infected children aged 8-18 years from the Academic Medical Center in Amsterdam, and 37 age-, sex-, ethnicity- and socio-economic status-matched uninfected controls. We measured markers of inflammation, endothelial activation (using MesoScale Discovery), and coagulation (using enzyme-linked immunosorbent assays) in blood samples from all participants and in cerebrospinal fluid (CSF) from HIV-infected participants. Using 3-Tesla MRI, we determined CBF (using arterial spin labeling), gray matter (GM) volume, white matter (WM) lesion volume, and WM diffusivity (using diffusion tensor imaging). We explored whether CBF and vascular health markers were associated with MRI abnormalities, and cognitive performance (among others intelligence, processing speed, and visuomotor integration) in HIV-infected children using linear and ordered logistic regression analyses.
Results: HIV-infected children showed higher CBF in WM, caudate nucleus, putamen, nucleus accumbens and thalamus, as well as higher blood levels of CRP and sVCAM-1. Blood and CSF levels of CRP, sVCAM-1, and sICAM-1 were strongly correlated (Table 1). Higher levels of CRP were associated with higher WM mean diffusivity (blood: coef=2.09; P=.029; CSF: coef=2.27; P=.029), and lower GM CBF was associated with higher WM lesion volume (coef=-0.053; P=.001). Vascular markers were not associated with GM volume, WM lesion volume, or CBF. Among cognitive outcomes, only higher blood sVCAM-1 was strongly associated with poorer visuomotor integration (coef=-17.6; P=<.001).
Conclusion: In HIV-infected children, lower GM CBF, and increased inflammation and endothelial activation were associated with WM injury and visuomotor integration. Vascular disease may thus play a role in pediatric HIV-associated cerebral and cognitive deficits. Longitudinal evaluation is warranted to assess whether CBF changes, inflammation and endothelial activation negatively affect white matter health and cognitive performance in this population over time.

826 NEUROPSYCHOLOGICAL OUTCOMES IN A TWO YEAR AFRICAN-BASED PEDIATRIC OBSERVATIONAL STUDY

Michael J. Boivin[1], Miriam Chernoff[2], Barbara Laughton[3], Mutsa Bwakura-Dangarembizi[4], Portia Kamthunzi[5], Linda Barlow-Mosha[6], Avy Violari[7], Mark Cotton[3], Paul Palumbo[8], for the IMPAACT P1104s Study Team
[1]Michigan State Univ, East Lansing, MI, USA, [2]Harvard Univ, Boston, MA, USA, [3]Stellenbosch Univ, Cape Town, South Africa, [4]Univ of Zimbabwe, Harare, Zimbabwe, [5]Univ of North Carolina Proj–Malawi, Lilongwe, Malawi, [6]Makerere Univ–Johns Hopkins Univ Rsr Collab, Kampala, Uganda, [7]Univ of the Witwatersrand, Johannesburg, South Africa, [8]Dartmouth-Hitchcock Med Cntr, Lebanon, NH, USA

Background: We compared neuropsychological outcomes over 48 weeks for HIV-infected (HIV), HIV-uninfected perinatally-exposed (HEU), and HIV unexposed (HU) children at 6 sub-Saharan sites.
Methods: IMPAACT P1060 compared Nevirapine (NVP) versus Lopinavir/Ritonavir (LPVr)-based ART in HIV-infected children 6 to 35 months of age. P1104s enrolled these children at 5-11 years of age and will evaluate their neuropsychological performance at 3 time points over 2 years, compared to age-matched HEU and HU controls. Evaluation tools included the KABC-II cognitive ability, TOVA attention/impulsivity, BOT-2 motor proficiency tests, and parental BRIEF executive function questionnaires. Cohorts were compared using linear mixed models adjusted for site, child's age and gender. Personal and social characteristics (child's growth, development, disability, caregiver's education and household socio-economic status) were screened (p<0.20) and incorporated in selected analyses.
Results: 611 (246 HIV, 183 HEU, 182 HU) of the 615 enrolled at 6 sites (South Africa [3], Zimbabwe, Malawi, Uganda) were compared across 2 assessment points (weeks 0 and 48). Mean age at enrollment was 7.2 years, 47% were male, and 69% were in school. 94% of caregivers were biological mothers, 32% had completed high school, 22% received social grants, 38% lived in urban areas, 29% judged family income as sufficient.Unadjusted and adjusted comparisons were consistent. The HIV cohort performed significantly worse than HEU and HU cohorts at both weeks 0 & 48 on KABC-II, TOVA, BOT-2 overall performance (P<0.01), but not on the BRIEF, where the HIV cohort performed similarly or

better at week 48. HU and HEU cohorts were comparable. On most major outcomes, there was either little change or improvement within each cohort from week 0 to week 48. The magnitude of HIV cohort deficits were consistent across time, although HIV children improved less than the HEU and HU on KABC-II Planning (Story Completion, Pattern Reasoning). KABC scaled scores were worse for children with lower developmental, higher disability scores (P<0.01) and for families with social grants (P-values depend on outcome, most <0.01). They were better for children whose caregivers had completed high school (P <0.01).
Conclusion: Testing at more than one time point allowed us to evaluate the consistency of deficits in neuropsychological development for HIV-affected children. Other social and environmental factors can compound these deficits.

827 PLASMA HEME OXYGENASE-1 IS ASSOCIATED WITH COGNITIVE DECLINE IN CHILDREN WITH HIV

David Bearden[1], Alexander J. Gill[2], Paige L. Williams[3], Dennis L. Kolson[2], Laura Schankel[4], Allison Agwu[5], Russell B. Van Dyke[6], Steven D. Douglas[4], for the Pediatric HIV/AIDS Cohort Study (PHACS) Network and the IMPAACT 219C Study Team
[1]Univ of Rochester, Rochester, NY, USA, [2]Univ of Pennsylvania, Philadelphia, PA, USA, [3]Harvard Univ, Boston, MA, USA, [4]Children's Hosp of Philadelphia, Philadelphia, PA, USA, [5]The Johns Hopkins Univ, Baltimore, MD, USA, [6]Tulane Univ, Metairie, LA, USA

Background: Heme oxygenase-1 (HO-1) is an inducible, detoxifying enzyme that has emerged as a critical effector for limiting cellular injury associated with oxidative stress and inflammation within the central nervous system (CNS) in several disease states, including HIV infection. HO-1 protein expression has been described in association with neurocognitive impairment and elevated CNS markers of immune activation in adults with HIV, but has not previously been studied in children.
Methods: Data and plasma samples were taken from the IMPAACT 219C cohort and plasma HO-1 levels were measured by ELISA in two separate populations. First, samples from subjects aged 6-16 with perinatal HIV (PHIV, 74 pre-HAART and 75 post-HAART) were compared to age-matched HIV-exposed uninfected (HEU) controls (n=24). In a second 219C population, PHIV subjects with neurocognitive decline (defined as a sustained drop in full scale IQ of 15 or more points on the WISC3 or WISC4 during the period of the study) were compared to PHIV controls without decline (n=65 per group) using adjusted conditional logistic regression models to account for matching.
Results: Plasma HO-1 levels were significantly elevated in PHIV subjects compared to HEU controls (mean 3.59 vs. 2.88, p=0.04). This difference was most pronounced in subjects prior to initiation of HAART (mean=3.71 vs. 2.88, p=0.01). HO-1 levels decreased after HAART initiation, and in the post-HAART group HO-1 was not significantly different than in controls (3.48 vs. 2.88, p=0.07). HO-1 levels correlated negatively with CD4 T-cell count (p = 0.04), and positively correlated with markers of macrophage activation, including sCD163 (p=0.001), sCD14 (p=0.04), and tumor necrosis factor receptor 1 and 2 (p<0.001). In the second study population, PHIV subjects in the highest quartile of HO-1 had increased risk of neurocognitive decline vs. those in the bottom three quartiles (OR 5.0, 95% CI 1.1-22.1, p=0.04). This association was significant after adjusting for age, race, sex, viral load, and CD4 count.
Conclusion: These results demonstrate a significant increase in HO-1 plasma levels in HIV infection and an association between HO-1 levels and cognitive decline. Plasma HO-1 may represent a novel peripheral marker of HIV neuropathogenesis.

828 BIOMARKERS OF COGNITIVE DECLINE IN PERINATALLY INFECTED CHILDREN WITH HIV

David Bearden[1], Alexander J. Gill[2], Paige L. Williams[3], Dennis L. Kolson[2], Laura Schankel[4], Allison Agwu[5], Russell B. Van Dyke[6], Steven D. Douglas[4], for the Pediatric HIV/AIDS Cohort Study (PHACS) Network and the IMPAACT 219C Study Team
[1]Univ of Rochester, Rochester, NY, USA, [2]Univ of Pennsylvania, Philadelphia, PA, USA, [3]Harvard Univ, Boston, MA, USA, [4]Children's Hosp of Philadelphia, Philadelphia, PA, USA, [5]The Johns Hopkins Univ, Baltimore, MD, USA, [6]Tulane Univ, Metairie, LA, USA

Background: Cognitive impairment is common in children with perinatally acquired HIV (PHIV). An association between immune activation, inflammation and cognitive impairment has been described in adults with HIV but there is limited data in PHIV children.
Methods: Data and plasma samples were obtained from IMPAACT 219C PHIV youth ages 6-16. 13 biomarkers of immune activation and inflammation were measured in plasma using ELISA or multiplex assays. PHIV youth with neurocognitive decline (defined as sustained drop in WISC3 or WISC4 full scale IQ ≥ 15 points during study follow-up) were compared to age-matched PHIV youth without decline (n=65 per group). Where possible, two samples were measured for each PHIV subject: one at the time of testing showing decline, and the other at the last assessment before the decline (baseline). Median interval between time points was 130 weeks (IQR 111-156 weeks.) Control samples were age-matched to both time points. Due to correlations between biomarkers, factor analysis was performed for variable reduction, and both unadjusted and adjusted linear and conditional logistic regression models were constructed to investigate associations between each factor and decline.
Results: Cases and controls were well matched on age and sex, but cases were more likely to be of Hispanic race, and had lower CD4 counts and higher viral loads. In the univariate analysis, higher levels of IL-8 and interferon gamma at baseline, and higher levels of sCD163 at time of decline were significantly associated with cognitive decline, as was an increase over time in CD40 ligand, CRP, and sCD14 (all p<0.05). Heme oxygenase-1 (HO-1) was significantly associated with the outcome (p=0.04), but had a high level of uniqueness in the factor analysis and thus was analyzed separately. In the multivariable analysis, a factor at baseline characterized by Tumor Necrosis Factor Receptor 1 and 2 (TNFR1, TNFR2), and IL6 was significantly associated with cognitive decline (β=0.19, p=0.003), as was a factor at time of decline characterized by CRP, TNF-alpha, TNFR1 and TNFR2 (β=0.06, p=0.001). This association persisted in a multivariable linear regression model after adjusting for age, race, sex, viral load, and CD4 count.
Conclusion: These results demonstrate a significant association between inflammatory biomarkers and cognitive decline in children with HIV. Further studies are necessary to confirm these associations and identify interventions that could reduce risk of cognitive decline.

829 MONOCYTES MAY BE ANTIVIRAL TARGETS TO LIMIT PEDIATRIC HIV-RELATED CNS MANIFESTATIONS

Erica L. Johnson, Dominika Swieboda, Christina Gavegnano, Rana Chakraborty, Raymond F. Schinazi
Emory Univ, Atlanta, GA, USA

Background: In 2015, approximately 150,000 new HIV-1 infections occurred in children. Combination antiretroviral therapy (cART) has decreased the risk and severity of HIV-1-associated neurocognitive disorders (HAND), however, current cART regimens neither eradicate HIV-1 and rarely improve CNS manifestations, underscoring the inability of most ARVs to penetrate the CNS and mitigate pro-inflammatory events associated with viral replication . A hallmark of CNS HIV-1 infection is increased activation of mononuclear phagocytes (MPs), conferring HIV-induced inflammation. These cells are poorly characterized in neonates particularly in regard to HIV-1 susceptibility and ARV pharmacology.
Methods: Cord blood was collected from 12 HIV-1 and HBV seronegative women (>18 years) at Emory Midtown and Grady Hospitals in Atlanta, GA. Peripheral blood was obtained from healthy adult donors. MPs were treated with various concentrations of AZT, 3TC, ABC, NVP, TDF, and RAL for 2 hr prior to or 6 days post infection with HIV-1BaL and maintained overtime before quantification of viral replication by HIV-1 p24, cytokine levels and cellular markers (CCR5, CD16, CD163, and HLA-DR) by FACS analysis. Data were analyzed using Student's t-test and Mann-Whitney test.
Results: Fetal monocyte-derived macrophages (MDM) were found to be more susceptible to HIV-1 than adult MDMs, and CCR5 was significantly upregulated on fetal CD14+ monocytes and MDM compared to adult subsets. CD163, a receptor that improves adherence of activated monocytes prior to CNS migration, is upregulated on fetal CD14+ compared to adults. In vitro HIV-1 infection of fetal monocytes induced further CCR5 and HLA-DR upregulation, along with CD16, which plays a role in monocyte trafficking to the brain. The overall fraction of fetal CD14+CD16+CCR5+ monocytes is also upregulated by HIV-1. All ARVs inhibited acute HIV-1 infection of fetal macrophages, however the antiviral potency of AZT, 3TC and ABC was significantly (p< 0.05) decreased in the fetal MDMs compared to the adults (EC50 0.1–1.4 μM versus 0.02-0.2 μM). In chronically-infected cells, TDF exhibited potent viral inhibition (EC90 2.25 μM). The ARVs had no effect on surface expression of CCR5 or relevant activation markers in uninfected or HIV-1-infected fetal macrophages.

Conclusion: Neonatal MPs may be important in the pathogenesis of pediatric AIDS and serve as a target to offset HAND in children. Current pediatric cART regimens may not be sufficient, therefore, novel therapeutics need to be developed.

830 CENTRAL NERVOUS SYSTEM PENETRATION OF ANTIRETROVIRAL THERAPY IN HIV-INFECTED CHILDREN

Malon V. Hof[1], Charlotte Blokhuis[2], Sophie Cohen[2], Henriëtte J. Scherpbier[2], Ferdinand Wit[3], Marcel Pistorius[1], Neeltje A. Kootstra[1], Charlotte E. Teunissen[4], Ron Mathot[1], Dasja Pajkrt[2]
[1]Academic Med Cntr, Amsterdam, Netherlands, [2]Emma Children's Hosp/Academic Med Cntr, Amsterdam, Netherlands, [3]Stichting HIV Monitoring and Academic Med Cntr, Amsterdam, Netherlands, [4]VU Univ Med Cntr, Amsterdam, Netherlands

Background: Despite optimal responses to combination antiretroviral therapy (cART), HIV-infected children continue to show neurocognitive deficits with macro- and microstructural brain injury and signs of neuroinflammation. Subtherapeutic central nervous system (CNS) drug levels may contribute to neuropathology in these children. Also, chronic HIV infection has been associated with blood-brain barrier (BBB) breakdown. Pediatric data on cerebrospinal fluid (CSF) cART penetration is scarce. We evaluated cART levels in CSF and plasma and assessed whether CSF drug penetration is related to BBB function, intrathecal inflammation and immune activation in HIV-infected children on suppressive cART.
Methods: This cross-sectional study included perinatally HIV-infected children between 8-18 years old from the Academic Medical Center, Amsterdam. CSF was collected from a subset of patients stable on cART in whom a lumbar puncture was indicated as part of routine patient care. CSF and plasma total drug levels were measured and CSF penetration was assessed using each drug's CSF-to-plasma concentration ratio. BBB permeability was defined as the albumin CSF-to-plasma ratio. Intrathecal inflammation/immune activation markers included CRP, IL-6, soluble CD14 and soluble CD163. Potential associations were explored using Spearman's rank correlation.
Results: Of the 36 perinatally HIV-infected children included, paired CSF and serum samples were available from 20 cART-treated children. All participants were virologically suppressed in blood and CSF. The median CSF penetration of lopinavir (0.12%), efavirenz (0.36%) and tenofovir (1.95%) was poor compared to lamivudine (34%), emtricitabine (35%), nevirapine (48%), zidovudine (52%) and abacavir (56%) (Figure 1). CSF penetration of lamivudine, abacavir, efavirenz and lopinavir was not associated with age or BBB permeability. There was no correlation between CSF penetration of these antiretrovirals and inflammation/immune activation markers soluble CD14, soluble CD163, CRP and IL6 in CSF.
Conclusion: Similar to adult patients, CSF penetration of lopinavir, efavirenz and tenofovir is poor in pediatric HIV. We found no associations between CSF penetration of cART and BBB permeability or inflammatory markers in CSF. This suggests cART-specific properties may be more important in CSF penetration than the studied host related factors. Alternatively, HIV related neuroinflammation in children might be at such a low grade, that BBB permeability remains unaltered.

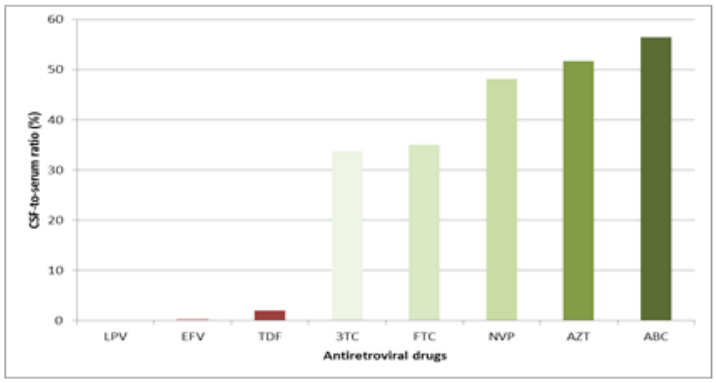
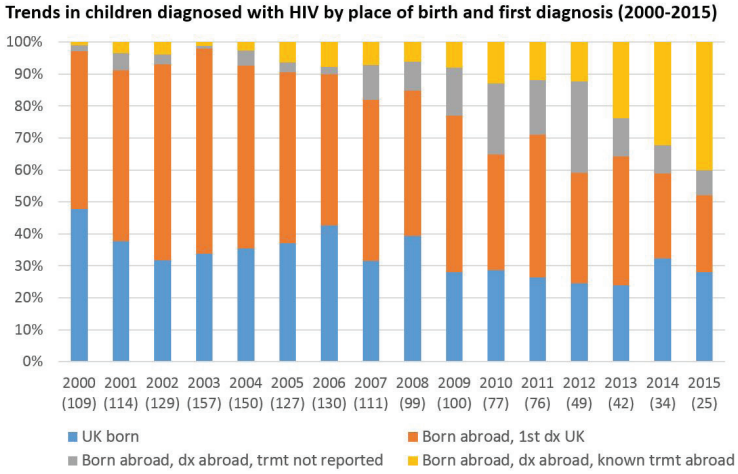


Figure 1: Penetration of different antiretrovirals in CSF in children
Abbreviations: LPV = lopinavir; EFV = efavirenz; TDF = tenofovir; 3TC = lamivudine; FTC = emtricitabine; NVP = nevirapine; AZT = zidovudine; ABC = abacavir

831 CURRENT TRENDS IN CHILDREN WITH HIV DIAGNOSED IN THE UK AND IRELAND

Helen Peters, Kate Francis, Intira J. Collins, Ali Judd, Claire Thorne
Univ Coll London, London, UK

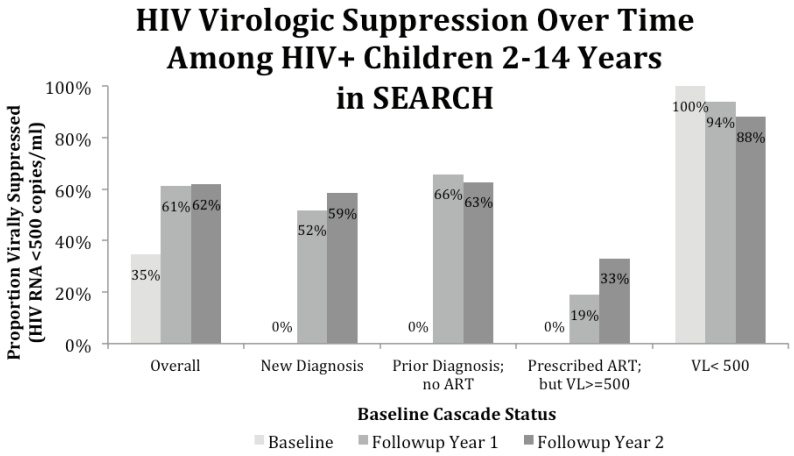
Background: Incidence of mother-to-child HIV transmission has declined to <0.5% among diagnosed HIV+ pregnant women delivering in the UK/Ireland (UK/I), however most children living with HIV in UK/I were born abroad. We describe evolving trends in the characteristics of children at diagnosis in the UK/I from 2000-15.
Methods: All children (<16y) diagnosed with HIV are reported to the National Study of HIV in Pregnancy and Childhood through an active surveillance system, including infants and children born in the UK/I to diagnosed and undiagnosed mothers, plus children born abroad arriving in the UK/I with unknown or known HIV status. HIV status is reconfirmed after arrival in the latter. Children receiving paediatric HIV care in UK/I are followed in the Collaborative HIV Paediatric Study (CHIPS). We report characteristics at time of UK/I diagnosis among those diagnosed in 2000-15.
Results: Overall 1,528 children were diagnosed, annual numbers peaking at 150 during 2003-4 and stabilising at 30-50 per year since 2012 (p<0.001). 53% (804/1517) were female, 97% (1369/1408) reported as vertically infected and 65% (999/1528) born abroad (mainly sub-Saharan Africa), with this proportion increasing to 73% (109/150) from 2012. Among UK/I-born children born <2005, median age at diagnosis was 9mth (IQR 3mth-3y) vs 3mth (0.5y-1y) for those born ≥2010; among children born abroad median ages were 6yr (3-9y) vs 3yr (2-3y) respectively. The proportion of children with CDC C or B symptoms at UK/I diagnosis declined from 26% (132/509) and 34% (171/509) of those diagnosed in 2000-3, to 2% (3/150) and 11% (17/150) since 2012 respectively (p<0.001, for both trends). Of children born abroad 23% (228/999) were diagnosed before entering the UK/I, increasing over time (8% in 2000-3 to 55% ≥2012, p<0.001). By arrival 49% (112/228) were ART experienced [Figure], median age at ART start was 6y (IQR: 2y, 9y). Of 88/112 with known regimen, 76% initiated on a NNRTI and 14% a boosted-PI based regimen. Of patients linked in CHIPS with ART data after entry (73/88), 23% switched to a new regimen (change across drug/within PI class) within 1 year of arrival in UK/I.
Conclusion: Annual numbers of newly diagnosed children in the UK/I continue to decline, with increasing proportions of children born abroad and treatment experienced at arrival. Median age at diagnosis has decreased significantly, although remains higher for children born abroad. An encouraging trend is the declining proportion presenting with CDC B/C symptoms.



832 BASELINE POPULATION HIV CASCADE AND 2-YR OUTCOME OF HIV+ CHILDREN IN THE SEARCH TRIAL

Laura B. Balzer[1], Norton Sang[2], Albert Plenty[1], Teri Liegler[1], Craig Cohen[1], Elizabeth A. Bukusi[2], Moses R. Kamya[3], Maya L. Petersen[4], Diane V. Havlir[1], Theodore Ruel[1]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Kenya Med Rsr Inst, Nairobi, Kenya, [3]Makerere Univ, Kampala, Uganda, [4]Univ of California Berkeley, Berkeley, CA, USA

Background: SEARCH (NCT01864603) is a community randomized trial evaluating an HIV test-and-treat strategy in rural Uganda and Kenya. We evaluated the population-level HIV care cascade among children (2-14years) at baseline and interim outcomes of HIV+ children receiving streamlined ART delivery in the 16 intervention communities.
Methods: At baseline residents were enumerated through a household census and HIV-serostatus was determined by multi-disease health campaigns and targeted home-based testing of at-risk (mother's HIV-status unknown/positive) non-attendee children. Streamlined ART including patient-centered care and viral load counseling was universally offered. HIV RNA levels were measured at health campaigns or with home-based testing at baseline and after 1 and 2 years. With multivariable adjustment for untested children, we estimated at baseline: the prevalence of HIV; the proportion of HIV+ children previously diagnosed; of those, the proportion receiving ART; and of those, the proportion virally suppressed (HIV RNA< 500 copies/ml). For HIV+ children at baseline, we estimated HIV viral suppression probabilities over 2 years, adjusted for missing measures and right-censoring with targeted maximum likelihood estimation.
Results: Of 70,511 baseline stable resident (in community >6mo/past year) children, we ascertained HIV status on 89%; 665 were HIV+. The adjusted baseline HIV prevalence was 1.1% (95%CI:1.0-1.2%) overall. Before the SEARCH intervention, 64% (95%CI:59-70%) of infected children had known status; of these, 84% (95%CI:79-89%) had been prescribed ART. Among those prescribed ART, 64% (95%CI:56-74%) were virally suppressed at baseline. The estimated population-level viral suppression among all HIV+ children was 35% (95%CI:29-41%) at baseline. Two years into SEARCH, the probability of viral suppression was 62% (95%CI:58-66%) overall, 59% (95%CI:51-66%) for new diagnoses, and 63% (95%CI:51-74%) for previous diagnoses newly initiating ART, but only 33% (95%CI:23-44%) among children on ART but not suppressed at baseline. 12% (95%CI:6-18%) of children suppressed at baseline were viremic at 2 years (Figure).
Conclusion: Within 2 years, SEARCH increased overall HIV viral suppression among HIV+ children from 35% to 62% with gains driven by new diagnoses and initiation of treatment in ART-naïve children. However, additional strategies to address retention, adherence, and drug resistance are needed to achieve and maintain higher rates of viral suppression.



833 COST-EFFECTIVENESS OF HIV SCREENING: US ADOLESCENTS AND YOUNG ADULTS (AYA) AGED 13–24

Anne M. Neilan[1], Richard Dunville[2], Cheryl B. Ocfemia[2], Joshua A. Salomon[3], Li Yan Wang[2], Katherine K. Hsu[4], Elizabeth DiNenno[2], Rochelle P. Walensky[1], Robert A. Parker[1], Andrea L. Ciaranello[1]
[1]Massachusetts General Hosp, Boston, MA, USA, [2]CDC, Atlanta, GA, USA, [3]Harvard SPH, Boston, MA, USA, [4]Massachusetts Dept of Pub Hlth, Boston, MA, USA

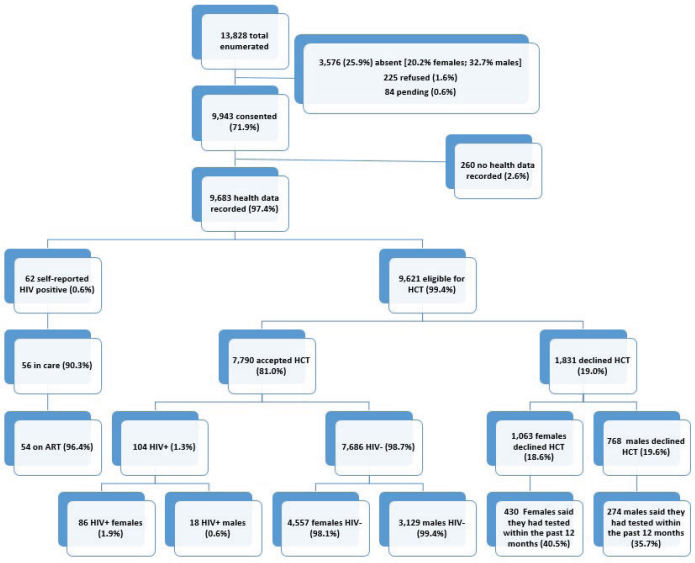
Background: Of new HIV diagnoses in the US, 22% occur in AYA. Despite 2006 CDC guidelines for one-time HIV screening, few AYA are screened. We projected the clinical and cost-effectiveness of HIV screening in AYA ages 13 to 24 without identified HIV risk factors.

Methods: We simulated a cohort of 12 year-olds who faced age-specific risks of HIV infection, ranging between 0.6 and 71.3 per 100,000 person-years, peaking at age 24. We examined a one-time screen ($36) at age 15, 18, 21, 25, or 30, each in addition to current US screening practices (13% ever screened by age 18, 30% by age 24). We used published data on the HIV care continuum: screen acceptance (80%); linkage to care and ART initiation (76%); and disease progression; ART response; and HIV care costs. Model outcomes included CD4 count at diagnosis; HIV care continuum care outcomes (proportions HIV-diagnosed, linked to care, retained in care, and virally suppressed); life expectancy and lifetime costs; and incremental cost-effectiveness ratios (ICERs) in $/year of life saved (YLS). In sensitivity analyses, we varied HIV incidence, current practice screening rates, linkage rates, and screen cost.
Results: All one-time screens detected only a small proportion of lifetime infections (0.1-10.3%), most of which occurred after age 24. An additional one-time screen at age 25 compared to current US screening practice modestly reduced the proportions of all HIV-infected persons being diagnosed via OI (35 vs. 39%) and never being diagnosed during their lifetime (11 vs. 12%). A screen at age 25 also led to the most favorable continuum of care outcomes at age 25 compared to current US screening practice, including proportion diagnosed (77 vs. 51%), linked to care (71 vs. 50%), retained in care(61 vs. 34%) and virally suppressed (49 vs. 32%). A screen at age 25 provided the greatest clinical benefit, and was cost-effective (ICER $61,900/YLS) by US standards (<$100,000/YLS) compared to the next most effective screen. In sensitivity analyses, this finding was robust to wide ranges of HIV incidence, current practice screening rates, linkage rates, and screen cost; it was most sensitive to peak age of incidence.
Conclusion: For AYA in the US general population, a one-time routine HIV screen at age 25, after the peak of incidence, would optimize clinical outcomes and be cost-effective. Focusing screening on AYA ages 18 or younger is a less efficient use of a one-time screen among AYA than screening at a later age.

834 COMMUNITY INTERVENTION IMPROVES ADOLESCENT HIV STATUS KNOWLEDGE: HPTN 071 STUDY ZAMBIA

Kwame Shanaube[1], Mwate J. Chaila[1], David Macleod[2], Ab Schaap[1], Sian Floyd[2], Conred Jani[1], Graeme Hoddinott[3], Richard Hayes[2], Sarah Fidler[4], Helen Ayles[5]
[1]Zambart, Lusaka, Zambia, [2]London Sch of Hygiene and Trop Med, London, UK, [3]Univ of Stellenbosch, Cape Town, South Africa, [4]Imperial Coll London, London, UK, [5]London Sch of Hygiene and Trop Med, Lusaka, Zambia

Background: The PopART for Youth (P-ART-Y) study aims to evaluate the acceptability and uptake of a HIV prevention package, including universal HIV testing and treatment (UTT), among young people. It also assess the need for specific youth targeted interventions in the context of community wide UTT. The study's primary outcome is uptake of HIV counselling and testing (HCT) in the previous 12 months among 15-19 year old adolescents. The study is nested within the HPTN071 (PopART) trial, a 3-arm community randomized study in 21 communities in Zambia and South Africa. Arm A of the study provides the "full" combination HIV prevention package including home based HCT which is delivered in annual rounds by Community HIV Care Providers (CHiPs) to all household members irrespective of age.
Methods: Adolescents contacted in their homes were offered participation in the PopART intervention which included HCT and linkage to prevention and treatment. Uptake of the intervention was recorded electronically by the CHiPs during household visits. We present data on the uptake of HCT in 4 Arm A communities in Zambia among adolescents aged 15-19 years. Data were analysed for the second annual round of the intervention, October 2015 to June 2016.
Results: A total of 13,828 adolescents were enumerated of which 71.9% (n=9,943) agreed to participate in the intervention; 1.6% (n=225) refused and 25.9% (n=3,576) were not found at home (figure 1). More males (2,052/6,267; 32.7%) than females (1,524/7,561; 20.2%) were not found at home. Acceptance of HCT was similar in females, 81.4% (4,643/5,706) and males, 80.4% (3,147/3,915). HIV prevalence as tested by the CHiPs was 1.3% (104/7,790) and varied by sex (Males, 0.6%; Females, 1.9%). Following the CHiPs' visit, using the definition that they either reported they were HIV positive (n=62), or were tested by the CHiPs (n=7,790) or reported to have been tested in the previous 12 months (n=704 among those who declined, and n=1803 among those who accepted, HCT by CHiPs), knowledge of HIV status increased from 26.5% (2569/9,683) to 88.4% (8,556/9,683).
Conclusion: Through a home-based approach of offering a combination HIV prevention package the percentage of adolescents who knew their HIV status increased from ~27% to ~90%, among those who were contacted and consented to participate. Delivering a community level door-to-door combination HIV prevention package is acceptable but complementary strategies tailored to finding more males maybe required.



835 A NOVEL MODEL OF COMMUNITY COHORT CARE FOR HIV-INFECTED ADOLESCENTS IMPROVES OUTCOMES

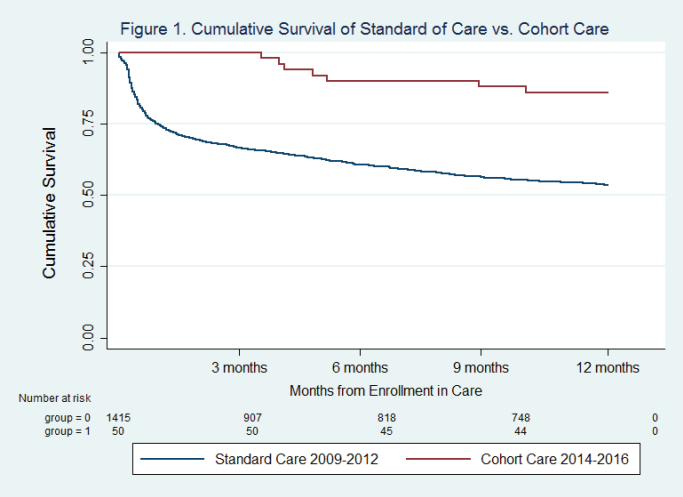
Lindsey Reif[1], Rachel Bertrand[2], Vanessa Rivera[3], Bernadette Jospeh[2], Benedict Anglade[2], Jean W. Pape[3], Daniel Fitzgerald[3], Margaret McNairy[3]
[1]Columbia Univ, New York, NY, USA, [2]GHESKIO, Port-au-Prince, Haiti, [3]Weill Cornell Med, New York, NY, USA

Background: Adolescents account for 40% of new HIV infections in Haiti and have worse outcomes than other age groups. A novel model of community cohort care was implemented to improve retention and viral load suppression among HIV+ adolescents in Port-au-Prince, Haiti. The intervention addressed barriers of social isolation, stigma, and long visits reported among adolescents.
Methods: Adolescents 10-20 years, who newly tested HIV+ were enrolled in cohorts of 8-10 peers, stratified by age group – 10-15 and 16-20. Cohorts met monthly for integrated clinical care, counseling, and social activities in a community setting. All clinical services (laboratory tests, ART initiation/management, and pharmacy refills) were performed during the cohort meeting by a nurse; group counseling was provided by a peer counselor. Retention at 12 months was defined as being alive with a visit between 11 and 13

months from enrollment. Viral load suppression was defined as <1000 copies/ml. Retention was compared between cohort care participants and teens receiving standard care at the Adolescent Clinic between 2009 and 2012. Kaplan-Meier methods estimated incidence of retention.

Results: Fifty adolescents enrolled in cohort care between Nov 2014-Sept 2015 – 80% females, median age of 18 (IQR 15-19), and median CD4 count 537 cells/mL (IQR 339-805). In standard care, 710 adolescents enrolled in care from Jan 2009-Dec 2012 – 80% female, median age 18 (IQR 16-19), and median CD4 count 414 cells/mL (IQR 238-604). In cohort care, 100% of adolescents were assessed for ART eligibility on the day of testing, 22 (44%) were eligible for ART with CD4 <500 cells/uL, and 100% started ART with median time to initiation of 0 days. In standard care, 462 (65%) adolescents were assessed for eligibility, 330 (46%) were eligible with CD4 <350 cells/uL, and 305 (92%) started ART with median time to initiation of 20 days. At 12 months from enrollment, 86% (95% CI: 74-92) of adolescents in cohort care were retained compared to 66% (95% CI: 63-67) in standard care (p<.001) (Fig 1). In cohort care, among those with a viral load measurement 6-12 months from ART initiation, 5/19 (26%) had viral suppression. Viral load was not routinely collected prior to 2016.

Conclusion: Community-based cohort care for HIV+ adolescents in Haiti significantly improved retention by an absolute difference of 20% and decreased time to ART initiation. Viral suppression remains poor indicating a need for increased efforts to improve adherence to ART among adolescents.



836 LOCAL SOCIAL NETWORKS PREDICT RETENTION & SUPPRESSION IN YOUNG WOMEN IN SEARCH TRIAL

Lillian Brown[1], Wenjing Zheng[2], James Ayieko[3], Asiphas Owaraganise[4], Florence Mwangwa[4], Tamara D. Clark[1], Edwin D. Charlebois[1], Moses R. Kamya[5], Diane V. Havlir[1], Maya L. Petersen[2]

[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Univ of California Berkeley, Berkeley, CA, USA, [3]Kenya Med Rsr Inst, Nairobi, Kenya, [4]Infectious Diseases Rsr Collab, Kampala, Uganda, [5]Makerere Univ, Kampala, Uganda

Background: Young women in sub-Saharan Africa are at high risk of HIV infection, poor retention in HIV care, and virologic failure on ART. Peer support between HIV+ women may improve care cascade outcomes, but community-level social network data to inform network-based interventions are limited. We used comprehensive social network and HIV testing data from the intervention arm of the SEARCH test-and-treat trial (NCT01864603) to evaluate whether having HIV+ social network contacts predicted retention and viral suppression among young HIV+ Kenyan women.

Methods: All adult (≥ 15) residents in 3 rural Kenyan communities were enumerated during a baseline census and asked to name social contacts that provided support in five domains: health, money, emotional support, food, and free time. Named contacts were matched to enumerated residents to build social networks among 15,162 stable adult residents; 85% of these residents were tested for HIV at baseline. We evaluated whether having gender-specific social network contacts with HIV predicted retention in care (not more than 90 days late to scheduled clinic visit) and viral suppression (HIV RNA < 400 copies/ml) at 12 months among young (15-24 years) HIV+ women who linked to care following baseline testing. We used Cox proportional hazards models and logistic regression with robust standard errors to adjust for prior HIV care and pre-ART CD4 count.

Results: Baseline HIV prevalence was 14% among adults and 10% among young women. Of the 162 young women who linked to HIV care, 31% of young women named ≥1 HIV+ contact in any domain, 17% named ≥1 HIV+ female contact in any domain, and 6% named ≥1 HIV+ female contact in the health domain [Table]. At 12 months, 83% (95% CI: 76,88) of young women who linked were retained in care and 70% (95% CI: 62,78) of those in care were virally suppressed. Women with an HIV-infected female contact were more likely to be retained in care (aHR 2.63; 95% CI: 1.10, 14.3). Among those retained, young women with any HIV+ contact (aOR 3.2; 95% CI: 1.1,9.8), and specifically, those with a female HIV+ health contact (aOR 3.5; 95% CI: 1.1,12.7) were more likely to be suppressed.

Conclusion: HIV+ female peers in the local social networks of young Kenyan women may support their engagement in HIV care. Interventions that strengthen existing social connections between HIV-infected women and increase social support in the health sector may contribute to improved clinical outcomes.

837 TEENAGE PREGNANCY: A CRITICAL BARRIER TO RETENTION ON ANTIRETROVIRAL THERAPY

Harriet Nuwagaba-Biribonwoha[1], Agnes Kiragga[2], Constantin Yiannoutsos[3], Beverly Musick[3], Kara K. Wools-Kaloustian[3], Elaine J. Abrams[1], Batya Elul[4], for the International Epidemiologic Databases to Evaluate AIDS (IeDEA) East Africa Collaboration

[1]ICAP at Columbia Univ, New York, NY, USA, [2]Makerere Univ, Kampala, Uganda, [3]Indiana Univ, Indianapolis, IN, USA, [4]Columbia Univ, New York, NY, USA

Background: Retention on ART is essential for reducing HIV-related morbidity and mortality. We compared loss to follow-up (LTFU) among adolescents and adults initiating ART in East Africa.

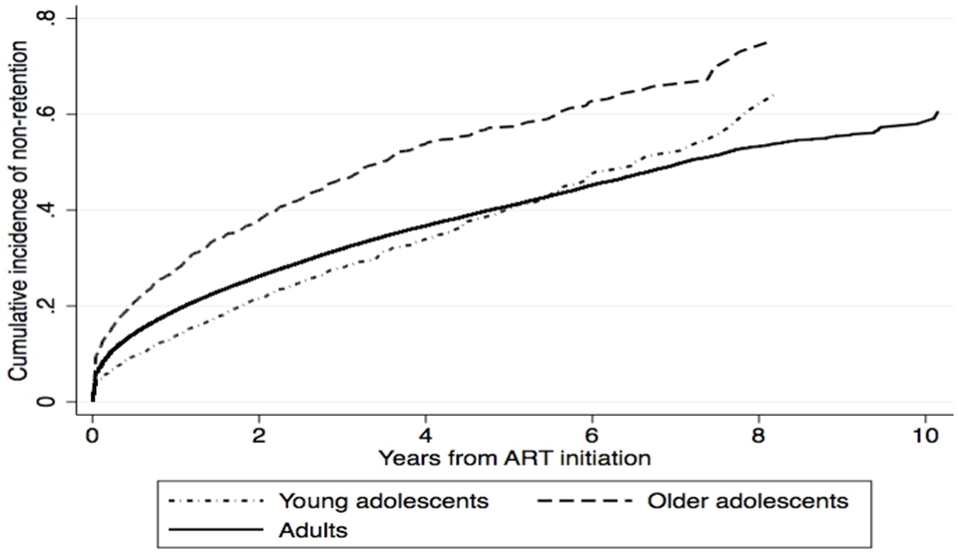
Methods: We conducted a retrospective cohort analysis using routinely collected clinical data on patients enrolling into HIV care as young adolescents, YA (10-14 years), older adolescents, OA (15-19 years) and adults (20 years and older). We analyzed data from 2000-2012 at 33 health facilities participating in the IeDEA collaboration in Kenya, Uganda and Tanzania. We compared adolescent and adult LTFU (no clinic visit for 3 months) after ART initiation using competing risk methods. Patient- and site-level correlates of LTFU were examined using the Fine and Gray competing regression model, with death as a competing risk.

Results: A total of 2,709 YA, 4,179 OA and 154,792 adults were enrolled, the majority female (56% YA, 84% OA, and 67% adults). One percent of YA, 27% OA and 9% adults were pregnant at enrolment. Median CD4 count (IQR) at ART initiation was 179 cells/μL (51-328) among YA, 186 cells/μL (72-329), among OA and 146 cells/μL (63-236) among adults. Cumulative probability of LTFU at 24 months after ART initiation was highest among OA (32%), lowest among YA (19 %), and 21% among adults, Figure 1. Compared to YA, the OA had 50% higher risk of LTFU adjusted Hazard Ratio (aHR) 1.50 (95% Confidence Interval, CI: 1.32-1.71), P<0.001, and aHR 1.04 (0.94 – 1.16) P=0.252 among the adults. Among OA,

the highest hazard ratios for LTFU were observed among pregnant females (aHR 1.90, 95% CI 1.50-2.42) and non-pregnant females (aHR 1.57 95% CI 1.19-2.08), when compared to males. OA had lower hazard of LTFU if enrolled at health facilities which provided group adherence counselling (aHR 0.61, 95% CI: 0.53-0.70), and if they attended tertiary health facilities vs. primary health facilities (aHR 0.64, 95% CI: 0.46-0.90). Availability of adolescent-specific clinics and outreach services were not statistically significantly associated with LTFU after ART initiation.

Conclusion: Older adolescents enrolling in care experienced higher risk of LTFU compared to younger adolescents and adults, and should be targeted with supportive interventions such as group counselling. Specific retention interventions are needed for teenage girls, especially those who are pregnant at enrolment into HIV care.

Figure 1: Cumulative incidence of lost to follow-up (with death as a competing risk) among adolescents and adults in initiating ART at IeDEA East Africa clinics.



838 IMPACT OF SUBSTANCE USE, MENTAL HEALTH, AND AGE ON RETENTION AND VIRAL SUPPRESSION

Brian C. Zanoni[1], Sara Lammert[1], Jessica Haberer[1], Gregory K. Robbins[1], Heidi M. Crane[2], Michael J. Mugavero[3], Katerina Christopoulos[4], Kenneth H. Mayer[5]
[1]Massachusetts General Hosp, Boston, MA, USA, [2]Univ of Washington, Seattle, WA, USA, [3]Univ of Alabama at Birmingham, Birmingham, AL, USA, [4]Univ of California San Francisco, San Francisco, CA, USA, [5]Fenway Hlth, Boston, MA, USA

Background: Adolescents and young adults living with HIV in the United States have lower retention in care and viral suppression rates than older adults. The extent to which modifiable factors such as substance use, mental health and lack of insurance contribute to these outcomes has not been fully characterized.

Methods: We evaluated the correlation of self-reported current substance use, moderate to severe anxiety and/or depression and lack of health insurance on retention in care and viral suppression among individuals initiating antiretroviral therapy (ART) between January 1, 2010 and September 30, 2014 at 6 centers in the United States as part of the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. We used univariable and multivariable logistic regression to evaluate the association between current substance use, moderate to severe anxiety and/or depression, insurance status, and categorical age (18-24, 25-49, 50+ years) on retention in care (2 visits within first year separated by ≥90 days) and viral suppression (viral load <200 copies/ml after 6 and 12 months on ART). We included interaction terms to evaluate for effect modification based on age.

Results: Among the 3,465 individuals in the CNICS cohort with self-reported outcomes, we found higher rates of current substance use, moderate to severe anxiety/depression and lack of health insurance in younger compared to older adults (Table). Current substance use was associated with lower retention in care (AOR=0.53; 95% CI 0.36 – 0.78; p<0.001), lower 6-month (AOR=0.51; 95% CI 0.28 – 0.93; p=0.029;) and 12-month (AOR=0.38; 95% CI 0.19 – 0.72; p=0.003) viral suppression rates. Despite these differences, there was no difference in retention in care, 6-month, or 12-month viral suppression rates among younger compared to older adults. Adjusting for substance abuse, anxiety/depression, and insurance status, age was not associated with lower retention in care or viral suppression. In addition, there was no effect modification based on age. There were no significant differences in primary outcomes when adjusting for baseline CD4 or time from initial linkage to ART initiation.

Conclusion: HIV programs such as the CNICS network which incorporate routine screening for mental health disorders and substance use show no difference in retention in care and viral suppression among youth compared to older adults. Incorporating screening may improve outcomes for HIV-infected youth in other settings.

	18 – 24 years n= 528	25 – 49 years n= 2486	50+ years n= 451	p-value
Current substance use	55% (96)	52% (505)	36% (64)	<0.001
Anxiety and/or depression	63% (122)	61% (672)	52% (116)	0.034
Uninsured	20% (107)	13% (322)	11% (48)	<0.001
Retained in care	81% (430)	82% (2029)	82% (268)	0.995
Viral suppression 6 months	90% (327)	91% (1540)	94% (283)	0.275
Viral suppression 12 months	88% (261)	91% (1229)	91% (221)	0.292

839 THE MACARTI STUDY: CLOSING THE GAPS IN HIV CARE AMONG YOUTH IN ATLANTA, GA

Andres Camacho-Gonzalez[1], Scott Gillespie[1], Lateshia Thomas-Seaton[2], Krystal Frieson[3], Sophia A. Hussen[1], Ashley Murray[4], Zaneta Gaul[6], Madeline Sutton[4], Chanda Graves[1], Rana Chakraborty[1]
[1]Emory Univ, Atlanta, GA, USA, [2]Children's Hlthcare of Atlanta, Atlanta, GA, USA, [3]Atlanta VA Med Cntr, Decatur, GA, USA, [4]Emory Univ, Atlanta, GA, USA, [5]CDC, Atlanta, GA, USA, [6]ICF Intl, Atlanta, GA USA

Background: Georgia ranks 5th among US states for new HIV diagnoses; black youth and young adults are disproportionately affected. Ensuring early diagnosis and HIV care are vital steps to decrease the HIV burden in Georgia, consistent with the National HIV/AIDS Strategy.
Methods: Newly identified HIV+ young people aged 18-24 years were enrolled into the Metropolitan Atlanta Community Adolescent Rapid Testing Initiative (MACARTI) intervention and compared to standard of care (SOC) participants. MACARTI combined a formative phase that informed a later strategy of non-traditional venue HIV testing, pre-test and post-test motivational interview sessions, and case management support. Demographic, behavioral, and clinical variables along with linkage (within 3 months of diagnosis) and retention rates (missed visit rate/100 visits) were collected. Means and standard deviations (SD) were calculated for continuous variables; frequencies and percentages with 95% confidence intervals (CI) are shown at baseline and at 12-month follow-up time. Clinical values were compared between arms using parametric and non-parametric statistical tests.
Results: Ninety-eight participants were enrolled; 49 each in the MACARTI and SOC arms; 85% were male; 91% were Black; mean age=21 years (SD:1.8). The MACARTI study screened 435 participants for an HIV-positivity rate of 11.3%. Overall 64% of participants were linked to care; linkage was higher for the MACARTI arm compared with SOC (88% vs. 41%, p≤0.001). Mean linkage time for MACARTI participants compared to SOC was 0.46 (IQR: 0.23-0.85) vs. 5.31 (IQR:1.35-17.03) months (p<0.001). Missed visit rates in the MACARTI arm were significantly lower than the SOC arm [14.4 (95% CI:10.3 – 19.8) vs. 26.1 (CI:20.8- 32.2) attended visits per 100 visits scheduled, respectively]. Mean CD4+ T-cell counts increased within both arms, however, values were significantly higher in the MACARTI arm at 12-month follow-up (474 vs. 278 cells/mm3; p=0.006). Also, mean HIV-1 RNA levels decreased in both arms at 12-month follow-up, with borderline significance across the MACARTI arms and SOC arm [79 vs. 283 copies/ml p=0.068 respectively].
Conclusion: The MACARTI intervention successfully identified and linked HIV-positive black youth to care in Atlanta. The intervention also decreased missed visit rates and improved CD4 counts and viral suppression rates. MACARTI may serve as an HIV linkage and care model for other areas with HIV-affected black youth.

840 RETENTION, ART USE, AND VIRAL SUPPRESSION AMONG YOUNG ADULTS NEWLY LINKED TO HIV CARE

Fidel A. Desir[1], Peter F. Rebeiro[2], Richard D. Moore[1], Heidi M. Crane[3], Karyn Gabler[4], Joseph B. Margolick[1], Ronald Bosch[5], Michael A. Horberg[6], Michael J. Silverberg[7], Keri N. Althoff[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Vanderbilt Univ, Nashville, TN, USA, [3]Univ of Washington, Seattle, WA, USA, [4]BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada, [5]Harvard Univ, Boston, MA, USA, [6]Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, [7]Kaiser Permanente Northern California, Oakland, CA, USA

Background: Retention in care (RIC), antiretroviral therapy use (ART), and HIV viral suppression (VS) are critical milestones for persons living with HIV (PLWH) to achieve soon after an HIV diagnosis. The United States (US) National HIV/AIDS Strategy specifies subgroups of particular importance, including young black men who have sex with men (MSM), black women, and Hispanics. Our objective was to examine trends in these indicators among important subgroups of young adults newly linked to care in the US.
Methods: Young adults (18-<30 years) with ≥1 CD4 or HIV RNA measure within 5 years of linking to care in 15 US clinical cohorts in the North American AIDS Cohort Collaboration on Research and Design were included. We evaluated 3 Department of Health and Human Services indicators: 1) RIC was the percentage of patients with ≥1 HIV care visit in January to June who also had visits in each following semester of a 24-month period, ≥60 days apart; 2) ART was the percentage with ≥1 HIV care visit who were prescribed ART for ≥1 month; and 3) VS was the percentage with ≥1 HIV care visit and ≥1 HIV RNA measure who had an HIV RNA ≤200 copies/mL at their last measurement in the calendar year. Cross-sectional annual estimates from 2004-14 were produced for each subgroup. Log binomial models with generalized estimating questions for repeated measures and an ordinal variable for calendar time were used to estimate p-values for trend. Changes over time in disparities between subgroups were evaluated using an interaction term and a nested models approach.
Results: Among 9,432 young adults newly linked to care, ART and VS increased in all subgroups over time (all p-trends<.01; Figure 1). However, there was no change in RIC (all p-trends>.05). Black MSM had lower RIC and VS compared to white and Hispanic men, with a widening of the disparity in VS over time relative to white men (p-interaction<.001). Hispanic men had higher percentages of ART compared to black MSM and white men, with a narrowing disparity over time relative to white men (p-interaction<.001). Compared to Hispanic women, black and white women had lower percentages of RIC and ART. The disparity in ART relative to white women decreased for Hispanic and black women over time (p-interaction=.035).
Conclusion: The low proportions of RIC, ART, and VS in young adults newly linked to care, and changes over time in disparities between key subgroups, demonstrate the need for continued efforts to improve the percentages of young PLWH that achieve these milestones.

841LB WITHDRAWN

842 RACIAL DISPARITIES IN HIV PREVALENCE AND COMPOSITION OF RISK NETWORKS, HPTN 037

Florence Momplaisir[1], Mustafa Hussein[2], Danielle Fiore[3], Laramie Smith[4], David Bennett[5], Carl Latkin[6], David Metzger[3]
[1]Drexel Coll of Med, Philadelphia, PA, USA, [2]Univ of Wisconsin-Milwaukee, Milwaukee, WI, USA, [3]Univ of Pennsylvania, Philadelphia, PA, USA, [4]Univ of California San Diego, La Jolla, CA, USA, [5]Drexel Univ, Philadelphia, PA, USA, [6]The Johns Hopkins Univ, Baltimore, MD, USA

Background: HIV prevention interventions in the US have failed to reduce racial disparities in HIV prevalence. The purpose of this analysis is to evaluate individual and network factors associated with racial disparity in HIV prevalence among people who inject drugs using HIV Prevention Trial Network 037 data in Philadelphia.
Methods: We measured racial consistency of risk networks (all members share the same race); network HIV prevalence by race of index participant; and network risk behaviors for drugs and sex among 232 index participants who regularly injected drugs and 464 network members. We then performed a logistic regression with a two level random intercept to evaluate the association between HIV status, individual and network characteristics.
Results: Racial consistency was high among blacks and whites (79% and 70% respectively) while the majority of Hispanics were in racially mixed networks (racial consistency for Hispanics was 31%). HIV prevalence was 25% among networks of black index participants compared to 15% and 7% among networks of white and Hispanics index participants. Drug network risk behavior was significantly lower and sex risk behaviors similar in black compared to white and racially mixed networks: needle sharing was 23% in black, 48% in white, 46% in racially mixed networks (p<0.001). The number of unprotected sex events in the past week and number of sexual partners in the past month averaged around 2 in all networks. In our multivariable logistic regression, women (AOR 2.0, 95% CI 1.0-4.1), blacks (AOR 3.2, 95% CI 1.4-7.1), homeless individuals (AOR 2.2, 95% CI 1.1-4.5) and cocaine injectors (AOR 2.4, 95% CI 1.1-5.2) were more likely to be HIV positive compared to men, whites, housed individuals, and injectors who did not use cocaine (Table 1). Being in a network where members have multiple sex partners was negatively associated with HIV status (AOR 0.8, 95% CI 0.7-1.0).
Conclusion: Despite having lower drug risk behavior, blacks were disproportionately HIV positive. HIV prevention interventions need to go beyond individual risks and consider social context and the composition of risk networks.

843 CONCURRENCY IN THE SEXUAL NETWORKS OF RACIALLY DIVERSE YMSM

Patrick Janulis, Gregory Phillips, Brian Mustanski, MIchelle Birkett
Northwestern Univ, Chicago, IL, USA

Background: Black young men who have sex with men (YMSM) experience substantially higher incidence rates of HIV despite reporting fewer risk behaviors. Concurrency (i.e., overlapping sexual partnerships) is a feature of sexual networks that could explain this contradiction, given that reporting more concurrent partners has been shown to increase the spread of disease through a sexual network, even with the same levels of contact. Accordingly, this study leverages recent advances in modeling sexual networks to a) model variation in concurrency across race among YMSM and b) examine unobserved 'whole network' structural features based on these models.
Methods: Data for this analysis come from an ongoing cohort study of YMSM in Chicago (RADAR). Participants (n = 574) completed a comprehensive inventory of their sexual partners. Using a series of egocentric exponential random graph models, we examined if the tendency to have fewer than 2 current partners varies across race, while controlling for other features of sexual networks such as racial homophily. Finally, we simulated sexual networks using these models in an effort to estimate risk metrics that cannot be observed in egocentric network data.
Results: Results suggest that YMSM have a disinclination for concurrency. However, providing separate estimates for concurrency for each racial group did not improve the fit of the model, and this tendency did not significantly vary between Black and White YMSM ($z = 1.9$, $p = 0.051$). Contrastingly, the tendency for same-race sexual partners was significantly greater among Black YMSM ($z = 3.2$, $p = 0.001$). Sexual networks simulated from these models suggest that Black YMSM are more closely connected to individuals perceived to be HIV-positive but are less likely to be in a large connected component, relative to their White peers.
Conclusion: These results suggest racial differences in concurrency are not observed among YMSM in Chicago, and therefore differences in concurrency are unlikely to explain racial disparities in HIV. Yet, existing racial disparities may be partially maintained through higher levels of racial homophily among Black YMSM. Furthermore, HIV prevalence in the sexual networks of Black YMSM place them at risk for HIV acquisition. Yet, White YMSM are more likely to be in connected components, suggesting a similar paradox to individual level risk behavior.

844 HIV TRANSMISSION IN TIJUANA, MEXICO: REAL-TIME IDENTIFICATION OF A NEW CLUSTER

Antoine Chaillon[1], Patricia Gonzalez-Zuniga[1], Tommi O. Gaines[1], Horacio Almanza[2], Jose R. Chavez[2], Jesus Vera[1], Thomas L. Patterson[1], Davey M. Smith[3], Steffanie A. Strathdee[1], **Sanjay R. Mehta**[1]
[1]Univ of California San Diego, San Diego, CA, USA, [2]Autonomous Univ of Baja California, Tijuana, Mexico, [3]Univ of California San Diego, La Jolla, CA, USA

Background: Tijuana's proximity to the border and a large transient population has led to a thriving red light district and illicit drug market, creating populations at high risk for acquiring and transmitting HIV. Policy decisions designed to clear homeless individuals from the canal region along the US border have driven some of these behaviors "underground". Benefiting from continued surveillance in Tijuana between 2004 and 2016, we applied molecular epidemiologic techniques to infer the presence and monitor the development of putative transmission clusters to help target HIV prevention efforts.
Methods: Participants from eight research studies in Tijuana were screened for HIV infection at baseline, and in two of these studies participants were screened longitudinally on a six-month basis in follow-up. After quality filtering, a total of 288 sequences were obtained from unique individuals sampled between 2004-2016. Phylogenetic and genetic network analyses were performed to infer putative relationships between these HIV sequences. Correlates of identified clusters were evaluated.
Results: Among individuals with reported demographic data, 46.4% (116/250) were MSM, 42.1% (99/235) reported transactional sex, and 27.8% (65/234) reported injection drug use (PWID). 32 individuals seroconverted during the observation period from 2011-2016, of which 21 had available sequence data and were included in the analysis. 123/288 (42.7%) of sequences were linked with at least one other sequence, forming 37 transmission clusters (ranging size: 2-14) (Fig.1). 27/123 (22.8%) of the clustering subjects were FSWs, and these individuals were found in four out of the five clusters linking to individuals residing in San Diego. We identified one cluster of five seroconverters who were all PWID. Two were diagnosed in 2012, and three were diagnosed April-May, 2016. Another three individuals with no sequence data seroconverted during this period. Notably, nearly all individuals diagnosed in April-May 2016 reported moving to a new "underground" shooting gallery away from the canal region, and 3 reported an interaction with police one month prior to their HIV diagnosis. These results were shared with the Mexican authorities.
Conclusion: These data suggest a dynamic HIV transmission pattern reflecting transmissions across risk groups. However, our surveillance also allowed us to identify a rapidly growing transmission cluster in a demographically and geographically focused population impacted by policy change.

845LB IDENTIFYING AND INVESTIGATING A RAPIDLY GROWING HIV TRANSMISSION CLUSTER IN TEXAS

Analise C. Monterosso[1], Sydney Minnerly[1], Samuel Goings[1], Allyson Morris[1], Anne Marie France[2], Sharoda Dasgupta[2], Alexandra Oster[2], Miranda Fanning[1]
[1]Texas Dept of State Hlth Services, Austin, TX, USA, [2]CDC, Atlanta, GA, USA

Background: Analysis of HIV nucleotide sequence data collected through the National HIV Surveillance System can identify rapidly growing transmission clusters. The Centers for Disease Control and Prevention (CDC) identified a molecular cluster in Texas that grew substantially during July 2015–June 2016. CDC and the Texas Department of State Health Services investigated to define the extent of the cluster, identify relationships between cases, characterize the epidemiology and factors facilitating transmission, characterize timing of viral suppression, and prioritize intervention.
Methods: Persons in the molecular cluster were considered confirmed cluster cases. Based on partner services interview records, we identified HIV-infected persons without nucleotide sequences available for analysis who were named sex or needle sharing partners of confirmed cases, partners of sex or needle sharing partners, or social network contacts of confirmed cases. During August–October 2016, we reviewed medical records and partner services interview records to collect data on demographics, risk behaviors, partner meeting sites, and time to achieve viral suppression.
Results: From 27 confirmed cluster cases, we identified 112 additional cluster cases. Of 27 confirmed cases, 12 (44%) were connected through named partners or social contacts into one large cluster; no links were identified for 15. Of 76 confirmed and other cluster cases with records available, 76 (100%) were male at birth, 59 (78%) were aged 13–29 y, 66 (87%) were Hispanic, and 68 (89%) reported sex with men. Reported lifetime sex partners ranged from 2–300; 18 (24%) reported anonymous partners and 18 (13%) had an STD diagnosis within 12 months before HIV; none were on PrEP. In all, 31 (41%) had evidence of viral suppression within 6 months of diagnosis (figure); 10 (13%) have never had a viral load test. After this investigation, 25 people were initiated for reengagement in care.
Conclusion: Our investigation identified an actively growing transmission cluster of primarily young Hispanic MSM that was substantially larger than the molecular cluster; this network is likely even larger, given the large number with anonymous partners or without identified links to the cluster. High risk sexual behavior coupled with delays in achieving viral suppression among some cluster cases likely contributed to rapid growth. These findings reveal opportunities for prioritization of persons associated with this cluster for linkage to care and PrEP referral.

846 SEXUAL NETWORKS OF CIS AND TRANSGENDER PEOPLE WITH & AT-RISK FOR HIV, KING COUNTY, WA

Julia Hood[1], David A. Katz[2], Lindley A. Barbee[2], Sara N. Glick[2], Amy Bennett[1], Susan Buskin[1]
[1]Pub Hlth–Seattle & King County, Seattle, WA, USA, [2]Univ of Washington, Seattle, WA, USA

Background: In King County (KC), Washington, HIV is concentrated among cisgender ("cis") men who have sex with men (MSM). The number of transgender ("trans") people in KC is unknown, complicating estimates of disease burden. We triangulated several health department data sources to describe characteristics of trans people known to be HIV-positive and to assess the extent to which trans sexual networks overlap with HIV-negative cis MSM and people living with diagnosed HIV (PLWDH).

Methods: Data sources are outlined in the Table. We describe the number and characteristics of PLWDH known to be trans; the percent of HIV-negative trans men and trans women who reported cis male sex partners; and the percent of PLWDH and HIV-negative cis MSM who reported trans sex partners. Unless otherwise indicated, questions about sex partners referred to the prior 12 months.
Results: Of 7071 PLWDH presumed living in KC in 2015, 5286 (75%) were cis MSM and 60 (<1%) were trans. Compared to cis PLWDH, proportionally more trans PLWDH were Hispanic (28% vs. 13%), <35 years (25% vs. 15%), virally unsuppressed (25% vs. 19%), diagnosed with AIDS within 1 year of HIV diagnosis (35% vs. 29%), and had a history of injection drug use (27% vs. 13%) Of Trans Pride Survey respondents who were assigned male at birth and identify as a woman and/or non-binary, 2% reported an HIV-positive sex partner, 35% a cis male partner, 43% cis female partner, and 41% trans partner. The corresponding percentages for respondents who were assigned female at birth and identify as a man were 1%, 27%, 43%, and 34%. Among PLWDH, a recent trans sex partner was reported by 0.8% of newly diagnosed cases and 0.1% of HIV care patients who participated in MMP. Among HIV-negative cis-MSM, 4% of Pride Survey respondents reported a recent trans partner and 3% of STD Clinic patients reported ever having a trans partner.
Conclusion: The PHSKC HIV surveillance system includes a small number of trans people. Along with evidence of limited overlap between trans sexual networks and people with HIV or at high-risk for HIV, this may suggest a lower burden of HIV among trans people in KC than reported in other areas. These findings are impacted by data collection methods and may not be generalizable. Evaluations of sexual network characteristics may be informative, especially when case counts and population denominators cannot be reliably estimated. Efforts to more systematically monitor HIV among trans persons are needed.

DESCRIPTION OF HOW INFORMATION ABOUT GENDER IDENTITY IS COLLECTED BY PUBLIC HEALTH - SEATTLE & KING COUNTY'S HIV/STD PROGRAM

Data Source	Design	Years & # of Records Included in Analysis	Population	How gender of respondent was assessed:	How gender of sex partners was assessed:
People with Diagnosed HIV					
Enhanced HIV/AIDS Reporting System	HIV surveillance registry	2015 (N=7071)	HIV-diagnosed people presumed living in King County in 2015	Sex at birth. {M, F} Gender or Identity Change. {MTF, FTM}	(Not available)
Partner Services (PS)	Interview with about 75% of all cases newly diagnosed with HIV	2010-16, N=1293	People newly diagnosed with HIV who participated in PS.	"What was your assigned gender at birth?" {M, F} "What is your current gender?" {M, F, MTF, FTM, trans-unspecified, other-specify}	"In the last 12 months, have you had • Oral sex with a transgendered person? • Vaginal/anal sex with a transgender partner?"
Medical Monitoring Project (MMP)	Complex Survey Design	2009-15, N=1088	Adults in HIV care who participated in MMP.	"What was your sex at birth?" {M, F} "Do you consider yourself to be male, female, or transgender?"	"During the past 12 months, how many transgender persons have you had sex with?"
MSM, excluding those who self-reported being HIV-positive					
STD Clinic Intake Form[1]	Client Intake Form	2012-2015 N_{Visits}=7596	STD Clinic patients who reported being a cisgender gay man without known HIV.	"Are you male, female, or transgender?"	"Have you ever had sex with a transgender person?"
Pride Survey[2]	Serial cross-sectional convenience survey at Pride Parade	2014-2016, N=1245	Respondents who reported being a cisgender man, without known HIV, who has sex with men; HIV self-reported	"What is your primary gender identity today?" {M, F, non-binary, none of the above} "What was your sex at birth?" {M, F}	"In the last 12 months, were any of your sex partner transgender?"
Transgender respondents, excluding those who self-reported being HIV-positive					
Trans Pride Survey[3]	Serial cross-sectional convenience survey at Trans Pride Event	2014-2016, N_{MTF}=130 N_{FTM}=83	MTF=reported male sex at birth and current gender female or non-binary. FTM= reported female sex at birth and current gender male.	"What is your primary gender identity today?" {M, F, non-binary, none of the above} "What was your sex at birth?" {M, F}	"In the last 12 months were any of yours sex partners... *[*Cisgender'= gender corresponds to sex at birth]* • Cisgender men • Cisgender women • Transgender men • Transgender women • Partner(s) with a gender identity not listed here"

[1]STD Clinic implemented a more nuanced question in May 2016; [2] 2014-15 Pride Survey used a 1-part question to assess gender; [3] Trans 2014 Pride Survey used a different 2-part question.

847 SPATIAL CLUSTERING OF HIV IN KENYA MAY NOT MATCH WELL-KNOWN EPIDEMIC PATTERN

Anthony Waruru[1], Thomas Achia[2], James Nganga[3], Joyce Wamicwe[4], **James Tobias**[5], Mary Mwangi[1], Evelyn Muthama[1], Emily Zielinski-Gutierrez[2], Tom Oluoch[6], Thorkild Tylleskär[7]
[1]US CDC (CDC), Nairobi, Kenya, [2]US CDC, Nairobi, Kenya, [3]Natl Bureau of Statistics, Nairobi, Kenya, [4]Natl AIDS and STI Control Prog (NASCOP), Nairobi, Kenya, [5]US CDC, Atlanta, GA, [6]US CDC, Atlanta, USA, [7]Univ of Bergen, Bergen, Norway

Background: In a spatially well-known and dispersed HIV epidemic, identifying geographic clusters with significantly higher HIV-prevalence is important for focusing interventions. We conducted geo-spatial analysis on data from a nationally representative Kenya AIDS Indicator Survey 2012 to identify clusters with high number of HIV-infected persons 15-64 years old in Kenya.
Methods: We used Kulldorff spatial-scan statistics implemented in SATScan™ program to assess whether HIV prevalence is randomly distributed over space or whether a cluster can be detected with higher than random distribution of PLHIV by using a Poisson-based model. We classified HIV-infected persons as belonging to high vs. lower prevalence (HP/LP) clusters. Using this classification, we assessed distributions and associations of clustering with socio-demographic and bio-behavioral HIV risk factors. We used a χ-square test to compare weighted proportions.
Results: Out of 358 survey clusters, 238 (66.5%) had at least one HIV-infected person (Figure 1). Of those, 41(17%) were HP, with 1.05-4.15 times greater PLHIV observed than expected. Fewer respondents in HP clusters (4.3%, 95% CI 3.2-5.3) had no formal education compared to respondents in LP clusters (7.8%, 95% CI 6.2-9.5), p=0.0025. Half of respondents in HP clusters (50.0%, 95% CI 40.1-59.9) were living in rural areas compared to 66.7% (95% CI 62.5-70.9) in LP clusters, p=0.0097. Fewer respondents in HP clusters

had travelled away in the past 12 months (42.3%, 95% CI 38.9-45.6) than in LP clusters (53.0%, 95% CI 50.7-55.2), p<0.0001. Fewer respondents in HP clusters vs. LP clusters had tested for HIV only once, 26.0% (95% CI, 23.7-28.4) and 32.1% (95% CI, 30.3- 33.8) respectively, p<0.001. Among men, 22.1% in HP clusters had ever been clients of female sex workers (FSW) compared to 16.3% in LP clusters, p=0.0064. More respondents in HP clusters had greater HIV acquisition risk perception or were already known to be HIV-infected than in LP clusters (p<0001).
Conclusion: HIV infection in Kenya exhibits localized geographic clustering that is dependent on socio-demographic and behavioral factors revealing disproportionate exposure to higher HIV-risk. Identification of these clusters reveals the right places for targeting priority-tailored HIV interventions.

848 A FRAMEWORK FOR PREDICTING PHYLOGENETIC CLUSTERS OF HIV AT HIGH RISK FOR GROWTH

David McVea[1], Richard Liang[2], Jeffrey Joy[2], P. Richard Harrigan[2], Art Poon[3]
[1]Univ of British Columbia, Vancouver, Canada, [2]BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada, [3]Western Univ, London, Ontario, Canada
Background: Phylogenetic clustering of HIV from infected individuals facilitates the rapid detection of outbreaks and may augment traditional surveillance. However, we lack a quantitative understanding of cluster behaviour. Here, we examine the growth and characteristics of 224 phylogenetic clusters of >5 individuals from British Columbia (BC). In particular, we sought characteristics that could identify clusters likely to grow rapidly in the short- and long-term.
Methods: The BC phylogenetic research program uses anonymized genotypes from the BC drug treatment program annotated with demographic, risk-factor, and treatment data. Phylogenetic clusters are assembled from groups of >5 individuals based on short distances between sequences in a phylogenetic tree. We divided clusters into large (≥ 20 members) and small (< 20 members). We also divided clusters into currently growing rapidly (≥ 5 new members in the past year) and slowly (≤ 4 new members in the past year). We then compared cluster demographic and risk-factor data to identify which ones varied most between large- and small-, and slowly- and rapidly-, growing clusters.
Results: Both cluster size at one year and the maximum-ever growth rate increased with larger cluster size. A threshold of 5 new members within the first year, and 0.6 new members per month, were most efficient at identifying eventual large clusters. Using these thresholds, clusters could be classified into large or small with sensitivity of 1 and specificity of 0.76 based on maximum ever growth rate, and with sensitivity of 0.43 and specificity of 0.95 based on size at one year of age. Regarding current growth, the ratio of MSM in each cluster increased with current growth rate, and a threshold ratio of 0.5 MSM/Non-MSM was the most efficient at differentiating rapidly- from slowly-growing clusters. Using this threshold, clusters could be identified as rapidly- or slowly-growing with sensitivity of 1 and specificity of 0.54.
Conclusion: As the bulk of the HIV epidemic slows in developed countries, further control will rely on targeted interventions, such as pre-exposure prophylaxis in limited sub-populations at elevated risk of HIV infection. Simple characteristics of phylogenetic clusters may predict short- and long-term growth, identifying sub-groups most at risk of infection. While such rules will need to be validated and refined in each unique context, they offer an opportunity to target interventions to maximize their impact and cost-effectiveness.

849 NETWORK VIRAL LOAD: A CRITICAL METRIC FOR HIV ELIMINATION

Britt Skaathun[1], Aditya Khanna[1], Ethan Morgan[1], Samuel R. Friedman[2], **John A. Schneider**[1]
[1]Univ of Chicago, Chicago, IL, USA, [2]Natl Development & Rsr Insts, New York, NY, USA
Background: Previous associations have been observed between an aggregate viral load measure, the community viral load (CVL) and new HIV diagnoses. The CVL, however, is prone to ecological fallacy due to the presumption that transmission occurs between individuals in the same community. We develop a new and more precise metric, the Network Viral Load (NVL) to measure the composite viral load within a risk network of an HIV negative individual.
Methods: We examined the relationship between NVL and HIV infection among a population-based sample of Young Black Men who have Sex with Men (YBMSM) in Chicago. Networks were generated using Respondent Driven Sampling. NVL was defined as the average viral load of HIV-seropositive individuals from a sample of one's risk network. Multivariate logistic regression analyses were performed to assess the association between NVL and HIV serostatus. Permutation tests were conducted to account for dependency in the sampling scheme.
Results: Of 457 respondents, 100% were Black. HIV seroprevalence was 39%. After controlling for total connections, age, substance use during sex, syphilis diagnosis (previous 12 months), and frequency of anal sex (previous 6 months), we found a positive association between NVL and HIV infection. Compared to a network with all HIV-seronegative members, the odds of HIV infection with a NVL of <200 to <10k copies/mL were 2.17 times higher, the odds of a NVL of >10k to <60k copies/mL were 2.38 times higher, and a NVL of >60k copies/mL were 2.80 times higher (all 95% CIs between 1.08-7.25) in the multivariate regression analysis.
Conclusion: We found a positive association between NVL and HIV seroprevalence. NVL may have substantial public health implications for HIV-seronegative persons most at risk for HIV infection given that this novel metric avoids overreliance on individual level behavior or broad community indices.

Multivariate Logistic Regression: Factors Associated with HIV serostatus: uConnect Study (n=425)

		OR	95% CI	p-value
Age		1·09	1·02-1·18	0·01
Syphilis Diagnosis (previous year)	No	1·00	-	-
	Yes	4·16	2·28-7·57	<0·0001
Frequency of anal intercourse (previous 6 months)		1·02	0·99-1·04	0·09
Number of social & sexual connections (Degree)		0·98	0·94-1·02	0·36
Sex Drug Use	No			
	Yes	1·39	0·82-2·29	0·20
Average Network Viral Load	0	1·00	-	-
(copies/mL)	1-9k	2·17	1.34-3·52	0·002
(copies/mL)	10k-59k+	2·38	1·27-4·47	0·007
(copies/mL)	60k+	2·80	1·08-7·25	0·03

OR=Odds Ratio, CI=Confidence Interval

850 IDENTIFYING A GEOSPATIAL RELATIONSHIP BETWEEN COMMUNITY-LEVEL RISK AND HIV PREVALENCE

Laurence Palk, Sally Blower
Univ of California Los Angeles, Los Angeles, CA, USA
Background: Many countries in sub-Saharan Africa show considerable geographic variation in the severity of their HIV epidemics. We hypothesize that geographic variability in HIV prevalence may be due to differences among communities in risk behavior. To test this hypothesis we determine if there is a significant geospatial association between the size of the high-risk group (in a community) and the prevalence of HIV. We use Malawi as a case study.

Methods: We use geo-referenced HIV testing data from the 2010 Malawi Demographic and Health survey; a national representative survey of 7,091 women and 6,497 men aged 15-49. We construct gender-stratified HIV prevalence maps. We also construct gender-stratified, community-level, risk maps that show the proportion of the community who have engaged in high-risk behavior; defined as three or more lifetime sex partners for women and four or more for men. We quantify the spatial correlation between areas of high risk and high prevalence by calculating local bivariate Moran's and plotting cluster maps. We then conduct a regression at the district level, adjusting for the spatial auto-correlation of errors, to determine the extent to which community-level risk behavior explains local prevalence.
Results: Average HIV prevalence is 13% in women, 9% in men. Maps show prevalence varies geographically from 1% to 29% in women, and from 1% to 20% in men. Large-scale spatial patterns are apparent. Notably there is a north-south trend. Maps of risk behavior show the proportion in the high-risk group varies from 0% to 40% in women, and from 16% to 58% in men. A north-south trend is apparent; more discernable in women than in men. Cluster maps show a strong, positive, correlation between community-level risk and HIV prevalence. The regression model shows that variation in the size of the women's high-risk group, within a community, explains 75% of the variation in the prevalence of HIV in women and 65% of the variation in the prevalence of HIV in men. When high-risk women are more than ~15% of the community, the prevalence in women and men will be above average.
Conclusion: Our results support our hypothesis. Geographic variation in community-level high-risk sexual behavior in women generates the large-scale spatial patterns in the HIV epidemic in Malawi, and can explain the north-south trend in increasing HIV prevalence. Our study suggests a simple and plausible explanation for the high degree of geographic variation in the severity of HIV epidemics in sub-Saharan Africa.

851 THE EPIDEMIOLOGY OF HIV IN PEOPLE BORN OUTSIDE THE UNITED STATES, 2010–2014

Roxanne P. Kerani[1], Anna S. Johnson[2], Susan Buskin[3], Deepa Rao[1], Matthew R. Golden[1], Xiaohong Hu[2], Irene Hall[2]
[1]Univ of Washington, Seattle, WA, USA, [2]CDC, Atlanta, GA, USA, [3]Pub Hlth–Seattle & King County, Seattle, WA, USA
Background: Previous estimates of HIV among migrants to the United States (US) preceded data availability from all states.
Methods: We analyzed National HIV Surveillance System data for persons with HIV diagnosed 2010-2014. Country of birth (COB) is included on HIV case report forms, but data reporting is incomplete. If COB was missing, nativity (US, including US dependent areas, or outside the US) was imputed with covariates age, race/ethnicity, HIV transmission category, and stage at diagnosis. Transmission category was imputed for cases with missing risk factor information.
Results: Among 210,888 children and adults with HIV diagnosed from 2010-2014, 36,324 (17.2%) were estimated to be migrants after imputing COB for 37,670 (17.9%). Migrants accounted for 9,700 (22.2%) and 26,624 (15.9%) of female and male cases, respectively. Among 30,043 migrants with known COB, the most frequent regions of birth (ROB) were Mexico/Central America (MCA, 10,778, 35.9%), the Caribbean (6,327, 21.1%), and Africa (5,336, 17.8%). The most frequent ROB among females were Africa (3,193, 39.5%) and the Caribbean (2,185, 27.0%), while among males, these were MCA (9,322, 42.4%) and the Caribbean (4,142, 18.9%). Migrants comprised 19,756/48,914 (40.4%) of Hispanics/Latinos; 10,571/93,955 (11.3%) of blacks, 2,552/4,031 (63.3%) of Asians/Pacific Islanders, and 2,300/55,852 (4.1%) of whites. Relative to US-born individuals, migrants were more frequently female (26.7% versus 19.5%); however, males outnumbered females among migrants from all ROB except Africa (59.8% female). Compared with US-born persons, a higher percentage of migrants acquired HIV heterosexually (males, 17.7% vs 9.8%; females, 91.2% vs. 82.9%) and had stage 3 disease (AIDS) at HIV diagnosis (34.7% vs. 25.8%). Over one-third of migrants (11,706, 39.0%) resided in the South. African and Caribbean migrants accounted for 13.9% of the 2014 US foreign-born population, but together represented 38.8% of HIV cases with known COB among migrants. Migrants from South America and the Caribbean were the most geographically concentrated, with 60.8% and 69.2% of cases, respectively, residing in the five metropolitan statistical areas with the largest number of cases from each population.
Conclusion: African and Caribbean migrants are disproportionately affected by HIV. Characterizing migrants with HIV is essential for development of effective HIV interventions, particularly in areas with large migrant populations.

852 CHANGES IN HIV RISK FACTORS AMONG MEN WHO HAVE SEX WITH MEN AND WOMEN, 2008–2014

Wade Ivy[1], Thema Chapple[2], Gabriela Paz-Bailey[1], for the NHBS Study Group
[1]CDC, Atlanta, GA, USA, [2]Morehouse Coll, Atlanta, GA, USA
Background: Since 2008, HIV diagnoses have consistently declined among African American (black) women. Molecular surveillance data have suggested that nearly one-third of HIV infections among heterosexual women are linked to HIV infections attributable to male-to-male sexual contact. We used National HIV Behavioral Surveillance (NHBS) data to evaluate changes in behaviors and access to care among men who have sex with men and women (MSMW). We hypothesize that reductions in risk behaviors and improved HIV treatment coverage among MSMW may contribute to the declining trends in HIV diagnoses among black women.
Methods: We used cross-sectional data from NHBS among MSM recruited using venue-based sampling in 20 US cities in 2008, 2011, and 2014. Data from men who reported sex with both men and women in the past 12 months were analyzed using GEE to determine changes over time in access to healthcare, HIV testing and antiretroviral (ARV) treatment, and HIV risk behaviors, controlling for city of residence and accounting for clustering around venue recruitment. Models were run separately using each of the variables under investigation as outcomes.
Results: Among the 3,339 MSMW in this analysis, the percentage who reported a recent (past 12 months) HIV test (55%, 64%, 65%; $p < 0.0001$) and current health insurance (51%, 59%, 65%; $p = <0.0001$) increased significantly from 2008 to 2014. High-risk sexual behaviors increased or remained stable over time. Anal sex without a condom with a man in the past 12 months increased significantly (44%, 46%, 51%; $p = 0.0014$), and reporting 3 or more male (57%, 61%, 57%; $p = 0.4719$), or 3 or more female (39%, 34% 39%; $p = 0.6176$) sex partners in the past 12 months remained stable. Among HIV-positive MSMW, the percentage who reported being aware of their infection (31%, 40%, 55%; $p = <0.0001$) increased. Among those HIV-positive aware, the percentage on anti-retroviral treatment (47%, 64%, 80%; $p = <0.0001$) also increased significantly over time.
Conclusion: Although risk behaviors among MSMW increased over time in this analysis, there were increases in HIV testing, insurance coverage, HIV status awareness and being on ARV treatment. While HIV transmission from MSMW to women only comprise a portion of all HIV infections in women, targeting expansion of HIV treatment and access to care to MSMW may help further drive down HIV infection rates among women.

853 ASSOCIATION BETWEEN HOUSING STABILITY AND NEW HIV DIAGNOSIS IN SEEK AND TEST STUDIES

Bridget Whitney[1], Bridget Kruszka[1], Jennifer Lorvick[2], Gregory M. Lucas[3], Wendee Wechsberg[4], Irene Kuo[5], William E. Cunningham[6], Asa Clemenzi-Allen[7], Julie Franks[8], Heidi M. Crane[1]
[1]Univ of Washington, Seattle, WA, USA, [2]RTI Intl, Berkeley, CA, USA, [3]The Johns Hopkins Univ, Baltimore, MD, USA, [4]RTI Intl, Rsr Triangle Park, NC, USA, [5]George Washington Univ, Washington, DC, USA, [6]Univ of California Los Angeles, Los Angeles, CA, USA, [7]Univ of California San Francisco, San Francisco, CA, USA, [8]Columbia Univ, New York, NY, USA
Background: Housing instability can act as a barrier to timely HIV diagnosis and treatment. Studies have found that homelessness and living in marginal housing are associated with a variety of HIV risk behaviors, including higher rates of substance use and injection drug use. Using four studies from the Seek, Test, Treat, and Retain (STTR) HIV consortium, we examined the association between housing stability and HIV diagnosis. We hypothesized that new diagnosis of HIV would be highest in participants reporting marginal housing and homelessness.
Methods: We constructed a harmonized measure of housing stability, categorized as stable, marginally housed, and homeless. Participants were considered marginally housed if they reported living in a temporary facility or an informal settlement at baseline and were considered homeless if they self-reported homelessness or living in shelters. The outcome of interest was HIV diagnosis. Random-effects individual patient data (IPD) meta-analysis models, adjusted for age and gender, was used to assess the relationship between housing stability and HIV diagnosis.

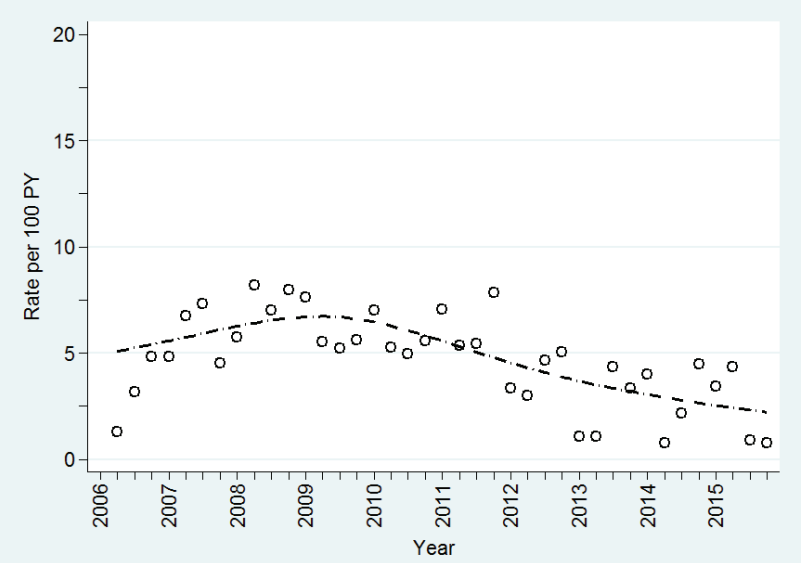
Results: 17,406 participants were included in the IPD analysis: 1,987 (11.4%) HIV-infected and 15,419 (88.6%) HIV-uninfected. The greatest proportion of people diagnosed with HIV were stably housed (12.0%), followed by marginally housed (9.8%), and homeless (9.6%). Median age was 30 in stably housed participants and 37 in marginally housed and homeless participants. The majority of individuals, overall, and by study, were male (89.3%), except the all-female WHC+. Compared to those in stable housing, living in marginal housing during the study reference period showed an inverse association with HIV diagnosis (overall OR: 0.63, 95% CI: 0.27-1.43), with the exception of WHC+ (OR: 1.66, 95% CI: 1.07-2.58). Overall, there was no association between homelessness and HIV infection at baseline (overall OR: 0.93, 95% CI: 0.60-1.42).
Conclusion: Counter to hypotheses and some extant literature, homelessness was not associated with HIV diagnosis, with individual studies showing associations in both directions. In contrast, recent marginal housing showed an inverse association with HIV diagnosis, which may indicate people in marginal housing are targeted by services that alter their HIV testing patterns. The models were sensitive to the inclusion of international studies, suggesting there may be heterogeneity in definition of marginal housing and homelessness between countries.

Study	Location	Sample Size	% Newly Diagnosed	Stable Housing	Marginal Housing OR (95% CI)	Homeless OR (95% CI)	Weight (%)
Overall		17,406	11.4%	Reference	0.63 (0.27-1.43)	0.93 (0.60-1.42)	100
ICC-IDU	India	13,083	12.9%	Reference	0.70 (0.49-0.98)	1.33 (1.15-1.56)	75
STAR	United States	1,897	8.0%	Reference	0.30 (0.17-0.53)	0.70 (0.49-0.99)	11
UHS II Cross-sectional	United States	2,025	1.4%	Reference	0.68 (0.09-5.03)	1.11 (0.53-2.32)	12
WHC+	South Africa	401	30.7%	Reference	1.66 (1.07-2.58)	0.93 (0.53-1.65)	2

854 HIV INCIDENCE AND RISK BEHAVIORS IN THE BANGKOK MSM COHORT STUDY, THAILAND, 2006–2015

Timothy H. Holtz[1], Anchalee Varangrat[2], Philip Mock[2], Warunee Thienkrua[2], Wannee Chonwattana[2], Wipas Wimonsate[2], Wichuda Sukwicha[2], Marcel Curlin[3], Eileen Dunne[4], Anupong Chitwarakorn[5]
[1]CDC, Atlanta, GA, USA, [2]Thailand Ministry of Pub Hlth–US CDC Collab, Nonthaburi, Thailand, [3]Oregon Hlth and Scis Univ, Portland, OR, USA, [4]US CDC, Nonthaburi, Thailand, [5]Thailand Ministry of Pub Hlth, Nonthaburi, Thailand

Background: We assessed 10-year HIV incidence trend and risk factors for incident infection among men who have sex with men (MSM), and transgender women (TGW), participating in the Bangkok MSM Cohort Study (BMCS) at the Silom Community Clinic (SCC) in Bangkok from 2006–2015.
Methods: MSM and TGW aged >18 years were enrolled into BMCS. Participants provided socio-demographic and sexual risk behavior data by computer-assisted self-interview every 4 months for up to 60 months. HIV testing was performed on oral fluid with serologic confirmation of all reactive specimens and nucleic acid amplification testing (NAAT) of all negative specimens obtained after February 2010. We calculated incidence per 100 Person Years (PY) and cumulative incidence by Kaplan-Meier survival analysis, determining risk factors for incident HIV infection using Cox regression analyses with time-varying covariates. We evaluated trends in HIV incidence per 100 Person Years (PY) by quarter using a restricted cubic spline for time in a Poisson regression.
Results: Among 1744 BMCS participants followed from 2006–2015, 1371 tested HIV-negative at baseline, and 1259 (72%) of these participants had follow-up. We detected 271 infections (n = 22 diagnosed by NAAT) in 4798 total person-years, for an overall HIV incidence density of 5.6 PY (95% CI: 5.0–6.4). HIV incidence rose from 1.3 PY in Q2/2006 to a peak of 8.2 PY in Q1/2008, then declined steadily (inverted U-shaped curve) (Figure). Cumulative incidence at 60 months of follow up was 23.6% overall, and varied by age group: 32.5% among 18-21 year olds; 25.0% among 22-29 year olds; and 16.3% among ≥30 year olds ($p < 0.001$). Multivariable risk factors for HIV incidence were younger age (adjusted Relative Risk [aRR] 2.18) and lack of HIV testing before enrolment (aRR 1.36). Significant covariates reported for the last 4 months of each individual follow-up visit were use of drugs for sexual pleasure (aRR 2.59); inconsistent condom use (aRR 1.73), group sex (aRR 1.60); receptive anal intercourse (aRR 1.57); anti-HSV-2 antibody (aRR 1.51); living alone or with a roommate (vs. with a partner or family) (aRR 1.43); and anti-HSV-1 antibody (aRR 1.39).
Conclusion: HIV incidence among MSM and TGW in Bangkok was as high as 8.2 PY. Combination HIV prevention interventions that reduce HIV transmission during receptive anal intercourse without a condom, especially targeting young men with a history of drug use, HSV, or multiple partners, could significantly impact the epidemic.



855 CHANGES IN RISK BEHAVIORS AFTER HIV SEROCONVERSION, BANGKOK MSM COHORT STUDY

Wipas Wimonsate[1], Sarika Pattanasin[1], Pikunchai Luechai[1], Jaray Tongtoyai[1], Wichuda Sukwicha[1], Chaiwat Ungsedhapand[1], Anupong Chitwarakorn[2], Michael Thigpen[3], Eileen Dunne[3], Timothy Holtz[3]
[1]Thailand Ministry of Pub Hlth–US CDC Collab, Nonthaburi, Thailand, [2]Thailand Ministry of Pub Hlth, Nonthaburi, Thailand, [3]US CDC, Nonthaburi, Thailand

Background: HIV seroconversion has been associated with change in HIV risk behaviors among men who have sex with men (MSM). We evaluated risk behaviors before and after HIV seroconversion in the Bangkok MSM cohort study (BMCS).
Methods: From 2006–2016, we enrolled Bangkok MSM aged ≥18 years into BMCS and followed them at 4-month intervals. At each visit, participants provided behavioral information using computer-assisted self-interview and were tested for HIV on oral fluid, and, if reactive, confirmed with three rapid tests on serum. We used the McNemar test to compare proportions of each risk behavior reported at the study visit immediately before seroconversion with the visit immediately after seroconversion, and with the visit at 12 months after seroconversion. We compared these behaviors between the visit immediately after seroconversion with the visit at 12 months after seroconversion. We used the binomial distribution to calculate the estimates of the percentage reduction in risk behaviors with associated 95% confidence intervals [CI].
Results: Among 1744 enrollees, 1259 (72.2%) were initially HIV-negative and returned for at least one follow-up visit: 249 (19.8%) individuals acquired HIV during the follow-up period. Among 183 who returned for follow-up both immediately before and after seroconversion and provided information for the comparison of behaviors, there was a 64% reduction in group sex after seroconversion (95% CI 0.50-0.76), an 82% reduction in condomless anal intercourse (CAI) with a steady male partner (95% CI 0.71-0.90), and a 79% reduction in CAI with a casual partner (95% CI 0.66-0.88). Among 150 who were available at visits pre-seroconversion and 12-month after seroconversion, there was a 74% reduction in group sex at 12-month after seroconversion (95% CI 0.59-0.85), an 84% reduction in CAI with a steady male partner (95% CI 0.72-0.93), and an 82% reduction in CAI with a casual partner (95% CI 0.68-0.92). Among 158 who were available at visits immediately post-seroconversion and 12-month after seroconversion, there were no significant differences in the proportions with these behaviors. There were no significant changes in recreational drug use and erectile dysfunctional drug use before and after seroconversion.
Conclusion: In this cohort, three high-risk sexual behaviors decreased in frequency for at least 12 months after HIV seroconversion. This change in behaviors could prevent further onward transmission of HIV, especially during the critical period after HIV acquisition.

856 AN EMPIRIC RISK SCORE TO GUIDE PREP UPTAKE IN MSM IN COASTAL KENYA

Elizabeth Wahome[1], Alexander N. Thiong'o[1], Oscar Chirro[1], Evans Gichuru[1], John Mwambi[1], Matt A. Price[2], Susan M. Graham[3], Eduard Sanders[4]
[1]KEMRI Wellcome Trust Rsr Prog, Kilifi, Kenya, [2]Intl AIDS Vaccine Initiative, New York, NY, USA, [3]Univ of Washington, Seattle, WA, USA, [4]Kenya Med Rsr Inst, Kilifi, Kenya

Background: The World Health Organization recommends preexposure prophylaxis (PrEP) for populations with high HIV-1 incidence (≥3% per year). While Kenyan guidelines recommend PrEP for men who have sex with men (MSM), HIV-1 acquisition risk is heterogeneous. We set out to develop an empiric risk score to target PrEP use among MSM in Kenya, using data from a cohort of high-risk MSM followed on the Kenyan coast.
Methods: Poisson regression was used to identify predictors of incident HIV-1 infection in MSM followed in the period 2005-2016 in Coastal Kenya. We assigned a predictor score to each statistically significant predictor based on its model coefficient, summing predictor scores to calculate a risk score for each participant. We then determined which risk score cut-off would correspond to an HIV-1 incidence ≥3%. We evaluated risk score algorithm performance, and assessed whether higher risk scores correlated with higher HIV-1 incidence. We then calculated the proportion of MSM who should start PrEP, if this algorithm was used.
Results: A total of 741 MSM contributed a median follow-up time of 15.0 (interquartile range: 5.6-33.1) months, for an average of 117 MSM followed per calendar year (range: 11-208). HIV-1 incidence was 7.0 [95% confidence interval (CI), 5.7–8.5] per 100 person-years. Independent predictors of HIV-1 infection and corresponding risk scores were: 1 for exclusive sex with men, receptive anal intercourse, any unprotected sex, and group sex; and 2 for age 18-24 years. While laboratory-confirmed urethral or rectal gonorrhea infection was the strongest predictor of HIV-1 infection, we did not include this in the model as few providers have access to such information. The area under the receiver operator curve (AUC) for predictive ability of the risk score was 0.71 (95% CI, 0.66-0.76). A risk score ≥1 corresponded to an HIV-1 incidence ≥3% (Table). A unit increase in risk score strongly correlated with an increase in observed HIV-1 incidence (test for trend: $p<0.001$). A total of 79.6% of MSM participating in this cohort met eligibility criteria for PrEP start.
Conclusion: An empiric risk score based on the summation of four reported risk behaviors and age strongly correlated with increased HIV-1 incidence in our cohort. This risk score may help Kenyan health providers to assess HIV-1 acquisition risk in MSM and encourage PrEP uptake. MSM with recent laboratory-confirmed gonorrhea infection qualify for PrEP a priori but should be evaluated for acute HIV infection prior to initiation.

Table. HIV-1 Incidence and 95% CI stratified by risk score among 741 MSM in Kilifi, Kenya, 2005-2016.

Risk Score	HIV-1 incidence cases/ Per 100 PY	Total No. of MSM	HIV-1 Incidence (95% CI)
0	3/299.6	151	1.0 (0.3-3.1)
1	13/345.4	166	3.8 (2.2-6.5)
2	19/293.2	181	6.5 (4.1-10.2)
3	21/261.9	127	8.0 (5.2-12.3)
4	23/117.8	81	19.5 (13.0-29.4)
5	16/43.8	53	36.6 (22.4-59.7)

CI, confidence interval; PY, person-years

857 VALIDATION OF A RISK SCORE FOR HIV ACQUISITION IN YOUNG AFRICAN WOMEN WITH FACTS 001

Emma K. Burgess[1], Sinead Delany-Moretlwe[2], Pedro Pisa[2], Khatija Ahmed[3], Sydney Sibiya[4], Cynthia Gama[5], Busiswe Nkala[6], Gustavo Doncel[7], Glenda Gray[6], Helen Rees[2]
[1]Global Hlth Fellows Internship at USAID, Arlington, VA, USA, [2]Wits Reproductive Hlth and HIV Inst, Johannesburg, South Africa, [3]Setshaba Rsr Cntr, Pretoria, South Africa, [4]Qhakaza Mbokodo Rsr Clinic, Ladysmith, South Africa, [5]MatCH, Durban, South Africa, [6]Perinatal HIV Rsr Unit, Soweto, South Africa, [7]CONRAD, Arlington, VA, USA

Background: Adolescent Girls and Young Women (AGYW) in South Africa are at high risk of HIV, and understanding which factors may be predictive of their level of risk could improve the efficiency of recruitment into HIV research and targeting AGYW for the prevention programs they urgently need. Using baseline data from the FACTS 001 1% tenofovir gel trial, we sought to externally validate a risk scoring tool to predict HIV-1 acquisition in African women that was derived by Balkus et al. with the VOICE cohort.
Methods: We compared FACTS data collected from women across 9 South African sites in 2011 to 2014, to the findings in the VOICE cohort. The full score included 7 items with a maximum total of 11: age, living with a partner, partner provides financial support, partner exclusivity, alcohol use, detection of curable STIs, and HSV-2 serostatus. Scores of ≥5 were associated with HIV incidence of >5/100 PY and identified 91% of infections among only 64% of the women. The score was applied to FACTS participants and evaluated using sensitivity, specificity, and area under the curve (AUC). The 7 risk score factors were also assessed in a multivariate Cox proportional hazards model.
Results: Among 2,059 enrolled FACTS participants, 1,115 (54%) had complete data for all 7 indicators. Of these, 81 acquired HIV infections over 1876 person years of follow-up (incidence=4.32/100 PY). Cutting off scores at ≥5 had a sensitivity of 84% and specificity of 23%, therefore, 77% of the women were needed to identify 84% of the infections. Scores of ≥5 were loosely associated with incidences of >3/100 PY. The AUC was 0.56, indicating poor discriminative accuracy. In the full model only 3/7 risk factors had a significant association with HIV: not receiving financial support from a partner (aHR=0.50, CI 0.26, 0.99), not living with one's partner (aHR=2.48, CI 1.13, 5.45), and being HSV-2 positive (aHR=1.56, CI 1.11, 2.25).
Conclusion: Our external validation in FACTS found that the score could not differentiate well between women at lower and higher risk of HIV acquisition as incidence was comparable across risk score categories. The null and opposing risk associations could be attributable to FACTS being a younger cohort, hence the score's poor discriminative ability in FACTS compared to VOICE. This analysis warrants further investigation for framing a risk score for South African AGYW in high incidence settings, in particular that can be used to identify potential users who would benefit from new HIV prevention options.

858 SELF-ASSESSED HIV RISK 3 YEARS AFTER HIV "TEST AND TREAT" IMPLEMENTED IN SEARCH

James Ayieko[1], Dalsone Kwariisima[2], Catherine A. Koss[3], Craig Cohen[3], Elizabeth A. Bukusi[1], Tamara D. Clark[3], Edwin D Charlebois[3], Moses R. Kamya[4], Maya L. Petersen[5], Diane V. Havlir[3]
[1]Kenya Med Rsr Inst, Nairobi, Kenya, [2]Makerere Univ Joint AIDS Prog, Kampala, Uganda, [3]Univ of California San Francisco, San Francisco, CA, [4]Makerere Univ, Kampala, Uganda, [5]Univ of California Berkeley, Berkeley, CA

Background: Data are limited regarding self-perception of HIV acquisition risk where HIV test and treat is ongoing or on how self-perception correlates with true risk. We compared self-assessed HIV risk to an empirically-based risk score for HIV seroconversions to inform PrEP implementation in SEARCH.
Methods: Seroconversion data from the SEARCH intervention (HIV test and treat) arm were analyzed using machine-learning to build an HIV risk score that maximized observed seroconversion coverage under a minimized number of persons to be provided PrEP. The risk score included age, sex, marital status, polygamy, education, circumcision, occupation, and alcohol use. After 3 years of HIV test and treat, we measured self-assessed HIV risk (SAR) through structured survey among HIV-uninfected adults in the rural Kenyan community of Nyatoto. We evaluated gender-specific predictors of SAR and its relation to our empirically-derived risk score.
Results: Baseline community HIV prevalence was 15%. Overall, 15% of HIV-uninfected adults (N=4159) perceived themselves at risk of HIV. Among men and women, predictors of SAR included age 25-35 yrs (OR 2.3,95%CI:1.6,3.1; OR 1.6, 95%CI:1.2,2.2, relative to 15-25 yrs), employment in the high-risk informal (non-government regulated) sector (OR 3.0,95%CI: 1.9,4.9; OR 2.4,95%CI:1.1,5.3, relative to formal sector) or low-risk informal sector (OR 1.4; 95%CI:1.1,1.9; OR 1.4,95%CI:1.1,1.9, relative to formal sector), polygamous marriage (OR 1.9,95%CI 1.2,1.9; OR 1.8,95%CI:1.4,2.5), and greater than primary education. Among women, SAR was higher among those with an HIV+ spouse (OR 8.5,95%CI:2.0,35.7). Among men, alcohol use predicted SAR (OR 2.6,95%CI:1.5,4.5 for >7 days drinking/month, relative to not drinking). Among both men and women, HIV SAR was higher among those identified as high-risk using our empirically-derived score (OR 1.7,95%CI:1.3,2.4; OR 1.7,95%CI:1.3,2.2). Among all (N=858) persons identified as empirically high-risk, 21% perceived themselves at risk.
Conclusion: After 3 years of HIV test and treat,15% of HIV-uninfected subjects perceived themselves at risk of HIV acquisition. Although an empirically-derived risk score predicted self-assessed risk, only 21% of individuals empirically targeted for PrEP perceived themselves at high-risk for HIV. These data suggest that optimizing the uptake of empirically targeted PrEP will require new community sensitization approaches to help persons recognize actual HIV risk.

859 HIV RISK FACTORS AND RISK PERCEPTION AMONG ADOLESCENT GIRLS AND YOUNG WOMEN IN MALAWI

Joan T. Price[1], Nora E. Rosenberg[1], Bertha Maseko[2], Savvy Brar[2], Twambilile Phanga[2], Audrey Pettifor[1], Linda-Gail Bekker[3]
[1]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Univ of North Carolina Proj–Malawi, Lilongwe, Malawi, [3]Univ of Cape Town, Cape Town, South Africa

Background: The high HIV incidence among adolescent girls and young women in sub-Saharan Africa has been associated with a range of individual, social, and structural risk factors. Perceived risk of HIV is a key element in the uptake of prevention programming; an understanding of the association between HIV risk factors and perceived risk in a vulnerable group can inform intervention planning and targeting.

Methods: Adolescent girls and young women 15-24 years old were recruited from four government-run health clinics in Lilongwe, Malawi to participate in a study evaluating four models of HIV service delivery. They completed a baseline survey assessing risk factors, and if HIV-uninfected or HIV-unknown, their risk perception. Risk perception was elicited by assessing lifetime chances of acquiring HIV with three possible responses: "no chance", "small chance", or "high chance". This variable was then dichotomized for analysis into "any chance" or "no chance". We analyzed associations between risk perception and five HIV risk factors: inconsistent or no condom use, more than one lifetime sexual partner, >5 year age difference with a current partner, transactional sex, and forced sex with a current partner.
Results: In a cohort of 1000 adolescent girls and young women, 967 reported being HIV-negative or of unknown status at baseline and were included in this analysis. The median age of respondents was 19 (IQR 17–21). 69% used condoms inconsistently or not at all; 54% had >1 lifetime sexual partner; 15% had a partner >5 years older; 21% reported current transactional sex; and 46% reported forced sex from a current partner. 41% reported no perceived lifetime risk of HIV. Inconsistent condom use (OR 1.86, 95% CI 1.40–2.47), >1 lifetime partner (OR 1.65, 95% CI 1.26–2.15), transactional sex (OR 1.50, 95% CI 1.07–2.11), and forced sex (OR 1.71, 95% CI 1.30–2.25) were associated with any perceived lifetime risk of HIV. Despite association between risk factors and risk perception, 35% of those with one or more risk factor perceived no lifetime risk of acquiring HIV.
Conclusion: Adolescent girls and young women in this cohort have a high prevalence of HIV risk factors. However, many participants with these risk factors perceive no risk of HIV acquisition. As a critical gap in the HIV prevention cascade, accurate risk perception is needed to tailor effective and sustained combination prevention strategies for this vulnerable population.

860 GENDERED PATTERNS OF MOBILITY PREDICT HIV PREVALENCE IN UGANDA/KENYA IN SEARCH STUDY

Carol S. Camlin[1], Tor Neilands[1], Jane Kabami[2], Gabriel Chamie[1], Elizabeth A. Bukusi[3], Tamara D. Clark[1], Moses R. Kamya[4], Maya L. Petersen[5], Diane V. Havlir[1], Edwin D. Charlebois[1]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Infectious Diseases Rsr Collab, Kampala, Uganda, [3]Kenya Med Rsr Inst, Nairobi, Kenya, [4]Makerere Univ, Kampala, Uganda, [5]Univ of California Berkeley, Berkeley, CA, USA

Background: Geographic mobility is highly prevalent in Sub-Saharan Africa and challenges HIV prevention and treatment goals: it can break bonds between individuals and care systems, link geographically separate epidemics, and intensify transmission. However, research on links between mobility and HIV has yielded discordant findings, due in part to suboptimal measures that do not capture the full dimensions of mobility, including its gender-specific forms. We therefore sought to characterize relationship between HIV prevalence and mobility in an ongoing HIV test and treat study (SEARCH, NCT01864603).
Methods: We examined associations between measures of mobility and baseline HIV prevalence among 134,752 census-enumerated adults aged ≥15 years in 32 rural communities in Uganda and Kenya participating in the ongoing Sustainable East Africa Research in Community Health (SEARCH) trial. Multilevel logistic regression analyses, containing random intercepts for community, were conducted with Stata 13 stratified by gender.
Results: Controlling for region, age, education level, marital status and household wealth index, HIV prevalence was significantly associated with number of nights spent in main household of residence in past month and migrated in past year in both men and women. Relative to those with no past year migration, odds of infection were 35% higher in migrant men (OR 1.36 [95%CI 1.17,1.59]) and women (OR 1.35 [95%CI 1.12,1.63]). Relative to those who spent few or no nights in household in past month, men who spent every night had lower odds of HIV infection (OR 0.79 [95% CI 0.72, 0.88), as did women who spent most nights (OR 0.88 [95%CI 0.78,0.99) or every night (OR 0.79 [95%CI 0.71,0.89]). In addition, the number of months living outside household in past year was associated with HIV prevalence in men only. The adjusted odds of infection were 20% higher in men who had spent 6 or more months away from the household in past year, relative to men who were more residentially stable (OR 1.21 [95%CI 1.04,1.4]).
Conclusion: Gender-specific patterns of mobility were associated with HIV prevalence, controlling for important confounders. Absence from households in past year was a stronger predictor in men, but residence change (migrated in past year) had similar effects in men and women. Even very recent mobility (nights away in past month) was associated with higher HIV prevalence. Causal pathways may be complex and bidirectional, and require further investigation with longitudinal data.

861 HIGH RISK BEHAVIOR IN MARRIED PEOPLE LIVING WITH HIV: IMPLICATIONS FOR PREVENTION

Zachary A. Kwena[1], Catherine K. Makokha[1], David O. Ang'awa[1], Elizabeth A. Bukusi[2]
[1]Kenya Med Rsr Inst, Kisumu, Kenya, [2]Kenya Med Rsr Inst, Nairobi, Kenya

Background: Global efforts to end HIV by 2030 focus on reducing and eventually eliminating new infections in priority populations. Preventing high risk sexual behaviors among people living with HIV/AIDS is a cornerstone for such efforts. We sought to establish HIV high risk behavior among married people living with HIV/AIDS in the fishing communities on Lake Victoria within Kenya.
Methods: In 2015, we conducted a resurvey of 545 couples who had previously been enrolled in a cross-sectional survey conducted between September 2011 and June 2012. Although the target was to trace and re-interview all couples, we only contacted 903 individuals of whom 89.5% were couples. Among those contacted were 175 individuals who had tested HIV positive during the first survey and referred to care. On contact, the participants were asked to return to the study clinic to participate in a resurvey. Returning participants were consented and invited for face-to-face interviews in private rooms. We asked them whether or not they had enrolled in care and time to enrolment. In addition, we asked them about their sexual behavior including extramarital partnerships and condom use in marriage and extramarital partnerships. We defined high risk sexual behavior as reporting (1) extramarital sex in the preceding 12 months and, (2) inconsistent marital and extramarital condom use regardless of partners HIV status.
Results: Overall, 61% of the participants were involved in high risk sexual behavior. Marital condom use was low with 46% reporting inconsistent condom use in their marriages. This did not improve even among those in serodiscordant relationships where 38% reported inconsistent condom use. One third (33%) reported extramarital sex in the preceding 12 months; 35% reporting unprotected sex in their most recent extramarital sexual encounter. Half (53%) of those who reporting unprotected extramarital sex also reported unprotected marital sex. Enrolment in HIV care was associated with reduced odds of engaging in high risk sexual behavior (aOR 0.14; 95%CI: 0.03-0.66) after controlling for age, spouse HIV status, education level and wealth index.
Conclusion: Married people living with HIV/AIDS in these fishing communities on Lake Victoria engage in high risk sexual behavior that can result in new infections within their marriages and sexual networks. Rigorous process of ensuring linkage to care after people test HIV positive and ensuring enrolment into care could prevent involvement in high risk behavior and new infections.

862 HIV AND SYPHILIS COINFECTION IN MEN WHO HAVE SEX WITH MEN, BANGKOK, 2005–2016

Chaiwat Ungsedhapand[1], Kanokpan Panchroen[1], Anuwat Sriporn[1], Wichuda Sukwicha[1], Wipas Wimonsate[1], Nutthawoot Promda[1], Santi Winaitham[1], Anupong Chitwarakorn[2], Eileen F. Dunne[3], Michael Thigpen[3]
[1]Thailand MOPH–US CDC Collab, Nonthaburi, Thailand, [2]Thailand MOPH, Nonthaburi, Thailand, [3]US CDC, Nonthaburi, Thailand

Background: We evaluated HIV and syphilis infection among men attending Silom Community Clinic for HIV voluntary counseling and testing (VCT) services in Bangkok, Thailand over 10 years.
Methods: We tested VCT clients for HIV and syphilis, and collected basic demographic information. Serological testing for syphilis used a 2-step algorithm with rapid plasma reagin and if reactive, treponemal specific testing (Immunochromatography assay). Serological testing for HIV infection followed the Thailand national 3-step algorithm using rapid tests. We used multivariable logistic regression to evaluate factors associated with coinfection at the first visit. We also described HIV only, syphilis only, or both HIV and syphilis (dual) seroconversion. We used Wilcoxon Signed Ranks Test to compare the time to seroconversion between HIV and syphilis.
Results: From September 2005-June 2016, there were 10,014 unique clients. Among these, 786 (7.8%) had prevalent HIV and syphilis coinfection, 1,953 (19.5%) had HIV infection only, 458 (4.6%) had syphilis only, and 6,817 (68.1%) had neither infection. Prevalent coinfection increased with each calendar year from 1.3% in 2006 to 9.5% in 2015 ($p<0.05$). Coinfection was more common among those ≥ 22 years (aOR 1.8, 95% CI 1.4-2.2), clients not born in Bangkok (aOR 1.3, 95% CI 1.1-1.6), and Thai clients (aOR 2.0, 95% CI 1.5-2.7).

Among 3,044 clients, 292 (9.6%) had HIV seroconversion only, 317 (10.4%) had syphilis seroconversion only, and 78 (2.6%) had dual HIV and syphilis seroconversion. Among those with dual seroconversion, the median time to HIV infection was 2.1 years (25-75 Interquartile Range [IQR] 1.3-3.5) and the median time to syphilis infection was 2.8 years (25-75 IQR 1.4-4.0) (p=0.354).
Conclusion: Over 10 years, prevalent HIV and syphilis coinfection was common and increased each year; 2.6% of clients had dual HIV and syphilis seroconversion. Continued surveillance for HIV and syphilis infection among MSM will support prevention efforts.

863 SUBSEQUENT AND RECURRENT STI AMONG THAI MSM AND TG IN TEST AND TREAT COHORT

Akarin Hiransuthikul[1], Supanit Pattanachaiwit[1], Nipat Teeratakulpisarn[1], Parinya Chamnan[2], Panita Pathipvanich[3], Suchart Thongpaen[4], Supabhorn Pengnonyang[1], Deondara Trachunthong[1], Nittaya Phanuphak[1], for the Thai MSM/TG Test and Treat Study Group
[1]The Thai Red Cross AIDS Rsr Cntr, Bangkok, Thailand, [2]Sanpasitthiprasong Hosp, Ubonratchathani, Thailand, [3]Lampang Hosp, Lampang, Thailand, [4]Mahasarakham Hosp, Mahasarakham, Thailand
Background: Men who have sex with men (MSM) and transgender women (TG) are at increased risk for sexually transmitted infections (STI). However, the information on the incidence and characteristic of those who have subsequent and recurrent STI are lacking.
Methods: During December 2012 - December 2013, Thai MSM and TG aged ≥18 years were enrolled into the Test and Treat study. Participants who came to follow-up visit were analyzed for subsequent STI; and recurrent STI was analyzed from those who had ≥1 STI at baseline. Blood collected for syphilis and pharyngeal swab, urine, anal swab, and neovaginal swab (for TG) for gonorrhea and chlamydia screening at baseline, month 12, and month 24 were used to identify subsequent and recurrent STI (defined as any subsequent STI diagnosed over a 24-month period). Cox proportional hazards regression was used to identify potential predictors of recurrent STI among baseline covariates.
Results: From 811 MSM and TG enrolled, 448 (55.2% of total) came to follow-up visit and had STI test. Subsequent STI incidence was 2.2 per 100 person-months. Common subsequent STIs were anal chlamydia (1.1 per 100 person-months), pharyngeal and anal gonorrhea, and syphilis (0.6 per 100 person-months each). Baseline HIV-positive status increased risk of subsequent STI (adjusted hazard ratio [aHR] 1.8; 95% CI 1.2-2.8, p=0.006). Other independent risk factors were low income, baseline anal chlamydia, syphilis, had/unsure of previous STI, and popper use (p<0.05). Of 448 participants, 154 (34.4%) had baseline STI, 50 (32.5% of 154) were HIV-positive and 96 (62.3% of 154) had recurrent STI within a 24-month period. The incidence for recurrent STI was 3.8 per 100 person-months. Those with baseline anal chlamydia, pharyngeal chlamydia, and anal gonorrhea had the highest incidence rate of recurrent infection with the same respective diseases (2.6, 2.2, and 1.6 per 100 person-months, respectively). Baseline HIV-positive status (aHR 1.8; 95% CI 1.14-2.85, p=0.012) and circumcision (aHR 2.2; 95% CI 1.12-4.32, p=0.021) were associated with increased risk for recurrent STI.
Conclusion: Among Thai MSM and TG enrolled into the Test and Treat study, baseline HIV-positive status increased the risk of both newly acquired and re-acquired STI over a 24-month period. Targeted STI educational campaigns and increased frequency of STI screening for earlier diagnosis and treatment are needed to improve STI outcome among MSM and TG in both HIV prevention and treatment programs.

864 RISK FACTORS AND INCIDENCE OF SYPHILIS IN HIV-INFECTED PERSONS, THE HOPS, 1999–2015

Richard Novak[1], Abdelhamid Ghanem[1], Rachel Hart[2], Douglas Ward[3], Carl Armon[3], Kate Buchacz[4]
[1]Univ of Illinois at Chicago, Chicago, IL, USA, [2]Cerner Corp, Kansas City, MO, USA, [3]Dupont Circle Physicians Group, Washington, DC, USA, [4]CDC, Atlanta, GA, USA
Background: The incidence of syphilis has been increasing, especially among gay, bisexual and other men who have sex with men (MSM) for at least a decade in the United States (US). We assessed incidence, temporal trends and associated risk factors for newly diagnosed syphilis infections among HIV-infected patients in care during a 15-year period.
Methods: We analyzed data from the HIV Outpatient Study (HOPS) cohort participants seen at ten US HIV clinical practice sites from January 1, 1999 to June 30, 2015. New syphilis cases were defined based on a combination of established laboratory parameters as well as clinical diagnoses. We assessed incidence rates of syphilis by patient sociodemographic, clinical and behavioral characteristics, and performed multivariable Cox proportional hazards regression analyses of risk factors for new syphilis infections.
Results: We studied 6888 HIV-infected participants, among whom 641 had one or more new syphilis diagnoses during a median follow-up of 5.2 years (interquartile range: 2.0 to 10.8). Most study participants were male (78%) and aged 31-50 years (Table) and 56% of participants were MSM, 28% heterosexuals, 10% persons who inject drugs (PWID) and 6% other/unknown risk. There were a total of 799 syphilis diagnoses for an overall incidence of 1.8 per 100 person-years (95% Confidence Interval [CI] 1.6-1.9). The crude incidence rate was higher among MSM than heterosexuals (2.6 vs. 0.7, P <0.001), was higher among participants aged 18-30 years than over 50 years (3.0 vs. 0.8, P<0.001), and was elevated among non-Hispanic blacks vs. white and Hispanic/Latino participants (Table). Rates of diagnosed syphilis were highest in the most recent time period, 2011-2015, as compared with prior periods (Table). In multivariable analyses, the independent risk factors for syphilis included (all P< 0.001): being aged 18-30 years (hazard ratio [HR] 1.8, CI 1.5-2.1) vs older, having MSM HIV risk (HR 4.4, CI 3.6-5.5) vs other HIV risks, being black, non-Hispanic (HR 1.8, CI 1.5-2.1) vs other race/ethnicities, and being observed during 2011-2015 (HR 2.3, CI 1.7-3.0) vs earlier periods.
Conclusion: The steady increases in the syphilis incidence rate through 2015, particularly among HIV-infected patients who are younger, black, non-Hispanic and MSM, reflect ongoing sexual risk. Results highlight need for enhanced and targeted prevention interventions in this population.

865 INCIDENT SYPHILIS INFECTIONS DECLINED IN WELL-CHARACTERIZED COHORT OF HIV+ PERSONS

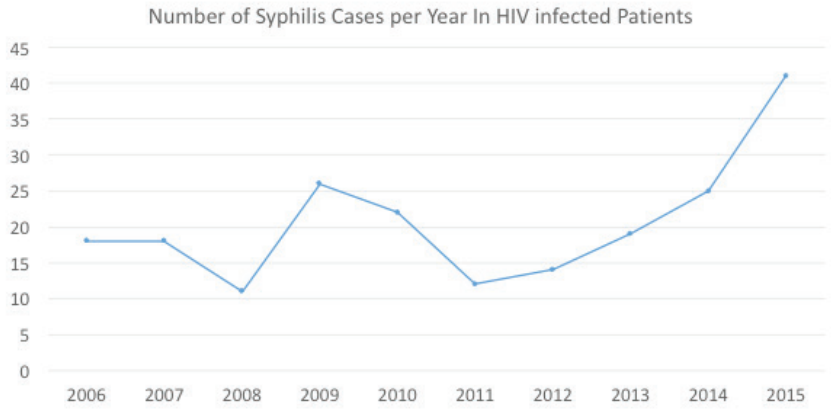
Anuradha Ganesan[1], Xun Wang[2], Robert Deiss[3], Julie Pavlin[3], Tomas Ferguson[4], Thomas O'Bryan[5], Jason Okulicz[6], Ryan Maves[7], Karl Kronmann[8], Grace Macalino[3]
[1]Uniformed Services Univ of the Hlth Scis, Rockville, MD, USA, [2]Henry M. Jackson Fndn for the Advancement of Military Med, Rockville, MD, USA, [3]Tripler Army Med Cntr, Honolulu, HI, USA[4]Uniformed Services Univ of the Hlth Scis, San Antonio, TX, USA, [5]San Antonio Military Med Cntr, San Antonio, TX, USA, [6]Naval Med Cntr San Diego, San Diego, CA, USA, [7]Naval Med Cntr Portsmouth, Portsmouth, VA, USA
Background: Since 2000, syphilis rates have increased in the US; racial minorities are disproportionately represented. We used results of serially collected Non-Treponemal tests (NTrt) to examine incident syphilis infections in the US Military HIV Natural History Study (NHS), a cohort of HIV-infected Department of Defense beneficiaries
Methods: We included all NHS subjects with visits since 2004.Syphilis was diagnosed with a positive NTrt confirmed by treponemal testing. Descriptive statistics included temporal trends between 2004 and 2015 and sexual risk behavior data from a computer-assisted self-interview (administered since 2014). Time-updated Poisson regression was used to examine incidence rate ratios, while logistic regression was used to examine sexual risk behavior correlates.
Results: 2719 participants contributed 14,504 person years (PY) of follow-up. Since 2004, 423 incident infections (99.3% male, 57.2% African- American, 27%- Caucasian) were recorded in the NHS database. Syphilis incidence was highest during calendar years 2004-2007 [3.2/100 PY (2.7, 3.7)], and lowest between 2012-2015 [2.4/100 PY (2.0, 2.9); p=0.03]. Rates in 2008-2011 were similar to those observed in 2004-2007 [3.1/100 PY (2.6, 3.6); p=0.74]. While overall rates were highest among African-American [3.9/100 PY (3.4, 4.4)], they declined only in this ethnic group over time (Table). Of 1,328 individuals completing the questionnaire, 53 men were subsequently diagnosed with syphilis. Compared to those without syphilis, subjects with syphilis often perceived themselves as being at medium or high risk for infection (45% vs.17%, p=<.0001). In a univariate model, ethnicity, drug use, higher numbers of male sex partners, participating in oral or anal intercourse, and use of social media to seek partners were associated with syphilis. In a selected multivariate model AA ethnicity [compared to Caucasian, OR 2.4 (1.2-4.8)] and participation in anal intercourse [OR 3.0 (1.5-6.2) remained independently associated with infection
Conclusion: Syphilis rates in the NHS have declined, especially among AA, though this group remains disproportionately affected. Nonetheless, in spite of high self-perception of risk, subjects with syphilis still had high prevalence of high risk sexual behaviors. Given the observed association with social media use and subsequent infection, using social media to target high risk groups for prevention messages is a strategy worth pursuing in this setting.

		Cases	Years of Follow-Up	Rate (95% CI)	P-value
Overall		**423**	**14504.57**	**2.92 (2.64,3.21)**	
Race					
	Caucasian	114	6205.72	1.84 (1.52,2.21)	Ref
	African-American	242	6186.34	3.91 (3.43,4.44)	<.0001
	Hispanic/Other	67	2112.51	3.17 (2.46,4.03)	0.0004
African-American					
	2004-2007	104	2184.45	4.76 (3.89,5.77)	Ref
	2008-2011	81	2208.26	3.67 (2.91,4.56)	0.0784
	2012-2015	57	1793.63	3.18 (2.41,4.12)	0.0142

866 INCIDENT SYPHILIS INFECTIONS IN HIV-POSITIVE PATIENTS IN CARE

Raynell Lang[1], Ron Read[2], Soheil Ramazani[3], John Gill[2]
[1]Alberta Hlth Services, Calgary, Canada, [2]Univ of Calgary, Calgary, Canada, [3]Southern Alberta Clinic, Calgary, Canada

Background: Syphilis is a reemerging global infectious disease and in the province of Alberta rates of diagnosis have doubled between 2014-2015. The Southern Alberta Clinic (SAC) and Calgary STI Clinic identified a rising number of incident syphilis infections in patients successfully engaged in HIV care. The medical and demographic characteristics of those engaging in high-risk sexual behavior contracting syphilis were examined to enhance targeted preventative strategies.
Methods: Syphilis serology has been undertaken routinely with bloodwork used for monitoring HIV care for ten years in SAC. All cases of incident Syphilis infections (initial and reinfection) in HIV positive patients between 2006 and 2016 were reviewed. Data was retrospectively collected through a comprehensive medical chart review combined with manual data abstraction from an EMR database in both the Calgary STI clinic and SAC. Data was pooled and statistical analysis was performed.
Results: We identified were 231 cases involving 188 individuals over 10 years. Of the 231 cases, 170 (74%) were the patients first syphilis infection, whereas the remaining 61 (26%) cases were repeat infections. Since 2011(12), cases had doubled by 2014 (25) and more than tripled by 2015 (41). The vast majority of those acquiring syphilis were males (94%) of Caucasian race (72%). Of the males 76% are MSM, 21% heterosexual and 3% IDU. The average age of this population is 42 years with a range of 21-72 years. 52% of the population admitted to current or prior excessive alcohol use, 27% to smoking and 27% to recreational drug use. The average length of time between HIV infection and incident syphilis infection was 7.8 years with 31% of the population having been HIV positive for over 10 years. HIV viral loads were fully suppressed in 64% of the population prior to contracting syphilis. 80% of the individuals were on ART at the time of syphilis co-infection. There was no significant change in CD4 counts or HIV viral loads prior to and following syphilis infection .
Conclusion: We identified a dramatic increase in incident syphilis infection in the gay male Caucasian population while receiving HIV care over last three years. HIV positive population demonstrates an emerging public health concern. As part of a quality assurance program we have identified demographic features and disease trends that may be used for development of targeted preventive strategies.



867 SCREENING FOR EXTRAGENITAL CT/GC AMONG HIV-INFECTED MSM: A COMPARISON OF 4 NAATS

Jodie Dionne-Odom, Kristal Aaron, Mary Banasiewicz, Sarah Dougherty, Brice Daniels, James Raper, Edward Hook, Barbara Van Der Pol
Univ of Alabama at Birmingham, Birmingham, AL, USA

Background: CDC recommends annual screening for Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (GC) using NAAT at sites of exposure in adults with HIV. NAAT is highly sensitive but testing is not FDA-approved at rectal and pharyngeal sites and several testing platforms have become available. Although HIV-infected MSM have high incidence rates of rectal and pharyngeal CT/GC, clinic screening rates are suboptimal.
Methods: HIV-infected MSM who presented to clinic for routine care and reported receptive anal intercourse in the past 30 days were eligible to participate. Self-collected rectal swabs, urine, and provider-collected pharyngeal samples were run on at least two of four platforms and positivity rates for CT and GC were determined. Data for all visits were

included for subsequent analyses. Comparison across platforms was performed using repeated measures analysis to test for within-subject effects. Estimates of sensitivity and specificity were obtained separately relative to the composite infection standard (CIS) for rectal and urine samples. For oropharyngeal samples, estimates of sensitivity and specificity were obtained relative to the patient infection standard (PIS) in which two NAATs had to be positive. All statistical analyses were performed using SAS 9.4.
Results: Of 151 men enrolled, the median age was 35 and 19.9% had GC or CT detected at one or more of three sites. There were 48 positive tests in this group (27 CT, 21 GC). CT was identified in 16.4% of rectal swabs, 2.1% of urine, and 0.0% of oropharyngeal swabs; while GC was identified in 7.5% of rectal swabs, 2.1% of urine, and 4.9% of oropharyngeal swabs. All of the NAAT CT/GC platforms had statistically similar test characteristics (p=0.06). CT sensitivity estimates ranged from 83.3%-100.0% using CIS and specificity was >98.2% for all sample types. Sensitivity ranged from 63.6%-100.0% using CIS and 75.0-90.0% using PIS for detection of GC infections; and specificity for GC infections was >98.3%.
Conclusion: CT or GC was detected in 1 of 5 HIV-infected MSM who reported receptive anal intercourse in the past 30 days. Most extragenital infections would have been missed with urethral screening alone. Each of the four testing platforms performed similarly at rectal and pharyngeal sites.

	Sensitivity (%, n, range)				Specificity (%, n, range)			
Sample Type	Panther	Viper	Cobas	GeneXpert	Panther	Viper	Cobas	GeneXpert
Rectal CT	95.2% [20/21] (76.2-99.9%)	91.3% [21/23] (72-98.9%)	83.3% [20/24] (62.6-95.3%)	91.7% [22/24] (73-99%)	98.2% [159/162] (94.7-99.6%)	98.8% [161/163] (95.6-99.9%)	99.4% [160/161] (96.6-100%)	99.4% [157/158] (96.5-100%)
Urine CT	100.0% [3/3] (29.2-100%)	100.0% [3/3] (29.2-100%)	100.0% [3/3] (29.2-100%)	100.0% [3/3] (29.2-100%)	100.0% [182/182] (98-100%)	100.0% [182/182] (98-100%)	100.0% [182/182] (98-100%)	100.0% [175/175] (97.9-100%)
Pharyn-geal CT	N/A	100% [1/1] -	N/A	N/A	99.5% [183/184] (97-100%)	100.0% [183/183] (98-100%)	N/A	N/A
Rectal GC	100.0% [8/8] (63.1-100%)	63.6% [7/11] (30.8-89.1%)	90.0% [9/10] (71.4-100%)	90.0% [9/10] (71.4-100%)	98.9% [173/175] (97.3-100%)	100.0% [175/175] (97.9%-100%)	98.9% [173/175] (97.3-100%)	99.4% [171/172] (96.8-100%)
Urine GC	100.0% [1/1] (2.5-100%)	100.0% [1/1] (2.5-100%)	100.0% [1/1] (2.5-100%)	100.0% [1/1] (2.5-100%)	98.9% [182/184] (96.1-99.9%)	99.5% [183/184] (97-100%)	100.0% [184/184] (98-100%)	100.0% [177/177] (97.9-100%)
Pharyn-geal GC	75.0% [9/12] (42.8-94.5%)	90.0% [9/10] (55.5-99.8%)	N/A	N/A	99.4% [170/171] (96.8-100%)	98.3% [170/173] (95-99.6%)	N/A	N/A

868LB NALTREXONE IMPLANT IMPROVES HIV TX OUTCOMES VS ORAL NTX IN OPIATE ADDICTED PATIENTS

Evgeny Krupitsky[1], Edwina Zvartau[1], E. Blokhina[1], Elena Verbitskaya[1], D. Lioznov[1], T. Yaroslavtseva[1], Sabrina Poole[2], **Robert Gross**[2], George Woody[2]
[1]First Pavlov State Med Univ of St. Petersburg, St. Petersburg, Russian Federation, [2]Univ of Pennsylvania, Philadelphia, PA, USA,

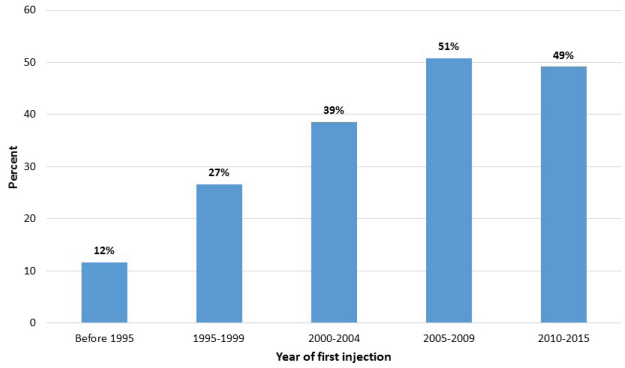
Background: Aim: HIV+ opiate users often have poor adherence to antiretroviral therapy (ART). An earlier study found that a one-gm extended release naltrexone implant (NI) prevents relapse for ~ 3 months and improves addiction treatment outcomes. We aimed to assess the impact of NI compared to 50 mg daily oral naltrexone (ON) on ART outcomes.
Methods: Methods: 200 detoxified HIV+ opiate addicted patients starting ART in St. Petersburg were randomized 1:1 to 12 months of NI + ON placebo (NI group), or ON + NI placebo (ON group). All were offered every other week drug counseling. The primary outcome was plasma HIV RNA (LLQ = 400 copies/ml) at month 12; secondary outcomes were adherence to addiction treatment, retention in ART and ART adherence indexed by MEMS, CD4 count, and adverse events.
Results: Results: Baseline characteristics were similar between groups. HIV RNA suppression was more common in NI than ON (66% vs 50%; OR [95% CI] = 1.94 [1.10-3.43]), addiction treatment was more often completed in NI than ON (32% vs 17%, respectively, p<0.05), and retention in ART care was better in NI than ON (46% vs 32%; p<0.05). The proportion of ART doses taken was higher in completers vs. dropouts: 73.7% (95% CI: 67.2-80.2%) vs. 64.9% (95% CI: 59.7-70.1%; F1, 198 = 4.37; P= 0.038). CD4 count increase was greater in those who continued naltrexone regardless of group assignment as seen by CD4 change at end of treatment compared to baseline for completers vs. drop outs: +206.2 cells/mm3 ±201.8 vs. +67.3 cells/mm3 ±159.4 (p<0.001). The groups did not differ in adverse events (32% for ON vs. 30% for NI).
Conclusion: Conclusions: NI improved HIV treatment outcome and retention compared to ON in patients addicted to opioids and initiating ART in St. Petersburg, Russia. Extended release naltrexone may be a useful alternative to methadone or buprenorphine maintenance for opioid addicted patients starting ART who are not interested in agonist-based medication assisted therapy or where it is difficult to access or otherwise unavailable. Supported by: NIDA grants R01 DA026336; K05 DA 17009; U10DA013043

869 "HOOKED ON PAINKILLERS" PRIOR TO FIRST INJECTION AMONG PWID IN 16 US CITIES

Dita Broz[1], Maria Zlotorzynska[2], Michael Spiller[1], Gabriela Paz-Bailey[1], for the NHBS Study Group
[1]CDC, Atlanta, GA, USA, [2]Emory Univ, Atlanta, GA, USA

Background: Misuse of prescription opioids (PO) increased dramatically in the US since the early 2000s and may lead to increases in heroin use and drug injection. Understanding the role of PO in injection initiation is key to preventing injection-related harms, including HIV and hepatitis C. We assessed factors associated with PO abuse prior to first injection (prior PO abuse) among people who inject drugs (PWID).
Methods: PWID ages ≥18 years were recruited for the 2015 National HIV Behavioral Surveillance using respondent-driven sampling. Data on prior PO abuse ("hooked on painkillers before you injected for the very first time") among PWID who injected opioids (heroin, PO; alone or in combination) were available in 16 cities. We estimated Poisson regression models with generalized estimating equations clustered on recruitment chain and adjusted for sampling design covariates to assess factors associated with prior PO abuse. We report adjusted prevalence ratios (aPR) and 95% confidence intervals (CI).
Results: Of 7,454 PWID, 2,208 (30%) reported prior PO abuse. Prior PO abuse was higher among PWID who began injecting in more recent years (Figure). PWID reporting prior PO abuse compared to other PWID were more likely to be younger (mean age 34 vs. 47 years, p<0.0001), female (32% vs 26%, aPR 1.22, CI 1.13-1.31), non-Hispanic white (65% vs. 33%, aPR 2.14, CI 1.85-2.47), have high school education or higher (74% vs 68%, aPR 1.21, CI 1.12-1.30) and receptively shared syringes (44% vs 33%, aPR 1.28, CI 1.19-1.37). PWID who reported prior PO abuse were less likely to test HIV-positive, even after controlling for age and race/ethnicity (2% vs 6%, aPR=0.59, 95%CI 0.41-0.84). Common sources of first ever PO were prescription by a physician (41%), purchased from friends, family or others (36%), and given by friends (29%). Mean time between first ever PO use and first injection was 5 years (SD=6.4, median 3).
Conclusion: Prior PO abuse was substantially higher among PWID who began injecting during the opioid epidemic (i.e., since 2000). PWID with prior PO abuse differed in socio-demographic characteristics and despite lower HIV prevalence, were more likely to engage in practices that increase risk of infection. Efforts to prevent HIV transmission and other blood-borne infections would benefit from injection prevention interventions for people who abuse PO and increased understanding of barriers and facilitators to effective prevention delivery for those already injecting.

Figure. "Hooked on painkillers" prior to drug injection initiation by year of first injection among persons who inject drugs in 16 U.S. cities.



870 OPIOID SUBSTITUTION THERAPY AND INITIATION INTO INJECTION DRUG USE IN SAN DIEGO, CA

Maria Luisa Mittal[1], Devesh Vashishtha[1], Xiaoying Sun[1], Sonia Jain[1], Richard S. Garfein[2], Steffanie A. Strathdee[2], Dan Werb[1]
[1]Univ of California San Diego, La Jolla, CA, USA, [2]Univ of California San Diego, San Diego, CA, USA

Background: Opioid substitution therapy (OST) is the gold standard of care for the management of opioid use disorder. OST is also known to reduce HIV risk behaviors among people who inject drugs (PWID) by reducing the frequency of injecting. Given that data suggest that PWID play a key role in initiating others into drug injecting through exposing others to injecting behaviors, our objective was to explore whether an association existed between OST enrollment and initiating others into injecting among PWID.
Methods: Preventing Injecting by Modifying Existing Responses (PRIMER; NIDA DP2-DA040256-01), is a multi-site cohort study assessing the impact of a range of socio-structural factors on the risk that PWID initiate others into injection. Preliminary results were drawn from a single participating cohort of PWID in San Diego ≥ 18 years old who reported injection drug use 6 months prior to baseline (STAHR-II; NIDA R01DA031074). PRIMER survey items were measured at 24-month follow up, and the outcome was defined as reporting ever initiating others into injecting; sustained OST enrollment was defined as being enrolled at 2 or more study visits (i.e., ≥1 year). Logistic regression modeling was used to identify associations.
Results: Participants (N=360) were predominantly male (n=253, 71%), with a mean age of 47 (Interquartile Range [IQR]: 38-55), and a median of 24 years injecting (IQR: 13-35). Thirty-nine percent (n=139) of participants reported ever enrolling in OST and 19% (n=70) reported being enrolled in OST during the study period. Less than half of participants (n=135, 38%) reported ever initiating others into injecting. In multivariable models, males who reported sustained enrollment in OST had decreased odds of initiating others into injecting (Adjusted Odds Ratio [AOR]: 0.23, 95% Confidence Interval [CI]: 0.10-0.50; p<0.01). Additionally, each year increase in age was associated with decreased odds of initiating others (AOR: 0.94, 95% CI: 0.91-0.97; p<0.01), and a higher number of years injecting was independently associated with increased odds of initiating others into injecting (AOR: 1.03, 95% CI: 1.00-1.06, p=0.05).
Conclusion: OST may improve community health and reduce HIV risk behaviors by reducing the incidence of injection drug use initiation. While preliminary, this study highlights the need to further investigate whether OST may, along with reducing injection-related harms, also impact the risk that individuals initiate injection drug use.

871 CHANGES IN PRESCRIPTION OPIOID, METH, AND COCAINE USE AMONG MSM IN 20 US CITIES

Brooke Hoots, Dita Broz, Lina Nerlander, Gabriela Paz-Bailey
CDC, Atlanta, GA, USA

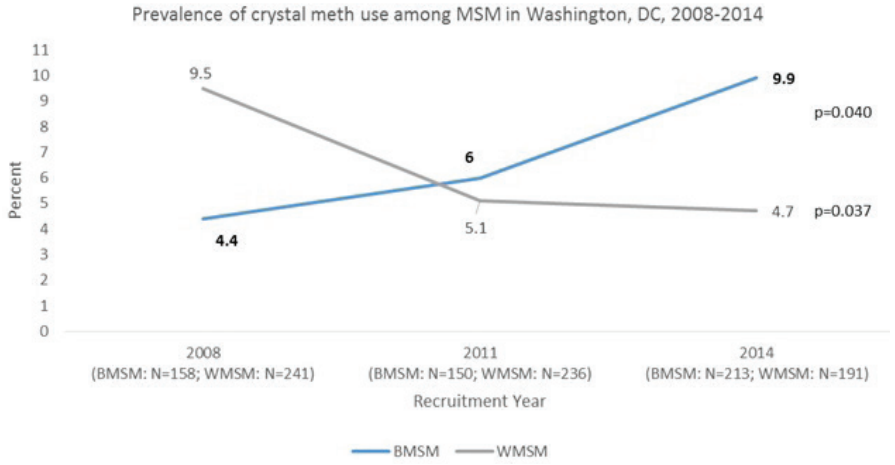
Background: Men who have sex with men (MSM) have higher rates of drug use compared with the general population and are at increased risk of contracting HIV. The United States is currently experiencing an opioid epidemic, but few studies have examined opioid use among MSM. Previous studies have focused on crystal meth, cocaine, and other drugs. We analyzed data from MSM participating in the National HIV Behavioral Surveillance to determine the prevalence of non-injected use of prescription opioids, meth, and cocaine by key characteristics, and to evaluate changes from 2008 to 2014.
Methods: Men were recruited using venue-based, time-space sampling in 20 US cities in 2008, 2011, and 2014. Non-injected use of meth, cocaine, and prescription opioids (e.g., Oxycontin, Vicodin, and Percocet) in the past 12 months were self-reported. Prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated from log-linked Poisson regression models to estimate the change in prevalence of drug use per three-year increase overall, and by demographic group.
Results: Meth use was more frequent among MSM who were white, had lower education and income, lived in Western cities, and were HIV-positive. There were no differences in meth use over time, with 7.8% reporting use in 2008, 6.6% in 2011, and 8.0% in 2014 (P=.76). Cocaine use was more frequent among MSM who were white and 'other' race and younger. Cocaine use was also stable over time, although much more frequent than meth use, with 18.6% reporting use in 2008, 16.9% in 2011, and 19.0% in 2014 (P=.75). Opioid use was on par with meth use and was more common among MSM who were white, younger, low education and income, and who lived in Western cities. Opioid use also did not increase overall, with 7.5% reporting use in 2008, 7.7% in 2011, and 7.8% in 2014 (P=.87). However, after adjusting for covariates, increases in opioid use were seen among black MSM (adjusted PR [aPR], 1.24, CI: 1.06-1.45) and those with less education (aPR 1.21, CI: 1.02-1.43) and low income (aPR 1.23, 95% CI: 1.02-1.49).
Conclusion: Overall, there were no changes in reported use of meth, cocaine, and opioids among MSM from 2008 to 2014. Opioid use was as frequent as meth use and is increasing among black MSM and those of low socioeconomic status. HIV prevention interventions need to consider assessing use of opioids and other commonly abused drugs among MSM and offer early treatment for drug dependence to prevent transition to injection.

872 CHANGING PATTERN OF CRYSTAL METH USE IN BLACK & WHITE MSM, WASHINGTON, DC, 2008–2014

Irene Kuo[1], Rudy Patrick[1], Jenevieve Opoku[2], Anthony Rawls[1], Manya Magnus[1], James Peterson[1], Michael Kharfen[2], Alan Greenberg[1]
[1]The George Washington Univ, Washington, DC, USA, [2]District of Columbia Dept of Hlth, Washington, DC, USA

Background: Crystal meth use is associated with increased sexual risk behavior, particularly among men who have sex with men (MSM). Despite evidence of declining methamphetamine use among MSM, it is unknown whether this is occurring across different racial groups. We explored trends in crystal meth use between black MSM (BMSM) and white MSM (WMSM) in Washington, DC over time.
Methods: Data from National HIV Behavioral Surveillance in 2008, 2011, and 2014 were used. MSM recruited via venue-based sampling completed an interviewer-administered survey regarding past year drug use and sexual behaviors and tested for HIV. The prevalence of self-reported past year crystal meth use was calculated for each data collection year by race; a chi-square test for trend assessed changes in prevalence over time. Multivariable logistic regression were stratified by race and identified independent correlates of crystal meth use, including year of data collection as a covariate.

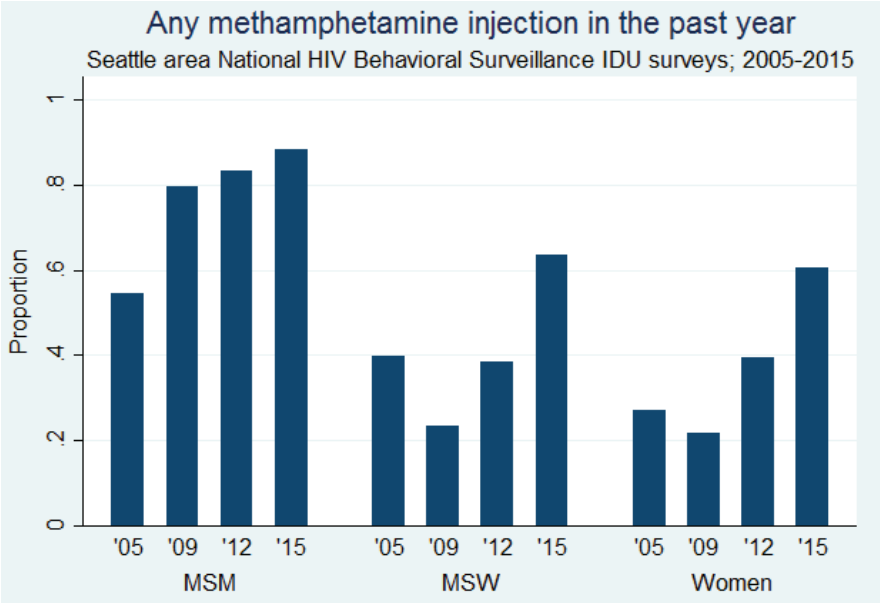
Results: Overall, 521 BMSM and 668 WMSM were analyzed. The age distribution and HIV prevalence was constant for WMSM across time, but BMSM were older in 2011 and had a higher HIV prevalence in 2014 versus other years. In 2008, 2011, and 2014, the prevalence of crystal meth use among BMSM was 4.4%, 6.0% and 9.9% (p=0.04) and 9.5%, 5.1%, and 4.7% respectively among WMSM (p=0.04). Among BMSM, independent correlates of crystal meth use were having ≥4 sex partners vs 1-3 (AOR: 2.7; 95% CI: 1.3, 5.8) and being HIV positive (AOR: 4.2; 95% CI:1.8, 9.7); there was an elevated odds of crystal meth use in 2014 versus 2008 (AOR: 2.5; 95% CI: 1.0, 6.5). Among WMSM, being older (AOR:2.5; 95%CI: 1.0,5.9), earning <$20K per year vs >$50K (AOR: 8.5; 95% CI: 3.1, 23.0), having ≥4 sex partners (AOR: 3.2; 95% CI: 1.3, 7.9), and being HIV positive (AOR: 10.6; 95% CI: 4.4, 25.3) were associated; there was reduced odds of crystal meth use over time for WMSM (2011: AOR: 0.4; 95% CI: 0.2, 0.9 and 2014: AOR: 0.3; 95% CI: 0.1, 0.7 vs 2008). Condomless anal sex was not associated with crystal meth use for either racial group.
Conclusion: We observed an increase in crystal meth use among venue-attending BMSM and a decrease among WMSM between 2008-2014. There is a need to better understand the changing pattern of use that might impact HIV risk, particularly for BMSM. Across both races, recent crystal meth use was associated with more sex partners and HIV-positivity, highlighting the continued need for interventions among crystal meth users to reduce HIV transmission risks.



873 INCREASING METHAMPHETAMINE USE AMONG NON-MSM WHO INJECT DRUGS IN KING COUNTY, WA

Sara N. Glick[1], Richard Burt[2], Kim Kummer[1], Joe Tinsley[2], Caleb Banta-Green[1], Matthew R. Golden[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Pub Hlth - Seattle & King County, Seattle, WA, USA

Background: In King County, WA, men who have sex with men (MSM) who inject methamphetamines (meth) are among the populations at highest risk for HIV infection, while HIV prevalence among other people who inject drugs (PWID) is low. Local drug problem indicators suggest recent increased meth use. It is not known if this increase is among MSM or non-MSM men and women, and if these networks are connected through injection equipment sharing. We investigated temporal trends in meth use among PWID in King County and estimated frequency and characteristics of injection equipment sharing.
Methods: We used data from two serial cross-sectional surveys of PWID in King County. From 2005-2015, four National HIV Behavioral Surveillance (NHBS) IDU surveys used respondent-driven sampling to survey PWID about their drug use behaviors (N=2,103). From 2004-2015, the Public Health–Seattle and King County Needle Exchange (NX) conducted 5 behavioral surveys of all NX clients over a two week period (N=1,964). These analyses were restricted to PWID who reported any sex in the past year and stratified by MSM, men who have sex with women (MSW), and women. We calculated frequencies and evaluated temporal trends using multivariable Poisson regression with a log link adjusting for age, gender, race, and NHBS field site locations.
Results: Any meth injection in the past year increased significantly among PWID – including MSM, MSW, and women – in King County between 2005-2015 (see Figure). NX survey data were nearly identical. In NHBS-IDU, the magnitude of change was greatest among women with reported meth use increasing from 27% in 2005 to 61% in 2015. Among MSW, meth use increased from 40% to 63%, and among MSM from 55% to 88%. These trends remained statistically significant after adjusting for potential confounders. Among NHBS-IDU meth injectors, sharing any drug injection equipment in the last year was reported by 54% of MSM, 73% of MSW, and 78% of women. Among meth injectors who were not MSM, 6% of men and 12% of women reported sharing injection equipment with someone who was likely to be a MSM in the previous 12 months. Likewise, 25% of MSM meth injectors reported sharing injection equipment with a MSW or woman.
Conclusion: Meth use has increased dramatically among PWID in King County over the past decade. Given non-trivial rates of sharing injection equipment with meth-using MSM – a population with an HIV prevalence of 35-40% – non-MSM men and women who inject meth could be an emerging population at risk for HIV.



874 REDUCING ALCOHOL CONSUMPTION IMPROVED HIV VIRAL SUPPRESSION IN WOMEN

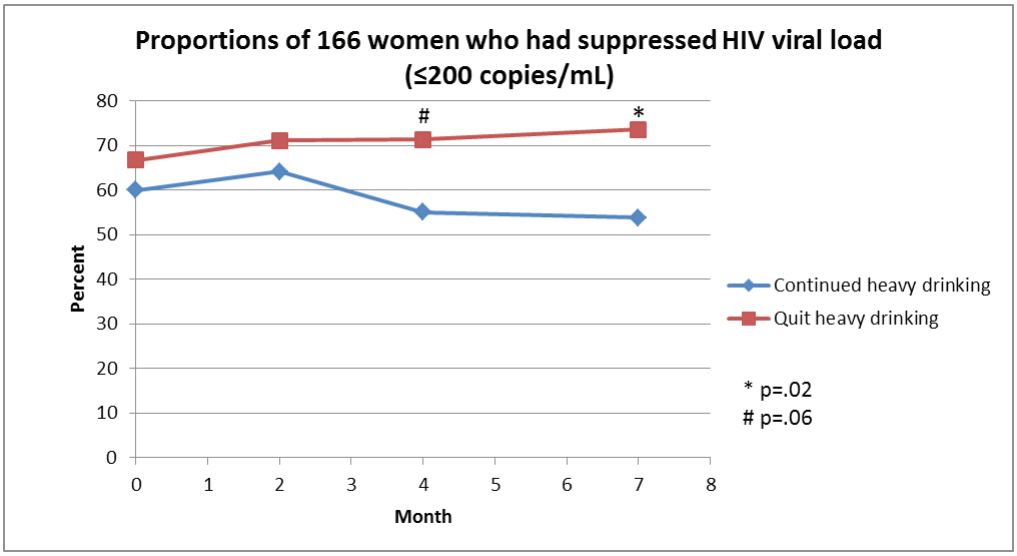
Robert L. Cook[1], Zhi Zhou[1], Maria J. Miguez[2], Babette Brumback[1], John Lewis[3], Luis Espinoza[3], Kendall J. Bryant[4]
[1]Univ of Florida, Gainesville, FL, USA, [2]Florida Intl Univ, Miami, FL, USA, [3]Univ of Miami, Miami, FL, USA, [4]Natl Inst on Alcohol Abuse and Alcoholism, Bethesda, MD, USA

Background: Alcohol use is common among persons living with HIV/AIDS (PLWH) and is associated with poor HIV-related outcomes. However, it is not clear whether interventions to reduce drinking will improve health outcomes among PLWH. We conducted an observational study of women participating in a randomized clinical trial to determine whether reduced drinking after alcohol intervention is associated with improvements in HIV viral suppression (NCT01625091).

Methods: From December, 2012 to August, 2016 we enrolled 194 women with HIV infection who exceed recommended alcohol drinking levels (>7 drinks/week or ≥2 binge sections/month). Women were randomly assigned to receive oral naltrexone or placebo for 4 months. Alcohol consumption and HIV viral loads were assessed at 2-, 4-, and 7-months after enrollment. We analyzed data from 166 women who completed the 7 month visit. Women were categorized as "quitting heavy drinking" or not based whether they had reduced to non-heavy drinking (<7 drinks/week) or complete abstinence at the 7-month timepoint. Logistic regression models with propensity score weighting were constructed to determine whether quitting heavy drinking was associated with improved HIV viral load suppression (≤200 copies/mL).

Results: Of the 166 women, 11%, 85%, and 4% were Hispanic, black, or white; the mean age was 48 years; and 96% were receiving antiretroviral therapy (ART). The majority of women (76%) had quit heavy drinking at 7 months. At baseline, there was no statistically significant difference in the quitters and non-quitters in HIV viral suppression (67% vs. 60%, p=0.44), or having >95% ART adherence (61% vs 59%, p=0.86). However, viral suppression improved over time in those who reduced drinking and the proportion of women with viral suppression at 7 months was significantly better in than those who quit vs. those who did not quit (74% vs. 54%, p=0.02). In the weighted logistic regression analysis, quitting heavy drinking was significantly associated with achieving HIV viral suppression (Adjusted OR: 2.62, 95% CI: 1.02, 6.69), when adjusting for baseline HIV viral load level.

Conclusion: In this sample of heavy drinking women living with HIV, those who successfully reduced drinking were significantly more likely to achieve HIV viral suppression. The findings support continued efforts to screen and intervene to reduce hazardous drinking in persons with HIV, especially those who have not achieved consistent HIV viral suppression.



875 THE RELATIVE IMPACTS OF ART AND HARM REDUCTION ON HIV INCIDENCE IN BRITISH COLUMBIA

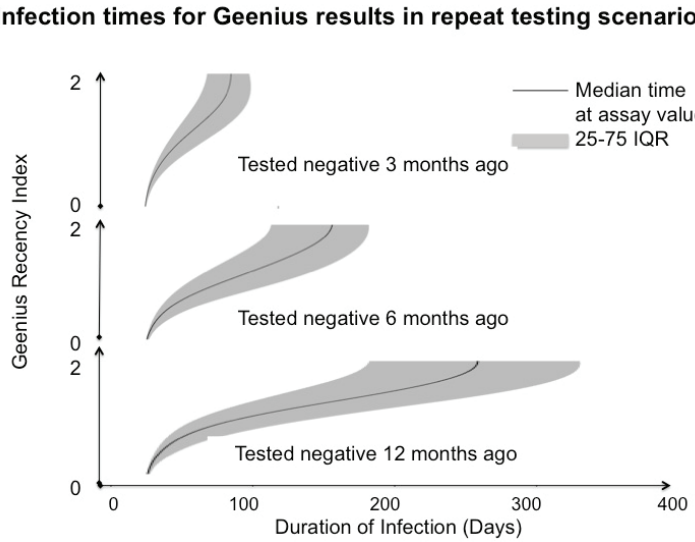
Bohdan Nosyk, Xiao Zang[1], Jeong E. Min, Emanuel Krebs, Viviane D. Lima, M-J Milloy, Jean A. Shoveller, Rolando Barrios, Evan Wood, Julio S. Montaner
BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada

Background: Access to antiretroviral therapy and harm reduction services have been cited as key contributors to the control of the HIV epidemic, however the specific contribution of the latter has been questioned due to uncertainty in the true efficacy of ART in prevention HIV transmission through needle sharing. We aimed to isolate the independent effects of the provision of opioid agonist treatment (OAT) and needle distribution (or harm reduction services), and the secondary preventive benefits of ART through needle sharing on HIV incidence in British Columbia, from 1996-2013.
Methods: Using comprehensive linked population-level data, we populated a dynamic, compartmental transmission model to simulate the HIV/AIDS epidemic in BC from 1996-2013. HIV incidence, mortality among PLHIV, and quality-adjusted life years (QALYs) were estimated. We further incorporated rates of OAT utilization and syringe distribution volumes to estimate their impact on the selected outcomes. We estimated scenarios designed to isolate the independent effects of ART on transmission via needle-sharing (assuming 50% (10%-90%) efficacy) and harm reduction services in reducing HIV incidence through needle sharing– both among PWID and at the population-level. Structural and parameter uncertainty was investigated.
Results: We estimated that 3240 (2394-4562) incident HIV cases were averted between 1996 and 2013 as a result of the combined effect of the expansion of harm reduction services and ART coverage on HIV transmission via needle sharing. Decomposing the effects of these services, we estimate harm reduction services alone would have accounted for 77% (62%-95%) of averted HIV incidence, while ART alone would have accounted for 44% (10%-67%) of incident cases. Due to high distribution volumes, provision of sterile syringes predominantly accounted for incidence reductions attributable to harm reduction services, however OAT provided substantially greater QALY gains.
Conclusion: The scale-up of harm reduction services had a profound impact on the course of the HIV epidemic in BC, with an impact on HIV incidence comparable to ART access. Harm reduction services such as needle distribution and OAT should be viewed as critical and cost-effective tools in a combination implementation strategy to reduce the public health and economic burden of HIV/AIDS.

876 ASSESSING UTILITY OF HIV INCIDENCE ASSAYS IN ESTIMATING INDIVIDUAL INFECTION TIMES

Christopher D. Pilcher[1], Shelley Facente[1], Eduard Grebe[2], Sheila Keating[3], Reshma Kassanjee[4], Matt A. Price[5], Michael P. Busch[3], Gary Murphy[6], Alex Welte[2], Travis C. Porco[1]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Stellenbosch Univ, Stellenbosch, South Africa, [3]Blood Systems Rsr Inst, San Francisco, CA, USA, [4]Univ of Cape Town, Cape Town, South Africa, [5]Intl AIDS Vaccine Initiative, New York, NY, USA, [6]Pub Hlth England, London, UK

Background: In HIV antibody-positive seroconverters, infection time can be estimated from negative and positive test dates. Even in frequent repeat testing situations (e.g. 3-12 monthly) this interval may not allow precise estimates. We explored whether modern tests for recent HIV infection could be used to narrow a 3-12 month interval and improve infection time estimates in HIV seroconverters.
Methods: We examined a panel comprising 196 ART-naïve timepoints from 96 HIV seroconverters with first viremia documented and followed up to 2 years.We focused on three commercial assays that provide information on HIV recency: Sedia LAg Avidity assay (ODn); Architect Ag/Ab screening assay (S/CO) and Geenius supplemental test (recency index). Growth curves were derived by linear interpolation within the observed range, and extrapolation of a semiparametric growth curve outside the observed range for each subject. The distribution of infection times associated with a particular result was obtained by repeatedly randomly sampling the entire population of curves at some prior distribution of infection times: this sampling time frame ranged from 0 to 3, 6 or 12 months in alternative testing scenarios. Quantiles derived from the simulation procedure were then smoothed with splines (degrees of freedom, 5), and truncated for test values larger than the value for which the largest median time was observed.
Results: The range of infection times seen at any test result was reduced by about half (42-56%) when compared to the prior distribution of plausible infection times, for all assays and scenarios. The Figure shows the median and 25-75%IQR of infection times associated with first Geenius results and a prior negative test in 3, 6 or 12 months prior. At lower assay values and in more frequent testing scenarios, the infection times associated with a given value were earlier and the IQR of these times was narrower. In the 3 monthly testing scenario, the average IQR was 22 days for LAg, 21 days for Geenius and 25 days for Architect.
Conclusion: Commercial diagnostic and incidence assays can inform infection time estimates newly HIV Ab-positive individuals. For a given result, however, both the estimate and its precision depend on prior information from the testing history. When the plausible interval defined by the history is short, timing estimates can be made with precision similar to Fiebig staging (IQR11 days). These findings have implications for targeting HIV prevention, cure research and vaccine trial design.



877 A MULTIPLEX ASSAY FOR MONITORING RECENT HIV-1 TRANSMISSION IN LOCALIZED OUTBREAKS

Kelly Curtis, Ellsworth Campbell, Krystin A. Price, William M. Switzer
CDC, Atlanta, GA, USA

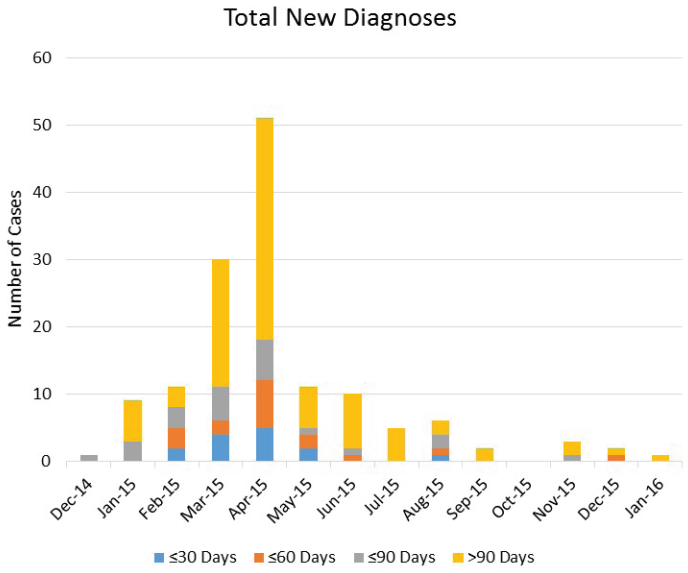
Background: Assays for determining recent HIV-1 infection are important public health tools for estimating HIV incidence. These assays provide a measurable distinction between recent and long-term infection due to differential antibody reactivity to specific HIV antigens. We developed a bead-based, multiplex assay which measures antibody binding and

avidity to multiple HIV antigens for determining recent HIV infection. Due to the sensitivity and dynamic range characteristics of the assay, we demonstrated that some antibody biomarkers are remarkably predictive of time since seroconversion which may have additional applications, such as inferring recent transmission events. Identification of early HIV infection (< 3 months since seroconversion) may be useful for determining the efficacy of emergency responses and other interventions in outbreaks, and to infer a timeline for the outbreak.

Methods: Plasma samples from persons (n=142) who inject drugs involved in a recent HIV-1 outbreak in rural Indiana were tested with a customized HIV-1 multiplex assay, based on the Bio-Rad Bio-Plex platform, which measures the antibody response to gp120, gp160, and gp41 antigens. Assay cutoffs for each analyte were established to determine whether seroconversion occurred within 30, 60, or 90 days of the sample collection date. The cutoffs were estimated based on the assay values from well-characterized, longitudinal seroconversion panels (n=608) with known last negative/first positive antibody test dates. In addition to each individual analyte, an algorithm incorporating three different analytes and their respective cutoffs was applied to the Indiana data to determine early infection status.

Results: Sensitivity/specificity of the multiplex assay for predicting seroconversion within 30, 60, 90 days, based on the training data set, was 90.5%/95.4%, 94.1%/90%, and 89.4%/82.9%, respectively. Of the 142 new diagnoses in Indiana between December 2014 and January 2016, the majority of early infections (≤3 months since seroconversion) were estimated to have occurred between February and May. During this period, 13 persons were inferred to have seroconverted within 1 month of the diagnosis, 27 within 2 months, and 42 within 3 months.

Conclusion: The HIV-1 multiplex antibody assay can identify and monitor trends in recent infection during a localized epidemic, help assess the impact of public health interventions, and may also be useful for inferring a timeline for the outbreak.



878 INFERENCE OF HIV-1 INFECTION DATES IN AN OUTBREAK USING ANTIBODY-BASED RECENCY ASSAYS

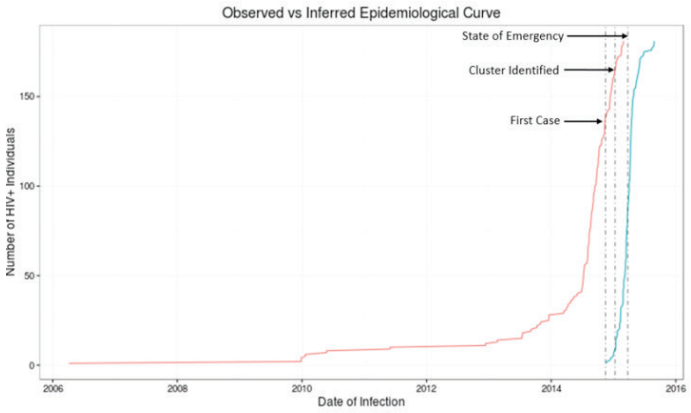
Ellsworth Campbell[1], Kelly Curtis[1], Krystin A. Price[1], Debra Hanson[1], Sara J. Blosser[2], Joan Duwve[3], Pam Pontones[2], Philip J. Peters[1], William M. Switzer[1]
[1]CDC, Atlanta, GA, USA, [2]Indiana State Hlth Dept, Indianapolis, IN, USA, [3]Indiana Univ, Indianapolis, IN, USA

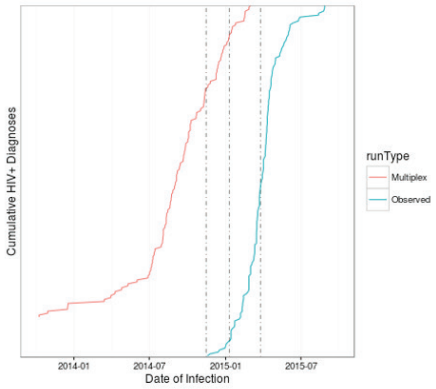
Background: Serologic assays for determining recent HIV-1 infection are used to estimate HIV incidence by differentiating recent from long-term infection. While an effective public health tool at a population-level, they may also benefit outbreak investigations that are subject to common biases of respondent-driven sampling. Given dates of diagnosis and serologic results we used plasma samples collected from persons who injected drugs during a 2015 HIV outbreak in rural Indiana and from a seroconverter panel of data used to characterize the incidence assays to infer the incidence curve during the outbreak.

Methods: Plasma samples (n=608) from recent seroconverters with known last negative/first positive test dates were tested with a customized HIV-1 multiplex assay which measures antibody avidity to three envelope (gp120, gp160, and gp41) antigens. A 4-parameter logistic (4PL) function was fit to a principal component score computed from multiplex assay analytes. Statistics from these training data and the principal component eigenvalues were applied to plasma samples from 142 persons involved in a recent HIV-1 outbreak, collected between November 2014 and March 2016, to compute scores used to predict duration of recent infection (DRI) from the 4PL model parameters. By subtracting the inferred DRI from the date of diagnosis we inferred possible dates of infection (DOI).

Results: The earliest HIV-positive diagnoses during the HIV outbreak in rural Indiana occurred between November 2014 and January 2015. Beginning in January 2015, the shape of the curve of cumulative diagnoses over time is more representative of outbreak response efforts than actual incidence during the outbreak. Inferred DOIs suggest that over 70% of HIV infections occurred prior to the first diagnosis and 90% occurred prior to the identification of the transmission cluster. In March 2015, extensive HIV prevention measures were implemented. Although >50% of HIV infections were diagnosed after March 2015, this inferred DOI model indicates that all sampled HIV infections occurred prior to the implementation of these HIV prevention interventions.

Conclusion: We developed a novel but simple algorithm for inferring HIV infection dates using results of a multiplex incidence assay. We show that serologic incidence assays can aid outbreak investigations by inferring estimates of infection duration and by overcoming sampling biases inherent to respondent driven investigations that can inaccurately represent true epidemic curves.





879 IDENTIFICATION AND VALIDATION OF AN INCIDENCE-TESTING ALGORITHM FOR HIV-1 SUBTYPE C

Oliver Laeyendecker[1], Jacob Konikoff[2], Douglas Morrison[3], Ronald Brookmeyer[3], Jing Wang[4], Connie L. Celum[5], Charles S. Morrison[6], Quarraisha Abdool Karim[7], Audrey Pettifor[8], Susan H. Eshleman[9]

[1]NIAID, NIH, Baltimore, MD, USA, [2]The Johns Hopkins Univ, Baltimore, MD, USA, [3]Univ of California Los Angeles, Los Angeles, CA, USA, [4]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [5]Univ of Washington, Seattle, WA, USA, [6]FHI 360, Durham, NC, USA, [7]CAPRISA, Durban, South Africa, [8]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [9]The Johns Hopkins Univ, Baltimore, MD, USA

Background: Accurate methods for estimating HIV incidence are needed for surveillance and to assess prevention efforts, particularly in HIV subtype C endemic areas where the burden of disease is the greatest. We evaluated assays and multi-assay algorithms (MAAs) for cross-sectional HIV incidence estimation in subtype C settings.

Methods: We analyzed 2442 samples from 278 adults with known duration of infection (0.1 to 9.9 years after seroconversion). Samples were collected in 3 studies conducted in Zambia, Zimbabwe, and South Africa (CAPRISA; Hormonal Contraception and Risk of HIV Acquisition; HPTN 039). The following assays were evaluated: the Limiting Antigen Avidity assay (LAg, cut-offs: 0.5 to 3 normalized optical density [OD-n]); the Johns Hopkins modified BioRad Avidity assay (BioRad, cut-offs: 30 to 100% avidity index); CD4 cell count (cut-offs: 50 to 500 cells/mm3); and viral load (cut-offs: 400 to 10,000 copies/mL). We evaluated >25,000 MAAs, varying the assays used and cut-off for each assay. For each assay or MAA, we computed the mean window period (mean duration individuals are classified as 'recent'); mean duration of recent infection (MDRI, mean duration individuals are classified as 'recent' in the first 2 years of infection); shadow (how far back in time incidence is being measured); and false recent rate (FRR, fraction of individuals infected >2 years misclassified as 'recent'). We selected MAAs with the largest mean window period, where the upper 95% confidence interval (CI) of shadow was <1 year. Assays and MAAs were compared to the LAg standard algorithm (LAg <1.5 OD-n + VL > 1000) and were used to estimate HIV incidence in a longitudinal cohort from South Africa (HPTN 068).

Results: The table shows data from the LAg standard algorithm (I: LAg <1.5 + VL >1000); two clade B algorithms (II: BioRad <40% + LAg <2.9, III: BioRad <85% + LAg <2.8 + VL >400 + CD4 >50); LAg alone (IV: LAg <0.7); BioRad alone (V: BioRad <40%); and the overall optimal MAA (VI: BioRad <95% + LAg <2.8 + VL >400). The optimal MAA (VI) estimated incidence in the HPTN 068 cohort with an error that was 3-fold less than the LAg standard algorithm, with CIs for the incidence estimate that were half as wide.

Conclusion: We identified an optimized MAA for cross-sectional HIV incidence in subtype C settings. This MAA, which includes the LAg assay, BioRad assay, and viral load, is more accurate than the LAg standard algorithm currently in use for global HIV surveillance.

880 VALIDATION OF LIMITING ANTIGEN AVIDITY ASSAY TO ESTIMATE HIV INCIDENCE IN EAST AFRICA

Oliver Laeyendecker[1], Ronald H. Gray[2], Kate Grabowski[2], Steven Reynolds[1], Anthony Ndyanabo[3], Joseph Ssekasanvu[2], Gilad Bismut[2], Maria Wawer[2], David Serwadda[4], Thomas C. Quinn[1]

[1]NIAID, Baltimore, MD, USA, [2]The Johns Hopkins Univ, Baltimore, MD, USA, [3]Rakai Hlth Scis Prog, Kalisizo, Uganda, [4]Makerere Univ, Kampala, Uganda

Background: Cross-sectional incidence testing will be used for Population-based HIV Impact Assessments in several East African countries. These will use a combination of the Limiting-Antigen (LAg) Avidity Assay with viral load (VL) >1000 copies/mL to estimate population level incidence. We aimed to validate the capacity of the LAg-Avidity + VL algorithm to estimate incidence in a subtype A and D epidemic compared to cohort observed incidence.

Methods: We tested all samples from a single survey round of the Rakai Community Cohort (2008-2009) which had previously determined HIV subtype distribution and an observed incidence from individuals who were also surveyed in the prior round. The observed incidence was 1.05/ 100 person years (95% CI 0.90, 1.23). The sample set included 544 individuals infected >2years, for which a site-specific false recent rate (FRR) was determined. We compared incidence results per protocol (mean duration of recent infection [MDRI] of 130 days using a normalized optical density [OD-n] of 1.5 and 0% FRR after excluding those on ARV and VL<1000), to recent independent recommendations (MDRI 141 days and site specific FRR). Samples from HIV positive individuals who self-reported ARV use or with clinical records of ARV treatment were excluded from the analysis.

Results: There were 9973 participants present at both surveys, with 1253 HIV+ subjects of whom 866 were not on ART. 822/866 HIV positive subjects not on ART had samples available for testing. 94/822 samples had LAg-Avidity values < 1.5 OD-n, and 49/94 had detectable VL. The site specific FRR was 1.1% (95% CI 0.4-2.4% [6/544]). Of the 161 individuals who seroconverted over the 18 months between surveys, the LAg-Avidity+ VL identified 27 as recently infected. The estimated incidence per protocol was 1.73% (95% CI 1.03, 2.22), 65% higher than the observed point estimate. Using the updated MDRI of 141 days and a site determined FRR of 1.1%, the incidence estimate was 1.38% (95% CI 0.83, 1.93), 33% higher than the observed cohort incidence.

Conclusion: Revised MDRI and locally-estimated FRR improved the incidence estimate. The LAg-Avidity + VL estimate of incidence using revised performance characteristics was still 33% higher than the observed estimate, though confidence intervals overlapped. Nearly half of individuals with low LAg-Avidity values, with no self-reported or clinical record of ARV use had undetectable VL.

881 MISCLASSIFICATION RATE OF HIV ANTIBODY AVIDITY ASSAYS IN INDIVIDUALS FROM CAMEROON

Briana Lynch[1], Eshan Patel[2], Colleen R. Courtney[3], Aubin J. Nanfack[3], Thomas Quinn[2], Oliver Laeyendecker[4], Phillipe N. Nyambi[3], Ralf Duerr[3], Andrew D. Redd[5], for the Medical Diagnostic Center, Yaoundé, Cameroon

[1]NIH, Bethesda, MD, USA, [2]The Johns Hopkins Univ, Baltimore, MD, USA, [3]New York Univ, New York, NY, USA, [4]NIAID, Baltimore, MD, USA, [6]NIAID, Bethesda, MD, USA

Background: Accurate estimates of HIV incidence are critical to surveillance and prevention efforts. Current cross-sectional incidence testing strategies are dependent on antibody dynamics during recent and chronic infection, and many individual and population-level factors can affect their performance. Limited information exists on the

performance of cross-sectional incidence assays on samples from West and Central Africa, though population-based HIV impact assessments, which will use this methodology, are planned in Cameroon and Cote D'Ivoire in 2017.

Methods: This study examined plasma samples of participants from the MDC cohort in Cameroon. Samples were collected from 2011-2015 from individuals known to be HIV-infected more than one year (n=129). CD4 counts and HIV-subtype were previously determined for this cohort. All the samples were tested by the Limited Antigen (LAg) Avidity assay and the Johns Hopkins modified (JHU) BioRad-Avidity assay. The proportion of samples infected greater than one year being misclassified as recent were examined using previously determined cut off values, specifically: (1) LAg Avidity at <1.5 normalized optical density (OD-n), (2) LAg Avidity at <1.5 OD-n and >1000 HIV RNA copies/mL, and (3) LAg Avidity at <1.5 OD-n, >1000 HIV RNA copies/mL, and JHU BioRad-Avidity Assay at an avidity index (AI) < 40%.

Results: The median CD4 count for this population was 364 (interquartile range, 249-521), and the majority of individuals with known HIV subtype data were infected with an AG recombinant virus (59% [23/39]). Overall, 16.3% (21/129, 95% CI 1.4, 23.8) of samples were misclassified using the LAg-Avidity assay with a cutoff ≤ 1.5 OD-n. This was reduced to 1.71% (2/117, 95% CI 0.19, 5.49) for LAg-Avidity assay <1.5 OD-n and >1000 HIV RNA copies/mL. The two individuals that misclassified had a JHU BioRad HIV Avidity index of 53% and 55%, therefore the false recent rate was reduced to zero for the third algorithm

Conclusion: Individuals in the Cameroon cohort were shown to be misclassified when assessing the LAg-Avidity alone. However, the LAg-Avidity assay (<1.5 ODn) with viral load testing algorithm yielded a false recent rate less than 2%, which could be improved by adding the JHU BioRad assay at a cut-off of 40%. Further studies are needed to determine if there is a subtype specific misclassification in West-Central Africa.

882 WITHDRAWN

883 HIGH HIV INCIDENCE AMONG PWID AND MSM ATTENDING INTEGRATED CARE CENTERS IN INDIA

Allison M. McFall[1], Sunil S. Solomon[1], Gregory M. Lucas[1], Aylur K. Srikrishnan[2], Muniratnam S. Kumar[2], Santhanam Anand[2], Canjeevaram K. Vasudevan[2], David D. Celentano[1], Shruti H. Mehta[1]

[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]YR Gaitonde Cntr for AIDS Rsr and Educ, Chennai, India

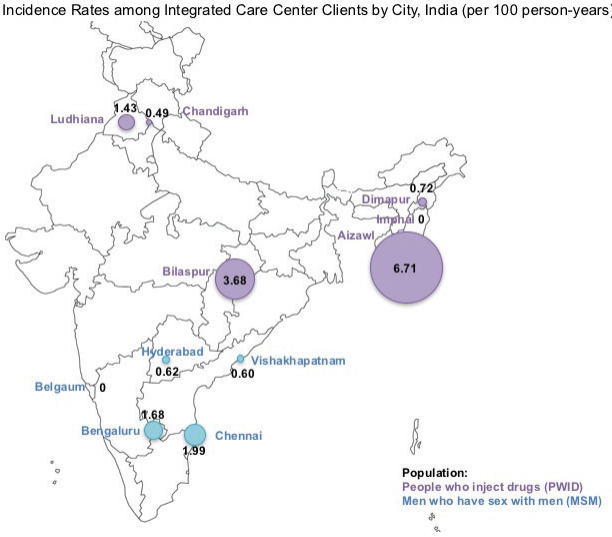
Background: In India, similar to other lower- and middle-income countries, HIV incidence has declined over the past decade following scale-up of HIV prevention and treatment services for heterosexual populations. While prevalence data among people who inject drugs (PWID) and men who have sex with men (MSM) suggest increasing burden, HIV incidence data among these groups are sparse.

Methods: As part of a cluster-randomized trial among PWID and MSM in India, integrated care centers (ICCs) were established in 11 cities (6 PWID and 5 MSM) and have been running for nearly two years. ICCs provide core and PWID- or MSM-focused HIV prevention and treatment services, including HIV counseling and testing, in a single venue. HIV negative clients are actively tracked to promote annual HIV testing. HIV incidence rates were calculated for clients with ≥2 HIV tests and negative on the first test. Multi-level Poisson regression models were used to explore correlates of HIV incidence.

Results: 5,012 ICC clients (3,430 PWID and 1,582 MSM) who were initially HIV negative were included. Median age was 28 years and 8.9% of PWID were women. There were 48 PWID and 13 MSM seroconverters resulting in HIV incidence rates of 1.30 per 100 person-years (PY) (95% confidence interval [CI]: 0.98 - 1.73) and 0.99 per 100 PY (95% CI: 0.58 - 1.71), respectively. There was considerable variability across cities with a range of 0 - 6.71 for PWID and 0 - 1.99 for MSM (Figure). Among PWID, HIV incidence was higher among women (adjusted incidence rate ratio [aIRR]: 2.54) and those with traditional risk factors - recent injection drug use (aIRR: 2.77), sharing needles/syringes (aIRR: 17.7), and a higher number of sexual partners (aIRR for ≥3 partners vs. none: 3.05). Lower incidence was observed among those receiving opioid substitution therapy >2 times/week (aIRR: 0.21) and receiving at least one session of safe sex counseling (aIRR: 0.23); however, those using needle/syringe exchange were at higher risk (aIRR: 2.41). Among MSM, the only factor significantly associated with HIV incidence was a recent sexually transmitted infection diagnosis (aIRR: 9.51).

Conclusion: PWID and MSM attending HIV-focused care centers in India experience high HIV incidence. Specific sub-groups of clients continue to engage in high-risk behaviors and should be targeted for additional harm reduction services and biomedical prevention approaches such as pre-exposure prophylaxis (PrEP), particularly PWID who have not been the focus of PrEP programs thus far.

Figure: HIV Incidence Rates among Integrated Care Center Clients by City, India (per 100 person-years)



884 TRENDS IN HIV INCIDENCE AMONG PWID, MSM AND CSW USING PREVENTION SERVICES IN UKRAINE

Kostyantyn Dumchev[1], Olga Varetska[2], Yana Sazonova[2], Pavlo Smyrnov[2]

[1]Ukrainian Inst on Pub Hlth Policy, Kyiv, Ukraine, [2]Alliance for Pub Hlth, Kyiv, Ukraine

Background: HIV epidemic in Ukraine is one of the largest in Europe, with estimated 223,000 people living with HIV and 10,500 new HIV cases annually. The epidemic was mainly driven by people who inject drugs (PWID), 21.9% of whom are HIV infected, and to lesser extent by other key groups such as men who have sex with men (MSM, 8.5% prevalence) and commercial sex workers (CSW, 7% prevalence). Prevention programs supported by the Global Fund through Alliance for Public Health in Ukraine rapidly grew since 2004 to

reach more than 300,000 clients during 2015. This study analyzed HIV prevention program data to estimate incidence trends over time and assess the effect of prevention services on seroconversion.

Methods: Data were extracted from the SyrEx database developed by Alliance to monitor service provision. The dataset included data on all HIV tests from Jan 2010 to Dec 2015 performed in all HIV prevention programs in Ukraine. Unique client coding system allowed tracking of individual testing history. Clients who had two or more tests were included in incidence calculation. Seroconversion was defined as a positive test after a negative one. Person time calculated as time between first negative test and last negative (or midpoint between last negative and first positive tests) was distributed across calendar years spent between the tests. Exact Poisson confidence intervals were calculated.

Results: From 568,194 individual clients who received at least one prevention service in 2011-2015, 58.8% had at least one HIV test. Of those, 42.8% had a negative first test and were tested at least once more and contributed person time. Overall five-year incidence rate per 100 person-years was 0.65 for PWID (95% CI 0.61-0.69), 0.48 for MSM (0.40-0.57), and 0.24 for CSW (0.20-0.30). Over five years, there was a significant declining trend among PWID, but no meaningful change among MSM and CSW. Detailed results are presented in the Table.

Conclusion: Electronic program monitoring tools, such as SyrEx, are becoming a useful source of strategic information on HIV epidemic. Incidence among Ukrainian prevention clients is low compared to data from other studies on key populations in Ukraine. The declining trend among PWID may reflect the impact of continuously high prevention coverage, whereas the stable incidence among CSW and MSM may warrant improvements both in coverage and quality of services. Association between service utilization and seroconversion will be the subject of further analysis.

Table. Incidence among clients of HIV prevention program in Ukraine, 2011-2015

	Year	Unique clients reached	Clients tested during the period	Clients who contributed person-time	Number of seroconversions	Incidence rate per 100 person-years	95% Confidence interval (Poisson)
PWID	2011	153,692	15,723	9,894	22	0.62	(0.39 - 0.94)
	2012	182,075	57,498	40,056	313	1.24	(1.11 - 1.39)
	2013	221,738	71,122	61,948	336	0.72	(0.65 - 0.80)
	2014	217,787	68,287	73,728	275	0.46	(0.41 - 0.52)
	2015	230,730	154,549	83,187	254	0.51	(0.45 - 0.58)
	2011-2015	**436,791**	**249,412**	**106,876**	**1200**	**0.65**	**(0.61 - 0.69)**
MSM	2011	16,746	3,781	1,918	3	0.31	(0.06 - 0.92)
	2012	20,318	6,702	5,667	18	0.45	(0.27 - 0.72)
	2013	22,821	8,076	9,103	33	0.48	(0.33 - 0.67)
	2014	23,937	9,380	11,035	42	0.44	(0.32 - 0.60)
	2015	33,503	26,034	13,186	40	0.56	(0.40 - 0.76)
	2011-2015	**59,041**	**38,840**	**15,191**	**136**	**0.48**	**(0.40 - 0.57)**
CSW	2011	25,691	5,190	2,945	2	0.16	(0.02 - 0.57)
	2012	29,588	11,035	9,020	15	0.26	(0.14 - 0.42)
	2013	38,813	14,012	13,465	30	0.29	(0.20 - 0.42)
	2014	38,724	12,394	15,601	22	0.17	(0.11 - 0.26)
	2015	38,496	27,872	16,072	28	0.29	(0.19 - 0.42)
	2011-2015	**72,362**	**45,866**	**21,086**	**97**	**0.24**	**(0.20 - 0.30)**

885 IMPROVED EVALUATION OF HIV PREVALENCE ADJUSTING FOR INFORMATIVE NONPARTICIPATION

Linbo Wang[1], Erik VanWidenfelt[2], Chloe Auletta-Young[1], Nealia Khan[1], Etienne Kadima[2], Unoda Chakalisa[2], Tendani Gaolathe[2], Eric Tchetgen Tchetgen[1], Kathleen Wirth[1]
[1]Harvard Univ, Boston, MA, [2]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana

Background: HIV prevalence is routinely estimated from household surveys. Estimates may be biased if HIV-infected persons are less likely to participate. A design-based method leveraging interviewer features as instrumental variables (IV) for non-ignorable missing data can be used to account for such bias. A valid IV satisfies two conditions: (A) it is a strong correlate of participation and (B) it is not directly related to a subject's HIV status. Using an IV, we examined the presence and magnitude of bias due to missing data on HIV status within a large randomized trial in Botswana.

Methods: The Botswana Combination Prevention Project is an ongoing cluster-randomized trial evaluating the effect of a combination prevention package on HIV incidence. From 2013 to 2015, a random 20% sample of households in 30 communities was selected for participation. A household representative enumerated all members with their age, gender, residency status and relationship to head of household. Present and consenting members aged 16-64 years who were (or married to) a Botswana citizen completed a survey and submitted to HIV testing in the absence of evidence of positive HIV status. For each interviewer, we obtained data on years of prior work experience as an IV which we used to estimate upper and lower bounds of HIV prevalence consistent with (A) and (B). Under a third condition (C) that selection bias does not vary with interviewer years of experience, we obtained HIV prevalence estimates overall and by community.

Results: A total of 15,475 eligible household members were enumerated by 58 interviewers. Median (25th, 75th percentile) years of prior work experience among interviewers was 3.1 (0.7, 8.0) years. Field staff consented and enrolled 12,610 persons. The most common reason for non-participation was refusal (10%), followed by inability to locate the person in the household (9%). Among the 12,570 subjects with a known HIV status, 3,596 (28.6%; 95% CI: 26.4%-31.0%) were HIV-infected. Under (A) and (B), the estimated lower and upper bounds of HIV prevalence were 29.5% and 35.4%. Under (A), (B) and (C), estimated HIV prevalence was 32.3% (95% CI: 30.1%-34.0%). Figure 1 presents bias-corrected prevalence estimates by community. We found empirical evidence for selection bias overall and in nine communities.

Conclusion: HIV prevalence estimates which ignore non-participation may be downwardly biased. Investigators should consider including IVs in the study design to safeguard against non-participation-induced bias.

886 RISK- AND SYMPTOM-BASED SCREENING IMPROVES IDENTIFICATION OF ACUTE HIV INFECTION

Maartje Dijkstra[1], Godelieve J. de Bree[2], Ineke Stolte[1], Udi Davidovich[1], Eduard Sanders[3], Maria Prins[1], Maarten F. Schim van der Loeff[1]
[1]Pub Hlth Service Amsterdam, Netherlands, [2]Academic Med Cntr, Amsterdam, Netherlands, [3]Kenya Med Rsr Inst, Kilifi, Kenya

Background: Identifying patients with acute HIV infection (AHI) is important; (1) patients with AHI benefit from immediate start of antiretroviral therapy (ART), (2) early treatment of AHI could have a significant impact on the ongoing HIV epidemic, (3) patients who start ART during AHI may offer insight into the potential for post treatment HIV control. The recent development of point-of-care HIV RNA tests has made prompt diagnosis of AHI possible at time of care seeking. However, these tests are expensive and guidelines on whom to test for AHI are lacking.

Methods: A case definition for possible AHI based on literature and expert opinion – including 14 symptoms associated with AHI – was evaluated using data from the Amsterdam Cohort Studies (ACS), the Netherlands. We optimized the risk score by constructing 2 multivariable logistic regression models: one including only symptoms and one combining symptoms with known risk factors for HIV seroconversion, using generalized estimating equations. Points were assigned to each of the symptoms and risk factors equal to the beta coefficients. Several risk scores were generated and the optimal risk score was validated using data of the Multicenter AIDS Cohort Study (MACS), USA.
Results: Using data from 1,562 MSM with 17,271 seronegative and 175 seroconversion visits in the ACS, the area under the curve (AUC) for the case definition was 0.70. Sensitivity was 45.7% (95%CI 38.2-53.4) and specificity 89.5% (95%CI 89.1-90.0). The optimal risk score included 4 symptoms (oral thrush, fever, lymphadenopathy, weight loss) and 3 risk factors (self-reported gonorrhea, receptive condomless anal intercourse, more than 5 sexual partners, all in the preceding 6 months) and yielded an AUC of 0.82. Sensitivity was 76.3% (95%CI 68.2-83.2) and specificity 76.3% (95%CI 75.6-77.0). Validation in the MACS resulted in an AUC of 0.78, sensitivity of 56.0% (95%CI 48.5-63.4) and specificity of 88.5% (95%CI 0.74-0.82). Using this risk score as a screening tool, 11.7% (MACS) to 24.2% of men (ACS) would be indicated for AHI testing.
Conclusion: A risk score for AHI including risk factors and symptoms performed better than a risk score including only symptoms. The optimal risk score had good performance in the ACS and performed comparable (but lower sensitivity) in the validation study. Screening for AHI with our optimal risk score would increase the efficiency of HIV RNA testing and potentially enhance early diagnosis and immediate treatment.

Table. Performance of 2 risk scores for AHI among participants of the Amsterdam Cohort Studies, 1984-2009; and Multicenter AIDS Cohort Study, 1984-2010.

Risk score	Cut-off	Seroconversions among visits with a positive risk score	Seroconversions among visits with a negative risk score	Sensitivity % (95% CI)	Specificity % (95% CI)	Overall AUC (95% CI)	% to be tested
Development of a risk score in Amsterdam Cohort Studies							
AHI case definition	2	80/1888	95/15555	45.7 (38.2-53.4)	89.5 (89.1-90.0)	0.70 (0.66-0.74)	10.8
Optimal risk score: 4 symptoms and 3 risk factors	1.5	103/3675	32/11517	76.3 (68.2-83.2)	76.3 (75.6-77.0)	0.82 (0.79-0.86)	24.2
Validation of the optimal risk score in MACS							
Optimal risk score: 4 symptoms and 3 risk factors	1.5	102/4049	80/30521	56.0 (48.5-63.4)	88.5 (88.2-88.9)	0.78 (0.74-0.82)	11.7

AHI, acute HIV infection; AUC, area under the curve; CI, confidence interval; MACS, Multicenter AIDS Cohort Study.

887 IMPLEMENTATION OF A RAPID TRAJECTORY TO IDENTIFY ACUTE HIV INFECTION IN AMSTERDAM

Maartje Dijkstra[1], Elske Hoornenborg[1], Udi Davidovich[1], Arjan Hogewoning[1], Henry J.C. de Vries[1], Sylvia Bruisten[1], Maria Prins[1], Maarten F Schim van der Loeff[1], Godelieve J. de Bree[2]
[1]*Pub Hlth Service Amsterdam, Netherlands,* [2]*Academic Med Cntr, Amsterdam, Netherlands*

Background: Immediate diagnosis of acute HIV infection (AHI) is important from both patient as well as public health perspective. First, patients benefit from immediate start of antiretroviral therapy (ART) during the early phase of infection. Second, AHI is an important cause of onward transmission given high viral load and unawareness of infection. The recent development of point-of-care HIV-RNA tests has made prompt diagnosis of AHI at time of care seeking possible. We implemented an on-going rapid AHI diagnostic and referral trajectory at the Amsterdam Public Health Service in 2015, including the use of a point-of-care HIV-RNA test. We present the first experiences with this new AHI trajectory.
Methods: Men who have sex with men (MSM) were assessed for eligibility after being referred by a media campaign through a dedicated website (hebikhiv.nl, with a self-referral screening tool), by their general practitioner (GP), or during routine STI screening at the Public Health Service. Eligibility was based on a score of symptoms in combination with condomless anal sex in the previous 3 months. If eligible, a rapid HIV antibody test was performed. If negative, both a point-of-care HIV-RNA test (GeneXpert, Cepheid) and a HIV antigen/antibody test (Murex on LiaisonXL) were performed. AHI was defined as an HIV-RNA positive test result and an antigen/antibody negative or only positive for antigen (Fiebig I-II) test result.
Results: From August 2015 through September 2016, 192 MSM with possible AHI presented themselves for testing, of whom 157 men were eligible. Of these 157 men, 47.8% were referred by the website/campaign, 7.6% by their GP and 31.2% via routine STI screening. The median age was 33 years (IQR 26-43). The average time between intake and test results was 4 hours. In total, 14/157 men were newly diagnosed with HIV. Seven were diagnosed with AHI (Fiebig I-II), 5 with recent HIV infection (Fiebig III-V) and 2 with established HIV infection (Table). All 14 were referred to an HIV treatment center the same day for immediate start of ART.
Conclusion: The AHI trajectory resulted in a high prevalence (12/157; 7.6%) of acute or recent HIV infection. The addition of the point-of-care HIV-RNA test provided same-day results and early start of ART. Moreover, 2 extra cases of AHI were diagnosed relative to only using antigen/antibody assays. Further evaluation including (cost)effectiveness analyses will contribute to our knowledge of optimizing early diagnosis and immediate start of treatment.

Table. Test results of 14/157 MSM newly diagnosed with HIV through the rapid AHI diagnostic and referral trajectory at the Public Health Service of Amsterdam, August 2015 through 15 September 2016

Case	Age	rCLAI[1]	iCLAI[1]	RNA	Combo		Rapid test	Blot	Fiebig	Diagnosis
					P24	Ab				
1	33	Yes	Yes	+	-	-	-	NP	I	AHI
2	25	Yes	Yes	+	-	-	-	NP	I	AHI
3	41	Yes	Yes	+	+	-	-	-	II	AHI
4	47	No	No	+	+	-	-	-	II	AHI
5	58	Yes	Yes	+	+	-	-	-	II	AHI
6	38	Yes	No	+	+	-	-	-	II	AHI
7	29	Yes	No	+	+	-	±[2]	-	II	AHI
8	22	Yes	No	+	+	+	-	-	III	Recent HIV
9	23	Yes	Yes	+	-	+	-	-	III	Recent HIV
10	25	Yes	Yes	+	+	+	±[2]	±	IV	Recent HIV
11	58	No	No	+	+	+	±[2]	±	V	Recent HIV
12	21	Yes	Yes	+	+	+	±[2]	+	V	Recent HIV
13	47	Yes	Yes	NP	+	+	+	+	VI	Established HIV
14	34	Yes	Yes	+	+	+	+	+	VI	Established HIV

Ab, antibodies; AHI, acute HIV infection; MSM, men who have sex with men; iCLAI, insertive condomless anal intercourse; NP, not performed; rCLAI, receptive condomless anal intercourse; +, positive; -, negative; ±, indeterminate

[1]In the 2 weeks to 3 months preceding the visit

[2]Rapid test failed or showed minimal antibody response

888 COMPARISON OF SELF-REPORT TO BIOMARKERS OF RECENT INFECTION

Katherine E. Schlusser[1], Shweta Sharma[2], Pola de la Torre[3], Giuseppe Tambussi[4], Rika Draenert[5], Angie N. Pinto[6], Julia A. Metcalf[7], Danielle German[1], James Neaton[2], Oliver Laeyendecker[7]

[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Univ of Minnesota, Minneapolis, MN, USA, [3]Cooper Univ Hosp, Camden, NJ, USA, [4]Ospedale San Raffaele, Milano, Italy, [5]Klinikum der Univ Munich, Munich, Germany, [6]Kirby Inst, Sydney, Australia, [7]NIAID, Bethesda, MD, USA

Background: Identifying individuals with recent HIV infection is critical to research related to viral reservoirs, outbreak investigations, and intervention applications. Currently, the reliability of self-report of recent infection is unknown.

Methods: We tested samples from individuals of the Strategic Timing of Antiretroviral Treatment (START) trial for biomarkers associated with recent HIV infection. These included 3 groups: 1) 167 individuals who self-reported being infected < 6 months before enrollment (recent infection group); 2) 771 individuals with an unknown date of infection (unknown infection group), and 3) 199 randomly selected individuals who were diagnosed with HIV ≥2 years before enrollment (control group). Participants in the first two groups were diagnosed with HIV in the 6 months before enrollment. Samples from all individuals were tested by a multi assay algorithm (MAA), where subjects had to have a low titer and avidity (based on the Limiting-Antigen Avidity Assay), and detectable viral load to be classified as recently infected. Comparisons within groups were done using chi-square tests for proportions and Wilcoxon rank sum test for medians. Multivariate logistic regression was used to determine predictors of recent infection.

Results: A significantly higher proportion of individuals in the self-reported recent infection group appeared recently infected by the MAA compared to individuals from the control group (65% [109/167] vs. 2.5% [5/199], p<0.001, see table), and had lower Limiting-Antigen Avidity Assay values (normalized optical density 1.86 [IQR 0.99, 3.01] vs. 4.53 [3.84, 4.99], p<0.001. Within the recent infection group, there were no significant differences in age, sex, race, geographic location, or HIV history when comparing those classified as recent versus not by the MAA. 27% (206/771) of individuals of the self-reported unknown infection group appeared recent by the MAA. Individuals who appeared recently infected by the MAA were similar, irrespective of knowing their infection date.

Conclusion: Self-report of recency of infection seems reliable as a majority of such individuals' claims were corroborated with biomarkers associated with that infection state. Discrepancies observed between self-report and biomarkers associated with recent HIV infection do not seem to be correlated with age, race, gender, geographic location, or HIV history.

Table 1. Baseline characteristics of individuals within each self-report group by duration of infection determined by biologic testing.

Biologic Recent vs Non-Recent Testing by Duration of Infection Claim						
	Diagnosis Date ≤ 6 months					
	Recent Infection Group		Unknown Infection Group		Control Group	
	Recent Med[IQR], N(%)	Not Recent Med[IQR], N(%)	Recent Med[IQR], N(%)	Not Recent Med[IQR], N(%)	Recent Med[IQR], N(%)	Not Recent Med[IQR], N(%)
No. Pts	109	58	206	565	5	194
Demographics						
Age (years)	30 [25, 39]	28 [25, 34]	32 [26, 41]	34 [28, 42]	34 [32, 47]	39 [32, 46]
Gender (female)	8 (7.3)	5 (8.6)	28 (13.6)	183 (32.4)	3 (60.0)	65 (33.3)
Race						
Asian	13 (11.9)	7 (12.1)	32 (15.5)	34 (6.0)	2 (40.0)	15 (7.7)
Black	14 (12.8)	8 (13.8)	32 (15.5)	218 (38.6)	2 (40.0)	82 (42.3)
Latino/Hispanic	15 (13.8)	12 (20.7)	31 (15.0)	63 (11.2)	0 (0.0)	16 (8.2)
White	62 (56.9)	26 (44.8)	103 (50.0)	215 (38.1)	1 (20.0)	74 (37.9)
Other	5 (4.6)	5 (8.6)	8 (3.9)	35 (6.2)	0 (0.0)	7 (3.6)
Geographic Location						
US/Europe/Australia (High)	53 (48.6)	24 (41.4)	90 (43.7)	155 (27.4)	1 (20.0)	89 (45.9)
S America/Africa/Asia (Low-Mid)	56 (51.4)	34 (58.6)	116 (56.3)	410 (72.6)	4 (80.0)	105 (53.8)
HIV History						
Likely mode of HIV infection						
MSM	89 (81.7)	49 (84.5)	143 (69.4)	266 (47.1)	1 (20.0)	89 (45.2)
Heterosexual	15 (13.8)	6 (10.3)	48 (23.3)	265 (46.9)	4 (80.0)	90 (46.2)
Injection drug use	2 (1.8)	0 (0.0)	2 (1.0)	5 (0.9)	0 (0.0)	3 (1.5)
Blood products/other/unknown	3 (2.8)	3 (5.2)	13 (6.3)	29 (5.1)	0 (0.0)	12 (6.2)
Laboratory Results						
CD4 (cells/mm^3)	663 [595, 810]	650 [590, 740]	659 [573, 771]	665 [589, 796]	911 [585, 1012]	635 [585, 710]
CD8 (cells/mm^3)	1083 [802, 1448]	1090 [929, 1444]	945 [698, 1317]	1023 [751, 1350]	1139 [808, 2150]	1071 [832, 1430]
HIV RNA (copies/mL)	26323 [7490, 81945]	19114 [8176, 48127]	30079 [8200, 77959]	9920 [2203, 35800]	11000 [1834, 13444]	8084 [1703, 31012]
HIV RNA ≤ 400 copies/mL	0 (0.0)	4 (6.9)	0 (0.0)	72 (12.7)	0 (0.0)	16 (8.2)

889 USE OF TESTING HISTORY TO IDENTIFY HIV-INFECTED PEOPLE AT HIGH RISK OF TRANSMISSION

Laurie Linley[1], Richard M. Selik[1], Xiaona Qian[2], Alexandra Oster[1]
[1]CDC, Atlanta, GA, USA, [2]ICF Intl, Atlanta, GA, USA

Background: Acute HIV infection (AHI) is more infectious than later stages of infection, but only a small percentage of HIV infections are recognized as acute at diagnosis. Detecting AHI could provide an opportunity to reduce transmission. Information on the interval between a previous negative HIV test result and the diagnosis of HIV infection could help identify AHI, but laboratory reports of previous negative results are often not available at diagnosis. We compared diagnoses for which lab reports of the last negative test result was available with those for which the last negative test was available only from other sources of testing history (e.g., patient, provider) to assess the usefulness of testing history from lab reports and other sources in identifying AHI.
Methods: We analyzed National HIV Surveillance System data for persons aged ≥13 years with HIV diagnosed during 2008-2014 from 21 US jurisdictions that collected data on dates of last negative HIV tests from both lab reports and other sources. We defined AHI as HIV infection in which the reported date of last negative test was < 60 days before diagnosis. We divided AHI cases into those based on lab report and those based on other sources, and compared viral load (VL) and results from incidence assays (BED HIV-1 incidence IA or CDC-modified Bio-Rad HIV-1/HIV-2 plus O avidity IA; a "recent" result indicates duration of infection within 6-8 months post-seroconversion on average).
Results: Of 220,195 diagnoses, 6% had a last negative test by lab report, of which 18% were AHI; 23% had a last negative test from other sources, of which 6% were AHI (Table). Among AHI cases with VL data, the percentage with a VL ≥ 100,000 copies/mL was higher for lab report-based AHI (65%) than for other source-based AHI (30%, p<0.001). Among AHI cases with incidence assay results, the percentage with results indicating recent infection was higher for lab report-based AHI (85%) than for other source-based AHI (38%, p<0.001).
Conclusion: Persons with AHI based on lab report were more than twice as likely to have a high VL or an incidence test indicating recent infection as those with AHI based on other sources. These findings indicate that data on last negative tests from other sources are not as accurate as those from lab reports for identifying AHI. Improving collection of the last negative HIV test results from laboratory reports could improve the ability of HIV surveillance programs to identify persons with AHI, and thereby to prevent further transmission.

Table. Identification of acute HIV infection (AHI) through use of testing history among persons with diagnosed HIV, by source of testing history information—21 U.S. jurisdictions, 2008-2014.

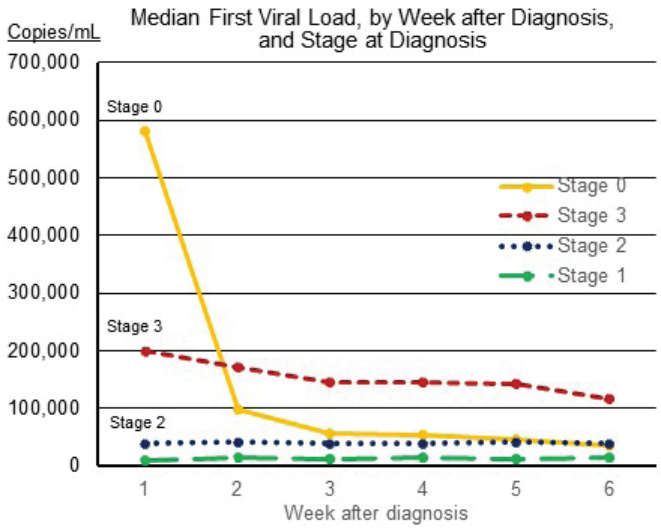
	Source of information on last negative HIV test	
	Laboratory report	Other sources (e.g., patient, provider)
Diagnoses with date of last negative HIV test information (among all diagnoses)	13,881/220,195 (6%)	51,122/220,195 (23%)
AHI (among cases with a last negative HIV test)	2,524/13,881 (18%)	3,216/51,122 (6%)
AHI cases with VL ≥ 100,000 copies/mL (among AHI cases with VL data)	1,359/2,077 (65%)	638/2,129 (30%)
AHI cases with recent incidence assay result (among AHI cases with incidence assay results)	677/800 (85%)	521/1,377 (38%)

Note: AHI determined by a date of last negative HIV test < 60 days before date of HIV diagnosis.

890 VIRAL LOADS NEAR HIV DIAGNOSIS: VARIATION WITH STAGE (0, 1, 2, OR 3) AT DIAGNOSIS

Richard M. Selik, **Laurie Linley**, Mi Chen
CDC, Atlanta, GA, USA

Background: Diagnosis of HIV infection at an early stage may provide an opportunity to prevent transmission because early (including acute) infection has been associated with viral loads much higher than those in later stages. We aimed to confirm this association by comparing viral loads in the first 6 weeks after diagnosis (or on the same date), by week and stage of disease at diagnosis.
Methods: We analyzed data on the 163,215 infections diagnosed in 2012-2015 reported to the US National HIV Surveillance System through June 2016. Diagnosis and staging were based on the 2014 US surveillance case definition for HIV infection, in which early infection is stage 0. We limited the analysis to records with exact specimen collection dates, and to first viral loads to minimize the effect of antiretroviral therapy and reveal the natural history of viral loads.
Results: 95,606 infections (59% of the total) were reported with a quantifiable first viral load within 6 weeks after diagnosis and with enough criteria to determine the stage at diagnosis. Of these, 3,473 (3.6%) were stage 0; 26,894 (28.1%) stage 1; 35,135 (36.8%) stage 2; and 30,104 (31.5%) stage 3. The median first viral load among infections diagnosed in stage 0 fell from 581,501 copies/mL in week 1 to 97,564 in week 2, and 36,806 by week 6; among infections in stage 1, it was 8,980 in week 1, and ranged from 13,094 to 15,170 in week 2 through week 6; among infections in stage 2, it ranged from 39,495 to 42,070 in week 1 through week 6; among infections in stage 3, it dropped from 201,000 in week 1 to 170,213 in week 2, and 116,000 by week 6 (see figure). The percentage of infections with a first viral load of ≥500,000 copies/mL among those in stage 0 fell from 53.8% in week 1 to 27.7% in week 2, and to 11.4% by week 6; among infections in stage 1, it dropped from 6.6% in week 1 to 2.9% in week 2, and 1.1% by week 6; among infections in stage 2, it decreased from 10.9% in week 1 to 5.2% in week 2, and 2.8% by week 6; among infections in stage 3, it declined from 27.1% in week 1 to 24.0% in week 2, and 18.9% by week 6.
Conclusion: In the 1st week after diagnosis, viral loads are generally much higher among infections diagnosed in stage 0 than among infections in other stages. By the 2nd week, they are generally less than those in stage 3. These findings imply that the period when early infections are highly infectious lasts only about 1 week after diagnosis, so prevention of transmission should start as soon as possible after diagnosis.



891 HIV SELF-TEST (HIVST) AWARENESS, EXPOSURE, AND USE, NEW YORK CITY, 2015–2016

Paul M. Salcuni, Zoe R. Edelstein, Demetre C. Daskalakis, Julie Myers
New York City DHMH, Queens, NY, USA

Background: The HIV self-test (HIVST) can increase status awareness, but barriers to access exist along a proposed continuum from awareness to use. Among a large, urban sample of men and transgender people who have sex with men (MTSM) who participated in an HIVST Giveaway (HTG), we examined associations between sociodemographic and behavioral factors and prior HIVST awareness, pharmacy exposure, and use.
Methods: Data were derived from online eligibility and follow-up surveys, 11/2015-4/2016. Participants were recruited through dating apps and sites. Adult NYC residents who were MTSM and reported no prior HIV diagnosis were eligible. Data included sociodemographic factors (age, race/ethnicity, education, income), recent HIV-related behaviors [timing of last HIV test before HTG; last condomless anal sex (CAS; <1/1-3/>3 months ago/never); gender(s) and HIV status of partners; number of CAS partners (0-1/>1); sexually transmitted infection (STI) diagnosis; pre-exposure prophylaxis (PrEP) use; recreational drug use]. Outcomes were HIVST awareness, pharmacy exposure (ever seen at a pharmacy), and use (ever) prior to HTG. Factors associated with outcomes in bivariate analysis ($p<0.05$) were included in logistic regression models adjusted for age, race/ethnicity, education, and income.
Results: Eighty-five, 57% and 23% of respondents were aware of, had seen, and had used the HIVST, respectively (Table). After adjusting for sociodemographics, all outcomes were associated with higher income and recent HIV testing. Awareness did not differ by age or race/ethnicity; exposure and use were associated with both. Among HIV-related behaviors, awareness was associated with recent PrEP use [adjusted odds ratio (aOR) 1.85, 95% CI 1.12-3.06] and having an HIV-positive partner (aOR 2.35, CI 1.20-4.63); similar relationships existed for exposure. Awareness was also associated with CAS in the past month vs. never (aOR 3.26, CI 1.61-6.57) and partnering only with men (aOR 2.10, CI 1.05-4.18). Among behaviors examined, use was associated with >1 recent CAS partner (aOR 1.68, CI 1.22-2.31).
Conclusion: While most respondents knew about the HIVST prior to HTG, fewer had seen one, and only 1 in 4 had used one. Associations with recent HIV testing suggest that less frequent testers may not be adequately informed of this option. Disparities along an HIVST continuum by income suggest that barriers to access are present even before purchase, underlining the importance of efforts to bring this testing strategy to diverse populations.

Table. Select associations with HIV self-test continuum outcomes by select sociodemographic and behavioral characteristics among HIV Self-Test Giveaway participants prior to the HIV Self-Test Giveaway, New York City, 2015-16

	Awareness			Pharmacy exposure[1]			Use		
Characteristic	n/N	%	aOR* (95% CI)	n/N	%	aOR* (95% CI)	n/N	%	aOR* (95% CI)
Overall	974/1151	85%	--	635/1115	57%	--	267/1155	23%	--
Age									
18-24	178/216	82%	0.82 (0.39 - 1.74)	109/204	53%	1.79 (1.05 - 3.04)	41/217	19%	1.49 (0.78 - 2.85)
25-34	501/587	85%	0.86 (0.44 - 1.68)	337/573	59%	1.82 (1.15 - 2.88)	157/589	27%	1.88 (1.07 - 3.29)
35-44	193/231	84%	0.69 (0.34 - 1.41)	138/226	61%	1.97 (1.19 - 3.26)	47/235	20%	1.23 (0.66 - 2.30)
45+	102/117	87%	Ref	51/112	46%	Ref	22/117	19%	Ref
Race/ethnicity									
Black, NH	116/130	89%	1.53 (0.81 - 2.89)	78/123	63%	1.36 (0.87 - 2.12)	31/124	25%	0.99 (0.61 - 1.60)
Hispanic	267/315	85%	1.19 (0.77 - 1.84)	180/305	59%	1.18 (0.85 - 1.63)	63/315	20%	0.74 (0.51 - 1.07)
Other[2]	141/174	81%	0.75 (0.46 - 1.20)	82/173	47%	0.60 (0.41 - 0.87)	31/180	17%	0.55 (0.35 - 0.88)
White, NH	433/510	85%	Ref	283/494	57%	Ref	138/513	27%	Ref
Income									
$40,000+	527/609	87%	1.66 (1.14 - 2.41)	360/593	61%	1.49 (1.12 - 1.97)	161/611	26%	1.54 (1.11 - 2.15)
<$40,000	346/427	81%	Ref	218/415	53%	Ref	84/430	20%	Ref
Time since last HIV test									
<= 1y ago	578/662	87%	2.73 (1.67 - 4.46)	405/644	63%	2.21 (1.45 - 3.38)	191/662	29%	5.59 (2.64 - 11.86)
> 1y ago	265/317	84%	1.85 (1.08 - 3.16)	146/302	48%	1.20 (0.76 - 1.90)	58/321	18%	2.83 (1.28 - 6.25)
Never tested	98/135	73%	Ref	58/132	44%	Ref	9/135	7%	Ref

aOR: adjusted odds ratio; NH: Non-Hispanic

*Adjusted for age, race/ethnicity, education, and income.

[1]Pharmacy exposure is defined as having ever seen an HIV self-test at a pharmacy.

[2]Other race includes Asian/Pacific Islander; Native American; mixed race, non-Hispanic; and those reporting other race.

892 ETEST: A "SMART" HOME HIV TESTING SYSTEM ENABLING REAL-TIME FOLLOW-UP AFTER TESTING

Tyler B. Wray[1], Philip A. Chan[2], Don Operario[1], Erik Simpanen[1]
[1]*Brown Univ, Providence, RI, USA,* [2]*The Miriam Hosp, Providence, RI, USA*

Background: Men who have sex with men (MSM) are at high risk for HIV, but many do not test as frequently as recommended. Home-based self-testing (HBST) for HIV could encourage more regular testing and potentially detect some new infections earlier, but providing sufficient follow-up after testing is a challenge. A more active approach to post-test follow-up with HBST may be needed, so that those who receive reactive (preliminary positive) results can be efficiently linked with care, and those who test negative can be connected with other key prevention services (e.g., safe sex supplies, sexually transmitted infection [STI] testing, pre-exposure prophylaxis [PrEP] consultation).
Methods: We developed the "eTEST" system, which uses Bluetooth low energy beacons (BLE) and a smartphone app to remotely monitor when HBST kits have been opened (see Fig. 1), allowing Qualified HIV Test Counselors (QHTCs) to actively follow up with users over the phone after testing. In this 7 month study, we recruited 60 high-risk MSM who had not tested in the last year from MSM-oriented "hookup" apps and randomly assigned them to receive one of the following in the mail at baseline, 3-months, and 6-months: either (1) "eTEST" HBST kits, (2) standard HBST kits, or (3) reminders to seek clinic-based testing. Those in the "smart" HBST condition received follow-up calls from QHTCs within 24 hours, while those in the "standard" group had no follow-up.
Results: Between-groups comparisons suggested that more participants in the HBST conditions reported having tested for HIV (98% vs. 40%, t=0.93, p<.05) and other STIs compared with the control condition (45% vs. 10%, t=1.98, p<.05), but these rates did not differ between the "smart" and standard HBST groups. However, compared with control and standard HBST conditions, more in the "smart" HBST group received HIV risk reduction counseling (65% vs. 25%, t=2.98, p<.05), safe sex supplies (55% vs. 17%, t=2.45, p<.05), and were referred for PrEP consultation (55% vs. 0%, t=3.61, p<.05). More "smart" HBST participants also began PrEP (15% vs. 0%), but this difference was not significant.
Conclusion: Initial results suggest that HBST may encourage more regular HIV and STI testing among high-risk MSM, and that the eTEST system in particular may be useful for engaging individuals with other critical services. Further research is needed to determine whether eTEST facilitates earlier detection of new infections and linkage to care.

893 PEER-LED ORAL HIV-SELF TESTING FINDS UNDIAGNOSED HIV AMONG MSM IN MALINDI, KENYA

Elisabeth M. van der Elst[1], Mahmoud Shally[1], Clifford Oduor[1], Oscar Chirro[1], Fauz Ibrahim[2], Bernadette Kombo[1], Susan M. Graham[3], **Eduard Sanders**[4]
[1]*KEMRI Wellcome Trust Rsr Prog, Kilifi, Kenya,* [2]*Kilifi County Dept of Hlth, Kilifi, Kenya,* [3]*Univ of Washington, Seattle, WA, USA,* [4]*Kenya Med Rsr Inst, Kilifi, Kenya*

Background: Men who have sex with men (MSM) in Kenya experience structural and social barriers to HIV-testing, and have a high burden of undiagnosed HIV. We assessed whether oral HIV self-testing (OST) extended by MSM lay counsellors would be acceptable and feasible compared to clinic-based HIV testing and counseling (HTC) of mobilised MSM in an area known for sex work.
Methods: We compared HIV-prevalence and time to immediate ART initiation among newly diagnosed MSM who were mobilised either for clinic-based HTC or for OST, using trained lay counsellors. For HTC, 5 MSM recruiters mobilised between 20 and 30 MSM per week during 6 months. Clinic-based HTC followed national testing guidelines (i.e., two positive rapid tests needed to confirm HIV positive status). OST was facilitated by six MSM lay counsellors who each extended 5 OST kits to their peers per week. Irrespective of the OST result, all MSM who did OST were asked to report for confirmatory HTC per national guidelines at the clinic. All newly HIV-diagnosed MSM were offered immediate ART at a Government hospital serving key populations.
Results: During July-December 2015, 690 MSM with median age 27.0 years (interquartile range (IQR): 22-33) underwent HCT, and 24 (3.5%) were newly diagnosed. Of these, 20 (83.3%) MSM initiated ART at the hospital after a median 5 days (IQR: 3-14). During March-June 2016, 337 MSM were provided with OST, and 333 (99.1%) MSM with median age 26.0 years (IQR:23-32) reported for confirmatory testing. A total of 29 MSM (8.7%, p<0.001) were newly diagnosed. Of these, 24 (82.8%, p=1.0) started ART on the day of HIV-confirmation. MSM were highly motivated to participate in OST, which they considered an activity they owned.
Conclusion: In Malindi, peer-led OST followed by confirmatory testing was feasible and identified a higher prevalence of undiagnosed HIV-infection in MSM compared to HCT. Men who underwent OST had high rates of retesting, and tended to accept immediate ART treatment. OST appeared a feasible strategy to engage MSM for HIV testing and care.

894 ROLE OF PARTNER VIOLENCE IN WOMEN'S ABILITY TO DISTRIBUTE SELF-TESTS TO MALE PARTNERS

Elisabeth Schaffer[1], Kawango Agot[2], Harsha Thirumurthy[1]
[1]*Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA,* [2]*Impact Rsr and Development Org, Kisumu City, Kenya*

Background: Offering multiple HIV self-tests to women in sub-Saharan Africa is a promising way to increase male partner testing and couples testing. Recent findings indicate that women are willing and able to safely distribute self-tests to their partners, yet the extent to which prior history of intimate partner violence limits the potential of this approach is unknown.

Methods: This secondary analysis used data from a cohort study in Kenya to examine the association between recent intimate partner violence and the likelihood of partner and couples testing. From January-March 2015, 176 HIV-negative women were recruited from antenatal and postpartum care clinics and offered multiple oral fluid-based HIV test kits. Participants received instructions on how to use the self-tests and modest encouragement to offer them to their primary sexual partners. Using multinomial logistic regression, we assessed whether self-testing outcomes reported by participants at 3 months were associated with the history of physical or sexual violence in 12 months prior to study enrollment. The primary outcome had 3 categories indicating whether: the partner did not test; partner testing occurred but couples testing did not; or couples testing occurred. Logistic regression was used to further examine partner dynamics associated with couples testing. We estimated relative risk ratios (RRR) and odds ratios (OR), adjusting for key covariates.
Results: Recent physical or sexual violence was reported by 20% of participants at enrollment. Compared to women who did not experience recent physical or sexual violence, women who experienced recent physical or sexual violence were less likely to report that partner testing occurred (0.10 aRRR, 95% CI: 0.02-0.47) or that couples testing occurred (0.13 aRRR, 95% CI: 0.03 - 0.54). Recent partner violence was not significantly associated with whether a male partner tested himself vs. as a couple. However, couples-testing was less likely to occur if the male partner had a neutral or negative reaction to the offer of a self-test (0.32 aOR, 95% CI: 0.12 - 0.87) or if it was not easy to persuade the partner to use a self-test (0.25 aOR, 95% CI: 0.09 - 0.76).
Conclusion: Women are capable of deciding for themselves whether to offer self-tests to their partners. However, women who had experienced physical or sexual violence from their partner were less likely to achieve partner or couples testing with self-tests. This finding underscores the need to address intimate partner violence.

895 INFORMING HIV SELF-TESTING SERVICES IN MALAWI USING DISCRETE CHOICE EXPERIMENTS

Pitchaya Indravudh[1], Marc D'Elbee[2], Moses Kumwenda[1], Augustine Choko[3], Doreen Sakala[1], Thokozani Kalua[4], Cheryl Johnson[5], Karin Hatzold[6], Liz Corbett[3], Fern Terris-Prestholt[2]
[1]Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi, [2]London Sch of Hygiene & Trop Med, London, UK, [3]London Sch of Hygiene & Trop Med, Blantyre, Malawi, [4]Malawi Dept of HIV and AIDS, Lilongwe, Malawi, [5]WHO, Geneva, Switzerland, [6]Pop Services Intl, Harare, Zimbabwe
Background: HIV self-testing (HIVST) has potential to improve equity in access to HIV testing and reach populations, including men and adolescents, underserved by standard-of-care services. This study examines relative preferences for HIVST services using Discrete Choice Experiments (DCE).
Methods: Two DCEs were conducted with adults in four rural, high HIV prevalence districts in Malawi. The DCE was administered to randomly selected household members with disproportionate allocation to either a DCE on a) HIVST delivery (n=771) or b) linkage to a confirmatory test and ART initiation after a positive self-test (n=554). Choice bundles of HIVST service characteristics were offered to participants, including option of standard-of-care. Preference heterogeneity was examined by sex and age using multinomial logit and latent class models.
Results: Respondents preferred home delivery of HIVST kits to distribution through health facilities or mobile clinics. Local lay distributors were stronger drivers of HIVST uptake compared to alternative providers, including intimate partners and health workers. Oral HIVST kits were preferred to provider-delivered HIV testing or finger-prick HIVST. Small user fees (US$0.07 to 0.21) were strong disincentives, especially among women. Delivery options relating to pre-test support did not affect choice, though there was negative preference for the HIVST instruction leaflet as the sole means of post-test guidance. Following a positive self-test, respondents preferred receiving information on confirmatory testing or HIV care by telephone compared to a leaflet, SMS reminder, or in-person support. Regarding location, respondents had negative preference for linking to mobile clinics over health facilities and their homes. For facility-based HIV care, service fees (US$0.14) and long waiting times (3 hours) were disincentives. HIV-specific service areas at clinics were significant drivers of linkage to care. Sex and age significantly affected willingness to be tested. Men and younger people were more likely to choose to test for HIV, potentially due to outstanding demand. Similar age trends were observed for linkage to care, with older respondents less likely to access services.
Conclusion: Preferences elicited in the DCEs support proactive and low-cost distribution by lay providers and minimal support linking to facility-based care services. Sex and age-differentiated responses suggest that some aspects of HIVST services could be configured to reach more men and adolescents.

896 PROVIDING USER SUPPORT FOR HIV SELF-TESTING BEYOND INSTRUCTIONS-FOR-USE IN MALAWI

Pitchaya Indravudh[1], Moses Kumwenda[1], Melissa Neuman[2], Blessings Chisunkha[1], Karin Hatzold[3], Chiwawa Nkhoma[4], Thokozani Kalua[5], Cheryl Johnson[6], Miriam Taegtmeyer[7], Liz Corbett[8]
[1]Malawi–Liverpool–Wellcome Trust Clinical Rsr Prog, Blantyre, Malawi, [2]London Sch of Hygiene & Trop Med, London, UK, [3]Pop Services Intl, Harare, Zimbabwe, [4]Pop Services Intl, Blantyre, Malawi, [5]Malawi Dept of HIV and AIDS, Lilongwe, Malawi, [6]WHO, Geneva, Switzerland, [7]Liverpool Sch of Trop Med, Liverpool, UK, [8]London Sch of Hygiene & Trop Med, Blantyre, Malawi
Background: HIV self-testing (HIVST) devices provide a convenient option for home-based testing, but comprehension of standard manufacturer instructions-for-use can be highly variable.
Methods: Commercial OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test Kits packaged for HIVST were procured with pictorial IFUs accompanied by text in both English and ChiChewa. Ease-of-use was assessed through cognitive interview with literate adults (age ≥16 years) attending HIV testing services in rural and urban Blantyre. Participants were provided with the packaged kits containing IFUs but no other assistance. A standardised questionnaire and observation record was administered during self-testing. Feasibility was then evaluated in two rural villages, with 342 participants from randomly-selected households and community peer groups (age ≥16 years and not on antiretrovirals). Respondents were offered the options of self-testing, receiving standard HIV testing, or not testing and were administered baseline and exit questionnaires. Respondents opting to self-test received a brief demonstration on kit content and usage. HIVST results were compared to a reference standard (2 parallel rapid blood-based kits by a trained professional).
Results: Numerous problems occurred in 20 cognitive interviews, including difficulty in package opening and misinterpretation of translated phrases ("two pouches"; "test stand") and imagery. Abstract symbolisation (e.g. knife and fork for eating; traffic crosses for 'do not') was poorly recognised. Although 18/20 completed HIVST, these difficulties greatly affected timeliness and confidence in validity. In contrast, all 291 feasibility participants (80.0% literate) who opted to self-test completed the test following standardised demonstration. Self-read results agreed with reference for 12/13 HIV-positive participants (sensitivity 92.9%, 95%CI 66.1%-99.8%) and 276/277 HIV-negative participants (specificity 99.60%, 95%CI 98%-100%). Uptake was high, with 85.1% of participants opting to self-test. Respondents also reported high levels of ease and satisfaction, with 100% recommending HIVST to friends and family.
Conclusion: In settings where commercially packaged self-assembly products are rarely encountered, literacy may not guarantee ability to follow HIVST IFUs unless accompanied by demonstration of use. Cognitive interviewing provides a rapid and convenient way to alert self-testing implementers of this need in their communities.

897 ACCEPTABILITY OF SELF-COLLECTED RECTAL SWABS FOR HIV EXPOSURE TESTING AMONG MSM/TGW

Hong Van Tieu[1], Maria Lemos[2], Michele Andrasik[2], Ira Fleming[2], Vijay Nandi[1], Geneva Ortiz[1], Debbie Lucy[1], Martin Musuruana[3], Julie McElrath[2], Beryl A. Koblin[1]
[1]New York Blood Cntr, New York, NY, USA, [2]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [3]Univ of Illinois, Peoria, IL, USA
Background: HIV biomedical prevention trials lack a reliable, sensitive method to measure HIV exposure and condomless sex. A pilot, prospective cohort study assessed the acceptability of self-collected rectal swabs and feasibility of testing for HIV-1 RNA and Y chromosome short tandem repeats (STRs) as biomarkers for HIV exposure and condomless receptive anal sex among MSM and transgender women (TGW) in NYC. Data on acceptability of and adherence to self-administered rectal swab collections for detection of HIV exposure biomarkers are presented here.
Methods: Eligibility criteria were assigned male at birth, age 18-50 years, HIV-negative, ≥2 male anal sex partners of HIV+/unknown status and receptive anal sex without condoms ≥3 times in last month, reside in NYC. 30 participants (ppts) were recruited via websites and referrals. They were randomized to daily vs. sex act-based self-administered rectal swab collection for 2 months. Self-administered online surveys on risk behaviors and acceptability (based on Likert scale 1 to 5), HIV testing, and blood sample collections

were performed at baseline and month 2 visits. Ppts were asked to complete daily mobile app-based sex diaries. Presence of human and Y chromosome DNA (Quantifiler Duo PCR) was used to distinguish successful collections from empty rectal swabs.
Results: Of 29 MSM and 1 TGW enrolled, 32% were 18-29 years, 30% Black and 23% Latino. Ppts reported median 6 sex partners and median 8 receptive anal sex acts in the last 60 days. The proportion of swab returns vs. expected was 59.7% in the daily arm and 49.7% in the sex act- based arm (p=0.27). Acceptability measures based on comfort level (mean Likert score=4.4 [SD 0.8] for both groups) and ease (mean 4.3 [SD 0.8] for both groups) in self-collecting rectal swabs were high. Ppts reported that having information about HIV detection in rectal swabs after condomless anal receptive sex to lower their HIV infection risk was very important (mean Likert score=4.0 [SD 1.5]). In comparing human and Y chromosome DNA results from rectal swabs to matching mobile app self-reported data on anal sex and condom use, adherence in swab collection was higher in the sex act-based arm compared with daily arm (87.2% vs. 71.9%, p=0.0054).
Conclusion: Self-administered rectal swab collection for testing of biomarkers for HIV exposure and condomless anal sex was acceptable among MSM/TGW, with higher adherence in the sex act-based arm. Methods to improve adherence to rectal swab collection and return should be explored.

898 FEASIBILITY AND REACH OF A HOME-TEST GIVEAWAY IN NEW YORK CITY, 2015–2016

Zoe R. Edelstein[1], Paul M. Salcuni[1], Benjamin Tsoi[1], Paul Kobrak[1], Adriana Andaluz[1], David A Katz[2], Demetre C. Daskalakis[1], Julie Myers[1]
[1]New York City DHMH, Queens, NY, USA, [2]Univ of Washington, Seattle, WA, USA

Background: The home HIV test may increase HIV status awareness. Advantages include convenience and privacy; barriers include cost and limited access. New York City (NYC) Health Department distributed HIV self-tests (HIVST) to men and transgender people who have sex with men (MTSM) at no charge by mail. We examined the feasibility and reach of our HIVST Giveaway (HTG) model.
Methods: Participants were recruited on dating applications and websites. Eligibility was limited to adult NYC residents who were MTSM and not previously HIV-diagnosed. Eligible participants were emailed a code to redeem on the manufacturer's website for a HIVST. Data collected via online eligibility survey included age, race/ethnicity, and time since last HIV test. Approximately 2 months after distribution ended, an online follow-up survey was used to collect information on test receipt, use, experience, result and, if appropriate, confirmatory testing. Sociodemographic factors and behaviors related to risk of HIV exposure were also assessed. To examine representativeness of those who followed up, we compared eligibility survey responses of all code redeemers to test receivers (reported on follow-up) (Chi-square test).
Results: Recruitment concluded in 23 days with 2500 codes distributed. Among those screened, 74% were deemed eligible (Table). Among eligible participants, 71% were code redeemers. Response to the follow-up survey was 48%. Among respondents, 74% of test receivers had used the test. Most test users (72%) were <35 year-old, 41% were of color, 18% had income <$20,000/year, 86% reported risk of HIV exposure (past 6 months), and 14% and 28% reported never testing and testing >1 year prior, respectively. Most test users (71%) reported testing sooner than usual or for the first time and 98% reported being likely to recommend HTG to a friend. Among 868 test users, 7 reported a reactive result (0.8%), of whom 5 reported no previous diagnosis; among the latter, 80% (4/5) reported receiving a confirmatory test. No differences were detected comparing all code redeemers to test receivers (p<0.05).
Conclusion: The HTG rapidly distributed a large volume of tests to a diverse set of NYC MTSM, many of whom had never tested or not tested recently. Despite reaching those at higher risk of HIV exposure, reported seropositivity was relatively low. Findings have motivated future HTG adaptions, including partnership with community-based organizations to recruit those at risk of HIV exposure who may not be reached online.

Table. Characteristics related to feasibility and reach of the New York City HIV Self-Test (HIVST) Giveaway, 2015-16

Characteristic	n/N	%
Screening, Eligibility and Code Redemption		
% eligible[1]	2493/3355	74%
% redeemed code and sent home test[2]	1763/2493	71%
Follow-up Survey and Test Use		
% response to follow-up survey[2]	1194/2493	48%
% received HIVST[3]	1103/1194	92%
% used HIVST[3]	884/1194	74%
% used HIVST within 1 week of receiving[4]	617/864	71%
% reporting testing sooner or for the first time[4]	591/836	71%
% reporting being likely to recommend HTG to a friend[4]	864/884	98%
Reach: Characteristics among HIVST Users		
% < 35 years old[4]	635/884	72%
% MTSM of color[4]	352/862	41%
% income <$20,000/year[4]	144/785	18%
% with risk of HIV exposure (past 6 months) [4]	761/883	86%
% with 2 or more condomless anal sex partner in past 6 months [4,5]	284/819	35%
% never tested for HIV prior to Giveaway[4]	118/858	14%
% last test more than 1 year prior to Giveaway[4]	244/858	28%
Reported HIVST Results		
% reactive results[4]	7/868	0.8%
% reactive results and no previous HIV-positive results[4]	5/868	0.6%

[1]Among those screened; [2]Among eligible participants; [3]Among follow-up survey participants; [4]Among HIVST users; [5]Report of any of the following in past 6 months: any condomless anal sex, post-exposure prophylaxis (PEP) use, sexually transmitted infection (STI) diagnosis, sex with an HIV-infected partner, stimulant (powder or crack cocaine, methamphetamine, MDMA) or injection drug use

899 STATE-LEVEL ESTIMATES OF HIV INCIDENCE, PREVALENCE, AND UNDIAGNOSED INFECTIONS

Anna S. Johnson, Ruiguang Song, Irene Hall
CDC, Atlanta, GA, USA

Background: The burden of HIV infection, the range of testing, and health outcomes for people living with HIV vary widely across the United States. Understanding the current status of HIV prevention and care outcomes in states informs efforts to achieve local HIV prevention and care goals and the goals of National HIV/AIDS Strategy.

Methods: Data from the National HIV Surveillance System on HIV diagnoses among persons aged ≥13 years and their first CD4 test result after diagnosis were used to produce state-level estimates of HIV incidence, prevalence, and percentage of undiagnosed infections during 2008–2014 for each of the 50 states and the District of Columbia. The indicators were derived from estimates of diagnosis delays based on a CD4 depletion model. Estimated annual percentage changes (EAPCs) in incidence, prevalence, and percentage undiagnosed were calculated and considered as significant if p-value is less than 0.05.
Results: During 2008–2014, among 36 jurisdictions with numerically stable estimates (>100 HIV diagnoses per year) there were significant increases (EAPCs 1-4%) in HIV prevalence in 23 jurisdictions and significant decreases (EAPCs 3-8%) in percentages of undiagnosed HIV infection in 7 jurisdictions. Estimated annual numbers of HIV infections decreased (EAPCs 2-10%) in 9 jurisdictions. In 2014, HIV prevalence ranged from an estimated 2,359 persons in Nebraska to 145,916 in New York. The estimated annual number of HIV infections ranged from 68 in Nebraska to 5,082 in California. Estimated percentages of undiagnosed HIV infections ranged from10% in Pennsylvania to 19% in Texas. Five jurisdictions (California, Georgia, Florida, New York, and Texas) accounted for 52% of HIV infections and 51% of undiagnosed infections in 2014. In 2014, by region, states located in the South accounted for 45% of persons living with HIV, 51% of HIV infections, and 50% of undiagnosed HIV infections.
Conclusion: Estimates of and changes in HIV incidence, prevalence, and undiagnosed HIV infection varied by state and geographic region. Differences in HIV outcomes between states and regions are due to a complex array of social, demographic, economic, and political factors in addition to the capacity of public health, health care systems, and the community to address HIV. Public health officials in the South and states with high percentages of undiagnosed infection should consider tailoring HIV prevention and testing initiatives to their unique environments.

900 ESTIMATING THE UNDIAGNOSED FRACTION: A COMPARISON OF NEW METHODS

Jeanette Birnbaum[1], Jason Carr[2], Martina Morris[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Washington State Dept of Hlth, Olympia, USA

Background: Estimating the number of undiagnosed HIV infections is critical for measuring the HIV care cascade but methodologically challenging. Estimates of undiagnosed HIV in the US are typically derived from the CDC's recently updated back-calculation model, which relies on the AIDS incubation distribution and is not recommended for use at the local level. We developed an alternative approach that leverages testing history data and can be applied at the local level (Fellows et al, 2015). In this paper, we seek to increase the precision of the method by incorporating data on CD4 at diagnosis, and to compare with the original and CDC estimates for WA State.
Methods: The "testing history" method (TH) relies on inter-test interval data. For newly diagnosed cases with a previous negative test, the last negative test date and date of diagnosis define a window of possible infection. For individuals diagnosed on their first test, a conservative assumption is made, and missing data are treated as missing at random. The TH "Base Case" assigns uniform probability of infection across the window, and uses the standard convolution equation to back-calculate quarterly HIV incidence and undiagnosed cases. But if individuals test after a risky exposure, this assumption would overestimate the time spent undiagnosed. To address this, we modified the TH method to incorporate data on CD4 count at diagnosis ("CD4 Case"). We reassigned 50% of the probability of infection to lie within the median untreated interval from seroconversion to CD4 established in the literature, for those with longer windows.
Results: The overall estimates from all three methods were relatively close, ranging from 9.9-11.0%. Incorporating CD4 had a small impact in the expected direction, decreasing the Base Case estimate by 0.6 percentage points (about 6%). The MSM-only estimates revealed large differences between the CDC method and both TH methods. The TH Base Case estimate of the undiagnosed fraction for MSM was 42% lower than the CDC estimate (Table 1).
Conclusion: The TH method relies on observed HIV testing patterns, while the CDC method estimates testing rates using a Bayesian approach. This may partially explain the discrepancy with CDC estimates for MSM, and may allow the TH method to more accurately reflect the impact of successful testing interventions. Incorporating CD4 data into the TH method had minimal impact here because the majority of those with high CD4 counts already had a short inter-test interval.

Table 1. Point estimates for the percent of PLWH who are undiagnosed in WA State, 2012. "TH" stands for the "testing history" method.

	*Point Estimate**			*Percent Difference*	
Population	**TH Base Case**	**TH CD4 Case**	**CDC****	**TH CD4 Case vs TH Base Case**	**TH Base Case vs CDC**
Total	10.5	9.9	11.0	-5.7%	-4.5%
MSM	6.8	6.4	11.7	-5.9%	-41.9%

* Standard errors are not presented as the diagnosed cases are a census of cases known, so there is no sampling uncertainty. The primary uncertainty derives from the model assumptions and is reflected in the point estimate differences.
**Source: CDC back-calculation model, WA State Department of Health

901 HIV TESTING MOTIVATIONS OF US MEN WHO HAVE SEX WITH MEN IN A NATIONAL ONLINE SURVEY

David A. Katz[1], Patrick Sullivan[2], Robert C. Sineath[2], Jennie McKenney[2], Maria Zlotorzynska[2], Susan Cassels[3], Joanne Stekler[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Emory Univ, Atlanta, GA, USA, [3]Univ of California Santa Barbara, Santa Barbara, CA, USA

Background: The Centers for Disease Control and Prevention recommends at least annual HIV testing for sexually active men who have sex with men (MSM) and testing every 3-6 months for those at greatest risk. Understanding reasons for seeking testing may help develop and evaluate interventions to increase frequent, regular testing.
Methods: US MSM aged 18-39 were recruited from social networking and MSM-focused online venues to participate in a study of online informed consent strategies. Surveys included questions about reasons for HIV testing. Chi-square and rank-sum tests were used to compare characteristics of never, regular, and non-regular testers and result of last test by reason for testing.
Results: Of 1413 MSM with HIV testing data (89% of total), 1106 (78%) reported prior HIV testing, of whom 105 (9%) had tested positive. Among HIV-negative ever testers, 51% reported currently testing on a regular schedule, of whom 1% reported testing monthly, 33% quarterly, 38% every 6 months, 22% annually, 3% every 2 years, and 3% on another schedule. The Table compares characteristics of regular, non-regular, and never testers. Regular testers had tested more recently than non-regular testers (median of 3 v. 10 months since last test; p<.0001). Among ever testers, reasons for last test were: routine testing (31%), HIV-positive partner (5%), other potential exposure (28%), new relationship (8%), healthcare provider recommended (7%), HIV/STD symptoms (6%), or other (14%). Among ever testers, 24% reported ever having tested in response to symptoms they thought might be acute HIV infection. The proportion who reported testing positive at last test differed by reason for last test: positive partner (30%), HIV/STD symptoms (15%), other exposure (7%), provider recommended (5%), routine testing (4%), new relationship (1%), and other (5%) [p<0.0001]. HIV-negative MSM thought they should test on a regular schedule (80%), after HIV exposure (29%), if they have HIV symptoms (22%), and between new partners (32%); this differed by testing history (Table). Most thought they should test at least annually (88%), including 85% of never testers.

Conclusion: Regular testing and perceived HIV exposures were important drivers of HIV testing among MSM, but one-fifth reported never having tested. Messages regarding frequent, regular HIV testing have reached these men but have not necessarily resulted in desired testing behaviors. Strategies for translating knowledge into practice, particularly for never testers, are needed.

902 INCREASES IN HIV TESTING FREQUENCY AMONG MEN WHO HAVE SEX WITH MEN, UNITED STATES

Qian An, Riuguang Song, Teresa Finlayson, Cyprian Wejnert, Gabriela Paz-Bailey
CDC, Atlanta, GA, USA

Background: Since 2006, CDC has recommended annual HIV testing among men who have sex with men (MSM). Knowing the HIV testing frequency and its temporal changes can inform the adherence to HIV testing recommendations. The objective of this analysis is to estimate the mean HIV inter-test interval (ITI) and assess its temporal trends among HIV-negative black and white MSM who reported previous HIV tests.

Methods: Using National HIV Behavioral Surveillance System (NHBS) data collected in 2008, 2011, and 2014, we estimated the mean HIV ITI for each year by age among black/African American (black) and white MSM with a negative NHBS HIV test who reported ever tested for HIV. We used separate statistical models based on renewal process theory by fitting exponential distributions using PROC NLIN with Newton-Raphson method. We compared the mean HIV ITI lengths by assessing whether the 95% confidence intervals overlap.

Results: Among 4406 HIV-negative black MSM and 8500 HIV-negative white MSM, 383 (8.7%) black MSM and 558 (6.6%) white MSM reported no previous HIV test. Among MSM who reported the most recent HIV test date (black: n=3945 and white: n=7776), the estimated mean HIV ITI decreased from 2008 to 2014 in each age group for both black (from 9.3 months to 6.5 months) and white (from 10.6 months to 7.7 months, table). There were differences in ITI by age. In 2014, the estimated HIV ITI in months among black MSM was: 5.5 among 18-29 years, 7.6 among 30-39 years, and 9.7 months among 40 years and older. Among white MSM it was: 6.0 among 18-29 years, 7.3 among 30-39 years and 10.5 months among 40 years and older.

Conclusion: Black and white MSM in NHBS cities who previously tested for HIV on average adhere to CDC HIV testing recommendations and the average HIV testing frequency has increased since 2008. Young MSM aged 18-29 years had a shorter mean testing interval than other age groups. Young black MSM tested more frequently than young white MSM.

Table. Estimated mean HIV ITI (months) among black and white men who have sex with men by age, National HIV Behavioral Surveillance, 20 cities, United States, 2008, 2011, 2014

		Number and percentage of participants								Estimated mean HIV ITI (months)		
		Total		2008		2011		2014		2008	2011	2014
Race	Characteristics	N	%	N	%	N	%	N	%	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Black	**Total**	3945		1093	28	1413	36	1439	36	9.3 (9.0-9.6)	7.8 (7.5-8.0)	6.5 (6.3-6.7)
	Age (years)											
	18-29	2342	59	648	59	861	61	833	58	7.9 (7.6-8.1)	6.9 (6.7-7.1)	5.5 (5.3-5.7)
	30-39	814	21	252	23	258	18	304	21	10.7 (10.0-11.4)	8.3 (7.9-8.7)	7.6 (7.2-7.9)
	>=40	789	20	193	15	294	21	302	21	15.8(14.9-16.7)	11.0(10.5-11.5)	9.7(9.2-10.1)
White	**Total**	7776		2528	33	2649	34	2599	33	10.6(10.2-10.9)	9.2(8.9-9.5)	7.7(7.4-7.9)
	Age (years)											
	18-29	2636	34	842	33	900	34	894	34	8.6(8.3-8.9)	7.7(7.4-7.9)	6.0(5.8-6.3)
	30-39	2112	27	743	29	673	25	696	27	11.2(10.7-11.7)	8.9(8.5-9.2)	7.3(7.0-7.6)
	>=40	3028	39	943	37	1076	40	1009	39	12.9(12.5-13.3)	11.8(11.4-12.1)	10.5(10.2-10.8)

903 UNDIAGNOSED HIV AND HCV IN A NEW YORK CITY EMERGENCY ROOM, 2015

Lucia V. Torian[1], Uriel Felsen[2], Qiang Xia[3], Eric Rude[3], Herbert Rose[4], Angelica Bocour[3], Gary J. Williams[5], Bob F. Bridgforth[5], Lisa A. Forgione[3], Barry S. Zingman[4]
[1]New York City DHMH, New York, NY, USA, [2]Albert Einstein Coll of Med, Bronx, NY, USA, [3]New York City DHMH, Long Island City, NY, USA, [4]Montefiore Med Cntr, Bronx, NY, USA, [5]Quest Diagnostics, San Clemente, CA, USA

Background: Undiagnosed HIV and HCV infection are missed opportunities for care and prevention of secondary transmission. CDC estimates that 13% of HIV-infected and 50% of HCV-infected persons nationwide are undiagnosed/unaware of their infection; a blinded Emergency Room (ER) HIV serosurvey in New York City (NYC) in 2010 found 14% undiagnosed/unaware. We sought to measure the prevalence of HIV and HCV, the proportion of undiagnosed/unaware, and the proportion coinfected in persons presenting to a high-volume NYC ER in 2015.

Methods: We conducted a blinded cross-sectional serosurvey using remnant serum from specimens originally drawn for clinical indications. Serum was deduplicated and matched to (1) the hospital's electronic medical record for demographic and clinical data and (2) the HIV and HCV surveillance registries for evidence of previous diagnosis prior to being de-identified and tested using standard 2- and 3-step clinical testing protocols.

Results: Among unique individuals successfully tested for HIV, 250/4990 (5.0%, 95% CI 4.4,5.7) were positive for HIV infection. Among patients tested for HCV, 372/4989 (7.5%, 95% CI 6.7,8.2) were anti-HCV-antibody positive; 196 (3.9%, 95% CI 2.8,5.1) were positive by HCV RNA PCR, indicating current infection. Overall, 12/250 patients testing positive for HIV (4.8%, 95% CI 2.5,8.2) were undiagnosed; 148/372 persons testing positive for anti-HCV antibody (39.8%, 95% CI 34.8,45.0) were undiagnosed; and 38/196 (19.2%, 95% CI 11.4,27.0) patients with detectable HCV RNA were undiagnosed. Among 250 HIV-positive individuals, 246 had sufficient serum for HCV testing; 79 (32.1%; 95% CI 26.3,38.3) were HCV-antibody positive, and 39 (15.7%, 95% CI 7.4,24.0) were currently HCV infected. Among 372 anti-HCV-positive patients, 79 (21.2%, 95% CI 17.2,25.8) were HIV-positive; among 196 HCV-infected patients, 39 (19.4%, 95% CI 12.8,26.0) were HIV-positive.

Conclusion: A reduction in the proportion of HIV-infected but undiagnosed/unaware persons presenting to the NYC ER setting between 2010 and 2015 was coterminous with legislation, funding and aggressive programming to increase HIV testing and diagnosis in NYC. Undiagnosed HCV was high, suggesting that initiatives similar to those directed toward HIV should be mounted to improve HCV diagnosis and linkage to care and treatment.

904 EXAMINATION OF UNRECOGNIZED AND MISREPORTED HIV STATUS IN BALTIMORE MSM AND PWID

Danielle German[1], Kate Shearer[1], Colin Flynn[2], Carl A. Latkin[1], Oliver Laeyendecker[3], Thomas Quinn[1], William Clarke[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Maryland DHMH, Baltimore, MD, USA, [3]NIAID, Baltimore, MD, USA

Background: Identifying individuals with unrecognized HIV infection is critical to deploying HIV testing, prevention, and surveillance resources. This measure is most commonly assessed using self-reported data about prior HIV testing and results. The accuracy of this measure can vary depending on the survey. In a previous study (2008), 33% of men who have sex with men (MSM) in Baltimore who were classified with unrecognized HIV infection had evidence of recent antiretroviral (ARV) medication. The current study

used ARV biomarkers to validate self-reported HIV infection in recent data collection waves among MSM and people who inject drugs (PWID) in Baltimore to assess changes in misrepresentation and obtain a better assessment of unrecognized HIV infection over time.
Methods: Sera from HIV+ participants in National HIV Behavioral Surveillance-Baltimore MSM (2011, n=177 and 2014, n=121) and PWID (2012, n=132) was tested for the presence of ARVs using liquid chromatography-high resolution accurate mass (HRAM) mass spectrometry (Thermo Fisher Q-Exactive) which detects 20 antiretroviral (ARV) drugs. Factors associated with unrecognized infection and misreported HIV status were assessed.
Results: Of participants originally classified with unrecognized HIV infection, 47.0% (55/117) of MSM in 2011, 52.5% (21/40) of MSM in 2014, and 58.3% (21/36) of PWID in 2012 tested positive for non-prophylactic ARV drugs. Compared to MSM who self-reported HIV+ status and ARV use, MSM misreporters in 2011 and 2014 were more likely to be non-Hispanic Black, lowest income, bisexual, and report female sex partners. MSM misreporters in 2014 also had less education, more social instability, and more substance use compared to those who disclosed HIV+ status. Among PWID, misreporters had lower education and employment and increased binge drinking. Recalculated prevalence of unrecognized HIV infection among HIV+ MSM was 35.0% in 2011 and 15.7% in 2014. Recalculated prevalence of unrecognized HIV infection among HIV+ PWID was 11.4%.
Conclusion: ARV testing reduced unrecognized HIV infection by half due to misreporting. This bio-behavioral approach across time points and populations highlights a set of persistent characteristics among those more likely to misreport HIV status. There is a critical need to enhance assessment of this important metric and to understand the role of economic and social factors such as perceived stigma and social desirability on self-report validity related to HIV status in epidemiological research.

905 SPATIAL VARIATION ALONG THE HIV CARE CONTINUUM IN WASHINGTON, DC, 2014–2015

Arpi Terzian[1], Naji Younes[1], Jenevieve Opoku[2], Johnathan Hubbard[1], Rena R. Jones[3], Princy Kumar[1], Amanda D. Castel[1], for the DC Cohort Executive Committee
[1]The George Washington Univ, Washington, DC, USA, [2]District of Columbia Dept of Hlth, Washington, DC, USA, [3]NCI, Bethesda, MD, USA

Background: Neighborhood level features have been found to influence a person's ability to connect to a HIV care provider and remain in care. The objective of this analysis was to: 1) identify clusters of geographic areas with poor outcomes along the HIV care continuum and 2) assess person-level factors associated with residing in clusters among persons living with HIV (PLWH) enrolled in the DC Cohort study, a city-wide clinical cohort in Washington, DC.
Methods: Among PLWH with ≥ 1 year of follow-up in the DC Cohort, retention in care (RIC), prescribed antiretroviral therapy (ART), and viral suppression (VS) were estimated by residential ZIP code from June 2014 to June 2015. RIC was defined as evidence of ≥ 2 HIV-related encounters ≥90 days apart in 12 months. ART prescription was among those RIC. VS was defined as VL <200 copies/mL at last visit among those RIC and on ART. Clusters of adjacent ZIPs with similar outcomes were identified using Moran's I and Getis-Ord Gi*. $\chi 2$ statistics were used to assess differences in person-level attributes by cluster status.
Results: Among 4,413 PLWH, they resided in 20 ZIP codes. Median RIC was 71% (range: 41-79%) with clustering of low RIC ZIPs in the West ($p<0.05$). Median percentage on ART was 97% (range: 85-100%) with no clustering. Median VS was 89% (range: 75-100%) with clustering of low VS ZIPs and high VS ZIPs in the SE and NW, respectively ($p<0.05$). RIC in PLWH living in clusters of low RIC was 10% lower than in other ZIPs, though the difference was not significant (64% vs74%; $P>0.05$). This group was less likely to be non-Hispanic (NH) black (18% vs 83%), more likely to be employed (47% vs 19%), permanently housed (90% vs 78%), and privately insured (55% vs 20%). VS in PLWH living in clusters of high VS was 19% higher (100% vs 84%; $P<0.05$, Figure 1); this group was less likely to be NH Black (40% vs 83%), more likely to be employed (29% vs 20%), permanently housed (83% vs 78%), privately insured (37% vs 20%) and older (median: 57 vs 50 years).
Conclusion: Consistent with prior research, person-level and neighborhood-level retention may relate to yet not fully predict VS – even in the setting of high ART coverage. Clinically stable PLWH may see their HIV providers less often thus, while they may be virally suppressed, they may not meet current definitions of retention in care. Spatial analyses may inform the development of geographically targeted interventions to reduce drop offs along the continuum.

906 TRENDS AND DISPARITIES IN ART USE AMONG PERSONS WITH HIV IN SAN FRANCISCO, 2006–2015

Ling Hsu, Sandy Schwarcz, Susan Scheer
San Francisco Dept of Pub Hlth, San Francisco, CA, USA

Background: Early entry in care and initiation of antiretroviral therapy (ART) among persons diagnosed with HIV is essential to achieve optimal treatment outcomes. However not all people with HIV receive ART and some delay initiation. In 2010, SFDPH recommended universal treatment for all persons with HIV regardless of stage of disease. We used SFDPH HIV surveillance data to examine ART use among persons diagnosed with HIV before and after the City's universal ART policy.
Methods: San Francisco residents aged ≥ 13 years diagnosed with HIV between 2006 and 2015 were divided into two time periods (2006-2010, 2011-2015). ART use and reasons for not starting ART were obtained from medical chart review. Persons whose medical records were unavailable but were virally suppressed (<200 copies/mL) were assumed to have received ART. Sociodemographic and risk characteristics of persons diagnosed in each time period who received ART were compared to those who did not using the Chi-Square test. The Kaplan-Meier product limit method was used to calculate time from HIV diagnosis to ART initiation. Logistic regression was used to identify factors associated with delayed ART initiation, defined as not starting ART within 6 months of diagnosis.
Results: Eighty-seven percent of the 2529 persons diagnosed with HIV in 2006-2010 and 88% of the 1902 diagnosed in 2011-2015 received ART. Lower ART use was observed in both time periods among persons who injected drugs (PWID), homeless, without health insurance at diagnosis, and diagnosed at counseling and testing sites. ART use was significantly lower among African Americans compared to other races in 2011-2015. Median time from diagnosis to ART initiation was 9 months in 2006-2010 and 1 month in 2011-2015. Median days from diagnosis to ART initiation decreased from 77 days in 2011 to 18 days in 2015. The most frequently documented reasons for not initiating or delaying ART were patient refusal (19%) and asymptomatic (13%). Factors independently associated with delayed ART initiation in both time periods were being African American (OR 0.74, 95% CI 0.6-1.0; OR 0.57, 95% CI 0.4-0.8, respectively) and MSM-PWID (OR 0.57, 95% CI 0.4-0.7; OR 0.60, 95% CI 0.4-0.9, respectively).
Conclusion: Overall treatment uptake after HIV diagnosis is high in San Francisco and time from diagnosis to ART significantly reduced in the last 10 years. However disparities remained. Efforts to improve timely linkage to care and treatment should target identified underserved populations.

907 CARE CONSTANCY AND VIRAL SUPPRESSION AMONG ADULTS IN HIV CLINICAL CARE, UNITED STATES

Heather Bradley, Kate Buchacz, Yunfeng Tie, Oluwatosin Olaiya, R. L. Shouse
CDC, Atlanta, GA, USA

Background: It is important to assess the frequency of HIV laboratory testing for monitoring ART efficacy to describe patterns of care usage and to improve our understanding of how care constancy is associated with viral suppression. Clinical HIV care guidelines recommend patients receive at least 1 viral load test every 6 months and 1 CD4 test every 12 months.
Methods: We used 2013–2014 data from the Medical Monitoring Project, a surveillance system producing nationally representative information about adults receiving HIV care in the US These data include 24 retrospective months of medical record data for 8,787 participants. We calculated weighted prevalence estimates of care constancy, defined as receiving 1 viral load test in each 6-month period and 1 CD4 test in each 12-month period. Using bivariate and multivariate logistic regression, we examined the association between care constancy and viral suppression (<200 copies/mL) at last test. Analyses were stratified by first CD4 count during the 24-month period (<350 vs. >350 cells/μL2).
Results: Overall, 52% [95% confidence interval (CI): 50–54] of patients met the care constancy definition over 24 months, though patients had a median of 7 clinical visits. Those with a lower first CD4 count were less likely than those with a higher first CD4 count to meet care constancy [48% (CI: 45–52) vs. 54% (CI: 52–56)] and to achieve viral suppression [74% (CI: 71–76) vs. 87% (CI: 85–89)]. Among patients with a lower first CD4 count, 83% (CI: 81–85) of those meeting care constancy were virally suppressed at last test compared to 65% (CI: 61–68) of those not meeting care constancy. Those with a higher first CD4 count who met care constancy were also more likely to be virally suppressed than those not meeting care constancy [93% (CI: 92–94) vs. 80% (CI: 76–85)]. After adjusting for characteristics that may confound the association between care constancy and viral suppression,

the prevalence ratio of viral suppression among those who did vs. did not meet care constancy was 1.24 (CI: 1.19–1.29) among patients with a lower first CD4 count and 1.15 (CI: 1.10–1.21) among those with a higher first CD4 count.

Conclusion: Only half of patients in HIV care met the care constancy definition over 24 months. It may be particularly important for persons with lower CD4 counts to receive laboratory tests at recommended intervals, as they have a considerably lower prevalence of viral suppression when care constancy is not met.

908 BEYOND THE STATIC HIV CONTINUUM: CAPTURING THE DYNAMIC PROCESS OF RETENTION

Hana Lee[1], Xiaotian Wu[1], Michael J. Mugavero[2], Stephen R. Cole[3], Bryan Lau[4], **Becky L. Genberg**[1], Joseph Hogan[1]
[1]Brown Univ, Providence, RI, USA, [2]Univ of Alabama at Birmingham, Birmingham, AL, USA, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]The Johns Hopkins Univ, Baltimore, MD, USA

Background: Retention in care is essential to maximizing antiretroviral therapy coverage and compliance and optimizing patient outcomes. Researchers often rely on cross-sectional snapshots of binary patient status to estimate retention rates and to identify predictors of attrition. This approach provides only a macro-level view, and does not make full use of longitudinal patient information that may describe cyclical processes of engagement, disengagement, and re-entry into care spanning the care continuum. We characterized the longitudinal dynamics and estimated effects of patient-level covariates related to retention in care.

Methods: We represent the process of engagement and retention in care using four states: Engaged in care, disengaged from care, lost from care (LFC), and deceased. Then various patient behaviors are described in terms of transition from one state to another such as transition from engaged to engaged (retention), engaged to disengaged, continued disengaged, disengaged to engaged (re-entry into care), disengaged to LFC, and mortality. The state space modeling (SSM) approach for longitudinal data was used to identify barriers of retention and sub-groups at higher risk of cycling out from care. This analysis includes data from the CFAR Network of Integrated Clinical Systems (CNICS), including 31,376 patients who enrolled and followed from 8 different sites in the US between 1996 and 2015.

Results: Following enrollment, we ascertained patient state membership every 200 days to reflect CNICS patient monitoring guidelines. Among engaged patients, probability of retention, disengagement, and death are 86%, 13%, and 1%. Once disengaged, probability of return to care, continued disengagement, LFC, and death are 24%, 58%, 16%, and 2%. The SSM identified some important prognostic factors of retention and other transition dynamics, after controlling for variation due to site and cohort entry year (see Table). In particular, patients with lower CD4 counts, higher viral load, and not on ARV have lower retention rates. Heterosexual males have lower retention rates compared to men who have sex with men. In addition, gender, race/ethnicity, age, and AIDS are associated with disengagement and/or LFC.

Conclusion: Beyond binary retention status, more comprehensive longitudinal patient behaviors uncover dynamic patterns of care engagement. Our findings can be used for policy, clinical, and programmatic purposes to enhance retention in care among those at greatest risk.

Table. Relative risk ratio (RRR) for effect of some key covariates on the state transition rates (relative to transition to engagement in care state), after controlling for effect of site, calendar year, and cohort entry year are presented. Significant (at alpha=0.05 level) factors are indicated as *. MSM represents men who sex with men, IDU represents injection drug use, and HSC represents heterosexual contact. Other than listed covariates, race, Hispanic ethnicity, age, alcohol use, and smoking status are also significantly associated with (some of) the state transitions.

	Transition from engaged			Transition from disengaged			
■Covariates	Retained in care	disengaged	death	Return to care	disengaged	LTFU	Death
♣CD4: 250-500	__	0.84*	0.28*	__	0.97	0.98	0.48*
♣CD4: >500	__	0.78*	0.16*	__	0.88*	0.88*	0.28*
$\log_{10}$ (viral load)	__	1.25*	1.27*	__	1.06*	0.99	1.26*
Initiated ARV	__	0.83*	0.64*	__	0.82*	1.13*	0.75*
°MSM IDU	__	1.07	1.31*	__	1.06	0.93	1.65*
°Male HSC no IDU	__	1.10*	1.41*	__	0.87*	0.81*	1.01
°Male HSC IDU	__	1.19*	1.74*	__	1.20*	0.79*	1.89*
°Female HSC no IDU	__	0.99	1.04	__	0.95	0.97	0.94
°Female HSC IDU	__	0.88*	1.04	__	0.95	0.87	1.21
AIDS	__	0.75*	2.79*	__	0.82*	0.86*	1.32*

■: CD4 counts, viral load, ARV initiation status, and AIDS defining illness are time-varying covariates
♣: reference category is CD4 counts <200
°: reference category is MSM no injection drug use

909 ASSOCIATION BETWEEN 4 MEASURES OF RETENTION IN CARE AND VIROLOGIC FAILURE

Mariah M. Kalmin, Amanda D. Castel, Alan Greenberg, Heather Young, Heather Hoffman, for the DC Cohort Executive Committee
George Washington Univ, Washington, DC, USA

Background: The relationship between retention in care (RIC) and achievement of viral suppression (VS) varies depending on the method used to measure retention. Furthermore, PLWH often cycle between VS and virologic failure (VF). We sought to apply different RIC measures to assess the relationship with VF as a recurrent event.

Methods: Data used were collected by the DC Cohort study, a longitudinal, observational study of HIV-infected patients receiving care at 13 clinics in Washington, DC. Patients ≥18 yrs enrolled between Jan 2011 and Sep 2014, on antiretroviral therapy, with an undetectable viral load at consent and with at least 12 months of study follow-up were included. RIC measures included no 6-month gaps in care, 4-month visit constancy, the Institute of Medicine (IOM) measure defined as >2 visits at least 90 days apart in a 12-month period, and the Health and Human Services (HHS) measure defined as >1 visit in each 6-month interval in 24-months with >60 days between visits. VF (viral load >200 copies/ml) was modeled as a recurrent event in order to describe the cyclical nature of VF followed by VS before again experiencing VF. Cox proportional hazards regression was used to evaluate the relationship between retention and time to VF.

Results: Among 1,958 participants, the median percent of follow-up time in which participants met each RIC measure was 50% for the HHS measure, 67% for the 4-month visit constancy and IOM measures, and 100% for the no 6-month gaps in care measure. VF was experienced by 18.8% of participants with 4% achieving VS before experiencing at least one subsequent VF event. During the first 2 yrs of follow up, an increased percentage of time not spent in a gap in care >6 months was associated with an increased rate of VF (aHR: 1.24, 95% CI: 1.06-1.45). During the last 2 yrs of follow-up, an increased percentage of time in which the IOM measure was met was associated with a decreased rate of VF (aHR: 0.74, 95% CI: 0.62-0.89). Other RIC measures were not associated with time to VF.

Conclusion: Early in follow up, meeting the no 6-month gap in care measure significantly increased the rate of VF; however, after 2 yrs, the rate of VF declined when the more stringent IOM measure was met, while other RIC measures did not impact time to VF. Our results suggest that the clinical implications of monitoring patient care and its effect on VF may vary depending on how retention is defined. Further follow up is needed to determine whether these patterns are maintained over time.

Associations between Measures of Retention in HIV Care and Time to Virologic Failure among Patients with Undetectable Viral Load at Study Enrollment			
	Retention Measure[1]	Follow-up time	Hazard ratio (95% CI)
Analysis #1: Patients with at least 12 months of follow up (N=1,958)[2]	% of time not spent in a gap > 6 months	0-2 yrs	**1.24 (1.06-1.45)**
		2-4 yrs	0.896 (0.676-1.19)
	% of time meeting 4-month visit constancy	0-2 yrs	1.03 (0.912-1.17)
		2-4 yrs	0.84 (0.658-1.07)
	% of time meeting IOM continuous care	0-2 yrs	0.97 (0.880-1.07)
		2-4 yrs	**0.74 (0.615-0.885)**
Analysis #2: Patients with at least 24 months of follow up (N=1,617)[2]	% of time meeting HHS retention in medical care	0-2 yrs	0.97 (0.902-1.05)
		2-4 yrs	0.87 (0.761-0.982)[3]

[1] Retention measures modeled as per 25% increase in retention

[2] Adjusted for baseline age, sex, race/ethnicity, insurance type, HIV transmission risk, site type, duration of follow up, baseline CD4 count, baseline ART regimen type, change in ART regimen during follow up, and baseline AIDS status

[3] Not statistically significant under the Bonferroni corrected p-value for multiple comparisons

910 USING SURVEILLANCE DATA TO MEASURE PROGRESS ALONG THE HIV CARE CONTINUUM

Nancy A. Hessol[1], Ling Hsu[2], Sharon Pipkin[2], Susan Scheer[2]

[1]Univ of California San Francisco, San Francisco, CA, USA, [2]San Francisco Dept of Pub Hlth, San Francisco, CA, USA

Background: HIV viral suppression is necessary to prevent HIV disease progression and reduce forward transmission of HIV. Routinely collected HIV surveillance data can measure progress along the HIV care continuum and evaluate changes overtime.

Methods: Newly diagnosed (2009-2014) HIV cases reported to San Francisco California Surveillance were analyzed to measure temporal trends in the HIV care continuum. Care was defined as the presence of a CD4 or HIV viral load test, viral suppression as an HIV viral load <=200 copies and retention in care as a subsequent CD4 or HIV viral load test within 6-12 months of the first laboratory test. The one-sided Cochran-Armitage test was used to test for trends. Kaplan-Meier time to event analyses assessed time to linkage to care, ART initiation, HIV viral suppression, AIDS diagnosis and death by year of HIV diagnosis.

Results: In San Francisco from 2009 through 2014 there were 2,544 newly diagnosed HIV cases and a decline in the annual number of diagnoses from 474 in 2009 to 335 in 2014. The proportion of cases who were male (P= <0.001), Asian/Pacific Islander or Latino (P= 0.01), or men who have sex with men (P= 0.002) increased. Linkage to care within three months of diagnosis increased from 86% in 2009 to 92% in 2014 (P=0.04). Among the 2390 cases who did not move out of San Francisco within the first 12 months of their diagnosis, ART initiation and viral suppression within 12 months of diagnosis increased; 63% in 2009 to 96% in 2014 (P <0.001) and 49% in 2009 to 88% in 2014 (P <0.001), respectively. The proportion who died within 12 months of diagnosis declined from 27% in 2009 to 16% in 2014 (P <0.001). Time to care, time to ART initiation and time to viral suppression were significantly shorter in more recent years of diagnosis (logrank P<0.001). Time from HIV to AIDS diagnosis was significantly longer in more recent years (logrank P<0.001). There was no significant difference for time to death by year of diagnosis.

Conclusion: Routinely collected surveillance data provides a population-based data source to measure progress along the HIV care continuum and success of HIV prevention and care programs. We observed declining numbers of HIV diagnoses and improvements in each of the HIV care continuum indicators over time.

911 IMPROVED HIV CARE OUTCOMES FOR INMATES REFERRED TO COMMUNITY PROGRAMS IN PHILADELPHIA

Makeda Carroll[1], Tanner Nassau[1], Melissa Miller[1], Cody Poerio[2], Hannah Zellman[3], Bruce Herdman[4], Coleman Terrell[1], Kathleen Brady[1]

[1]Philadelphia Dept of Pub Hlth, Philadelphia, PA, USA, [2]Action Wellness, Philadelphia, PA, USA, [3]Philadelphia FIGHT, Philadelphia, PA, USA, [4]Philadelphia Prison System, Philadelphia, PA, USA

Background: HIV-infected prison inmates constitute a vulnerable population for which information regarding long-term health outcomes post-release is lacking. We aimed to characterize predictors of care after release for inmates diagnosed in the Philadelphia Prison System (PPS).

Methods: We used data from HIV surveillance, PPS and two community referral programs (CRP) who work within PPS to identify all persons diagnosed with HIV within PPS from 2009-2013. CRPs provide advocacy, support, education, and linkages to medical care and supportive services to HIV-infected inmates upon release. Outcomes of interest included: (1) Linkage to care 90 days post-release from PPS, (2) Retention in care 1 year post-release (> 2 CD4 or viral loads (VL) at least 90 days apart), and (3) Viral suppression 1 year post-release (VL <200 copies/ml at the last measure). Multivariable logistic models evaluated factors associated with each outcome. All models were adjusted for AIDS status, length of diagnosis, prior to release length of incarceration, gender, age at release, race/ethnicity, mode of transmission, and CRP status.

Results: Of 410 inmates diagnosed within PPS, 41% were linked to care within 90 days after release, 35% and 10% were retained in care and virally suppressed at 1 year after release. Forty percent of those diagnosed in PPS were linked to a CRP. Those diagnosed for greater than 5 years were 3.2 times as likely (95% C.I. 1.9-5.4) as those diagnosed ≤ 6 months to be linked to and retained in care. Race significantly predicted retention, as black inmates were 49% less likely than whites (AOR, (95% CI 0.3-0.9) to be retained 1 year after release. Individuals that were connected to a CRP for post-release follow up were 2.4 times as likely (AOR, 95% C.I. 1.5-3.6) to be linked to care, and were 2.5 times as likely (95% C.I. 1.9-5.4) to be retained in care, as those not referred to a program. No significant predictors of viral suppression were identified.

Conclusion: HIV-infected inmates have low rates of post-release linkage to care, retention in care and viral suppression. Inmates connected to CRPs that work with newly diagnosed HIV were more likely to link to care within 90 days of release, and to be retained in the 1 year after release compared to inmates that did not access such programs. This evidence supports the need to increase referral of soon-to-be discharged inmates to CRPs as these programs can be a valuable resource in improving long-term health outcomes for this high-risk population.

912 HEALTH LITERACY AND DEMOGRAPHIC DISPARITIES IN HIV-1 VIRAL SUPPRESSION

Peter F. Rebeiro[1], Tristan McPherson[2], Kathryn Goggins[1], Megan M. Turner[1], Sally S. Bebawy[1], Lauren Brinkley-Rubinstein[3], Anna K. Person[1], Timothy R. Sterling[1], Sunil Kripalani[1], April C. Pettit[1]
[1]Vanderbilt Univ, Nashville, TN, USA, [2]Columbia Univ, New York, NY, USA, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: HIV viral suppression (VS) is critical for reducing HIV disease progression and transmission. Age, racial, and regional disparities in VS, as well as health literacy, have been noted in the US. Studies of the influence of health literacy on VS are lacking from the Southern US, and those from other regions have yielded conflicting results. We therefore examined health literacy and demographic disparities in VS in a large southern HIV clinical cohort.
Methods: Adults enrolled at Vanderbilt's Comprehensive Care Clinic (Nashville, TN) from 1998-2012 contributed person-time until final visit, death, or end of study. Health literacy was assessed by Brief Health Literacy Screen (BHLS), which is scored 3-15. VS was defined as a final viral load (VL) of <200 copies/mL, among those with ≥1 VL, in each calendar year. Modified Poisson regression with BHLS score, age, sex, race, years of education, HIV acquisition risk, insurance, year of enrollment, baseline CD4+, and baseline log10 VL, was used to estimate adjusted relative risks (RR) and 95% confidence intervals (CI) for not having VS. Generalized estimating equations accounted for multiple individual outcomes; restricted cubic splines with 3-4 knots captured the association between BHLS score, age, education, year of enrollment and VS.
Results: Among 568 individuals with BHLS score and ≥1 VL, median BHLS score was 13.5 (IQR: 11-15), median age was 40 (IQR: 33-46 years), 152 (27%) were female, 246 (43%) were black, and 65 (11%) had a history of injection drug use (IDU). Of 3,618 person-years contributed, 56% met criteria for VS. Older (mean difference=-1.74; CI=-2.89,-0.59 for 60 vs. 40-year-olds), black (mean difference=-0.59; CI=-1.09,-0.09 vs. white), and IDU risk (mean difference=-1.24; CI=-1.80,-0.69 vs. MSM) individuals had lower average BHLS scores. In the adjusted model, lower BHLS score (RR=1.16; CI=1.01,1.32 for 7 vs. 13.5), black race (RR=1.28; CI=1.14,1.44 vs. white), and younger age (RR=1.35; CI=1.09,1.66 for 20 vs. 40-year-olds) were associated with higher risk of not having VS (Table).
Conclusion: In this Southern US HIV clinical population, lower health literacy significantly increased the likelihood of not achieving VS; further, age and racial disparities in VS persisted even after accounting for health literacy differences. Improving health literacy, though a worthy goal, may not be sufficient to narrow demographic disparities in VS outcomes in this population.

913 FOOD INSECURITY AND HIV TREATMENT OUTCOMES IN THE WOMEN'S INTERAGENCY HIV STUDY

Sheri Weiser[1], Lila A. Sheira[1], Kartika Palar[1], Tracey Wilson[2], Lisa Metsch[3], Adaora Adimora[4], Igho Ofotokun[5], Eryka Wentz[6], Phyllis Tien[1], Edward A. Frongillo[7]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]SUNY Downstate Med Cntr, Brooklyn, NY, USA, [3]Columbia Univ, New York, NY, USA, [4]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [5]Emory Univ, Atlanta, GA, USA, [6]The Johns Hopkins Univ, Baltimore, MD, USA, [7]Univ of South Carolina, Columbia, SC, USA

Background: Food insecurity (the limited or uncertain availability of nutritionally adequate, safe foods), affects 18 million households in the U.S and is more prevalent among women. While food insecurity is a known contributor to increased HIV-related morbidity and mortality, there is little longitudinal research on this issue, particularly among women. This study assessed whether changes in food insecurity were associated with changes in HIV health outcomes among women in a nationally representative sample of women with or at risk for HIV.
Methods: We analyzed longitudinal data from the Women's Interagency HIV Study (WIHS), a multi-site prospective cohort study of women with or at risk for HIV. Data on 6778 observations from 2027 women with HIV were collected from spring 2013 to fall 2015 at 6-month intervals. Food insecurity was measured with the US Household Food Security Survey Module. Outcomes included 1) logarithm of viral load (copies/ml) and detectable versus undetectable viral load, 2) CD4 count (cells/mm3), and 3) physical health status (SF-36 scale). We used longitudinal multiple tobit, logistic, and linear regression models with random effects for examining associations between food insecurity and these outcomes, adjusting for age, race/ethnicity, income, education, child dependents, time on ART, CD4 nadir, current smoking, and hazardous drinking (>7 drinks/week).
Results: Over one-third of the women (37%) were food-insecure. One-third (34%) had detectable viral loads; 8% had CD4<200 cells/mm3. In adjusted analyses, having very low food security was associated with 2.4 times higher viral loads (95% CI=1.4, 4.0, p<0.0001) and 1.6 times higher odds of having a detectable viral load (95% CI=1.1, 2.1; p<0.01), compared to those with high food security (See Table 1). Those with very low food security had 24.0 cells/mm3 lower CD4 cells (p<0.01), and 2.4 points lower physical health composite scores (p<0.001), compared to those with high food security.
Conclusion: Food insecurity was associated with worse HIV treatment outcomes among HIV-infected women in the US. These results provide strong evidence that food insecurity is associated with poor health among HIV-infected women, and should be addressed as part of comprehensive HIV care delivery. Studies are needed to determine the best intervention strategies to improve food security in different contexts and sub-populations in order to improve control of the US HIV epidemic.

914 HIV STATUS AWARENESS AND ART COVERAGE AMONG FEMALE SEX WORKERS IN JUBA, SOUTH SUDAN

Avi Hakim[3], Victoria Achut[1], Alfred Okiria[2], Alex Bolo[3], Jennifer Wesson[4], Joel Katoro[3], Golda Caesar[1], Acaga Taban[2], Lee Hundley[5]
[1]South Sudan Ministry of Hlth, Juba, South Sudan, [2]IntraHlth Intl, Juba, South Sudan, [3]CDC–South Sudan, Juba, South Sudan, [4]IntraHlth Intl, Chapel Hill, NC, USA, [5]Emory Univ, Atlanta, GA, USA

Background: South Sudan's HIV prevalence is estimated at 2.7% in the general population, but no biobehavioral data exist on female sex workers (FSW). We conducted a survey of FSW in Juba, South Sudan, to estimate HIV prevalence, awareness of HIV status, and treatment coverage.
Methods: We used respondent-driven sampling to recruit 846 FSW in Juba from November 2015 to March 2016. Eligibility criteria included age ≥15 years; received money, goods, or services for sex in the last 6 months; lived or worked in Juba for at least 1 month; and able to speak English, Juba Arabic, or Swahili. Participants completed a face-to-face interview and were tested for HIV. Bivariate and multivariate analyses were conducted in RDS-A and SAS to assess factors associated with being unaware of one's HIV infection. All results are weighted.
Results: One-third (34.0%) of FSW in Juba were South Sudanese and 78.8% had ever tested for HIV. HIV prevalence was 37.9% (95% CI: 33.6-42.2). Among HIV-positive FSW, 37.1% (95% CI: 29.7-43.8) were unaware of their infection, 64.8% had a CD4< 500 and 46.4% were on treatment. Among FSW who had accessed care, 54.2% had their last clinic visit in Juba. In bivariate analysis, the odds of being unaware were higher among FSW who were South Sudanese (OR: 10.2, 95% CI: 4.3-24.3) or Congolese (OR: 4.1, 95% CI: 2.1-7.7), had not received condom information in the last 12 months (5.1, 95% CI: 3.0-8.9), and did not have a condom break in the last 6 months (2.8, 95% CI: 1.4-5.4). In multivariate analysis, a greater odds of being unaware of her HIV infection was observed among women <15 years old at first sex versus those who waited longer and women who had never spoken with a peer educator or outreach worker about HIV versus those who had (OR: 4.7, 95% CI: 1.4-16.3; 3.1, 95% CI: 1.3-7.5 respectively).
Conclusion: HIV prevalence among FSW in Juba is very high compared to the national HIV prevalence of 2.7% and treatment coverage is far below the UNAIDS goal of 90%. More than one-third of FSW are unaware they have HIV and thus are not on treatment. Outreach activities should be strengthened to increase access to HIV testing and improve linkages to treatment for FSW. With the majority of FSW eligible for treatment with a CD4< 500, FSW should be prioritized for test and start to increase treatment coverage in Juba. Retention efforts should focus on FSW who obtain care in other countries to mitigate possible treatment interruptions.

915 "TEST AND TREAT" ANTIRETROVIRAL THERAPY AMONG FEMALE SEX WORKERS IN KAMPALA, UGANDA

Yunia Mayanja, Onesmus Kamacooko, Daniel Bagiire, Gertrude Namale, Janet Seeley
MRC/UVRI Uganda Rsr Unit on AIDS, Entebbe, Uganda

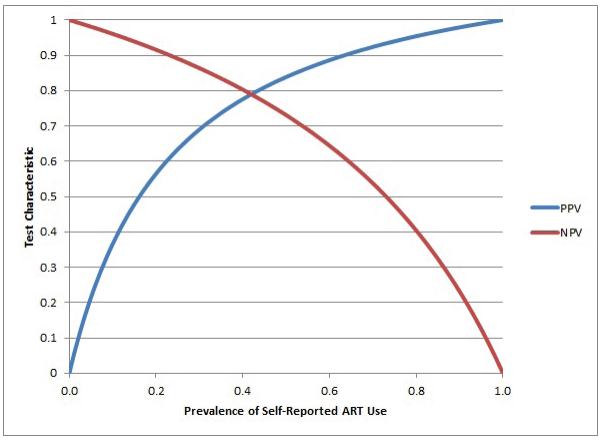
Background: Current guidelines on use of antiretroviral treatment (ART) recommend immediate treatment upon HIV positive diagnosis, regardless of CD4 count or WHO clinical stage (Test and Treat). Data on implementation of the guidelines among female sex workers (FSWs) in sub Saharan Africa are limited. We describe uptake of test and treat, and associated factors among FSWs attending a research clinic in Kampala, Uganda.

Methods: A cohort of FSWs was established in 2008 and followed up at a research clinic (Good Health for Women Project) in Kampala. At quarterly visits, data are collected on HIV and other sexually transmitted infections, socio-demographics, reproductive health, substance use, and partner violence; CD4 tests are done 6 monthly. HIV-positive women were initiated on ART using CD4 and WHO clinical stage criteria until August 2014, when test and treat was implemented. Previously enrolled HIV-positive women who had not been eligible for ART under the CD4/WHO criteria, newly enrolled HIV-positive women and HIV sero-converters became eligible for immediate treatment. Factors associated with uptake of test and treat August 2014- July 2016 were analyzed using logistic regression.
Results: We enrolled 502 ART naïve women, 56% of whom were enrolled after implementation of test and treat. Their mean age was 30.2 (± 6.3) years and 57% had CD4 >500 cells/ml at baseline. Forty-four percent self-identified as FSWs; the rest reported `other' or `no job' of whom 70.2% also engaged in transactional sex. Partner violence was reported by 27.3% of women with 52.3% perpetrated by casual partners. During the study period, 73.5% (n=369) of women initiated ART, of whom 27.4% initiated same day treatment. The median time to ART initiation was 3 months. Women who: reported partner violence (OR 0.57; 95% CI 0.33-1.00); had CD4 >500 cells/ml (OR 0.58; 95% CI 0.35-0.98), has shorter follow up duration at the clinic (OR 0.32; 95% CI 0.17-0.61) and self-identified as FSWs (OR 0.43; 95% CI 0.19-0.99) were less likely to take up test and treat. Women who worked in the hospitality industry (OR 2.63; 95% CI 1.01-6.85) and those reporting other/no job (OR 3.31; 95% CI 1.36-8.07) were more likely to take up test and treat compared to those who self-identified as FSWs.
Conclusion: Most FSWs initiate ART within two years but relatively few initiate same day treatment. Women who: self-identify as FSWs, report partner violence, have high CD4 counts and have shorter follow up need targeted interventions to increase ART uptake.

916 VALIDATING SELF-REPORTED USE OF ANTIRETROVIRAL THERAPY IN AGINCOURT, SOUTH AFRICA

Jennifer Manne-Goehler[1], Julia K Rohr[2], Livia Montana[2], Guy Harling[2], Xavier Gomez-Olive[3], Pascal Geldsetzer[2], Ryan Wagner[4], Stephen Tollman[5], Kathleen Kahn[5], Till Baernighausen[6]
[1]Beth Israel Deaconess Med Cntr, Boston, MA, USA, [2]Harvard Univ, Cambridge, MA, USA, [3]Tintswalo Hosp, Acornhoek, South Africa, [4]Univ of the Witwatersrand, Acornhoek, South Africa, [5]Univ of the Witwatersrand, Johannesburg, South Africa, [6]Heidelberg Univ, Heidelberg, Germany

Background: Knowledge of antiretroviral therapy (ART) use is essential to healthcare providers and those planning policy. Population-level testing for biological exposure to ART (BE-ART) is often not feasible and self-reported ART use (SR-ART) may be inaccurate or biased. We therefore conducted a validation study of SR-ART based on measured BE-ART in a cohort of older HIV-positive adults in South Africa, in order to understand reporting patterns and correlates of accurate self-reporting.
Methods: The Health and Aging in Africa: Longitudinal Studies of an INDEPTH community in South Africa (HAALSI) Study is a cohort of 5,059 adults aged 40+ in rural Mpumalanga, South Africa. In the baseline survey conducted in 2014-2015, HAALSI asked about socio-demographic characteristics, self-reported HIV status and ART use. HIV-positive participants also underwent dried blood spot (DBS) testing for emtricitabine (FTC) and lamivudine (3TC). Either FTC or 3TC or both have been included in any of the first- and second-line regimens ever used in the country. We calculate sensitivity and specificity of self-reported ART use for the total population and stratified by sex and age. We plot the positive predictive value (PPV) and negative predictive value (NPV) by ART prevalence. Finally, we use multivariable logistic regression to assess the association between accurate SR-ART use and socio-demographic characteristics.
Results: Baseline HIV prevalence in the HAALSI cohort was 23% (n=1,048 of 4,560 with valid DBS results). Of those who were HIV-infected and tested for ART exposure (n=1,035), 662 (64%) were positive for at least one ART drug: 573 (87%) for FTC, 84 (13%) for 3TC and 5 (1%) for both. Among those who were ART exposed only 450 (68%) reported ever accessing an ART program. The sensitivity of SR-ART use was 68% (95% CI: 64–72%) and the specificity 87% (95% CI: 83-90%). Assuming true ART use was 64%, PPV was 90% (95% CI: 87-93) and NPV 61% (95% CI: 56-65). The PPV and NPV are displayed over the full range of prevalence of self-reported ART use in Figure 1. Accurate SR-ART use was not significantly associated with participants' age, gender, educational attainment or wealth.
Conclusion: Large proportions of ART patients will disclose their ART status; and almost everyone who states they are on ART is de facto on ART. In this high-HIV prevalence community in South Africa, the PPV of SR-ART use is very high and NPV moderate. Thus, SR-ART is a useful way to measure ART use in the absence of biological exposure data.



917 REDUCING THE DEMAND FOR VIRAL-LOAD MONITORING IN THE CONTEXT OF TREATMENT FOR ALL

Denise Evans[1], Mouhamed Abdou Salam Mbengue[1], Dorina Onoya[1], Charles Chasela[1], Matthew Fox[2]
[1]Univ of the Witwatersrand, Johannesburg, South Africa, [2]Boston Univ, Boston, MA, USA

Background: From September 2016 South Africa will offer antiretroviral treatment for all, regardless of CD4 count. Eliminating CD4 count thresholds for ART eligibility has a number of challenges, including providing adequate resources for treatment and monitoring for the estimated 164,000 additional patients who are expected to start treatment each year. We aim to develop a clinical predictor score (CPS) to screen patients at 6 months on ART, and identify those who need a viral load test. Since most patients fail treatment after the first 12 months on ART, targeting those who need a viral load test at 6 months and reducing the number of tests required may be a reasonable strategy to cope with the extra numbers starting ART.
Methods: Prospective cohort study among HIV-positive ART-naïve adults initiating standard first-line ART at Themba Lethu Clinic, Johannesburg between 02/2012-05/2014. We developed a CPS to identify patients likely to have a viral load ≥400copies/ml at 6 months on ART, and should be targeted for viral load testing. Baseline demographic and clinical characteristics, changes from baseline to 6 months, number of missed visits and self-reported adherence at 6 months were included in the CPS. We obtained a risk score by summing adjusted relative risks and determined the overall discriminative value of the score using the area under the ROC curve (AUC) and dichotomized the score using several cut-offs. We determined sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of the cut-offs compared to viral load (gold standard).

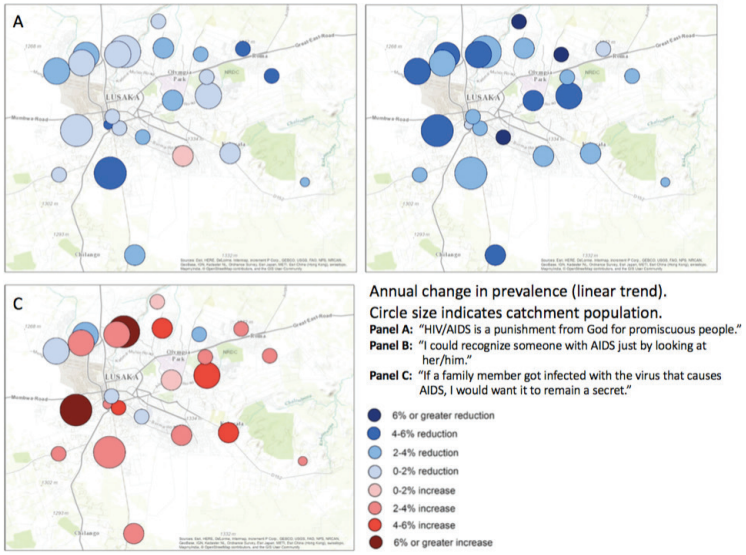
Results: 296 patients were included (64% males; median age 37.2 years). Factors associated with viral load ≥400copies/ml included male gender, platelet count <150/uL, visual analog scale <95%, missing at least two ARV visits by ≥7 days and change in mean cell volume <14.5fL. The optimal diagnostic accuracy was obtained using a risk score ≥5 (Se 65%; Sp 46.7%). CPS performed better than self-reported adherence measures (Se <60%). CPS for targeted viral load testing at 6 months correctly identified 65% (47/72) of patients with a detectable viral load, while reducing viral load testing by more than 40%. False negatives (25/72) would later receive a 12 month viral load test according to current guidelines.
Conclusion: CPS may be useful for targeted viral load testing. Results need to be validated in the context of treatment for all, in the absence of CD4 thresholds for ART eligibility.

918 STIGMA ASSOCIATED WITH HIV/STI INCIDENCE AMONG NIGERIAN MEN WHO HAVE SEX WITH MEN

Cristina Rodriguez-Hart[1], Rebecca G. Nowak[2], Rashelle Musci[1], Danielle German[1], Ifeanyi Orazulike[3], Uchenna Ononaku[4], Hongjie Liu[5], Trevor Crowell[6], Stefan Baral[1], Man Charurat[2]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Univ of Maryland, Baltimore, MD, USA, [3]Intl Cntr on Advocacy and Rights to Hlth, Abuja, Nigeria, [4]Inst of Human Virology Nigeria, Abuja, Nigeria, [5]Univ of Maryland, Coll Park, Coll Park, MD, USA, [6]US Military HIV Rsr Prog, Bethesda, MD, USA
Background: Sexual stigma, due to same-sex practices among men who have sex with men (MSM), may contribute to onward transmission of HIV and other sexually transmitted infections (STIs) in Nigeria, impeding achievement of the UNAIDS 90-90-90 treatment goals. Pathways through which this occurs are not well understood. This study assessed whether sexual stigma was associated with HIV and STI incidence and if poor mental health and sexual risk behavior contributed to the pathways between stigma and risk for HIV and STIs.
Methods: From March 2013 to February 2016, the TRUST/RV368 study recruited 1,480 MSM in Abuja and Lagos, Nigeria, into a prospective cohort that provides HIV and STI diagnosis and treatment every three months. HIV was diagnosed according to national guidelines using parallel rapid tests. Chlamydia and gonorrhea were diagnosed by PCR on rectal swab and urine specimens. Participants were classified into low (n=633), medium (n=663), and high (n=184) stigma subgroups, based on a latent class analysis of nine stigma indicators. Associations between stigma and HIV and STI incidence were assessed using $\chi 2$ tests. The components of the path analysis were hypothesized to have the following order: disclosure, stigma, suicidal ideation, condomless sex, HIV and/or STI incidence and were clustered by city. Model fit was assessed: $\chi 2$ goodness-of-fit test p-value>.05, Root Mean Square Error of Approximation (RMSEA)<.05, Comparative Fit Index (CFI)>.90, and Tucker-Lexis Index (TLI) >.90.
Results: As stigma increased in severity, incident STIs increased in a dose response relationship (STIs: 8.1%, 12.2%, 16.3% p-value=.003) (Figure 1). Incident HIV infection was less common and increased non-significantly with increasing severity of stigma (HIV: 2.8%, 3.2%, 3.8% p-value=.798). The path analysis found that all direct relationships in the model were significant and that suicidal ideation and condomless sex were significant mediating factors of the association between stigma and HIV and/or STI incidence. The model had good fit across all fit statistics ($\chi 2$ p-value=.077, RMSEA=.021, CFI=.979, and TLI=.965).
Conclusion: Increasing severity of stigma was associated with risk of HIV and STIs. The integration of stigma mitigation strategies, such as screening and treating for mental health, into combination HIV programming may facilitate the success of important biomedical tools including pre-exposure prophylaxis and treatment as prevention to reduce onward transmission.

919 POPULATION TRENDS IN HIV STIGMA IN LUSAKA, ZAMBIA, 2004–2011

Margaret P. Kasaro[1], Marie Stoner[2], Sujit Rathod[3], Tessa Roberts[3], Jennifer Winston[2], Richard Banda[4], Thankian Kusanthan[5], Jeffrey S. Stringer[2], Benjamin H. Chi[2]
[1]Univ of North Carolina, Lusaka, Zambia, [2]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [3]London Sch of Hygiene & Trop Med, London, UK, [4]Central Statistical Office, Lusaka, Zambia, [5]Univ of Zambia, Lusaka, Zambia
Background: Perceptions about HIV, including HIV-related stigma, can be an important barrier to treatment coverage, particularly as antiretroviral therapy (ART) programs expand globally.
Methods: We studied the trends in HIV stigma in Lusaka, Zambia during a period of rapid ART expansion (2004-2011). Using data from a 12-round, repeat cross-sectional survey – sampled across the entire Lusaka urban district – we compared responses to six questions over time: HIV can be transmitted through meals, HIV can be transmitted by sharing toilets, unwillingness to care for relatives infected with HIV, HIV is a punishment from God for promiscuity, those infected with AIDS can be recognized, desire to keep HIV infection of a family member a secret. We analyzed the linear trend over time for each question. For those with greater than 2% change per year (yr), we mapped the linear changes by each clinic catchment area
Results: We observed the following annual change in participant responses: HIV can be transmitted through meals (-0.86%/yr), HIV can be transmitted by sharing toilets (-0.65%/yr), unwillingness to care for relatives infected with HIV (-0.69%/yr), HIV is a punishment from God for promiscuity (-4.28%/yr), those with AIDS can be recognized (-2.17%/yr), desire to keep HIV infection of a family member a secret (+3.21%/yr). P for trend was <0.001 for all. When we mapped changes in the latter three questions (i.e., those with >2.0%/yr) by clinic catchment area, rates of change differed geographically (figure).
Conclusion: We observed encouraging trends in HIV stigma in the city of Lusaka during a period of rapid ART scale-up. Five of six indicators declined over this 8-year period, though at varying rates. Over time, an increasing proportion of respondents also preferred to keep HIV infection of a family member a secret. Efforts to reduce HIV stigma remain an important component of expanding HIV programs.



920 DEPRESSION AND ART INITIATION AMONG HIGH-RISK HIV SERODISCORDANT COUPLES IN AFRICA

Jennifer Velloza[1], Connie L. Celum[1], Haberer Jessica[2], Kenneth Ngure[3], Elizabeth Irungu[3], Nelly Mugo[3], Jared Baeten[1], Renee Heffron[1], for the Partners Demonstration Project Team
[1]Univ of Washington, Seattle, WA, USA, [2]Cntr for Global Hlth, Massachusetts General Hosp, Boston, MA, USA, [3]Kenya Med Rsr Inst, Nairobi, Kenya

Background: Depression is known to reduce antiretroviral therapy (ART) adherence and HIV care engagement, especially among women. Less is understood about the impact of depression on ART initiation, a key upstream factor on the HIV treatment cascade.

Methods: We analyzed data from 1013 Kenyan and Ugandan HIV-infected participants in the Partners Demonstration Project, an open-label study of integrated pre-exposure prophylaxis (PrEP) and ART delivery for HIV serodiscordant couples. Participants completed quarterly visits over two years; depression and stigma were assessed at enrollment, 12-month, and 24-month visits. Depression was measured with the 16-item Hopkins Symptom Checklist (HSCL; mean score ranges from 1-4; scores >1.75 indicate "probable depression"). Stigma was measured with the sum from the 6-item Internalized HIV-Related Stigma Scale (score ranges from 0-6). Using multivariable Cox proportional hazards regression, we determined whether time-varying depressive symptoms and internalized stigma independently affected ART initiation among ART-eligible participants.

Results: Most participants were female (67.0%), the median time since learning of HIV serodiscordancy was 1 month (IQR: 0.8-3 months), and the median age was 28 years (IQR: 23-35 years). At enrollment, 162 (16.0%) participants experienced probable depression and this proportion decreased during follow-up. The median stigma score was 2.0. Women were more likely to experience probable depression than men (12.8% vs. 7.5% of visits; RR=1.18; 95% CI=1.14-1.22; p<0.001) and reported higher levels of internalized HIV-related stigma across all visits (mean score of 2.4 vs. 2.0; p<0.001). Greater depressive symptom severity was associated with a higher ART initiation rate after adjustment for gender, stigma, HIV viral load, and CD4 count (aHR=1.32; 95% CI=1.01-1.73; p=0.04). This association was similar for men and women and remained when somatic items were removed from the HSCL in sensitivity analyses. Internalized stigma had no effect on ART initiation after controlling for gender, viral load, and CD4 count (aHR=0.97; 95% CI=0.93-1.02; p=0.11).

Conclusion: In this demonstration project for HIV serodiscordant couples, depression and stigma were infrequently reported although women had significantly greater risk of depression and stigma than men. Depression and stigma did not hinder ART initiation and depressive symptoms should not prevent providers from encouraging all HIV-infected individuals to initiate ART.

921 HIV STIGMA, DEPRESSION, ADHERENCE, AND VIRAL LOAD AMONG HIV+ AFRICAN-AMERICAN WOMEN

Lauren Lipira[1], Emily C. Williams[1], David Huh[1], Patrick J. Heagerty[1], Audrey French[2], Susan E. Cohn[3], Janet M. Turan[4], Michael J. Mugavero[4], Deepa Rao[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Ruth M. Rothstein CORE Cntr, Chicago, IL, USA, [3]Northwestern Univ, Chicago, IL, USA, [4]Univ of Alabama at Birmingham, Birmingham, AL, USA

Background: African-American women are disproportionately affected by HIV, have high levels of HIV stigma, and poor HIV outcomes. The purpose of this cross-sectional study is to explore relationships between HIV stigma, depressive symptoms, adherence to antiretroviral treatment (ART), and viral load among a sample of African-American women living with HIV.

Methods: From 2013-2015, African-American women living with HIV in Chicago and Birmingham were recruited for a stigma-reduction intervention. Baseline data from women on ART were included in this analysis. Using logistic regression, the association between stigma (14-item Stigma Scale for Chronic Illness) and viral suppression at baseline (< 200 copies/mL) was estimated. Then, depressive symptoms (PHQ-8) and adherence (missed doses in last 30 days) were tested as mediators using the Karlson, Holm and Breen method for comparing coefficients of nested nonlinear probability models. Finally, a generalized path analysis evaluated a model of 1) stigma predicting depressive symptoms (linear regression), 2) depressive symptoms predicting adherence (negative binomial regression), and 3) adherence predicting viral suppression at baseline (probit regression). Models were adjusted for study site, age and education.

Results: Among 194 African-American women, mean stigma score was 33.2 (SD=13.4), mean PHQ-8 score was 7.73 (SD=6.2), mean number of missed ART doses was 1.8 (SD=3.9), and 81% were virally suppressed at baseline. Higher stigma was associated with decreased odds of being virally suppressed at baseline (OR = 0.97, 95% CI: 0.94 – 1.00, p=0.03). This association did not appear to be mediated by depressive symptoms or adherence. However, when estimated simultaneously, higher stigma was associated with higher depressive symptoms (β = 0.27, 95% CI: 0.22 – 0.33, p<0.001); higher depressive symptoms were associated with a higher rate of missed ART doses (IRR = 1.04, 95% CI: 1.00 – 1.10, p =0.04); and a higher number of missed doses was associated with decreased odds of being virally suppressed at baseline (OR = 0.93, 95% CI: 0.88 – 0.99, p = 0.02).

Conclusion: These results suggest that HIV stigma is negatively associated with psychosocial and disease outcomes among African-American women living with HIV in urban settings. Longitudinal analysis of similar measures may provide important causal insights.

922 THE CAUSAL EFFECT OF DEPRESSION ON VIRAL SUPPRESSION AMONG ADULTS IN HIV CARE

Alison Hughes, Susan Scheer
San Francisco Dept of Pub Hlth, San Francisco, CA, USA

Background: Depression has been associated with lower adherence to antiretroviral treatment (ART) and lower likelihood of viral suppression. We sought to use causal inference methods to quantify how much the proportion of viral suppression may increase if current depression could be eliminated among HIV-positive adults in HIV care in San Francisco, California.

Methods: The causal effect of current depression on subsequent sustained viral suppression was estimated using causal inference methods. Data from the 2012-2014 cycles of the San Francisco Medical Monitoring Project (MMP) were collected from June 2012 through May 2015. Current depression was measured during the patient interview using the Patient Health Questionnaire Depression Scale-8 (PHQ-8) scale and was defined as a score ≥10. Sustained HIV viral suppression, which was defined as all reported viral loads within 12 months after interview being suppressed (≤200 copies/mL or "undetectable" result) was obtained through the HIV surveillance registry. Targeted minimum loss estimation (TMLE) was utilized to estimate the difference in the counterfactual proportion of HIV-positive adults virally suppressed if all adults in HIV care in San Francisco did not have current depression compared to the proportion of HIV-positive adults virally suppressed with the current level of depression. Non-parametric bootstrap was used to obtain 95% confidence intervals.

Results: There were 692 adults in our sample. The prevalence of current depression was 20.1% and 87.7% of adults in HIV care had sustained viral suppression for the 12 months after interview. The counterfactual proportion of adults virally suppressed would increase by 4.6% (95% CI: 3.4%-5.8%) if current depression could be eliminated from its current prevalence in adults in HIV care in San Francisco.

Conclusion: The results from this analysis highlight that current depression has a causal effect on sustained viral suppression among adults in HIV care in San Francisco. The percentage of adults virally suppressed at the current prevalence of depression fell short of the UNAIDS 90-90-90 goal, which aims to get 90% of persons living with HIV virally suppressed by 2020. If depression could be eliminated, through effective treatment, the proportion of adults virally suppressed in HIV care in San Francisco would increase from its current level of 87.7% to 92.3% (95% CI: 91.1%-93.5%), which exceeds the 90-90-90 target.

923 SOCIAL ECOLOGICAL FACTORS ASSOCIATED WITH SEX WORK AMONG TRANSGENDER WOMEN IN JAMAICA

Carmen H. Logie[1], Ying Wang[1], Nicolette Jones[2], Uzma Ahmed[1], Kandasi Levermore[2], Tyrone Ellis[2], Ava Neil[2], Annecka Marshall[3], Ashley A. Lacombe-Duncan[1], Peter A. Newman[1]
[1]Univ of Toronto, Toronto, Canada, [2]Jamaica AIDS Support for Life, Kingston, Jamaica, [3]Univ of the West Indies, Mona Campus, Kingston, Jamaica

Background: Transgender women are disproproportionately impacted by HIV. Transgender women involved in sex work may experience exacerbated violence, social exclusion, and HIV vulnerabilities, in comparison with non sex work involved transgender women. Scant research has investigated sex work among transgender women in the Caribbean, including Jamaica, where transgender women report pervasive violence. The study aim was to examine social ecological factors associated with sex work involvement among transgender women in Jamaica.

Methods: In 2015 we implemented a cross-sectional survey using modified peer-driven recruitment with transgender women in Kingston and Ocho Rios, Jamaica, in collaboration with a local community-based AIDS service organization. We conducted multivariable logistic regression analyses to identify factors associated with paid sex and transactional sex. Exchanging oral, anal or vaginal sex for money only was categorized as paid sex. Exchanging sex for survival needs (food, accommodation, transportation), drugs or alcohol, or for money along with survival needs and/or drugs/alcohol, was categorized as transactional sex.

Results: Among 137 transgender women (mean age: 24.0 [SD: 4.5]), two-thirds reported living in the Kingston area. Overall, 25.2% reported being HIV-positive. Approximately half (n=71; 51.82%) reported any sex work involvement, this included sex in exchange for: money (n=64; 47.06%); survival needs (n=27; 19.85%); and drugs/alcohol (n=6; 4.41%). In multivariable analyses, paid sex and transactional sex were both associated with: intrapersonal (depression), interpersonal (lower social support, forced sex, childhood sexual abuse, intimate partner violence, multiple partners/polyamory), and structural (transgender stigma, unemployment) factors. Participants reporting transactional sex also reported increased odds of incarceration, forced sex, homelessness, and lower resilience, in comparison with participants reporting no sex work involvement.

Conclusion: Findings reveal high HIV infection rates among transgender women in Jamaica. Sex work involved participants experience social and structural drivers of HIV, including violence, stigma, and unemployment. Transgender women involved in transactional sex also experience high rates of incarceration, forced sex and homelessness in comparison with non sex workers. Findings can inform multi-level interventions to advance the social determinants of health and HIV prevention and care cascades with transgender women in Jamaica.

924 SEXUAL ORIENTATION DIFFERENCES IN HEALTH AND WELLBEING AMONG WOMEN WITH HIV IN CANADA

Carmen H. Logie[1], Ashley A. Lacombe-Duncan[1], Ying Wang[1], Angela Kaida[2], Alexandra de Pokomandy[3], Kath Webster[2], Tracey Conway[4], Mona Loutfy[4]
[1]Univ of Toronto, Toronto, Canada, [2]Simon Frasier Univ, Vancouver, Canada, [3]McGill Univ, Montreal, Canada, [4]Women's Coll Rsr Inst, Toronto, Canada

Background: Scant research has examined wellbeing among sexual minority women (SMW) living with HIV despite well-documented sexual minority health disparities. The study objective was to examine sexual orientation differences in clinical, psychosocial and structural outcomes among women living with HIV (WLH) in Canada. We hypothesized that SMW living with HIV would experience poorer health and wellbeing than heterosexual WLH.

Methods: Cross-sectional baseline data was analyzed from a national Canadian cohort study conducted with WLH between August 2013 and May 2015. This included 1,420 participants (SMW: n=180; heterosexual: n=1240). SMW participants (median age: 38 years, IQR: 13) included bisexual (58.9%), lesbian (17.8%) and other sexualities (gay, queer, Two-spirit) (23.3%). We assessed sexual orientation differences in clinical, psychosocial and structural outcomes. Univariate and multivariate logistic regression analyses were conducted to determine the adjusted risk ratio for sexual orientation.

Results: SMW were younger than heterosexual participants (median age 38 years vs. 43 years; p<.001). Caucasian was the highest reported ethnicity category for both heterosexual (40.4%) and SMW (46.1%) participants; the second most frequent ethnicity was African, Caribbean or Black among heterosexuals (31.9%) and Indigenous among SMW (35.6%). A higher proportion of SMW (73.5%) compared to heterosexuals (64.3%, p<0.05) reported an annual household income of < $20,000. Multivariate logistic regression analyses controlling for age, poverty, education, and ethnicity revealed that compared to heterosexual WLH, SMW living with HIV reported clinical (<80% ARV adherence vs. 100% ARV adherence [AOR: 2.57, 95% CI: 1.45-4.56]), psychosocial (childhood abuse history [AOR: 2.93, 95% CI: 1.83-4.70], sex work [AOR: 2.87, 95% CI: 1.71-4.81], current injection drug use [IDU] vs. never IDU [AOR: 4.54, 95% CI: 2.70-7.61], prior IDU vs. never IDU [AOR: 2.35, 95% CI: 1.51-43.65], depression [AOR: 1.06, 95% CI: 1.03-1.08], lower resilience [AOR: 0.96, 95% CI: 0.95-0.98]), and structural (barriers to HIV support services [AOR: 1.76, 95% CI: 1.15-2.69], unstable housing [AOR: 1.72, 95% CI: 1.11-2.69], gender discrimination [AOR: 1.04, 95% CI: 1.02-1.06], racial discrimination [AOR: 1.03, 95% CI: 1.02-1.05]) outcome differences.

Conclusion: SMW with HIV experience social and health disparities relative to heterosexual WLH. Tailored multi-level interventions are needed to promote health equity among SMW with HIV.

925 HEALTH OUTCOMES ASSOCIATED WTIH GENDER-BASED VIOLENCE AMONG WOMEN WITH HIV IN CANADA

Carmen H. Logie[1], Angela Kaida[2], Alexandra de Pokomandy[3], Erin Ding[4], Nadia O'Brien[3], Uzma Ahmed[1], Tracey Conway[5], Val Nicholson[2], Mona Loutfy[5]
[1]Univ of Toronto, Toronto, Canada, [2]Simon Frasier Univ, Vancouver, Canada, [3]McGill Univ, Montreal, Canada, [4]BC Cntr for Excellence in HIV Rsr, Vancouver, Canada, [5]Women's Coll Rsr Inst, Toronto, Ontario

Background: Gender-based violence (GBV) is a global epidemic that disproportionately impacts women living with HIV (WLWH). We aimed to assess factors associated with experiencing GBV among WLWH in Canada.

Methods: Baseline survey data were analyzed for WLWH (≥16 years) enrolled in a community-based research cohort study in British Columbia, Ontario, and Québec. GBV was assessed through self-report of ever experiencing physical, sexual, emotional, or verbal abuse in adulthood (>16 years). Multivariable logistic regression identified socio-demographic, clinical and psychosocial factors associated with having experienced any adulthood GBV, and each type of violence separately.
Results: Of 1320 participants, the median age was 43 (IQR=36-51) years; 22% identified as Indigenous, 28% African, Caribbean or Black (ACB), 42% White, and 8% other. Most (80%) women reported experiencing any adulthood GBV, including physical (62%), sexual (43%), verbal (73%), and emotional (46%). In adjusted analyses (n=1241), women who had ever experienced GBV had higher odds of marginalization across social axes, including: incarceration history (AOR: 6.03, CI: 3.47, 10.45), food insecurity (AOR: 2.96, CI: 1.48, 5.93), racial discrimination (AOR: 1.03, CI: 1.01, 1.05), and older age (1.02, 95% CI: 1.00, 1.04). GBV was associated with increased odds of substance use: recent cannabis use (AOR: 7.33, CI: 1.71, 31.47), current cigarette use (AOR: 4.31, CI: 2.50, 7.44) and past 3 months recreational drug use (AOR: 4.08, CI: 1.18, 14.07). GBV was associated with increased odds of poor health: previous cancer diagnosis (AOR: 3.66, CI: 1.55, 8.61), Hepatitis C co-infection (AOR: 2.48, CI: 1.64, 3.75), sub-optimal antiretroviral adherence (<80% vs. >95%) (AOR: 2.31, CI: 1.11, 4.81), current post-traumatic stress disorder (AOR: 2.30, CI: 1.53, 3.45), and delayed access to HIV medical care after diagnosis (AOR: 2.22, CI: 1.40, 3.53). Correlates varied for each type of violence. Sexual violence was associated with lower income, depression, Hepatitis B, gender discrimination, and sharing needles/syringes. Physical violence was higher among participants who were Indigenous, had lived in a group home, and had a history of sharing needles/syringes. Emotional violence was associated with HIV-related stigma.
Conclusion: Most (80%) WLWH experienced violence in adulthood. Violence was associated with social marginalization and poorer clinical and psychosocial outcomes, demonstrating the need to address and screen for GBV in HIV care.

926 TRANS WOMEN WITH HIV IN CANADA: RESULTS OF A NATIONAL COMMUNITY-BASED COHORT STUDY

Ashley A. Lacombe-Duncan[1], **Yasmeen Persad**[2], Greta R. Bauer[3], Carmen H. Logie[1], Angela Kaida[4], Alexandra de Pokomandy[5], Nadia O'Brien[5], Mona Loutfy[6], for the CHIWOS Research Team
[1]Univ of Toronto, Toronto, ON, Canada, [2]The 519, Toronto, ON, Canada, [3]Western Univ, London, Ontario, Canada, [4]Simon Fraser Univ, Vancouver, Canada, [5]McGill Univ, Montreal, Canada, [6]Women's Coll Rsr Inst, Toronto, Ontario, Canada

Background: Globally, transgender (trans) women are disproportionately affected by HIV. Drivers of HIV vulnerability, including gendered stigma and discrimination, poor social determinants of health (SDoH), and violence have been well documented. Less is known about the experiences of trans women with HIV in Canada. Our study's purpose was to compare SDoH including healthcare access and mental health outcomes between trans and cisgender (cis) women living with HIV in Canada. We hypothesized that poor SDoH and HIV-related healthcare access would be higher among trans women with HIV compared to cis women with HIV in Canada.
Methods: We analysed baseline survey data from the Canadian HIV Women's Sexual and Reproductive Health Study (CHIWOS), a multi-province (British Columbia, Ontario, Quebec), community-based cohort study. We computed descriptive statistics and compared distribution among trans (n=53) and cis (n=1362) women using chi-square and ANOVA.
Results: Transgender (trans) women in CHIWOS reported a mean age 41 years (SD=10). Most were heterosexual (57%), and born in Canada (71%), while ethnicity was Indigenous (36%), White (36%), Other ethnicity (20.8%) and Black (7.5%). Similar to cis women, many reported clinical depression (44%), PTSD (44%), past incarceration (45%), and food insecurity (64%). Compared to cis women, more trans women reported a household income <$20,000/year (92% vs. 64%,p<.001), unstable housing (25% vs. 10%,p<.001), current use of recreational drugs (45% vs. 17%,p<.001), sex work for income (9% vs. 2%,p<.05), childhood violence (88 vs. 68%,p<.001), and never accessing HIV healthcare (8% vs. 3%,p<.05). Over 80% of trans women reported sometimes/many times being made fun of or called names for being trans, hearing that trans people were not normal, and being fetishized sexually because they were trans.
Conclusion: These descriptive findings highlight a multitude of factors across the SDoH that shape the health and wellbeing of trans women with HIV in Canada, including economic insecurity, mental health issues, violence, and stigma, adding to the growing body of literature about trans women and HIV globally. These findings inform an urgent need to work with multiple stakeholders (e.g., trans women, organizations, government) in order to address SDoH disparities and health outcomes for trans women with HIV.

927 THE HEALTH IMPACT OF SEXUAL VIOLENCE AMONG WOMEN IN A PLATINUM MINING BELT

Meiwen Zhang[1], Sarah Jane Steele[1], Amir Shroufi[1], Gilles van Cutsem[1], Junaid Khan[2], Garret Barnwell[2], Julia Hill[1], Kristal Duncan[1]
[1]MSF, Cape Town, South Africa, [2]MSF, Rustenburg, South Africa

Background: Physical and sexual intimate partner violence (IPV) and forced-sex or sexual acts by non-partners (NP-rape) are common in South Africa. Access to effective medical services for survivors, such as post exposure prophylaxis (PEP) for HIV prevention and sexually transmitted infections (STIs), counseling and social services is often severely limited by individual (e.g. awareness) and service-level factors (e.g. location), leaving health consequences of rape and IPV largely unaddressed. Rustenburg Municipality (RM) is South Africa's platinum mining capital and one of Africa's fastest growing cities, with a population of 301,795 men and 247,780 women living in informal settlements near the mines. We quantified the prevalence of IPV and NP-rape in this setting, and estimated the associated disease burden. By considering this alongside levels of access to services, we describe the extent to which opportunities to address this disease burden are realized.
Methods: Cluster-randomized household survey of women 18-49 years living in RM conducted (Nov– Dec, 2015) to determine the prevalence of IPV and NP-rape. We used WHO estimates of disease risk to determine population attributable fractions (PAF) and applied the PAFs to the population distribution (2011 Statistics SA Census) and local disease prevalence estimates obtained through literature review to determine burden of disease.
Results: Eighty-five percent (n=882) of eligible women participated. Lifetime prevalence of IPV was 45% – >82000 women. Lifetime prevalence of NP-rape was 18% – >28000 women and girls. Very few sought care – 5% told a health care professional about their experiences, 4% a counselor, and 3% a social worker. Of the estimated 35,680 women in RM living with HIV, 6765 cases can be attributed to IPV (19%; Table 1). The burden of IPV on induced abortion is 1296. IPV resulted in 5022 major depression disorder (MDD) cases and 2 suicides. An additional 2012 MDD cases are attributed to NP-rape.
Conclusion: IPV and NP-rape were extremely common among women and girls living in RM, contributing to a large disease burden, including 1/5 of HIV prevalence and more than 1/3 of major depressive disorders. Much of this disease burden could be prevented, through improved access to quality medical services including PEP for HIV and STI prevention, counseling and social services. Current low levels of access mean that this is not achieved, leaving major opportunities for improved health of this very vulnerable population unrealized.

Domain	Disease	IPV		NP-FS	
		PAF (95% CI)^	Disease burden	PAF (95% CI) ^	Disease burden
Mental health	Alcohol use disorders	27.9 (1.8, 49.5)	-	19.3 (17.2, 21.6)	-
	Major depressive disorders	30.4 (20.1, 40.0)	5022	22.3 (3.0, 46.0)*	2012**
	Suicide	61.4 (26.0, 82.7)	2	-	-
Sexual health	HIV/AIDS	19.0 (1.3, 35.6)	6765	-	-
	Syphilis infection	21.5 (9.8, 32.7)	-	-	-
Reproductive health	Induced abortion	34.3 (28.4, 40.1)	1296	-	-

* Major depressive disorder combined with anxiety disorders

** Major depressive disorder

^Risk of disease estimated from: Global and regional estimates of violence against women: prevalence and health effects of intimate partner violence and non-partner sexual violence

928 ASSOCIATION OF SEX AND RACE WITH HIV-/NON-HIV–RELATED DEATH IN TREATED HIV INFECTION

David B. Hanna[1], Donald R. Hoover[2], Qiuhu Shi[3], Uriel Felsen[1], Mark H. Kuniholm[4], Mindy S. Ginsberg[1], Howard D. Strickler[1], Kathryn Anastos[1]
[1]Albert Einstein Coll of Med, Bronx, NY, USA, [2]Rutgers, the State Univ of New Jersey, New Brunswick, NJ, USA, [3]New York Med Coll, Valhalla, NY, USA, [4]State Univ of New York at Albany, Rensselaer, NY, USA

Background: Whether there are systematic survival differences by sex and/or race among HIV+ individuals treated with antiretroviral therapy (ART) remains unclear. We assessed associations of sex and race with mortality among HIV+ patients initiating ART in a large US health system.
Methods: The Einstein/Rockefeller/CUNY Center for AIDS Research's HIV Clinical Cohort Database contains electronic medical records of HIV+ patients receiving care in the Montefiore Health System, the largest provider of HIV care in Bronx, New York. Inclusion criteria included intake at one of >15 outpatient clinics and ART initiation between 2006 and 2012. Self-reported race was categorized as black (Hispanic and non-Hispanic), white (Hispanic and non-Hispanic), and Hispanic of other, unspecified, or >1 race; all others were excluded. Deaths were ascertained by linkage to the National Death Index. Cox regression assessed associations of sex and race with time to death, adjusted for age, HIV transmission risk group, peak HIV-1 RNA and nadir CD4+ count as of ART initiation, neighborhood socioeconomic status, insurance type, and hepatitis C virus infection.
Results: Of 2,108 eligible patients, 41% were female, 52% black, 8% white and 40% Hispanic of other or unspecified race. Median CD4+ count at ART initiation was 240 cells/uL (interquartile range 99-365). Patients were followed for a median 3.6 years, 7,044 person-years in total. Of 227 reported deaths (11% of the cohort), 58% were HIV-related based on underlying cause ICD-10 codes. Men had a greater overall hazard of death than women (adjusted hazard ratio [aHR] 1.4, 95% CI 1.1-1.9), and black patients had a greater hazard of death (aHR 1.8, 95% CI 1.04-3.2) than white patients. For HIV deaths, blacks had a higher hazard of death than whites (aHR 2.8, 95% CI 1.2-6.4). However, there was no difference in HIV-related mortality in men versus women (aHR 1.1, 95% CI 0.7-1.5). For non-HIV deaths, there was no association with race, but there was an association of male versus female sex with mortality (aHR 2.2, 95% CI 1.4-3.4).
Conclusion: Among patients initiating ART, greater HIV-related mortality was observed among blacks than whites, whereas there was no difference by sex. Further understanding of the causes of this disparity is warranted to eliminate preventable HIV-related deaths. Our finding of higher mortality due to non-HIV causes in men versus women is comparable to findings in HIV-uninfected populations.

929 IMPACT OF INJECTION DRUG USE AND SELECTED COMORBIDITIES ON HEALTHY LIFE EXPECTANCY

Robert S. Hogg, Oghenowede Eyawo, Wendy Zhang, Paul Serada, Mark Hull, Jean A. Shoveller, Karyn Gabler, Viviane D. Lima, Julio S. Montaner, for the Comparative Outcomes And Service Utilization Trends (COAST) Study
BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada

Background: We sought to understand the impact of select comorbidities [cancers, diabetes, heart, liver, lung and renal diseases, hepatitis B and C (HCV, HBV)] and history of injection drug use on life expectancy among persons living with HIV (PLHIV). We hypothesized that persons who inject drugs (PWID) would be more impacted by these select comorbidities, especially HCV, HBV and liver diseases, and spend less time in a healthy state than other PLHIV in British Columbia (BC), Canada.
Methods: The Comparative Outcomes And Service Utilization Trends (COAST) study follows a retrospective cohort study design and includes individuals aged 19 years or older at baseline or during study follow-up. A cohort of PLHIV was constructed from all adults (≥20 years) known to be HIV-positive in BC who had a record of at least one detectable HIV plasma viral load, AIDS defining illness, or CD4 cell count; and who initiated highly active antiretroviral therapy (HAART) in BC between 25 June 1996 and 31 December 2012. Prevalence of select comorbidities was determined using case-finding algorithms based on a set of validated International Classification of Diseases, version 9 and 10 codes. All deaths were obtained from the vital event registry in BC. A healthy state was defined as the proportion of life expectancy comorbid free. We estimated comorbid-specific healthy life expectancy from 20 years of age and by history of injection drug use (IDU).
Results: Our study consisted of 5,636 PLHIV with known IDU status aged ≥20 years on HAART. Compared to other PLHIV, PWID were more likely to be women, to be Indigenous and to have initiated HAART at CD4 counts below 200 (all p-values <0.001). PWIDs had significantly higher crude and adjusted mortality rates and shorter overall life expectancies without any comorbidities than other PLHIV [29.5 (1.1, standard error) vs. 53.2 (1.1) years, p<0.001]. Differences length of the healthy state between the two groups were largest for: having one or more of eight select comorbidities (53.6 vs. 70.3%), liver disease [76.6 vs. 92.2%], and Hepatitis B (76.7 vs 97.0%) (see Figure).
Conclusion: While HAART has substantially improved the life expectancy for many PLHIV, PWID have not benefitted to the same degree and spend significantly less time in a healthy state due to the fact that they are more impacted by liver-related conditions.

930 LONGITUDINAL ASSOCIATION BETWEEN HIV STATUS AND MEDICALLY SIGNIFICANT FALLS

Julie A. Womack[1], Terrence E. Murphy[2], Harini Bathulapalli[1], Jonathan Bates[2], Cynthia L. Gibert[3], Maria Rodriguez-Barradas[4], Phyllis Tien[5], Michael T. Yin[6], Cynthia A. Brandt[1], Amy Justice[1]
[1]VA Connecticut Hlthcare System, West Haven, CT, USA, [2]Yale Univ, New Haven, CT, USA, [3]Washington, DC, VA Med Cntr, Washington, DC, USA, [4]Baylor Coll of Med, Houston, TX, USA, [5]Univ of California San Francisco, San Francsico, CA, USA, [6]Columbia Univ, New York, NY, USA

Background: As HIV infected (HIV+) individuals age, prevention of geriatric syndromes, particularly falls, is an important focus of research and clinical care. Using a machine learning algorithm to identify medically significant falls, we explored the relationship between HIV infection and falls.

Methods: Using data from the Veterans Aging Cohort Study, we identified falls by external cause of injury codes and a machine learning algorithm that identified falls in radiology reports. As verified with chart review, reliability and accuracy of this algorithm were excellent: sensitivity 94.5, and positive predictive value 92.6. In addition to HIV status, falls models included adjustment for race, sex, BMI, number of prescription medications taken in the past year (excluding antiretrovirals), specific medications associated with falls (antihypertensives, hypoglycemics, antipsychotics, benzodiazepines, hypnotics, muscle relaxers, and opiates), and comorbid conditions identified by ICD9 codes (HCV, anemia, coronary artery disease, heart failure, osteoarthritis, diabetes, COPD and pneumonia, end stage liver disease, hypertension, stroke, dementia, end stage renal disease, major depression, alcohol and drug use/abuse). With the exception of demographics, all covariates were time updated. We used general estimating equations (GEE) to assess the longitudinal association between HIV infection and falls in repeated six month intervals.
Results: 130,107 Veterans were included (34% HIV+, 2% women, 48% Black, and 8% Hispanic, mean age 47±10 years). Falls incidence was 30/1000 person-years among HIV+ and 27/1000 person-years among uninfected persons ($p<0.0001$). HIV was associated with falls in unadjusted (odds ratio: 1.09; 95% confidence interval: 1.06, 1.12; $p<0.0001$) but not in fully adjusted models (Table).The strongest predictors included HCV infection, alcohol use/abuse, anemia, dementia, stroke, greater number of prescription medications taken, and the use of antipsychotics, benzodiazepines, and opiates.
Conclusion: Falls are more common among HIV+ vs uninfected individuals but appear to be mediated by comorbid conditions known to be associated with falls (stroke and dementia) and by potentially modifiable factors: polypharmacy, opiate use, alcohol abuse, anemia and HCV infection. Efforts to reduce polypharmacy and hazardous medication use should be explored, especially in patients with high-risk comorbidities. Further research is needed to explore the role of HCV treatment in mitigating falls risk.

931 VIREMIA COPY-YEARS & MORTALITY IN HIV+ MEN STARTING ART: HOW MUCH HISTORY IS NEEDED?

Ruibin Wang[1], Sabina Haberlen[1], Frank J. Palella[2], Joseph B. Margolick[1], Bernard Macatangay[3], Otoniel Martínez-Maza[4], Lisa Jacobson[1], Alison Abraham[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Northwestern Univ, Chicago, IL, USA, [3]Univ of Pittsburgh, Pittsburgh, PA, USA, [4]Univ of California, Los Angeles, Los Angeles, CA, USA
Background: HIV replication while on combination antiretroviral therapy (cART) may reduce survival. Current methods to assess cumulative viral burden are limited by the need for extensive historical viral load (VL) data. We aimed to develop a prognostic metric of cumulative viral burden that requires less VL data.
Methods: HIV+ men in the Multicenter AIDS Cohort Study (MACS) who started cART between 1995 and 2014 were included. Viremia copy-years (VCY) was calculated as the area under the VL curve since cART initiation. This overall metric was compared to 20 different time-updated VCY metrics (10 calculated VCY over the most recent 1 to 10-year period; 10 calculated VCY over 1 to 10-year period immediately after cART initiation) and 3 cross-sectional VL metrics (VL at cART initiation, first post-cART VL and current VL). Men who did not have a VL measured in >1 year were censored. Lognormal survival models were used to assess the associations of VCY and cross-sectional VL metrics with all-cause mortality after cART initiation. Measure of association was the relative time (RT) to death, with a lower value indicating worse survival outcome. All models were adjusted for age, race, year of study entry, study center, baseline and current CD4 T cell count, and history of clinically-defined AIDS. A second model incorporated both VCY metrics and the 3 cross-sectional VLs. Model fit was evaluated using Akaike Information Criteria (AIC), a lower value indicating better fit.
Results: Among 841 HIV+, cART-initiating men, 22% were black. At cART initiation, mean age was 43y; mean CD4 361 cells/μL; mean $\log_{10}$VL 4.5. Median follow-up was 5 years; 74 died. For the 10 recent VCY metrics, each $\log_{10}$ increase in VCY was independently associated with 23% or more decrease in survival time (RT 0.72-0.77, Table). These RTs were similar to that of the overall VCY (RT 0.76). When further adjusted for cross-sectional VLs, only VCY over the recent 2 years remained significantly associated with death (RT 0.75, 95% CI 0.57-0.98). The model with VCY in the recent 2 years alone had the best fit based on AICs (Table).
Conclusion: These results among cART-initiators suggest that the prognostic value of VCY over the most recent 2 years was similar to that of the overall VCY since cART initiation, while requiring much less viral load data. VCY over the most recent 2 years could potentially serve as a useful measure of mortality risk among cART-treated HIV+ persons.

Table. Adjusted relative times of all-cause mortality for cumulative and cross-sectional viral load metrics

	$\log_{10}$ Median	Full-adjusted model		Including all 3 cross-sectional VLs‡	
		RT (95% CI)	AIC	RT (95% CI)	AIC
Overall VCY*	3.06	0.76 (0.58-0.99)	452.3	0.85 (0.61-1.19)	457.4
Recent 1-year VCY*	1.60	0.77 (0.64-0.92)	448.8	0.75 (0.56-1.00)	454.4
Recent 2-year VCY*	1.90	0.75 (0.61-0.91)	447.5	0.75 (0.57-0.98)	453.5
Recent 3-year VCY*	2.10	0.75 (0.61-0.92)	448.6	0.77 (0.58-1.02)	454.5
Recent 4-year VCY*	2.26	0.74 (0.59-0.92)	448.4	0.76 (0.57-1.02)	454.3
Recent 5-year VCY*	2.39	0.72 (0.57-0.92)	447.5	0.73 (0.53-1.01)	453.4
Recent 6-year VCY*	2.51	0.72 (0.56-0.92)	447.5	0.73 (0.52-1.02)	453.5
Recent 7-year VCY*	2.61	0.73 (0.56-0.94)	448.8	0.75 (0.54-1.05)	454.6
Recent 8-year VCY*	2.70	0.72 (0.56-0.94)	449.1	0.76 (0.53-1.07)	454.9
Recent 9-year VCY*	2.78	0.74 (0.57-0.96)	450.3	0.79 (0.56-1.10)	455.9
Recent 10-year VCY*	2.85	0.75 (0.58-0.97)	451.1	0.81 (0.58-1.13)	456.5
1-year VCY since cART*	2.17	0.84 (0.70-1.01)	454.7	0.92 (0.68-1.25)	458.3
2-year VCY since cART*	2.47	0.80 (0.65-0.98)	452.6	0.86 (0.64-1.15)	457.4
3-year VCY since cART*	2.62	0.78 (0.63-0.98)	452.1	0.85 (0.63-1.14)	457.1
4-year VCY since cART*	2.74	0.76 (0.60-0.97)	451.2	0.81 (0.59-1.11)	456.4
5-year VCY since cART*	2.79	0.75 (0.58-0.97)	450.9	0.80 (0.57-1.12)	456.3
6-year VCY since cART*	2.88	0.76 (0.59-0.98)	451.5	0.82 (0.58-1.15)	456.8
7-year VCY since cART*	2.93	0.77 (0.60-0.99)	452.5	0.86 (0.62-1.19)	457.5
8-year VCY since cART*	2.97	0.77 (0.59-0.99)	452.4	0.86 (0.61-1.19)	457.5
9-year VCY since cART*	2.99	0.77 (0.59-0.99)	452.5	0.86 (0.62-1.20)	457.6
10-year VCY since cART*	3.02	0.77 (0.59-1.00)	452.5	0.86 (0.62-1.20)	457.6
VL at cART†	4.44	0.93 (0.76-1.13)	458.1	--	--
Current VL†	1.60	0.84 (0.72-0.98)	453.8	--	--
First post-cART VL†	2.07	0.86 (0.72-1.03)	455.8	--	--

Blue indicates $p<0.05$. *Per $\log_{10}$ increase in copy-years/mL; †Per $\log_{10}$ increase in copy/mL; ‡Cross-sectional VLs included VL at cART, current VL and first post-cART VL. ***Abbreviations:*** VCY, viremia copy-years; VL, viral load; cART, combination antiretroviral therapy; RT, relative time; CI, confidence interval; AIC, Akaike Information Criteria.

932 LOW-LEVEL VIREMIA IS ASSOCIATED WITH VIROLOGIC FAILURE IN A LARGE MILITARY COHORT

Christie Joya[1], Seung Hyun Won[2], Karl Kronmann[3], Jason Okulicz[4], Timothy Whitman[1], Robert Deiss[5], Christina Schofield[6], Julie Pavlin[5], Brian K. Agan[5], Anuradha Ganesan[5]
[1]Walter Reed Natl Military Med Cntr, Bethesda, MD, USA, [2]Henry M. Jackson Fndn for Advancement of Military Med, Bethesda, MD, USA, [3]Naval Med Cntr Portsmouth, Portsmouth, VA, USA, [4]Brooke Army Med Cntr, San Antonio, TX, USA, [5]Uniformed Services Univ of the Hlth Scis, Rockville, MD, USA, [6]Madigan Army Med Cntr, Takoma, WA, USA
Background: Current treatment guidelines recommend against antiretroviral therapy (ART) changes until the viral load (VL) is greater than 200 copies/mL on two or more determinations. Whether VLs between 50 and 200 copies, i.e. persistent low level but quantifiable viremia (pLLV) predicts virologic failure (VF) is unclear. We used data from the US Military HIV Natural History Study (NHS), a well-characterized cohort of HIV-infected military members, to examine virologic outcomes and the association of pLLV and VF.

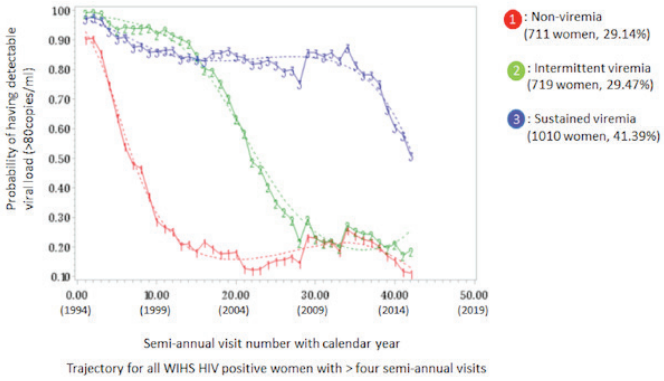
Methods: NHS subjects who initiated ART after 1996 were included, if they had two or more viral loads (VLs) measured utilizing an assay with a lower limit of detection of 50 copies/mL; for each subject, one VL had to be measured 6-18 months after ART initiation. The NHS definition of ART, which complies with the definitions discussed in the treatment guidelines, was used in this analysis. VF was defined as a viral load ≥200 copies on two separate determinations. Subjects with VLs ranging from 51 to 199 copies in over 25% of their measured values, while receiving ART, were classified as having pLLV. Continuously suppressed subjects were those with VL <50 copies/mL on all measurements. Descriptive statistics and chi-square were used to compare individuals with/without VF; variables found significant ($p<0.05$) in a univariate analysis were used in a multivariate logistic regression analysis.
Results: 1675 NHS subjects [95% male, 42% African- American, 39% Caucasian] met our inclusion criteria. 801 (47.8%) subjects were continually suppressed, while 141(8.4%) had pLLV. Of the 1675 subjects, 430 (25.7%) experienced VF during follow up. In comparison, 51 (36%) of the 141 subjects with pLLV met criteria for VF. In a multivariate analysis, presence of pLLV, younger age at ART initiation, HIV diagnosis prior to 1996, the use of antiretrovirals (ARV) that did not meet the NHS definition (usually mono or dual therapy) before ART initiation, and use of unboosted protease inhibitor (PI) based regimens were associated with VF (table).
Conclusion: In this large well characterized cohort with free access to care and limited confounders pLLV was associated with an increased risk of VF. Other factors identified were consistent with prior reports. Our results suggest that subjects with pLLV should be evaluated for their risk of VF including evaluation of medication adherence, adverse effects, and the need for ART modification.

Factors Associated VF			
Effect	Multivariate OR	95% CI	
pLLV (Referent No)	1.754	1.112	2.766
Gender (Referent Male)	0.978	0.554	1.728
Race (Referent Hispanic)			
African-American	1.314	0.897	1.926
Caucasian	1.044	0.704	1.549
HIV diagnosis era (Referent Prior to 1996)			
1996-2000	1.135	0.665	1.936
2001-2009	0.385	0.225	0.660
2010-Current	0.059	0.029	0.120
ARV before ART (Referent None)	3.527	2.119	5.871
CD4 count at ART initiation (for every 50 cell increase)	0.992	0.956	1.029
ART regimens (Referent Unboosted PI based regimens)			
Triple Nucleotide regimens	0.554	0.319	0.961
Boosted PI based regimens	0.595	0.354	0.998
Non Nucleotide Reverse Transcriptase based regimens	0.469	0.318	0.691
AIDS dx prior to ART initiation (Referent none)	1.466	0.779	2.761
Age at ART initiation (for each year increase)	0.949	0.933	0.966

933 LONGITUDINAL VIRAL TRAJECTORY AMONG WOMEN IN THE WOMEN'S INTERAGENCY HIV STUDY

Seble Kassaye[1], Cuiwei Wang[1], Jeff Collmann[1], Tracey Wilson[2], Kathryn Anastos[3], Mardge H. Cohen[4], Ruth Greenblatt[5], Joel Milam[6], Steven Gange[7], Michael Plankey[1]
[1]Georgetown Univ, Washington, DC, USA, [2]SUNY Downstate Med Cntr, Brooklyn, NY, USA, [3]Albert Einstein Coll of Med, Bronx, NY, USA, [4]John H.Stroger Jr. Hosp of Cook County, Chicago, IL, USA, [5]Univ of California San Francisco, San Francisco, CA, USA, [6]Univ of Southern California, Los Angeles, CA, USA, [7]The Johns Hopkins Univ, Baltimore, MD, USA

Background: The HIV treatment cascade provides a cross-sectional estimate of success in achievement of viral suppression, with the global goal of viral suppression in 90% of treated patients. We sought to determine the probability of sustained viral suppression by determining the longitudinal HIV viral trajectories (LHT) among women enrolled in the Women's Interagency HIV Study (WIHS).
Methods: Women were recruited in 1994-1995, 2001-2002, and 2011-2012. Logistic trajectory modeling was performed to identify longitudinal HIV RNA trajectories among women with >4 semi-annual visits to determine the probability of achieving HIV RNA >80 c/mL. Multinomial regression analysis was conducted to determine risk factors associated with the sustained viremia trajectory (SAS v9.2).
Results: 2,440 women contributed 56,209 visits from 1994-2015. The baseline median age was 36.4 years, 58.2% were African American, with a median CD4+ T lymphocyte count of 464/µl and median HIV RNA of 7000 c/mL. Three HIV viral trajectories were identified: sustained viremia (N=1010); intermittently viremic (N=719), and; non-viremic (N=711). Cumulative years of viral suppression were 20 years (non-viremic), 13 years (intermittent-viremia), and 5 years (non-viremic) across groups. The proportion of women with intermittent viremia declined then plateaued starting around 2008, alongside a sharp decline in the proportion with sustained viremia starting in 2012. Significant predictors of sustained viremia in both univariate and multivariate analyses were younger age, African American, depression with CES-D ≥16, illicit drug use, alcohol use >7 drinks/week, self-reported adherence < 95%, or not being on antiretrovirals and enrollment site.
Conclusion: This novel approach to determine LHT provides a rich perspective of challenges and successes in achieving and maintaining viral suppression over a long period of time. Long-term viral suppression was uncommon in this non-clinic based cohort, and a surprisingly high proportion of women exhibit intermittent viral suppression. The recent viral trajectories we observe likely reflect availability of potent, well tolerated antiretrovirals, and evolving treatment guidelines that promote universal treatment. Treatment success to achieve current treatment targets of 90-90-90 must address the psychosocial elements that we identify as deterrents to long term viral suppression.



Trajectory for all WIHS HIV positive women with > four semi-annual visits

934 PREP USED IN PREGNANCY DOES NOT INCREASE POOR BIRTH OUTCOMES

Renee Heffron[1], Nelly Mugo[2], Ting Hong[1], Elizabeth A. Bukusi[2], Elly T. Katabira[3], Stephen Asiimwe[4], Mark A. Marzinke[5], Connie L. Celum[1], Jared Baeten[1], for the Partners Demonstration Project and Partners PrEP Study Teams
[1]Univ of Washington, Seattle, WA, USA, [2]Kenya Med Rsr Inst, Nairobi, Kenya, [3]Makerere Univ, Kampala, Uganda, [4]Kabwohe Clinical Rsr Cntr, Kabwohe, Uganda, [5]The Johns Hopkins Univ, Baltimore, MD, USA

Background: Current recommendations for women using PrEP who become pregnant include counseling with the choice to continue or discontinue PrEP. However, safety data from women using PrEP throughout pregnancy are very limited.
Methods: In an open-label delivery study of PrEP integrated with ART for high risk HIV serodiscordant couples in Kenya and Uganda (the Partners Demonstration Project), women who became pregnant while using PrEP were counseled and offered the opportunity to continue using PrEP throughout pregnancy. Using age-adjusted generalized estimating equations with a logistic link, we compared birth outcomes from babies with exposure to FTC/TDF PrEP throughout pregnancy to those without any exposure, using data from the placebo arm of the Partners PrEP Study clinical trial, which was conducted in the same setting.
Results: Women in the open-label study who became pregnant were a median of 25.8 years (interquartile range [IQR]: 21.0-28.8) and had 2 (IQR: 1-2) children prior to study engagement. Of 34 who became pregnant while using PrEP, 30 (88%) elected to continue PrEP use. Objective adherence measures indicated at least two-thirds of expected doses were taken: a median of 71% of days (IQR: 28%-93%) had a pill bottle opening recorded via MEMS caps and 74% (116/156) of plasma samples collected from women during pregnancy had tenofovir detected, including 35% (54/156) with >40ng/ml detected. Birth outcomes from these pregnancies were compared with 96 pregnancies occurring among 88 women in the Partners PrEP Study clinical trial (median age=28 (IQR: 24.5-33.0), children=3 (IQR: 2-5)). There was no increase in the frequency of pregnancy loss (16.7% PrEP-exposed versus 32.3% PrEP-unexposed, adjusted odds ratio [aOR]=0.29, 95% CI 0.17-1.52) or preterm delivery (0 versus 7.7%, [aOR]=0.4 (0-2.32), exact p=0.4). No congenital anomalies occurred among PrEP-exposed babies.
Conclusion: To our knowledge, these are the first data to report birth outcomes from a study where women used PrEP throughout pregnancy and compare to a similar cohort without PrEP exposure. PrEP-exposed pregnancies had similar rates of pregnancy loss and preterm delivery to PrEP-unexposed women. These data provide some reassurance that PrEP use can safely continue during pregnancy.

935 PREGNANCY INCIDENCE AND OUTCOMES AMONG WOMEN USING THE DAPIVIRINE VAGINAL RING

Bonus Makanani[1], Jennifer Balkus[2], Thesla Palanee-Phillips[3], Yamikani Mbilizi[1], Jeanna Piper[4], Kenneth Kintu[5], Tchangani Tembo[6], Lisa Noguchi[7], Helen Rees[3], Jared Baeten[8]
[1]Malawi Coll of Med–Johns Hopkins Univ Rsr Proj, Blantyre, Malawi, [2]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [3]Wits Reproductive Hlth and HIV Inst, Johannesburg, South Africa, [4]NIH, Bethesda, MD, USA, [5]Makerere Univ–Johns Hopkins Univ Rsr Collab, Kampala, Uganda, [6]Univ of North Carolina Proj–Malawi, Lilongwe, Malawi, [7]The Johns Hopkins Univ, Baltimore, MD, USA, [8]Univ of Washington, Seattle, WA, USA

Background: The dapivirine vaginal ring has been shown to be safe and effective for HIV prevention. Understanding the safety of exposure during pregnancy is important for the potential roll-out of the dapivirine ring among reproductive aged women. In the MTN-020/ASPIRE trial, use of a highly effective contraceptive method was a criterion for study participation and a range of methods were offered to study participants. However, pregnancies did occur, resulting in short-term exposure to study product during the periconception period. This analysis assessed pregnancy incidence and outcomes among women randomized to receive the dapivirine ring versus matching placebo.
Methods: ASPIRE was a randomized, double-blind, placebo-controlled phase III safety and effectiveness study of the dapivirine vaginal ring for HIV-1 prevention. Sexually active women aged 18-45 from Malawi, South Africa, Uganda, and Zimbabwe were enrolled. Pregnancy tests were performed monthly and, if positive, study product was withheld during pregnancy and breastfeeding. Pregnancy incidence by arm was calculated and compared using an Andersen-Gill proportional hazards model with censoring at HIV infection. Pregnancy outcomes and infant congenital anomalies were determined by participant report and medical record review.
Results: Of 2629 women enrolled, 78 reported prior history of tubal ligation, leaving 2551 women for analysis. A total of 179 pregnancies were detected in 169 women, resulting in 180 pregnancy outcomes (86 in the dapivirine arm and 94 in the placebo arm). Pregnancy incidence in the dapivirine arm was 4.0 per 100 person-years (95% CI 3.1-5.1) versus 4.3 per 100 person-years (95% CI 3.4-5.5) in the placebo arm (HR=0.93, 95% CI 0.68-1.26). Pregnancy outcomes were similar by arm (see Table). Among 114 pregnancies that resulted in live births, data on potential congenital anomalies were available for 107, with any anomaly seen in 4 (8%) in the dapivirine arm versus 4 (7%) in the placebo arm and no pattern of anomalies for those assigned dapivirine.
Conclusion: Pregnancy rates did not differ between women randomized to dapivirine ring versus placebo in the ASPIRE trial. Pregnancy outcomes and the frequency of site-identified congenital anomalies were also similar by arm, suggesting that dapivirine use in the periconception period is not associated with adverse effects on pregnancy. Additional studies are needed to further assess the safety of the dapivirine ring use throughout pregnancy.

Table. Pregnancy outcomes by study arm among women who became pregnant in the ASPIRE trial

	Dapivirine N=86	Placebo N=94
Full term live birth	52 (60%)	53 (56%)
Preterm birth	0 (0%)	9 (10%)
Stillbirth/Intrauterine fetal demise	2 (2%)	2 (2%)
Spontaneous abortion	18 (21%)	21 (22%)
Therapeutic/elective abortion	13 (15%)	8 (9%)
Ectopic pregnancy	1 (1%)	1 (1%)

936 PREFERENCE AND CHOICE OF MULTIPURPOSE PREVENTION TECHNOLOGIES IN YOUNG AFRICAN WOMEN

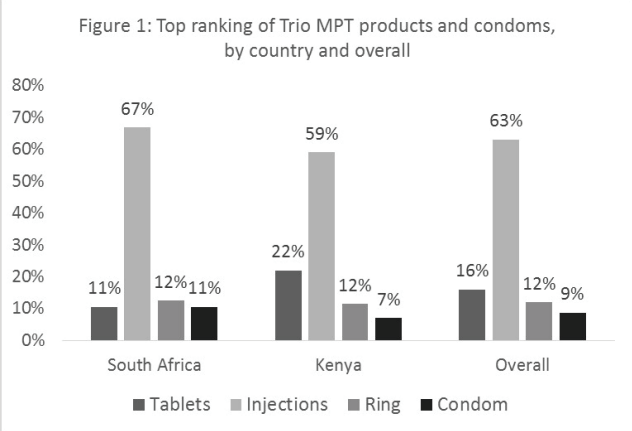
Ariane van der Straten[1], Helen Cheng[1], Kawango Agot[2], Khatija Ahmed[3], Rachel Weinrib[1], Kgahlisho Manenzhe[3], Fredrick Owino[2], Alexandra Minnis[1], for the Trio Study Team
[1]RTI Intl, San Francisco, CA, USA, [2]Impact Rsr and Development Org, Kisumu, Kenya, [3]Setshaba Rsr Cntr, Pretoria, South Africa

Background: Preventing HIV and unintended pregnancies are key health priorities in young African women. We evaluated product preference and choice in a cross-over study of 3 multipurpose prevention technology (MPT) placebo delivery forms: vaginal ring, injections or daily pills.

Methods: We enrolled 277 HIV-negative, sexually active, non-pregnant women aged 18-30 in a randomized cross-over study to use each MPT for one month. Participants were provided male condoms at every visit. Participants ranked the 3 products and condoms (from #1 top to #4 bottom), at enrollment and month-3. Next they chose one MPT for an additional 2-month usage period. We examined changes in product ranking between enrollment and month-3 (Wilcoxon signed-rank test), and, in multivariable logistic regression, the relationships of age (<25 vs. 25+) and country with the product ranked #1 at month-3, adjusting for past use of the contraceptive delivery form.

Results: Among the 214 participants who have reached their month-3 visit, 109 are from Kenya (51%) and 105 from South Africa, mean age is 23.2 years and 94% currently have a main partner. Product ranking significantly increased between enrollment and month-3 for injections (p<.001) and for ring (p<.001), but decreased for pills (p<.0001) and condoms (p=0.02). At month-3, 63% top-ranked injections, 16% top-ranked pills, 12% top-ranked ring and 9% top-ranked condoms (Figure 1). Age or country were not associated with top-ranking injection or ring at month-3; however, more Kenyans ranked pills as their #1 preference (AOR=2.3, 95% CI 1.1-5.1), compared to South Africans. MPT choice for the usage period mimicked preference ranking: 64% chose injections, 22% chose pills and 14% chose ring. "Ease of use" was the most common reason for choosing any of the three MPT; for injections or ring, infrequent dosing was another common reason, while lack of side effects was cited for pills.

Conclusion: Compared to male condoms, an existing MPT, all Trio products ranked similarly or higher. Injections were the top preference for a majority, while pills and rings each were most preferred by fewer than 1 in 5 participants, with some variation by country. MPT ranking changed following actual experience with each product, and it aligned well with product choice. User convenience appeared as paramount for selecting an MPT.



937 MODERN CONTRACEPTIVE USE AND UNPROTECTED SEX IN HIGH-RISK HIV-POSITIVE WOMEN IN KENYA

Diya Surie[1], Krista Yuhas[1], Kate Wilson[1], Linnet N. Masese[1], Juma Shafi[2], John Kinuthia[3], Walter Jaoko[2], R. Scott McClelland[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Univ of Nairobi, Nairobi, Kenya, [3]Kenyatta Natl Hosp, Nairobi, Kenya

Background: As antiretroviral therapy is scaled-up across sub-Saharan Africa, millions of women with HIV can expect to survive through their reproductive years. Modern contraceptives help women prevent unintended pregnancy while allowing them to choose the timing and spacing of childbearing. However, concerns remain that women with HIV who use modern contraceptives may engage in more unprotected intercourse because of their decreased risk of unintended pregnancy. This study evaluated whether modern contraceptive use by high-risk, HIV-positive women was associated with increased frequency of unprotected sex, measured by detection of prostate-specific antigen (PSA) in vaginal secretions and self-reported unprotected sex.

Methods: Women who were HIV-positive and reported transactional sex in Mombasa, Kenya were included in this analysis. Pregnant and post-menopausal women were excluded. At enrollment and quarterly follow-up visits, a pelvic speculum examination with collection of vaginal secretions was conducted for detection of PSA. In addition, women were interviewed for current contraceptive methods and sexual risk behavior at enrollment and monthly follow-up visits. We used log-binomial generalized estimating equations regression to test for associations between modern contraceptive use and detection of PSA in vaginal secretions and self-reported unprotected sex. Data from October 1, 2012 through September 30, 2014 were included in this analysis.

Results: Overall, 330 women contributed 1,746 quarterly examination visits and 3,868 monthly visits. There was minimal difference in PSA detection at contraceptive-exposed versus contraceptive-unexposed visits (adjusted RR [aRR] 1.16, 95% CI 0.85–1.58). However, self-reported unprotected sex was higher when women used contraceptives (aRR 1.65, 95% CI 1.04–2.63).

Conclusion: Modern contraceptives were not associated with increased risk of objective evidence of unprotected sex, but may influence reporting of unprotected sex in this population.

Table 1. Risk of Unprotected Sex and Sexual Risk Behavior by Exposure to Modern Contraceptives, Mombasa, Kenya, 2012–2014

Outcome	Visits using modern contraception n (%)	Visits not using modern contraception n (%)	Unadjusted		Adjusted	
			RR (95% CI)	*P* value	aRR (95% CI)	*P* value
Biologic outcomes						
Semen detection by PSA	104/533 (19.5)	203/1213 (16.7)	1.17 (0.85–1.60)	0.34	1.16 (0.85–1.58)	0.35
Self-reported behavior in the past week						
Self-reported unprotected sex	137/1183 (11.6)	226/2685 (8.4)	1.38 (0.84–2.25)	0.20	1.65 (1.04–2.63)	0.034
Abstinence	494/1183 (41.8)	1203/2685 (44.8)	0.93 (0.75–1.15)	0.52	0.93 (0.76–1.15)	0.52
100% condom use	552/689 (80.1)	1256/1482 (84.8)	0.95 (0.85–1.05)	0.30	0.95 (0.85–1.05)	0.30
>1 sex partner	237/689 (34.4)	675/1482 (45.6)	0.76 (0.55–1.03)	0.08	0.77 (0.57–1.02)	0.07
>2 sexual encounters	204/689 (29.6)	562/1482 (37.9)	0.78 (0.57–1.07)	0.12	0.92 (0.71–1.19)	0.52

938 INTERACTION BETWEEN ETONOGESTREL-RELEASING IMPLANT AND 3 ANTIRETROVIRAL REGIMENS

Regis Kreitchmann[1], Alice Stek[2], Brookie Best[3], Edmund Capparelli[3], Jiajia Wang[4], David E. Shapiro[4], Nahida Chakhtoura[5], Sandra Burchett[6], Mark Mirochnick[7], for the IMPAACT P1026s Protocol Team

[1]Irmandade da Santa Casa de Misericordia de Porto Alegre, Porto Alegre, Brazil, [2]Univ of Southern California, Los Angeles, CA, USA, [3]Univ of California San Diego, La Jolla, CA, USA, [4]Harvard Univ, Boston, MA, USA, [5]NICHD, Bethesda, MD, USA, [6]Boston Children's Hosp, Boston, MA, USA, [7]Boston Med Cntr, Boston, MA, USA

Background: Long acting reversible contraceptives are highly efficacious and used to prevent unplanned pregnancies in HIV infected women worldwide. There are limited data on pharmacokinetic (PK) interactions between the etonogestrel releasing implant (ENG) and antiretroviral therapy. We evaluated both the effect of ENG on the PK parameters of 3 highly active antiretroviral (ARV) regimens including: ritonavir boosted atazanavir (ATV/r), ritonavir boosted lopinavir (LPV/r) or efavirenz (EFV) and the effect of these antiretrovirals on ENG levels in HIV infected postpartum women.

Methods: IMPAACT P1026s is an ongoing, non-blinded international study of ARV PK in pregnancy and postpartum. We enrolled postpartum women who desired to use ENG implants and were taking ATV/r, LPV/r, or EFV-based regimens for at least 2 weeks. ENG implant was inserted between 2 and 12 weeks postpartum. PK sampling was performed before and 6 to 7 weeks after insertion. ARV and ENG concentrations (conc) were measured using liquid chromatography-mass spectrometry. The P1026s target minimum AUC for ATV, LPV and EFV were 29.4, 52 and 40 µg*hr/mL (10th percentile in non-pregnant historical controls), respectively. Median (range) ENG conc within the first few weeks of use in women not receiving ARV's is 400 pg/mL (250-500 pg/mL). ENG conc >90 pg/mL is believed to reliably suppress ovulation.

Results: PK data are available for 62 postpartum women (6 Black, 49 Hispanic, 7 Asian). Median (range) age at enrollment was 26.9 (15.8-41.1) yr, weight 62.7 (38.7-157.9) kg, median duration of LPV/r, ATV/r and EFV use before implant insertion was 30.0, 32.1 and 4.4 weeks, respectively. Median CD4 was 584/mm3 (79-1578) in 61 women and VL was <400 in 40/54 women (74.1%) before ENG initiation. Table 1 presents ENG concentrations and ARV AUCs among these three arms. Median ENG conc of EFV arm was <10% of the other two arms. ARV AUCs before and after ENG insertion did not differ significantly. Proportions of women meeting ARV PK targets before and after ENG insertion were: 77% and 66% for ATV/r, 84% and 84% for LPV/r and 90% and 81% for EFV (p=0.73).

Conclusion: No significant change in ATV/r, LPV/r and EFV exposure was seen after ENG insertion. EFV use was associated with greatly decreased ENG conc to levels that may impair contraceptive efficacy. Co-administration of LPV/r and ATV/r with ENG resulted in adequate ENG conc, suggesting that these combinations should have no impact on implant efficacy.

ENG Concentration and ARV AUC Comparisons between Different Arms

Characteristic		Study arm ATV/r/TFV+ENG (N=24)	EFV+ENG (N=12)	LPV/r+ENG (N=26)	P-Value
ENG Concentration (pg/mL)	N	22	9	26	
	Min, Max	260, 2,400	2.0, 280.0	225, 3,680	
	Median (Q1, Q3)	604 (436, 838)	41.5 (26.7, 136.0)	469 (366, 565)	<.001*
ENG Concentration < 90 pg/mL	Yes	0 (0%)	6 (67%)	0 (0%)	<.001**
	No	22 (100%)	3 (33%)	23 (100%)	
	Unknown	2	3	3	
ARV AUC (mcg*hr/mL)	N***	21	11	26	
Pre-ENG AUC	Median (Q1, Q3)	53.9 (29.6, 80.9)	62.6 (48.4, 93.5)	116.0 (97.3, 129.1)	
Post-ENG AUC	Median (Q1, Q3)	52.3 (26.4, 65.4)	57.6 (43.6, 113.9)	100.2 (72.9, 131.5)	
Pre/Post-ENG AUC Ratio	GMR (90% CI)	1.11 (0.83, 1.47)	1.08 (0.85, 1.37)	1.24 (0.97, 1.59)	

Abbreviations: N: Number with PK result available; ARV: Either ATV, EFV, or LPV, respectively; AUC: Area under the Curve; GMR (90% CI): Geometric Mean Ratio (90% confidence interval)
*Kruskal-Wallis Test
**Fisher's Exact Test
***Excludes 4 women (3 ATV and 1 EFV) who had a pre-ENG AUC but not a post-ENG AUC.

939 FERTILITY AND REPRODUCTIVE OUTCOMES OF HIV+ AND HIV- WOMEN IN THE CARMA COHORT STUDY

Clara E. Van Ommen[1], Arianne Y. Albert[2], Ariel Nesbitt[1], Shanlea Gordon[3], Evelyn J. Maan[3], Helene C. Cote[1], Neora Pick[1], Deborah M. Money[1], Melanie C. Murray[1], for the CIHR Team on Cellular Aging and HIV Comorbidities in Women and Children (CARMA)

[1]Univ of British Columbia, Vancouver, Canada, [2]Women's Hlth Rsr Inst, Vancouver, Canada, [3]Oak Tree Clinic, Vancouver, Canada

Background: Many women living with HIV are of reproductive age and desire children, yet the belief remains that HIV reduces fertility. The majority of studies exploring fertility and birth rates among HIV+ women are from the pre-combined antiretroviral therapy (cART) era, and report that HIV decreases fertility by 25-40%. There is little data on the impact of controlled HIV infection on reproduction in HIV+ women, though increased birth rates among women on cART versus the pre-cART era were reported. We hypothesize that Canadian women, with full access to cART, may experience a level of fertility similar to their HIV- peers.

Methods: Lifetime self-reported obstetric history was collected from 269 HIV+ and 215 HIV- women enrolled in the CARMA cohort from December 2008 to March 2016. Total number of pregnancies, live births, spontaneous and therapeutic abortions, and ectopic pregnancies were compared between the groups. Total pregnancy and live birth rates were then analyzed using negative binomial regressions for count data to calculate unadjusted and adjusted (for age, ethnicity, education, and substance use history) incident rate ratios (IRR).
Results: HIV+ women were younger, (38.3y vs. 42.2y p=0.007), more likely to be of Black ethnicity (19.7% vs. 3.3% p<0.0001), without a high school diploma (31.2% vs. 24.7%, p<0.0001) and with a history of substance use (37.9% vs. 32.6% p=0.005) compared with HIV- peers. HIV+ women had a greater number of pregnancies [median (IQR) 3 (1-4) vs. 2 (0-3) p<0.0001] and live births [2 (1-3) vs. 1 (0-2) p=0.003] as compared with controls. HIV+ and HIV- rates of spontaneous abortion (16.4% vs. 18.2% p=0.65) and ectopic pregnancy (1.3% vs. 0.6% p=0.10) were similar, while proportion of pregnancies ending with therapeutic abortion trended toward being higher (22% vs. 17% p=0.06). Given the differences between the groups, particularly as age is a major predictor of fertility, a model adjusted for the significant factors above was used to compare number of live births, and pregnancies between the groups. In the adjusted model the HIV+ group still had a higher rate of pregnancies (IRR=1.63 p<0.0001) and live births (IRR=1.54 p<0.0001) compared to HIV- controls.
Conclusion: Our data demonstrate pregnancy and live birth rates among HIV+ women in the CARMA cohort are 1.5 and 1.6 times greater than HIV- controls respectively. This suggests that in the post cART era, HIV+ women experience similar reproductive potential to their HIV- peers.

940 EARLY ONSET MENOPAUSE AMONG WOMEN LIVING WITH HIV IN CANADA

Nisha Andany[1], Angela Kaida[2], Alexandra de Pokomandy[3], Lu Wang[4], V. Logan Kennedy[1], Mark Yudin[5], Kath Webster[6], Anita Benoit[7], Mona Loutfy[1], for the CHIWOS Research Team
[1]Women's Coll Rsr Inst, Toronto, Ontario, Canada, [2]Simon Fraser Univ, Burnaby, British Columbia, Canada, [3]McGill Univ, Montreal, Canada, [4]BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada, [5]St. Michael's Hosp, Toronto, Ontario, Canada, [6]CHIWOS Study, Vancouver, Canada, [7]Univ of Toronto, Toronto, Ontario, Canada
Background: The interplay between HIV and aging has become crucial. Menopause is a pivotal age-related transition for women. Women with HIV are most likely to experience early menopause (EM) (menopause between 40-45years) and premature ovarian failure (POF) (menopause <40 years). We measured the prevalence and correlates of EM and POF in a cohort of post-menopausal Canadian women with HIV.
Methods: We used baseline survey data from the Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS), a prospective community-based study of 1425 women with HIV aged >=16 years in British Columbia, Ontario and Quebec enrolled from October 2013 to June 2015. Analyses were restricted to post-menopausal women and excluded women who had never had menses, were pregnant, or using hormonal contraception. Multivariable logistic regression models assessed independent correlates of EM and POF combined (i.e. menopause <45 years).
Results: 232 women were included. Median age was 55 (IQR=51,59) and years since HIV diagnosis was 15 (IQR=10,20); 53% of women were White, 22% African/Caribbean/Black and 19% Indigenous; 39% had history of injection drug use (IDU), 95% were on ART and 87% had viral loads <50 copies/mL. Median age of menopause was 48 years (IQR=43,51); 29.3% of women had menopause <45 years: 16.4% with EM and 12.9% with POF. In univariate analyses, menopause <45 years was associated with (trend) longer duration of HIV (p=0.05), recreational drug use (p=0.02), IDU (p=0.005), and hepatitis C (p=0.006). Older age at interview (P<0.001), being born outside of (p=0.041) and having high-school education or higher (p=0.009) reduced risk of EM/POF. The multivariable model demonstrated a trend for increased risk of EM/POF with longer duration of HIV (aOR 1.04,95%CI=0.0.99-1.09). EM/POF was less likely with older age at interview (aOR 0.86,95%CI=0.81-0.92); having high-school education or higher (aOR 0.48,95%CI=0.22-1.01) was borderline significant. IDU was not independently associated with EM/POF in the multivariate model (aOR 1.43,95%CI=0.73-2.77).
Conclusion: In this cohort of post-menopausal women with HIV, median age of menopause was 48 years; 3 years lower than the general population; 29% of women had menopause <45 years, and 13% had POF, substantially higher than the 1% rate of POF in Canada. Menopause <45 years was associated in univariate analyses with age, duration of HIV, region of birth, education, drug use and hepatitis C, but only age at interview remained significant in multivariate analyses.

941 COST-EFFECTIVENESS OF 2 METHODS TO TREAT CERVICAL DYSPLASIA IN HIV-POSITIVE WOMEN

Naomi Lince-Deroche[1], Craig Van Rensburg[1], Jane Phiri[1], Pamela Michelow[2], Jennifer Smith[3], **Cindy Firnhaber**[4]
[1]Hlth Economics and Epi Rsr Office, Johannesburg, South Africa, [2]NHLS, Johannesburg, South Africa, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]Right to Care, Johannesburg, South Africa
Background: HIV-positive women are at high risk of acquiring human papillomavirus and developing cervical cancer. Fortunately cervical cancer is preventable when early screening and treatment are available. We aimed to estimate the costs and cost-effectiveness of cryotherapy and large loop excision of the transformation zone (LLETZ) for treating cervical intraepithelial neoplasia or greater (CIN2+) in HIV-infected women taking antiretroviral treatment (ART) in Johannesburg, South Africa.
Methods: Effectiveness data were derived from a clinical trial completed at a large, public, outpatient ART clinic. HIV-positive women with CIN2+ and eligible for cryotherapy (i.e. whole lesion visible, squamocolumnar junction visible, and lesion on less than 75% of the ectocervix) were randomly assigned to cryotherapy or LLETZ. Six months post-treatment, women had a Pap smear and colposcopic biopsy (CB); if CIN2+ was present, LLETZ was performed regardless of initial assignment. At 12 months, Pap and CB were repeated; having no evidence of CIN2+ was considered successful treatment. Micro-costing was conducted from the provider perspective. We included personnel, supplies, equipment and laboratory costs. Service volume assumed full productivity for an eight-hour work day. Capital costs were annualized using a discount rate of 3% and depreciation periods recommended by the South African Revenue Service. Costs reflect USD 2015.
Results: During the study, 166 women were randomized to treatment: 86 LLETZ, 80 cryotherapy. LLETZ was performed by medical officers, cryotherapy by primary health care nurses. Table 1 provides the total average cost per procedure alone, total costs per group, and the cost per case cured for each treatment group. Total costs and cost per case cured include diagnostics and follow-up LLETZ treatment if needed. LLETZ was more costly – both in total average costs and the cost per case cured, mostly due to high laboratory costs (87.6% of the total costs). Bivariate sensitivity analysis did not alter the comparative cost findings.
Conclusion: South African guidelines indicate that LLETZ should be offered freely in the public sector. In practice access is limited. In this analysis, cryotherapy followed by LLETZ at 6 months, if necessary, was more cost-effective in treating CIN2+ in eligible HIV-positive women. Despite higher costs, access to LLETZ remains important as not all women are eligible for cryotherapy, and LLETZ may be required for follow-up treatment.

Table 1. Treatment outcomes, total average cost and cost per successfully treated case of CIN2+

	LLETZ	Cryotherapy
Number of HIV-positive women randomized to group	86	80
Number successfully treated (12 months) (n (%))	66 (76.7%)	67 (83.8%)
Total average cost per procedure*	54.38	3.46
Personnel	2.21 (4.1%)	1.45 (42.0%)
Consumables	2.71 (5.0%)	0.98 (278.4%)
Equipment	1.83 (3.4%)	1.03 (29.7%)
Laboratory	47.62 (87.6%)	0.0 (0.0%)
Total cost for all women in randomization group**	13,982.33	9,541.55
Cost per successfully treated woman**	211.86	142.41

NB: Costs reflect USD 2015.
* The total average cost per procedure represents the procedural costs only.
** The total costs per treatment group and cost per successfully treated case represent the initial treatment (or procedural) costs, follow-up LLETZ costs if needed, and Pap smears and CBs at 6 and 12 months.

942 FERTILITY DESIRES OF HIV-POSITIVE MEN AND WOMEN IN THE US

Susan E. Cohn[1], **Lisa B. Haddad**[2], Christina S. Hayford[1], Anandi N. Sheth[2], Justin A. Schmandt[1], Joan S. Chmiel[1]
[1]Northwestern Univ, Chicago, IL, USA, [2]Emory Univ, Atlanta, GA, USA

Background: A nationally representative US sample of HIV-infected women and heterosexual men in 1998 reported that 28-29% desired children in the future. Data on whether men who have sex with men want children in the future are limited. We examined the fertility desires among HIV-infected men and women initiating one of three modern antiretroviral therapy (ART) regimens.
Methods: We included 1660 (all men and women aged ≤45 years who completed necessary questionnaires) of the 1809 participants in A5257. Self-reported questionnaire data were analyzed from baseline to 96 weeks after initiating ART. We defined MSM as men who have ever had sex with a man; MSW as men who have never had sex with a man; and W as all women enrolled. Primary outcome was desire to have children in the future (yes/maybe versus no) as reported at baseline and at 96 weeks. Multivariable logistic regression models were used to evaluate associations between sociodemographic variables at baseline and fertility desire at 96 weeks after ART initiation.
Results: Participants' characteristics were: 36% white, 40% black, and 22% Hispanic; median age was 36 years; 69% were MSM, 13% MSW, 18% W. At baseline, 42% desired children in the future (42% MSM, 38% MSW and 45% W) and 41% desired children at 96 weeks (41% MSM, 37% MSW, and 43% W). Fertility desire changed from baseline to 96 weeks in 20% of participants, with 9.5% of those not desiring children changing to desiring children, while 10.5% changed to no longer desiring children. Among women who desired children, 13.1% had had a tubal ligation or hysterectomy at baseline, whereas among MSM and MSW who desired children, only 1% had had vasectomies. Multivariable analyses found that being black, having >high school degree, being <30 years old, and having no children were positively associated with desiring children in the future. Within the 3 subgroups, these same factors generally predicted wanting future children, with the exception of being black among W and MSW, of whom well over half were black.
Conclusion: During modern ART, about 40% of HIV-infected W and MSW desire more children before and 2 years after ART initiation. A similar proportion of MSM also desire future children. These results highlight the need for 1) regular assessment of family planning goals in HIV care settings; 2) access to comprehensive reproductive health, fertility, and contraceptive services, and; 3) prevention of vertical and heterosexual HIV transmission.

943 CHANGES IN GENITAL-TRACT HIV TARGET CELLS WITH THREE PROGESTIN-BASED CONTRACEPTIVES

Lisa B. Haddad[1], Alison S. Kohlmeier[2], Richard Haaland[2], Nakita Brown[1], David Lupo[2], Christina Mehta[1], Anandi N. Sheth[1], Kehmia Titanji[1], Clyde Hart[2], Igho Ofotokun[1]
[1]Emory Univ, Atlanta, GA, USA, [2]CDC, Atlanta, GA, USA

Background: Recent findings suggest that the injectable contraceptive Depot Medroxyprogesterone acetate (DMPA) may increase the risk of HIV acquisition for women but the risk for other progestin-based contraceptives is not known. We evaluated the effect of DMPA, Etonogestrel Implant (Implant) and Levonorgestrel Intrauterine Device (IUD) use on HIV target cells in the genital mucosa of adult premenopausal HIV-negative women.
Methods: Paired cervicovaginal lavage (CVL) and blood samples were prospectively obtained from eligible subjects pre (weeks 0, 2), and post (weeks 14, 16) contraceptive initiation, with contraception initiated at week 2. Genital tract leukocytes enriched from CVL and peripheral blood mononuclear cells (PBMC) were examined for T-cell markers (CD3, CD4) and HIV susceptibility, activation and trafficking markers (CCR7, CCR5, CD38, HLA-DR) by multicolor flow cytometry. Repeated-measures analyses using linear mixed models were used to estimate and compare study endpoints.
Results: Participants in this analysis included 10 DMPA, 11 Implant, and 9 IUD users of African American (76.7%) and non-Hispanic white (20.7%) races with a mean age of 35.6 +/- 8.1 years. The percentage of genital tract CCR5+ CD4+ T cells increased after implant initiation (E=16.9, p=0.007) and with DMPA use (E=14.8, p =0.039) but only when samples with <100 CD3+ lymphocytes were excluded from the DMPA analysis. Genital tract CCR7+ CCR5+ CD4+ T-cell percentages increased with Implant use (E=10.9, p=0.005) but not with DMPA or IUD; CD38+ and HLA-DR+ CD4+ T-cell percentages did not change with these 3 contraceptives. PBMCs had increased CCR5+ CD4+ T-cell percentages with DMPA use (E=2.2, p=0.004) and increased CCR7+CCR5+ CD4+ T-cell percentages with implant use (E=10.9, p=0.005).
Conclusion: DMPA and Etonogestrel Implant but not Levonorgestrel IUD use was associated with increased HIV target cell percentages in female genital tract lymphocytes. Implant use was associated with increased percentages of CCR5+ HIV target cells in the genital tract and blood capable of trafficking (CCR7+) to lymphoid organs. How these changes in genital tract HIV targets among progestin-based contraceptive users may affect their risk of HIV acquisition deserves further investigation.

944 DEPOT MEDROXYPROGESTERONE ACETATE INCREASES HIV-1 REPLICATION IN MUCOSAL TISSUE

Charlene S. Dezzutti[1], Seo Young Park[1], Ingrid Macio[2], Kenneth Marks[3], Sidney Lawlor[3], Catherine Chappell[4], Katherine Bunge[4]
[1]Univ of Pittsburgh, Pittsburgh, PA, USA, [2]Univ of Pittsburgh Med Cntr, Pittsburgh, PA, USA, [3]Magee-Womens Rsr Inst, Pittsburgh, PA, USA, [4]Magee-Womens Hosp of UPMC, Pittsburgh, PA, USA

Background: Women recruited into clinical trials evaluating HIV prevention products use effective forms of contraception or do not have sex with men. Exogenous progestins, such as hormonal contraceptives, could affect the capacity of mucosal tissue to replicate HIV-1. This study aimed to determine the effect of contraception on genital HIV replication using the ex vivo challenge assay, which collects cervical (CVX) and vaginal (VAG) tissue and exposes it to HIV-1. We hypothesize that tissue collected from women using depot medroxyprogesterone acetate (DMPA) will replicate HIV-1 to significantly higher levels than other contraceptive methods.
Methods: Healthy women (18-45 years old) using no hormonal contraception (no HC) (N=54), DMPA (N=30), levonorgestrel-intrauterine device (LNG-IUD) (N=37), or copper-IUD (Cu-IUD) (N=30) were enrolled. Two CVX and two VAG biopsies from each woman were collected using Tischler forceps and immediately treated with HIV-1BaL. After washing, the tissues were placed in culture with fresh medium. On days 3, 7, and 11, supernatants were collected for HIV-1 p24 quantification by ELISA. ANOVA F-tests with a Tukey post-hoc test were used to compare groups. The intraclass correlation coefficients (ICC) for CUM p24 for CVX and VAG tissues were calculated to evaluate intra-person variability.

Results: DMPA users had significantly higher CVX CUM p24 than the no HC (p<.0001) and Cu-IUD (p=.0048) users. LNG-IUD users had a trend of higher CVX CUM p24 compared to no HC (p=.0764) users. DMPA and LNG-IUD users had significantly higher VAG CUM p24 than the no HC users (p=.0029 and p=.0025, respectively). No difference in CUM p24 was found between no HC and Cu-IUD users for CVX and VAG tissues. There was high intra-person variability in CUM p24 for both tissues with an ICC of ≤0.234.
Conclusion: DMPA and to a lesser degree LNG-IUD use increased HIV-1 replication in mucosal tissue, which supports the epidemiological findings of increased HIV acquisition among DMPA users. Our data suggest that DMPA users should be considered for inclusion into clinical trials and controlled for in the analysis where the ex vivo challenge assay is used. HIV-1 replication in CVX and VAG tissues showed high p24 variability within the same woman suggesting baseline biopsies are not needed for the ex vivo challenge assay so long as a placebo group is included in the study.

945 ZIM-CHIC: IMPACT OF CONTRACEPTIVE INITIATION ON IMMUNE CELLS IN THE CERVIX AND PBMCS

Sharon L. Achilles[1], Feliz Mhlanga[2], Leslie A. Meyn[1], Kevin A. Stoner[3], Allen T. Matubu[2], Zvavahera M. Chirenje[2], Sharon L. Hillier[1]
[1]Univ of Pittsburgh, Pittsburgh, PA, USA, [2]Univ of Zimbabwe, Harare, Zimbabwe, [3]Magee–Womens Rsr Inst, Pittsburgh, PA, USA

Background: Injectable contraceptives have been linked to increased susceptibility to HIV. Our objective was to prospectively evaluate the impact of three injectable contraceptives (depot medroxyprogesterone actetate [DMPA], norethisterone enanthate [Net-EN], medroxyprogesterone acetate and ethinyl estradiol [MPA-EE]), two implantable contraceptives (levonorgestrel [LNG], etonogestrel [ENG]) and the copper IUD on HIV-target cells including CD4 T-cells expressing CCR5 and CD69 and antigen presenting cells (APCs) expressing CD11c, 90-days after initiation.
Methods: 193 women in Harare, Zimbabwe aged 18-34 who had not used hormonal or intrauterine contraception for >30 days or DMPA for >10 months were enrolled. Women were negative for sexually transmitted infections and HIV, and were confirmed by mass spectrometry to be free of exogenous hormones and in the follicular phase of the menstrual cycle. Cervical cytobrush samples and PBMCs were obtained at baseline and 90-days after contraceptive initiation. Immune cell populations were quantified by flow cytometry and gating was independently performed by three scientists masked to contraceptive group. Paired changes were evaluated using the Wilcoxon Signed Rank test.
Results: Women initiating Net-EN had significant increases in both the number and percent (%) of local and systemic CD4 cells expressing CCR5 (Fig) as well as CD4 cells expressing the activation marker CD69 (p=.001 in cervical cytobrushes and p=.03 in PBMCs). Women initiating copper IUD use had an increase in the number of CD4 cells expressing CCR5 (Fig) and CD69 (p=.002) as well as the number and % of CD11c+ APCs in the cytobrush (p=.002 and .007 respectively). Women initiating DMPA, MPA-EE or implantable progestins had no significant change in the number or % of CD4 cells expressing CCR5 or CD11c cells in the cytobrush or PMBCs.
Conclusion: Initiation of the injectable contraceptive Net-EN was associated with increases in CCR5 and CD69 on CD4 lymphocyte populations in the genital tract and systemically, a finding not observed following initiation of DMPA or MPA-EE. These data suggest that any increased susceptibility to HIV associated with MPA may occur through an alternative mechanism. The ECHO trial is comparing HIV incidence among women randomized to contraception with DMPA, LNG implants, or copper IUDs. Because initiation of copper IUDs was associated with local changes in immune cells, IUDs should not be considered as placebos when evaluating the impact of contraceptives on HIV risk.

946 HIV GENITAL-TRACT SHEDDING WHILE ON PROGESTIN CONTRACEPTION

Julie A. Nelson[1], Jeff Wiener[2], Jennifer H. Tang[1], Lameck Chinula[3], Stacey Hurst[2], Gerald Tegha[3], Albans Msika[3], Mina C. Hosseinipour[3], Lisa B. Haddad[4], Athena Kourtis[2]
[1]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA[2]CDC, Atlanta, GA, USA, [3]Univ of North Carolina Proj–Malawi, Lilongwe, Malawi, [4]Emory Univ, Atlanta, GA, USA

Background: During a randomized trial of the Depot Medroxyprogesterone Acetate injectable (DMPA) and the Levonorgestrel (LNG)-implant that was designed to evaluate the effects of the two progestin contraceptives on HIV genital shedding in HIV-infected women, multiple genital specimens were collected up until 6 months after contraceptive initiation. Previous analysis indicated no difference in HIV RNA shedding between the two contraceptive arms using cervicovaginal lavage (CVL) among the subset of women who were taking antiretroviral therapy (ART).
Methods: Both CVL and cervical TearFlo Strips (TFS) were collected at 2 time points before and 4 time points after contraceptive initiation. HIV RNA levels were measured (Abbott RealTime HIV-1 Assay) from CVL and TFS at all 6 time points. In addition, cell pellets from CVL were extracted for DNA and measured by Droplet Digital PCR for HIV DNA. Among women on ART, detectable genital HIV RNA was compared for the two specimen types between study arms using repeated measurements models fit by generalized estimating equations.
Results: Among the 73 HIV-infected women who were randomized to either contraceptive, 68 (93%) were taking ART (35 using DMPA and 33 using LNG-implant) and included in this analysis. Overall, the TFS showed higher viral loads (max 300,000 cp/ml) than CVL (max 3700 cp/ml), and more frequently detectable HIV RNA overall (9.6% vs 3.7%). Despite more frequent detection of shedding with TFS, the risk of genital shedding of HIV was not different between the DMPA and LNG-implant arms (RR [95%CI] 1.19 [0.52-2.72] for TFS and 0.92 [0.22-3.83] for CVL adjusted for HIV viral load and CD4 count). There was also no increased risk for shedding after initiation of progestin contraception, either in TFS or CVL. Using TFS, the highest frequency of shedding was in the follicular phase prior to contraceptive initiation (14.9%), whereas with CVL, the highest frequency of shedding was 3 days after contraceptive initiation (4.7%). HIV DNA was detected in only one CVL cell pellet from a woman whose CVL and TFS HIV RNA measures were detectable.
Conclusion: Among women on ART, there was no difference in the frequency of genital HIV RNA shedding between the DMPA and LNG-implant arms or before and after initiation of progestin contraception, regardless of the specimen type used. HIV RNA was detectable more often using TearFlo. HIV RNA in CVL fluid and HIV DNA in CVL cells are less frequently detected in the same women.

947 HORMONAL CONTRACEPTION DOES NOT AFFECT ART EFFECTIVENESS OR GENITAL HIV SHEDDING

Rena Patel[1], Jared Baeten[1], Renee Heffron[1], Ting Hong[1], Nicole Davis[2], Kavita Nanda[3], Robert Coombs[1], Elizabeth A. Bukusi[4], Athena Kourtis[2], Nelly Mugo[5]
[1]Univ of Washington, Seattle, WA, USA, [2]CDC, Atlanta, GA, USA, [3]FHI 360, Durham, NC, USA, [4]Kenya Med Rsr Inst, Nairobi, Kenya, [5]KEMRI, Nairobi, Kenya

Background: To explore the association between hormonal contraceptive use and antiretroviral therapy (ART) effectiveness and genital HIV shedding among HIV-positive women on ART.
Methods: We analyzed plasma viral load and genital viral RNA shedding from 1,079 HIV-positive women initiating ART who were followed prospectively in three HIV prevention studies in sub-Saharan Africa. Plasma and endocervical swab samples were collected every six months. Self-reported contraceptive use was categorized into injectable, implant, oral, or non-hormonal/no contraception. We used multivariate Cox regression to assess time to plasma viral suppression and logistic regression with generalized estimating equations to assess genital viral shedding for each contraceptive method.
Results: At the time of ART initiation, there were 211 (20%) injectable, 69 (6%) implant, 50 (5%) oral, and 749 (69%) non-hormonal or no method users. Viral suppression was high (90% by 6 months) and hormonal contraceptives did not significantly diminish time to viral suppression as compared to non-hormonal or no methods [adjusted hazard ratios were: injectables 0.89 (95% CI 0.75-1.1), implants 0.91 (0.68-1.2), and oral methods 1.3 (1.1-1.7)]. Genital viral shedding at any time after ART initiation was uncommon (only 9% of samples had detectable viral shedding) and hormonal contraceptives were not significantly associated with changes in detection of genital viral shedding [adjusted odds ratios were: injectables 1.1 (0.73-1.7), implants 0.67 (0.30-1.5), and oral methods 0.55 (0.18-1.6)].
Conclusion: Hormonal contraceptive use was not significantly associated with reduced ART effectiveness or increased genital HIV shedding among HIV-positive women on ART. HIV-positive women should continue to be offered the full range of contraceptive options that best meet their needs.

948 ASYMPTOMATIC ANAL CHLAMYDIA AND GONORRHEA ARE ASSOCIATED WITH CD8+ T-CELL ACTIVATION

Vinícius A. Vieira[1], Natalia B. Cerqueira[1], Dayane A. Costa[1], Priscilla R. Costa[1], Vivian I. Avelino-Silva[2], Ricardo D. Vasconcelos[2], Jose Valdez Madruga[2], Valdilea Veloso[3], Beatriz Grinsztejn[3], Esper G. Kallas[1]

[1]Univ of Sao Paulo, Sao Paulo, Brazil, [2]Centro de Referência e Treinamento DST/AIDS–SP, Sao Paulo, Brazil, [3]Oswaldo Cruz Fndn–Fiocruz, Rio de Janeiro, Brazil

Background: PrEP is effective in preventing HIV transmission, but concerns about a potential upsurge in rates of sexually transmitted infections (STI) are reported. The most prevalent STI are the Chlamydia trachomatis (CT) and Neisseria gonorrheae (NG), often seen in extra-genital sites and as asymptomatic infections in men who have sex with men (MSM). Recent data demonstrate that T cell activation and lower T regulatory cell frequency are associated with increased risk for sexually acquired HIV. In this study, we examined the association between asymptomatic anal CT/NG infection and immune activation among healthy MSM enrolled in a PrEP study.

Methods: From the 546 complete sample of the open-label demonstration study PrEP Brasil, 34 asymptomatic participants with a positive anal swab for CT and/or NG while negative for other STIs were selected as cases; 35 controls were randomly selected based on sample availability among asymptomatic participants with negative anal swab. Groups were similar regarding demographic and clinical characteristics. Peripheral blood mononuclear cells samples were analyzed by flow cytometry

Results: Compared to controls, individuals with asymptomatic CT and/or NG infection had a higher frequency of HLA-DR+CD38+ CD8+ T cells (1.5 vs. 0.9% $p<0.005$), trends toward higher proportions of activation markers in the memory phenotype (naïve/NA:0.2 vs. 0.1%, $p=0.09$; central memory/CM:2.9 vs. 1.9%, $p=0.07$; transitional memory/TM:2.4 vs. 1.2%, $p=0.02$; effector memory/EM:2.0 vs. 1.4%, $p=0.06$; and terminal effector/TE:1.9 vs. 1.9%, $p=0.4$). Exhaustion and senescence markers were also statistically higher. The percentage of activated CD8+ T cell expressing PD-1 (0.9 vs. 0.5%, $p<0.01$), CD95 (1.5 vs. 0.8%, $p<0.01$) and co-expressing both markers (0.9 vs. 0.5%, $p<0.01$) were significantly higher.

Conclusion: Asymptomatic CT/NG anal infection are associated with systemic activation of the CD8+ T cells, potentially increasing the risk of sexually-acquired HIV. These findings were observed in CM, TM and EM subsets which reinforced the data by a shift toward non-naïve phenotype. Considering the effect of immune activation on HIV-transmission risk and the prevalence of asymptomatic STIs among MSM, either persistent diagnosis strategies or regular empiric treatment should be explored as additional HIV-preventive tool. Rather than merely increasing the risk of other STIs, PrEP provides an excellent opportunity to identify patients with asymptomatic STIs and offer counseling, screening and treatment.

949 MUCOSAL INFLAMMATION ABROGATES TENOFOVIR-GEL–MEDIATED PROTECTION FROM HIV INFECTION

Lyle McKinnon[1], Lenine Liebenberg[2], Nonhlanhla Yende[2], Lindi Masson[3], Angela Kashuba[4], Derseree Archary[2], Quarraisha Abdool Karim[2], Salim Abdool Karim[2], Jo-Ann Passmore[2], for the CAPRISA Mucosal Immunology Collaboration

[1]Univ of Manitoba, Winnipeg, Manitoba, Canada, [2]CAPRISA, Durban, South Africa, [3]Univ of Cape Town, Cape Town, South Africa, [4]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: Partial efficacy in preventing HIV infection has been demonstrated by several trials of pre-exposure prophylaxis (PrEP). While adherence is a major predictor of PrEP efficacy, whether additional, biological factors related to HIV susceptibility predict how well PrEP prevents HIV in various sub-groups remains unclear. We addressed this in a prospective cohort analysis of mucosal inflammation in the context of the CAPRISA 004 trial of tenofovir (TFV) 1% gel.

Methods: All available cervicovaginal lavage (CVL) specimens from HIV uninfected visits (n=2,144 visits in n=774 participants) were assayed for cytokine analysis using Biorad multiplex kits. Inflammation was defined by the number of elevated cytokines (upper quartile) as per our published analyses (Masson et al Clin Infect Dis 2015). Survival analyses using Cox regression were used to determine TFV efficacy in inflammation-defined strata. Adherence was defined by >50% of sex acts covered by gel as per Abdool Karim et al Science 2010. Multivariate analyses were used to control for potential confounders.

Results: Using a cytokine score to define inflammation we confirmed that inflammation was associated with HIV outcome at the cohort level in a prospective survival analysis (n=774). HIV risk increased in a step-wise fashion in those with 3, 4, 5, 6, and 7 elevated cytokines (all $p<0.05$), providing strata for subsequent TFV efficacy sub-analyses. TFV efficacy was not observed in any of the groups where inflammation was present, with estimates ranging from 4 to -136% (all $p>0.1$). Conversely, those without inflammation were protected by TFV with efficacy ranging from 39 to 59% ($p<0.05$ for 4 of 5 comparisons). Efficacy was further enhanced in the group without inflammation and good adherence, with estimates of 76, 63, and 57% in those with fewer than 3, 4, and 5 or more elevated cytokines and who used the gel at >50% of sex acts (all $p<0.05$). In contrast, TFV efficacy estimates in high adherers with inflammation were -13, -9, and -19% for the same groups (all $p>0.1$).

Conclusion: Individuals with mucosal inflammation were not protected by TFV gel, and adherence to gel, while protective overall, was of no benefit in the group where inflammation was present. Together, these data suggest mucosal inflammation, combined with adherence, is a major determinant of TFV gel efficacy. The mechanisms that underlie this observation, and validation of these findings in additional cohorts including those using other PrEP regimens, require further study.

950 IS SYNDROMIC DIAGNOSIS OF REPRODUCTIVE TRACT INFECTIONS ANTIQUATED IN THE HIV ERA?

Harriet Nuwagaba-Biribonwoha[1], Hannah Chung[1], Asungushe Kayombo[2], Deodatha Mugisha[1], Kokuhumbya Kazaura[3], Oscar Ernest[1], Gissenge J. Lija[4], Deborah Kajoka[4], Jessica E. Justman[1], Elaine J. Abrams[1]

[1]ICAP at Columbia Univ, New York, NY, USA, [2]Natl Inst of Med Rsr, Mwanza, Tanzania, [3]CDC Tanzania, Dar es Salaam, Tanzania, [4]Tanzania Ministry of Hlth, Community Development, Gender, Elderly and Children, Dar es Salaam, Tanzania

Background: Syndromic diagnosis (SD) of reproductive tract infections (RTIs), based on patient signs and symptoms, is a widely implemented strategy in sub-Saharan Africa. We assessed sensitivity and specificity of SD against laboratory testing for RTIs among recently-diagnosed HIV-infected patients in Tanzania.

Methods: A cross-sectional study was conducted among sexually-active HIV-positive adults ≥ 18 years (y) newly enrolling at the regional hospital HIV clinic in Bukoba Tanzania, 2012-14. Study procedures included an interview on current RTI symptoms (sores, discharge, dysuria), and a genital exam. A study nurse made the SD according to national RTI guidelines, verified by a medical doctor. Regardless of symptoms, laboratory testing of blood, urine samples and genital swabs for chlamydia trachomatis, neisseria gonorrhoea, herpes simplex virus 1/2, and treponema pallidum was conducted. Among women, we also tested for trichomonas vaginalis, bacterial vaginosis and vaginal candidiasis. We analyzed the sensitivity and specificity of syndromic RTI diagnosis against a gold standard of laboratory testing, and determined the positive and negative predictive values (PPV, NPV).

Results: We enrolled 615 participants: 301 men, median age 35.8y (IQR (30-41) and 314 women, median age, 33.2y (IQR 27-38). Half the men (56.2%) and 42.7% of women were married, median number of sexual partners in the previous 6 months was 1 for both. Median CD4 cell count was 249cells/µL (IQR 82-398) among men and 294cells/µL (IQR 132-486), among women. One third of men were circumcised (34.2%) at a median age of 10 years (IQR 3-19). Among 301 men, 58(19.3%) reported genital symptoms, 53(17.6%) had signs on examination; and 83(27.6%) had a syndromic RTI diagnosis. Among women 117(37.3%) reported symptoms, 67 (21.3%) had signs, and 184(58.6%) had a syndromic RTI diagnosis. On laboratory testing, 108 (35.9%) men and 247 (78.7%) women has RTIs. Among men, SD had a sensitivity of 37% (95% CI 28%-47%) and a specificity of 77% (95% CI 71%-83%), with a PPV of 1.66 (1.16-2.38) and NPV of 0.81 (0.69-0.95). Among women, SD had a sensitivity of 62% (95% CI 55-68%) and a specificity of 52% (95% CI 40%-65%), with a PPV of 1.29 (0.98-1.68) and a NPV of 0.74 (0.56-0.97).

Conclusion: RTI prevalence was high. SD underestimated RTI prevalence in comparison to laboratory testing, particularly among men. Routine RTI screening through physical exam and laboratory testing should be implemented for all adults recently diagnosed with HIV.

951 DOES THE E138A MUTATION IN ASPIRE SEROCONVERTERS AFFECT SUSCEPTIBILITY TO DAPIVIRINE?

Kerri Penrose[1], Breanna J. Goetz[1], Kelley C. Gordon[1], Daniel W. Szydlo[2], Marla J. Husnik[2], Thesla Palanee-Phillips[3], Jared Baeten[4], John Mellors[1], Urvi Parikh[1], for the MTN020/ASPIRE Study Team

[1]Univ of Pittsburgh, Pittsburgh, PA, USA, [2]Statistical Cntr for HIV/AIDS Rsr and Prevention (SCHARP), Seattle, WA, USA, [3]Wits Reproductive Hlth and HIV Inst, Johannesburg, South Africa, [4]Univ of Washington, Seattle, WA, USA

Background: The reverse transcriptase (RT) polymorphism E138A occurs naturally in 5% of treatment-naïve HIV-1-subtype C-infected individuals, but is also selected by the diarylpyrimidine (DAPY) class of NNRTIs causing 3-fold resistance to etravirine and rilpivirine. E138A could reduce the protective efficacy of the vaginal ring candidate dapivirine (DPV) in preventing HIV-1 infection. DPV resistance was investigated among recombinant subtype C viruses with E138A derived from seroconverters in ASPIRE.

Methods: ASPIRE was a safety and effectiveness study of a DPV vaginal ring for HIV-1 prevention conducted at 15 sites in South Africa, Zimbabwe, Malawi and Uganda. Population sequencing of protease and RT (amino acids 1-560) was performed on plasma samples from 164 seroconverters with HIV-1 RNA levels ≥200 copies/ml using an in-house assay. Drug resistance mutations (DRM) were identified using the Stanford HIVdb program v7.0. DPV susceptibility of plasma-derived recombinant HIV-1 containing bulk-cloned full-length RT sequences from ASPIRE seroconverters with E138A was determined in TZM-bl cells. Fold-change (FC) values were calculated using a mean IC_{50} from a matched number of seroconverters without E138A from each arm. Statistical significance was calculated using Fisher›s Exact and Likelihood Ratio tests.

Results: The frequency of E138A was not significantly different (p=1.0) between seroconverters in the DPV arm (3 of 68; 4.4%) vs. placebo arm (5 of 96; 5.2%) of ASPIRE. Of participants with E138A, 2 of 3 from the DPV arm (2.2-FC and 5.9-FC) and 2 of 5 from the placebo arm (3.4-FC and 4.1-FC) had significantly (p<0.05) higher IC_{50} compared to participants with wild type virus (Table). Mean IC_{50} values for E138A-containing HIV-1 from the DPV arm (2.1 nM) was not different from the placebo arm (2.7 nM; p=0.70).

Conclusion: E138A is a naturally occurring polymorphism in HIV subtype C that is associated with modest reductions in DPV susceptibility in some RT backgrounds but not others. The frequency and extent of reduced susceptibility associated with E138A as the major variant was independent of the ASPIRE study arm. Although the low frequency of E138A limited the sample size, these phenotypic data provide reassurance that the E138A mutation was not selected by the DPV vaginal ring and is unlikely to reduce efficacy of the DPV vaginal ring for HIV-1 prevention.

Arm	Genotype	N	IC50 ±St Dev (nM)[a]	Fold-Change[b]	p-value[c]
DPV	wild type	3	0.7 ± 0.1		
DPV	E138A, V179D	1	0.6 ± 0.1	0.8	1
DPV	E138A, V179I/T	1	4.2 ± 1.4	5.9	<0.001
DPV	V108I/V, E138A	1	1.6 ± 0.4	2.2	0.009
Placebo	wild type	5	1.2 ± 0.5		
Placebo	E138A	1	1.1 ± 0.2	0.9	1
Placebo	E138A	1	2.7 ± 0.3	2.3	0.058
Placebo	E138A	1	1.2 ± 0.1	1	1
Placebo	E138A	1	3.9 ± 1.2	3.4	0.002
Placebo	K101E, E138A	1	4.7 ± 2.0	4.1	0.001

[a] IC_{50} values were generated for each sample in three independent experiments.

[b] Fold-Change was calculated as IC_{50} of mutant/wildtype in each arm.

[c] p-values were adjusted for multiple comparisons using the Bonferroni correction.

952 NNRTI-CONTAINING ART IS EFFECTIVE FOR DAPIVIRINE RING BREAKTHROUGH HIV-1 INFECTION

Sharon Riddler[1], Jennifer Balkus[2], John Mellors[1], Urvi Parikh[1], Carolyne Akello[3], Sufia Dadabhai[4], Felix Mhlanga[5], Colin O'Rourke[2], Jared Baeten[6], for the MTN-015 and MTN-020/ASPIRE Study Teams

[1]Univ of Pittsburgh, Pittsburgh, PA, USA, [2]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [3]Makerere Univ-Johns Hopkins Univ Rsr Collab, Kampala, Uganda, [4]The Johns Hopkins Univ, Baltimore, MD, USA, [5]Univ of Zimbabwe, Harare, Zimbabwe, [6]Univ of Washington, Seattle, WA, USA

Background: A vaginal ring containing dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), was safe and effective in preventing HIV-1 infection in African women. Among women who acquired HIV-1 infection during the ASPIRE study conducted by the Microbicide Trials Network (MTN-020), NNRTI resistance associated mutations were detected in both dapivirine ring and placebo ring recipients with no significant difference between arms. NNRTI-based antiretroviral therapy (ART) remains the first-line standard of care in many regions of the world. The impact of dapivirine ring use at the time of HIV-1 acquisition on the subsequent response to NNRTI-containing ART is unknown.

Methods: The virologic failure rate following initiation of ART was assessed among women who acquired HIV-1 infection during participation in MTN-020, a randomized, placebo-controlled trial of a monthly dapivirine vaginal ring. Virologic failure was defined as lack of suppression of plasma HIV-1 RNA to <200 copies/ml by 6 months after ART initiation or viral rebound to ≥200 copies/ml after initial suppression at any time.

Results: Among 168 participants with incident HIV-1 infection during dapivirine or placebo ring use in MTN-020, 158 (94%; 65 dapivirine, 93 placebo) had at least 1 follow-up visit, of whom 78 (49%) initiated NNRTI-containing ART during follow-up (29 dapivirine, 49 placebo). The median time from estimated HIV-1 seroconversion to ART initiation was 10.3 months. The median time from ART initiation to HIV-1 RNA <200 copies/ml was approximately 90 days for both dapivirine and placebo ring recipients. The Cox proportional hazards model estimate for the likelihood of virologic suppression between the dapivirine ring and placebo ring arms was 1.0 (95% confidence interval 0.6-1.6). Among 57 women with at least 6 months of post-ART follow-up, 10 (17.5%) experienced virologic failure, 6/36 (16.7%) placebo ring recipients and 4/21 (19%) dapivirine ring recipients (P=0.82).

Conclusion: Compared to placebo, we observed no difference in the time to virologic suppression or the risk of virologic failure for women who had received the dapivirine vaginal ring and then initiated NNRTI-containing ART. These results provide reassurance that standard WHO-recommended ART regimens are effective in the setting of breakthrough HIV-1 infection in women who had received the dapivirine vaginal ring, although continued monitoring of viorologic response is warranted.

953 ACUTE INFECTION WITH A WILD-TYPE HIV-1 VIRUS IN PREP USER WITH HIGH TDF LEVELS

Elske Hoornenborg[1], Godelieve J. de Bree[2], for the Amsterdam PrEP Project in the HIV Transmission Elimination Amsterdam Consortium (H-Team)
[1]Pub Hlth Service Amsterdam, Amsterdam, Netherlands, [2]Academic Med Cntr, Amsterdam, Netherlands

Background: Clinical trials show that pre-exposure prophylaxis (PrEP) with tenofovir/emtricitabine is highly effective against acquisition of HIV-infection. World-wide, only one case of PrEP failure was reported in an individual infected with a multi-class resistant virus under adequate tenofovir-diphosphate (TFV-DP) levels. We report a case with potentially very high HIV-1 exposure who was infected with wild-type HIV-1 while adhering well to a daily PrEP regimen.
Methods: A 50-year-old men who has sex with men (MSM) started daily PrEP via the Amsterdam PrEP (AMPrEP) study. At enrollment, he tested HIV negative (4th generation HIV Ag/Ab test and HIV RNA test). Pill counts and daily diary information indicated adequate adherence of 7 pills per week. This was confirmed by a TDF-DP level in DBS of 2234 and 2258 fmol/punch at respectively 6 and 8 months after start of PrEP. HIV Ag/Ab tests during follow-up were repeatedly negative at 1, 3 and 6 months after starting PrEP. The number of episodes of condomless anal sex (CAS) was remarkably high (table 1).
Results: Eight months after PrEP start, HIV seroconversion was observed with an indeterminate HIV Ag/Ab test (Ab positive, Ag negative). At the same day, the patient had a negative serum HIV RNA test (LOD 50 copies/mL) and western blot showed an atypical pattern characterized by a single p160 band. We were not able to detect HIV by nested pol PCR (DNA and RNA) on bulk peripheral blood mononuclear cells and sigmoid biopsies. Based on these findings and fear of inducing drug resistance, PrEP was stopped and the patient was monitored at weekly intervals. Three weeks after Ab seroconversion, HIV RNA was detected in his plasma (40,000 cop/ml) without detectable resistance mutations using routine clinical sequencing. Combination antiretroviral therapy was started resulting in an undetectable viral load after one month.
Conclusion: Wild-type HIV-1 infection, despite confirmed adherence to PrEP, occurred in a MSM with potentially high HIV-1 exposure. It remains speculative why the patient seroconverted. The presence of an aberrant immune response under appropriate serum TDF levels raises the possibility that a very high HIV exposure, possibly in combination with inadequate TDF levels in gut mucosa may have led to infection. This case underscores the importance of counseling and monitoring PrEP users, including frequent HIV testing. Furthermore, we should be alert for atypical seroconversion resulting in indeterminate HIV Ag/Ab test in individuals on PrEP.

Table 1: Sexual risk behaviour of PrEP user who seroconverted for HIV with high tenofovir-diphosphate levels

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8
Anal sex partners[a]	75	56	56	50	38	49	66	12
Number of days he reported CAS[a]	21/31	12/30	13/31	15/31	15/29	19/31	17/30	3/20
Median [IQR] number of sex partners per day he reported CAS[a]	3 [1-7.5]	4.5 [2.25-8.5]	4 [1.5-6]	4 [1-5]	2 [1-5]	3 [1-4]	5 [2-6]	5 [1-5]
CAS partners[b]	90		51			missing		
CAS episodes[b]	100		100			missing		

a: per month, data collected via daily diary via application for mobile phone
b: in 12-week periods, collected through computer-assisted self-reported questionnaires
CAS: condomless anal sex

954 HIV GENETIC DIVERSITY TO INFER PREP ADHERENCE AT THE ESTIMATED TIME OF INFECTION

Olivia Council[1], Susan Ruone[1], Philip Mock[2], George Khalil[1], Marcel Curlin[3], Walid Heneine[1], Kachit Choopanya[4], Michael Martin[2], **Gerardo Garcia-Lerma**[1]
[1]CDC, Atlanta, GA, USA, [2]Thailand MOPH-US CDC Collab, Nonthaburi, Thailand, [3]Oregon Hlth and Scis Univ, Portland, OR, USA, [4]Bangkok Tenofovir Study Group, Bangkok, Thailand

Background: Adherence in pre-exposure prophylaxis (PrEP) trials can be inferred by measuring drug concentrations at the time of HIV diagnosis. However, results do not necessarily reflect pill taking behavior around the time of HIV infection. The Bangkok Tenofovir Study (BTS) evaluated the efficacy of daily oral PrEP with tenofovir (TDF) among persons who inject drugs. We used molecular tools and adherence diaries from BTS participants to define pill taking behavior at the estimated time of infection
Methods: HIV genetic diversity was studied in 11 participants who became infected with HIV during periods of daily directly observed therapy (DOT) with TDF and in 13 placebo recipients. HIV env (V1-V5) was amplified from plasma collected at the first nucleic acid test positive (NAT+) visit using single genome amplification. The diversity structure of the virus population seen in this sample was used to estimate time since infection (±95% confidence interval) using the Poisson-Fitter tool. The number of TDF doses taken within the confidence interval of infection were then computed from adherence diaries
Results: The estimated time since infection in the TDF group ranged from 8 (95%CI=1-16) to 75 (49-100) days (median=41) and did not differ from that seen in the placebo group (median=15 days; p=0.433). Analysis of missed TDF doses within the estimated period when HIV infection occurred showed perfect adherence in 5/11 (45%) participants, nearly perfect adherence in two (67/69 and 95/100 possible doses taken), low adherence in one (52 out of 71 possible doses taken) and non-adherence (no TDF taken) in three. The 2-5 missed doses in the two participants with nearly perfect adherence were recorded immediately before (3-4 days) or after (1-2 days) the estimated day of infection. TDF exposure in adherent participants was associated with low plasma virus loads at the first NAT+ visit (13,465 RNA copies/ml vs. 294,000 in placebo infections; p=0.033) and infection with single variants (8/8 vs.8/13 in the placebo group; p=0.063) although the latter was not significant at the 0.05 level
Conclusion: We used molecular tools to characterize adherence to PrEP at the estimated time of HIV infection, and demonstrated breakthrough infections under conditions of perfect or near perfect adherence to TDF. These results highlight the utility of molecular tools to improve computation of the biological efficacy of PrEP. Pre-diagnosis drug activity by PrEP reduces acute viremia and may favor the transmission of single variants

955 CHARACTERIZATION OF HIV SEROCONVERTERS IN A TDF/FTC PREP STUDY: HPTN 067

Mariya V. Sivay[1], Yinfeng Zhang[1], Sarah E. Hudelson[1], Maoji Li[2], Estelle Piwowar-Manning[1], Mark A. Marzinke[1], Kevin Bokoch[3], Robert Grant[4], Susan H. Eshleman[1], for the HPTN 067 Study Team
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [3]FHI 360, Durham, NC, USA, [4]Univ of California San Francisco Gladstone Insts, San Francisco, CA, USA

Background: HPTN 067/ADAPT evaluated tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) regimens for pre-exposure prophylaxis (PrEP). HIV-uninfected women (South Africa) and men who have sex with men (Thailand, US) received 5 weekly observed doses of TDF/FTC (DOT), and were then randomized to a daily, time-driven (twice weekly + post-sex dose), or event-driven (before and after sex) TDF/FTC regimen. We analyzed data from subjects who seroconverted in the study.

Methods: Two HIV rapid tests were performed at each visit; infections were confirmed with an HIV RNA assay. Samples were analyzed retrospectively at the HPTN Laboratory Center using two 4th generation assays; a qualitative HIV RNA assay; a viral load assay; Western blot; an HIV-1/HIV-2 discriminatory assay; HIV genotyping; next generation sequencing (NGS); and antiretroviral drug (ARV) testing.
Results: Twelve subjects acquired HIV infection. In 4 cases, at least 1 rapid test was non-reactive at the seroconversion visit. Six subjects were not randomized (3 had acute infection at enrollment, 2 were infected during the DOT phase, 1 was not randomized due to pregnancy and was infected months later). One subject had acute infection at the end of the DOT phase but was not diagnosed for 3-4 months after randomization because HIV rapid tests were non-reactive; resistance testing failed in this case because HIV RNA levels were persistently low/undetectable. Five subjects were infected after randomization. In 4 cases, ARV test results were consistent with infrequent drug use (event-driven arm) or poor adherence (daily or time-driven arm); one woman in the time-driven arm had ARV levels prior to infection indicating PrEP use with 4+ doses/week. She developed HIV resistance consistent with TDF/FTC use (K65R + M184I). Mutations associated with TDF/FTC use were also detected after 4 weekly DOT doses in two subjects who had acute infection at enrollment (one K65R; one M184I). In 2/3 cases, resistance was only detected using NGS.
Conclusion: All but one infection in this study was acquired when subjects were not on PrEP, were in the once-weekly DOT phase, or had ARV levels indicating infrequent dosing. Early infections were often missed by HIV rapid testing, but were detected using a sensitive HIV RNA assay and 4th generation tests. One subject who continued PrEP with undiagnosed infection had persistent low/undetectable HIV RNA. Resistance was detected in 2 subjects who received only 1 TDF/FTC dose/week.

956 A PRAGMATIC RANDOMIZED CLINICAL TRIAL OF RAPID HIV SCREENING IN EMERGENCY DEPARTMENTS

Jason Haukoos[1], Michael S. Lyons[2], Douglas A. White[3], Emily Hopkins[1], Meggan Bucossi[1], Sarah Pfeil[3], Andrew Ruffner[2], Danielle Signer[4], Richard Rothman[4], for the HIV TESTED Trial Investigators
[1]Denver Hlth Med Cntr, Denver, CO, USA, [2]Univ of Cincinnati Coll of Med, Cincinnati, OH, USA, [3]Highland Hosp, Oakland, CA, USA, [4]Johns Hopkins Univ, Baltimore, MD, USA
Background: HIV screening in emergency departments (EDs) is a major focus of national HIV prevention efforts. Screening strategies, including risk-based (targeted) and non-risk-based (nontargeted), have been endorsed by the CDC and the USPSTF; however, little is known about their comparative effectiveness. The objective of this study was to evaluate targeted and nontargeted rapid opt-out HIV screening strategies when fully-integrated into EDs with the principal hypothesis that targeted screening using the Denver HIV Risk Score (DHRS) would be superior to nontargeted screening for identifying newly-diagnosed HIV infections.
Methods: Design: Prospective pragmatic randomized clinical trial. Setting: Four urban EDs in Baltimore, MD, Cincinnati, OH, Denver, CO, and Oakland, CA with an annual combined census of 300,000 visits. Population: Patients were eligible if: (1) ≥ 16 years of age; (2) not critically ill or mentally altered; and (3) not already HIV diagnosed; or (4) with an anticipated length of stay < 30 minutes. Interventions: Consecutive patients underwent concealed balanced randomization to 1 of 3 arms: (a) nontargeted HIV screening; (b) enhanced targeted HIV screening, using the DHRS as a validated HIV risk prediction tool; or (c) traditional targeted HIV screening, using conventional risk behaviors as defined by the CDC. 4th-generation HIV testing was performed based on results of screening and opt-out consent. Outcomes: Newly-diagnosed HIV infection and disease stage. Analyses: Intention-to-treat using risk ratios (RRs) with 95% confidence intervals (CIs) and patient visit as the unit of analysis.
Results: During the 22-month study period, 76,561 patient visits were randomized with outstanding balance (Table). Of these, 25,469 underwent nontargeted screening, 25,453 enhanced targeted screening, and 25,639 traditional targeted screening, with a total of 14,405 completed HIV tests and 25 (0.2%) confirmed new HIV infections. Of the 25 new diagnoses, only 6 (24%) were AIDS defined and 1 (4%) was acute. The RR between the combined targeted screening strategies vs nontargeted screening and new HIV diagnoses was 0.5 (95% CI: 0.2–1.2), and the RR between enhanced targeted screening vs nontargeted screening was 0.7 (95% CI: 0.3–1.6).
Conclusion: Among ED patients, targeted rapid opt-out HIV screening was not superior to nontargeted rapid opt-out HIV screening. All three strategies identified comparable numbers of newly diagnosed HIV-infected patients, although the overall prevalence of disease was low.

Table. Patient characteristics and outcomes for The HIV TESTED Trial.

	Nontargeted (n = 18,059)		Enhanced Targeted* (n = 17,867)		Traditional Targeted† (n = 18,079)	
Characteristics (Patient Level)	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Age, years (median, IQR)	39	(28 – 54)	39	(28 – 53)	39	(28 – 53)
Female gender	9,325	(52)	9,165	(51)	9,303	(51)
Race/ethnicity						
Asian	469	(3)	481	(3)	481	(3)
Black	6,878	(38)	6,670	(37)	6,967	(39)
Hispanic	3,865	(21)	3,782	(21)	3,762	(21)
White	5,967	(33)	6,036	(34)	6,050	(33)
Other / Unknown	880	(5)	888	(5)	819	(4)
Payer						
Commercial	3,927	(22)	3,882	(22)	4,025	(22)
Medicaid	7,498	(42)	7,491	(42)	7,552	(42)
Medicare	2,195	(12)	2,070	(12)	2,113	(12)
Self-Pay	2,515	(14)	2,511	(14)	2,484	(14)
Other / Unknown	1,924	(11)	1,913	(11)	1,905	(10)
	(n = 25,469)		(n = 25,453)		(n = 25,639)	
Outcomes (Patient Visit Level)	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Increased risk‡	–		13,883	(55)	7,099	(28)
Agree to testing	9,313	(37)	6,010	(24)	4,164	(16)
Completed testing	6,744	(26)	4,488	(18)	3,173	(12)
Confirmed HIV infections	23	(0.09)	19	(0.07)	12	(0.05)
Confirmed new HIV infections	12	(0.05)	8	(0.03)	5	(0.02)
AIDS defined (CD4 <200 cells/mm^3)	2	(16)	1	(13)	3	(60)
CD4 (cells/mm^3) (median, 95% CI)	241	(182 – 578)	406	(206 – 588)	22	(0 – 664)
Viral load (copies/mL) (median, 95% CI)	34,788	(13,230 – 310,548)	15,900	(3,272 – 40,916)	106,000	(786 – 610,243)

Abbreviations: IQR = interquartile range; CI = confidence interval; "–" = not applicable.
* Enhanced Targeted HIV Screening involved administering the Denver HIV Risk Score, an empirically-derived and validated HIV risk prediction instrument, and offering rapid HIV testing for all patients who were identified as "increased risk".
† Traditional Targeted HIV Screening involved asking conventional risk behavior questions as defined by the CDC (MMWR, 2001) and offering rapid HIV testing for all patients who were identified as "increased risk".
‡ Defined by a Denver HIV Risk Score =30 for Enhanced Targeted HIV Screening or =1 affirmative behavioral risk response for Traditional Targeted HIV Screening.

957 OPT-OUT HIV/HCV TESTING AMONG JAIL INMATES

Carolina De La Flor[1], Esmaeil Porsa[2], Ank E. Nijhawan[1]
[1]Univ of Texas Southwestern Med Cntr, Dallas, TX, USA, [2]Parkland Hlth and Hosp Systems, Dallas, TX, USA
Background: Incarceration provides an opportunity to provide HIV/HCV screening in high-risk and hard-to-reach individuals. The Centers for Disease Control recommends routine opt-out HIV testing in jails and prisons, however only 19% of prisons and 35% of jails offer this service. HCV testing is recommended for those born between 1945-1965 ("baby boomer" cohort) and with risk factors such us injection drug use, and incarceration. The aim of our study is to describe the results of an opt-out combined HIV and HCV testing program in a criminal justice setting.

Methods: Opt-out HIV/HCV testing was offered to individuals entering the Dallas County Jail between October 2015 and July 2016 at the time of a scheduled blood draw. Basic demographics were collected on all participants. For those who tested HIV positive, risk factors, prior engagement in care (seen by an HIV provider within 6 months previous to incarceration), and re-engagement in care (receipt of HIV care during incarceration) were assessed.
Results: HIV opt-out testing Overall, 1.3% (41/3155) had a positive HIV screening test. Of these, 24% were false positives (positive 4th generation Ag/Ab test with negative HIV1/2 Ab differentiation test). Of those remaining, 16% were newly diagnosed, of whom 100% were linked to care. Among those previously known to be HIV-positive, one-third were not engaged in care before incarceration though 88% were linked back to HIV care in jail. HCV opt-out testing Overall, 16% (500/3042) had a positive HCV Ab screening test. Mean age was 49, 80% were men, and our cohort was racially diverse (43% White, 42% Black, and 15% Hispanic). One-third of inmates self-reported HCV positivity before being tested. Only 52% of the HCV-positive were baby boomers. Racial differences were observed within the baby boomer group, with 74% of blacks v. 35% of whites belonging to this cohort.
Conclusion: Routine opt-out HIV/HCV testing in a jail setting identified multiple HIV and HCV infections. New HIV diagnoses were relatively rare, though linkage to care and re-engagement in HIV care was high. The rate of HCV Ab positivity was high and one-third was already aware of this diagnosis. Testing only those in the baby boomer cohort would have missed approximately half of HCV infections, predominantly among whites. Opt-out HIV/HCV screening in the criminal justice system is a unique opportunity to reach underserved individuals, who may otherwise not seek testing and are at high risk of transmitting these infections.

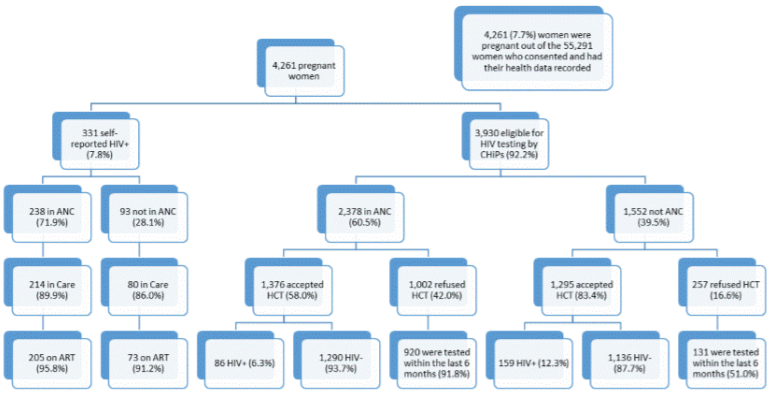
958 STRENGTHENING MALE-PARTNER TESTING IN ANTENATAL CARE: FINDINGS FROM SOUTH AFRICA

Amy M. Medley[1], Nienke van Schaik[2], Carlos Toledo[1], Makungureyi Mlambo[3], Sello Moremi[2], Kabelo Baloyi[2], Nompumelelo Khanyile[3], Sphindile Magwaza[3], Cila Kabongo[4], John Tumbo[4]
[1]CDC, Atlanta, GA, USA, [2]Hlth Systems Trust, Durban, South Africa, [3]US CDC, Pretoria, South Africa, [4]Rustenburg Sub-District Office, Rustenburg, South Africa
Background: Knowing both partners' HIV status during pregnancy is associated with improved maternal and infant outcomes and reduced risk of horizontal and vertical HIV transmission and acquisition. Despite high uptake of testing among women, male partner testing within antenatal clinics (ANC) remains low. This study aimed to increase the proportion of men and couples tested within ANC through promotion of facility and home-based HIV testing services.
Methods: The study was conducted at four health facilities in the Bojanala District, South Africa from January 2015 - September 2016. All women, regardless of HIV status, attending their first ANC visit received education on the importance of partner HIV testing. Women were then offered letters inviting male partner(s) to the health facility for an HIV test or the option of home-based services. Information about partner testing and women's clinical status were abstracted from patient medical charts and records post-partum. Numbers and proportions of male partner testing were assessed before and after the intervention. A multivariable logistic regression model, adjusted for clustering and study phase, was used to identify predictors of male partner testing.
Results: In our preliminary analysis, a total of 1,342 women (600 in the pre-intervention, 742 in the post-intervention) had delivered (mean age: 26 years, 27% HIV-positive) of which 76% were single and 27% were primigravida. The proportion of women self-reporting partner testing for HIV increased from 14% to 33% ($p<0.0001$). Post-intervention, 59 couples tested at home, 110 tested at a study facility, and 64 tested elsewhere. Clinic records indicate that 690 couples tested at the four health facilities overall (14% concordant positive, 9% sero-discordant), while 181 couples tested in the home (8% concordant positive, 3% sero-discordant). In multivariable analysis, significant predictors of partner testing included being HIV-negative (OR: 1.4, 95% CI: 1.2, 1.6, $p=0.002$) and in the post-intervention cohort (OR: 3.2, 95% CI: 1.6, 6.5, $p=0.001$).
Conclusion: Scaling-up HIV testing coverage among men is critical to achieving international goals aimed at ending the HIV epidemic. Our findings indicate that promotion of facility testing and targeted home-based HIV testing may be an effective strategy for increasing the number of male partners who receive an HIV test during the woman's pregnancy. Additional efforts are also needed to increase HIV testing coverage among men.

959 HPTN 071 HOME-BASED TESTING IMPROVES UPTAKE OF HCT AMONG PREGNANT WOMEN IN ZAMBIA

Stable Besa[1], Ab Schaap[1], Mwate J. Chaila[1], S. Floyd[2], Richard Hayes[2], Sarah Fidler[3], Kwame Shanaube[1], H. Ayles[4], for the Zambart Study Group
[1]Zambart, Lusaka, Zambia, [2]London Sch of Hygiene and Trop Med, London, UK, [3]Imperial Coll London, London, UK, [4]London Sch of Hygiene and Trop Med, Lusaka, Zambia
Background: The HPTN071 (PopART) trial is a 3-arm community randomized trial in 12 communities in Zambia and 9 communities in South Africa evaluating the impact of a combination HIV prevention package, including a universal test and treat intervention, on HIV incidence. In Zambia, almost 88% of ANC attendees receive HCT during any given pregnancy however, data are limited for pregnant women who have not attended ANC (non-ANC). Therefore, we assessed what contribution home based testing does to knowledge of HIV status among pregnant women in Zambia.
Methods: All household members, including pregnant women, were offered a combination HIV prevention package by the Community HIV-care Providers (CHiPs) through a door-to-door approach. Uptake of different components of the PopART intervention, including HIV testing, were recorded electronically. We present data on the uptake of HCT among pregnant women in 4 Arm A communities in Zambia? During the first annual round of the intervention (November 2013 to June 2015).
Results: A total of 55,703 women consented to participate in the intervention of whom 99.3% (55,291/55,703) had their health data recorded. 7.7% (4,261/55,291) of the women were pregnant with 7.8% (331/4,261) self-reporting as HIV positive (figure 1), while the remaining 92.2% (3,930/4,261) were offered HCT. Among the latter 60.5% (2,378/3,930) had attended ANC for their current pregnancy, with 96.6% (2,296/2,378) either agreeing to HIV testing by the CHiPs (n=1,376) or reporting to have been tested within the last 6 months (n=920). Of those who had not yet attended ANC, 91.9% (1,426/1,552) either agreed to HIV testing by CHiP's (n=1,295) or reported to have been tested in the last 6 months (n=131). The HIV prevalence among those testing was nearly double for the non-ANC compared to ANC women [12.3% (159/1,295) versus 6.3% (86/1,376)]. Of the 576 pregnant women that knew their HIV-positive status following the intervention, 43% were tested HIV+ by CHiPs. Knowledge of HIV status defined as self-reported HIV-positive, tested by CHiPs or tested elsewhere within the past 6 months, increased from 60.0% before the intervention to 95.1%
Conclusion: Community based HIV testing may enhance HIV case finding among women not yet in ANC.

Figure 1: Uptake of HIV testing among pregnant women



960 DOES HIV TREATMENT AVAILABILITY ENCOURAGE PEOPLE TO LEARN THEIR HIV STATUS?

Ellen Moscoe[1], Jacob Bor[2], Frank Tanser[3], Deenan Pillay[4], Till Baernighausen[5]
[1]Harvard Univ, Boston, MA, USA, [2]Boston Univ, Boston, MA, USA, [3]Africa Cntr for Pop Hlth, Mtubatuba, South Africa, [4]Africa Hlth Rsr Inst, Mtubatuba, South Africa, [5]Heidelberg Univ, Heidelberg, Germany

Background: A crucial first step toward obtaining HIV care is knowing one's own HIV status. A large proportion of HIV-infected persons in South Africa do not know their status, and men are typically less likely than women to be aware of their serostatus. Expansion of HIV treatment may increase disclosure, reduce stigma, and increase testing. We estimate how a person's ART eligibility affects their household member's HIV status knowledge.
Methods: We conducted a regression discontinuity analysis that exploits the CD4 count threshold for ART eligibility in South Africa to evaluate the causal intent-to-treat (ITT) effect of ART eligibility on the patient's household members. Using data from 2007-2012 in a large population-based cohort in rural South Africa run by the Africa Health Research Institute, we compared outcomes among household members of patients who had a CD4 count just below the 200-cell threshold (and were thus eligible for ART) with household members of patients with CD4 counts just above the cut-off (and were thus less likely to be eligible for ART). We assessed effects on self-reported knowledge of HIV status and conducted sub-group analyses by the gender of the patient and the gender of household members.
Results: ART led to a large increase in HIV status knowledge among the patient's male household members (ITT causal effect of 17 percentage points, 95% CI 12, 22). This effect represents a three-fold increase in the likelihood that a male household member reported knowing their HIV status relative to the baseline rate of 7%. The effect was concentrated among men living in households where women became eligible for ART, and there was no effect for female household members. The results for men were robust to sensitivity analyses including variation in bandwidths and inclusion of covariates.
Conclusion: Living with someone who is eligible for ART increased men's likelihood of reporting that they knew their HIV status. This effect may be due to increased testing, or to updating of beliefs about HIV status based on partner's status even in the absence of test results. In designing the next generation of ART programs, such household-level spillover effects could be harnessed to increase HIV status knowledge and ART uptake among men. Although prior studies have noted a correlation between ART expansion and testing rates, this study is among the first to causally link ART initiation to increased awareness of HIV status among household members.

Table 1: Effect of ART eligibility on household members' knowledge of HIV status

	Full sample			Male household members		
Eligible for ART (CD4<200)	0.07	0.05	0.03	0.17***	0.10***	0.08***
	(0.046)	(0.034)	(0.023)	(0.047)	(0.038)	(0.028)
Eligible*distance to 200 cutoff	-0.00	0.00	0.00	0.00	-0.00	0.00
	(0.006)	(0.002)	(0.001)	(0.006)	(0.002)	(0.001)
Distance to 200 cutoff	0.00	-0.00	0.00	0.01	0.00	0.00
	(0.004)	(0.002)	(0.001)	(0.004)	(0.002)	(0.001)
Constant	0.30***	0.33***	0.33***	0.16***	0.18***	0.21***
	(0.034)	(0.026)	(0.018)	(0.029)	(0.026)	(0.020)
Bandwidth (200 +/-)	13	27	54	13	27	54
Observations	3,214	7,430	14,964	1,265	3,044	5,976
Number of households (clusters)	397	841	1608	280	596	1163
R-squared	0.002	0.001	0.000	0.014	0.005	0.003

Notes: Coefficients are percentage points, with standard errors in parenthesis. Standard errors are clustered at the household level. Bandwidths are selected based on minimizing squared bias plus variance; 13 is the optimal bandwidth with 27 and 54 shown to demonstrate robustness to variation in bandwidth size.

961 FEASIBILITY OF A PHARMACIST-RUN HIV PREP CLINIC IN A COMMUNITY PHARMACY SETTING

Elyse Tung[1], Annalisa Thomas[1], Allyson Eichner[1], Peter Shalit[2]
[1]Kelley-Ross Pharm, Seattle, WA, USA, [2]Univ of Washington, Seattle, WA, USA

Background: Reduction of new HIV infections and increased access to HIV testing continue to be of high priority for health organizations. For years, pharmacists have demonstrated success in managing disease states, such as hypertension, via clinic-based protocols. Management of HIV pre-exposure prophylaxis (PrEP) involves a similar level of

care as these other proven pharmacist-managed protocols. By collaborating with a local HIV primary care clinic, we created an innovative pharmacist-managed HIV PrEP clinic in a community pharmacy setting called One-Step PrEP™.
Methods: One-Step PrEP™ was created in March 2015 under physician oversight with a collaborative drug therapy agreement (CDTA). This service is located at Kelley-Ross Pharmacy in Seattle, Washington. One-Step PrEP™ allows for a single patient encounter to provide access to PrEP. Pharmacists meet with patients individually, take a medical and sexual history, make a risk assessment, perform laboratory testing, provide patient education, and prescribe and dispense tenofovir DF/emtricitabine when appropriate. Pharmacists also provide all follow up care as recommended by the practice guidelines. Here we report data on the first year of operating the clinic.
Results: From March 2015 through March 2016, 373 individuals sought PrEP services from One-Step PrEP™. Of those, 251 (67%) were evaluated in person, and 57 (23%) reported having a primary care provider. Among those seen in clinic, 245 (98%) initiated PrEP, and 210 (84%) identified as men who have sex with men (MSM). The mean age was 34 years (range 18-64 years). A total of 26 diagnoses of bacterial sexually-transmitted infections were made, and there was one HIV seroconversion. A retention rate of 75% was seen during the first year of operation. A majority of patients (235 or 96%) paid $0 per month for their PrEP medication. Financial viability of the clinic was determined based on the areas of revenue versus clinic costs. Initial startup costs were recouped at 9 months of clinic operations.
Conclusion: We have found that a pharmacist-run HIV PrEP clinic in a community pharmacy is logistically feasible and financially viable. We observed a higher-than-expected response from MSM patients seeking PrEP care in a community pharmacy setting. The high retention rate indicates that patients find value in our service. The One-Step PrEP™ clinic model proves to be financially sustainable by demonstrating a return on investment in less than one year of clinic operation.

962 ASSESSING THE EFFICACY AND FEASIBILITY OF A RETAIL PHARMACY-BASED HIV TESTING PROGRAM

Bryan C. Collins, Heather W. Bronson, Elaine G. Martin
Virginia Dept of Hlth, Richmond, VA, USA

Background: The Virginia Department of Health (VDH) initiated a public/private partnership to launch an HIV testing program in 32 retail pharmacies which also conducted screening for other chronic diseases. We estimated that testing in retail pharmacies would lead to higher service uptake among first-time testers, that clients would reflect the racial/ethnic composition of communities where pharmacies were located, and that the public/private partnership would be more cost-effective than community-based HIV testing.
Methods: VDH selected stores in census tracts that were >30% Black/Latino, and where >10% of the population lived in poverty. Clients could request walk-in testing using a one-minute HIV rapid test whenever the pharmacy was open. Clients who tested positive were referred to confirmatory testing at a local nonprofit organization or health department.
Results: Between June 1, 2014 and June 30, 2016, Walgreens pharmacists performed 3,221 HIV tests, including 25 positive tests, for a 0.8% positivity rate. Among all clients in the pharmacy testing program, 46% had never been tested or were unsure, versus 31% of clients in community-based HIV testing programs. Among HIV-positive clients in the pharmacy testing program, 64% had never been tested or were unsure, versus 17% of clients in community-based HIV testing programs. Only 39% of tests were performed during business hours, while 61% were provided at night or over the weekend. Statewide, 61% of clients were Black or Latino, more than double the minimum selection criteria. The cost per positive test was $4,300, versus $14,900 in community-based HIV testing programs.
Conclusion: Retail pharmacy-based HIV testing effectively facilitates access to HIV testing for clients who will not seek testing from established testing venues, such as Community-Based Organizations (CBO) and Local Health Departments (LHD). Retail pharmacy-based HIV testing is an effective venue for HIV testing, specifically in geographically large or low incidence states, where it can provide services in areas not feasible for CBOs or LHDs. Public/private partnerships present potential cost savings over community-based HIV testing programs.

963 MIDWEST PHARMACISTS' KNOWLEDGE OF & WILLINGNESS TO PROVIDE PREEXPOSURE PROPHYLAXIS

Jordan Broekhuis, Kimberly K. Scarsi, Harlan Sayles, Donald Klepser, Joshua Havens, Susan Swindells, Sara H. Bares
Univ of Nebraska, Omaha, NE, USA

Background: Pharmacist provision of pre-exposure prophylaxis (PrEP) through collaborative practice agreements with local physicians could expand access for those at risk of HIV infection. We sought to characterize pharmacists' knowledge about and willingness to provide PrEP services in Nebraska and Iowa.
Methods: An 18-question survey was distributed via email to members of the American Society of Health-System Pharmacists in Nebraska and Iowa and to University of Nebraska Medical Center pharmacy preceptors (n=1140). The survey was organized into three parts: demographics, experience, and beliefs. Descriptive analyses were performed for all questions. Pearson chi-square tests identified characteristics based on gender, age, years in practice, and HIV experience. Wilcoxon rank-sum was used to compare responses to number of HIV-infected patients treated annually. P-values less than 0.05 were considered significant.
Results: Of the 140 respondents, 54% were female, 96% were white, 58% practiced in an urban setting, and mean age was 45 years. Less than half of respondents were familiar with the use of PrEP (42%) or the CDC guidelines for its use (25%). Respondents who were older (p=.015) and in practice longer (p=.005) were less likely to be familiar with the use of PrEP. Overall, 54% indicated that they were fairly or very likely to provide PrEP services as part of a collaborative practice agreement and after additional training. While familiarity with PrEP use or guidelines did not affect respondents' willingness to provide PrEP, respondents were more likely to express an interest in providing PrEP services if they had prior experience counseling HIV-infected patients on antiretroviral therapy (p=0.023) or PrEP (p=0.013), and if they recently completed HIV-related continuing education (p=0.032) [see Table]. Respondents were "moderately concerned" or "very concerned" about the following issues: time burden (61%), inadequate compensation for services (55%), outside skill set (39%), adherence (63%), loss to follow-up (56%), and promotion of drug resistance (51%). Only 13% of respondents identified ethical concerns related to PrEP.
Conclusion: Pharmacist respondents in Nebraska and Iowa had limited knowledge and experience with PrEP, but most indicated willingness to provide PrEP through collaborative practice agreements after additional training. Attention to concerns about time burden, workflow disruption and compensation may facilitate development of this innovative model of PrEP delivery.

	N	How likely do you think you would be to provide PrEP services to clients at risk for HIV after completion of additional training and participation in a collaborative practice agreement?		p-value
		Somewhat, A little, or Not at all likely	Very or Fairly likely	
I have counseled HIV-infected patients receiving antiretroviral therapy. n (%) Yes No	123	 14 (25) 42 (75)	 30 (45) 37 (55)	0.023
I have completed HIV-related continuing education in the past year. n (%) Yes No	123	 7 (13) 49 (88)	 19 (28) 48 (72)	0.032
I am familiar with the use of Truvada (tenofovir/emtricitabine) as pre-exposure prophylaxis (PrEP) for the prevention of HIV. n (%) Yes No	123	 22 (39) 34 (61)	 32 (48) 35 (52)	0.346
I am aware of the current CDC guidelines for PrEP use. n (%) Yes No	123	 12 (21) 44 (79)	 19 (28) 48 (72)	0.378
I have counseled patients on antiretroviral therapy for PrEP use. n (%) Yes No	123	 3 (5) 53 (95)	 14 (21) 53 (79)	0.013
How many HIV-infected patients have you cared for in the past year as part of your practice? mean (sd)	113	14 (70)	38 (144)	0.003

964 TEXT MESSAGING IS ASSOCIATED WITH IMPROVED RETENTION IN A CLINIC-BASED PREP PROGRAM

Christine M. Khosropour[1], Richard T. Lester[2], Matthew R. Golden[1], Julia C. Dombrowski[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Univ of British Columbia, Vancouver, British Columbia, Canada

Background: Text messaging and short message service (SMS) interventions are associated with improved medication adherence among HIV-positive individuals. The impact of SMS on retention in a clinic-based pre-exposure prophylaxis (PrEP) program is unknown.

Methods: From September 2015 to June 2016 we invited all patients receiving PrEP through an STD clinic in Seattle, Washington to enroll in an SMS program (provided by WelTel) that included three components: automated weekly "check-in" messages, automated appointment reminders, and bi-directional open communication via SMS with clinic staff. Per routine clinic practice, PrEP patients return to the clinic one month following enrollment and then every three months. Patients cease to receive PrEP from our clinic if they do not return to the clinic and do not respond to multiple phone calls or if they notify the clinic that they are discontinuing PrEP. We used chi-square tests to compare characteristics of patients who did and did not enroll in the SMS program and to examine differences in retention in the PrEP program among those did and did not enroll in SMS. We used log binomial regression to examine the adjusted relative risk (aRR) of the association between enrollment in SMS and dropping from our clinic's PrEP program.

Results: There were 225 patients who received PrEP from our clinic during the study period. Most (95%) were men who have sex with men, 53% were white non-Hispanic and the average age was 31. Of 225 PrEP patients, 159 (71%) opted to enroll in the SMS program; 5 (3.1%) later requested to be withdrawn. Enrollment in SMS was highest for Asian patients (91.3% enrolled) and lowest for black patients (55.6% enrolled). Patients aged 16-24 years were more likely to enroll in SMS compared to those >25 years (82.5% vs. 66.5%, P=0.02). Overall, 70 men stopped receiving PrEP from our clinic during the study period, including 44 (27.7%) of 159 patients enrolled in SMS and 26 (39.9%) of 66 patients not enrolled in SMS (P=0.08). Adjusting for age, race/ethnicity and gender, patients enrolled in SMS were 34% less likely to discontinue PrEP from our clinic compared to those who were not enrolled (aRR=0.66; 95% confidence interval=0.45-0.97).

Conclusion: Among PrEP patients in our STD clinic, the majority opted to receive SMS messages and those who did were less likely to discontinue PrEP. These findings suggest that implementing SMS as part of PrEP clinical care is acceptable and may improve retention.

965 BRIEF BEHAVIORAL INTERVENTION INCREASES PREP DRUG LEVELS IN A REAL-WORLD SETTING

Sarit A. Golub[1], Stephanie Pena[2], Amy Hilley[3], John Pachankis[4], Asa Radix[2]
[1]City Univ of New York, New York, NY, USA, [2]Callen-Lorde Community Hlth Cntr, New York, NY, USA, [3]Hunter HIV/AIDS Rsr Team, New York, NY, USA, [4]Yale Univ, New Haven, CT, USA

Background: The effectiveness of pre-exposure prophylaxis (PrEP) depends on optimizing adherence; however, few (if any) brief counseling interventions have demonstrated efficacy improving PrEP adherence in real-world settings. This analysis presents data from SPARK, a PrEP demonstration/implementation project conducted at a community-based health center in New York City.

Methods: Participants were 301 men who have sex with men and transgender women (ages 18-63; 49% white) who were patients at the health center and chose to start PrEP. SPARK tested the efficacy of two brief interventions: a sexual health intervention (SHI) designed to frame PrEP use as part of sexual health, and a PrEP adherence intervention (AI) designed to provide detailed information about the rationale for daily dosing and concrete logistical adherence support. Each intervention was tested against an educational control, based on existing clinic protocols (i.e., treatment as usual (TAU)). Participants were randomly assigned to one of four conditions, in which they received SHI only, AI only, both, or neither. Adherence was monitored using dried blood spot testing at 3- and 6-month follow-up visits.

Results: Overall adherence in the study was high; almost 93% of participants demonstrated drug levels consistent with >= 4/week dosing (TDF ≥ 700 fmol) at 3M and 90.3% demonstrated these levels at 6M. At 3M, participants who had received one or both of the brief interventions demonstrated significantly higher adherence, compared to those who received neither. Specifically, 96.6% of participants who received at least one brief intervention demonstrated adherence ≥700fmol, compared to only 84% among those who received TAU (p = .002). TAU participants also reported more missed pills, compared to the intervention groups (p = .04). Adherence at 3M did not differ by demographic factors (age, race, income, education, insurance). At 6M there was a trend toward greater adherence in the intervention conditions (92.1% vs. 85.7%), but this difference was not statistically significant. Participants with <700fmol at 6M were more likely to be Black; there were no other demographic factors associated with lower adherence.

Conclusion: A brief client-centered counseling intervention can significantly improve PrEP adherence in a real world setting, even among patients who are highly motivated to adhere. Additional "boosters" may be needed at follow-up visits to better support highest priority patients.

Table 1. *PrEP Adherence by Condition (N = 301)*

	Total Sample (N=301)	SHI/AI (n=75)	SHI only (n=72)	AI only (n=75)	TAU (n=79)	X2
***Persistence**, n (%)*						
On PrEP at 3M	279 (92.7)	70 (93.3)	65 (90.3)	71 (94.7)	73 (92.4)	1.01, p = .78
On PrEP at 6M	264 (87.7)	65 (86.7)	63 (87.5)	65 (86.7)	71 (89.9)	.50, p = .92
***Drug Levels**, n (%)*						
TDF 700 fmol or higher 3M	259 (91.8)	66 (94.3)	63 (98.4)	68 (97.1)	62 (84.9)	**12.99, p = .005**
TDF 700 fmol or higher 6M	234 (90.3)	56 (90.3)	59 (93.7)	59 (92.2)	60 (85.7)	2.76, p = .43
***Missed Pills**, n (%)*						
> 3 missed pills 3M	25 (9.3)	3 (4.5)	7 (10.8)	3 (4.6)	12 (16.4)	**8.15, p = .04**
> 3 missed pills 6M	28 (10.7)	6 (9.1)	9 (14.5)	4 (6.3)	9 (12.9)	2.79, p = .42

Note. SHI = Sexual Health Intervention. AI = Adherence Intervention. TAU = Treatment as Usual (no behavioral intervention).

966 FOUR-YEAR TRENDS IN AWARENESS AND USE OF HIV PREP AMONG GBMSM IN VANCOUVER, CANADA

Moliehi Khaketla[1], Nathan J. Lachowsky[2], Heather L. Armstrong[3], Zishan Cui[3], Mark Hull[3], Paul Sereda[3], Robert S. Hogg[3], Julio S. Montaner[3], Eric Roth[2], David Moore[1]
[1]Univ of British Columbia, Vancouver, Canada, [2]Univ of Victoria, Victoria, Canada, [3]BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada

Background: Gay, bisexual and other men who have sex with men (gbMSM) are at highest risk for incident HIV infection in British Columbia (BC), Canada. Pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate/emtricitabine was licensed in Canada in February 2016 but is currently not publicly funded in British Columbia (BC). We explored 4-year trends in, and factors related to awareness and use of PrEP among an gbMSM cohort in Vancouver, BC.
Methods: We analyzed data from the Momentum Health Study, a longitudinal cohort study of gbMSM in Vancouver, BC. MSM aged ≥16 years were recruited through respondent-driven sampling and completed a computer-assisted self-interview at enrolment with follow-up every 6 months. Stratified by HIV status, we examined awareness and use of PrEP among participants using data from February 2012 to February 2016. We conducted univariable and multivariable generalized linear mixed effect model analyses to examine trends in the proportion of participants aware of and using PrEP, and then to identify factors associated with PrEP awareness over time among HIV-negative gbMSM.
Results: 2991 study visits were completed by 732 participants (median follow-up 2.5 years), of whom 27.9% were HIV-positive, 75.7% Caucasian and median age was 34 years. The proportion of HIV-negative men who were aware of PrEP increased from 18% in 2012 to 80% in 2016 ($p<0.001$ for trend); among HIV-positive men, awareness increased from 35% to 77% ($p<0.001$). While 73% of HIV negative men reported to have insurance that covered prescription medication, only 8 (2%) reported using PrEP in any 6-month period. In the final model, HIV-negative men were more likely to be aware of PrEP if they had annual incomes ≥$60,000 (aOR=2.24), had more than a high school education (aOR=2.10), were aged 28 – 40 (aOR=1.66) reported viral load sorting as an HIV prevention practice (aOR=2.56), had used ecstasy in the past 6 months (aOR=1.46), scored higher on the Sensation Seeking Scale (aOR=1.04) and had reported ≥2 previously diagnosed STIs (aOR=1.97); gbMSM who were Aboriginal (aOR= 0.36) or Latino (aOR=0.40), who were single (aOR=0.70) and who had received drugs for sex (aOR=0.22) were less likely to be aware of PrEP.
Conclusion: PrEP awareness increased dramatically over time, and was associated with several HIV risk behaviours among HIV-negative gbMSM. However, only a small proportion of HIV-negative gbMSM reported PrEP use, highlighting that PrEP access should be expanded for at-risk gbMSM in BC.

967 KNOWLEDGE ABOUT PREP AMONG MSM AND TRANS* METHAMPHETAMINE USERS IN SEATTLE

Vanessa McMahan[1], Aleks Martin[2], Lindsay Garske[2], Jared Baeten[1], Caleb Banta-Green[1], Joanne Stekler[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Proj NEON, Seattle, WA, USA

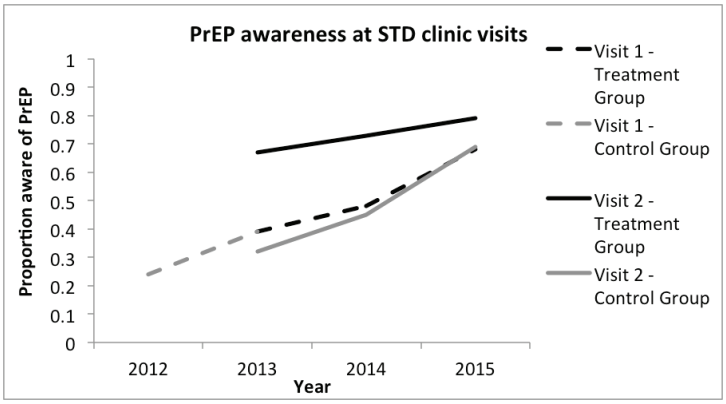
Background: Men who have sex with men (MSM) who use crystal methamphetamine (meth) are at particularly high risk of HIV acquisition. However, meth-using MSM are under-represented in PrEP programs in Seattle, WA. It is critical to understand the knowledge of and concerns about PrEP in this population to better target effective HIV prevention services.
Methods: In August 2016 we administered an anonymous, online, 17-item survey to meth users. Respondents were recruited by peer educators from Project NEON, a harm reduction program for gay, bi, and trans* male meth users. Eligibility criteria included reporting cisgender male or trans* identity, sex with male or trans* partners in the past year, meth use in the past 3 months, and negative or unknown HIV status. The survey collected demographic characteristics, frequency of meth use, and knowledge of PrEP and barriers to use. Participants were sent a $10 gift card for survey completion.
Results: The majority of the 221 participants identified as male (97.7%) with a median age of 31 years (IQR 25-35, range 19-53). 84.2% reported having sex only with men, 9.1% with men and women, 5.4% with men and trans* partners, and 1.4% with women and trans* partners. 159 participants were white (71.9%), 46 were black (20.8%), and 16 reported other racial identities (7.2%). Approximately one-third were currently homeless (35.8%). 214 participants had insurance (96.8%) and, of those insured, 79.0% had Medicaid and 20.1% private insurance. 6.8% participants reported using meth daily, 77.8% weekly, 13.1% monthly, and 2.3% less frequently. The majority of respondents had "heard of PrEP before" (96.4%); however, only 7 had ever used it (3.3%). Out of the 206 who had heard of PrEP but not used it 93.2% knew where to access PrEP. Despite the rare use of PrEP in this high-risk population, most participants reported no concerns about it (58.7%). Of the 88 reporting concerns, the most common were that it would not prevent HIV (47.7%), meth may impact PrEP's efficacy (31.8%), and that it would not be safe to use while using meth (30.7%).
Conclusion: A high number of participants had heard of PrEP, knew where to access it, and did not have insurance-related barriers to PrEP. Despite this, a very small minority had ever used it. Additional research is needed to assess what education about PrEP may be needed for meth users and understand barriers to uptake in order to increase access to effective HIV prevention services among the highest-risk individuals.

968 A CLINICAL HIV PREEXPOSURE PROPHYLAXIS EDUCATION INTERVENTION AMONG MSM

Julia Raifman[1], Catherine E. Oldenburg[2], Amy Nunn[3], Madeline C. Montgomery[3], Alexi Almonte[4], Allison Agwu[1], Renata Arrington-Sanders[1], Philip A. Chan[4]
[1]The Johns Hopkins Univ, Baltimore, MD, [2]Univ of California San Francisco, San Francisco, CA, USA, [3]Brown Univ, Providence, RI, USA, [4]Miriam Hosp, Providence, RI, USA

Background: Pre-exposure prophylaxis (PrEP) effectively prevents HIV among high-risk groups, including men who have sex with men (MSM), but implementation has been slow. While sexually transmitted diseases (STD) clinics are increasingly implementing PrEP education programs, the impact of PrEP education programs on awareness and use has not been established. We evaluated the impact of a brief education intervention on PrEP awareness and use among MSM attending a STD clinic in Rhode Island.
Methods: We reviewed data on HIV-negative MSM presenting to the Rhode Island STD Clinic between 2012-2015. We estimated the impact of a brief (≤5 minutes) clinic-wide PrEP education intervention for all MSM at their first visit on PrEP awareness and use at a second clinic visit. We considered all MSM whose first clinic visit occurred before intervention

initiation to be in the "control" group and all MSM whose first clinic visit occurred after intervention initiation to be in the "treatment" group. We estimated a difference-in-differences linear regression model, comparing PrEP awareness and use at second visit among MSM in the treatment group relative to the control group.
Results: Of 967 HIV-negative MSM receiving care at the STD clinic, 316 (33%) presented two or more times. Non-Hispanic Black MSM had statistically significantly lower PrEP awareness relative to non-Hispanic white MSM at their first visit (adjusted odds ratio: 0.36, p=0.03). Time trends in PrEP awareness (p=0.53, Figure 1) and use (p= 0.63) were equivalent between the treatment and control groups at the first clinic visit. At the second clinic visit, MSM who had received the PrEP intervention during their first clinic visit were 19 percentage points (pp; p<0.01) more likely to be aware of PrEP (Figure 1) and 3.6 pp (p=0.04) more likely to use PrEP, relative increases of 47% for PrEP awareness and 133% for PrEP use relative to the period prior to the intervention.
Conclusion: A brief, scalable PrEP education intervention at an STD clinic led to significantly increased PrEP awareness and use among MSM. Healthcare providers should consider implementing brief PrEP education interventions in sexual healthcare settings. It is particularly important for such interventions to reach non-Hispanic Black MSM due to lower levels of PrEP awareness in this population.



969 PREP GUIDELINES HAVE LIMITED ACCURACY IDENTIFYING YOUNG MSM PRIOR TO SEROCONVERSION

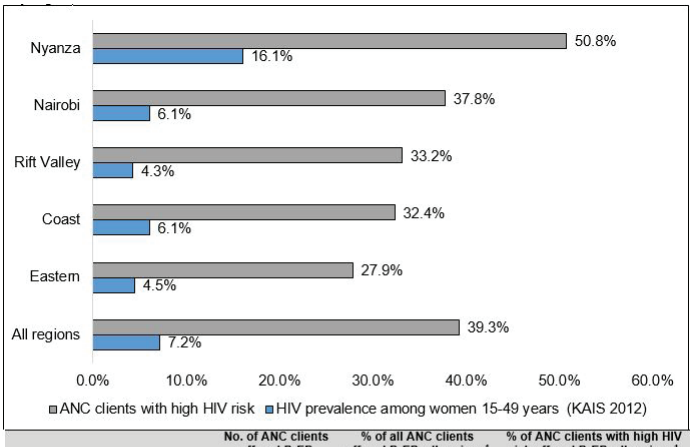
Nicola Lancki, Ellen Almirol, Leigh Alon, Moira McNulty, **John A. Schneider**
Univ of Chicago, Chicago, IL, USA

Background: Identification of clients at highest risk of acquiring human immunodeficiency virus (HIV) is a critical component to PrEP implementation. CDC published clinical practice guidelines for identifying individuals as PrEP candidates in 2014 and developed a risk-screening tool: HIV Incidence Risk Index for MSM (HIRI-MSM). Gilead also listed factors to identify individuals at high risk in the package insert. We examined the performance of CDC guidelines, HIRI-MSM and Gilead recommendations in identifying eligible PrEP candidates, including seroconverters, in a population-based sample of young Black men who have sex with men (YBMSM).
Methods: We followed a population-based cohort of YBMSM aged 16-29 years during PrEP roll-out in Chicago from 2013-2016 (n=618). We computed the proportion of YBMSM with indications for PrEP using CDC guidelines, HIRI-MSM, and Gilead recommendations. We also calculated the sensitivity and specificity of guidelines in predicting HIV seroconversion. HIV seroconversion was measured using 4th generation and NAAT testing at three time points. Incidence Rate Ratios using Poisson regression were computed to compare sociodemographic and network factors associated with HIV incidence.
Results: In the study cohort, 300 HIV uninfected YBMSM contributed 390.4 person-years (PY) of follow-up. The mean age at baseline was 22.3 years (SD=3.07), HIV incidence was 8.5 cases per 100 PY (95% CI, 6.0-11.9). Overall, 49% had an indication for PrEP using CDC guidelines; 72% using HIRI-MSM, and 86% using Gilead recommendations. HIV seroconverters (n=33) were identified as PrEP eligible prior to seroconversion with sensitivity/specificity of CDC, HIRI-MSM and Gilead guidelines of: 52%/52%; 85%/30%; and 94%/15%. HIV incidence did not differ significantly by individual risk behaviors that comprise indications for PrEP: condomless anal sex (IRR 1.2, 95% CI: 0.6-2.3); drug use (IRR 1.2, 0.6, 2.3); serodiscordant partnership (IRR 0.3, 95% CI 0.04, 1.9). Having a partner ≥ 10 years older was predictive of HIV incidence (IRR 2.1, 95% CI 1.0-4.5).
Conclusion: Low sensitivity of CDC guidelines and limited specificity of HIRI-MSM and Gilead screening tools is of concern for PrEP implementation in most at risk populations. Consideration of local epidemiology and network factors may better guide identification of clients who could benefit the most from PrEP.

970 IDENTIFYING PREGNANT WOMEN FOR PREP USING ROUTINE ANTENATAL CARE INDICATORS IN KENYA

Jillian Pintye[1], Benson Singa[2], Kennedy Wanyonyi[2], Janet Itindi[2], John Kinuthia[3], Lucy Ng'ang'a[4], Agnes Langat[4], Abraham Katana[4], Christine J. McGrath[5], Grace John-Stewart[1]
[1]Univ of Washington, Seattle, WA, USA, [2]Kenya Med Rsr Inst, Nairobi, Kenya, [3]Kenyatta Natl Hosp, Nairobi, Kenya, [4]US CDC, Nairobi, Kenya, [5]Univ of Texas Med Branch, Galveston, TX, USA

Background: PrEP could prevent HIV acquisition in pregnancy, however, implementation strategies have not been established for pregnant women in high HIV prevalence settings. Regional HIV prevalence and indicators assessed in antenatal care (ANC) could be used to prioritize PrEP. Data from a Kenyan national survey of 62 ANC facilities were used to estimate the proportion of women at potential risk for HIV who could be prioritized for PrEP.
Methods: Facilities were selected using stratified random sampling by ANC volume. Data were abstracted from the first 10% of initial ANC visits per facility per year from 2011-2013. High HIV risk was defined as having syphilis and/or a male partner of unknown or positive HIV status. Survey weights and clinic-level clustering were applied. Kenya Demographic and Health Survey 2014 data were used for projected estimates.
Results: Overall, 9250 records from first ANC visits of HIV-uninfected women were abstracted, of which 8634 (93%) met inclusion criteria (had syphilis or partner HIV status data); partner HIV status and syphilis data were available for 85% and 69% of records, respectively. Median age was 24 years and 18% of women were <20 years; 86% were married and 37% were primagravidas. Having a male partner of unknown HIV status was common (46%) and higher in Nyanza, a high HIV prevalence region, than in other regions (50% vs. 32%, p=0.04). Couples HIV counseling and testing was low (3%), without regional differences. Few women reported HIV-infected partners (1%) and 1% had syphilis infection. Overall, 39% of women had potential high HIV risk (as defined by syphilis and/or partner HIV status among women with data on either variable) with similar rates between 2011 and 2013; prevalence of high HIV risk was highest in Nyanza (51%) than other regions (Prevalence Ratio 1.5, 95% CI 1.1-2.2). In all regions combined, prioritizing PrEP to pregnant women with these ANC indicators would decrease the number of women offered PrEP by 61% while providing PrEP to all women at potential high HIV risk (Figure 1). An HIV prevalence-guided approach with PrEP provision only to all women in the highest prevalence region (Nyanza) would reduce the number of women exposed to PrEP by 74%, but exclude 63% of high-risk women nationally.
Conclusion: A combination of prevalence and risk assessment strategies may be useful to strategically deliver PrEP in pregnancy. Many pregnant women remain unaware of partner HIV status; enhancing partner HIV testing could improve PrEP provision.



	No. of ANC clients offered PrEP	% of all ANC clients offered PrEP, all regions[1]	% of ANC clients with high HIV risk offered PrEP, all regions[1]
All pregnant women, all regions[2]	1,134,634	100%	100%
Only pregnant women with high HIV risk, all regions[3]	447,046	39%	100%
All pregnant women, Nyanza only[4]	295,005	26%	37%
Only pregnant women with high HIV risk, Nyanza only[5]	149,862	13%	37%

KAIS = Kenya AIDS Indicator Survey
[1]Regions include Eastern, Coast, Rift Valley, Nairobi and Nyanza.
[2]The number of pregnant women for all regions was estimated by multiplying the total number of pregnant women nationally (1.53 million, Kenya Demographic and Health Survey [KDHS] 2014) by the proportion of women in Eastern, Coast, Rift Valley, Nairobi and Nyanza regions (74%, KDHS 2014).
[3]The number of pregnant women with high HIV risk was estimated by multiplying the total number of pregnant women in Eastern, Coast, Rift Valley, Nairobi and Nyanza regions by the proportion of pregnant women with high HIV risk (39%) in all regions combined.
[4]The number of pregnant women in Nyanza was estimated by multiplying the total number of pregnant women nationwide (1.53 million, KDHS 2014) by the proportion of women in Nyanza (26%, KDHS 2014).
[5]The number of pregnant women in Nyanza with high risk for HIV was estimated by multiplying the total number of pregnant women in Nyanza by the proportion of pregnant women with high HIV risk in Nyanza (51%).

971 PREP UPTAKE DISPARITIES IN A DIVERSE ON-LINE SAMPLE OF US MEN WHO HAVE SEX WITH MEN

Kenneth H. Mayer[1], Katie Biello[2], David S. Novak[3], Douglas Krakower[4], Matthew J. Mimiaga[2]
[1]Fenway Hlth, Boston, MA, USA, [2]Brown Univ, Providence, RI, USA, [3]On-Line Buddies, Inc, Cambridge, MA, USA, [4]Beth Israel Deaconess Med Cntr, Boston, MA, USA

Background: Although the CDC estimates that >400,000 US men who have sex with men (MSM) are PrEP candidates, uptake initially was slow. Monitoring recent trends is important to ensure wider access to those at greatest HIV risk.
Methods: An on-line survey was mounted on 2 popular MSM partner seeking sites during March 2016 to assess PrEP use. Factors independently associated with PrEP use were evaluated using multivariable logistic regression with backward selection.
Results: Of 4,698 MSM respondents, 21% were 18 to 24 y.o., 41% were 25 to 39, and 38% were 40 or older. Almost half (47%) identified as White, 25% as Black, 11% as Latino. Almost 12% were born outside the US The largest number of respondents were from the Southeast (26%) or Mid-Atlantic (20%). Nearly 60% had private health insurance; 12% had none. Almost 2/3 reported condomless anal intercourse (C.A.I.) at least once in the prior 3 months. Bacterial STIs were common (8% reporting gonorrhea, 8% chlamydia, and 6% syphilis in the prior year). Almost 8% had used PEP previously. Almost 15% of respondents (N=684) reported using PrEP. PrEP users resided in 45 different states, 491 zipcodes. Factors independently associated with PrEP use in a multivariable model depicted by aOR and (95% CI) were: Age over 25 years: 1.9 (1.3, 2.7) (REF: 18-24 years old) Black race: 0.7 (0.6, 0.9) (REF: White) Born outside US: 0.7 (0.4, 0.9) (REF: native-born) Private insurance: 3.8 (2.4, 6.0) (REF: No insurance) Urban zip code: 1.02 (1.01, 1.02) (REF: non-urban zipcode) 2 or more CAI acts*: 2.9 (2.2, 3.8) (REF: 0 CAI) (*in past 3 months) Bacterial STI**: 3.1 (2.4, 3.9) (REF: no STI) (** in past year) Ever used PEP: 6.5 (4.7, 9.0) (REF: no prior PEP use)
Conclusion: In this online MSM sample, those who engaged in condomless anal sex with non-monogamous partners, who had a bacterial STI and/or had used PEP were more likely to report PrEP use. Those who were younger, Black, immigrant and/or uninsured MSM were less likely to report PrEP use, despite frequent condomless anal sex. Programs to address economic and sociodemographic disparities are needed to ensure wider PrEP access to those who might benefit most.

972 IMPACT OF INSURANCE COVERAGE ON PREEXPOSURE PROPHYLAXIS FOR HIV PREVENTION

Rupa R. Patel[1], Leandro Mena[2], Amy Nunn[3], Timothy McBride[1], Laura C. Harrison[1], Catherine E. Oldenburg[4], Jingxia Liu[1], Kenneth H. Mayer[5], Philip A. Chan[6]
[1]Washington Univ in St. Louis, St. Louis, MO, USA, [2]Univ of Mississippi, Jackson, MS, USA, [3]Brown Univ, Providence, RI, USA, [4]Univ of California San Francisco, San Francisco, USA, [5]Fenway Hlth, Boston, USA, [6]The Miriam Hosp, Providence, RI, USA

Background: Antiretroviral pre-exposure prophylaxis (PrEP) has the potential to reduce HIV acquisition among high-risk populations in the United States. The effect of insurance coverage on PrEP uptake has not been fully assessed in recent trials where participants often obtained the medications for free. We assessed individual insurance coverage and its effect on PrEP uptake in three diverse clinic settings.
Methods: We reviewed demographic, behavioral and insurance data from patients enrolled in an observational PrEP clinical cohort recruited in 3 US cities (Jackson, Mississippi, St. Louis, Missouri and Providence, Rhode Island) from January 2014 to December 2015. Inclusion criteria included patients who were prescribed PrEP for least three months. The primary outcome was PrEP utilization, defined as patients who reported taking PrEP at their three-month follow up evaluation. Multivariable logistic regression analysis was performed to assess the relationship of sociodemographics, including income and insurance coverage, on PrEP utilization. Rhode Island was the only state of the three to have expanded Medicaid during the study period.
Results: Of the 201 patients included in the analyses, 34% were from Jackson, 28% from St. Louis, and 38% from Providence. Almost all (91%) were male with a median age of 29 years (IQR 24-37); 51% were White, 34% were African American, and 6% were Latino. Majority (65%) were college graduates with a median income of $25,000 (IQR $7,200-$50,000). Overall, 79% were insured, although this varied by site: 95% were insured in Providence, 49% in Jackson and 95% in St. Louis (P<0.0001). Eighty-two percent of patients reported taking PrEP at three-month follow up. After adjusting for age, race, education, income, and state Medicaid expansion, insured patients had four times the odds of taking PrEP at three months compared to the uninsured (OR: 4.49, 95% CI: 1.68-12.01; P<0.003).

Conclusion: Insurance coverage had a significant and positive impact on PrEP utilization. Disparities in insurance coverage may impede PrEP uptake in non-trial clinical settings and may exacerbate disparities in PrEP access. These findings from three diverse areas suggest state- and local-level PrEP implementation efforts should address barriers to insurance coverage as a critical component to successful programmatic efforts.

973 CONCORDANT POPULATION-LEVEL INCREASES IN PREP FOUND WITH NOVEL PUBLIC HEALTH METHODS

Susan Buskin[1], Julia Hood[1], Sara N. Glick[2], Warren Dinges[3], Matthew R. Golden[2]
[1]Pub Hlth–Seattle & King County, Seattle, WA, USA, [2]Univ of Washington, Seattle, WA, USA, [3]Seattle Infectious Disease Clinic, Seattle, WA, USA

Background: PrEP (pre-exposure prophylaxis) is a highly effective means of HIV prevention yet limited data are available regarding trends in PrEP use. We estimated local PrEP uptake among men who have sex with men (MSM) in King County, WA using data from surveys of medical providers, behavioral surveillance, and community surveys.
Methods: Annual provider surveys were conducted in King County 2014-2016. Those surveyed had volunteered to be in state or county PrEP provider lists or had used HIV RNA testing >2 times for HIV testing. Providers estimated their number of patients who were currently taking PrEP, and the percent of MSM using PrEP was calculated assuming 5.7% of King County men aged >14 years were MSM, an estimate from a local probability survey. Annual surveys of MSM were conducted at the 2014-2016 Seattle Pride festivals using convenience sampling. Finally, the Seattle area National HIV Behavioral Surveillance (NHBS) system used venue-based sampling of MSM in the second half of 2014. "High risk" status was defined by any of the following in the past year: a bacterial STI diagnosis, methamphetamine or popper use, condomless intercourse with a sero-discordant partner, or 10 or more MSM partners.
Results: Participation in the PrEP provider survey ranged from 82% of 22 providers in 2014 to 76% of 150 providers in 2016. The sum of patients of provider-participants using PrEP increased from 330 in 2014 to 3,347 in 2016 (402 to 4,404 after non-response adjustment). Among providers included in both 2014 and 2016, current PrEP patients increased from 311 to 1,678. The NHBS survey included 424 HIV- MSM and the Seattle Pride data included 371 to 505 seronegative participants each year. Highly consistent findings were present from the disparate methods (see graphic). In 2016, we estimate that 10.6% and 10.2% of MSM were on PrEP based on provider survey and Pride data, respectively. High risk MSM reported more PrEP use than lower risk men: 9% vs. 0-2% from Pride and NHBS in 2014; 34 vs. 3% from Pride in 2015; and 29 vs. 4% from Pride in 2016.
Conclusion: Data from both providers and MSM document that PrEP use is rapidly expanding in King County, and increasing more steeply among high risk MSM. While uncertainty in the representativeness of surveyed populations and our estimate of the number of MSM in King County limit the precision of our findings, the consistency of our results supports their validity and demonstrate the utility of our approach to monitoring PrEP uptake at the population-level.

974 RACIAL/ETHNIC DISPARITIES IN PERSISTENCE AMONG PREP USERS IN SAN FRANCISCO

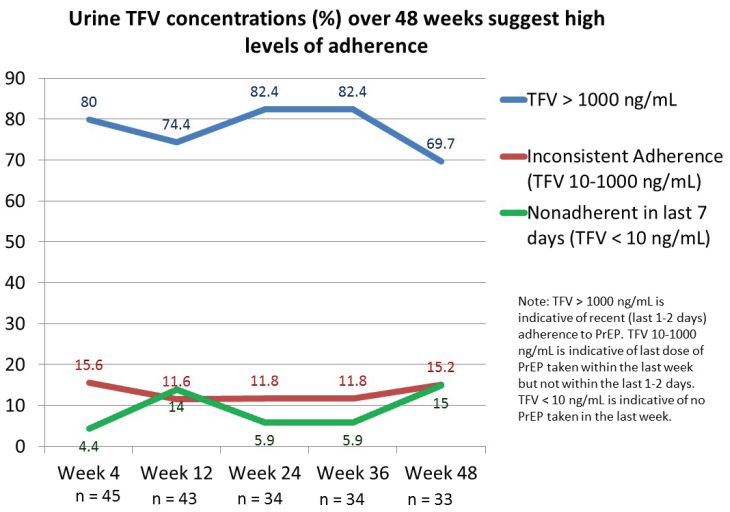
Hyman Scott[1], Miranda Nordell[1], Anne Hirozawa[1], Monica Gandhi[2], Catherine James[1], Hali Hammer[1], Susan Buchbinder[1], Susan Scheer[1]
[1]San Francisco Dept of Pub Hlth, San Francisco, CA, USA, [2]Univ of California San Francisco, San Francisco, CA, USA

Background: Dissemination of Pre-Exposure Prophylaxis (PrEP), a highly effective HIV prevention tool, is a priority for San Francisco's Getting to Zero campaign to reduce new HIV infections citywide. However, there are limited data available on persistence (staying on PrEP) among those who've initiated, an important component of the PrEP cascade.
Methods: Patients receiving PrEP within the San Francisco Department of Public Health Primary Care (SFPC) clinics are included in a centralized PrEP registry to monitor metrics such as uptake and persistence. Patients were included in the PrEP registry if they received a PrEP prescription from a SFPC medical provider and were not in the HIV registry, had no HIV positive laboratory tests, and were not on post-exposure prophylaxis. Patients receiving PrEP at any time from 2/1/2015 to 2/29/2016 were included in this analysis, regardless of initiation date, and median time on PrEP was calculated. PrEP persistence, the proportion of patients who remained on PrEP through 4/1/2016, was determined via medical chart abstraction, and stratified by age, race/ethnicity, and clinic.
Results: Overall, there were 220 patients who received PrEP over the evaluation period; most (85%) were men. The largest proportion of patients (39%) were 30-39 years old, 9% were 18-24, 20% were 25-29 years, 16% were 40-49, and 17% were >50 years old. Forty-three percent of patients were white, 18% Latino, 9% Black, and 8% Asian/Pacific Islander. At the end of the study period, PrEP persistence was 67% among patients receiving PrEP within SFPC clinics, and the median time on PrEP was 217 days. Persistence was lowest for those aged 25-29 (61%) and 40-49 (60%); and highest for those >50 years old (73%). Black patients had the lowest persistence (50%), followed by Latino patients (57%). Median duration on PrEP was lower for Black patients (115 days, $p<0.01$), and Latino patients (183 days, $p<0.01$), compared with White patients (347 days). The primary reason for PrEP discontinuation based on chart review was being lost to clinical follow-up, although discontinuation reason was often missing from the medical record.
Conclusion: Age and racial/ethnic disparities in PrEP persistence were identified among patients receiving PrEP in public health clinics in San Francisco. To maximize the preventive impact of PrEP, and reverse HIV-related disparities at a population level, further efforts are needed to understand reasons for PrEP discontinuation and remove barriers to appropriate PrEP persistence.

975 URINE TENOFOVIR TESTING TO MEASURE PREP ADHERENCE AMONG YOUTH IN A REAL WORLD SETTING

Linden Lalley-Chareczko[1], Devon Clark[1], Ganesh S. Moorthy[2], Athena Zuppa[3], Caitlin Conyngham[1], Karam Mounzer[1], Pablo Tebas[2], **Helen C. Koenig**[2]
[1]Philadelphia FIGHT, Philadephia, PA, USA, [2]Univ of Pennsylvania, Philadephia, PA, USA, [3]Children's Hosp of Philadelphia, Philadephia, PA, USA

Background: Pre-exposure prophylaxis(PrEP) for HIV prevention with daily TDF/FTC is effective when taken consistently. Young men who have sex with men(yMSMc) and transgender women of color(TWc) have the highest risk of new HIV infections. Currently there is no objective way to monitor adherence to PrEP in the clinic. Urine has been shown to be highly correlated with plasma tenofovir(TFV) levels, with urine TFV levels >1000 ng/mL demonstrating recent(last 1-2 days) adherence, levels 10-1000 ng/mL demonstrating adherence within the previous week but not in the last 1-2 days, and levels <10 ng/mL indicative of no TFV in the previous week(Abstr. 975, CROI 2015).
Methods: PrEP was administered to 50 yMSMc and TWc at a youth drop-in center using a needs-based dispensation schedule(weekly, biweekly, monthly) over 48 weeks. Primary objectives were retention at 48 weeks (defined as having a study visit at end-of-study and completing ≥50% of medical pick-ups), and adherence as assessed by urine TFV levels. Risk behaviors and STI diagnoses were also collected.
Results: Participant mean age was 22.4 years, 10% were transgender women, 64% were African American, and mean time on PrEP prior to study initiation was 35.2 weeks. Retention was 70%(35 subjects) at 48 weeks. 11 withdrew and 4 were lost-to-follow-up. The proportion of subjects with urine TFV concentrations consistent with recent adherence to PrEP was 80% at week 4, 74.4% at week 12, 82.4% at weeks 24 and 36, and 69.7% at week 48. The proportion of subjects with evidence of inconsistent adherence was 15.6% at week 4, 11.6% at week 12, 11.8% at weeks 24 and 36, and 15.2% at week 48. The proportion of subjects who demonstrated nonadherence over the previous 7 days was 4.4% at week 4, 14% at week 12, 5.9% at weeks 24 and 36, and 15% at week 48. 61 STIs were diagnosed over 231 screenings: 6 subjects had rectal gonorrhea/chlamydia at screening; 9 additional subjects tested positive between weeks 2-24, and 12 subjects between weeks 25-48($p=0.43$ for change over study period). No subjects seroconverted. At week 48, more than half of subjects endorsed an increase or no change in condom use, an increase in ability to discuss HIV with partners, and no change in number of sexual partners from baseline.
Conclusion: PrEP can be successfully delivered to a young high-risk population with high program retention and medication adherence measured through objective urine testing.



976 COMBINING MEASURES OF ADHERENCE CAN ASSESS PATTERNS OF PREP DRUG-TAKING

Andrew M. Abaasa[1], Craig Hendrix[2], Monica Gandhi[3], Peter Anderson[4], Anatoli Kamali[5], Eduard Sanders[6], Gaudensia Mutua[7], Frances Priddy[5], Haberer Jessica[8]
[1]MRC/UVRI Uganda Rsr Unit on AIDS, Entebbe, Uganda, [2]The Johns Hopkins Univ, Baltimore, MD, USA, [3]Univ of California San Francisco, San Francisco, CA, USA, [4]Univ of Colorado, Aurora, CO, USA, [5]Intl AIDS Vaccine Initiative, New York, NY, USA, [6]Kenya Med Rsr Inst, Kilifi, Kenya, [7]Univ of Nairobi, Nairobi, Kenya, [8]Cntr for Global Hlth, Massachusetts General Hosp, Boston, MA, USA

Background: Measuring patterns of drug-taking with PrEP remains a challenge. In phase 1/2 PrEP trials in East Africa, we use non-pharmacokinetic (non-PK) and pharmacokinetic (PK) adherence metrics in combination to assess patterns of drug-taking.

Methods: From Oct 2009 to Mar 2010, the International AIDS Vaccine Initiative (IAVI) randomized participants to daily tenofovir, disoproxil fumarate(TDF)/emtricitabine(FTC) or placebo or intermittent TDF/FTC or placebo in Uganda (Ug) and Kenya (Ke). Eligible participants were HIV-negative aged 18-49 years, followed at Weeks 1, 2, 4 and then monthly for 4 months. Adherence was measured by 5 metrics: Electronic Monitoring (EM), Self-Report (SR), and concentrations of drug levels in plasma & cryopreserved peripheral blood mononuclear cells (PBMC) (short-term) and hair (long-term). The EM and SR data were averaged over the duration of exposure represented by the 3 PK measures. We categorized adherence as low, moderate and high (table) by each metric and assessed patterns of drug-taking via the 3 PK measures. A discriminant (C-statistic) analysis for single or combined methods for adherence measuring was assessed by logistic regression models with outcome as high versus moderate or low and displayed by receiver operating characteristic (ROC) curve area.

Results: The analysis involved 48 participants with a mean age of 29.2 (SD=6.9). Discrimination for the EM measure was poor for SR (AROC 0.53) and best for the hair (AROC 0.87). A short-term PK metric (PBMC) did not improve discriminant ability. Using 3 measures, the highest percent of variability in EM adherence was explained with SR plus hair and PBMC in Ug (24.6%) and with SR plus plasma and hair in Ke (63.5%). The combination of the 3 PK metrics in Ug revealed high adherence in the short-term and low adherence in the long-term. In Ke, combining the 3 metrics showed high adherence just prior to study visits, but low adherence prior to that.

Conclusion: SR adherence in PrEP is of low utility. Combining short-term (plasma) and long-term (hair) PK metrics of adherence can reveal patterns of drug-taking during PrEP.

Adherence level	EM	SR doses per week	Plasma TFV ng/ml	Hair TFV ng/mg	PBMC TFV-DP fmol/10^6 cells
Low	0 - <29%	0 - 2	≤5.9	≤0.012	≤11
Moderate	29% - <71%	3 - 5	>5.9 - <52.2	>0.012 - <0.038	>11 - <42
High	71% - 100%	6 - 7	52.2+	0.038+	42+
Median (IQR)	Ug 7(6,7) Ke 5(4,7)	7(7,7) 7(6,7)	70.5(38.9,94.6) 81.1(40.0,148.5)	0.07(0.05,0.11) 0.07(0.03,0.08)	23.3(13.6,34.6) 10.4(2.5,23.2)

977 SUBSTANCE-USING MSM ON HIV PREEXPOSURE PROPHYLAXIS HAVE BETTER ADHERENCE

Martin Hoenigl[1], Sonia Jain[2], David J Moore[1], Deborah Collins[3], Xiaoying Sun[2], Peter L. Anderson[4], Katya Calvo[5], Michael Dube[6], Sheldon Morris[1], for the California Collaborative Treatment Group (CCTG) 595 Team
[1]Univ of California San Diego, San Diego, CA, USA, [2]Univ of California San Diego, La Jolla, CA, USA, [3]Long Beach HHS, Long Beach, CA, USA, [4]Univ of Colorado Denver, Aurora, CO, USA, [5]Los Angeles Biomed Rsr Inst at Harbor–UCLA Med Cntr, Torrance, CA, USA, [6]Univ of Southern California, Los Angeles, CA, USA

Background: The effectiveness of tenofovir/emtricitibine (TDF/FTC) for HIV preexposure prophylaxis (PrEP) strongly depends on maintaining adherence. We hypothesized that among men who have sex with men and transgender women enrolled in a randomized controlled PrEP trial, substance users would have lower levels of PrEP adherence.

Methods: CCTG 595 was a randomized controlled trial of individualized texting versus standard care for adherence to daily TDF/FTC. We examined alcohol and substance use over 48 weeks for association with dried blood spot (DBS) intracellular tenofovir diphosphate (TFV-DP) levels at weeks 12 and 48 (i.e., composite outcome, see Table; cutoff ≥719 fmol/punch that approximates ≥4 doses in the past week). Substance use was assessed (for the past 3 months) at all study visits using a SCID screening questionnaire for "No use", "Some use" (1-4 times) and "Heavy use" (5 or more times) of any substance of abuse combined (marijuana and alcohol excluded) and also for each substance separate. Problematic use was assessed using the DAST-10 and AUDIT. We also assessed whether alcohol and substance use impacted study completion and incident sexually transmitted infections (STIs). Fisher's exact test and logistic regression were used.

Results: Of 394 subjects at baseline, any substance use was reported by 73% and alcohol use by 83% of participants. Overall, 71% of the 394 participants had TFV-DP levels ≥719 fmol/punch at week 48. Ongoing "Heavy" substance use (any) and "Some" or "Heavy" alcohol use were significantly associated with better adherence in logistic regression (Table), while problematic use had no significant impact on adherence. No particular substance contributed more to this association and notably METH users did not have worse adherence than non-METH users. In general, intensity of alcohol or substance use at baseline was not associated with study completion. Any substance use, but not alcohol use, was strongly associated with incident STI on study (Odds ratio of 2.5 and 2.6 for "Some" and "Heavy" use compared to "No" use; p<0.001).

Conclusion: While substance users had increased STI rates, indicating higher risk behavior, PrEP adherence was not lowered by substance or alcohol use. In fact, likelihood to reach TFV-DP levels above the cut-offs appeared to be higher in participants with substance use suggesting that these individuals may have insight into HIV risk and appropriately be more diligent with PrEP adherence.

978 OLDER AGE ASSOCIATED WITH BOTH ADHERENCE AND RENAL DECLINE IN THE PREP DEMO PROJECT

Monica Gandhi[1], Peter Bacchetti[1], Catherine A. Koss[1], Chengshi Jin[1], Howard Horng[1], Richard Elion[2], Michael Kolber[3], Stephanie E. Cohen[4], Susan Buchbinder[4], Albert Y. Liu[4]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]The George Washington Univ, Washington, DC, USA, [3]Univ of Miami, Miami, FL, USA, [4]San Francisco Dept of Pub Hlth, San Francisco, CA, USA

Background: Pharmacokinetic (PK) metrics (drug levels in a matrix such as plasma, dried blood spots, or hair) provide objective measures of adherence and exposure to TDF/FTC-based PrEP. As PrEP use expands in diverse, "real-world" populations, PK metrics from demonstration projects can be used to assess predictors of adherence to and safety of PrEP.
Methods: The US PrEP Demonstration Project (PrEP Demo) enrolled HIV-negative MSM and transwomen (TGW) in San Francisco, Miami and DC and provided 48 weeks of TDF/FTC-based PrEP. Tenofovir (TFV) and FTC levels were measured in hair in a subset of participants using validated LC/MS-MS assays. Multivariate logistic regression models were used to analyze predictors of TFV hair levels ≥0.023 ng/mg, consistent with ≥4 doses of PrEP/week. The associations of time-dependent factors, including exposure, with visit-to-visit changes in GFR estimated by MDRD were assessed using linear mixed models.
Results: From 10/2012-1/2014, 557 MSM and TGW enrolled in PrEP Demo. 280 participants (50% of total) provided hair. Among hair study participants, median age was 34 (range 19-65); 23% identified as Latino; 78% White, 5% Black, 9% Asian, 17% other; 99% MSM; 79% reported condomless receptive anal sex; 14.8% used amphetamines in the past 3 months; median baseline GFR was 98 ml/min/1.73m2. TFV hair levels were consistent with ≥4 PrEP doses taken/week in 82% of 876 person-visits at which hair was collected. Predictors of ≥4 doses/week included older age (OR 1.42 per decade, 95% CI 1.0-2.0, p=0.05); condomless receptive anal sex with a known HIV+ partner (OR 2.3, 95% CI 1.4-4.5, p=0.01); and amphetamine use (OR 2.5, 95% CI 0.93-6.5, p=0.07). Overall, GFR declined by median -4.2% (range -37 to +68) over 48 weeks. In a multivariate model, each decade of age was associated with -2.8% (-0.4 to -5.2, p=0.02) more decline in GFR; each 2-fold increase in baseline GFR was associated with -14.6% (-5.4 to -22.9, p=0.003) more decline; each doubling in FTC hair level was associated with -2.4% (-0.4 to -4.3, p=0.02) more decline. Hypertension and PrEP duration were not substantially associated with GFR decline.
Conclusion: In this subset of PrEP Demo participants, older age, condomless sex with a known HIV+ partner, and amphetamine use were each associated with taking ≥4 doses/week of PrEP. Older age, higher GFR at baseline, and higher TFV/FTC exposure were associated with greater declines in renal function. MSM who initiate PrEP at older ages may require more frequent safety monitoring.

979 CHANGES IN SEXUAL BEHAVIOR AND STI DIAGNOSES AMONG MSM USING PREP IN SEATTLE, WA

Michalina A. Montano, Julia C. Dombrowski, Lindley A. Barbee, Matthew R. Golden, Christine M. Khosropour
Univ of Washington, Seattle, WA, USA

Background: Whether and how MSM modify sexual behaviors after initiating PrEP has not been well studied in non-research settings and is of particular importance as PrEP becomes more widely used.
Methods: We measured changes in sexual behavior among MSM attending an STD clinic in Seattle, WA who initiated PrEP. Sexual behavior during prior 30 days was reported in a computer-assisted self-interview (CASI) administered at PrEP initiation and subsequent clinic visits every 3 months. Bacterial sexually transmitted infections (STI) diagnosed during the periods before and after PrEP initiation were identified via STI surveillance records. MSM were asked about number of sexual partners, sexual positioning, and condom use with HIV-positive, HIV-negative, and unknown-status partners during the prior 30 days. We used linear regression to assess significance of behavioral trends. We describe the proportion of MSM reporting each behavior at each visit. We present the proportion of MSM diagnosed with chlamydia (CT), gonorrhea (GC), or syphilis in the 12 months prior to baseline for MSM who completed a baseline CASI, and the proportion of MSM diagnosed with CT, GC, or syphilis while taking PrEP, for those who completed at least one follow-up CASI.
Results: 220 men began PrEP during Sept 2014 – June 2016, and completed the behavioral section of the baseline CASI. Mean age of participants was 31 (SD: 8.5), and 63% were white. Mean number of sex partners and proportion of sex with each type of partner was stable during the study period (Table). The proportion of men reporting never using condoms for any anal sex or never using condoms during receptive anal intercourse with HIV-positive partners increased over the study period, but there were no clear trends with other position and partner serostatus combinations. 24% of men were diagnosed with GC, 17% with CT, and 19% with syphilis at baseline or during the 12-months prior to PrEP initiation. Among men with at least one follow-up visit (n=76; average follow-up time = 8.6 months), 34% were diagnosed with GC, 37% with CT, and 9% with syphilis while on PrEP.
Conclusion: MSM in our clinic reported decreased condom use during receptive anal intercourse with HIV-seropositive partners after initiating PrEP. The proportion of men diagnosed with CT and GC was higher in the time period after PrEP initiation, which could reflect increased risk behavior, increased detection during routine screening, or temporal increases in STD risk in the population.

Reported Sexual Behaviors Over Time

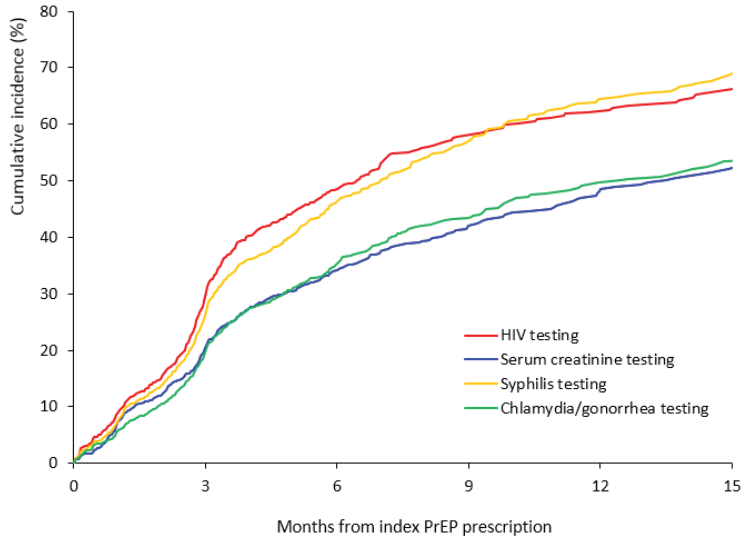
Behavior	Baseline (Pre-PrEP) N=220	3-Month Visit N=76	6-Month Visit N=58	9-Month Visit N=41	p-Value (Linear Trend)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
# Male Sex Partners	3.9 (4.0)	4.3 (7.5)	3.6 (3.8)	5.0 (4.3)	0.4
Anal Sex Partner Type	N (%)	N (%)	N (%)	N (%)	
Any HIV-positive Partners	49 (25.3)	16 (24.4)	14 (28.6)	11 (30.6)	0.1
Any HIV-negative Partners	173 (89.2)	60 (90.9)	43 (87.8)	30 (83.3)	0.2
Any Unknown Status Partners	74 (38.1)	16 (24.2)	7 (14.3)	14 (38.9)	0.9
Condom Use during Anal Sex					
Never uses condoms	28 (15.0)	10 (15.6)	9 (18.8)	8 (24.2)	**0.05**
Never uses condoms during receptive anal sex with HIV+ Partner	7 (25.9)	3 (30.0)	4 (36.4)	4 (50.0)	**0.04**
Never uses condoms during receptive anal sex with HIV- Partner	19 (13.5)	6 (13.3)	6 (18.8)	8 (32.0)	0.1
Never uses condoms during receptive anal sex with Unknown Status Partner	6 (12.5)	3 (27.3)	0 (0.0)	1 (14.3)	0.7
Never uses condoms during insertive anal sex with HIV+ Partner	12 (29.3)	5 (38.5)	5 (38.5)	5 (62.5)	0.1
Never uses condoms during insertive anal sex with HIV- Partner	22 (17.7)	8 (17.4)	7 (22.6)	10 (43.5)	0.1
Never uses condoms during insertive anal sex with Unknown Status Partner	9 (18.4)	3 (23.1)	1 (20.0)	3 (33.3)	0.2

980 LABORATORY TESTING OF A US COHORT OF PRIVATELY INSURED USERS OF HIV PREP, 2011–2014

Ya-Lin A. Huang, Guoyu Tao, Taraz Samandari, Karen W. Hoover
CDC, Atlanta, GA, USA

Background: Antiretroviral (ARV) preexposure prophylaxis (PrEP) is highly effective in preventing HIV infection but requires laboratory monitoring. CDC recommends initial testing for renal function (serum creatinine), HIV, and hepatitis B infections; and ongoing testing for renal function, HIV, and sexually transmitted infections (STIs). To assess the uptake of these recommendations, we examined laboratory testing rates before and after PrEP initiation.
Methods: Using Marketscan, a commercial insurance claims database, we followed a cohort of HIV-uninfected persons aged 18-64 years who started PrEP during 2011-2014. Their first PrEP prescription date was the index date. The sample was limited to persons continuously enrolled in the health plan for ≥ 6 months pre-index. PrEP users were followed until the earliest occurrence of a) evidence of HIV infection, b) health plan disenrollment, or c) December 31, 2014. We estimated the incidence of laboratory testing at baseline (≤ 3 months pre-index) and conducted Kaplan-Meier analyses to estimate the cumulative incidence of follow-up tests. We used Cochrane-Armitage trend test to assess if testing rates varied by index year.
Results: Our cohort of 2,140 new PrEP users were followed for a median duration of 142 days (interquartile range=79-237). Prior to PrEP initiation, 53% of the cohort was tested for HIV, 32% for hepatitis B, and 28% for serum creatinine. Among the 1,261 persons who were prescribed PrEP for ≥ 3 months, at 3 months after PrEP initiation, 30% had their first monitoring testing for HIV and 20% for creatinine; at 12 months, 62% had testing for HIV and 49% for creatinine. At 6 months after PrEP initiation, 46% of the cohort had testing for syphilis and 35% for chlamydia/gonorrhea. When stratified by index year, both baseline and follow-up testing rates increased significantly from 2011 to 2014 for all tests except for creatinine. For example, the rate of baseline HIV testing was 26% in 2011 and 54% in 2014 (Ptrend < 0.001).
Conclusion: For these PrEP users, laboratory testing was less frequent than recommended, although most of the testing rates improved as the number of PrEP prescriptions increased. Monitoring for HIV infection is crucial for early detection and to avoid ARV drug resistance. Other tests are important to detect possible renal toxicity of PrEP and incident STIs. There are opportunities to increase laboratory testing for PrEP users, especially for serum creatinine. Our analysis provides estimates for future evaluation.

Figure: Kaplan-Meier plot of first HIV, serum creatinine, syphilis, and chlamydia/gonorrhea test after PrEP initiation, privately insured patients, United States, 2011-2014



981 BONE CHANGES WITH TDF-CONTAINING AND NON–TDF-CONTAINING PREP IN US MEN AND WOMEN

Todd Brown[1], Timothy Wilkin[2], Kenneth H. Mayer[3], Raphael J. Landovitz[4], Ying Q. Chen[5], Alicia Young[6], Mark A. Marzinke[1], Wairimu Chege[7], Marybeth McCauley[8], Roy M. Gulick[2]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Weill Cornell Med, New York, NY, USA, [3]Fenway Hlth, Boston, MA, USA, [4]Univ of California Los Angeles Cntr for Clinical AIDS Rsr & Educ, Los Angeles, CA, USA, [5]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [6]Statistical Cntr for HIV/AIDS Rsr and Prevention, Seattle, WA, USA, [7]NIAID, Bethesda, MD, USA, [8]FHI 360, Washington, DC, USA

Background: TDF-containing PrEP has been associated with decreases in bone mineral density (BMD) in both men and women. The BMD effects of non-TDF-containing PrEP regimens have not been reported.
Methods: The HPTN 069/ACTG 5305 study randomized US men and women at risk for HIV-infection to one of 4 double-blinded, placebo-controlled regimens: maraviroc (MVC), MVC+emtricitabine (FTC), MVC+TDF, or TDF+FTC to test the safety and tolerability of these regimens. BMD was measured at the lumbar spine (LS) and hip by dual-energy x-ray absorptiometry (DXA) at baseline and 48 weeks. Adherence was assessed by detectable plasma drug concentrations (TFV and FTC: 0.31 ng/mL; MVC: 0.5 ng/mL) at 24 and 48 weeks. Percentage change in LS and hip BMD was compared between the TDF- and non-TDF (MVC±FTC) containing arms by multivariate linear regression adjusting for sex, race and baseline BMI.
Results: At baseline (n=397), the median age was 32 years, 53% male, 46% black, and median Z-scores were -0.6 and -0.4 at the LS and hip respectively. Overall at the LS, the percentage change in BMD was +0.19% in the TDF arms and +0.66 % in the non-TDF arms (between group difference, -0.48% (95% CI, -1.22, 0.26)). Overall at the hip, the percentage change in BMD was -0.85% in the TDF arms and 0.09% in the non-TDF arms (between group difference, -0.94 (95% CI, -1.74, -0.13)). Among those who had detectable drugs concentrations at 24 and 48 weeks, at the LS (n=129), the percentage change in BMD was +0.89% in the TDF arms and +1.11% in the non-TDF arms (between group difference, -0.22% (95% CI, -1.36, 0.92), p=0.70). At the hip (n=131), the percentage change in BMD was -2.89% in the TDF arms and -0.95 % in the non-TDF arms (between group difference, -1.94% (95% CI, -3.23, -0.65), p=0.003). The between-group differences in percentage change in BMD did not differ by sex at either the LS or hip.
Conclusion: TDF-containing PrEP was associated with greater bone loss compared to non-TDF MVC±FTC PrEP at the hip, but not the lumbar spine in both men and women.

982 PREDICTORS OF MEDICAL MALE CIRCUMCISION UPTAKE BY MEN AGED 25-39 YEARS IN NYANZA

Donath Emusu[1], **Kawango Agot**[2], Jonathan Grund[3], Paul K Musingila[4], Frankline Onchiri[5], Edward Mboya[2], Jacob Onyango[2], Eunice Omanga[2], Elijah Odoyo-June[1], Boaz Otieno-Nyunya[1]
[1]US CDC, Nairobi, Kenya, [2]Impact Rsr and Development Org, Kisumu, Kenya, [3]CDC, Atlanta, GA, USA[4]US CDC, Kisumu, Kenya, [5]Seattle Children's Rsr Inst, Seattle, WA, USA

Background: Uptake of voluntary medical male circumcision (VMMC) as an intervention for the prevention of HIV is low among men aged ≥25 years in Nyanza region, Kenya. We evaluated the baseline prevalence and cofactors of VMMC among men 25-39 years who were targets of interventions to improve VMMC uptake.
Methods: As part of a cluster randomized controlled trial (cRCT) to evaluate tailored interventions to improve uptake of VMMC, we conducted a survey of men from the Luo, traditionally non-circumcising ethnic community who were aged 25-39 years and residing in non-contiguous administrative locations selected as cRCT sites. We determined their circumcision status, estimated VMMC prevalence and assessed predictors of being circumcised using univariate and multivariate Generalized Estimating Equations logistic regression to account for study design.
Results: While 9,711 men were screened, 5,639 (58.1%) consented and were enrolled into cRCT. Of these 5,639 used for this analysis, 2,851 (50.6%) self-reported being circumcised. Uncircumcised men aged 25-39 years residing or planning to continue living in the study village for the next 9 months were included in the study. Circumcised men aged 39 years who were non-resident or planning to move away from the study village within 9 months after enrolment were excluded. Three-quarters of enrolled men consented to visual verification of circumcision status of whom 2,195 (52.0%) were confirmed fully or partially circumcised. The odds of being circumcised, as self-reported, were significantly higher for men with secondary school education (adjusted Odds Ratio (aOR)=2.15; 95% CI: 1.11-4.13, p =0.023), college (aOR=2.12; 95% CI: 1.12-4.00, p=0.021), and university (aOR=2.86; 95% CI: 1.53-5. 34, p=0.001) education compared to no education; for non-Christians (aOR=2.03; 95% CI: 1.28-3.21, p=0.003) compared to Christians; and for the employed (aOR=1.32; 95% CI: 1.09-1.59, p=0.004). The odds were lower for men with history of being divorced/separated/widowed (aOR=0.59; 95% CI: 0.41-0.85, p=0.005) compared to being single; and for men aged 35-39 years (aOR 0.83; 95% CI: 0.41-0.85, p=0.003) compared to men aged 25-29 years.
Conclusion: Among the Luo community in Nyanza region of Kenya, men aged 35-39 years with post-primary education, non-Christians and employed are more likely to be circumcised. VMMC providers seeking to improve uptake among men aged 25-34 years should target men who are or were married, the less educated and the unemployed.

983 MALE CIRCUMCISION AND RISK COMPENSATION IN KWAZULU-NATAL, SOUTH AFRICA

Katrina F. Ortblad[1], Guy Harling[1], Joshua A. Salomon[1], Frank Tanser[2], Deenan Pillay[3], Tinofa Mutevedzi[3], Till Baernighausen[4]
[1]Harvard Univ, Boston, MA, USA, [2]Africa Cntr for Pop Hlth, Mtubatuba, South Africa, [3]Africa Hlth Rsr Inst, Mtubatuba, South Africa, [4]Heidelberg Univ, Heidelberg, Germany

Background: Voluntary medical male circumcision (VMMC) has been proven in a number of randomized clinical trials (RCTs) to reduce HIV transmission by 60%. However, the benefits of circumcision might be negated by risk compensation, i.e., increases in risky sexual behaviors because of the biological HIV risk reduction following circumcision. To date, data on risk compensation in sub-Saharan Africa has been largely limited to RCTs. We test the risk compensation hypothesis for the first time using data from a population-based cohort study in sub-Saharan Africa.
Methods: A population-based cohort in KwaZulu-Natal, South Africa was followed longitudinally from 2003 to 2014. Self-reported circumcision status and sexual behavior was collected for all individuals annually, 2009-2014. Four variables were used to measure sexual behavior: (1) condom use at last sex, (2) regular condom used, (3) number of partners in the last 12 months, and (4) number of concurrent partners. Multivariable models with individual fixed effects were used to determine the impact of circumcision uptake on the self-reported sexual behavior variables.
Results: From 2009 to 2014 14,997 unique men reported their circumcision status (median age 25 years, IQR: 19-41 years). During this time circumcision prevalence rose dramatically (2% in 2009 to 12% in 2014) and 954 individuals partook in circumcision interventions (as indicated by changes in their circumcision status over time). No significant changes in sexual behaviors were observed before and after circumcision uptake. The odds of condom use at last sex were 1.1 (95% CI: 0.4 – 3.0) for individuals post-circumcision compared to pre-circumcision and individuals post-circumcision had 0.9 times (95% CI: 0.7 – 1.2) the reported number of sexual partners in the past 12 months compared to number of partners reported pre-circumcision.
Conclusion: We find no evidence for risk compensation following circumcision in a community in rural KwaZulu-Natal. The often-hypothesized risk compensation phenomenon is unlikely to reduce the impact of VMMC campaigns on population HIV incidence in this and similar real-world settings. Circumcision should continue to be vigorously scale-up as a key HIV prevention strategy and newly circumcised males should continue to be counseled on the importance of condom use post-circumcision.

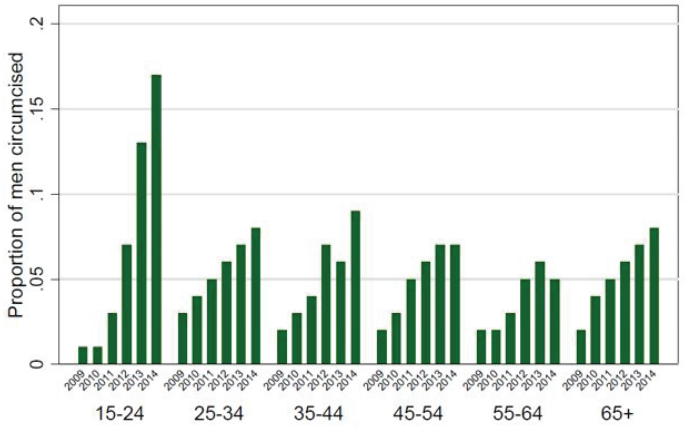


Figure 1. Circumcision prevalence among males in KwaZulu-Natal South Africa from 2009 to 2014, by 10-year age groups.

984 RISK COMPENSATION OVER 2 YEARS AMONG MEN IN A NATIONAL VMMC ROLL-OUT IN ZIMBABWE

Daniel E. Montano[1], Danuta Kasprzyk[1], Deven T. Hamilton[1], Mufuta Tshimanga[2]
[1]Univ of Washington, Seattle, WA, USA, [2]Univ of Zimbabwe, Harare, Zimbabwe

Background: Three randomized control trials (RCTs) demonstrated at least 60% protection of voluntary medical male circumcision (VMMC) against HIV acquisition, and protection against acquisition of ulcerative STIs and HPV. This protection may be offset by risk compensation (RC). Prior RC studies involved men who were part of or follow-on to the RCTs, with men exposed to safe sex messages each time they were seen. This is the first study of RC among men circumcised in a national VMMC program, who were not exposed to safe sex messages each time they were surveyed.

Methods: We assessed change in sexual risk behavior over 2 years among circumcised versus uncircumcised men. We enrolled a cohort of 2,379 HIV-negative men aged 18-40 in 2 urban areas in Zimbabwe: 1,196 circumcised near recruitment, 1,183 eligible for VMMC but declined it. Men were surveyed at baseline, 6, 12, and 24-months with extensive sexual behavior measures including number of partners in last 6-, 12-months, and lifetime, sex with sex workers, condom use, concurrent partnerships, and alcohol and drug use. Longitudinal analyses were performed using generalized estimating equations to test for main and interaction effects of study group and time on sexual risk measures, adjusting for baseline differences.
Results: Cohort groups differed at baseline on marital status, income and education, but not on sexual behavior. Study group was significant for only 3 measures: circumcised men were more likely to have had a partner in past 6 and 12 months, and less likely to drink alcohol before sex. Time was significant for 12 measures, with increases in: had a partner in the previous 6 months, 2+ partners in previous 6 and 12 months, had a partner of unknown HIV status, had concurrent partners, concurrent partners and did not use a condom at last sex, 2+ non-spouse partners, suspected partner had other partners, and being drunk in the past 30 days. There was a significant decrease in using a condom at last sex, consistent condom use with spouse, and having an STI Dx/Sx in the previous 6 months. Group by time interaction was significant only for drinking before sex.
Conclusion: Lack of group by time interaction indicates no evidence for RC after VMMC. Of concern is the strong evidence for increased risk behavior among both groups over time. This study coincided with increased availability of ART in Zimbabwe. Possible emphasis on treatment at the expense of behavioral prevention may lead to viewing HIV as a chronic condition, so greater risk behavior.

985 WITHDRAWN

986 AGREEMENT OF SELF-REPORTED AND PHYSICALLY VERIFIED MALE CIRCUMCISION STATUS IN KENYA

Elijah Odoyo-June[1], Kawango Agot[2], Edward Mboya[2], Jonathan Grund[3], Paul K. Musingila[1], Donath Emusu[1], Leonard Soo[1], Boaz Otieno-Nyunya[1]
[1]US CDC, Nairobi, Kenya, [2]Impact Rsr and Development Org, Kisumu City, Kenya, [3]CDC, Atlanta, GA, USA
Background: Self-reported male circumcision (MC) status is frequently used to estimate MC prevalence, although its accuracy varies by setting. Nevertheless, self-reported MC status remains essential because it is the most feasible method of collecting MC status data in community surveys; and its accuracy is an important determinant of data reliability. We assessed the accuracy of self-reported MC status among adult men during a household survey in non-circumcising communities within Nyanza region of Kenya where MC for HIV prevention is being rolled out.
Methods: A total of 5,656 men aged 25-39 years from four counties were enrolled and a baseline questionnaire that captured information on self-reported MC status administered to 4,232 consenting men. Thereafter, a trained research assistant physically verified their MC status as fully circumcised (no foreskin), partially circumcised (foreskin is past coronal sulcus but covers less than half of the glans) or uncircumcised (foreskin covers half or more of the glans). The sensitivity and specificity of self-reported MC status were calculated using physically verified MC status as the gold standard. The data were pooled for analysis and did not account for the study design.
Results: Out of 4,232 men, 2,197 (51.9%) reported being circumcised of whom 99.0% (2,176/2,197) were confirmed as fully circumcised on physical examination. Among the 2,035 men who reported being uncircumcised, 93.7% (1,907/2,035) were confirmed uncircumcised by physical examination. Kappa agreement between self-reported and physically verified MC status was high, K= 0.9858 (95% CI, 0.981-0.991), p<0.001. The sensitivity of self-reported MC status was 99.59% and specificity was 98.97%, and did not differ significantly by age group; the sensitivity range was 99.3% - 99.6%, and the specificity range was 98.7 % - 99.6%. Similarly, the Kappa agreement was high for all age groups: range 0.9805 - 0.9917.
Conclusion: In this study population, the accuracy of self-reported MC status was high at 99.0%; therefore in this setting MC coverage estimates based on self-reported MC status are accurate and applicable for planning. We recommend similar studies to validate accuracy of self-reported MC status in other populations where MC is being rolled out.

987 VOLUNTARY MEDICAL MALE CIRCUMCISION FOR NONCOMMUNICABLE DISEASE CASE FINDING, NAMIBIA

Nikki Soboil[1], Shawn J. Rooinasie[2], Catherine Laube[3], Abubakari Mwinyi[1], Amir Shaker[2]
[1]Jhpiego, Swakopmund, Republic of Namibia, [2]Ministry of Hlth and Social Services, Erongo Regional Directorate, Swakopmund, Republic of, [3]Jhpiego, Baltimore, MD, USA
Background: The burden of non-communicable diseases (NCDs), including hypertension (HTN), is growing in sub-Saharan Africa (SSA), particularly in urban areas, with evidence of considerable under-diagnosis. An estimated 38% of urban Namibians are living with HTN. HTN is more prevalent in African males, and prevalence increases with age. A systematic review of HTN in SSA found less than 40% of people with HTN had been previously diagnosed. Males, whose health seeking is less common than females', are particularly likely to suffer from undiagnosed HTN and other NCDs in Namibia. Voluntary medical male circumcision (VMMC) is one of few health services catering to males, and thus a rare opportunity for HTN screening. Jhpiego launched high volume nurse-led voluntary medical male circumcision VMMC services at Swakopmund State Hospital in Erongo Region, Namibia in May 2016, and more than 90% of the clients served to date have been aged 20 years and above, in contrast to VMMC clients across East and Southern Africa to date, the majority of whom have been aged between 10 to 19 years.
Methods: Jhpiego abstracted data from client records for males registered for VMMC services between 13 May and 31 July 2016, including pre-operative physical screening data, to characterize the proportion of clients with blood pressure above 140/90 mm Hg. A random sample of 28 hypertensive clients were contacted post-hoc to determine whether they had been previously diagnosed.
Results: Of the 1,266 males screened for VMMC between 13 May and 31 July 2016, 367 (29%) were hypertensive. Of hypertensive clients, 136 (37%) were Stage 1 (140-159/90-99 mm Hg), 89 (24%) were Stage 2 (160-179/100-109 mm Hg), and 142 (39%) were isolated systolic (>140/<90 mm Hg). Of the random sample of 28 hypertensive clients contacted post-hoc, 15 (53%) were newly diagnosed.
Conclusion: VMMC can be a critical platform for HTN and other NCD screening, particularly in programs serving mature clients. VMMC programs seeking to attract a greater proportion of males aged 15-29 should prioritize careful pre-operative physical screening, as well as a systematic approach to deferrals and active referrals for clients diagnosed with HTN. Service delivery models integrated/co-located with primary care may help reduce loss to follow up for males newly diagnosed with HTN. Research is needed to better understand the full NCD disease burden in VMMC clients within and outside of Namibia.

988 BOTSWANA'S PROGRESS TOWARDS THE THIRD "90": VIRAL SUPPRESSION IN THE MASA PROGRAM

Madisa Mine[1], Julia Ngidi[1], Lesego Gabaititi[2], Joseph N. Jarvis[3], Modiri Tau[1], Ava Avalos[1], Tendani Gaolathe[4], Dinah Ramabyaa[5], Bornaparte Nkomo[5]
[1]Natl Hlth Lab, Gaborone, Botswana, [2]Univ of Botswana, Gaborone, Botswana, [3]CDC Botswana, Gaborone, Botswana, [4]Botswana Harvard AIDS Inst Partnership, Gaborone, Botswana, [5]Ministry of Hlth, Gaborone, Botswana
Background: Botswana launched the first African national HIV/AIDS treatment program known as "Masa" in 2002, with viral load monitoring as a part of the standard of care. To assess national progress towards the UNAIDS 90-90-90 targets cross-sectional programmatic data were used to determine national viral suppression rate among patients who had at least one viral load between in 2015.
Methods: Electronic records for patients who had at least one viral load at laboratories using the Integrated Patient Management System (IPMS) in Botswana during 2015 were extracted and anonymised. In the case of repeat samples the most recent result was used for analysis. Viral suppression was defined as value <400 copies/mL. Logistic regression models were used to explore association between age and viral suppression.
Results: Fifty-seven percent patients (n=159,535) on treatment had at least one viral load test; 64.7% were female, and the mean age was 40 ±13years. Of these, 98.3% had complete data and were included in the analysis. One point four percent (n=2,145) were pediatric patients (<10 years), 4.6% (n=7,270) were adolescent (10-19 years), 2.9% (n=4,584) young adults (19-24 years), 87.7% (n=137,573) adults (24-65 years) and 3.3% (n=5,296) seniors (>65 years). The overall rate of viral suppression was 96.4% (95% CI

96.3-96.5), with females having slightly higher viral suppression rates of 96.6% (95% CI 96.5-96.7) compared to 96.1%, (95% CI 95.9-96.3, P<0.001) in males. Young adults had the lowest rates of viral suppression (88.6%, 95% CI 87.7-89.5), followed by adolescent (90.6%, 95% CI 89.8-91.2), and pediatric patients (91.1%, 95% CI 89.8-92.3) (p<0.001). The senior age group had the highest rates of viral suppression of 98.1% (95% CI 97.7-98.4). Young adults were almost seven times less likely to be virologically suppressed compared to oldest age group (OR 0.15, 95% CI 0.12-0.19).
Conclusion: The Masa data show that a very high proportion of patients actively engaging in HIV care in Botswana achieve viral suppression levels These laboratory based data do not capture individuals defaulting care who are less likely to be virologically suppressed, thus may overestimate overall virological suppression rates in the treatment program. Among those in care, age-disaggregated data analysis showed lower rates of virological suppression among young adults, adolescents and pediatric patients. To fully achieve 90-90-90 targets treatment programs must pay particular attention to the needs of young adults and adolescents.

989 POPULATION-LEVEL VIRAL-LOAD MONITORING TO MEASURE PROGRESS TOWARDS THE "THIRD 90"

Maia Lesosky[1], Nei-Yuan M. Hsiao[1], Wolfgang Preiser[2], Jean Maritz[3], Landon Myer[1]
[1]Univ of Cape Town, Cape Town, South Africa, [2]Stellenbosch Univ, Cape Town, South Africa, [3]NHLS, Cape Town, South Africa
Background: Global targets for antiretroviral therapy (ART) programmes call for 90% of those on ART to achieve sustained viral suppression (VS) by the year 2020, but there are few programmatic data from viral load (VL) monitoring in sub-Saharan Africa to help measure progress towards this goal.
Methods: Using routine laboratory data from the South African National Health Laboratory Service, we examined results of VL monitoring conducted in all adult patients on ART in the public health care system of the Western Cape province from 2009-2015. In this setting there have been major efforts to decentralise ART services during this period. Routine VL monitoring is conducted 6m and 12m after ART initiation and annually thereafter; repeated VL testing is done for those with suspected virologic failure. In this analysis we defined VS as any VL <1000 copies/mL and analysed the proportion of VS test results by patient age, calendar period (month/quarter) and health facility.
Results: Data include 964,184 VLs from 217 facilities; the average number of VL tests/month increased from 7,291 in 2009 to 17,841 in 2015. The overall proportion of VS results <1000 copies/mL remained consistent between 80-86% during the period, with an increasing trend of 1% per year (p<0.001). There was marked heterogeneity in the proportion of VS tests between facilities (Figure 1a), with larger sites having higher proportions of VS tests (p<0.001): while only 12% of all facilities had an average of >90% VS during 2015, these facilities contributed 23% of all VL tests done in the period. Across the period, younger patients were less likely to have VS (Figure 1b) but formed a minority of the patient population: for example 16-24 year-olds were 8-10% less likely to have VS at any time point, but comprised only 6-8% of all VL tests performed in the period.
Conclusion: In this setting, achieving the 'third 90' remains an ongoing challenge despite significant progress in increasing ART access, and reaching this target will likely require increasingly targeted interventions. At a facility level, the heterogeneity in VS rates points to the need for targeted strengthening of services at specific facilities. At a patient level, young people clearly remain a key population for adherence support. More generally these data demonstrate the value of VL monitoring systems to gauge progress and focusing efforts to achieve global treatment targets.

990 CONTEMPORARY DISENGAGEMENT FROM ANTIRETROVIRAL THERAPY IN KHAYELITSHA, SOUTH AFRICA

Samantha Kaplan[1], Christa Oosthuizen[2], Kathryn Stinson[2], Francesca Little[2], Jonathan Euvrard[2], Meg Osler[2], Katherine Hilderbrand[2], Andrew Boulle[2], Graeme Meintjes[2]
[1]Yale Univ Sch of Med, New Haven, CT, USA, [2]Univ of Cape Town, Cape Town, South Africa
Background: Retention in care is an essential component of meeting the UNAIDS "90-90-90" targets. In Khayelitsha township (population ~500,000) in Cape Town, South Africa, >50,000 patients have received ART since the inception of this public sector program in 2001. Disengagement from care remains an important challenge. We sought to determine incidence of and risk factors associated with disengagement from care in 2013-4, and outcomes for those who disengaged.
Methods: We conducted a retrospective cohort study of all patients >=10 years who visited one of the 13 Khayelitsha ART clinics in 2013-14 regardless of the date they initiated ART. We described the cumulative incidence of first disengagement (>180 days) in the study window by time on ART and time in the study, as well as risk factors for disengagement based on a Cox proportional hazards model. We ascertained outcomes after disengagement using province-wide health databases and the National Death Registry.
Results: Of 39,895 patients meeting our eligibility criteria, the median time on ART to 31 Dec 2014 was 33.6 months (IQR 12.4-63.2). Of the total study cohort, 595 (1.5%) died in the study period, 1,231 (3.1%) formally transferred out, 984 (2.5%) were "silent transfers" and visited another provincial clinic within 180 days, 9008 (22.6%) disengaged, and 28,077 (70.4%) remained "in care." Cumulative incidence of disengagement from care was 25.1% by two years in the study and 37.7% by ten years on ART estimated from time contributed in the study window. Key factors associated with disengagement were younger age, male sex, pregnancy at ART start, and lower last CD4 count; protective factors were ART club membership and lower baseline CD4 (Table 1). Of those who disengaged (excluding silent transfers), the two most common outcomes by 30 June 2015 were return to ART care after six months (33.0%), and being alive but not in care in the Western Cape (25.0%). After disengagement, a total of 1464 (16.3%) were hospitalized and 238 (2.6%) died.
Conclusion: One quarter of patients in Khayelitsha disengaged from ART care at least once in a contemporary two-year period. Although the majority either subsequently returned to care or remained alive without hospitalization, a challenge to meeting the 90-90-90 targets is finding service adaptations to accommodate mobile populations and retain them in long-term care. This should be guided by risk factors for disengagement as observed in this study.

Variable / Description		Hazard Ratio	95% CI
Age (years)	*10 - 20*	1.39	(1.23; 1.54)
	20 - 30	1.44	(1.37; 1.52)
	30 - 40	ref	ref
	40 - 50	0.9	(0.85; 0.96)
Sex/ pregnancy	*Nonpregnant women*	ref	ref
	Pregnant women	1.57	(1.47; 1.68)
	Men	1.14	(1.09; 1.20)
Baseline CD4 count (cells/mm^3)	*>350*	ref	ref
	200-350	0.62	(0.57; 0.67)
	50-200	0.53	(0.49; 0.57)
	<50	0.49	(0.44; 0.55)

Variable / Description		Hazard Ratio	95% CI
Most recent CD4 count (cells/mm^3)	*>350*	ref	ref
	200-350	1.89	(1.79; 2.01)
	50-200	2.63	(2.45; 2.82)
	<50	2.65	(2.33; 3.01)
Most recent NRTI drug 1	*Other/missing*	ref	ref
	Stavudine (d4T)	1.69	(1.54; 1.84)
Provincial clinic (vs. City)		1.15	(1.09; 1.20)
Previous gap in care of >180 days, prior to study entry		1.61	(1.51; 1.72)
Viral load undetectable ever during ART		0.52	(0.48; 0.57)
ART club membership ever during ART		0.27	(0.24; 0.30)

991 SELF-REPORTED AND BIOMARKER HIV TREATMENT CASCADES FOR OLDER SOUTH AFRICAN ADULTS

Julia K. Rohr[1], Jennifer Manne-Goehler[2], Xavier Gomez-Olive[3], Joshua A. Salomon[4], Pascal Geldsetzer[5], Ryan Wagner[6], Molly Rosenberg[7], Chodziwadziwa Kabudula[4], Kathleen Kahn[4], Till Baernighausen[7]

[1]Harvard Univ, Cambridge, MA, USA, [2]Beth Israel Deaconess Med Cntr, Boston, MA, USA, [3]Tintswalo Hosp, Acornhoek, South Africa, [4]Univ of the Witwatersrand, Acornhoek, South Africa, [5]Indiana Univ, Bloomington, IN, USA, [6]Univ of the Witwatersrand, Johannesburg, South Africa, [7]Heidelberg Univ, Heidelberg, Germany

Background: HIV treatment cascades are important for highlighting gaps in care, yet data sources for constructing cascades vary, and often include self-reported information or are based from clinical cohorts. We compare treatment cascades from biomarker data and self-report in a population-based cohort of older South African adults, who constitute a growing segment of the HIV+ population in South Africa.

Methods: Data came from the Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI) 2015 baseline survey, which includes 5,059 adults aged 40+ years, sampled from the Agincourt Health and Demographic Surveillance System. At-home interviews asked about HIV testing, knowledge of status, linkage to care, and antiretroviral therapy (ART). Dried bloodspots (DBS) were screened for HIV, ART, and viral load. We calculated proportions and 95% confidence intervals for each stage of the treatment cascade, conditional on completion of the previous stage, using (1) self-reported responses (2) biomarker data and (3) combined self-report or biomarker evidence, where screening positive for ART was considered positive for earlier stages. Cascades were framed within the UNAIDS 90-90-90 target. We explored variations in the cascade through stratification by age, sex and wealth.

Results: There were 4,560 participants with valid DBS results. 1,048 (23%) screened positive for HIV and formed the denominator for the cascades. The biomarker cascade showed that 63% (95% CI: 60-66) were on ART and 46% (95% CI: 43-49) were virally suppressed, which is significantly lower than the UNAIDS target (Figure 1). Self-report under-estimated testing, diagnosis, and ART (only 47% [95% CI: 44-50] reported ART use). The combined cascade indicated high HIV testing (89% [95% CI: 87-91]), but lower awareness of being HIV+ (71% [95% CI: 68-74]), and while nearly all who identified themselves as HIV+ were linked to care, only 72% (95% CI: 68-75) of individuals on ART had viral suppression. Cascades were similar by age and sex, but the lowest wealth quintile had a lower cascade compared to the highest quintile (leading to 43% (95% CI: 37-49) vs. 49% (95% CI: 41-57) virally suppressed).

Conclusion: Combining self-reported information with biomarker data reveals the limitations of self-report for HIV cascade construction, and improves cascade depth and accuracy. We find that major gaps in care for older South Africans with HIV persist, in particular at the HIV diagnosis and viral suppression stages.

992 MISDIAGNOSED HIV INFECTION IN PREGNANT WOMEN INITIATING UNIVERSAL ART IN SOUTH AFRICA

Allison Zerbe[1], Nei-yuan Hsiao[2], Tamsin Phillips[3], Kirsty Brittain[3], Elaine J. Abrams[1], Landon Myer[3], for the Maternal Child Health - Antiretroviral Therapy (MCH-ART) Study

[1]ICAP at Columbia Univ, New York, NY, USA, [2]Div of Med Virology, Cape Town, South Africa, [3]Univ of Cape Town, Cape Town, South Africa

Background: Rapid diagnostic tests (RDTs) are used globally to diagnose HIV infection, but with universal ART eligibility there is concern that false positive (FP) RDTs could result in misdiagnosis of HIV infection and inappropriate ART initiation. The use of confirmatory viral load testing before ART initiation (pre-ART VL) is suggested to identify FP RDT results but there are few insights into the potential consequences of universal pre-ART VL testing.

Methods: The study took place in a public sector primary care facility in Cape Town, South Africa, where HIV diagnosis employs two RDTs following WHO algorithms. As part of a larger study of ART in pregnancy, we conducted pre-ART VL testing (Abbott RealTime HIV-1) in consecutive HIV+ pregnant women making their 1st antenatal clinic (ANC) visit who were not on ART or ARV prophylaxis according to interview and antenatal record review. We describe the final HIV status of women based on pre-ART VL testing and other investigations, including the proportion of women found to be erroneously started on ART due to FP RDT results, and estimate the costs to identify one erroneous ART initiation using pre-ART VL testing.

Results: In 952 pregnant women diagnosed HIV+ based on RDT algorithms and reporting no current ART use, the median CD4 cell count was 352 cells/mm3 (IQR, 236-509). In pre-ART VL testing, 37 women (4%) were aviraemic with no detectable VL and were investigated further as suspected FP from RDTs. Of these, 22% (8/37) were subsequently confirmed to be on ART from medical records and 13% (5/37) had detectable virus on subsequent VL measurements; the remaining 24 underwent additional testing using ELISA. In the ELISAs conducted, 2 women were found to be HIV-negative, representing 5% of all aviraemic women (2/37) and 0.2% (2/952) of all women identified as HIV-infected by the public sector health services using RDT. Based on this we estimate that approximately $9520 USD (uncertainty interval, $7140-$11,900) would be spent on confirmatory pre-ART VL testing, with further ELISA for aviraemic women, to identify 1 patient erroneously initiated on ART. By contrast, immediate use of an ELISA alone as a confirmatory test would cost $1666 ($1428-$1904) to identify one patient erroneously initiated on ART.

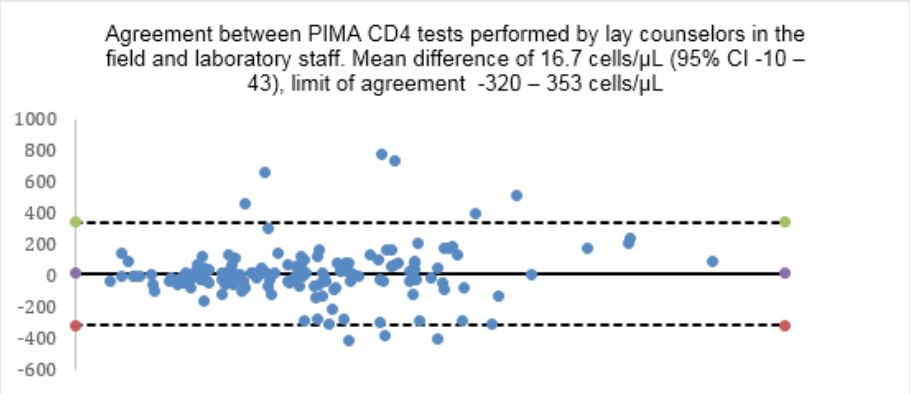
Conclusion: False-positive RDT may lead to patients erroneously initiated on ART, but routine pre-ART VL testing appears inefficient compared to ELISA only as an approach to confirm infection before ART initiation.

993 ACCURACY OF HIV AND CD4 FIELD TESTING IN THE BOTSWANA COMBINATION PREVENTION PROJECT

Ebi Bile[1], **Pamela J. Bachanas**[2], Fiona Maurice[1], Sylvia Modise[1], Liziwe Chebani[3], Vongai Makovore[1], Peter Fonjungo[2], Mary Grace Alwano[1], William Bapati[4], Joseph N. Jarvis[1]
[1]US CDC Botswana, Gaborone, Botswana, [2]CDC, Atlanta, GA, USA, [3]Botswana Ministry of Hlth, Gaborone, Botswana, [4]Tebelopele Voluntary Counseling and Testing Cntr, Gaborone, Botswana

Background: Ensuring correct HIV test results are given to participants is critical for both large field-based prevention trials and national HIV-testing programs. During the Botswana Combination Prevention Project (BCPP), a cluster randomized trial designed to evaluate the impact of a combination prevention package on population level HIV incidence in Botswana, robust quality assurance (QA) measures have been implemented to ensure lay counselors deliver accurate test results in the field.
Methods: BCPP conducted home-based and mobile HIV testing campaigns in 15 intervention communities from October 2013-February 2016. Lay counselors (130) were trained to conduct rapid HIV testing and point of care PIMA CD4 testing with annual refresher training, weekly internal Quality Control (QC) panel testing, and proficiency testing (PT) 3 times/year. In the first community, 100% of field samples were retested in the reference laboratory using EIA HIV testing. In subsequent communities a random sample of 5-10% of samples were retested. Laboratory based PIMA CD4 counts were repeated on samples from 155 field PIMA CD4 counts. Monthly supervision and monitoring visits were conducted.
Results: Weekly QC panels conducted on 1000 positive and 975 negative HIV tests in the field using Determine and First Response assays produced 100% accurate results. Overall, 89% of counselors achieved a pass on PT increasing from 78% at baseline to 96% and 97% in the final two rounds. Repeat EIA testing of 3002 DBS samples demonstrated a 99.6% agreement between field and laboratory HIV-test results, with a kappa score of 0.99, $p < 0.0001$. Of the 12 discordant results, 4 were false negative and 8 were false positive in field-testing. The overall pass rate for PIMA CD4 PT was 89% (81%, 93%, 95%, and 88% rounds 1-4). Levels of agreement between field and lab PIMA CD4 results are shown in figure 1, with a mean difference of 16.7 cells/μL (95% CI -10 – 43). At the CD4 threshold of 350 there was 86% agreement (21 of 155 misclassified).
Conclusion: With a strong training, monitoring, and QA program, BCPP lay counselors conducted HIV-testing in field settings accurately and to a high standard. This indicates that lay counselors can competently and correctly implement HIV testing at scale in field settings, and gives very high confidence in BCPP HIV-test results. Concordance between PIMA CD4 field results and lab results were within expected ranges.

Figure



994 PATIENTS' OUT-OF-POCKET EXPENDITURES FOR ART IN SWAZILAND

Maria Vaikath[1], **Shaukat Khan**[2], Emma Mafara[2], Ndumiso Dlamini[2], Phiwayinkhosi Dlamini[2], Nothando Ndzinisa[2], Njabulo Simelane[2], Velephi Okello[3], Till Baernighausen[4], Pascal Geldsetzer[1]
[1]Harvard Univ, Boston, MA, [2]Clinton Hlth Access Initiative, Mbabane, Swaziland, [3]Swaziland Ministry of Hlth, Mbabane, Swaziland, [4]Heidelberg Univ, Heidelberg, Germany

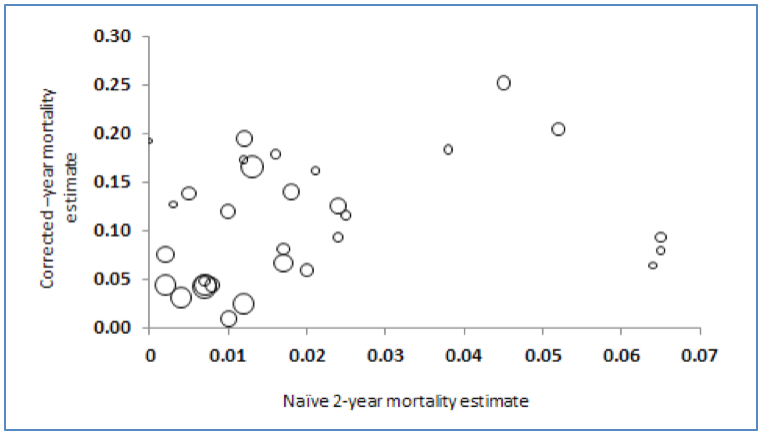
Background: There is limited evidence on patient expenditures for antiretroviral therapy (ART) in the public-sector health systems in sub-Saharan Africa. This knowledge gap is becoming increasingly problematic as countries expand ART treatment eligibility, dramatically increasing the number of people eligible for ART. Carried out as part of the Early Access to ART for All (EAAA) health systems trial in Swaziland, this study aims to determine patients' out-of-pocket expenditures for attending ART care in Swaziland.
Methods: The study took place at 14 healthcare facilities, including high- and low-volume facilities and one regional hospital, in the Hhohho region of Swaziland from July 2014 to August 2016. We administered questionnaires in patient exit interviews on randomly selected clinic-days, eliciting data on costs for transport, food, consultation fees, medicines, child care, and phone calls, as well as on lost income due to time away from work. Costs in the local currency were converted to US dollars using the average exchange rate for the data collection period. Standard errors were clustered at the level of the healthcare facility.
Results: The questionnaire was administered to a total of 742 patients. 25% (95% CI: 18–32%) of patients reported not having incurred any expenditure on the day of the interview. The average total out-of-pocket expenditure for an ART visit was $2.2 (95% CI: $1.5–2.8) across all interviewed patients, and $2.8 (95% CI: $2.1–3.5) for those who reported any expenditure. 11% (95% CI: 8–13%) of patients indicated that they lost income as a result of the time required to attend today's ART visit-mean income loss was $34 (95% CI: $18–87). On average across all respondents, 56% of costs were incurred from lost earnings to attend the visit, 36% on transport to the clinic, 3% on food during travel, 2% on consultation fees, 2% on medicines, 1% on child care, and 1% on phone calls.
Conclusion: Even though antiretroviral drugs are provided free-of-charge at the point-of-care in Swaziland's public-sector health system, patients still incur large costs to attend ART care. Because travel and lost income are the largest financial burdens on ART patients, alternative delivery models that do not require travel and time-consuming clinic visits should be considered for future transformations of the HIV treatment response, e.g., differentiated ART with a community-based pathway for stable patients.

995 MARKED MORTALITY AND RETENTION UNDER-REPORTING IN A LARGE HIV PROGRAM IN ZAMBIA

Charles Holmes[1], Izukanji Sikazwe[1], Ingrid Eshun-Wilson[2], Nancy Czaicki[3], Kombatende Sikombe[1], Sandra Simbeza[1], Carolyn Bolton Moore[4], Cardinal Hantuba[1], Nancy Padian[3], Elvin Geng[5]
[1]Cntr for Infectious Disease Rsr in Zambia, Lusaka, Zambia, [2]Stellenbosch Univ, Cape Town, South Africa, [3]Univ of California Berkeley, Berkeley, USA, [4]Univ of Alabama at Birmingham in Lusaka, Zambia, [5]Univ of California San Francisco, San Francisco, CA, USA

Background: Mortality and retention after entry into HIV care are crucial metrics of effectiveness of services in a region. However, under routine program conditions, deaths are underreported and overall estimates of mortality and retention and site-to-site variability in these outcomes may be biased. As a result, these vital metrics of performance cannot be reliably used for program improvement practices.

Methods: We undertook a multi-stage sampling approach in which we selected a probability sample of facilities from a network of 70 facilities offering HIV care and treatment in Zambia, and then selected a simple random sample of lost patients within each facility for intensive vital status ascertainment. Deaths and in-care patients identified by tracing lost patients were used to revise overall outcome estimates through probability weights.
Results: Among a cohort of 54,172 patients newly starting ART in 30 facilities (63% women, median age 35 years at enrollment (IQR: 29-42) and median ART initiation CD4 level of 266 cells/mm3 (IQR: 141-395)), 11,152 were lost to follow up over two years (20%). The median clinic-level loss to follow up was 26% (IQR: 22%-28%, range 20% to 40%). Among a random sample of 18% of all lost patients, 75% of outcomes were ascertained. Median clinic mortality among the lost across the 30 sites was 12% (IQR 8% to 17%, range 4% to 27%). Once outcomes among the lost were incorporated into overall estimates of mortality in the entire cohort, mortality at two years from ART rose from 2% (95% CI: 2% to 2%) to 9% (95% CI: 8% to 10%). Median site level mortality across the 30 sites was 9% (IQR: 5% to 15%, range 3% to 19%). The median ratio difference was 6% fold with IQR of 4-fold to 12-fold (Figure). Estimated retention across all sites was 61% at one year and 42% at two years, which rose to 86% and 78% upon incorporation of outcomes ascertained by tracing.
Conclusion: Routine program monitoring underestimated both mortality and retention outcomes, thus threatening to undermine assessments of public health effectiveness. A sampling based approach revealed that both the extent of underestimation and the actual revised mortality estimates differed markedly across facilities. Improved assessments of mortality and retention by facility can inform where to target efforts for improved outcomes.



996 DIFFERENTIAL UPTAKE OF HIV CARE AND TREATMENT BY SEXUAL RISK BEHAVIORS

Veena G. Billioux[1], Larry W. Chang[1], Kate Grabowski[1], Steven Reynolds[2], Gertrude Nakigozi[3], Joseph Ssekasanvu[1], Robert Ssekubugu[3], Ronald H. Gray[1], Maria Wawer[1], for the Rakai Health Sciences Program
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]NIAID, Washington, DC, USA, [3]Rakai Hlth Scis Prog, Kalisizo, Uganda
Background: The success of treatment as prevention is dependent upon uptake of HIV care and antiretroviral therapy (ART). HIV-positive individuals who are not on ART are a potential source of HIV transmission. The sexual behaviors of persons who are not engaged in HIV care and treatment are poorly understood. We use empirical survey data to explore the association of risky sexual behaviors with uptake of HIV care and ART in Rakai, Uganda.
Methods: 3,666 HIV-infected participants in the population-based Rakai Community Cohort Study (RCCS), surveyed between September 2013 and December 2015, provided self-reported information on engagement in care, ART use, and sexual behaviors. Engagement in care and treatment initiation was assessed using self-reports and clinical records. Prevalence risk ratios (PRR) of sexual behaviors and enrollment in care and ART initiation were estimated as using modified Poisson regression. Sex, age and community type (fishing, trading, and agrarian) were identified as potential confounders and were included in the multivariable models.
Results: We found modest but significant differences in engagement in HIV care and ART uptake by sexual risk behaviors. ART initiation was lower in persons reporting 3+ sexual partners (adjPRR 0.84, 95% CI 0.71–0.98) and among women aged 15-29 with 2 sexual partners (PRR 0.74, 95% CI 0.57–0.95). ART initiation was also lower in persons with non-marital sexual partners (adjPRR 0.90, 95% CI 0.82–0.98); particularly among men aged 15-29 (PRR 0.62, 95% CI 0.44–0.89). Persons with sexual partners outside the community were less likely to be enrolled in care (adjPRR 0.90, 95% CI 0.82–0.98) or to be on ART (adjPRR 0.87, 95% CI 0.78–0.96). ART initiation was lower in persons who used alcohol before sex (adjPRR 0.91, 95%CI 0.83-0.99).
Conclusion: In this population-based cohort, there was evidence of lower rates of adoption of HIV care and ART among persons reporting higher sexual risk behaviors. These factors likely reduce the population-level effectiveness of treatment as prevention programs. Tailored strategies are needed to engage HIV-positive persons at highest risk for onward transmission in HIV care.

997 HIV TESTING, LINKAGE TO CARE, AND VIRAL SUPPRESSION AMONG GAY MEN IN NIGERIA

Habib R. Omari[1], Uchenna Ononaku[2], Rebecca G. Nowak[1], Ifeanyi Orazulike[3], Trevor Crowell[4], Nicaise Ndembi[2], Hongjie Liu[5], Stefan Baral[6], Man Charurat[1]
[1]Univ of Maryland, Baltimore, MD, USA, [2]Inst of Human Virology Nigeria, Abuja, Nigeria, [3]Intl Cntr on Advocacy and Rights to Hlth, Abuja, Nigeria, [4]US Military HIV Rsr Prog, Bethesda, MD, USA, [5]Univ of Maryland Coll Park, Coll Park, MD, USA, [6]The Johns Hopkins Univ, Baltimore, MD, USA
Background: The UNAIDS 90-90-90 targets challenge healthcare systems to diagnose people living with HIV (PLHIV), link them to care, and support them to achieve viral suppression. In particular for key populations such as men who have sex with men (MSM), characterizing individual, network, and structural barriers to care is essential in order to inform interventions to achieve these goals. We characterize the HIV treatment cascade within the context of "test-and-treat" among MSM in Nigeria.
Methods: From March 2013-June 2016, TRUST/RV368 study used respondent-driven-sampling to recruit MSM into a "one-stop" clinic. Participants completed a structured survey and HIV testing. Those initiated antiretroviral therapy (ART) were considered linked into care and underwent HIV RNA testing every three months (Abuja) or six months (Lagos). Those with HIV RNA <1000 copies/ml at the latest follow-up visit were considered virally suppressed. Multivariate logistic regression models were used to calculate adjusted odds ratios (aOR) for factors associated with HIV testing, linking in care, and viral suppression.
Results: A total of 1604 MSM were recruited and 628 (39.1%) PLHIV were included in these analyses of treatment cascade (Figure 1). Higher education was associated with increased HIV testing while having no place to socialize was associated with decreased HIV testing. Factors associated with increased odds of being linked in care included education, senior secondary school vs < senior secondary school (aOR 2.4, 95%CI: 1.0–5.5), participation in HIV prevention meetings (aOR 1.9, 95% CI: 1.2–3.0), having an older partner 20-29 vs ≤19 years (aOR 2.6, 95%CI: 1.6–4.2), and having HIV-infected partners (aOR 1.9, 95%CI: 1.3–2.9). Ever being blackmailed (aOR 0.6, 95%CI: 0.3–1.0) and those

recruited at later waves (aOR 0.4, 95%CI: 0.3–0.6) were less likely to be linked in care. Viral suppression at six months was associated with having a partner with higher education senior secondary school (aOR 1.9, 95% CI: 1.0–3.6) and increased education (aOR 2.2, 95% CI: 1.2–4.1).
Conclusion: Social determinants of health potentiated engagement in HIV care whereas structural determinants including blackmail mitigated this engagement for MSM in Nigeria. Given the high HIV prevalence and incidence among these men, comprehensive programs and policies combined with implementation research to study optimal implementation is needed to support effective linkage and sustained retention in the HIV treatment cascade.

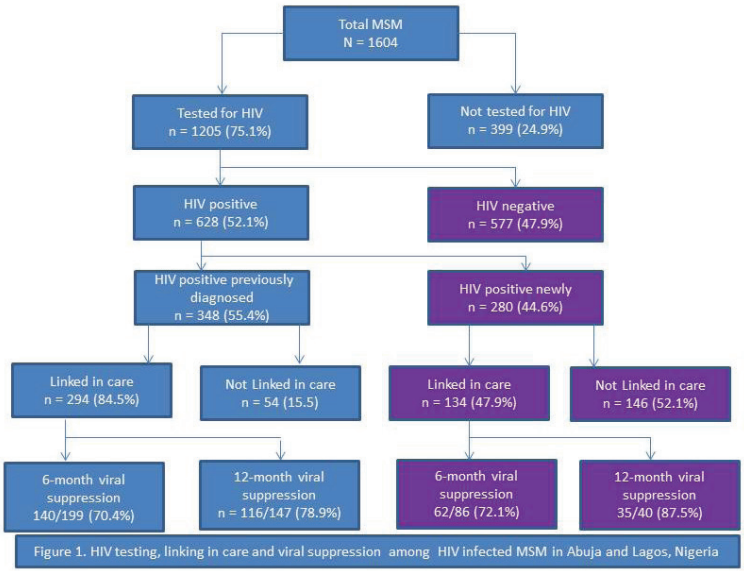


Figure 1. HIV testing, linking in care and viral suppression among HIV infected MSM in Abuja and Lagos, Nigeria

998 ART INITIATION AND RETENTION IN AFTER-HOUR VERSUS DAILY MALE HEALTH CLINICS

Tali Cassidy[1], Amir Shroufi[1], Sarah Jane Steele[1], Morna Cornell[2], Virginia de Azevedo[3], David Binza[4], **Rodd Gerstenhaber**[1]
[1]Médecins Sans Frontières, Cape Town, South Africa, [2]Univ of Cape Town, Cape Town, South Africa, [3]City of Cape Town Dept of Hlth, Cape Town, South Africa, [4]Western Cape Provincial Dept of Hlth, Cape Town, South Africa

Background: In large African antiretroviral therapy (ART) programs, disproportionately fewer men initiate ART, and at more advanced age and disease stage than women. Identifying and overcoming gender-specific barriers, at the individual and service delivery level, are critical to improving HIV/STI services for men. Previous research in Khayelitsha, a large, high HIV-prevalence township near Cape Town, found that despite increased male access to HIV counseling and testing (HCT), the proportion of men accessing treatment did not increase. MSF, the City of Cape Town and the Western Cape Provincial Department of Health, piloted two male services in Site B, Khayelitsha: Site B Male Clinic (SBMC) and a male after-hours clinic (MAC). Both facilities have all-male staff and offer HIV/STI services, including testing and treatment. SBMC is open daily 8:00-16:00 and MAC is open on Wednesdays 16:00-19:30. We compare the characteristics and outcomes of these two clinics.
Methods: Those on ART who initiated at another clinic are referred to as transfers-in (TFI) while known HIV-positives tested positive at another service before presenting. Summary statistics of patient characteristics and outcomes are presented, contrasting the two clinics where relevant.
Results: Between June 2014 and June 2016, 14193 visits took place; median: 588/month (IQR: 509-659). Most (88%) of these visits took place at SBMC. Compared to MAC, patients at SBMC were more likely to seek STI treatment(45% vs 21%). Over half of the HCT occurred at an STI-related visit and HCT yielded a 6.2% positivity rate. The median CD4 counts were 376 (IQR:260-505) cells/μL at testing. Of those found eligible for ART, 91% (42/46) ever initiated at MAC compared to 69% at SBMC (203/295). Compared with SBMC, a far higher proportion of MAC patients presented as known HIV-positive or TFIs (64% vs 14%). TFIs at MAC were on ART longer (median:3.3yrs[IQR:2.1-5.2] vs 1.9yrs[IQR:1-2.4] at SBMC) with similar retention in care 6 months after TFI(86%). Among new initiates 6-month retention in care was 95%(35/37) at MAC and 88%(140/159) at SBMC.
Conclusion: STI care is an excellent opportunity to link men to HIV services. While SBMC had more patients, MAC attracted a different patient population, and had higher initiation and retention rates. Given these contrasting successes, further research should investigate whether aspects of both services could be rolled out to attract more men to HIV services.

999 THE IMPACT OF CARE NAVIGATORS ON ENGAGEMENT IN HIV CARE IN WESTERN KENYA

Becky L. Genberg[1], Violet Naanyu[2], Alfred Keter[3], Anthony Ngeresa[3], Juddy Wachira[2], Joseph Hogan[4], Paula Braitstein[4]
[1]Brown Univ, Providence, RI, USA, [2]Moi Univ, Eldoret, Kenya, [3]Academic Model Providing Access to Hlthcare, Eldoret, Kenya, [4]Univ of Toronto, Toronto, Canada

Background: Retention in HIV care remains challenging in resource-limited settings. Peer interventions are a strategy for addressing contextual barriers, such as stigma and inefficient care delivery. The objective of this study was to determine the impact of peer care navigators (CN) on engagement in care among patients enrolling in the AMPATH (Academic Model Providing Access to Healthcare) HIV care program in western Kenya.
Methods: CNs were outreach or support staff living with HIV with excellent adherence. CNs received new patients and provided counseling and information. All patients newly accessing HIV care from September 2013 to June 2014 at two AMPATH facilities with CNs were eligible for inclusion. 1118 patients who received CN services and completed an initial encounter were matched on age, sex, facility, and date of enrollment (+/- 6 months) with up to 3 controls that did not use CNs. Differences in demographics by case status were examined with Chi-squared and Wilcoxon rank sum tests. Adjusted logistic regression models were used to examine the impact of CNs on further engagement in HIV care, controlling for potential confounders. Outcomes included: follow-up visit (>14 days from enrollment), CD4 testing (<45 days from enrollment), as well as ART initiation, lost-to-follow-up (LTFU), or death within 12 months of enrollment.
Results: Of 1025 cases and 2954 controls, 64% were female, with a median age of 32 years. There were no statistically significant ($p>0.05$) differences by case in sex, age, education, or travel time to clinic. Cases were less likely to have electricity ($p=0.001$) or piped water ($p=0.01$). Overall 85% had a follow-up visit and 26% had a CD4 test. At 12 months, 65% were on ART, 33% became LTFU, and 5% died. Cases were as likely as controls to have had a follow-up visit (adjusted odds ratio (AOR)=1.14, 95% confidence interval (CI): 0.91-1.43), initiated ART (AOR=0.99, 95% CI: 0.83-1.18), become LTFU (AOR=0.96, 95% CI: 0.81-1.13), or died (AOR=1.30, 95% CI: 0.94-1.79). Cases were less likely than controls to have had a CD4 test (AOR =0.61, 95% CI: 0.51, 0.74).

Conclusion: This study provided no evidence that CNs led to improved engagement in HIV care. Facility-based peers may not have an impact on further engagement in care following linkage. Since this analysis was restricted to patients already linked to care, the impact of peers on linkage to care is unknown. Additional research is needed to identify interventions to improve engagement in HIV care following linkage.

1000 IMPROVED RETENTION WITH LONGER FOLLOW-UP INTERVALS FOR STABLE PATIENTS IN ZAMBIA

Aaloke Mody[1], Nancy Padian[2], Nancy Czaicki[1], Monika Roy[1], Carolyn Bolton Moore[3], Charles Holmes[4], Elvin Geng[1], Izukanji Sikazwe[5]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Univ of California Berkeley, Berkeley, CA, USA, [3]Univ of Alabama at Birmingham–CIDRZ, Lusaka, Zambia, [4]The Johns Hopkins Univ–CIDRZ, Bethesda, MD, USA, [5]Cntr for Infectious Disease Rsr in Zambia, Lusaka, Zambia

Background: Extending appointment intervals for stable HIV-infected patients in sub-Saharan Africa can reduce opportunity costs to patients and decongest overcrowded facilities, but has not been prioritized as a strategy, with shorter intervals still being more common, in part due to concerns of waning engagement with longer absences.
Methods: As part of the Better Info study, we analyzed a cohort of stable HIV-infected adults (on treatment >6m, CD4 >200 cells/µl) who presented for a routine clinical visit from January 1, 2013 to July 31, 2015 in Zambia. We used missed visits (>14d late to next visit), gaps in medication (>14d late to next pharmacy refill), and loss to follow-up (LTFU, >90d late to next visit) as indicators of retention. We utilized multilevel logistic regression adjusting for patient characteristics-including an individual's prior retention history-to assess the association between scheduled appointment intervals and subsequent lapses in retention.
Results: 127,448 patients (66% female, median age 39y [IQR 33-46], median CD4 444 cells/µl [IQR 325-595]) made 857,900 routine visits to 71 sites. Most visit intervals were 30d (25-45d, 43%), followed by 60d (46-75d, 21%), and 90d (76-105d, 33%); 3.3% were <25d and 0.9% were >105d. Patients given longer follow-up (>76d) were slightly more on time to current visit and had a history of slightly fewer missed visits and slightly higher medication possession ratio, but were of similar age and gender makeup. Longer visit intervals were associated with improved probability of making the next visit on time (Figure). After adjustment and as compared to patients scheduled for 30d follow-up, patients with longer appointment intervals were less likely to have subsequent lapses: 60d follow-up (late aOR 0.82, p<0.001; medication gap aOR 0.91, p<0.001; LTFU aOR 0.96, p<0.03), 90d follow-up (late aOR 0.56, medication gap aOR 0.69, LTFU aOR 0.94; p<0.001 for all), and >106d follow-up (late aOR 0.37, medication gap aOR 0.59, LTFU aOR 0.71; p<0.001 for all). Patients with very short follow-up (<25d) were more likely to have retention lapses (late aOR 1.89, medication gap aOR 1.56, LTFU aOR 1.29; p<0.001 for all).
Conclusion: Longer visit intervals are associated with decreased lateness, gaps in medication, and LTFU in stable HIV-infected patients even when adjusting for prior retention history. Extending visit intervals to 3 months, and potentially up to 6 months, may represent a promising strategy to reduce patient burden of care and decongest clinics.

1001 EXPERIENCES WITH RETENTION IN CARE AND VIRAL SUPPRESION IN A PHARMACY REFILL PROGRAM

Arvind Kaimal[1], Barbara Castelnuovo[1], Martha Atwiine[1], Rachel Musomba[1], Maria S. Nabaggala[1], Rosalind P. Ratanshi[2], Mohammed Lamorde[1]
[1]Makerere Univ, Kampala, Uganda, [2]Univ of Cambridge, Cambridge, UK

Background: Following implementation of routine annual HIV-1 RNA monitoring at the Infectious Diseases Institute HIV clinic (Kampala, Uganda), a Pharmacy Refill plus Program (PRP) was introduced to reduce patient visit loads on doctors and nurses by incorporating pharmacy-only visits in patient monitoring algorithms. The PRP patients would have only 4 visits in a year(every 3 months) alternating a doctor visit and a pharmacy-only visit to pick up their drugs as opposed to standard of care where a doctor or nurse would be seen every 2 months. The PRP schema comprised: doctor visit (enrollment), pharmacy-only visit (month 3), doctor and adherence counseling visit (month 6), pharmacy-only visit (month 9), doctor visit (month 12). Patients were included into the PRP if they were stable on first-line antiretroviral therapy for at least 24 months, and had no opportunistic infections or non-communicable diseases. Pregnant women were excluded.
Methods: Between 10Aug15 and 23Sep16, 708 patients were screened of which 624 patients met program criteria. A cross sectional analysis was conducted including 288 patients who had at a minimum completed the month 3 visit. Data was extracted from the IDI electronic medical record (Integrated Clinic Enterprise Application) database and clinical records of patients that dropped out of the PRP were examined in detail by one reviewer. Median duration of time for patients to be dropped off the program for any reason and the proportion of patients with HIV-1 RNA suppression was calculated.
Results: Overall among patients enrolled; 354/624(56.7%) were females with median age 46[Interquartile range(IQR) 40-51] years and median CD4 492(IQR 367-653) cells/ul. Only 2/288 patients were discontinued from the program due to NCD diagnoses at months 3 and 11 resulting an overall retention at 99.3%. Median time among those on program was 11.1(IQR 5.0-12.4) months and 6.95(IQR 3.2-10.7) months among those who discontinued. Of the 84/624 completed a month 12 visit, 83/84(98.8%) had viral suppression at month 12.
Conclusion: Implementing a monitoring approach and incorporating pharmacy-only visits for stable patients was feasible in Infectious Diseases Institute HIV clinic (Kampala, Uganda). High retention rates and virologic suppression rates suggest that this approach should be considered for wider implementation

1002 VIROLOGIC OUTCOMES WHEN ANTIRETROVIRAL THERAPY IS USED FOR PREVENTION: HPTN 052

Jessica M. Fogel[1], Xinyi C. Zhang[2], Estelle Piwowar-Manning[1], Nagalingeswaran Kumarasamy[3], James G. Hakim[4], Beatriz Grinsztejn[5], Ying Q. Chen[2], Myron S. Cohen[6], Susan H. Eshleman[1], for the HPTN 052 Study Team
[1]The Johns Hopkins Univ Sch of Med, Baltimore, MD, USA, [2]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [3]YRG CARE, Chennai, India, [4]Univ of Zimbabwe, Harare, Zimbabwe, [5]Inst de Pesquisa Clinica Evandro Chagas, Rio de Janeiro, Brazil, [6]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background: In May 2011, an interim analysis of the HIV Prevention Trials Network (HPTN) 052 trial showed that early initiation of antiretroviral therapy (ART) prevented 96% of genetically-linked HIV infections in serodiscordant couples. ART was then offered to all index participants and the trial continued until May 2015. This report describes virologic outcomes in index participants who initiated ART in HPTN 052.
Methods: Virologic outcomes were evaluated in three study groups: (1) early ART arm (ART initiation at enrollment, CD4 350-550 cells/mm3), (2) delayed ART arm with ART initiation before May 2011 (ART initiation at CD4 <250 cells/mm3 or with an AIDS-defining illness), and (3) delayed ART arm with ART initiation after May 2011 (with ART initiation at any CD4 cell count). Viral suppression was defined as two consecutive viral loads ≤400 copies/mL. Virologic failure was defined as two consecutive viral loads >1,000 copies/mL >24 weeks after ART initiation.
Results: There was no significant difference in virologic outcomes in the three study groups (early ART arm [N=832]; delayed ART arm before May 2011 [N=204]; delayed ART arm after May 2011 [N=530]). Longer time to viral suppression was associated with higher baseline (pre-ART) viral load (p<0.0001), age (<25 years; compared to 25-39 years, p=0.0006, compared to ≥40 years, p=0.0002), and region (Africa; compared to Asia, p=0.005). Virologic failure was associated with higher baseline CD4 cell count (p=0.02), lack of viral suppression by 6 months (p<0.0001), age (<25 years; compared to ≥40 years, p=0.0005), region (Americas; compared to Africa, p=0.001), and education (none; compared to primary or secondary-schooling, p=0.004 and compared to post-secondary schooling, p=0.002).
Conclusion: Higher baseline CD4 cell count and higher baseline viral load were associated with worse virologic outcomes. Demographic factors such as age, region, and education were also associated with time to viral suppression and ART failure. In this study, awareness of the interim findings of the trial (personal health benefits and lower risk of HIV transmission with early ART initiation) did not improve virologic outcomes in those who initiated ART at higher CD4 cell counts. Additional resources may be needed to optimize treatment outcomes, especially among younger individuals and those who start ART at higher CD4 cell counts.

1003 USERS MAY LACK CONFIDENCE IN ART FOR HIV PREVENTION: A QUALITATIVE ANALYSIS

Monique A. Wyatt[1], Emily E Pisarski[1], Jared Baeten[2], Renee Heffron[2], Edith Nakku-Joloba[3], Timothy R. Muwonge[4], Elly T Katabira[3], Connie L. Celum[2], Norma C. Ware[1]
[1]Harvard Univ, Boston, MA, USA, [2]Univ of Washington, Seattle, WA, USA, [3]Makerere Univ, Kampala, Uganda, [4]Infectious Diseases Inst, Kampala, Uganda

Background: Antiretroviral-based approaches to HIV prevention have been shown to reduce new infections in both clinical trials and demonstration settings. To achieve optimal uptake of these strategies and anticipate barriers to effective rollout, it is critical to understand users' perspectives on the use of antiretroviral treatment (ART) for prevention of HIV transmission. We explored serodiscordant couples' understandings of and feelings about treatment as prevention (TasP) using qualitative data from the Partners Demonstration Project (PDP).
Methods: The PDP employed an integrated delivery strategy of daily oral pre-exposure prophylaxis (PrEP) and ART for serodiscordant couples in Kenya and Uganda. PrEP use was time-limited and discontinued after HIV-infected partners had been on ART for 6 months. Multiple in-depth interviews were conducted with a subset of 48 couples from the Kampala, Uganda site (N interviews=189). Interview topics included: (a) purpose and meanings of PrEP and ART; (b) adherence; (c) experiences of PrEP discontinuation; and (d) understandings of TasP. Interviews were inductively analyzed to identify themes representing couples' understandings of and feelings about using ART for prevention of HIV transmission. Categories were developed to represent the themes.
Results: Serodiscordant couples generally understood that ART prevents HIV transmission to uninfected partners. However, some individuals doubted that ART alone was "enough" to protect against HIV acquisition. Lack of confidence in ART for prevention took the following forms: (1) Concerns about the effectiveness of ART for prevention in the absence of other methods of protection (i.e., PrEP, condoms); (2) Misunderstandings about how viral suppression and sustained ART use lead to a reduction in infectiousness and HIV risk; (3) Uncertainty about partners' adherence to ART stemming from distrust in the relationship; and (4) A preference for multiple methods of protection used simultaneously.
Conclusion: Our findings suggest a lack of confidence in TasP among serodiscordant couples arising from unfamiliarity with new biomedical prevention strategies and reluctance to rely on partners for HIV prevention. Improved messaging about how ART works to achieve viral suppression and reduce transmission, along with supportive counseling, may address underlying concerns about HIV risk, helping to alleviate fears and increase trust in ART to prevent HIV.

1004 UPTAKE AND ADAPTATION OF COMMUNITY ADHERENCE GROUPS IN ZAMBIA

Monika Roy[1], Mpande Mukumbwa-Mwenechanya[2], Emilie Efronson[2], Mwansa Lumpa[2], Anjali Sharma[2], Izukanji Sikazwe[2], Nancy Padian[3], Carolyn Bolton Moore[4], Elvin Geng[1], Charles Holmes[5]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Cntr for Infectious Disease Rsr in Zambia, Lusaka, Zambia, [3]Univ of California Berkeley, Berkeley, CA, USA, [4]Cntr for Infectious Disease Rsr in Zambia, Lusaka, Zambia, [5]Johns Hopkins Univ, Baltimore, MD, USA

Background: The community adherence group (CAG) is a community-based HIV treatment model promoted to improve long-term retention in care. It combines clinical visit spacing, group drug-pick up and distribution in the community, and peer social support to reduce the high opportunity costs of clinic visits and promote patient self-management. Although existing data suggest that retention is higher in CAGs compared to facility-based care, the overall public health impact of CAGs depends on the fraction of eligible patients who take up the model.
Methods: We evaluated uptake and adaptation of CAGs in an ongoing cluster randomized trial of the CAG model using an implementation cascade for individuals offered CAGs. A systematic sample of eligible patients (HIV+, on ART > 6 months, not acutely ill, CD4 >=200/µl) were offered CAG participation between May 19, and July 31, 2016 at five primary care facilities in three provinces in Zambia. We recorded number of persons that were a) offered CAG group membership, b) accepted membership, c) successfully placed into a CAG group d) retained during assembly e) attended first CAG group meeting. Reasons for not accepting a CAG and number, mechanism, and sustainability of CAG group formation were documented. We characterized adaptation by documenting changes to intended group size (n=6) and drug-pick up frequency.
Results: Among 603 individuals, 543(90%) accepted, 495(82%) were placed into a CAG, 479(79%) were retained during assembly, and 478(79%) attended their first CAG group meeting. CAG acceptance varied by site (range:80-97%, median:92%) as did the proportion of those placed into CAGs among those who accepted (range:79-100%, median:91%). The primary documented reasons for not accepting a CAG included fear of HIV status disclosure in the community and concern over needing to find members to join their group. Of those who accepted CAG participation, 170(31%) were male, median age was 45 years [IQR:39-52], and median time on ART was 5.5 years [IQR:2.9-7.9]. Of 84 CAG groups formed, 74(88%) formed autonomously, 29(35%) adapted group size, and 82(98%) were sustained until the first meeting. Frequency of drug-pickup was adapted at one site from monthly to bimonthly.
Conclusion: Results of our evaluation document overall high, but heterogeneous uptake of the CAG intervention. Further evaluation of site-specific challenges with patient acceptance of the CAG model and CAG group formation are needed in order to optimize the public health benefit of this model at scale.

1005 ASSESSING RETENTION IN A CLUSTER RANDOMIZED TRAIL TO ACCELERATE ART INITIATION

Richard Katuramu[1], Fred Semitala[2], Gideon Amanyire[1], Jennifer Namusobya[1], Leatitia Kampiire[1], Jeanna Wallenta[3], David Glidden[3], Moses R. Kamya[2], Diane V. Havlir[3], Elvin Geng[3]
[1]Makerere Univ Joint AIDS Prog, Kampala, Uganda, [2]Makerere Univ Coll of Hlth Scis, Kampala, Uganda, [3]Univ of California San Francisco, San Francisco, CA, USA

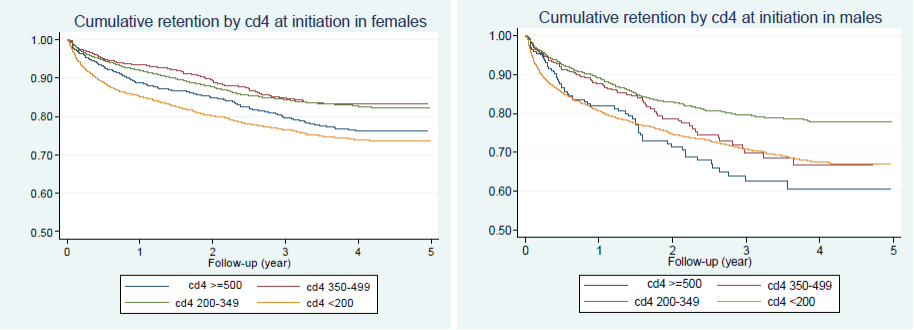
Background: Antiretroviral therapy (ART) initiation among treatment eligible HIV patients in Africa who have presented for clinical care is often delayed, but concerns exists that accelerating initiation – especially to the same day as ART eligibility – may compromise retention. We previously reported a cluster randomized trial in Uganda showing an increase in the ART initiation on the same day of eligibility from 18% to 71% after introduction of coaching, point of care technology and a reputational incentive. We now report the effect of same day ART initiation on retention using randomized intervention as an instrumental variable.
Methods: We evaluated all HIV positive, treatment eligible patients presenting for care in 20 public facilities in southwestern Uganda. We examine visit adherence (the fraction of appointments made within 7 days) using generalized estimating equations and the cumulative incidence of being 14 days late for an appointment using the Kaplan-Meier method. We treated the randomized behavioral intervention as an instrumental variable to assess the effect of same day ART initiation on retention. We assumed that the randomized intervention had no effect on retention other than through the timing of ART initiation, which permits causal inference even in the presence of unmeasured, post-randomization common causes of same day start and retention.
Results: Among 12,024 patients in 20 facilities, 63% female with a median CD4 count at eligibility of 310/ul (IQR: 179 to 424), the behavioral intervention did not change overall retention as measured by visit adherence (84.4% in intervention vs. 83.8% in control, p=0.18), but reduced overall the cumulative incidence of being 14 days late for an appointment at 12 months (44.4% to 38.8%, difference = 5.6%, 95% CI: 3.1% to 8.0%, p < 0.0001). The instrumental variable analysis found that same day ART initiation increased visit adherence (83.6% to 85.4%, RD=1.8%; 95% CI: 0.3% to 3.2%, p=0.014) and decreased the cumulative incidence of being 14 days late for a visit at 12 months by 11% in patients who would adopt same day ART initiation.
Conclusion: More rapid ART initiation through an intervention that offered providers new knowledge, technology and feedback on performance but left professional judgment intact did not diminish retention. Improving one step in the cascade can in some cases enhance, rather than undermine, subsequent steps.

1006 LOWER RETENTION IN CARE WHEN ART IS INITIATED WITH CD4 ≥ 500 CELLS/ML

Isabelle A. Meyer-Andrieux[1], Jim Todd[2], Robert Keango[3], Elisabeth Poulet[4], Prince Nkhoma[3], Elisabeth Szumilin[4], David Maman[5], Leon Salumu[4]
[1]MSF, Geneva, Switzerland, [2]London Sch of Hygiene & Trop Med, London, UK, [3]MSF, Lilongwe, Malawi, [4]MSF, Paris, France, [5]Epicentre, Cape Town, South Africa

Background: New WHO guidelines for Universal test and treat imply many will start antiretroviral therapy (ART) without symptoms. A critical question is whether patients who initiate ART at high CD4 achieve good retention in care while on ART in sub-Saharan Africa. In the MSF supported project of Chiradzulu, we assessed the association between high CD4 count at ART initiation, retention and survival.

Methods: All adults who started ART between 2011 and 2015 in Chiradzulu district were included. Lost to follow up was defined as 9 months after a clinic visit without contact, being dead or transferred out. All analysis were stratified by gender. Multivariate Cox regression models were used to present the effect of CD4 at initiation on retention, adjusted for WHO staging, Body Mass Index, and age.
Results: Of 21,705 patients aged ≥15 years who initiated ART between 2011-2015, 16,258 (10,021 females and 6,237 males) had a CD4 count at initiation. Median age at ART start was 38[IQR 32-45] for men and 33[IQR27-40] for women. Among men and women, 239(3.8%) and 1,393(13.8%) initiated ART at CD4>500 cells/μL, respectively. At end of follow-up, 12,757 (78.5%) patients were still in care, 2,538 (15.6%) were lost to follow-up and 661 (4.1%) were dead. Mortality rates were higher for men (2.8 (95%CI 2.5-3.0)) than for women (1.3(95%CI 1.2-1.4)). Survival estimates 48 months after initiation were similar between patients with baseline CD4≥500cells/μL and 350-499, for both women (98.3% vs 98.1%, p=0.95) and men (91.2% vs 92.0%, p=0.33). Retention in care 48 months after ART initiation was 75.4%, 82.1%, 81.9% and 72.1% among women with initial CD4 at ≥500, 350-499, 200-349 and <200 CD4 cells/μL (Log Rank Test, p<0.01) respectively. In the multivariate analysis, women with CD4≥500 cells/μL had a lower retention in care than those who initiated between 350-499 (aHR 0.72; 95%CI 0.60-0.88) and 200-349 cells/μL (aHR 0.82; 95%CI 0.71-0.95). Similar trends were observed for men but the differences were not statistically significant (≥500 vs 350-499 aHR 0.84; 95%CI 0.62-1.14).
Conclusion: Initiating ART at CD4>500 cells/μL was associated with lower retention in care when compared to those who initiated ART between 350-499 CD4 cells/μL. Even if these results come mainly from women on PMTCT B+, in the treat-all era, specific attention to those initiating at high CD4 is needed to ensure good retention. Figure:Kaplan-Meier retention curves stratified by gender and CD4 count at initiation, Chiradzulu, Malawi,2011-2015



1007 ART INITIATION FOR NEWLY DIAGNOSED PLHIV: IMPLICATIONS FOR TEST & TREAT, SOUTH AFRICA

Anna Larsen[1], Mireille Cheyip[1], Abraham Tesfay[2], Peter Vranken[1], Henry Fomundam[2], Anthony Wutoh[2], Getahun Aynalem[1]
[1]US CDC, Pretoria, South Africa, [2]Howard Univ, Pretoria, South Africa

Background: Despite a decade advancing South African HIV/AIDS treatment policy, 20% of people living with HIV (PLHIV) eligible for antiretroviral treatment (ART) remain uninitiated. South Africa maintains the highest number of PLHIV -18% of the global burden. In anticipation of "test and treat" in South Africa, this analysis describes ART initiation, timeliness, and determinants among newly diagnosed PLHIV.
Methods: This analysis used routine data extracted from 35 purposively selected primary health clinics in three high HIV burden districts of South Africa, Gert Sebande, uThukela, City of Johannesburg, from June 1, 2014 to March 31, 2015. Kaplan-Meier survival curves estimated rate of ART initiation. We identified predictors of ART initiation rate and timely initiation (within 14 days of eligibility determination) using Cox proportional hazards and multivariable logistic regression models respectively in Stata 14.1.
Results: Based on national guidelines, 6,869 patients were eligible for ART initiation. Most were women (69.65%) and half were under age 30 (50.24%). Under half of men and non-pregnant women were initiated on ART within 14 days (men: 39.78%, 95% confidence interval: 37.7 – 41.9; women: 40.1%, 38.4 – 42.0) with median time to ART initiation over 20 days (men: 22, range: 7-61; women: 23, range: 7-61) and under 70% initiated within 60 days (men: 69.9%, 67.9 – 71.8; women: 68.8%, 66.8 – 70.2). Pregnant women initiated at a faster rate (day of HIV diagnosis: 82.0%, 80.3 – 83.7; within 14 days: 87.6%, 86.1 – 89.0; within 60 days 91.7%, 90.4 – 92.8; median days to ART initiation: 1, IQR: 1-1). From cox proportional hazards and multivariable logistic regression models for men, TB co-infection versus no co-infection predicted lower (adjusted hazard ratio (aHR): 0.7, 0.6 – 0.9) and less timely ART initiation (adjusted odds ratio (aOR): 0.3, 0.2 – 0.4) (Table 1). ART initiation and timeliness varied significantly by district and facility location among both genders, with minimal variation by age, WHO stage, or CD4 count.
Conclusion: Men and non-pregnant women newly diagnosed PLHIV eligible for ART in South Africa show suboptimal timeliness of ART initiation. If treatment initiation performance is not improved, test and treat implementation will be challenging among men and non-pregnant women. Test and treat programming should be modeled after the successful implementation practices used to initiate pregnant women on ART at antenatal care in South Africa.

1008 TREATMENT NEED AND FAST-TRACK ART IN THE BOTSWANA COMBINATION PREVENTION PROJECT

Refeletswe Lebelonyane[1], Lisa A. Mills[2], Joe Theu[1], Lisa Block[3], Michael Kasonde[2], Tony Chebani[1], Shenaaz el-Halabi[1], Elliot Raizes[3], Shahin Lockman[4], Joseph N. Jarvis[2]
[1]Botswana Ministry of Hlth, Gaborone, Botswana, [2]CDC Botswana, Gaborone, Botswana, [3]CDC Atlanta, Atlanta, USA, [4]Harvard Univ, Boston, MA, USA

Background: To ensure the success of Universal Test and Treat (UTT) it is essential that untreated HIV-infected adults are identified and that there are no barriers to ART initiation. Since UTT implementation in June 2016 the Botswana Combination Prevention Project (BCPP) has offered fast-track ART initiation with enhanced counseling and ART at the first clinic visit. We evaluated the feasibility of identifying untreated adults in the community and the acceptability of fast-track ART initiation.
Methods: BCPP is a cluster randomized trial evaluating the impact of a combination prevention package on HIV incidence in 30 communities. This sub-analysis of the 15 intervention communities evaluates 1) the cohort of patients identified through enhanced BCPP testing and linkage activities between October 2013 and May 2016, and 2) all individuals initiating ART prior to the introduction of UTT (October 2013-May 2016) and following UTT (1 June-31 August 2016) when participants with a positive HIV-verification test were immediately referred for ART initiation.
Results: BCPP assessedHIV status in 40,628 individuals; 9,586 (24%) were HIV-infected. Among the 9,406 with complete data, 2,354 (25%) were not on ART, 34% of whom had CD4≤200; 1,120 qualified for treatment by pre-UTT national guidelines (CD4≤350), of whom 76% initiated ART.Overall, prior to UTT 1,775 HIV-infected treatment eligible participants attended HIV-clinics in the 15 intervention communities, of whom 1,359 (77%) initiated ART. Median time to ART initiation was 35 days, with 46% (571 of the 1,253 with a known start date) starting within 30 days. Following introduction of UTT and fast-track ART initiation 896 participants attended a clinic visit and had a positive HIV-verification test; 85% (629/743 with a known start date) initiated on the same day as their verification test, 95% (709/743) initiated ART within a week of their initial clinic visit, and 99% (735/743) initiated within 30 days. Only 15 (1.8%) of individuals initiating fast-track ART had a baseline creatinine clearance <60mls/min necessitating a clinic recall, and 4 (0.5%) required a treatment switch.

Conclusion: Significant numbers of untreated HIV-infected individuals, many with advanced disease, were identified through intensified community testing.Fast track ART was acceptable and safe and led to increased rates of ART initiation and reduced times from initial clinic visit to treatment start, and could help ART programs in Africa reach the ambitious UNAIDS 90-90-90 targets.

ART Initiation	Same Day	1-7 Days	8-14 Days	15-30 Days	>30 Days
Standard Initiation* (Pre-UTT)	0 (0%)	79 (6%)	171 (14%)	321 (26%)	682 (54%)
Fast-track Initiation* (Post-UTT)	629 (85%)	80 (11%)	16 (2%)	10 (1%)	8 (1%)
ART timing date was missing in 106 (8%) of the 1359 individuals who initiated ART prior to UTT, and in 75 (9%) of the 818 individuals who initiated ART in the fast-track period.					

1009 LINKAGE TO CARE OUTCOMES IN THE BOTSWANA COMBINATION PREVENTION PROJECT

Mary Grace Alwano[1], **Pamela J. Bachanas**[2], Catherine Motswere[1], Tafireyi Marukutira[1], Baraedi W. Sento[3], Nokuthula Majingo[4], Shahin Lockman[5], Molly Pretorius Holme[5], Huisheng Wang[6], Janet Moore[1]
[1]US CDC, Gaborone, Botswana, [2]CDC, Atlanta, GA, USA, [3]Tebelopele HIV Testing and Counseling Cntr, Gaborone, Botswana, [4]Ministry of Hlth, Gaborone, Botswana, [5]Harvard Univ, Boston, MA, USA, [6]Northrup Grumman, Atlanta, GA, USA

Background: To achieve UNAIDS 90 90 90 targets, the 90% of PLHIV who know their status must link to care and initiate treatment. We report linkage to care rates, time to link, and follow up provided to HIV-positive persons not on ART identified through the Botswana Combination Prevention Project (BCPP).
Methods: BCPP is a randomized controlled trial designed to evaluate the impact of a combination prevention (CP) package on HIV incidence in 30 communities in Botswana. HIV testing was conducted in the 15 CP communities and included home-based and mobile testing. Newly identified and known HIV-positive persons not on ART were given point of care CD4 tests, referrals to local HIV clinics, SMS appointment reminders, incentives for keeping appointments (US $2 airtime cards) and home and/or phone counselor visits for up to 90 days if not registered at the HIV clinic.
Results: Overall, 40,628 persons were assessed for HIV status (tested or showed documentation of HIV status); 24% (9,586/40,628) were HIV-positive. Among all HIV-positive persons identified, 2,593 not on ART were referred to the local HIV clinic. Of those referred, 77% (1,997/2,593) linked to care within 30 days, 82% (2,126/2,593) within 90 days, and 84% (2,182/2,593) within 1 year. For women age 16-24, linkage to care rates were 83%, but lower for same-age men (72%). Of persons over 24 years of age, linkage to care rates were similar for women (85%) and men (84%). Of those who linked, 68% (1,492/2,182) registered with only an SMS reminder, and 58% (858/1,492) of these received an incentive upon registering. Of the 32% (690/2,182) who did not keep initial appointments, counselors provided an average of 2.2 counseling visits and re-appointments before they linked to the clinic. Of HIV-positive persons who never linked (16%, 411/2,593), 70% were employed compared to 40% of those who did link. Persons who never linked reported being too busy, unable to miss school/work, or not ready to accept HIV status as reasons for not keeping appointments.
Conclusion: Most HIV-positive persons referred to the clinic linked within the first 30 days, and linked with minimal follow up needed. Both women and men linked to care at high rates; however, men age 16-24 and employed persons may need additional tracking and expanded availability of clinical care to ensure they initiate treatment. Tracking referrals is a critical intervention to ensure resources are spent on those who do not link and need additional intervention to access care and treatment.

1010 ART COVERAGE AFTER 2 YEARS OF A UTT INTERVENTION IN ZAMBIA: FINDINGS FROM HPTN071

Sian Floyd[1], Mwelwa Phiri[2], Ab Schaap[2], David Macleod[1], Kwame Shanaube[2], Sam Griffith[3], Nulda Beyers[4], Richard Hayes[1], Sarah Fidler[5], Helen Ayles[6]
[1]London Sch of Hygiene and Trop Med, London, UK, [2]Zambart, Lusaka, Zambia, [3]FHI 360, Durham, NC, USA, [4]Desmond Tutu TB Cntr, Western Cape, South Africa, [5]Imperial Coll London, London, UK, [6]London Sch of Hygiene and Trop Med, Lusaka, Zambia

Background: The lack of effect of a universal test-and-treat (UTT) intervention on population-level HIV incidence reported by the TasP study emphasized the importance of high ART coverage. HPTN 071(PopART) is a community-randomized trial in 21 urban communities in Zambia and South Africa, testing the impact on HIV incidence of a household-based combination HIV prevention approach provided by community-HIV-care-providers (CHiPs). In 4 Zambian communities, from November 2013 CHiPs have delivered the "PopART" UTT package in annual "rounds", during which they (re-)visit all households. CHiPs refer HIV-positive (HIV+) individuals to routine HIV clinic services, with re-visits to support linkage to care. We present data on ART coverage and retention from round 2 (R2) of delivering the intervention.
Methods: R2 was from June 2015–September 2016. Included in analysis are adults (≥18 years) who consented to participate, and who self-reported HIV+ or were newly diagnosed HIV+ by the CHiPs ("known HIV+"). Our main outcomes are the percentage on ART by the end of R2 and the percentage retained on ART at the time of consenting to participate in R2, both self-reported. To help understand how the ART coverage outcome was achieved, we used "time to event" methods to estimate the percentage who initiated ART by 6 months after referral to HIV care.
Results: Among adults resident during R2, 65% (34,538/53,486) of men and 87% (49,648/57,269) of women consented to participate. Of these, 10% (n=3,405) of men and 16% (n=7,995) of women were known HIV+. On the date of consenting to participate in R2, 64% (n=2,196/3,405) of known HIV+ men and 69% (n=5,504/7,995) of known HIV+ women were on ART, increasing with age from 41% overall among 18-24 year olds to 82% among those ≥55 years; 24% of men and 20% of women were newly diagnosed HIV+. Among those who reported ever taking ART, 92% (2,154/2,329) of men and 95% (5,424/5,730) of women were on ART and missed 0 pills in the last 3 days. By the end of R2, among those still resident according to the last CHiP visit, 78% of men and 79% of women were on ART, ranging from 59% among 18-24 year olds to 88% among those ≥55 years. Compared to R1, initiation on ART by 6 months after referral to HIV care increased from 40% to 60%.
Conclusion: By the end of R2, among adults known to be HIV+, the percentage on ART approached 80%, lower among younger than older adults, retention on ART was high, and the time to initiate ART after referral to care was shortened compared with R1.

1011 REACHING 90-90-90? FINDINGS AFTER 2 YEARS OF HPTN 071 (POPART) INTERVENTION IN ZAMBIA

Richard Hayes[1], Sian Floyd[1], Ab Schaap[2], Kwame Shanaube[2], Peter Bock[3], Sam Griffith[4], Nulda Beyers[3], Helen Ayles[5], Sarah Fidler[6], for the HPTN 071 (PopART) Study Team
[1]London Sch of Hygiene & Trop Med, London, UK, [2]Zambart, Lusaka, Zambia, [3]Desmond Tutu TB Cntr, Western Cape, South Africa, [4]FHI 360, Durham, NC, USA, [5]London Sch of Hygiene & Trop Med, Lusaka, Zambia, [6]Imperial Coll London, London, UK

Background: The UNAIDS 90-90-90 targets aim to substantially decrease HIV transmission but it is unknown whether they can be achieved at scale in generalised epidemics. We report data from HPTN 071 (PopART), the largest programme to deliver universal testing and treatment at population level in Southern Africa, to determine how close we are to reaching the targets after two years of intervention.
Methods: The intervention comprises annual rounds of home-based HIV counselling and testing delivered by Community HIV Care Providers (CHiPs) who also support linkage to care, retention on ART and other HIV-related services. CHiP data from four communities in Zambia receiving the full PopART intervention (including universal ART irrespective of CD4 count), were used to determine proportions of adults who knew their HIV-positive (HIV+) status before and after the second annual round (R2: Jun 2015 - Sep 2016), and the proportions of known HIV+ adults who were on ART. Extrapolating from these data, we estimated overall proportions of HIV+ adults in these communities who knew their HIV+ status (first-90) and the proportion of these who were on ART (second-90) before and after R2.
Results: By the end of August 2016, 45,616 households had been visited by CHiPs for the second annual round; 110,755 adult residents of these households (aged 18+) were enumerated, of whom 84,186 (76%) were contacted and consented to the intervention. Based on data from these participants, estimated total numbers of HIV+ adults in these four communities were 6,216 men and 10,341 women (Table), of whom 78% of men and 90% of women (86% overall) knew their HIV+ status following the R2 annual visit (first-90). Among these known HIV+ adults, 80% of men and 80% of women were estimated to be on ART by the end of R2 (second-90). For both targets, coverage was higher in those who had participated during R1 than in those who had not. Comparison of R1 and R2 estimates shows a continuing increase in coverage particularly for the second-90.
Conclusion: After two rounds of intervention, 86% of HIV+ adults were estimated to know their HIV+ status, close to the first-90. Of those known HIV+, an estimated 80% were on ART, approaching the second-90. Continuing efforts are needed to speed up linkage to care and ART initiation in order to reach the second-90. Lower coverage in the large number of clients who had not participated during R1 emphasises the need for annual re-visits in urban communities with high rates of mobility and migration.

Table: Estimates of knowledge of HIV-positive status and ART uptake in total adult population of 4 communities in Zambia after two years of PopART intervention and corresponding estimates after one year

		First 90: % of HIV+ who know HIV+ status		Second 90: % of known HIV+ on ART	
	Estimated No. HIV+	Before AR visit	Immediately after AR visit	Immediately after AR visit	End of Round
Men	**6216**	**65%**	**78%**	**71%**	**80%**
R1 participants	2695	87%	92%	79%	84%
R1 non-participants	3521	48%	67%	62%	75%
Women	**10341**	**75%**	**90%**	**71%**	**80%**
R1 participants	5668	89%	96%	79%	85%
R1 non-participants	4673	57%	84%	61%	74%
Overall*					
Round 2	**16557**	**71%**	**86%**	**71%**	**80%**
Round 1	17341	55%	84%	52%	73%

*Corresponding estimates of population coverage against the first 90 and second 90 targets are shown for Rounds 1 and 2 for men and women combined

1012 HEALTH CARE COVERAGE AND VIRAL SUPPRESSION PRE- AND POST-ACA IMPLEMENTATION

Heather Bradley[1], Joseph Prejean[1], Lindsey Dawson[2], Antigone Dempsey[3], Jennifer Kates[2], Pamela W. Klein[3], R. L. Shouse[1]
[1]CDC, Atlanta, GA, USA, [2]Kaiser Family Fndn, Washington, DC, USA, [3]HRSA, HIV/AIDS Bureau, Rockville, MD, USA

Background: The Affordable Care Act (ACA), fully implemented in 2014, expanded health care coverage options for many people living with HIV in the US It is unknown how health coverage among persons in HIV medical care has changed since ACA implementation and how such changes may be associated with prevalence of viral suppression.
Methods: We used 2012 and 2014 data from the Medical Monitoring Project (MMP) to examine pre- and post-ACA implementation changes in health care coverage types and viral suppression among adults receiving HIV medical care. MMP is a surveillance system utilizing a national probability sample of adults receiving HIV care in the US We computed weighted percentages of adults who were uninsured or had private, Medicaid, or Medicare coverage in each time period. We also assessed, in each time period, the percentage of adults receiving Ryan White HIV/AIDS Program services for low-income, un- and under-insured persons, and the percentage of persons virally suppressed (<200 copies/mL) at last test. All analyses were stratified by residence in a Medicaid vs. non-Medicaid-expansion (ME vs. NME) state, defined as expansion anytime in 2014.
Results: In 2012, 26% [95% confidence interval (CI): 20–31] of persons in HIV medical care were uninsured in NME states compared to 13% (CI: 10–16) in ME states. There was no change in health care coverage of persons receiving HIV care in NME states from 2012–2014. In ME states, the percentage uninsured declined from 13% to 7% (CI: 6–8), and Medicaid coverage increased from 39% (CI: 32–46) to 51% (CI: 46–56). The percentage of patients receiving Ryan White services was 42% (CI: 39–45) in both NME and ME expansion states in 2012 but increased to 55% (CI: 49–62) in NME states in 2014 with no accompanying change in ME states. Prevalence of viral suppression was 77% (CI: 75–79) in both NME and ME states in 2012, increasing to 83% (CI: 81–85) among patients in ME states and non-significantly to 81% among patients in NME states (CI: 76–86) in 2014.
Conclusion: Among patients in ME states, the percentage of persons in HIV care who were uninsured declined by nearly 50% from 2012–2014; this was driven by increases in Medicaid coverage. No decline in the percentage uninsured was found among patients in NME states. Viral suppression increased by 8% in ME states from 2012–2014. Future work will examine whether this increase in viral suppression is attributable to changes in health care coverage.

1013 HOUSING STABILITY IS ASSOCIATED WITH HIV VIRAL SUPPRESSION IN A HOUSING PLACEMENT RCT

Yaoyu Zhong[1], Ellen Wiewel[1], Vivian L. Towe[2], Rachel Johnson[1], Laura McAllister-Hollod[1], Joanne Hsu[1], Sarah Braunstein[1], John Rojas[1]
[1]New York City DHMH, Long Island City, NY, USA, [2]RAND Corporation, Arlington, VA, USA

Background: Homeless or unstably housed people living with HIV (PLWH) may have low rates of retention in HIV care and viral suppression (VS). Providing stable housing is complex. A randomized controlled trial of rapid rehousing, Enhanced Housing Placement Assistance (EHPA), tested whether at-residence case management could improve housing stability and health outcomes among low-income, homeless PLWH in New York City (NYC).
Methods: A total of 236 PLWH from 22 emergency housing facilities were randomly sampled and assigned to EHPA or usual housing placement assistance (HPA). Case managers visited EHPA persons at their emergency housing weekly up to 1 year, to help them find stable housing; HPA persons received in-office supportive services ≤3 months (the

standard for housing placement). Housing status, engagement in HIV care (any viral load [VL] or CD4 count) and VS (last VL ≤200 copies/mL) were measured in 6-month increments from enrollment through 24 months. For each time increment, housing stability was classified as "low" for continuous residence in emergency housing, "medium" for transit between stable housing (i.e., permanent housing or independent living) and emergency housing, and "high" for continuous residence in stable housing. Chi-square measured the difference in housing stability between EHPA and HPA in each time increment. Multilevel logistic regression measured improvement in VS over time by using an interaction term of study arm by time, and housing stability's impact on VS. Data came from surveys, the NYC HIV surveillance registry, and an emergency housing database.
Results: Over 65% of participants were male, Black or Hispanic, ≥40 years old, disabled or unemployed, and chronically homeless. EHPA had more persons with medium and high housing stability than HPA at each time increment (at 6 and 12 months, p≤0.01). People with low housing stability were least likely to be engaged in care, but the proportion engaged in care decreased over time among high housing stability persons in EHPA. Half of variance in VS was due to within-subject differences (ICC=0.49). Compared to HPA, VS of EHPA persons increased by 4% monthly (aOR 1.04, 95% CI: 1.01-1.07; Table). People with medium and high housing stability were >50% more likely to be virally suppressed than those with low stability.
Conclusion: Compared with HPA, enhanced housing stabilization services with at-residence case management were associated with improved housing and health outcomes for PLWH.

Table. Factors associated with HIV viral suppression based on multilevel logistic regression

Parameter		Adjusted Odds Ratio[1]	95% Confidence Interval
Housing stability level	*Low*[2]		
	Medium	1.88	(1.12, 3.15)
	High	1.55	(0.88, 2.76)
EHPA study arm * Time[3]		1.04	(1.01, 1.07)
History of incarceration at baseline	*Recent (within 2 years)* [2]		
	Past (before 2 years)	2.75	(1.38, 5.50)
	Never	2.05	(0.92, 4.56)
Gender	*Female*[2]		
	Male	4.04	(2.02, 8.08)
	Transgender	1.52	(0.35, 6.65)

1. Adjusted by age, race, and if had SSI or SSD at baseline; 2. Reference level; 3. 1-unit (month) time change for intervention arm

1014 ADVANCING "TASP" USING A MEDICAL-CARE COORDINATION MODEL IN LOS ANGELES COUNTY

Wendy H. Garland, Sonali P. Kulkarni
Los Angeles County, Los Angeles, CA, USA

Background: Despite effective antiretroviral therapies, only 35% of persons living with HIV nationally achieve the full benefit of treatment and there is a paucity of evidence based interventions to increase viral suppression. To advance "treatment as prevention," the Los Angeles County (LAC) Division of HIV and STD Programs evaluated the effectiveness of a Medical Care Coordination (MCC) model.
Methods: MCC was adapted from chronic disease models in which HIV patients at highest risk for poor health outcomes are targeted for integrated medical and psychosocial support services. In 2013, MCC services were delivered by multidisciplinary teams (nurse, social worker, caseworker) co-located in 35 safety net HIV clinics in LAC. Patient acuity was assessed at enrollment and guided service intensity. Service effectiveness was evaluated using a pre-post prospective cohort design with patients as their own controls. The proportion of patients with suppressed viral load (last test in past 6m ≤200 copies/mL) was compared at 12m pre-and post-enrollment in MCC using McNemar's chi-square.
Results: In 2013, 1,204 HIV+ patients were enrolled in MCC (49% Latino, 26% Black; 85% male; 54% aged 25-44; 78% ≤federal poverty level; 38% ever incarcerated; 17% homeless in past 6m). Acuity at enrollment was 52% moderate, 30% high,18% low and >1% severe. Patients received 18.3 median service hours of MCC (interquartile range=23.6) over 12m with higher acuity patients receiving significantly more hours (p<0.05). The proportion of virally suppressed patients increased significantly from 31% pre-MCC to 60% post-MCC (p<0.05) resulting in a relative improvement of 97%. The largest improvements in viral suppression pre-and post MCC were observed among patients who were high/severe acuity (19% pre-MCC vs 49% post-MCC; p<0.05); patients aged 12-24 years (25% pre-MCC vs 58% post-MCC; p<0.05); transgender patients (31% pre-MCC vs 65% post-MCC; p<0.05); and, men who have sex with men (MSM) (28% pre-MCC vs 60% post-MCC; p<0.05).
Conclusion: The results of this large scale intervention demonstrate that MCC model is effective at increasing the proportion of patients with viral suppression after 12 months. Significant improvements were also seen among vulnerable populations including those with highest acuity, youth, transgender and MSM. This promising strategy not only results in improved health status among patients but advances "treatment as prevention" by reducing the likelihood of forward HIV transmission.

1015 MIGRATION, GENDER, AND HIV INCIDENCE IN RAKAI, UGANDA

Oluwasolape M. Olawore[1], Aaron Tobian[2], Fred Nalugoda[2], Ronald H. Gray[1], Maria Wawer[1], Robert Ssekubugu[2], John Santelli[3], Larry W. Chang[2], David Serwadda[4], Kate Grabowski[1]
[1]The Johns Hopkins Univ, Baltimore, MD, USA, [2]Rakai Hlth Scis Prog, Kalisizo, Uganda, [3]Columbia Univ, New York, NY, USA, [4]Makerere Univ, Kampala, Uganda

Background: Higher HIV prevalence is commonly observed among migrant populations in Sub-Saharan Africa. However the extent to which migration is a cause or consequence of HIV infection is largely unknown. Here, we use population-based, longitudinal data to assess the association between duration of residence since migration into a community and HIV incidence in Rakai District, Uganda.
Methods: We used prospective data from HIV-negative participants residing in thirty communities under continuous surveillance between 1999 and 2015 in the Rakai Community Cohort Study (RCCS), an open population-based census and cohort of adults aged 15-49 in rural south-central Uganda. Migrants were identified during census and classified as individuals who moved to a new community with intention to stay. Newly HIV-positive individuals were considered incident HIV cases if they had an HIV-negative test result at a prior survey. Poisson regression with generalized estimating equations was used to estimate incidence rate ratios (IRR) of HIV infection associated with years since arrival for migrants relative to long term-residents with adjustment for demographics, sexual risk behaviors, and calendar time.
Results: HIV incidence was assessed among 13,991 HIV-negative individuals of whom 57% (n=8,049) were women and 34% (n=4571) were classified as migrants. Participants were followed for 85,654 person-years (pys) during which 802 incident HIV events were detected (n=313 in men; n=489 in women). Overall, incidence was 1.6/100pys in recent migrants (arrived <2 years), 0.97/100pys in non-recent migrants (>2 years), and 0.88/100pys among long-term residents. Among women, HIV incidence was significantly elevated in recent migrants relative to long-term residents before and after adjustment for potential confounders (IRR=1.86, 95%CI:1.43-2.41; adjIRR=1.60, 95%CI: 1.21-2.13) but not in non-recent migrants (IRR=0.89, 95%CI:0.71-1.12; adjIRR=0.97, 95%CI: 0.76-1.23). We observed no significant increases in HIV risk among recent (IRR=1.34, 95%CI:0.78-2.32; adjIRR=1.36, 95%CI:0.78-2.37) or non-recent migrant men (IRR=1.03, 95%CI:0.71-1.48; adjIRR=1.12, 95%C1: 0.77-1.64).

Conclusion: These data suggest that the earliest years after migration are associated with increased risk of HIV acquisition in women but not men in rural East Africa. These findings highlight the need for timely interventions targeted to migrant populations, particularly women, to reduce HIV incidence in Sub-Saharan Africa.

1016 OUTCOMES ALONG THE HIV CARE CONTINUUM AMONG UNDOCUMENTED IMMIGRANTS IN CLINICAL CARE

Jonathan Ross, Uriel Felsen, Chinazo Cunningham, Viraj V. Patel, David B. Hanna
Albert Einstein Coll of Med, Bronx, NY, USA

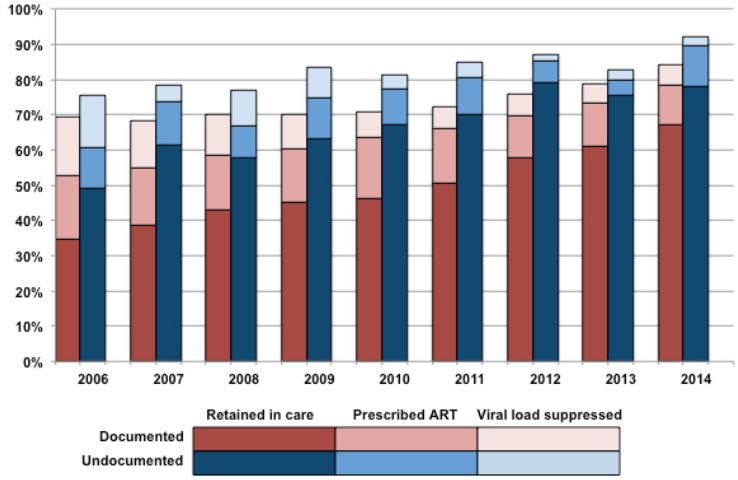
Background: HIV-infected undocumented immigrants face unique barriers to care yet little is known about clinical outcomes in this population. We compared outcomes along the HIV care continuum between undocumented and documented patients in a diverse, high HIV prevalence area where insurance and prescription medications are available to undocumented immigrants.

Methods: We performed a retrospective cohort analysis of HIV-infected persons ≥ 18 years who were linked to care between 2006-2014 at a large academic medical center that is the largest provider of HIV care in the Bronx, NY. Undocumented status was assessed based on an algorithm incorporating Social Security number and insurance status and was verified through medical chart review. We used adjusted Poisson regression models with generalized estimating equations to compare undocumented patients and documented patients with respect to retention in care (≥ 2 CD4 count or viral load measurements ≥ 90 days apart), antiretroviral therapy (ART) prescription (≥ 3 active antiretroviral agents in a year) and viral load suppression (HIV RNA < 200 copies/mL for the last measured viral load) for each year in care.

Results: A total of 7,551 eligible patients were followed for a median of 5 years (interquartile range 2-9). We classified 173 patients (2.3%) as undocumented. At entry to care, undocumented patients were younger (mean age 37.8 years vs 40.6 years, p<0.001), less likely to report injection drug use as their primary HIV risk factor (3% vs 18%, p<0.0001) and had lower median CD4 counts (in cells/mm3: 299 vs. 341, p<0.01). For each year of the analysis, higher proportions of undocumented immigrants were retained in care, prescribed ART and virally suppressed. After adjusting for age, race/ethnicity, sex, HIV risk factor, and comorbid substance use disorder, undocumented immigration status was associated with increased probability of retention in care (RR 1.05, 95% CI 1.01-1.10), ART prescription (RR 1.05, 95% CI 1.01-1.08) and viral load suppression (RR 1.13, 95% CI 1.08-1.19) compared to documented status.

Conclusion: Undocumented immigrants achieved retention in care, ART prescription and viral load suppression at modestly higher rates than documented persons, despite entering care with more advanced disease. When insurance and prescription medications are available to undocumented immigrants, similar outcomes along the HIV continuum of care may be achieved regardless of immigration status.

FIGURE. Proportion of patients retained in care, prescribed antiretroviral therapy and with suppressed viral load by immigration status, 2006-2014



1017 IMMIGRANTS AND BOTSWANA'S ART PROGRAM: POTENTIAL BARRIERS TO EPIDEMIC CONTROL

Tafireyi Marukutira[1], Mary Grace Alwano[1], Stephanie Behel[2], Joseph N. Jarvis[1], Unoda Chakalisa[3], Kathleen Powis[4], William Bapati[5], Gene Ussery[6], Refeletswe Lebelonyane[7], Pamela J. Bachanas[2]
[1]US CDC, Gaborone, Botswana, [2]CDC, Atlanta, GA, USA, [3]Botswana Harvard Partnership, Gaborone, Botswana, [4]Harvard Univ, Boston, MA, USA, [5]Tebelopele Voluntary Counseling and Testing Cntr, Gaborone, Botswana, [6]Northrop Grumman Corporation, Atlanta, GA, USA, [7]Botswana Ministry of Hlth, Gaborone, Botswana

Background: Models suggest that universal HIV testing and immediate antiretroviral therapy (ART) combined with enhanced prevention approaches could achieve epidemic control of HIV in southern Africa. Botswana may be close to UNAIDS 90-90-90 targets according to baseline data from the Botswana Combination Prevention Project (BCPP). Currently, Botswana's national HIV treatment program does not provide ART free of charge to non-citizens (immigrants). Access to free ART services for this population may limit the ability to achieve epidemic control even when 90-90-90 targets for Botswana citizens have been achieved.

Methods: The BCPP is a cluster randomized trial designed to evaluate the impact of a combination prevention package on population level HIV incidence in 30 rural or peri-urban communities in Botswana. HIV testing campaigns were conducted in the 15 intervention communities covering 80% of the households in each community from October 2013-February 2016 and included home-based and mobile testing. Interviews and HIV testing were offered to all persons >16 years, including non-citizens. HIV-positive participants not on ART, including non-citizens were referred to the local HIV clinic and offered support with linking to care.

Results: In the 15 Combination Prevention communities, 38,608 persons were assessed for HIV status (tested or showed documentation of status). Three percent (1,209/38,608) self-reported being non-citizens. Fifty-seven percent (695/1,209) of non-citizens were men, 41% (492/1,209) were women, and 22 (2%) were unknown. Eighteen percent (222/1,209) were HIV-positive: 64% (143/222) of whom were newly identified and 36% (79/222) had documentation of prior HIV positive status. Of all the HIV-positive non-citizens identified, only 27% (61/222) were on ART as compared to 71% (5,738/8,102) of citizens or spouses of citizens assessed.

Conclusion: Non-citizens accounted for 3% of participants in this community testing campaign, and had an HIV prevalence of 18%. The vast majority did not know their HIV status, were newly diagnosed, and were not on ART. Although the proportion of non-citizens is small, their knowledge of HIV status and ART use are very low. Given the high ART coverage rates in the general population in Botswana, lack of free ART coverage for non-citizens may result in a disproportionate contribution to incident HIV infections and modeling the estimated impact on epidemic control in Botswana is recommended.

1018 CASCADE OF CARE OF HIV SEROCONVERTERS IN THE CONTEXT OF UNIVERSAL "TEST AND TREAT"

Joseph Larmarange[1], Mamadou H. Diallo[1], Collins C. Iwuji[2], Joanna Orne-Gliemann[3], Nuala McGrath[4], Mélanie Plazy[3], Frank Tanser[5], Rodolphe Thiébaut[6], Deenan Pillay[5], François Dabis[6]
[1]IRD, Paris, France, [2]Univ Coll London, UK, London, UK, [3]INSERM, Bordeaux, France, [4]Univ of Southampton, Southampton, UK, [5]Africa Hlth Rsr Inst, Mtubatuba, South Africa, [6]Univ de Bordeaux, Bordeaux, France

Background: The ANRS 12249 TasP cluster-randomized trial aimed at evaluating the impact of a Universal Test and Treat (UTT) approach on population-based HIV incidence in rural KwaZulu Natal, South Africa. Previous results showed low rates of early linkage to HIV care and treatment and did not identify any incidence reduction. To optimize the impact of UTT, time to ART initiation and viral suppression must be shorten significantly, in particular among newly infected individuals. We describe here the longitudinal cascade of care for those seroconverting during the course of the TasP trial.
Methods: Every six months between March 2012 and June 2016, resident members aged ≥16 years old were offered rapid HIV testing at home and asked independently to provide dried blood spot (DBS) samples. Those testing positive or who self-reported their positive status were referred to local trial clinics for ART initiation, regardless of their CD4 count (intervention) or according to national guidelines (control). Cases of HIV seroconversion were identified using multiple sources: repeat DBS, repeat rapid tests, HIV+ self-reports and clinic visits. Date of seroconversion was estimated using a random point approach. The HIV care status, for each day following seroconversion (M0), was computed using additional data collected on CD4 count, ART prescription, viral load and migration out of the trial area. Follow-up was right-censored by dates of death or trial closure if alive.
Results: We observed 565 individuals acquiring HIV (244 in intervention arm; 321 in control arm). Among them, one year after seroconversion (M12), 22% out-migrated from the trial area. 57% were diagnosed (aware of their HIV status), 27% were actively in HIV care, 12% were on ART, and were 10% virally suppressed. The cascade was comparable in both trial arms, except for ART coverage, higher in the intervention arm (15%) than in the control arm (9%).
Conclusion: The observed cascade of care was suboptimal in seroconverters despite the introduction of UTT services and a trial environment. This poor outcome was aggravated in this rural setting by out-migration considered here as loss to the cascade. Newly HIV-infected individuals need time to (re)test, initiate ART and reach viral suppression. This is one of the plausible explanations of the lack of effect of the UTT strategy on HIV incidence in our setting. For a UTT approach to be effective, innovative strategies to identify seroconverters and support them to engage in ART care promptly are required.

1019 FACTORS ASSOCIATED WITH LATE PRESENTATION FOR HIV CARE IN SOUTH AFRICA

Henry Fomundam[1], **Abraham Tesfay**[1], Shelter Mushipe[1], Myriam Mosina[1], Carol Boshielo[1], Hanson Tebe[1], Anna Larsen[2], Mireille Cheyip[2], Getahun Aynalem[2], Yogan Pillay[3]
[1]Howard Univ, Pretoria, South Africa, [2]US CDC, Pretoria, South Africa, [3]South African Natl Dept of Hlth, Pretoria, South Africa

Background: Many people living with HIV (PLHIV) are not aware of their seropositive status and are diagnosed late during the course of HIV infection in South Africa. This study aims to assess factors associated with late presentation for HIV care among newly diagnosed PLHIV in three high HIV-burden districts of South Africa.
Methods: Data for this analysis were utilized from a study describing linkage and retention in HIV care and treatment among newly diagnosed PLHIV within 35 purposively selected facilities between June 2014 and March 2015. Patients with available CD4 results and/or documentation of WHO clinical staging were eligible for analysis and were categorized as "moderately" (CD4 count 351-500 cells/mm3 and WHO clinical stage I or II), "very" (CD4 count 201-350 cells/mm3 or WHO clinical stage III) or "extremely" (CD4 count < 200 cells/mm3 and/or WHO clinical stage IV) late presenters, or were deemed "early" presenters. Descriptive analysis was used to measure frequency of late presentation and variables independently associated with late presentation were assessed through ordinal multivariable regression analysis.
Results: Among 12,413 newly diagnosed PLHIV, 8,138 (66%) had CD4 measurement and/or WHO staging indicating presentation to HIV care. Most were female (69%) and 50% were age ≤ 30 years of age. A total of 78% (6,377) PLHIV presented to care late, of which 19% were moderately late, 27% were very late, and 33% were extremely late. Controlling for all other factors, men (AOR = 2.70; CI: 1.50 – 4.94), non-pregnant women (AOR 1.47; CI: 1.36 – 1.56), those older than 30 years (AOR = 2.60; CI: 1.99 – 4.92), and those accessing care in facilities within townships and inner cities (AOR = 1.52; CI: 1.06 – 2.20) were more likely to present extremely late versus early. Risk factors for very late and moderately late versus early presentation to care were not significant.
Conclusion: The majority of newly diagnosed PLHIV in this analysis presented for HIV care late in the course of HIV infection. While the existing South African health policies target pregnant women for linkage to HIV care and treatment services during antenatal care, similar policies should be developed to incentivize men, non-pregnant women, those over 30 years of age and those accessing care in facilities within inner city and urban townships toward early engagement with the health system.

1020 SOUTH AFRICA'S NATIONAL THIRD-LINE ART COHORT: DESCRIPTIVE ANALYSIS

Francesca Conradie[1], Matthew Fox[2], Michelle A. Moorhouse[1], Gary Maartens[3], Willem D. Venter[1], Mahomed-Yunus Moosa[4], Khadija Jamaloodien[5]
[1]Univ of the Witswatersrand, Johannesburg, South Africa, [2]Boston Univ, Boston, MA, [3]Univ of Cape Town, Cape Town, South Africa, [4]Univ of KwaZulu-Natal, Durban, South Africa, [5]South African Natl Dept of Hlth, Pretoria, South Africa

Background: The World Health Organization recommends that national antiretroviral therapy (ART) programs in resource limited settings develop policies for third-line ART. South Africa, with the largest HIV treatment program, is one of the only countries in sub-Saharan Africa that has access to third-line ART for patients who have failed both first-line non-nucleoside reverse transcriptase inhibitors (NNRTI) and second-line protease inhibitor (PI) based ART. We report on 152 public-sector patients in South Africa for whom third line treatment was requested. This may be the largest public sector cohort on third line agents in sub-Saharan Africa.
Methods: Third-line ART for adults in the public sector in South Africa is accessed through a national committee that assesses eligibility and makes regimen recommendation on each case. Criteria for third-line treatment include a minimum of one year of PI based ART with virologic failure despite adherence optimization and a genotypic antiretroviral resistance test (GART) showing PI resistance. We present a cross-sectional analysis and descriptive statistics on this cohort. PI resistance was defined by a resistance mutation score of ≥15 on the Stanford University HIV Drug resistance Database.
Results: 152 patients were submitted to the national third line committee between Aug 2013 and July 2014 and granted access to third line. Median age was 41 years (IQR: 24-47) and 60% were female. The median CD4 count and viral load was 170 (IQR: 127-337) and 17013 (IQR: 396-104178) respectively. In terms of second line ART, 5% started before 2005, 22% started second line between 2004 and 2009 and 62% started second-line between 2008 and 2011.Of the 146 (96%) patients with resistance test results, 74% and 77% had resistance (≥15) to efavirenz and nevirapine respectively. 85%, 72%, 69% and 92% had resistance to lamivudine, zidovudine, tenofovir and abacavir respectively, while 97% and 98% had resistance to lopinavir and atazanavir respectively. In addition 57% and 37% had resistance to darunavir and etravirine respectively. Of the 146, 145 were initiated on a third-line regimen containing either raltegravir (n=106), darunavir (n=145) or etravirine (n=33) or some combination thereof. Among those with at least one viral load post resistance testing (n=117), a large proportion (94%, n = 102) were able to resuppress their viral load to below 400 copies/ml
Conclusion: Despite high levels of resistance, viral suppression was high in a programmatic roll out of third line ART.

Resistance profiles of cohort

ARV class	ARV	%
NNRTI	efavirenz	74
	nevirapine	77
	etravirine	37
NRTI	lamivudine	85
	zidovudine	72
	tenofovir	69
	abacavir	92
PI	lopinavir	97
	atazanavir	98
	darunavir	57

1021 "I WON'T DIE WITH THE CAUSE OF AIDS": 10 YEARS ON ART IN SOUTH AFRICA'S HIV PROGRAM

Cheryl J. Hendrickson[1], Sophie Pascoe[1], Aneesa Moolla[1], Mhairi Maskew[1], Matthew Fox[2]
[1]*Univ of the Witwatersrand, Johannesburg, South Africa,* [2]*Boston Univ, Boston, MA*

Background: As South Africa enters the second decade of its National Antiretroviral Treatment (ART) program, it is important to take stock of a decade of achievement. This mixed-methods study describes 10-year treatment outcomes of patients initiated at the start of the rollout and explores what motivated testing, initiation and continued care.
Methods: We conducted a cohort analysis and in-depth interviews among adults initiating ART between April 2004 and March 2006 at a large public clinic in Johannesburg. We ascertained 10-year all-cause mortality and loss to follow-up (LTF) for two ten-year cohorts (Y1 initiated 04/2004-03/2005 and Y2 04/2005-03/2006). We describe associations using adjusted hazard ratios (aHR). Twenty-four patients were purposively selected and interviewed (09/2015-03/2016).
Results: 3003 adults (31.2% male) were followed for 18,687 person-years (median 6.9). Median ages at Y1 and Y2 were 35.3 and 35.0 and baseline CD4 counts were 78 and 87 cells/mm3 respectively. After ten years, 21.5% had died and 24.3% were LTF; 957 (31.9%) were still alive and in care. Being male (aHR=1.40 (1.18-1.66), older at initiation (>50 vs 18-30 aHR=1.56 (1.14-2.14) and WHO Stage III/IV (vs Stage I/II aHR 1.31 (1.09-1.58) increased the risk of mortality (Table 1). Patients were more likely to be LTF if they initiated in the second year of the treatment program (vs Y1 aHR=1.57 (1.29-1.91). Older initiators were less likely to be LTF (18-30 vs >50 aHR=0.39 (0.24-0.63). Interviewed individuals reported that having children, a strong desire to survive and being the only provider at home were strong facilitators for continued treatment. Patients cited supportive counselling and informal support groups prior to, and at, treatment initiation as key to their decision to start treatment. Observed quality of life improvement on ART encouraged long-term adherence and continued care. Conversely, conflicts in work/life commitments, health issues, side-effects, and clinic staff attitude were barriers. Few participants reported gaps in care during treatment (n=4); those who did indicated that severe side-effects, travel and domestic abuse resulted in them defaulting.
Conclusion: Many patients who initiated treatment at the beginning of the national programme have successfully remained on ART for ten years. A supportive and flexible clinic environment, which minimises negative aspects of treatment should be prioritised for continued long-term treatment and adherence, particularly as policy moves to test-and-treat.

Table 1: Clinical predictors of all-cause mortality and loss to follow-up after 10 years on ART at an urban HIV outpatient clinic in Johannesburg, South Africa

Variable		Mortality			Loss to follow-up		
	N	%	cHR	aHR	%	cHR	aHR
Year initiated*							
2004-2005	1404	21.2	1.00	1.00	13.8	1.00	1.00
2005-2006	1599	21.8	1.11 (0.95-1.30)	1.06 (0.89-1.25)	19.8	1.59 (1.33-1.90)	1.57 (1.29-1.91)
Gender							
Female	2065	18.8	1.00	1.00	17.8	1.00	1.00
Male	938	27.5	1.52 (1.30-1.78)	1.40 (1.18-1.66)	15.2	0.90 (0.74-1.09)	1.00 (0.81-1.24)
Age at initiation							
18-30	667	18.6	1.00	1.00	24.9	1.00	1.00
31-40	1500	19.5	0.99 (0.80-1.22)	0.97 (0.78-1.22)	16.1	0.60 (0.50-0.74)	0.58 (0.47-0.72)
41-50	622	25.4	1.28 (1.01-1.62)	1.21 (0.93-1.55)	13.5	0.50 (0.39-0.65)	0.52 (0.39-0.69)
>50	214	34.1	1.75 (1.31-2.34)	1.56 (1.14-2.14)	8.9	0.34 (0.21-0.54)	0.39 (0.24-0.63)
CD4 count category (cells/mm3 blood)							
0-50	915	27.2	1.00	1.00	13.8	1.00	1.00
51-100	603	23.4	0.81 (0.66-0.99)	0.85 (0.69-1.04)	15.3	1.03 (0.78-1.34)	1.03 (0.79-1.36)
101-200	918	18.3	0.64 (0.52-0.77)	0.68 (0.56-0.84)	20.8	1.42 (1.13-1.78)	1.31 (1.04-1.65)
201-350	161	11.2	0.39 (0.24-0.63)	0.45 (0.28-0.73)	21.7	1.49 (1.02-2.16)	1.27 (0.87-1.87)
>350	23	8.7	0.30 (0.08-1.22)	0.31 (0.08-1.26)	26.1	1.77 (0.78-4.02)	1.55 (0.68-3.53)
WHO Stage							
Stage I/II	1613	18.5	1.00	1.00	19.1	1.00	1.00
Stage III/IV	1390	25.0	1.39 (1.19-1.62)	1.31 (1.09-1.58)	14.5	0.79 (0.66-0.94)	0.83 (0.66-1.04)
TB at initiation of HAART							
Yes	546	22.3	1.00	1.00	15.9	1.00	1.00
No	2457	21.4	0.98 (0.81-1.20)	1.34 (1.06-1.70)	17.2	1.12 (0.89-1.40)	1.00 (0.74-1.35)

* 2004-2005 (Year 1): Initiated ART between 1 April 2004 and 31 March 2005; 2005-2006 (Year 2): Initiated ART between 1 April 2005 and 31 March 2006.

1022 OUTCOMES OF AHI SCREENING AND IMMEDIATE ART INITIATION IN COASTAL KENYA

Eduard Sanders[1], Oscar Chirro[2], Clifford Oduor[2], Juma Mangi[3], Elizabeth Wahome[2], Matt A. Price[4], Huub C. Gelderblom[4], Elisabeth M. van der Elst[2], Susan M. Graham[5]
[1]Kenya Med Rsr Inst, Kilifi, Kenya, [2]KEMRI Wellcome Trust Rsr Prog, Kilifi, Kenya, [3]Malindi Sub-County Hosp, Malindi, Kenya, [4]Intl AIDS Vaccine Initiative, New York, NY, USA, [7]Univ of Washington, Seattle, WA, USA

Background: The World Health Organization recommends treatment of all HIV-infected patients with ART upon diagnosis. However, patients with acute HIV infection (AHI) are rarely identified at care seeking in Africa, and data on linkage and ART initiation following AHI diagnosis is lacking. We assessed outcomes following AHI screening among outpatients seeking urgent care in a large Government hospital in coastal Kenya, estimating time to successful care linkage and time to ART initiation.
Methods: Patients aged 18-35 years with unknown HIV-status were eligible to be screened for prevalent and acute HIV when the sum of a 7-item published consensus risk score was ≥2 (age 18-29 years, reported fever, fatigue, body pains, diarrhea, and sore throat scored a "1", and genital ulcer disease a "3"). A 5-ml blood sample was used to diagnose prevalent HIV infection by two rapid tests (Determine and Unigold). AHI testing was conducted with a point-of-care X-pert Qual RNA test when rapid HIV tests were negative or discordant. Patients awaited X-pert results (1.5 hours), and all infected patients were offered immediate ART upon diagnosis, in accordance with Kenyan guidelines.
Results: From February-August 2016, 1058 (42.7%) of 2475 patients were eligible for screening, including 318 men and 720 women. Of these, 205 (64.5%) men and 496 (68.8%) women agreed to be screened (p=0.4). Eight (3.9%) men and 16 (3.2%) women had prevalent HIV (p=0.7). Six (1.3%) of 480 seronegative women had AHI, including 3 in Fiebig Stage II (RNA positive, seronegative) and 3 in Fiebig Stage III (RNA positive, discordant rapid tests). No men had AHI (p=0.1). Of 30 new HIV diagnoses, 10% were in women who would not otherwise have been diagnosed and 10% were in women with discordant test results, who may not have followed up with repeat testing as recommended. Overall, 22 (73.3%) HIV-infected patients (6 men and 16 women) registered for care after a median of 0 days (range: 0-51). Fifteen patients (50.0%, 6 men and 9 women) started ART after a median of 2 days (range: 0-71). Five of (83.3%) of 6 AHI patients started ART after a median of 0 days (range: 0-11).
Conclusion: Targeted AHI screening among young adult symptomatic outpatients identified a substantial number of undiagnosed prevalent HIV infections. Moreover, AHI screening led to an increase in confirmed diagnoses by 25% (from 24 to 30 cases). While the majority of AHI patients started ART immediately, same-day treatment initiation for all HIV patients needs strengthening.

1023 TEN YEARS OF SUPPORTING SCALE-UP OF HIV CARE AND EXPANSION OF ART IN 4 COUNTRIES

Chloe A. Teasdale, Chunhui Wang, Jessica E. Justman, David Hoos, Mark Hawken, Zenebe Melaku, Antonio Mussa, Wafaa M. El-Sadr, Elaine J. Abrams
ICAP at Columbia Univ, New York, NY, USA

Background: Scale up of HIV care and expansion of ART to reach all eligible patients has been a global priority for more than 15 years. We describe patient characteristics and attrition pre and post-ART among patients at 358 sites in four countries over 10 years.
Methods: We examined demographic and HIV disease characteristics at enrollment in care and ART initiation at PEPFAR-funded ICAP-supported clinics in Ethiopia, Kenya, Mozambique and Tanzania from 2005-2014. We analyzed the proportion of patients eligible for ART at enrollment based on prevalent WHO guidelines at enrollment and the proportion starting ART. We also examined attrition (loss to follow-up (LTF) and death) pre-ART initiation using competing risk estimators (ART as competing risk) and post-ART initiation with Kaplan-Meier estimators. LTF was defined as no visit within 6 months prior to ART and 12 months after ART start. We examined outcomes by year with Cochran-Armitage tests, Kendall Tau coefficients, log rank tests and unadjusted sub-distributional hazards models.
Results: From 2005-2014, 902,709 patients were enrolled in care at 358 ICAP-supported health facilities across four countries. Overall, 66.5% were female, median age was 32 years[IQR 26-40], 32.8% enrolled through VCT and 10.0% through PMTCT. At enrollment, 34.7% were WHO stage 3/4 and median CD4+ cell count was 235cells/mm3[IQR 104-427] (CD4 missing for 45.9%). As a result of changing WHO guidelines, ART eligibility at enrollment increased from 31.6% in 2005-2006 to 54.8% in 2013-2014(p<0.0001), however median CD4 increased from 172 cells/mm3[IQR 71-340] to 289 cells/mm3[IQR 132-484](p<0.0001). Overall, 484,621(53.7%) patients started ART; 44.1% were WHO stage 3/4 and median CD4 was 166 cells/mm3[IQR 79-260](CD4 missing for 31.1%). The proportion of patients starting ART increased from 53.1% in 2005-06 to 63.2% in 2013-14(p<0.0001). Attrition pre-ART at 12 months overall was 35.2% (95%CI 35.1-35.3) and decreased over time from 36.5%(95%CI 36.3-36.8) in 2005-06 to 25.7%(95%CI 25.3-26.1) in 2013-14(p<0.0001). Attrition post-ART at 12 months overall was 25.7% (95%CI 25.6-25.9) and increased over time from 22.6%(95%CI 22.3-23.0) in 2005-06 to 30.6%(95%CI 30.1-31.1) in 2013-14(p<0.0001).
Conclusion: Over 10 years of HIV care and treatment scale up in four countries, close to a million patients were enrolled in care and more than half started ART. Over time patients were healthier at enrollment, attrition decreased among pre-ART patients and increased among those on ART.

1024 DISTRIBUTION OF HIV TRANSMISSION BY NETWORK AND CLINICAL FACTORS AMONG US MSM

Johanna Chapin-Bardales[1], Samuel Jenness[1], Eli Rosenberg[1], Patrick Sullivan[1], Steven M. Goodreau[2]
[1]Emory Univ, Atlanta, GA, USA, [2]Univ of Washington, Seattle, WA, USA

Background: Men who have sex with men (MSM) continue to experience high HIV incidence in the United States. Sexual role, partnership types, infection stage, and care engagement strongly determine HIV transmission rates within serodiscordant MSM partnerships. Estimating the distribution of transmissions by these factors is critical to targeting prevention efforts. Previous studies to estimate the distribution of transmissions by these factors have yielded conflicting results and significant debate, likely due to heterogeneous populations and methods. We assessed all factors in one comprehensive US-based model in order to provide internally-consistent and actionable estimates.
Methods: A mathematical model simulated HIV transmission dynamics within sexual partnership networks of US MSM over a 10-year period. Parameters were estimated from HIV cohorts in Atlanta and national behavioral and clinical literature. We estimated population attributable fractions (PAFs) and 95% credible intervals by network and behavioral factors within partnerships and clinical status of the infected partner.
Results: Among all incident HIV infections, 42% occurred in main partnerships, 48% in casual partnerships, and 10% in one-time partnerships. Three-quarters (75%) of transmissions were to the receptive AI partner. One in five transmissions (21%) originated from an acute-stage partner, 60% from a non-AIDS chronic-stage partner, and 19% from a partner who progressed to AIDS. Nearly all infections resulted from AI with an infected partner who was undiagnosed (31%) or who was not retained in care (61%); few infections occurred during time on ART with partial (5%) or full (1%) viral suppression.
Conclusion: Our model suggests two high-value targets for prevention: MSM in non-main partnerships and in partnerships in which the infected partner has fallen out of HIV care. Assessing risk behavior specific to partnership type remains necessary to tailoring the delivery of HIV prevention tools. Targeting strategies may emphasize PrEP for HIV-negative MSM in non-main partnerships as partners' HIV status or care engagement may be unknown. Within main serodiscordant partnerships, strategies may include PrEP for the HIV-negative partner and support for the HIV-positive partner to remain effectively engaged in care. Because HIV-positive men not retained in care contribute the majority of ongoing HIV transmissions, efforts to engage these men individually and through their partnerships will be challenging but essential.

1025 HIV TRANSMISSION IN GENERALIZED, CONCENTRATED, AND MIXED EPIDEMICS IN WESTERN KENYA

Anna Bershteyn[1], Vibhuti Hate[2], Daniel J. Klein[1], Zindoga Mukandavire[3], Graham F. Medley[3], Wanjiru Mukoma[4], Michael K. Kiragu[4], Kristine Torjesen[5], Nduku Kilonzo[6], Katharine Kripke[7], for the OPTIONS Consortium

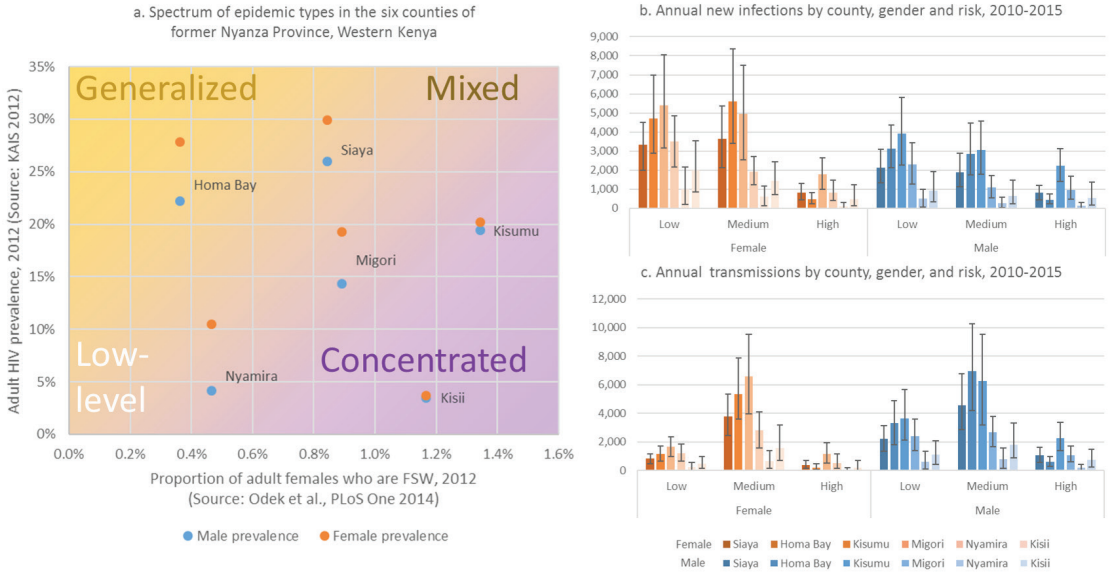
[1]Inst for Disease Modeling, Bellevue, WA, USA, [2]The George Washington Univ, Washington, DC, USA, [3]London Sch of Hygiene and Trop Med, London, United Kingdom, [4]LVCT Hlth, Nairobi, Kenya, [5]FHI 360, Durham, NC, USA, [6]Natl AIDS Control Council, Ministry of Hlth, Nairobi, Kenya, [7]Avenir Hlth, Washington, DC, USA

Background: HIV prevention planning requires information about those at highest risk of acquiring and transmitting HIV. Kenya exhibits a range of subnational HIV epidemic patterns including highly concentrated, highly generalized, and mixed HIV epidemics. This analysis identifies transmission patterns in each of the six counties of the former Nyanza province based on overall epidemic trends as well as high-risk sub-populations such as female sex workers (FSW) and their clients.

Methods: A literature review identified characteristics of FSW and their clients, defined here as "high" risk, and strata of the general population who were not FSW or clients but at increased risk of HIV infection, defined here as "medium" risk. Characteristics of FSW such as age, duration in sex work, population size based on a recent FSW enumeration, and number of clients were incorporated into an existing HIV microsimulation model, EMOD-HIV v2.5. Setting-specific data on fertility, mortality, traditional male circumcision and scale-up of voluntary male medical circumcision, HIV testing and treatment rates, and HIV treatment guidelines were incorporated and the model was fit to age and gender stratified HIV prevalence from four cluster-randomized surveys.

Results: Kenya counties were placed on a spectrum of generalized, concentrated, low-level, or mixed epidemics according to overall HIV prevalence and the proportion of adult females who were FSW in 2012 (Figure 1a). In every county, incidence rates were highest among FSW and their clients, but the overall number of new infections was higher in the general population (Figure 1b). In Kisii, which exhibits the most concentrated epidemic in Nyanza, numbers of new infections were similar in medium risk and high risk (FSW and clients). In other counties, new infections in medium risk exceeded those in FSW and clients. Surprisingly, the number of transmissions originating from medium risk exceeded those in high- and low-risk individuals in all counties, including Kisii.

Conclusion: While FSW and their clients experience the highest HIV incidence, the largest contribution to HIV transmission in the Nyanza region comes from more numerous "medium" risk individuals, defined as those at high risk of HIV infection in the general population, but not FSW or their clients. Broadly available and acceptable HIV prevention in the general population is needed to maximize the impact on the HIV epidemic.



1026 ANALYZING "MISSING MEN" IN THE UK HETEROSEXUAL HIV EPIDEMIC BY DSPS-HIV SIMULATIONS

Emma B. Hodcroft[1], Manon Ragonnet-Cronin[2], Joel O. Wertheim[3], Samantha Lycett[4], Sergei L. Kosakovsky Pond[5], Andrew Leigh Brown[6]

[1]Univ of Edinburgh, Edinburgh, Scotland, [2]Univ of Edinburgh, Midlothian, Scotland, [3]Univ of California San Diego, San Diego , CA, [3]Temple Univ, Philadelphia, PA, USA

Background: In the UK heterosexual HIV epidemic, there are six times as many clusters containing only women as containing only men. The abundance of female-only clusters implies a set of 'missing men' in currently available transmission networks, perhaps because these men are diagnosed later in infection, are not recruited to care, and/or are responsible for multiple onward transmissions. To investigate factors responsible for the excess of female-only clusters, we conducted a simulation to approximate the UK HIV epidemic, using the Discrete Spatial Phylo Simulator HIV (DSPS-HIV). In parallel, network analysis was undertaken on sequences from the UK HIV Drug Resistance Database (UK RDB) to identify characteristics of female-dominated and female-only clusters.

Methods: DSPS-HIV is an individual-based stochastic epidemic simulator that produces realistic viral phylogenies and sequences, allowing analysis of simulated data using the same methods as used on real data. We (i) allowed men to transmit at twice the rate of women, and (ii) delayed sampling in heterosexual men by approx. 6 months, while sampling heterosexual women approx. 6 months earlier. These effects were explored singly and jointly. Analysis of sequence data from UK RDB was with BEAST and the R package 'Network.'

Results: In baseline simulations, we found a mean ratio of 1.7 female-only to male-only clusters [FMC] due to women's risk from contact with bisexual men. Introducing gender-dependent transmission alone into the DSPS-HIV simulations elevated the mean FMC ratio to 3.0, and with delayed/early sampling it was 2.2. Combining the effects together yielded the FMC ratio of 4.4 (Table 1). Network analysis of UK RDB sequences showed that men have a mean degree of 1.9 (max=44) compared to 1.5 (max=27) for women. Identifying the nearest sequence to female-only clusters showed no significant difference in diagnosis date compared to the cluster.

Conclusion: Here we show the utility of simulations to investigate causal factors in real-world data. Both simulations and network analysis showed that the increased risk of male-to-female transmission plays an important role in the excess of female-only clusters. In combination with delayed/early sampling, we came close to recapitulating the observed FMC ratio, implying that sampling delays may also partially explain 'missing men.' Further work on the UK RDB and the DSPS-HIV will investigate subtype-specific differences in FMC, as subtypes represent different ethnic and risk groups in the UK.

1027 TEMPORAL EVOLUTION OF HIV SERODISCORDANCY AMONG STABLE COUPLES IN SUB-SAHARAN AFRICA

Susanne Awad, Hiam Chemaitelly, **Laith J. Abu-Raddad**
Weill Cornell Med Coll in Qatar, Doha, Qatar

Background: The objective of this study was to examine the temporal evolution of HIV sero-discordancy in six representative countries in sub-Saharan Africa (SSA) at different HIV epidemic scales. Historical (1980-2014) trends of seven sero-discordancy measures were assessed as the HIV epidemic emerged, peaked, and saturated. Future temporal evolution (2015-2030) of these measures was also assessed as antiretroviral therapy (ART) is scaled up and the HIV epidemic declines over the coming decades.
Methods: A pair-based deterministic mathematical model was constructed to describe HIV transmission dynamics in SSA. The model accommodated for different forms of sexual partnerships and infection statuses. Using nationally-representative epidemiological and demographic input data, trends of sero-discordancy were assessed in six countries at different HIV prevalence scales (low, intermediate, and high).
Results: Table 1 shows the definitions of these discordancy measures and their estimated values. In the emerging phase of the HIV epidemics, 54%-93% of couples affected by HIV were discordant. The proportion declined to 45%-88% at epidemic peak and stabilized during the saturated phase. The largest reduction was in high HIV prevalence countries. As the epidemics decline with future ART scale-up, the proportion of discordant couples among HIV affected couples is projected to increase to 70%-92% by 2030. The proportion of discordant couples among all couples increased as the epidemics emerged and peaked at 2%-20% as the epidemics peaked. As the epidemics saturated, this proportion declined following the decline in HIV prevalence. As the epidemics decline further in the future with ART scale-up, it is projected that 0.3%-16% of couples in the population will be discordant by 2030. Results on other discordancy measures can be found in Table 1.
Conclusion: Regardless of HIV epidemic scale across countries, HIV sero-discordancy varied with the evolution of the epidemic. However, the degree of variation depended on HIV epidemic scale. The largest variations in discordancy were observed in high HIV prevalence countries. Discordancy was projected to increase in most countries as the epidemic continues its decline with ART scale-up. These findings inform strategic planning and resource allocation for HIV intervention programming among discordant couples.

1028 EFFECTIVENESS AND COST-EFFECTIVENESS OF HIV SCREENING STRATEGIES ACROSS EUROPE

Guillaume Mabileau[1], Julia Del Amo[2], Kristi Rüütel[3], A. David Paltiel[4], Liis Lemsalu[3], Asunción Díaz[2], Jesús Martín Fernández[5], Rochelle P. Walensky[6], Kenneth Freedberg[6], Yazdan Yazdanpanah[1]
[1]INSERM, Paris, France, [2]Inst of Hlth Carlos III, Madrid, Spain, [3]Natl Inst for Hlth Development, Tallinn, Estonia, [4]Yale SPH, New Haven, CT, USA, [5]Univ Rey Juan Carlos, Madrid, Spain, [6]Massachusetts General Hosp, Boston, MA, USA

Background: In the eras of both Treatment as Prevention and PrEP, HIV testing has become critical to control the epidemic. We evaluated the clinical impact, costs, and cost-effectiveness of different testing strategies for both high-risk individuals and the general population in three European countries with different epidemic profiles.
Methods: We used a mathematical model of HIV disease, the Cost-Effectiveness of Preventing AIDS Complications (or "CEPAC") Model, with country-specific clinical & economic data to project discounted life expectancy, cost and incremental cost-effectiveness ratios (ICERs) of alternative HIV screening strategies in France, Spain, and Estonia. We compared these strategies to current HIV testing practices in adults aged 18-69 in the overall population, and among Men who have Sex with Men (MSM), and People Who Inject Drugs (PWID). Input data by country included (Estonia/France/Spain): HIV prevalence (Overall: 1.3%/0.4%/0.4%; MSM: 4%/17%/6%; PWID: 55%/18%/33%), incidence per 100py (Overall: 0.03/0.02/0.01; MSM: 1.0/1.0/0.6; PWID: 6.0/0.1/1.5), mean CD4 at ART initiation (Table), current screening performance including acceptance and linkage-to-care rates; and costs for ART, HIV tests, and HIV care. We labeled a strategy "cost-effective" if its ICER in 2015€ per year of life saved (YLS) was less than the annual per capita GDP of the country (20,000€/29,000€/24,300€).
Results: Frequent HIV testing among high-risk groups increased life expectancy in people living with HIV (PLWH) (Table). Among MSM, one test every 12 months in Estonia and France, and every 3 years in Spain, had an ICER of 16,200; 23,900; and 25,400€/ YLS. Among PWID, testing every month in Estonia, every 3 years in France, and every 6 months in Spain had ICERs of 11,000; 27,700; and 18,300€/YLS, respectively. In the general population, one additional lifetime test in France and Spain, and testing every 3 years in Estonia had ICERs of 37,100; 28,100; and 13,000€/YLS. Our findings were most sensitive to uncertainty in rates of HIV incidence, the screening frequency, and costs of HIV tests and ART.
Conclusion: In France and Estonia, MSM should be tested every 12 months; and in Spain every 36 months. In Spain and France, PWID should be tested every 6 and 36 months, while in Estonia, the frequency could be even higher. HIV testing in the general population has also proven to be cost-effective. For optimal value, HIV screening strategies in Europe should be tailored to each country's epidemic.

Table: Costs, effectiveness, and cost-effectiveness of HIV testing strategies among high-risk groups in Estonia, France, and Spain

Testing strategies:[1]	Estonia			France			Spain		
	Costs in PLWH (€)	LE[2] in PLWH	ICER (€/YLS)[3]	Costs in PLWH (€)	LE[2] in PLWH	ICER (€/YLS)[3]	Costs in PLWH (€)	LE[2] in PLWH	ICER (€/YLS)[3]
MSM	***PRE=4.0; INC=1.0; CD4=289***			***PRE=17.0; INC=1.0; CD4=465***			***PRE=6.2; INC=0.6; CD4=450***		
Current strategy	52,240	315.2	--	238,780	443.2	--	189,440	482.4	--
Every 3 years	62,930	334.0	8,900	249,940	449.3	dominated	205,050	492.7	**25,400**
Every year	67,330	342.0	**16,200**	259,410	453.7	**23,900**	213,460	498.2	31,300
Every 6 months	70,130	346.8	30,000	266,090	457.0	33,100	218,770	501.3	32,400
PWID	***PRE=55.0; INC=6.0; CD4=289***			***PRE=17.5; INC=0.1; CD4=316***			***PRE=33.1; INC=1.5; CD4=275***		
Current strategy	58,250	341.4	--	190,440	448.2	--	157,150	404.3	--
Every 3 years	68,010	358.5	dominated	235,080	470.3	**27,700**	204,960	435.8	dominated
Every 6 months	77,910	376.9	6,500	267,660	486.8	97,000	224,840	448.3	**18,300**
Every month	83,620	386.1	**11,000**	286,180	493.6	1,138,300	233,990	452.5	101,300

1 Only the most cost-effective strategies (bold) for each group are presented in the table, but the set of strategies tested included more testing frequencies; the current strategy (background testing) was included in each strategy, so each testing frequency was in addition to current practice; PLWH: People Living With HIV; MSM: Men who have Sex with Men; PWID: People Who Inject Drugs; PRE: HIV prevalence (%); INC: Annual incidence (per 100 person-years); CD4: CD4 counts at ART initiation (cells/μL)
2 LE: Life Expectancy in months
3 ICER: Incremental Cost-Effectiveness Ratio in Euros per Year of Life Saved (YLS): calculated from the 3% discounted outcomes in the total cohort (i.e. PLWH or not) when accounting for secondary transmission in Estonia and Spain (in France we used a 4% discount rate); the comparator strategy is always the next lowest, non-dominated, alternative; the 2015 GDP per capita was 20,000€ in Estonia, 29,000€ in France, and 24,300€ in Spain.

1029 COST-EFFECTIVENESS OF HIV SCREENING OF HETEROSEXUALS IN THE UNITED STATES

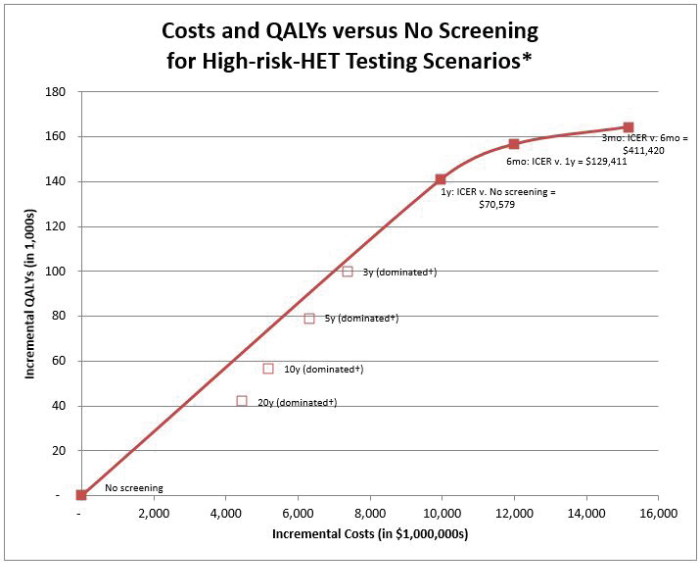
Angela B. Hutchinson[1], Katherine A. Hicks[2], Emine Yaylali[1], Emily Tucker[3], Evin Jacobson[1], Stephanie L. Sansom[1]
[1]CDC, Atlanta, GA, USA, [2]RTI Hlth Solutions, Rsr Triangle Park, NC, USA, [3]Univ of Michigan, Ann Arbor, MI, USA

Background: Previous analyses have demonstrated cost-effective screening frequencies for men who have sex with men and people who inject drugs. However, it is less clear how often heterosexuals (HETs) should be screened, particularly those at high risk of HIV.
Methods: We applied the HOPE model, a dynamic compartmental model of the HIV epidemic, to examine HIV screening at various frequencies for the mutually exclusive general HET and high-risk HET populations. The model examines HIV progression and transmission in the US population aged 13-64, stratified into 195 subpopulations based on HIV transmission risk, risk level and demographic characteristics. It includes 25 compartments defined by HIV disease and continuum-of-care stages. The general HET population

was defined as HETs who were sexually active within the past 12 months. High-risk HETs were defined as HETs living in urban, high-poverty, white-minority areas with high HIV prevalence. Symptomatic testing was considered in addition to screening. The model captures the benefits of HIV screening through changes in risk behavior upon diagnosis and viral suppression from antiretroviral therapy. Model outcomes from 2016-2035 include HIV incidence and prevalence, discounted costs and quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs).

Results: When screening the general HET population every 20 years, screening high-risk HETs as frequently as annually was cost-effective with an ICER of $63,200 per QALY gained compared to screening high-risk HETS at 3-year intervals. Screening high-risk HETs every 6 months, compared to annually, yielded an ICER of $129,400 per QALY gained (figure). Adding more frequent testing for the general HET population to testing for high risk HETS was outside acceptable cost effectiveness thresholds at $310,000 - $1.5 million per QALY for 10-year to 3-month screening intervals. Screening high-risk HETs annually compared to every 20 years reduced projected cumulative HIV incidence for the total population by 5%. Our findings were robust to a 20% variation in key parameters including per-act HIV transmission risks, testing compliance, probability of viral suppression and costs.

Conclusion: Screening high-risk HETS is cost-effective when conducted annually and could be considered economically attractive at 6-month intervals. HIV screening of the general HET population was beyond accepted thresholds of cost-effectiveness when conducted more frequently than 20-year intervals.



Cost-effectiveness plane (solid line) presenting the incremental costs and QALYs and the incremental cost-effectiveness ratio (ICER) for alternative testing frequencies of high-risk heterosexuals. Strategies to the right of the plane are eliminated by extended dominance.
y = years between screens
*General heterosexuals are screened every 20 years.
†Extended dominance = when a strategy has a higher ICER than a more effective option

1030 COST-EFFECTIVENESS OF DIFFERENT DELIVERY APPROACHES FOR HIV SELF-TESTING

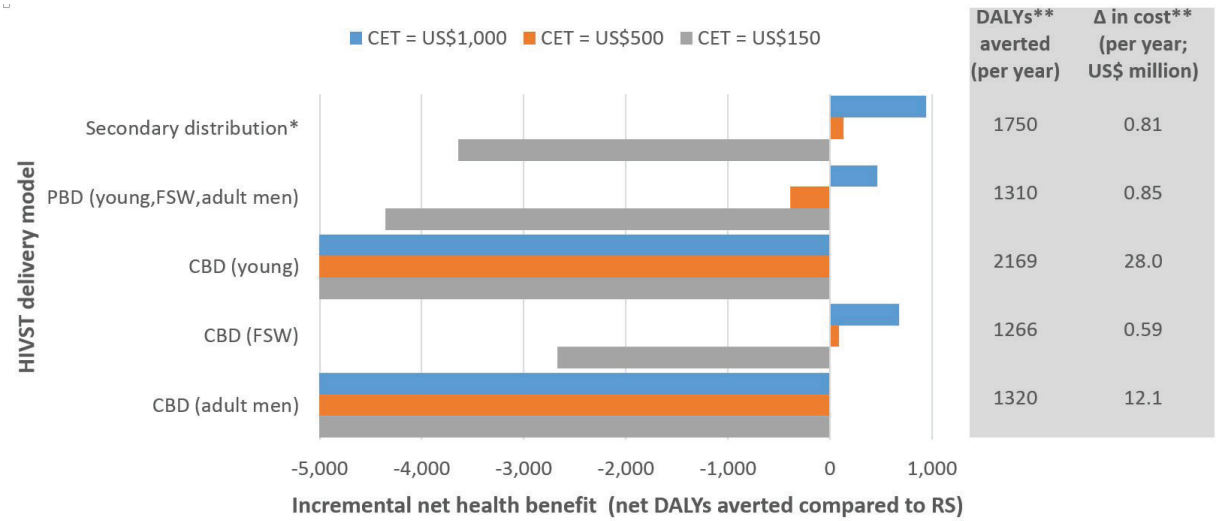
Valentina Cambiano[1], Cheryl Johnson[2], Carmen Figueroa[2], Paul Revill[3], Rachel Baggaley[2], Elizabeth L. Corbett[4], Tsitsi Apollo[5], Karin Hatzold[6], Frances Cowan[7], Andrew Phillips[1]
[1]Univ Coll London, London, UK, [2]WHO, Geneva, Switzerland, [3]Univ of York, York, UK, [4]London Sch of Hygiene & Trop Med, London, UK, [5]Zimbabwe Ministry of Hlth and Child Care, Harare, Zimbabwe, [6]Pop Services Intl, Harare, Zimbabwe, [7]Cntr for Sexual Hlth and HIV/AIDS Rsr, Harare, Zimbabwe

Background: HIV self-testing (HIVST) has been shown to be highly acceptable and able to reach people at high risk who might not otherwise test. This study assesses the cost-effectiveness of introducing HIVST in Zimbabwe for specific populations, considering different delivery models.

Methods: A dynamic model (HIV Synthesis) is used. The base case cost per HIVST kit is $4.8. Alternative strategies are compared to a reference scenario (RS) of no HIVST: a) secondary distribution of HIVST to partners of pregnant women (uptake in the population eligible in each year 40%; fully loaded cost/test $5.0); b) pharmacy-based distribution (PBD) of HIVST to young people (15-24), female sex workers (FSW) and adult men (25-49) (5%; $6.0); c) community-based distribution (CBD) to young people (65%; $7.2 for all CBD, as it is based on data including supervision), d) FSW (42%), e) adult men (55%). The incremental net health benefit (difference between health gains and health opportunity costs, calculated as costs divided by the cost-effectiveness threshold [CET]) of each strategy is compared to the RS. Alternative CETs are used: $1,000, $500, $150. A health care payer perspective is taken using 20 year time horizon.

Results: In the context of Zimbabwe, where we projected 85% of people with HIV know their status in 2016, the introduction of HIVST is likely to be cost-effective (CET of $500-1,000) when considering secondary distribution, PBD and CBD for FSW. Reductions in the cost of HIVST kit, which are believed to be possible, improve the cost-effectiveness of HIVST. However, higher cost of HIVST and lower linkage to care for people whose diagnosis is a consequence of a reactive HIVST result could lead to situations in which HIVST is not cost-effective.

Conclusion: In settings with high levels of HIV status awareness, interventions involving additional HIV tests (at the current cost) are unlikely to be cost-effective; our analysis suggests that HIVST strategies most likely to be cost-effective are secondary distribution, PBD and CBD for FSW. The most cost effective strategy is likely to involve a combination of distribution approaches and this will be evaluated as we move forward. In settings with lower testing coverage or if individuals found to be HIV-negative through HIVST were to link to HIV prevention (e.g. pre-exposure prophylaxis and voluntary medical male circumcision), it is likely that even other forms of HIVST distribution could become cost-effective, similarly if the CBD had to be performed less frequently.



CBD: community-based distribution; CET: cost-effectiveness threshold; DALYs: disability-adjusted life-years; FSW: female sex workers; PBD: pharmacy-based distribution; RS: reference scenario; *(to partners of pregnant women);**discounted at 3.5%/year;

1031 THE COST OF NOT RETESTING: HIV MISDIAGNOSIS IN THE ART "TEST-AND-OFFER" ERA

Jeffrey Eaton[1], Cheryl Johnson[2], Simon Gregson[1]
[1]Imperial Coll London, London, UK, [2]WHO, Geneva, Switzerland

Background: WHO recommends re-testing before starting ART, but this practice is not widely implemented. New recommendations for immediate ART initiation of all HIV-positive adults increase the risk that misdiagnosed HIV-negative persons will be initiated on lifelong ART. We compared the anticipated costs of re-testing persons before ART initiation to the expected cost of providing ART to misclassified HIV-negative persons.
Methods: We created a model to estimate the cost and outcomes of testing 10,000 persons using WHO-recommended serial HIV testing strategies in settings with 1% prevalence (3-test strategy) and 10% prevalence (2-test). The model calculated the expected number of misclassified HIV-negative persons initiated on ART assuming 98% test specificity (equating to 99.6% specificity for the two-test strategy and 99.9% for the three-test strategy), consistent with the real-world testing algorithm performance from a multi-country CDC study. Costs were 'fully-loaded' (including commodities, personnel, supply chain, and management) typical of LMIC settings. The first test and associated counseling cost US$8; each confirmatory test cost $6. ART provision to misclassified persons cost $450 per annum, for a total discounted (6%) lifetime cost of $6300 assuming a 30-year life expectancy after ART initiation. In the re-testing scenario, re-testing was assumed to occur just before ART initiation by an independent healthcare worker.
Results: In the 1% HIV prevalence setting, testing 10,000 cost $83,000, and 9 HIV-negative people would be misdiagnosed and initiated on ART; costing $58,000 in unnecessary ART costs. Re-testing all diagnosed HIV-positives cost $2,000, providing a net saving of $56,000. For 10% prevalence, testing 10,000 persons cost $87,000. 39 HIV-negative people are misdiagnosed, costing $243,000 in unnecessary ART. Re-testing cost $14,000, providing net savings of $226,000. Savings from averted ART costs were greater than expenditure on re-testing within 0.5 years and 0.8 years for the 1% and 10% prevalence scenarios, respectively. That averted ART costs quickly overtake re-testing costs was robust to varying test specificity from 92% to 99%, suggesting re-testing will be cost-saving even as HIV testing performance improves.
Conclusion: Countries should consider implementing re-testing before ART initiation as standard policy, particularly those moving to 'treat all'. This will ensure the quality and effectiveness of HIV programmes, and save significant financial and human resources.

1032 MODELING THE COST-EFFECTIVENESS OF ASSISTED PARTNER NOTIFICATION FOR HIV IN KENYA

Monisha Sharma[1], Jennifer Smith[2], Carey Farquhar[1], Roger Ying[3], Peter Cherutich[4], Beatrice Wamuti[5], Matthew R. Golden[1], Felix Abuna[5], Ruanne V. Barnabas[6]
[1]Univ of Washington, Seattle, WA, USA, [2]Imperial Coll London, London, UK, [3]Weill Cornell Med Coll, New York, NY, USA, [4]Ministry of Hlth, Nairobi, Kenya, [5]Kenyatta Natl Hosp, Nairobi, Kenya, [6]Univ of Washington, Seattle, USA

Background: Assisted partner services (aPS) or provider notification for sexual partners of persons diagnosed HIV-positive can increase HIV testing and linkage to care in sub-Saharan Africa (SSA) and is a high yield strategy to identify persons with undiagnosed HIV. However, aPS is resource intensive and its cost-effectiveness in SSA is not well-evaluated.
Methods: Using cost and effectiveness data from a randomized trial of aPS in Kenya, which found higher HIV testing in sexual partners in the aPS compared to control arm (41% vs. 9%), we parameterized a stochastic, dynamic mathematical HIV transmission model. The model incorporates partner concurrency, migration, coinfection with sexually transmitted infections, household structure, and health seeking behavior. We simulated 200 cohorts of 500,000 individuals and calculated the incremental cost-effectiveness of scaling up aPS in a region of western Kenya (formerly Nyanza Province) under different thresholds of antiretroviral (ART) initiation (CD4≤350, CD4≤500, and all HIV+ persons).
Results: Over a 10 year time horizon with universal ART initiation for HIV+ persons, adding aPS to standard of care in western Kenya is projected to achieve 11% population coverage and reduce HIV infections by 2.7%. In sexual partners receiving aPS, HIV-related deaths were reduced by 7.6%. The incremental cost-effectiveness ratio (ICER) of implementing aPS is $1,568 USD (range $1,162-4,477) per disability-adjusted life year (DALY) averted. Task-shifting delivery of the intervention from healthcare professionals to community health workers decreases the ICER to $1,156 (range $762-2,050) per DALY averted. The task-shifting scenario falls below Kenya's gross domestic product (GDP) per capita ($1,358) and is therefore considered very cost-effective, while the full program cost scenario is considered cost-effective under the higher threshold of 3-times Kenya's GDP per capita. Cost-effectiveness results were robust to all three ART initiation thresholds while health benefits to aPS partners increased with expanding ART initiation criteria.
Conclusion: APS is a cost-effective strategy to reduce HIV associated morbidity and mortality in western Kenya and similar settings. Task-shifting to community health workers will likely be necessary to increase program affordability.

1033 PREP TARGETING STRATEGIES FOR US ADOLESCENT SEXUAL MINORITY MALES: A MODELING STUDY

Steven M. Goodreau[1], Deven T. Hamilton[1], Patrick Sullivan[2], Samuel Jenness[2], Rachel A. Kearns[2], Li Yan Wang[3], Richard Dunville[3], Lisa C. Barrios[3], Eli Rosenberg[2]
[1]Univ of Washington, Seattle, WA, USA, [2]Emory Univ, Atlanta, GA, USA, [3]CDC, Atlanta, GA, USA

Background: Adolescent sexual minority males (ASMM) in the US have high HIV risk- one estimate is 7% prevalence at age 18-and thus may be good candidates for preexposure prophylaxis (PrEP). However, targeting PrEP to ASMM raises many issues, including identifying behavioral indications for prescription that are feasible to implement in clinical practice and which provide high epidemiological impact and efficiency.
Methods: We modified our mathematical model of HIV transmission among adult MSM to focus on ASMM. We explored 7 scenarios for PrEP indications, based on age (13-18 vs. 16-18) and sexual behavior (planning to initiate anal intercourse [AI], already initiated AI, >5 or >10 condomless AI acts in the past 6 months). The median duration remaining on PrEP was 48 weeks, with adherence rates based on preliminary results from the ongoing ATN113 trial. We considered 5 levels of coverage. Outcomes were % of infections averted (PIA) and number needed to treat (NNT, person-years on PrEP per infection averted).
Results: Our base scenario (40% coverage, indications = sexually active ASMM aged 16-18, PrEP initiated on average 6 months after debut) prevented 35.1% of infections, with an NNT of 33. Dropping eligibility age to 13 increases both the PIA (44.4%) and NNT (38) moderately. Initiating PrEP shortly before AI debut increased both further (48.3%, 41). Focusing on adolescents with the largest number of recent condomless AI acts yielded comparable PIA (35.2%-47.6% across scenarios), but much lower NNT values (27-32). Changing coverage demonstrated non-linearly increasing PIA values (20% coverage = 18.7% PIA, 60% coverage = 47.6% PIA), with slightly higher efficiency (lower NNT) for lower coverage (20% coverage = 33, 60% coverage = 36).
Conclusion: Our model demonstrates that PrEP could significantly reduce HIV incidence among US ASMM. There are multiple ways to achieve high epidemiological impact and efficiency, although each involves challenges to both public health infrastructure (increasing PrEP coverage capacity for ASMM) and clinical practice (having clinicians assess relevant sexual histories). The strategies targeted to the highest risk ASMM achieve levels of efficiency similar to some scenarios considered in our recently published adult MSM model. These results underscore the importance of developing approaches to reach and screen ASMM with the highest HIV risk, and to provide tailored support for their adherence and retention while on PrEP.

			Outcome (95% Cred. Int.)					
	PrEP eligibility criteria	Timing of PrEP initiation	Prevalence among 18 year-olds aging out of ASMM	Prevalence among ASMM	Incidence (per 100 py) among sexually initiated ASMM	NIA	PIA	NNT
No PrEP			6.76 (5.12-8.14)	2.87 (2.27-3.38)	2.01 (1.85-2.18)			
Scenario 1	16-18 and AI experienced	6 months after eligibility	4.46 (3.49-5.34)	1.99 (1.56-2.36)	1.30 (1.18-1.40)	705.9 (598.9- 836.3)	35.1 (29.9-41.1)	33 (28-39)
Scenario 2	13-18 and AI experienced	6 months after eligibility	3.84 (2.90-4.78)	1.62 (1.21-1.97)	1.12 (1.01-1.22)	891.9 (781.0- 996.1)	44.4 (38.8-49.2)	38 (33-42)
Scenario 3	13-18	at point of seeking first sex	3.40 (2.53-4.45)	1.44 (1.11-1.81)	1.04 (0.93-1.15)	970.6 (844.5-1079.4)	48.3 (42.4-53.2)	41 (36-46)
Scenario 4	16-18, >= 10 acts of UAI in prior 6 months	at point of eligibility	4.47 (3.23-5.42)	1.96 (1.47-2.37)	1.30 (1.17-1.42)	707.5 (586.7- 833.6)	35.2 (29.3-41.7)	27 (22-32)
Scenario 5	16-18, >= 5 acts of UAI in prior 6 months	at point of eligibility	4.36 (3.31-5.56)	1.91 (1.48-2.33)	1.26 (1.15-1.39)	744.8 (611.7- 848.2)	37.1 (30.5-42.2)	27 (22-32)
Scenario 6	13-18, >= 10 acts of UAI in prior 6 months	at point of eligibility	3.69 (2.88-4.58)	1.54 (1.21-1.80)	1.10 (0.99-1.19)	909.5 (812.3-1014.9)	45.3 (40.4-50.4)	30 (26-33)
Scenario 7	13-18, >= 5 acts of UAI in prior 6 months	at point of eligibility	3.52 (2.78-4.49)	1.45 (1.15-1.82)	1.05 (0.96-1.15)	958.4 (849.9-1050.4)	47.6 (42.6-51.7)	32 (29-36)
Scenario 1 with 20% coverage			5.51 (4.07-7.04)	2.42 (1.79-2.88)	1.63 (1.49-1.77)	375.9 (240.2- 507.5)	18.7 (11.9-25.3)	33 (23-49)
Scenario 1 with 30% coverage			4.97 (3.54-6.12)	2.17 (1.63-2.67)	1.47 (1.34-1.58)	541.2 (423.5- 662.3)	27.0 (21.3-33.1)	33 (26-41)
Scenario 1 with 50% coverage			3.98 (2.88-4.96)	1.77 (1.37-2.17)	1.17 (1.07-1.30)	836.9 (705.9- 940.8)	41.6 (35.4-46.5)	35 (31-41)
Scenario 1 with 60% coverage			3.62 (2.53-4.50)	1.67 (1.36-2.03)	1.05 (0.94-1.15)	957.3 (851.5-1055.7)	47.6 (42.4-52.5)	36 (32-40)

ASMM = adolescent sexual minority males
Cred. Int = credible interval from the range of simulations
NIA = number of infections averted, per 100k years of person-time at risk
PIA = percent of infections averted
NNT = number needed to treat = person-years on PrEP per case averted

1034 STI INCIDENCE AMONG MSM FOLLOWING HIV PREEXPOSURE PROPHYLAXIS: A MODELING STUDY

Samuel Jenness[1], Kevin Weiss[1], Steven M. Goodreau[2], Thomas Gift[3], Harrell Chesson[3], Karen W. Hoover[3], Dawn K. Smith[3], Patrick Sullivan[1], Eli Rosenberg[1]
[1]Emory Univ, Atlanta, GA, USA, [2]Univ of Washington, Seattle, WA, USA, [3]CDC, Atlanta, GA, USA

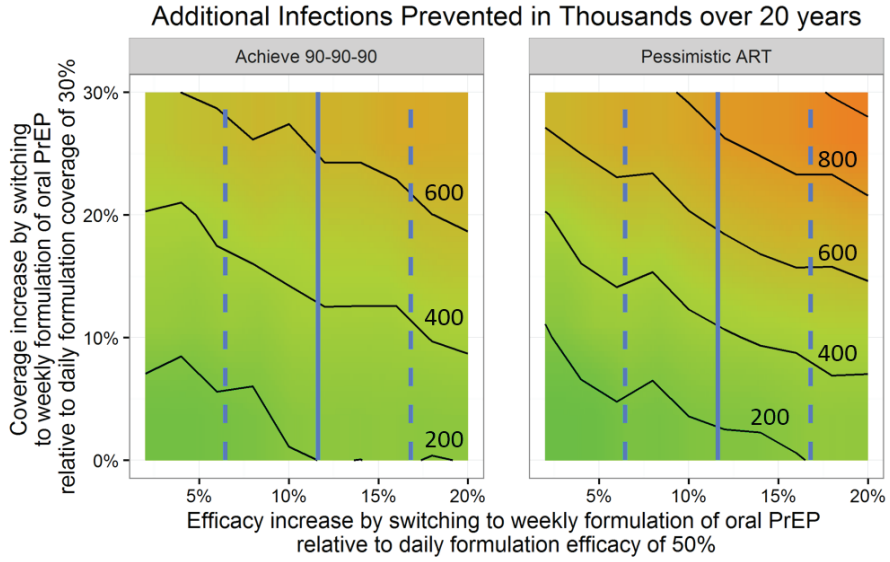
Background: Preexposure prophylaxis (PrEP) is highly effective for preventing HIV, but modest levels of risk compensation (RC) - such as reduced condom use - among men who have sex with men (MSM) have raised concerns about increased incidence of sexually transmitted infections (STIs). In contrast, CDC's PrEP guidelines recommend biannual STI screening, which may reduce STI incidence by treating STIs (e.g., asymptomatic rectal infections) that often remain undiagnosed. We used modeling to estimate the effect of these two potentially counteracting phenomena.
Methods: We expanded our network-based mathematical model of HIV among MSM to include transmission of rectal and urethral Neisseria gonorrhoeae (GC) and Chlamydia trachomatis (CT). PrEP use was simulated following the behavioral indications and ongoing HIV/STI screening recommendations in the CDC PrEP guidelines. Model scenarios varied PrEP coverage (the proportion of MSM indicated for PrEP who received it), the STI screening interval, and RC level (the reduction in the probability of condom use within partnerships).
Results: Under 20% PrEP coverage, the recommended biannual STI screening, and no risk compensation, an estimated 27.5% of GC infections and 31.2% of CT infections would be averted over the next decade. This occurred because PrEP-related STI screening resulted in a 2.1-fold and 2.8-fold increase in the treatment of rectal GC and CT, respectively. Screening at every 3 months (vs 6 months) would avert 33.9% of GC and 35.9% of CT. Doubling PrEP coverage to 40% (with biannual screening) would avert about half of GC and CT infections. At 50% RC (with 20% PrEP coverage & biannual STI screening), the incidence rates of GC and CT would be 1.6 and 1.5 times higher compared to 0% RC.
Conclusion: Implementation of the CDC clinical practice guidelines for PrEP may serve as a high-impact STI prevention intervention due to the salutary effects of the recommended STI screening schedule. The bio-behavioral indications for PrEP could also be well-suited to identify MSM at substantial risk of STI infections that would otherwise remain undiagnosed, including asymptomatic rectal GC and CT. Reducing the STI screening interval to quarterly may not be efficient, as this doubling of STI testing and treatment only reduces population-level STI incidence by a further 5–6%. RC increases STI incidence, but is unlikely to offset the STI prevention benefits of adherence to PrEP-related STI screening recommendations.

1035 ANTICIPATED ADHERENCE, EFFICACY, AND IMPACT OF WEEKLY ORAL PREEXPOSURE PROPHYLAXIS

Christian Selinger[1], Ameya Kirtane[2], Omar Abouzid[2], Robert Langer[2], Carlo G. Traverso[3], Anna Bershteyn[1]
[1]Inst for Disease Modeling, Bellevue, WA, USA, [2]Massachusetts Inst of Tech, Cambridge, MA, USA, [3]Brigham and Women's Hosp, Boston, MA, USA

Background: Advances in drug delivery will soon make week-long orally delivered controlled release of highly potent anti-retroviral drugs a possibility. We estimated the potential impact of developing these technologies into a weekly oral pre-exposure prophylaxis (PrEP) formulation as an alternative to presently available daily oral PrEP.
Methods: To estimate the most likely impact of weekly PrEP on efficacy, we performed a meta-analysis of the difference in adherence (defined as medication possession ratio (MPR)>80%) to preventative drugs for chronic medical conditions. The relationship between plasma drug concentration and medication possession was estimated based on measurements in the Partners PrEP Study. The relationship between plasma drug concentration of tenofovir disoproxil fumarate and PrEP efficacy was estimated from the VOICE, FEM-PrEP, iPrEx, iPrEx-OLE, Partners PrEP, and Partners Demonstration Studies. The population-level impact of weekly vs. daily oral PrEP on infections averted in South Africa was simulated using the microsimulation model EMOD-HIV v2.5. We assumed 30% baseline PrEP coverage and 50% baseline PrEP efficacy, and varied the increment in efficacy and coverage for weekly compared to daily formulations.

Results: Random effects meta-analysis estimated that weekly dosage forms were associated with a 9% (CI: 5%-13%) greater MPR than daily dosage for the same medical condition. When adherence is high, MPR is similar to pill count, and the latter had 84% sensitivity to identify individuals with detectable tenofovir in blood while taking daily oral PrEP. One percentage increase in fraction with detectable drug levels was associated with a 1.5% increase in efficacy of oral PrEP across studies. Taken together, this suggests that weekly formulation could increase PrEP efficacy by 12% (CI: 6%-17%). Modeling suggests that weekly PrEP could avert 200,000 to 800,000 additional infections over twenty years in South Africa (Figure). This range of uncertainty reflects uncertainty in the true impact of weekly PrEP formulation on efficacy, whether there is also a difference in coverage due to acceptability of weekly PrEP, and concurrent ART scale-up.
Conclusion: Weekly oral PrEP has the potential to substantially increase PrEP efficacy and population-level impact relative to daily oral PrEP. Drug potency and sustained delivery mechanisms should be a high priority in oral PrEP development.



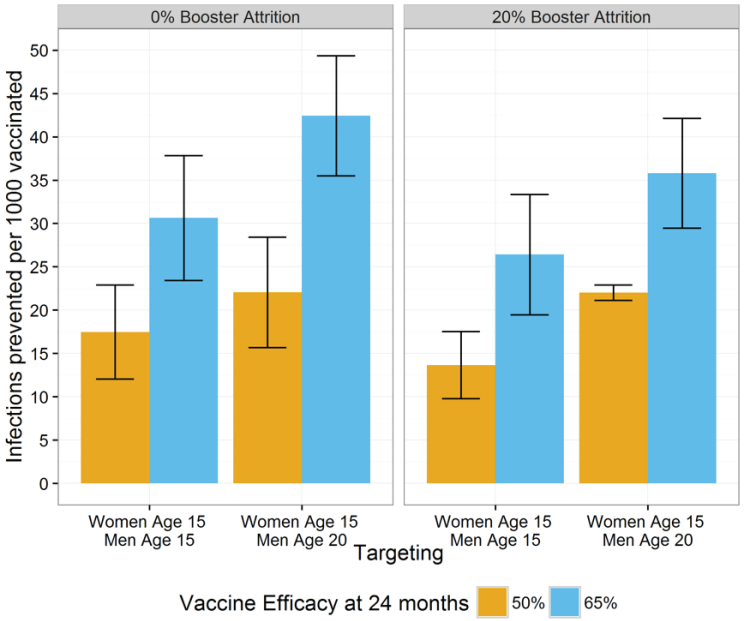
* Blue lines represent estimated efficacy increase and confidence intervals based on meta-analysis

1036 POPULATION-LEVEL IMPACT AND COST-EFFECTIVENESS OF AN HIV VACCINE IN SOUTH AFRICA

Christian Selinger[1], Anna Bershteyn[1], Dobromir Dimitrov[2], Timothy B. Hallett[3], Linda-Gail Bekker[4], Helen Rees[5], Glenda Gray[6], for the Pox-Protein Public-Private Partnership Global Access Committee

[1]Inst for Disease Modeling, Bellevue, WA, USA, [2]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [3]Imperial Coll London, London, UK, [4]Univ of Cape Town, Cape Town, South Africa, [5]Wits Reproductive Hlth and HIV Inst, Johannesburg, South Africa, [6]Perinatal HIV Rsr Unit, Soweto, South Africa

Background: The RV144 trial is to date the only demonstration of a partially effective HIV vaccine. Preliminary results from HVTN100 suggest similar immunogenicity for an ALVAC HIV clade C vaccine. Efficacy studies of ALVAC clade C with gp120 will include an additional booster at 12 months. Here, the population-level impact and maximum acceptable price of such a vaccine in South Africa are explored using EMOD, an individual-based network model.
Methods: The time profile of efficacy of an ALVAC/gp120 regimen with 12-month boost was fit to RV144 results or increased to 50% cumulative efficacy at 24 months. This time-varying efficacy profile was implemented in EMOD-HIV v2.5, a microsimulation model that has been fit to the HIV epidemic, and includes demographics, risk stratification, and HIV testing/cascade of care. In future projections, we varied the scale-up of treatment to examine its interplay with the 20-year impact of a vaccine to be started in 2027. Coverage was assumed to be 50% or 80% with boosters to continue two-yearly for ten years with up to 20% attrition per dose.
Results: A partially effective vaccine could reduce HIV incidence in South Africa by up to 21% with 80% coverage. The most efficient ages to start immunization are 15 in women and 20 in men, with 16-29 HIV infections averted per 1000 individuals vaccinated. If gender differences in vaccination age were impractical to implement, then ages 15 and 18 would be equally optimal for vaccination, with 10-23 HIV infections averted per 1000 vaccinated, a result highly sensitive to concurrent scale-up of ART. In contrast, combining HIV vaccination with the current HPV vaccine program among 9-11 year olds would result in less than one HIV infection averted per 1000 vaccinated due to waning immunity. Maximum cost-effective prices of a vaccine, calculated from the ratio of the net budget impact to DALYs averted, varied widely depending on cost-effectiveness thresholds and ART scale-up, and to a lesser extent on efficacy, age at vaccination, and attrition.
Conclusion: Partially effective HIV vaccines with rapid waning of immunity could substantially reduce HIV incidence if vaccination schedules were aligned with the ages of highest HIV incidence and high coverage levels were achieved. Reaching a new target population with a complex immunization schedule not aligned with other schedules may pose an implementation challenge in South Africa.



* Error bars reflect uncertainty about ART scale-up ranging from continuation of present-day trends to achievement of 90-90-90 targets.

1037 COST-EFFECTIVENESS OF PREEXPOSURE PROPHYLAXIS ACROSS COUNTIES IN WESTERN KENYA

Anna Bershteyn[1], Daniel J. Klein[1], Adam N. Akullian[1], Zindoga Mukandavire[2], Graham F. Medley[2], Wanjiru Mukoma[3], Michael K. Kiragu[3], Kennedy Mutai[4], Katharine Kripke[5], for the OPTIONS Consortium

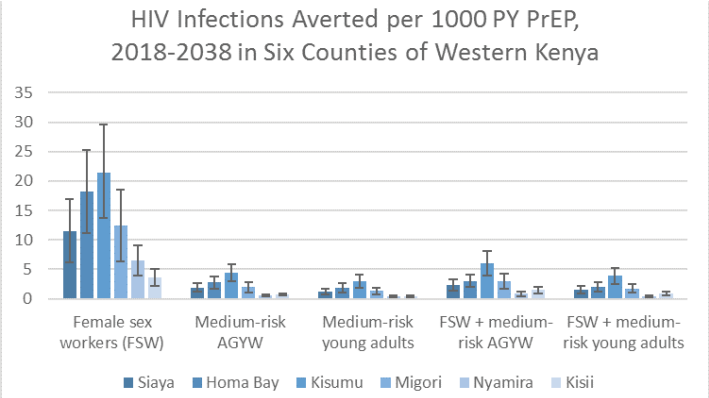
[1]Inst for Disease Modeling, Bellevue, WA, USA, [2]London Sch of Hygiene and Trop Med, London, United Kingdom, [3]LVCT Hlth, Nairobi, Kenya, [4]National AIDS Control Council, Ministry of Hlth, Nairobi, Kenya, [5]Avenir Hlth, Washington, DC, USA

Background: Pre-exposure prophylaxis (PrEP) is recommended when risk of acquiring HIV is high. Implementation planning for PrEP is now underway in Kenya. This analysis compares the estimated cost-effectiveness of PrEP in the six counties comprising the former Nyanza Province in Western Kenya, which exhibit a range of epidemic characteristics, including highly generalized, highly concentrated, and mixed epidemics.

Methods: The microsimulation model EMOD-HIV v2.5, fitted to demographic, programmatic, and epidemic data for six counties in Western Kenya, was used to assess the cost-effectiveness of PrEP. Female sex workers (FSW) were included based on a recent FSW enumeration; male clients of FSW were included to balance the number of clients reported by FSW. Projections with PrEP provision to FSW, "medium"-risk adolescent girls and young women (AGYW), who are not identified as FSW but still at elevated risk of HIV infection, and all medium-risk young adults were compared to projections without PrEP. The person-years of PrEP provided per HIV infection averted over a twenty-year time horizon was used as a proxy for PrEP cost-effectiveness. Upper bounds for PrEP impact assumed that present-day trends in antiretroviral therapy (ART) coverage continue; lower bounds for PrEP impact assumed achievement of UNAIDS 90-90-90 ART targets.

Results: Providing PrEP to FSW was more cost-effective compared to providing PrEP to "medium" risk adolescents and young adults in the general population. Regardless of PrEP coverage, the populations for which PrEP was most cost-effective were FSW in generalized or mixed epidemic contexts. In contrast, the cost-effectiveness of PrEP in a concentrated epidemic setting such as Kisii County, which had the second-highest proportion of adult women participating in FSW but an overall low HIV prevalence, was similar to that of providing PrEP to medium-risk AGYW in generalized or mixed epidemics. PrEP for medium-risk AGYW in mixed epidemics such as Kisumu was more cost-effective than PrEP for FSW in concentrated epidemics such as Kisii.

Conclusion: Transmission modeling suggests that the most cost-effective population for providing PrEP is FSW in mixed or generalized epidemic. FSW in concentrated epidemic contexts and high-risk AGYW in mixed or generalized epidemic contexts are both important populations to consider for PrEP.



1038 THE POTENTIAL IMPACT AND COST-EFFECTIVENESS OF MULTIPURPOSE PREVENTION TECHNOLOGIES

Ide Cremin[1], Jennifer Smith[1], Rebecca Geary[2], Timothy B. Hallett[1]
[1]Imperial Coll London, London, UK, [2]London Sch of Hygiene & Trop Med, London, UK

Background: Multipurpose prevention technologies (MPTs) to prevent both HIV and unintended pregnancy could create important opportunities in terms of cost efficiencies, higher acceptability and a reduced adherence burden for users. One such product in development is an intra-vaginal ring (IVR), and analyses of potential impact and cost-effectiveness will help guide development and delivery.
Methods: We developed a mathematical model to examine the impact and cost-effectiveness of four delivery strategies for an IVR MPT in South Africa. The first strategy assumes broad access to women of reproductive age (15-49 years) through existing public healthcare facilities. The second assumes enhanced coverage among younger women (15-29 years). The third and fourth prioritize an IVR for young women only and female sex workers, respectively. In accordance with acceptability data, coverage was assumed to vary between 5-10% of women in these target groups. Costs were assumed to range from US$16-163 per woman per year, depending on the assumed cost of the product and delivery strategy. We summarised HIV-related and reproductive health impacts as DALYs averted over a ten-year intervention period.
Results: HIV infections averted among women range from 2.7% (low efficacy ring) to 5.5% (high efficacy ring), when an IVR is prioritized to younger women (15-29 years old). Maternal deaths averted range from 1.7% (low efficacy ring) to 5.2% (high efficacy ring), assuming 50% displacement from other methods of contraception, and from 5.2% (low efficacy ring) to 6.5% (high efficacy ring) assuming all IVR ring users are new contraceptive users, when an IVR is provided to 15-49 year old women with enhanced coverage among younger women. Assuming a high-efficacy low-cost IVR, the cost per DALY averted would range from $176 to $1089 (depending on delivery strategy) with 50% displacement, and from $169 to $1070 if all IVR users are new contraceptive users.
Conclusion: The use of an MPT IVR has the potential to cost-effectively reduce new HIV infections and unintended pregnancies and their sequelae among women in South Africa, if low costs can be achieved through integration with existing services. New and forthcoming data on the efficacy and cost of delivery of dual use IVRs, and women's and couples' behaviours and preferences will be critical for optimising the use of dual use products for the prevention of HIV and unintended pregnancy.

1039 THE IMPORTANCE OF A LOCAL PERSPECTIVE IN MONITORING THE SUCCESS OF HIV PREVENTION

Sarah-Jane Anderson[1], Joanne Enstone[2], Geoff P. Garnett[3], Timothy B. Hallett[1]
[1]Imperial Coll London, London, UK, [2]Univ of Nottingham, Nottingham, UK, [3]Bill and Melinda Gates Fndn, Seattle, WA, USA

Background: Setting and monitoring progress towards targets for HIV prevention should ensure responsive programmes and the appropriate use of resources. However, because of the considerable diversity in the burden and characteristics of the epidemic it is unclear how to apply global targets for HIV control to local settings. Furthermore, a large number of indicators have been recommended for monitoring progress but it is unclear which are most informative.
Methods: We use location specific models, tailored to reflect available epidemiological data in each of the counties and major cities in Kenya, to project the future trajectory of each local epidemic. Because both the epidemic and response may change in many ways, multiple future trajectories were considered through varying future behaviours, treatment coverage and available prevention interventions. From these we are able to (1) look at the change in incidence in each location between 2015-2030 across simulations, and (2) assess which indicators are most indicative of a change in incidence.
Results: The future trajectory of the epidemic varies considerably between modelled locations, thus the impact of specific targets will differ according to local setting (only 10 of 48 locations experience a median reduction in incidence of >80% by 2030 across the scenarios considered). The strength of each indicator in predicting changes in incidence is highly dependent on local patterns of transmission and the extent to which the epidemic is concentrated or generalised (Figure 1). Most single indicators demonstrate only limited association with changes in incidence as changes in incidence depend upon the combined effect of changes in sexual behaviours and other intervention successes. Measures of the population prevalence of viral non-suppression show the most consistent associations with long-term changes in incidence across locations.
Conclusion: Targets and indicators need to be appropriate for the local epidemic and what can feasibly be achieved. If they are to be used to assess progress in controlling HIV they need to be informed by a good understanding of how they relate to HIV incidence. There is no one universally reliable indicator to predict future changes in HIV incidence, but population viral load may offer the most consistently predictive metric in some of the settings with large generalised epidemics.

1040 PAST AND FUTURE IMPACT OF ART SCALE-UP IN BRAZIL: PROGRAMME DATA ANALYSIS 1996–2014

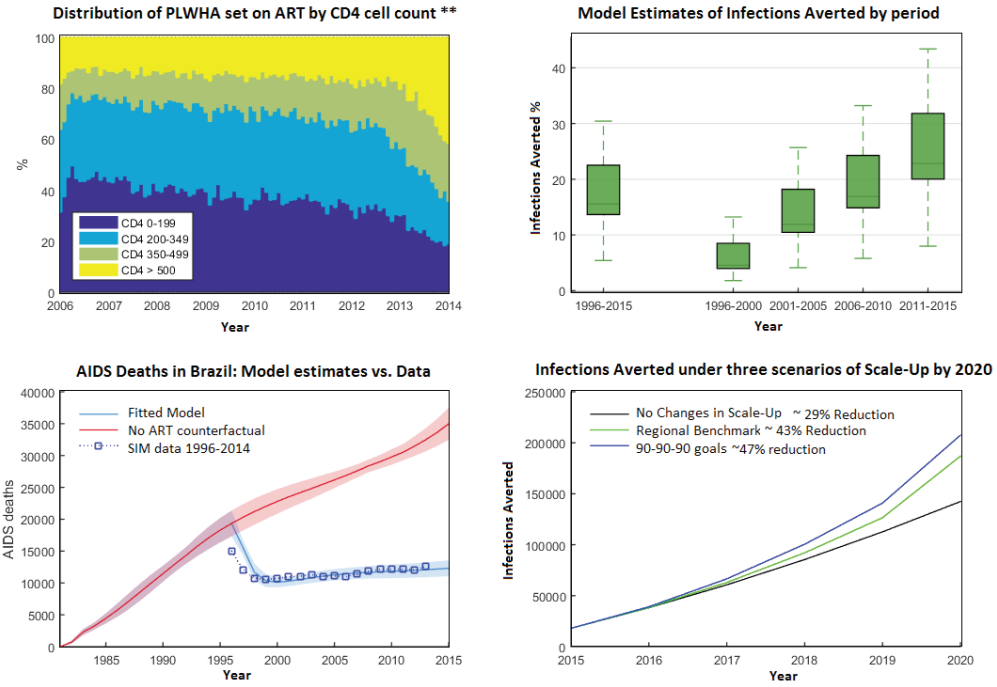
Juan F. Vesga[1], Ana R. Pati Pascom[2], Tara Mangal[1], Marcelo Freitas[2], Juliana M. Givisiez[2], Ronaldo de Almeida Coelho[2], Mariana Veloso Meirelles[2], Clarissa Habckost Dutra de Barros[2], Adele Benzaken[2], Timothy B. Hallett[1]
[1]Imperial Coll London, London, UK, [2]Ministry of Hlth, Brasilia (DF), Brazil

Background: Universal free access to ART is available in Brazil since 1996 and from 2013 it is offered to all living with HIV disregarding of their CD4 cell count. We combined mathematical modelling and extensive data analysis to assess, for the first time in the country, the impact of ART expansions and the prospects of future mortality and incidence reductions.
Methods: A network of models was developed to represent HIV transmission and the flow through stages of care in Brazil's five major regions. Four datasets (SISCEL, SICLOM, SINAN, and SIM) encompass Brazil's records on laboratories, treatment, surveillance, and mortality respectively with records dating as early as 1981 and updated up to 2014. These data together with prevalence studies were used during model calibration. Time trends in ART survival rates were estimated. The impact was assessed as incidence and mortality

reductions up to 2015 in the presence of ART, condoms, and needle exchange programs. Furthermore, three forward-looking scenarios were simulated to assess the impact as the cascade in Brazil moves towards 90-90-90 goals by 2020.

Results: We estimated that 18% to 22% of HIV infections were averted from 1996 to 2015 due to ART. In the recent period of 2011 to 2015, the reductions rose to 34% to 41%, matching the observed increments in the number of people treated for that period. ART has impacted Brazil's overall survival by contributing 1,660,000 Life-Years since 1996 – which is 0.005 years per person-year on ART. Levels of impact have been uplifted by the wealthier regions in southern Brazil where better and earlier access yielded reductions between 35% and 52% in the last five years. Forward projections show that between 22% and 35% of infections can be averted by 2020 if current levels of coverage stay unchanged. Additionally, if all regions reach the highest levels of coverage observed in the south, reductions reach levels between 37% and 49%. Finally, reaching 90-90-90 goals could produce reductions between 43% and 56% by 2020.

Conclusion: This is the first assessment of Brazil's wealth of data on the impact of ART on the HIV epidemic. ART expansions attained important reductions in incidence and mortality in a context of combined prevention. Substantial regional differences give scope for realistic projections of improved impact if all regions match the best-performing programs in the country. Further expansions to the 90-90-90 goals, would entail far-reaching changes, but would lead to an increase in impact.



*** Source: SISCEL & SICLOM databases, Ministry of Health Departamento de DST, Aids e Hepatites Virais, Brazil*

1041 EARLIER DIAGNOSIS AND TREATMENT REDUCES HIV TRANSMISSION IN MSM IN THE NETHERLANDS

Ard van Sighem[1], Daniela Bezemer[1], Eline Op de Coul[2], Judith Branger[3], Mark de Boer[4], Peter Reiss[5], for the ATHENA National Observational HIV Cohort
[1]Stichting HIV Monitoring, Amsterdam, Netherlands, [2]Natl Inst for Pub Hlth and the Environment, Bilthoven, Netherlands, [3]Flevoziekenhuis, Almere, Netherlands, [4]Leiden Univ Med Cntr, Leiden, Netherlands, [5]Stichting HIV Monitoring and Academic Med Cntr Amsterdam, Amsterdam, Netherlands

Background: Since 2012 treatment guidelines in the Netherlands recommend starting combination antiretroviral treatment (cART) immediately after HIV diagnosis, irrespective of CD4 cell counts. At the same time, cART effectiveness and tolerability improved considerably. We investigated to what extent the observed decrease in HIV diagnoses among men who have sex with men (MSM), from 766 in 2011 to 558 in 2015, could have been the result of earlier diagnosis and treatment.

Methods: We used an existing mathematical model describing HIV transmission, disease progression, and the effects of cART to study changes in the HIV epidemic among MSM. Treatment-related parameters were derived from data in the national ATHENA cohort, including time to viral suppression and rates of viral rebound. Viral suppression was defined as HIV RNA <1000 copies/ml; below this threshold HIV transmission is unlikely. We estimated changes over calendar time in duration from HIV infection to diagnosis, per-capita transmission rate (a proxy for risk behaviour), and annual number of newly acquired infections needed to explain annual data on HIV and AIDS diagnoses up to 2015. In a hypothetical scenario, we assumed treatment guidelines did not change in 2012.

Results: Median time to viral suppression in MSM diagnosed with asymptomatic HIV and CD4 counts ≥200 cells/mm^3 decreased from 0.97 (interquartile range, 0.29-3.30) years in 2000 to 0.76 (0.24-1.99) years in 2011 and 0.16 (0.10-0.25) years in 2015, and was shorter in MSM with CD4 <200 cells/mm^3, symptomatic HIV, or AIDS. During the same time, the proportion with viral rebound decreased from 55% to 11%. Our model estimated that HIV-positive individuals were diagnosed earlier: average time from infection to diagnosis decreased from 2.86 (95% confidence interval [CI], 2.72-3.02) years in 2000-2003 to 2.07 (1.93-2.19) years in 2012-2015, while the transmission rate increased by 20% (9-36). Annual number of newly acquired HIV infections decreased from a peak of 710 (95% CI, 650-780) in 2007 to 590 (540-650) in 2011 and 350 (320-400) in 2015. In 2012-2015, there were 1864 (1722-2074) estimated new HIV infections, which is 832 less than in a counterfactual scenario with no earlier treatment after 2011.

Conclusion: Our model suggests that immediate treatment, in combination with earlier diagnosis and less viral rebound, contributed to a substantial decrease in the annual number of new HIV infections in MSM in the Netherlands despite an increase in risk behaviour.

1042 ACHIEVING THE 90-90-90 TARGET BY 2020: THE EXPERIENCE IN BRITISH COLUMBIA, CANADA

Viviane D. Lima, **Martin St-Jean**, Jean A. Shoveller, P. Richard Harrigan, Bohdan Nosyk, Robert S. Hogg, Paul Sereda, Rolando Barrios, Julio S. Montaner
BC Cntr for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada

Background: Antiretroviral therapy (ART) scale-up is central to the global strategy to control the HIV/AIDS pandemic. To accelerate efforts towards ending the AIDS epidemic, the Joint United Nations Programme on HIV/AIDS released the "90-90-90" target. Thus, the present analysis was conducted to characterize the progress in British Columbia (BC), Canada, toward achieving the 90-90-90 target, and to predict whether BC is on track to reach this target by 2020.

Methods: Using linked individual-level data sets of people living with HIV (PLWH) in BC, we estimated the number of PLWH (aged ≥19 years) from 1996/1997 to 2013/2014. We modeled the trends in HIV prevalence and each of the steps of the 90-90-90 target using generalized additive models. Subsequently, we forecasted these outcomes for the fiscal years from 2014/2015 to 2019/2020. Lastly, we performed a sensitivity analysis to account for uncertainty associated with prevalence estimates based on four different scenarios with increasing prevalence, based on the upper 95% confidence interval bound of our original forecasted estimates, and based on a 5%, 10% and 15% increase in these same estimates.
Results: Among the estimated 10538 PLWH in BC in 2013/2014, 83% of PLWH were diagnosed, of these 81% were on ART, and among those who were on ART, 96% were virologically suppressed. Our model projections suggest further progress on these metrics in the next five fiscal years. By 2019/2020, the model projects that 93% of PLWH would be diagnosed, among these, 91% would be on ART and among those on ART, 97% would be virologically suppressed. Only one scenario in the sensitivity analysis met the 90-90-90 target by 2019/2020, the scenario based on the upper 95% confidence interval bound of our original forecasted prevalence estimates (90% of PLWH diagnosed). In the other scenarios, the proportion of PLWH diagnosed by 2019/2020 ranged from 81% to 88%.
Conclusion: As we approach 2020, BC is rapidly moving towards achieving the 90-90-90 target. Our results provide strong evidence that integrated comprehensive free programs that facilitate testing, and the delivery of treatment and care to this population can be effective in controlling, and eventually, ending the AIDS epidemic.

Table 1 Model Projections for Each of the Steps of the UNAIDS 90-90-90 Target by Fiscal Year, from 2014/2015 to 2019/2020, in British Columbia

	Estimates (95% Confidence Interval)			
		% of Target Reached		
Fiscal Year	Prevalence	Diagnosed	On ART	Suppressed
2014/2015	10499 (10408 - 10591)	8899 (8809 - 8989)	7372 (7241 - 7503)	7092 (6869 - 7316)
		85%	83%	96%
2015/2016	10470 (10338 - 10603)	9039 (8907 - 9171)	7645 (7447 - 7842)	7374 (7035 - 7713)
		86%	85%	97%
2016/2017	10441 (10266 - 10617)	9179 (9003 - 9355)	7917 (7652 - 8182)	7656 (7199 - 8114)
		88%	86%	97%
2017/2018	10412 (10194 - 10631)	9319 (9099 - 9539)	8189 (7855 - 8523)	7938 (7362 - 8515)
		90%	88%	97%
2018/2019	10383 (10121 - 10645)	9459 (9195 - 9724)	8462 (8059 - 8864)	8220 (7524 - 8917)
		91%	90%	97%
2019/2020	10354 (10049 - 10660)	9600 (9291 - 9908)	8734 (8262 - 9206)	8502 (7686 - 9319)
		93%	91%	97%

1043 THE CLINICAL AND ECONOMIC IMPACT OF ATTAINING NHAS TREATMENT TARGETS IN THE US

Ethan D. Borre[1], Emily P. Hyle[1], Paul E Sax[2], A. David Paltiel[3], Anne M. Neilan[1], Kenneth Freedberg[1], Rochelle P. Walensky[1]
[1]Massachusetts General Hosp, Boston, MA, USA, [2]Brigham and Women's Hosp, Boston, MA, USA, [3]Yale Univ, New Haven, CT, USA

Background: The US National HIV/AIDS Strategy (NHAS) aims to achieve 72% viral suppression among people living with HIV (PLWH) in the US by 2020. We examine the clinical and economic impact of reaching this target, both in the general population (US) and among Black MSM (BMSM).
Methods: We use a mathematical simulation (the CEPAC model) to project clinical outcomes, costs, and cost-effectiveness, over 5y and 20y, for two strategies: 1) Current Pace of detection, retention, and viral suppression; and 2) NHAS aspirational detection, linkage, and retention, resulting in 72% suppression by 2020. We assume that the US population of PLWH at model outset is 86% diagnosed, 37% diagnosed and in care, and 30% virally suppressed. For BMSM, these are 83%, 34%, and 28%. Under NHAS, we improve the average testing interval from 10 to 4 years, also incurring additional costs for testing ($32/test) and adherence to care interventions ($3,800/year). Transmission rates are HIV RNA-dependent (0.16-9.03/100PY) and include a reduction due to condom use (40% (US) and 10% (BMSM)). Annual ART costs are $25,000-$40,000. We define a strategy as "cost-effective" if its incremental cost-effectiveness ratio (ICER) is <$100,000/life-year saved (YLS). In sensitivity analyses, we examine alternative testing and adherence interventions and costs.
Results: NHAS improves viral suppression at 5y from 53% to 73% compared to Current Pace in the US (BMSM: 48% to 64%). Over 20y, NHAS will avert 265,900 (51,400) transmissions and 192,600 (30,200) deaths and save 2,008,000 (298,000) years of life. Over 20y, BMSM represent 18% of PLWH nationwide and account for 20% of transmissions averted under NHAS vs. Current Pace. NHAS increases costs by $191.1 billion ($19.8 billion) over 20y, with ART costs making up 86% (80%) of the budget. The ICER for scale up to NHAS compared to Current Pace is $96,000/YLS for US ($66,000/YLS). If the adherence intervention cost is doubled and efficacy halved, scale up to NHAS remains cost-effective in the US at $97,000/YLS ($75,000/YLS). Halving ART costs reduces the ICER of NHAS to $45,000/YLS ($26,000/YLS).
Conclusion: Reaching NHAS targets would yield substantial clinical benefits and be cost-effective in both the general US and BMSM populations. Interventions among BMSM will avert proportionally more transmissions at lower cost. The cost-effectiveness of NHAS scale up strategies is largely dependent on ART costs, less so on testing/adherence costs.

1044 IMPROVING THE PRISON CARE CONTINUUM REDUCES RACIAL HIV DISPARITIES: A MODELING STUDY

Brandon D. Marshall[1], Maximilian King[1], Alexandria Macmadu[2], Lauren Brinkley-Rubinstein[3], M.-J. Milloy[4], Curt G. Beckwith[1], Frederick Altice[5], Josiah D. Rich[1]
[1]Brown Univ, Providence, RI, USA, [2]The Miriam Hosp, Providence, RI, USA, [3]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [4]Univ of British Columbia, Vancouver, British Columbia, Canada, [5]Yale Univ, New Haven, CT, USA

Background: Prisons provide an opportunity for HIV screening and provision of antiretroviral therapy (ART). However, many individuals fail to re-engage with care post-release, increasing HIV transmission risk in the broader community. In this agent-based modeling study, we sought to determine how improved HIV diagnosis and ART initiation while incarcerated in prison-and continued transitional care post-release-could reduce HIV transmission and address racial HIV disparities in the non-incarcerated community.
Methods: Using Atlanta, Georgia as a case study, we developed an agent-based model to simulate HIV transmission in a dynamic, population-based sexual and drug-injecting network. The base case model was parameterized using city- and race-specific inputs for population characteristics, incarceration rates, sentencing lengths, and ART coverage. The model was calibrated to race-specific HIV incidence estimates for the Atlanta population in 2012. Then, in an "idealized" prison HIV care continuum scenario, all incarcerated agents were tested for HIV, initiated ART (for those testing positive), and were permanently maintained on ART post-release. Next, we compared projected community HIV incidence 10 years after implementation of the "idealized" correctional care continuum to that of the base case model.

Results: Compared to the base case, the idealized care continuum scenario reduced 10-year community HIV incidence by 23.7% (from 48.8 to 37.3 per 100,000 by 2022). The percentage reduction was larger among blacks (25.4%, 97.5 to 72.8 per 100,000 by 2022) than among whites (16.7%, 17.2 to 14.3 per 100,000; Figure 1). The overall reduction in community HIV incidence was larger (30.7%) in a sensitivity analysis in which HIV risk was doubled for 6 months post release.
Conclusion: Universal HIV testing and treatment in prisons, and programs to ensure retention in care post-release, may reduce HIV incidence in non-incarcerated populations. An optimized HIV care continuum in the prison setting and post-release may also significantly reduce racial HIV disparities, particularly if effective, culturally tailored linkage to care interventions can be implemented.

1045 THE COST-EFFECTIVENESS OF FINANCIAL INCENTIVES FOR VIRAL SUPPRESSION IN HPTN 065

Blythe J. Adamson[1], Deborah J. Donnell[2], Dobromir Dimitrov[2], Louis Garrison[1], Geetha Beauchamp[2], Theresa Gamble[3], Wafaa M. El-Sadr[4]
[1]Univ of Washington, Seattle, WA, USA, [2]Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA, [3]FHI 360, Durham, NC, USA, [4]ICAP at Columbia Univ, New York, NY, USA
Background: HIV viral suppression (VS) is associated with individual and societal health and economic benefits. The HPTN 065 study found providing $70 financial incentives (FI) for VS to HIV patients in Bronx, NY, and Washington, DC, resulted in a significantly higher proportion of patients with VS (revised as 3.7%) at sites randomized to FI compared to standard care. We developed a mathematical model to evaluate the cost-effectiveness of FI in HPTN 065.
Methods: A two-part semi-Markov model was used to simulate the cohort of HIV patients in care at study sites and their sexual partners during the two-year intervention. The effect on VS was assumed to diminish to zero over six months when FIs end, with patients and partners followed over a lifetime horizon. The number of HIV transmissions during the study period was estimated with transmission risk equations. Study budgets and staff time informed cost parameters; self-reported sexual activity informed the number of partners; patient utility projection relied on literature-based utility by CD4 count. Lifetime total costs, HIV transmissions, and quality-adjusted life years (QALYs) are predicted from a health-care sector perspective and discounted 3% annually. We assumed a US willingness to pay of 3xGDP per capita threshold of $150,000/QALY for cost-effectiveness.
Results: FIs for VS are likely to be highly cost-effective for HPTN 065 with an overall incremental cost-effectiveness ratio (ICER) of $7,371/QALY. Over two years, FI had a fixed cost of $167,714 per clinic for administration plus an average variable cost of $337 per patient for gift cards (Table 1). The resulting improvement in VS is projected to gain 19 patient QALYs and 20 partner QALYs in the population, and prevent 3 HIV infections for an average clinic with 456 patients on ART. Outpatient visits and ART costs increased 8.7% for FI patients; however, the estimated marginal increase in health care costs ($119 and $3,089 per patient respectively) are offset by savings from fewer HIV transmissions. A sensitivity analysis projected FI for VS cost-effective in all pre-specified sub-groups based on clinic size, type, baseline VS, and city with ICERs ranging from cost-saving to $79,471/QALY.
Conclusion: Financial incentives offer substantial value for money to improve the length and quality of life for HIV patients and their partners. This analysis provides evidence supporting the likely cost-effectiveness of an intervention to strengthen the clinical care continuum and reduce HIV transmission.

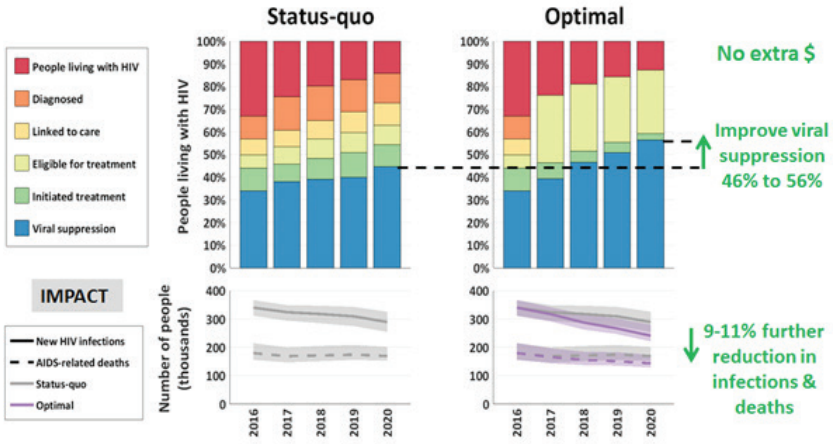
Table 1. Lifetime total costs and health outcomes for a two-year intervention providing $70 FI, at most provided quarterly, for VS in HIV patients compared to standard of care.

	Standard Care	Financial Incentives	Incremental Results
ICER (US$/QALY gained)			$7,371/QALY
TOTAL COSTS	$201 million	$202 million	$290,495
Program Administration Cost	0	$167,714	$167,714
FI Gift Card	0	$153,469	$153,469
Patient Lifetime Health Expenditures	$163 million	$164 million	$1.3 million
Partners Lifetime Health Expenditures	$39 million	$37 million	-$1.3 million
TOTAL QALYs	17,686	17,725	39
Patient QALYs	4601	4,621	19
Partners QALYs	13,084	13,105	20
HIV Transmissions to partners	66	62	-3.7

Study population includes a cohort of 456 HIV patients in care at an average clinic and a cohort of 774 sexual partners. Total costs (adjusted to 2015 USD) include the financial incentives program for HIV patients and the lifetime total health care expenditures associated with HIV for patients and partners using a 3% discount rate, lifetime horizon, and health care sector perspective. FI, financial incentives; VS, viral suppression; QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio.

1046 OPTIMIZING INTERVENTION MODALITIES TO IMPROVE 90-90-90 CONTINUUM IN SOUTH AFRICA

David Wilson[1], Andrew Shattock[2], Nicole Fraser[3], Zara Shubber[3], Marelize Gorgens[3], **David Wilson**[3], Richard Gray[2], Yogan Pillay[4]
[1]Monash Univ, Melbourne, Australia, [2]Univ of New South Wales, Sydney, Australia, [3]World Bank, Washington, DC, USA, [4]South African Natl Dept of Hlth, Pretoria, South Africa
Background: A large number of interventions and service modalities have been used in South Africa to increase the proportion of PLHIV aware of their status, initiated and retained on ART and achieving viral suppression. With limited resources, it is imperative that smart choices are made around the best combination of interventions to achieve maximal population health.
Methods: We collated detailed costing data and programmatic outcomes of 30 testing-, linkage-, retention-, care-, and treatment-related interventions in South Africa, further broken down by urban/rural locality. We developed a novel optimization model to test the hypothesis that re-allocation of projected future resources across these 30 interventions could potentially yield greater clinical outcomes towards attaining the UNAIDS 90-90-90 targets over 2017-2020 compared to current focus areas.
Results: We predict that 46% (43%-49%) of PLHIV in South Africa will achieve viral suppression by 2020 by maintaining current focus areas. Without additional funds, we estimate that the proportion of PLHIV achieving viral suppression by 2020 can increase to 56% (52%-59%) by optimally allocating resources and removing ART eligibility constraints; a 19% (13%-24%) relative increase. In the context of 90-90-90, we project that an estimated 85% of PLHIV will be diagnosed; 63% of them will receive ART, and 85% of them will be virally suppressed by 2020 according to current practices; but these values can increase to 87%-69%-94% by optimal prioritization. Our analyses suggest that mobile and door-to-door HIV testing services should be prioritized with client-initiated clinic-based testing and self-testing. Fast-track treatment initiation counselling should be scaled up at the expense of the classic ART initiation counselling model. Adherence support for PLHIV receiving ART should be a priority with a focus on text messaging services and enhanced adherence counselling by lay counsellors. Point-of-care viral load testing should be priority in rural settings, and decentralised delivery and adherence club services for treatment dispensing is also important. We estimate that 11% (9%-12%) of HIV infections and 9% (6%-11%) of AIDS-related deaths can be averted (2017-2020) by optimal resource allocation combined with South Africa's universal test and treat policy.
Conclusion: Targeting of investment to the right combination of service modalities across the HIV care continuum can yield important gains for population health.



1047 POPULATION-LEVEL IMPACT OF REACHING UNAIDS HIV PREVENTION TARGETS IN CÔTE D'IVOIRE

Mathieu Maheu-Giroux[1], Juan F. Vesga[2], Souleymane Dabate[3], Michel Alary[3], Stefan Baral[4], Douada Diouf[5], Kouame Abo[6], **Marie-Claude Boily**[2]
[1]Imperial Coll London, London, UK [2]Laval Univ, Quebec, Canada, [3]The Johns Hopkins Univ, Baltimore, MD, USA, [5]Enda Santé, Dakar, Senegal, [6]Ministère de la Santé et de l'Hygiène Pub, Abidjan, Cote d'Ivoire

Background: National responses need to be markedly accelerated to achieve UNAIDS' ambitious targets. We aimed to estimate the impact of various scale-up of antiretroviral treatment as prevention scenarios in Côte d'Ivoire.

Methods: An age-stratified dynamic model was developed and calibrated to epidemiological and programmatic data using a Bayesian framework, following a comprehensive review of the published and grey literature and site visits. The model represents sexual and vertical HIV transmission in the general population, female sex workers (FSW), and men who have sex with men (MSM). We estimated the impact of scaling-up interventions to reach the UNAIDS targets (90-90-90 by 2020 and 95-95-95 by 2030), and that of eight other scenarios, on HIV transmission in adults and children, compared to our baseline scenario that maintains 2015 rates of testing, antiretroviral therapy (ART) initiation, retention, treatment failure, and levels of condom use.

Results: In 2015, we estimated that 51% (95% Credible Intervals: 45-58%) of HIV positive individuals were aware of their status, 75% (59-85%) of those aware were on ART, and 77% (74-79%) of those on ART were virologically suppressed. Reaching the 2020 and 2030 UNAIDS targets on time would avert 49% (41-57%) of new adult HIV infections over 2015-2030 compared to 30% (25-36%) if the 90-90-90 target is only reached in 2025. Attaining the UNAIDS targets in FSW, their clients, and MSM - but not in the rest of the population - would avert a similar fraction of new infections (30%; 23-39%). Only 37% (23-49%) of all HIV infections would be averted if scaling-up of ART was accompanied by a 25% points drop in condom use from their 2015 levels among FSW and MSM.

Conclusion: Rapid scale-up of interventions, particularly HIV testing, ART initiation, and retention in the next five years is needed to halve HIV incidence by 2030. Reaching UNAIDS 90-90-90 targets with a five year delay reduces impact by two fifth (40%) and is not more effective than reaching UNAIDS targets in time among vulnerable key populations (MSM, FSWs and their clients) only. Results suggest that the importance of sustaining condom use in key populations while scaling-up ART should not be underestimated in order to maintain the prevention gains achieved in the past years and to realise the full potential of scaling-up treatment as prevention.

1048 ART RETENTION AND VIRAL SUPPRESSION KEY TO MAXIMISING TREATMENT AS PREVENTION IMPACT

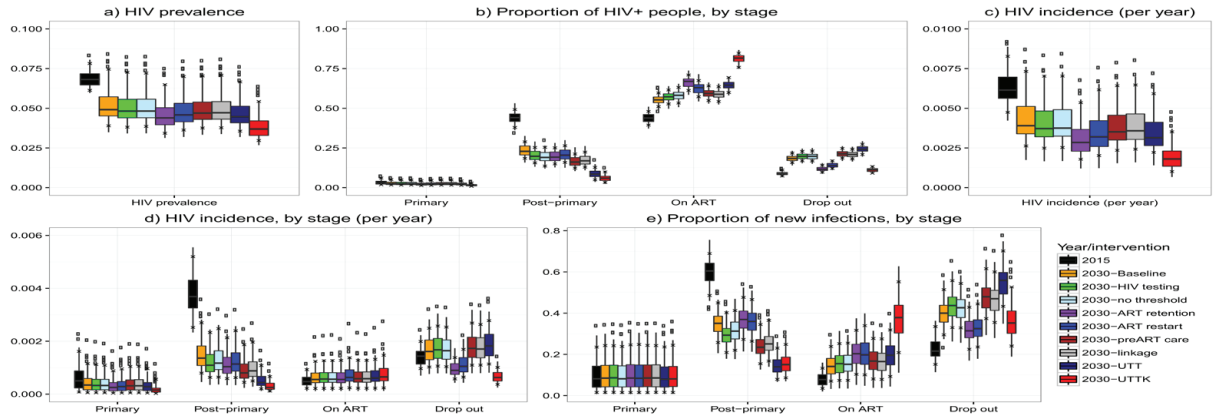
Nicky McCreesh[1], Ioannis Andrianakis[1], Mark Strong[2], Rebecca N. Nsubuga[3], Ian Vernon[4], Trevelyan J. McKinley[5], Jeremy E. Oakley[2], Michael Goldstein[4], Richard Hayes[1], Richard G. White[1]
[1]London Sch of Hygiene and Trop Med, London, UK, [2]Sheffield Univ, Sheffield, UK, [3]MRC/UVRI Rsr Unit on AIDS, Entebbe, Uganda, [4]Durham Univ, Durham, UK, [5]Exeter Univ, Exeter, UK

Background: UNAIDS call for fewer than 500,000 new HIV infections/year by 2020, with treatment-as-prevention being a key part of their strategy for achieving the target. A better understanding of the contribution to transmission of people at different stages of the care pathway can help focus intervention services at populations where they may have the greatest effect. We investigate this using Uganda as a case study.

Methods: An individual-based HIV/ART model was fitted using history matching. 100 model fits were generated to account for uncertainties in sexual behaviour, HIV epidemiology, and ART coverage up to 2015 in Uganda. A number of different ART scale-up intervention scenarios were simulated between 2016-2030. The incidence and proportion of transmission over time from people with primary infection, post-primary ART-naïve infection, and people currently or previously on ART was calculated.

Results: In all scenarios, the proportion of transmission by ART-naïve people decreases, from 70% (61%-79%) in 2015 to between 23% (15%-40%) and 47% (35%-61%) in 2030 (Figure). The proportion of transmission by people on ART increases from 7.8% (3.5%-13%) to between 14% (7.0%-24%) and 38% (21%-55%). The proportion of transmission by ART dropouts increases from 22% (15%-33%) to between 31% (23%-43%) and 56% (43%-70%).

Conclusion: People who are currently or previously on ART are likely to play an increasingly large role in transmission as ART coverage increases in Uganda. Improving retention on ART, and ensuring that people on ART remain virally suppressed, will be key in reducing HIV incidence in Uganda.



1049LB COST-EFFECTIVENESS OF A COMBINATION STRATEGY FOR THE HIV CARE CASCADE IN SWAZILAND

Elizabeth Stevens[1], Kimberly Nucifora[1], Qinlian Zhou[1], Lingfeng Li[1], Scott Braithwaite[1], Margaret McNairy[2], Averie B. Gachuhi[2], Matthew R. Lamb[3], Velephi Okello[4], Wafaa M. El-Sadr[2]

[1]New York Univ, New York City, NY, USA, [2]ICAP Columbia Univ, New York, NY, USA, [3]Columbia Univ, New York, NY, USA, [4]Swaziland Ministry of Hlth, Mbabane, Swaziland

Background: The Link4Health (L4H) study demonstrated that a combination strategy including point of care CD4 testing, rapid ART initiation, SMS reminders, financial incentives, and provision of health packages to motivate linkage and retention, significantly improved linkage to plus retention in care for HIV+ persons in Swaziland (SZ). We evaluated cost-effectiveness of the scale-up of L4H strategy in SZ.

Methods: We incorporated the observed effects and costs of L4H into a computer simulation of the HIV pandemic in SZ (increasing proportion of HIV-positive persons linked/retained in care and on ART from 39% to 53% with an annual program cost of $95 per person), comparing a scenario in which L4H was scaled up with a counterfactual scenario with no scale-up. The simulation combined a deterministic compartmental model of HIV transmission with a stochastic microsimulation of HIV progression, and was calibrated to SZ epidemiological data with the goal of replicating trends in SZ HIV prevalence, incidence, deaths, and persons with HIV from 1997 to 2015. We conservatively assumed that effects only persisted while the program was continued. Concordant with methodological guidelines, we assessed the incremental cost-effectiveness ratio from a societal perspective using $2015, a time horizon of 20 years, and a discount rate of 3%.

Results: In base case analyses, the L4H strategy reduced the number of new HIV infections over 20 years by 8,466 for total of 154,639 versus 163,105 HIV+ persons, reduced the number of HIV-related deaths over 20 years by 6,324 from 65,543 to 59,219; and reduced the overall infectiousness of HIV+ persons from 0.046 to 0.044 new infections per person per year. Incremental HIV treatment costs were reduced by $2 per person per year because of reduced AIDS cases. Overall, cost per HIV infection averted was $18,100 and cost per quality-adjusted life-year (QALY) gained was $3,820. Using time horizons of 5 years and 10 years rather than 20 years increased the incremental cost-effectiveness ratio of L4H to $12,380 and $6890, respectively. In other sensitivity analyses, the incremental cost-effectiveness ratio varied between $1500 and $5000 per QALY, indicating that L4H has favorable value in the context of estimated SZ GDP of $3000.

Conclusion: Our findings suggest that scale-up of the L4H strategy would substantially reduce HIV-related deaths, avert HIV infections, and would have favorable value in confronting the HIV epidemic in SZ over 10 year timeframe or longer.

1050 COST-EFFECTIVENESS OF SAME-DAY TREATMENT INITIATION IN SOUTH AFRICA

Lawrence Long[1], Mhairi Maskew[1], Alana Brennan[2], Constance Mongwenyana[1], Cynthia Nyoni[1], Given Malete[1], **Ian Sanne**[1], Matthew Fox[2], Sydney Rosen[2]

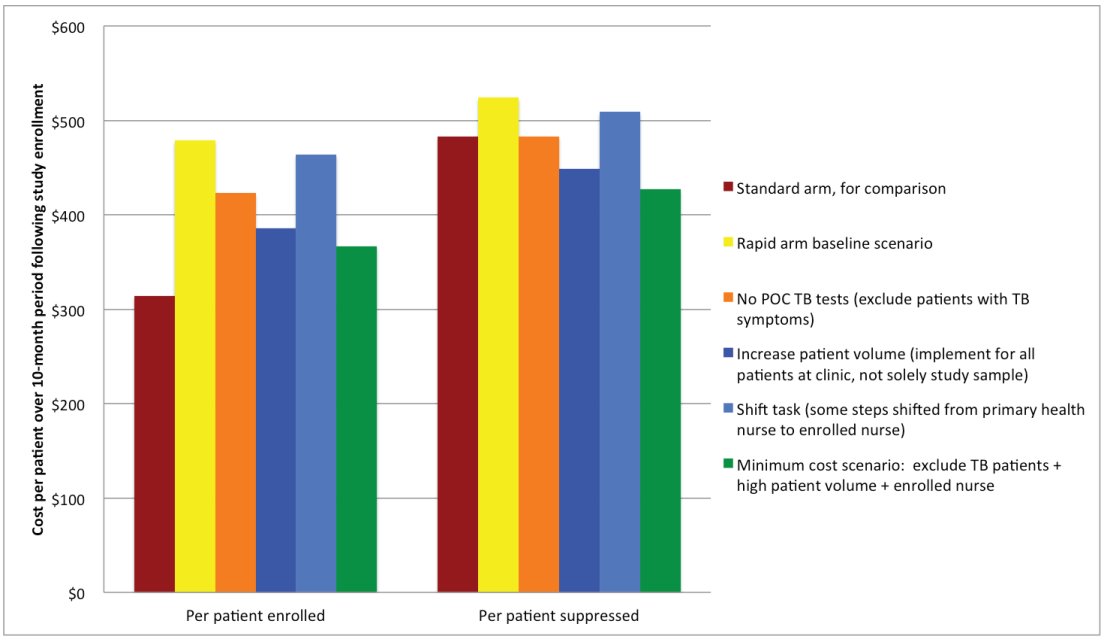
[1]Univ of the Witwatersrand, Johannesburg, South Africa, [2]Boston Univ, Boston, MA, USA

Background: The RapIT RCT of same-day ART initiation among non-pregnant adults using accelerated procedures and point-of-care (POC) laboratory instruments in Johannesburg, South Africa reported a 26% increase in viral suppression compared to standard initiation. We report the cost and cost-effectiveness of the rapid (same-day) strategy.

Methods: For the primary health clinic study site, we compared the provider cost per patient virally suppressed 10 months after study enrollment under the rapid strategy to the corresponding cost under standard care. We used study forms and routine patient records to estimate resource utilization for each patient over the 10-month observation period and multiplied the number of units of each resource used by the unit cost for the resource, estimated in rand and converted at R12.74/$1. We estimated the average and total cost per patient achieving the primary outcome and the incremental cost-effectiveness ratio (ICER) for the intervention and conducted sensitivity analysis for 3 key parameters: omitting the POC TB test; shifting some initiation tasks to junior nurses; and setting patient volume equal to the clinic's full patient load.

Results: In the standard arm, 46/108 (43%) patients were suppressed by 10 months, the average cost per patient suppressed was $483, and the total cost per patient suppressed (taking into account costs for patients not suppressed) was $836. In the rapid arm, 67/105 (63%) patients were suppressed by 10 months, the average cost per patient suppressed was $524, and the total cost per patient suppressed was $899. Standard and rapid arm patients averaged 9.9 and 6.9 clinic visits during the 10 month-period, respectively. Laboratory costs for baseline CD4 counts, TB tests, and other blood tests were much higher in the POC-based rapid arm, accounting for most of the difference; attributed fixed costs for infrastructure and management were lower in the rapid arm due to the smaller number of clinic visits. The ICER for the rapid strategy was $780 per additional patient suppressed by 10 months. Sensitivity analysis (see figure) indicates that omitting POC TB tests and increasing patient volume may reduce costs substantially.

Conclusion: Same-day treatment initiation using POC tests is more effective and more expensive than standard initiation. Variations on the strategy, in particular omitting POC tests at initiation and/or focusing on high volume clinics, have the potential to reduce costs substantially and should be evaluated in routine settings.



1051 COST OF STREAMLINED HIV CARE IN RURAL KENYAN AND UGANDAN CLINICS IN THE SEARCH STUDY

Starley B. Shade[1], Thomas Osmand[1], Florence Mwangwa[2], Asiphas Owaraganise[2], Tamara D. Clark[1], Edwin D. Charlebois[1], Moses R. Kamya[3], Maya L. Petersen[4], Diane V. Havlir[1], Vivek Jain[1]
[1]Univ of California San Francisco, San Francisco, CA, USA, [2]Infectious Diseases Rsr Collab, Kampala, Uganda, [3]Makerere Univ Coll of Hlth Scis, Kampala, Uganda, [4]Univ of California Berkeley, Berkeley, CA, USA

Background: The SEARCH Study-an HIV test-and-treat community-randomized trial-has achieved >90% HIV testing and antiretroviral (ART) treatment for all HIV+ stable adult residents. Our "streamlined" HIV care model reduces wait times and facilitates viral suppression (84%). Standard HIV care delivery is estimated to cost $224-$1089 per-person-per-year (ppy). We sought to estimate the cost of streamlined HIV care delivery in SEARCH, and to model the cost of streamlined HIV care under optimized scale-up conditions.
Methods: We estimated the cost ppy of streamlined HIV care delivery in 17 health facilities in intervention communities in Kenya and Uganda within the SEARCH Study (NCT:01864603). Streamlined HIV care utilizes a patient-centered, multi-disease approach in a supportive environment; nurse-driven appointments (q 3 months) with co-located clinical/phlebotomy/laboratory services; appointment reminders; telephone access to clinicians; and viral load (VL) testing and counseling (q 6 months). We calculated costs using standard micro-costing techniques, time-and-motion studies, interviews of supervisory staff, and administrative records review. Cost categories included clinical and supervisor staff salaries, ART medications, VL testing, and fixed and recurring costs. We modeled HIV care costs under optimal scale-up conditions: (1) transition to governmental personnel; (2) lowest available ART costs (using UNDP negotiated rates); and (3) actual costs of centralized VL testing.
Results: Streamlined HIV care delivery averaged $275 ppy. ART medications ($118/ppy for TDF/3TC/EFV) and VL testing ($110 ppy for 2 tests per year) dominated costs relative to staff salaries [$38 ppy for clinical ($37 ppy) and supervisory ($1 ppy) staff], fixed costs for infrastructure and equipment ($5 ppy) and other recurring goods and services ($4 ppy). In an optimized scale-up model featuring government salaries ($27 ppy), lowest available ART costs ($100 ppy) and annual VL testing ($12 ppy), the overall cost of streamlined HIV care dropped to $148 ppy.
Conclusion: Costs of streamlined HIV care within the SEARCH test-and-treat trial were similar to or lower than previous standard HIV care cost estimates, even after including costs for VL testing and counseling. Optimized models of care delivery would substantially reduce these costs below prevailing estimates. These data can inform global cost and policy formulations focused on financing the expansion of ART to achieve UNAIDS 90-90-90 targets.

1052 DIFFERENTIATED HIV RNA VIRAL-LOAD MONITORING IN UGANDA: A COST-EFFECTIVENESS ANALYSIS

Diana M. Negoescu[1], Zhenhuan Zhang[1], **Heiner C. Bucher**[2], Eran Bendavid[3], for the Swiss HIV Cohort Study
[1]Univ of Minnesota, Minneapolis, MN, USA, [2]Basel Inst for Clinical Epi and Biostatistics, Basel, Switzerland, [3]Stanford Univ, Stanford, CA

Background: Viral load (VL) monitoring for patients receiving antiretroviral therapy (ART) is recommended worldwide. However, the costs of frequent monitoring are a barrier to implementation in resource-limited settings. The extent to which personalized monitoring frequencies may be cost-effective is unknown.
Methods: We created a simulation model parameterized using person-level longitudinal data from the Swiss HIV Cohort Study to assess the benefits of flexible monitoring frequencies. Our data-driven model estimated CD4 evolution during and prior to virologic failure, and the relationship between virologic failure and self-reported adherence, duration on regimen, age, and gender. Our model tracked a population of HIV+ individuals for 10 years following ART initiation. Adherence was modeled as a time-varying process that depends on the patient's previous adherence status, age, gender, and education level. We used a Markov version of the model to optimize the interval between viral load tests as a function of patients' age, gender, education, duration since ART initiation, adherence behavior, and the willingness-to-pay threshold. We compared the cost-effectiveness of the personalized monitoring strategies to fixed monitoring intervals every 1, 3, 6, 12 and 24 months.
Results: Shorter fixed VL monitoring intervals yielded increasing benefits (6.034 to 6.221 quality-adjusted life-years (QALYs) per patient with monitoring every 24 to 1 month over 10 years, respectively, standard error 0.005 QALY), at increasing average costs: US$ 3445 (annual monitoring) to $5393 (monthly monitoring) per patient (standard error $3.7). The adaptive policy optimized for Uganda's context achieved 6.111 average QALYs at a cost of $3483 (incremental cost-effectiveness ratio of 490.8 USD/QALY compared to fixed 24-month monitoring). Compared to monitoring VL every 3 months, the adaptive policy optimized for middle-income resource settings yields 0.008 fewer QALYs per person, but saves $204. The adaptive policy optimized for high-income settings yields 0.007 fewer QALYs per person, but saves $1,180 compared to monthly monitoring.
Conclusion: Focusing on patients most at risk of virological failure improves the efficiency of VL monitoring. In low-income countries, adaptive policies achieve similar outcomes to fixed interval at lower costs. In middle- to high-income settings, adaptive policies may lead to significant reductions in costs compared to fixed interval monitoring policies.

1053 PROJECTING FUTURE DONOR ASSISTANCE FOR HIV/AIDS GLOBAL FUNCTION SUPPORT

Eran Bendavid[1], Marco Marco Schäferhoff[2], Jessica Kraus[2], Dean Jamison[3], Sebastian Martinez[2]
[1]Stanford Univ, Stanford, CA, USA, [2]SEEK Development, Berlin, Germany, [3]Univ of California San Francisco, San Francisco, CA, USA

Background: The resources available for the HIV response in aid-recipient countries reflect a balance between the financial needs to care for the growing HIV-infected population, donor resources, which have been mostly flat or declining, and domestic resources, which reflect national wealth and the prioritization of HIV. Increased prioritization of HIV aid for global functions, such as vaccine trials or surveillance, could offer high returns. In this context, the extent to which low and middle-income countries (LIC & MIC) can finance HIV control programs is poorly understood and could inform future planning.

Methods: To project the amount of potentially "repurposable" donor HIV resources, the amount of future domestic resources for HIV was calculated based on each country's total projected gross domestic product (GDP), the portion of GDP spent on health, and the share of overall disease burden made up by HIV. Percent of GDP spent on health was taken from observed trends relating GDP per capita and health spending, and HIV burden share was assumed to be stable at 2013 levels. We used UNAIDS estimates of full financing needs for HIV in each country through 2030 and assumed a stable gap between the full financing needs and actual financing of HIV programs. The difference between domestic plus donor resources and the financing needs was taken as repurposable donor resources.

Results: We estimate that domestic resources available for HIV could increase in LIC 2.5 fold between 2016-2030, from $13.3 million to $32.9 million on average per country (range $335,920 in Afghanistan to $407 million in Tanzania). The amount of repurposable HIV aid from increased domestic spending in LIC ranged from $0 in low-aid countries such as Burundi and Niger to upwards of $150 million in Ethiopia, Mozambique, Tanzania, and Uganda (58%-85% of current HIV aid levels). Between 2016-2030, we estimate that increasing domestic resources could enable repurposing $11.1 billion of HIV aid in LIC, $21.7 billion in lower-MIC, and $11.6 billion in upper-MIC.

Conclusion: If the GDP of low and middle-income countries grows according to projections, a substantial portion of HIV financial needs could be met with domestic resources. Although low-income countries receive the most aid, we project that more HIV aid could be repurposed from middle-income countries than low-income countries. Knowledge on financing trends can allow donors to make better-informed financing decisions.

1054 CHARACTERIZATION OF MORE THAN 10,000 ZIKA VIRUS TEST RESULTS IN THE US

Joseph M. Volpe[1], Dajie Luo[1], Arren Fisher[1], Mindy Nye[2], Barbara Body[2], Marcia Eisenberg[1]
[1]LabCorp, Durham, NC, USA, [2]LabCorp, Burlington, NC, USA

Background: The rapid emergence and spread of the Zika virus prompted the increased availability of screening assays in the US. LabCorp launched an RT-PCR-based test (RealStar® Zika Virus RT-PCR, Altona Diagnostics) to qualitatively detect Zika virus RNA in serum and urine (RNA test), and was the first commercial lab to provide the CDC's MAC-ELISA test for detection of Zika IgM antibodies in serum or CSF (IgM test). This analysis characterizes over 10,000 results from these two tests, providing age, gender, and geographical views of the results.

Methods: The data from Zika tests performed between June and mid-September 2016 for both RNA (June to mid-Sept) and IgM tests (mid-Aug to mid-Sept) were downloaded from the LabCorp database and were filtered such that only those with complete records were included in the analysis. The data were analyzed to determine frequencies of female and male testing, negative vs non-negative results, age distributions, and geography.

Results: A total of 11,129 result records, of which 6410 were from the RNA test and 4719 from the IgM test. We found negative result rates of 94.2% and 98.2% from the RNA and IgM assays, respectively. Testing in females represented 78.7% of all samples submitted and 83% of these samples came from patients between the ages of 21-40. Comparatively, 60.6% of male samples came from the 21-40 age group and 15% came from the 41-50 age demographic. For the RNA test, we found a concordance rate of 97% between the serum and urine results. For females, the concordance rate was 97.2%, and for males it was 96.3%. A statistically significant difference ($p=0.0001$) in the frequency of urine samples testing positive between females (4.39%) and males (6.67%) was observed, but was not seen between male and female serum results. Nearly half of the samples (48.6%) came from Florida, which demonstrated a negative rate of 97.8%.

Conclusion: Our data represents one of the first characterizations of Zika virus testing in the United States. This early review demonstrates that approximately one in every 25 samples results is presumptive positive/positive result. The high negative result rate from Florida is consistent with the broader screening approach that has occurred due to endemic Zika virus concerns. The significant difference in positive Zika RNA detection in the urine of males versus females was unexpected. The high rate of testing in males was generally a surprise because there is no screening algorithm for males.

1055LB ZIKA VIRUS PERSISTENCE IN BODY FLUIDS

Gabriela Paz-Bailey[1], Eli Rosenberg[2], Katherine Doyle[1], Jorge Munoz-Jordan[1], Gilberto Santiago[1], Liore Klein[3], Janice Perez[1], Stephen Waterman[1], Luisa Alvarado[4], Tyler Sharp[1]
[1]CDC, Atlanta, GA, USA, [2]Emory Univ, Atlanta, GA, USA, [3]Caduceus Healthcare Inc, Ponce, PR, USA, [4]Ponce Univ, Ponce, PR, USA

Background: A detailed understanding of the dynamics of the early stages of Zika virus (ZIKV) infection is needed to inform diagnostic testing algorithms and prevention interventions, as existing evidence is based on case reports and cross-sectional observations, primarily from returning travelers. To estimate the presence and duration of detection of ZIKV RNA in body fluids and anti-ZIKV IgM antibody in individuals with acute ZIKV infection, we established the Zika virus

Methods: Persons in whom ZIKV was detected by RT-PCR in urine or blood in a Puerto Rico enhanced arboviral clinical surveillance site were enrolled. Serum, saliva, urine, and semen/vaginal secretions were collected weekly for the first month and at 2, 4, and 6 months. All specimens were tested by RT-PCR and serum was tested by anti-ZIKV IgM ELISA. Among those with ZIKV RNA in any specimen at week 4, biweekly collection continued until all specimens tested negative. Time to loss of ZIKV RNA detection in each body fluid was estimated using parametric Weibull regression models. We estimated the 50th and 95th quantiles with their 95% confidence intervals (95% CI).

Results: Among 150 participants, 88% (132/150) of participants had detectable ZIKV RNA in ≥1 serum specimen, 62% (92/149) in urine, 10% (15/147) in saliva, 1/50 (2%) in vaginal secretions and 56% (31/55) in semen. The 50th and 95th percentile for days post-illness-onset until loss of ZIKV RNA detection were respectively, 14 (95% CI: 11-17) and 54 (95% CI: 43-64) in serum, 8 (95% CI: 6-10) and 39 (95% CI: 31-47) in urine, and 34 (95% CI: 28-41) and 81 (95% CI: 64-98) in semen. Few had detectable RNA in saliva and vaginal secretions. Conclusion: Our interim analyses provides crucial information about time to clearance of ZIKV RNA in persons with acute ZIKV infection and detectable ZIKV RNA at enrollment. Prolonged time to ZIKV RNA clearance in serum may have implications for diagnosis and prevention. Current sexual prevention guidelines recommend that men use condoms/abstain from sex for 6 months after ZIKV exposure; in this study 95% of men cleared ZIKV RNA from semen over this time period.

1056LB NEUROLOGIC CONSEQUENCES OF POSTNATAL ZIKA VIRUS INFECTION IN INFANTS

Maud Mavigner[1], Justin O'Neal[2], Siddhartha Bhaumik[1], Jakob Habib[1], Cameron Robinson[1], Maria Alvarado[3], Xiaodong Zhang[3], Jens Wrammert[1], Mehul Suthar[2], Ann Chahroudi[1]
[1]Emory Univ, Atlanta, GA, USA, [2]Emory Vaccine Center, Atlanta, GA, USA, [3]Yerkes Natl Primate Rsr Cntr, Atlanta, GA, USA

Background: Zika virus (ZIKV) infection can have devastating neurologic consequences for infants infected in utero, particularly during the first trimester. Little is known, however, about the impact of ZIKV infection close to the time of delivery or in the period of infancy.

Methods: To address this gap, we developed a model of postnatal ZIKV infection in infant rhesus macaques (RMs). Infant RMs were infected with 10(5) PFU of ZIKV strain PRVABC59 s.c. at five weeks of age. A subset of RMs was sacrificed soon after infection to determine tissue tropism of ZIKV in infants and another subset was followed longitudinally. Viral loads in plasma and tissues were measured by qPCR. Binding and neutralization antibody responses were quantified by ELISA and focus reduction neutralization test (FRNT), respectively. At three months of age, infant RMs underwent structural T1-weighted magnetic resonance imaging (MRI), resting-state functional MRI, and Diffusion Tensor Imaging (DTI). A Human Intruder task was used to quantify the response to acute stress.

Results: Six infant RMs were challenged with ZIKV with peak viral loads in plasma at day 2-3 that cleared by day 7 after infection. ZIKV was not detected in urine, saliva, or CSF. Infant RMs developed anti-ZIKV binding IgG and IgM antibodies as well as neutralization activity in plasma. In two infant RMs sacrificed at the peak of viremia, ZIKV RNA was detected in multiple lymph nodes and the spleen. In two infant RMs sacrificed two weeks after infection, ZIKV RNA was additionally detected in the frontal cortex, parietal cortex, occipital cortex, cauda equina, and trigeminal ganglion. MRI and DTI performed at three months of age revealed increased size of the lateral ventricles, microstructural alteration in the corpus callosum, and reduction in the functional connectivity of the primary motor (M1) and somatosensory (S1) cortices in ZIKV-infected infant RMs as compared to age-matched controls. ZIKV-infected infants also showed emotional dysregulation, failing to demonstrate the species-typical freezing behavior in response to an acute social stressor as compared to similarly reared controls.
Conclusion: In summary, we demonstrate for the first time that postnatal ZIKV infection of infants disseminates into the central nervous system and has structural and functional neurologic consequences. This model can be used to test therapeutic approaches to prevent or reverse the damage caused by ZIKV infection in infants.

1057LB ZIKA VIRUS PROTECTION BY A SINGLE LOW-DOSE NUCLEOSIDE-MODIFIED mRNA VACCINATION

Michael J. Hogan[1], Norbert Pardi[1], Rebecca S. Pelc[2], Hanne Anderson[3], Charles McGee[4], Michael J. Hope[5], Mark G. Lewis[3], Theodore C. Pierson[2], Barton F. Haynes[4], Drew Weissman[1]
[1]Univ of Pennsylvania, Philadelphia, PA, USA, [2]NIAID, Bethesda, MD, USA, [3]Bioqual, Inc, Rockville, MD, USA, [4]Duke Univ, Durham, NC, USA, [5]Acuitas Therapeutics, Vancouver, BC, Canada
Background: Zika virus (ZIKV) has recently emerged as an explosive pandemic associated with severe neuropathology in newborns and adults. There are no ZIKV-specific treatments or preventatives; thus, development of a safe and effective vaccine is a high priority. Messenger RNA (mRNA) containing modified nucleosides is emerging as a versatile and highly effective vaccine platform, which generates potent T follicular helper (Tfh) cell and neutralizing antibody responses to diverse viral pathogens. In this study, we developed a nucleoside-modified mRNA-based vaccine against ZIKV and determined its immunogenicity and protective efficacy in mice and non-human primates.
Methods: Nucleoside-modified mRNA encoding the pre-membrane (prM) and envelope (E) glycoproteins from a 2013 ZIKV outbreak strain (H/PF/2013) was transcribed with T7 phage RNA polymerase using 1-methylpseudouridine triphosphate in place of UTP. mRNA was purified by HPLC and incorporated into lipid nanoparticles (LNPs). Mice and rhesus macaques were immunized once intradermally with prM-E mRNA-LNPs. Serology was followed by IgG ELISA and three types of neutralization assay: plaque and focus reduction neutralization tests and reporter viral particle assay. Animals were challenged with ZIKV PRVABC59 (Puerto Rico, 2015) and viral loads were followed by quantitative RT-PCR.
Results: High and stable levels of Zika E-specific IgG and neutralizing antibody were generated after a single immunization of ZIKV mRNA-LNPs in both mice and rhesus macaques. Neutralizing titers in multiple assays exceeded levels that previously protected animals in passive transfer experiments. A single immunization with 30 µg of ZIKV mRNA-LNPs protected mice from detectable viremia (<200 copies/ml) following a ZIKV challenge at 2 weeks (short-term) or 5 months (long-term) post-vaccination. A single low-dose immunization with 50 µg (0.02 mg/kg) protected rhesus macaques from detectable viremia (<50 copies/ml) following a challenge at 5 weeks post-vaccination.
Conclusion: The ZIKV prM-E nucleoside-modified mRNA-LNP vaccine is potently immunogenic in mice and rhesus macaques. This vaccine platform requires only a single administration of a low dose of mRNA to generate a rapid, long-lived, and protective immune response, which is mediated by potent Tfh cell induction. Nucleoside-modified mRNA-LNP represents a new and advantageous vaccine candidate for a global public health campaign against ZIKV, with ongoing expansion to other pathogens.

DISCLOSURE OF FINANCIAL RELATIONSHIPS WITH COMMERCIAL CONCERNS

Disclosure information is presented generally as submitted by the corresponding presenting abstract author or invited speaker. The authors and speakers below provided their relevant disclosures of financial relationships with commercial entities for themselves and their spouses or partners, as well as funding provided to their institutions.

Abu-Raddad, Laith, J.
For self, paid to my institution: Research grant recipient from the Qatar National Research Fund

Achhra, Amit, C.
Self: Employee of NCBH Hosp and JJP VA Med Ctr, Bronx, NY

Achilles, Sharon, L.
Self: Consultant of Merck & Co, Inc

Adkison, Kimberly, K.
Self: Employee of ViiV Healthcare

Althoff, Keri, N.
Self: Consultant Gilead Sciences, Inc

Ananworanich, Jintanat
Self: Honoraria from ViiV Healthcare and Merck & Co, Inc
For self, paid to my institution: Research grant recipient from Cooperative agreements between The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., and the U.S. Department of the Army

Anderson, Jenny, L.
For self, paid to my institution: Contracted researcher Merck & Co, Inc

Anderson, Peter, L.
For self, paid to my institution: Research grant recipient from for contract work and study drug donation from Gilead Sciences, Inc

Anderson, Sarah-Jane
Self: Consultant for Bill and Melinda Gates Foundation and consultant for Avenir Health

Andrade, Adriana
Self: Board member of Ginseng Board of Wisconsin and research grant recipient Gilead Sciences, Inc

Andrew, Katende
Self: Employee of IFAKARA Health Institute

Ankrom, Wendy
Self: Employee of Merck & Co., Inc
Spouse or Partner: Contracted researcher for Certara

Anugulruengkitt, Suvaporn
Self: Research grant recipient from The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Grant Programme

Arribas, Jose, R.
Self: Research grant recipient from and speaker's bureau for ViiV Healthcare, JanssenTherapeutics, AbbVie, Bristol-Myers Squibb, and Gilead Sciences, Inc

Barber, Tristan
Self: Consultant and speaker's bureau for Gilead Sciences, Inc, Janssen Therapeutics, and ViiV Healthcare

Bares, Sara, H.
Self: Research grant recipient from Gilead Sciences, Inc.

Barnard, Richard
Self: Employee of Merck and Co., Inc

Bauer, Wolfgang
Self: Consultant of GlaxoSmithKline and Pharma GmbH

Bedimo, Roger
Self: Research grant recipient from and consultant for Merck & Co, Inc and Bristol-Myers Squibb

Bekker, Linda-Gail
For self, paid to my institution: Research grant recipient from The Desmond Tutu HIV Centre

Berenguer, Juan
For self, paid to my institution: Research grant recipient from ABBVIE, Gilead Sciences, Inc, Merck & Co, Inc, ViiV Healthcare
Self: Speaker's bureau for ABBVIE, Bristol-Myers Squibb, Gilead Sciences, Inc, Merck & Co, Inc, Janssen Therapeutics, and ViiV Healthcare

Bhattacharya, Debika
For self, paid to my institution: Research grant recipient from AbbVie, Bristol Myers Squibb, and Merck & Co, Inc

Boesecke, Christoph
Self: Consultant and speaker's bureau AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Merck & Co, Inc, and ViiV Healthcare
For self, paid to my institution: Research grant recipient from Deutsches Zentrum für Infektionsforschung (DZIF), Deutsche Leberstiftung, and NEAT ID

Boffito, Marta
Self: Consultant and speaker's bureau for Gilead Sciences, Inc, ViiV Healthcare, Bristol-Myers Squibb, Janssen Therapeutics, Mylan, Inc, and Teva
Self,For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc, ViiV Healthcare, Bristol-Myers Squibb, Janssen Therapeutics, Mylan, Inc, and Teva

Bollen, Pauline
For self, paid to my institution: Grant from ViiV Healthcare

Brehm, Jessica
Self: Employee of GlaxoSmithKline

Brinkman, Kees
Self: Consultant for Merck & Co, Inc, Gilead Sciences, Inc, ViiV Healthcare, Roche Diagnostics, Bristol-Myers Squibb, and Janssen Therapeutics

Brockmeyer, Norbert, H.
Self: Consultant Merck & Co, Inc
For self, paid to my institution: Research grant recipient from ViiV Healthcare, Bristol-Myers Squibb, and Janssen Therapeutics

Brown, Kimberley
Self: Janssen Therapeutics

Brown, Todd
Self: Consultant for Gilead Sciences, Bristol-Myers Squibb, Merck & Co, Inc, EMD-Serono, and Theratechnologies

Bucher, Heiner, C.
For self, paid to my institution: Research grant recipient from Gilead Sciences, Bristol-Myers Squibb, and ViiV Health Care

Butt, Adeel, A.
Self: Research grant recipient from Gilead Sciences, Inc, Merck & Co, Inc, and AbbVie

Cai, Suqin
Self: Employee of Monogram Biosciences

Calcagno, Andrea
Self: Consultant of Abbvie, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen-Cilag, Merck & Co, Inc, ViiV Healthcare
For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc, Bristol-Myers Squibb, ViiV Healthcare

Cambiano, Valentina
Self: Other for Merck & Co, Inc

Ceccherini Silberstein, Francesca
Self: Research grant recipient from consultant, and speaker's bureau for AbbVie, Abbott Molecular, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Merck & Co, Inc, Roche Diagnostics, ViiV Healthcare

Cento, Valeria
Self: Speaker's bureau for Abbvie, Bristol-Myers Squibb, Merck Sharp & Dohme, and Janssen Therapeutics

Chew, Kara, W.
Self,For self, paid to my institution: Research grant recipient from Merck & Co, Inc

Christopoulos, Katerina
Self: Other for Roche Diagnostics and Gilead Sciences, Inc

Clarke, Diana, F.
Self: Consultant for Merck & Co, Inc

Clement, Meredith
Spouse or Partner: Royalty holder (company not stated)

Cloherty, Gavin
Self: Employee of Abbott Laboratories

Coller, Kelly
Self: Employee of Abbott Laboratories

Corbin, John, A.
Self: Employee of Gilead Sciences, Inc

Costagliola, Dominique
Self: Consultant for Gilead Sciences, Inc and Innavirvax
For self, paid to my institution: Research grant recipient from ViiV Healthcare, Janssen-Cilagm, Merck & Co, Inc.

Cotte, Laurent
For self, paid to my institution: Research grant recipient from Merck & Co, Inc, ViiV

Custodio, Joseph, M.
Self: Employee of Gilead Sciences, Inc

Dean, Bonnie
Self: Research grant recipient from Cerner, Inc

DeJesus, Edwin
Self: Consultant of Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Merck & Co, Inc, and Vertex, Inc
For self, paid to my institution: Research grant recipient from Abbott Laboratories, Achillion Pharmaceuticals, Avexa, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline, LaRoche Diagnostics, Idenix, Janssen Therapeutics, Merck & Co, Inc, Pfizer, Sangamo, Taimed, Tobira, and Vertex, Inc

Devillé, Walter
For self, paid to my institution: Research grant recipient from Orasure Company

Dolci, Giovanni,
Self: Consultant of Gilead Sciences, Inc
Self,For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc

Dunham, Richard, M.
Self: Employee of GlaxoSmithKline

Durand, Christine
Self: Consultant Gilead Sciences
Research grant recipient from Merck Pharmaceuticals
Consultant Bristol-Myers Squibb

Durham, Phillip, G.
Self: Employee of RTI International

Eaton, Ellen, F.
For self, paid to my institution: Research grant recipient from Other Bristol Myers Squibb Virology Fellowship Recipient, Analyst on Merck-funded project

Eckard, Allison, R.
Self: Consultant Gilead Sciences
For self, paid to my institution: Research grant recipient from Bristol-Myers Squibb, Cubist Pharmaceuticals, and GlaxoSmithKline

Eckhardt, Benjamin,
Self: Research grant recipient from and consultant Gilead Sciences, Inc

Ellis, Ronald, J.
Spouse or Partner: Stockholder of Merck & Co, Inc, Abbott, and Johnson and Johnson

Emu, Brinda
Self: Consultant for Taimed and 3V Biosciences

Erlandson, Kristine
Self: Research grant recipient from and consultant for Gilead Sciences, Inc and Theratechnologies

Esser, Stefan
Self, For self, paid to my institution: Research grant recipient from Consultant Abbvie, BMS, Gilead, Merck & Co, Inc, Janssen, ViiV

Evans, Ceri
Self: Other for GlaxoSmithKline

Fleisher, Ilan
Self: Employee of MedStar Health Research

Flexner, Charles, W.
Self: Consultant for Merck & Co, Inc, Mylan, Inc, and ViiV Healthcare
For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc

Frange, Pierre
Self: Consultant for Merck & Co, Inc, ViiV Healthcare, Bristol-Myers Squibb, Janssen Therapeutics, and Gilead Sciences, Inc

Gandhi, Rajesh, T.
For self, paid to my institution: Grants from EBSCO Information Services, Gilead Sciences, Inc, Merck & Co, Inc, and ViiV Healthcare

Gatell, Jose, M.
Self: Consultant of Gilead Sciences, Inc, Merck & Co, Inc, ViiV Healthcare, and Janssen Therapeutics
For self, paid to my institution: Research grant recipient from ViiV Healthcare, Merck & Co, Inc, Gilead Sciences, Inc, and Janssen Therapeutics

Gaur, Aditya
For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc

Gerstenhaber, Rodd
Self: Employee of Medecins Sans Frontieres

Girardi, Enrico
Self: Speaker's bureau for Janssen Therapeutics, Gilead Sciences, Inc, Otsuka, and Angelini. Research grant recipient from Gilead Sciences, Inc

Golub, Sarit, A.
Self: Gilead provides free study drug to project participants and covers the cost of some testing

González-García, Juan
Self: Consultant and speaker's buerau for ViiV Healthcare, Gilead Sciences, Inc, Abbvie, and Merck Sharp Dohme
For self, paid to my institution: Research grant from ViiV Healthcare, Gilead Sciences, Inc, Merck Sharp Dhome, Abbvie, Bristol-Myers Squibb, and Janssen-Cilag

Gonzalez-Perez, Maria Paz
Self: Employee of (company not indicated)

Grattoni, Alessandro
Self: Stockholder of NanoMedical Systems

Grimwood, Ashraf
Self: Employee of Kheth'Impilo

Grinsztejn, Beatriz
Self: Employee of Fundação Oswaldo Cruz

Guaraldi, Giovanni
Self: Consultant and speaker's bureau for Gilead Sciences, Inc., Janssen Therapeutics, Bristol-Myers Squibb, GlaxoSmithKline. Grant recipient from ViiV Healthcareand Merck & Co, Inc

Gupta, Ravindra, K.
Self: Speaker's bureau for Janssen Therapeutics

Hagins, Debbie
For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc

Hamzah, Lisa
Self: Other from Gilead Sciences, Inc

Hayes, Richard
Self: Royalty holder from Chapman and Hall

Hileman, Corrilynn, O.
Self: Consultant for Gilead Sciences, Inc

Hill, Andrew
Self: Consultant for Merck & Co, Inc and Janssen Therapeutics

Hillier, Sharon, L.
Self: Consultant for Merck & Co, Inc, Cepheid, and Symbiomix, LLC

Hodder, Sally
Self: Consultant for Bristol-Myers Squibb, ViiV Healthcare, Gilead Sciences, Inc, and Janssen Therapeutics
Spouse or Partner: Consultant for Sanofi, Novartis, and Johnson & Johnson

Hogan, Michael, J.
Self: Recipient of Intellectual Property Rights from University of Pennsylvania

Holzmayer, Vera
Self: Employee of and stockholder of Abbott Laboratories

Hsu, Ricky,
Self: Research grant recipient from consultant, speaker's bureau, and contracted researcher for Gilead Sciences, Inc. Consultant and speaker's bureau for Janssen Therapeutics, and Bristol-Myers Squibb. Consultant for ViiV Healthcare. Speaker's bureau for Merck & Co, Inc

Huang, Wei
Self: Employee of Monogram Biosciences

Hultquist, Judd, F.
Self: Contracted researcher for Roche Diagnostics and consultant for BlueCatBio Ltd.

Imaz, Arkaitz
Self: Research grant recipient from consultant, and speaker's bureau for Gilead Sciences, Inc, ViiV Healthcare, Bristol-Myers Squibb, Janssen Therapeutics, Merck & Co, Inc, and Abbvie

Iwuji, Collins, C.
Self: Speaker's bureau for Gilead Sciences, Inc

Jarvis, Joseph, N.
For self, paid to my institution: Research grant recipient from for an investigator initiated award from Gilead Sciences, Inc

Keating, Sheila
Self: Other for Ortho Clinical Diagnostics

Khalilieh, Sauzanne
Self: Employee of Merck & Co., Inc.

Kosloski, Matthew, P.
Self: Employee of and stockholder of AbbVie

Koss, Catherine, A.
For self, paid to my institution: I am involved with a study for which Gilead Sciences, Inc awarded study drug to my institution.

Lansdon, Eric
Self: Employee of and stockholder of Gilead Sciences, Inc

Lathouwers, Erkki
Self: Employee of Janssen Therapeutics

Leal, Lorna
Self: Other for Gilead Sciences, Inc

Letendre, Scott
Self: Consultant for ViiV Healthcare, Gilead Scienced, Inc., Merck & Co, Inc, and Janssen Therapeutics

Levy, Itzchak
Self: Speaker's bureau for Gilead Sciences, Inc and Merck & Co, Inc
For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc

Lewis, Stanley
Self: Employee of TaiMed Biologics

Li, Jonathan
Self: Research grant recipient and consultant for Gilead Sciences, Inc and Merck & Co, Inc

Link, John, O.
Self: Employee and stockholder of Gilead Sciences, Inc

Longenecker, Chris, T.
Self: Consultant for Gilead Sciences, Inc

Macías, Juan
Self: Investigator in clinical trials supported by Roche Diagnostics, Bristol-Myers Squibb and Abbott Pharmaceuticals. Lectures fees from Roche Diagnostics, Gilead Sciences, Inc, Boehringer Ingelheim, and Bristol-Myers Squibb. Consulting fees from Boehringer Ingelheim

Maddon, Paul, J.
Self: Consultant and stockholder of CytoDyn Inc. Stockholder of Progenics Pharmaceuticals, Inc.

Majeed, Sophia, R.
Self: Employee and stockholder for Gilead Sciences

Makadzange, Azure, T.
Self: Consultant GSK
Self: Speaker's bureau Janssen Therapeutics

Maleche Obimbo, Elizabeth
Self: Stockholder Nairobi Securities Exchange

Mangia, Alessandra
Self: Research grant recipient from Gilead Sciences, Janssen-Cilag, Bristol-Myers Squibb, and Merck & Co, Inc

Marconi, Vincent, C.
Self: Research grant recipient from ViiV Healthcare

Margolis, David, A.
Self: Employee and stockholder for ViiV Healthcare

Martinez, Esteban
Self: Research grant recipient from Gilead Sciences, Inc, Janssen Therapeutics, Merck & Co, Inc, and ViiV Healthcare

Matheron, Sophie
For self, paid to my institution: Research grant recipient from Merck & Co, Inc

Mauss, Stefan
Self: Consultant, speaker's bureau and advisory board for: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, and ViiV Healthcare

McClelland, R. Scott
For self, paid to my institution: Research grant recipient from Hologic Corporation

McFarland, Elizabeth, J.
For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc

Meintjes, Graeme
Self: Other relationship with Gilead Sciences, Inc

Meissner, Eric, G.
For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc

Mills, Lisa, A.
Spouse or Partner: Employee of Leidos Biomedical

Mitchell, Michael, L.
Self: Employee of Gilead Sciences, Inc

Molina, Jean-Michel
Self: Consultant and speaker's bureau Gilead Sciences, Inc . Consultant for Merc & Co, Inc and ViiV Healthcare
For self, paid to my institution: Research grant recipient from Gllead Sciences

Morris, Sheldon
Self: Research grant recipient from Gilead Sciences

Moscicki, Anna-Barbara
Self: Other Merck & Co, Inc

Mothe, Beatriz
Self: Consultant Aelix Therapeutics, AlbaJuna Therapeutics

Murry, Jeffrey
Self: Employee of Gilead Sciences, Inc

Nijhawan, Ank, E.
Self: Research grant recipient from Gilead Sciences, Inc

Novak, Richard
Self: Consultant for Gilead Sciences, Inc. Contracted researcher for Merck & Co, Inc and GlaxoSmithKlien

Ofotokun, Igho
Self: Consultant for Accordant

Owen, Andrew
Self: Consultant Merck & Co, Inc and Norgine
For self, paid to my institution: Research grant recipient from Merck & Co, Inc, ViiV Healthcare, and AstraZeneca, Inc

Palella, Frank, J.
Self: Consultant and speaker's bureau Gilead Sciences, Inc, Janssen Therapeutics, Merck & Co, Inc, Bristol-Myers Squibb

Palma, Paolo
For self, paid to my institution: Research grant recipient from ViiV Healthcare

Pérez-Valero, Ignacio
Self: Other relationship with ViiV Healthcare, Gilead Sciences, Inc, and Bristol-Myers Squibb

Petoumenos, Kathy
Self: Research grant from Merck Sharp & Dohme; Gilead Sciences, Inc, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen-Cilag and ViiV Healthcare

Picker, Louis, J.
Self: Consultant Vir Biotechnology

Price, Richard, W.
Self: Consultant with Merck & Co., Inc

Riddler, Sharon
For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc and GlaxoSmithKline

Rijnders, Bart
Self: Research grant recipient from Merck & Co, Inc and Gilead Sciences, Inc. Consultant for GL-pharmaceuticals, Bristol-Myers Squibb, Merck & Co, Inc, Gilead Sciences, Inc, Janssen-Cilag, ViiV Healthcare. Contracted researcher for Gilead Sciences, Inc and ViiV Healthcare

Rodgers, Mary
Self: Employee and stockholder for Abbott Laboratories

Rose, Rebecca
Self: Consultant for BioInfoExperts

Rough, Kathryn
Self: Consultant for Bayer Pharmaceuticals

Ruelas, Debbie, S.
Self: Employee of Merck & Co, Inc

Sabin, Caroline
Self: Speaker's bureau for Gilead Sciences, Inc. Other relationship with ViiV Healthcare and Janssen-Cilag

Sax, Paul, E.
Self: Research grant recipient from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline, Merck & Co, Inc, and Janssen Therapeutics

Schalkwijk, Stein
For self, paid to my institution: Research grant from Bristol-Myers Squibb, Merck & Co, Inc, ViiV Healthcare and Janssen Therapeutics

Seydi, Moussa
For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc

Silverberg, Michael, J.
For self, paid to my institution: Research grant from Merck & Co, Inc and Pfizer, Inc

Soriano, Vincent
Self: Consultant and speaker's bureau for Gilead Sciences, Inc, Merck & Co, Inc, Janssen Therapeutics, Bristol-Myers Squibb

Squillace, Nicola
Self: Consultant for ViiV Healthcare. speaker's bureau for Merck & Co, Inc and Bristol-Myers Squibb. Other relationship with Janssen Therapeutics and Gilead Sciences, Inc

Squires, Kathleen
Self: Consultant for Bristol Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Merck & Co, Inc, and ViiV Healthcare
For self, paid to my institution: Research grant recipient from Clinical trials research grants to Thomas Jefferson University from Gilead Sciences, Inc

Tam, Edward
Self: Consultant and speaker's bureau for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Pharmaceutica, Merck & Co, Inc, and Pendopharm
For self, paid to my institution: Research grant recipient from AbbVie

Tan, Darrell, H.S.
For self, paid to my institution: Research grant recipient from ViiV Healthcare and Gilead Sciences, Inc

Telisinghe, L
For self, paid to my institution: Other QIAGEN provided non-financial support by providing the QuantiFERON®-TB Gold Plus kits free of charge to use in the study.

Thomsen, Nathan, D.
Self: Employee of Gilead Sciences, Inc

Thorne, Claire
For self, paid to my institution: Research grant recipient from AbbVie and ViiV Healthcare

Tieu, Hong Van
Self: Research grant recipient from Merck & Co, Inc

Todesco, Eve
Self: Speaker's bureau for Bristol-Myers Squibb

Tort, Olivia
For self, paid to my institution: Research grant recipient from Gilead Sciences, Inc

Tse, Winston, C.
Self: Employee of Gilead Sciences

Tung, Elyse
Self: Other relationship with Gilead Sciences, Inc

Ukaegbu, Chinyere
Self: Research grant recipient from Gilead Sciences, Inc

Utay, Netanya, S.
Self: Consultant for Gilead Sciences, Inc. Consultant and contracted researcher for Tobira Therapeutics, Inc and Entera Health, Inc

van der Heijden, Wouter, A.
For self, paid to my institution: Research grant recipient from Merck Sharp & Dohme, Merck & Co, Inc

van Sighem, Ard
For self, paid to my institution: Research grant from Janssen-Cilag and Viiv Healthcare

van Zoest, Rosan
For self, paid to my institution: Research grant from Gilead Sciences, Inc

Vannappagari, Vani
Self: Employee of ViiV Healthcare and stockholder of GlaxoSmithKline

Volpe, Joseph, M.
Self: Employee of LabCorp

Vos, Alinda,
Self: Employee of University Medical Center Utrecht, The Netherlands, Departmetn Julius Center.

Vourvahis, Manoli
Self: Employee and stockholder Pfizer, Inc

Wagner, Thor
Self: Research grant from Gilead Sciences, Inc

Wandeler, Gilles
Self: Research grant from Gilead Sciences, Inc

Warszawski, Josiane
For self, paid to my institution: Research grant from ViiV Healthcare and Parexel

Weinberg, Adriana
Self: Research grant recipient from GlaxoSmithKline and Medimmune
Spouse or Partner: Research grant recipient from and royalty holder from Merck & Co, Inc

Weinheimer, Steven
Self: Employee of TaiMed Biologics USA

White, Douglas, A. E.
Self: Research grant recipient from Gilead Sciences, Inc

White, Kirsten, L.
Self: Employee and stockholder of Gilead

Wiley, Dorothy, J.
Self: Research grant recipient from Merck Sharp & Dohme Corp, Merck & Co., Inc

Wong, Wingwai
For self, paid to my institution: Research grant recipient from United BioPharma
Self,For self, paid to my institution: Research grant from Gilead Sciences, Inc, Viiv Healthcare, Merck 7 Co, Inc, and Bristol-Myers Squibb

Yin, Michael, T.
Self: Consultant for Gilead Sciences, Inc

Zhang, Heather
Self: Employee and stockholder of Gilead Sciences, Inc

DISCLOSURE INDEX

The following have no relevant financial relationships to disclose. Any updates will be reflected in the mobile App.

Aamer, Hadega
Abaasa, Andrew, M.
Abdel Mohsen, Mohamed
Abdo, Mona
Abewe, Hosiana
Aboulnasr, Fatma
Abutaima, Rana
Adamson, Blythe, J.
Adewumi, Olubusuyi, M.
Adland, Emily
Agan, Brian, K.
Aghokeng, Avelin, F.
Agot, Kawango
Agrati, Chiara
Ahlgren, Erika
Ajibola, Gbolahan
Akay-Espinoza, Cagla
Alcaide, Maria, L.
Aldámiz-Echevarría, Teresa
Alessandra, Sacchi
Almirol, Ellen
Alvarez, Angeles
Alwano, Mary Grace
Amodo, Faizana
An, Qian
Ancona, Giuseppe
Andany, Nisha
Anderson, Albert
Anderson, Elizabeth, M.
Angelovich, Thomas, A.
Araújo, Marília, L.
Archary, Moherndran
Armstrong, Heather, L.
Arnedo, Mireia
Arpadi, Stephen, M.
Attia, Engi, F.
Avi, Radko
Avihingsanon, Anchalee
Avila-Rios, Santiago
Ayieko, James
Azzoni, Livio
Bachanas, Pamela, J.
Bachmann, Nadine
Badje, Anani, D.
Bai, Francesca
Bailin, Samuel
Baker, Jason
Balkus, Jennifer
Balogun, Kayode
Banga, Riddhima
Bangham, Charles, R.M.
Bardhi, Ariola
Barnabas, Ruanne, V.
Barocas, Joshua, A.
Batavia, Ashita, S.
Battalora, Linda
Baxter, Amy, E.
Bearden, David
Bebell, Lisa
Beck, Ingrid, A
Becker, James, T.
Becofsky, Katie
Bekker, Adrie
Belaunzaran-Zamudio, Pablo, F.
Beloukas, Apostolos
Bendavid, Eran
Bengtson, Angela
Bershteyn, Anna
Bertoli, Ada
Bhagwat, Priya
Bienczak, Andrzej
Biliotti, Elisa
Billioux, Veena, G.
Birnbaum, Jeanette
Bisson, Gregory
Blanco, José, L.
Blokhuis, Charlotte
Boehme, Catharina, C.
Boerekamps, Anne
Boivin, Michael, J.
Bonar, Michał
Bordoni, Veronica
Borges, Álvaro, H.
Borre, Ethan, D.
Bosman, Kobus
Boulougoura, Afroditi
Bowen-Test, Kevin, W.
Bozzi, Giorgio
Bracchi, Margherita
Bradley, Heather
Brenner, Bluma
Brittain, Kirsty
Broekhuis, Jordan
Brooks, Kristina, M.
Brown, Lillian
Broz, Dita
Bruce, Veronica
Brühl, Maria, C.
Brunet, Laurence
Buchacz, Kate
Buggert, Marcus
Bull, Marta, E.
Buranapraditkun, Supranee
Burchell, Ann, N.
Burdick, Ryan, C.
Burgener, Adam
Burgess, Emma, K.
Burke, Mark, W.
Buseyne, Florence
Bush, William, S.
Buskin, Susan
Butt, Zahid, A.
Cachay, Edward, R.
Camacho-Gonzalez, Andres
Camlin, Carol, S.
Campbell, Ellsworth
Cannizzo, Elvira, S.
Capoferri, Adam
Carrillo, Mayra, A.
Carroll, Makeda
Carryl, Heather
Casazza, Joseph, P.
Castagna, Antonella
Castel, Amanda, D.
Castelli, Francesco
Castillo-Mancilla, Jose, R.
Chaila, Mwate, J.
Chaillon, Antoine
Chaix Baudier, Marie-Laure
Chan, Austin, W.
Chan, Phillip
Chang, Ming
Chapin-Bardales, Johanna
Chattergoon, Michael
Chen, Mi
Cheng, Shu-Hsing
Chew, Glen
Chi, Benjamin, H.
Chow, Dominic
Christ, Frauke
Christensen-Quick, Aaron
Ciaranello, Andrea, L.
Cillo, Anthony, R.
Claassen, Mark
Coban, Hamza
Cocker, Alexander
Collins, Bryan, C.
Collins, Lauren, F.
Collins, Pamela
Connick, Elizabeth
Conradie, Francesca
Cote, Helene, C.F.
Cotugno, Nicola
Courtney, Colleen, R.
Crabtree- Ramírez, Brenda
Crane, Heidi, M.
Cremin, Ide
Crepaz, Nicole
Cummins, Nathan
Cunningham, Coleen, K.
Curtis, Kelly
Cuzin, Lise
Cyktor, Joshua, C.
Dabydeen, Sarah
Dagur, Raghubendra, S.
Dan, Jennifer, M.
Danboise, Brook
D'Antoni, Michelle, L.
D'arc, Mirela
Dasgupta, Sharoda
Daskalakis, Demetre, C.
Davis, Arielle, P.
Davis, Nicole
Davy, Thibaut
de Armas, Lesley, R.
De Francesco, Davide
De La Flor, Carolina
Debyser, Zeger
Del Amo, Julia
Delagreverie, Heloise, M.
Delaney, Kevin, P.
Delelis, Olivier
Delviks-Frankenberry, Krista
Derache, Anne
Desimmie, Belete, A.
Desir, Fidel, A.
Desmonde, Sophie
Dezzutti, Charlene, S.
Dhody, Kush
Dickey, Amy, K.
Dickinson, Laura
Dijkstra, Maartje
Dillon, Stephanie
Dingens, Adam
Dionne-Odom, Jodie
Dirajlal-Fargo, Sahera
Donnell, Deborah, J.
Drake, Alison, L.
Drechsler, Henning, J.
Dryden-Peterson, Scott
Duarte, Horacio, A.
Duenas Decamp, Maria Jose
Duerr, Ralf
Dumchev, Kostyantyn
Dumond, Julie, B.
Dunaway, Shelia
Eaton, Jeffrey
Edelstein, Zoe, R.
Egger, Matthias
El Kamari, Vanessa
Elliot, Emilie
Emery, Ann
Eshun-Wilson, Ingrid
Esmail, Hanif
Evans, Henry, W.
Fabbri, Gabriele
Falade-Nwulia, Oluwaseun
Fanjul, Francisco
Farhadian, Shelli
Faria de Oliveira, Michelli
Favarato, Graziella
Feinstein, Matthew, J.
Fenner, Lukas
Fernández McPhee, Carolina
Fielding, Katherine
Firnhaber, Cindy
Fisher, Bridget
Fitch, Kathleen, V.
Flerin, Nina, C.
Floyd, S
Fogel, Jessica, M.
Fox, Julie
Franco, Sandra
Freeman, Michael, L.
Freiman, J. Morgan
Frías, Mario
Fulcher, Jennifer, A.
Galvez Celada, Cristina
Gandhi, Monica
Ganesan, Anuradha
Ganser-Pornillos, Barbie, K.
Gantner, Pierre
Garcia, Erin, I.
García, Federico
Garcia-Lerma, Gerardo
García-Morales, Claudia
Garland, Wendy, H.
Gaseitsiwe, Simani
Gatechompol, Sivaporn
Gates, Thomas
Gathogo, Esther
Gavegnano, Christina
Geboy, Alexander
Gelman, Benjamin, B.
Genberg, Becky, L.
George, Varghese
Gerard, Laurence
Gervasoni, Cristina
Giacobbi, Nicholas, S.
Giacomet, Vania
Gianella, Sara
Gilada, Trupti, I.
Gill, Alexander, J.
Gill, John
Gingich, David
Giron, Leila, B.
Gisslén, Magnus
Glick, Sara, N.

Golden, Matthew, R.
Gonzalo-Gil, Elena
Goodreau, Steven, M.
Gorin, Aleksandr
Graham, Susan, M.
Greathead, Louise
Greene, Sharon, A.
Grund, Jonathan
Gu, Diane
Güerri-Fernández, Robert
Gupta, Amita
Gupta, Kushol
Gupte, Akshay
Gutierrez, Jose
Haaland, Richard
Haas, Andreas
Haberlen, Sabina
Hachiya, Atsuko
Haddad, Lisa, B.
Hader, Shannon, L.
Hakim, Avi
Hale, Malika
Hammarlund, Gustaf, O.
Hanan, Nathan
Hanna, David, B.
Harada, Shigeyoshi
Hassan, Amin, S.
Hassan, Jaythoon
Hassounah, Said
Havens, Peter, L.
Haworth, Kevin, G.
Hecht, Frederick, M.
Hector, Jonas
Heffron, Renee
Hellmuth, Joanna
Hendrickson, Cheryl, J.
Hensley-McBain, Tiffany
Hermans, Lucas, E.
Hermansson, Linn
Hernandez-Ramirez, Raul Ulises
Hessol, Nancy, A.
Hiener, Bonnie
Hijlkema, Simone, H.
Hikichi, Yuta
Hiransuthikul, Akarin
Hlupeni, Admire
Ho, Ya-Chi
Hodcroft, Emma, B.
Hoenigl, Martin
Hoepelman, Andy
Hof, Malon, Van den
Hofstra, Laura Marije
Hogg, Robert, S.
Holtz, Timothy, H.
Hood, Julia
Hoornenborg, Elske
Hoots, Brooke
Horner, Marie-Josephe
Howard, Andrea
Hoyte, Ashley, C.
Hsu, Denise, C.
Hsu, Hilary, K.
Hsu, Ling
Huang, Szuhan
Huang, Yunda
Hubbard, Mark
Hughes, Alison
Hughes, Stephen, H.
Huik, Kristi
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