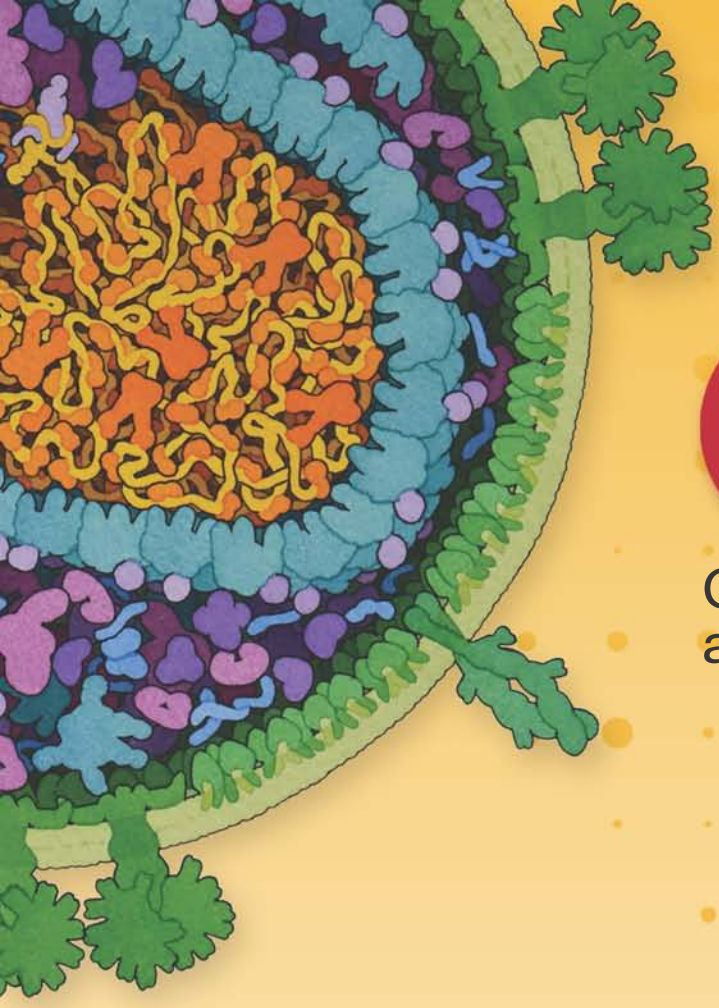

CROI

Conference on Retroviruses and Opportunistic Infections

Abstract eBook

Seattle
March 4-7, 2019

IAS–USA
International Antiviral Society–USA

CONTENTS

The contents of this Abstract eBook are current as of February 21, 2019. Please note that the contents may be periodically updated.

Embargo Policies and Social Media

Research presented at CROI 2019 is embargoed until the conclusion of its presentation at the conference. Oral abstract presentations are embargoed until the conclusion of their presentation at the conference, or at an official CROI press conference, whichever comes first. Poster presentations are embargoed until the beginning of the poster session in which they are presented.

CROI embargo policies apply to any public dissemination of research information presented at the conference, including electronic publications (eg, blogs) or social media (eg, Facebook, Twitter). No public dissemination of research information from the conference is permitted prior to the lifting of the conference embargo. Individuals or organizations that violate the conference embargo policy may have their conference credentials revoked and may forfeit the opportunity to participate in future conferences.

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ABSTRACT PROCESS

Scientific Categories

A. Virology
B. Pathogenesis: Human Studies and Animal Models
C. HIV-Associated Tumor Viruses
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 Neurologic Complications
G. Clinical Pharmacology
H. Antiretroviral Therapy: Pre-Clinical Data, Randomized Trials, Efficacy and Effectiveness Studies
I. HIV Drug Resistance
J. HIV Diagnostics
K. Hepatitis Viruses and Liver Complications
L. AIDS-Related Malignancies
M. Cardiovascular Complications of HIV Infection and Antiretroviral Therapy
N. Other Complications of HIV Infection and Antiretroviral Therapy
O. Tuberculosis and Other Opportunistic Infections
P. Maternal and Fetal HIV
Q. Pediatrics and Adolescents
R. Epidemiology
S. Testing
T. Prevention Interventions
U. Contraception, Sexually Transmitted Infections, and Reproductive Health
V. Implementation and Scale-Up of Treatment and Care
W. Population and Cost Modeling

Abstract Content

Author names, institutions, titles, and abstracts in the Abstract eBook and other materials are gernerally presented as submitted by the corresponding author.

Abstract Review Process

The PC and a panel of volunteer external reviewers reviewed more than 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 were identified and censored. Abstracts with high variability in scores were discussed individually during a series of conference calls for each scientific category. 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 (distinct from 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	1859
General abstracts accepted	992
General oral abstracts	92
General poster abstracts	900
Late-breaking abstracts submitted	189
Late-breaking abstracts accepted	35
Late-breaking oral abstracts	18
Late-breaking poster abstracts	17
Total abstracts submitted	2048
Total abstract accepted	1027

All Presenting Authors on Accepted Abstracts

Region	N	Percent
Africa	97	11
Asia	19	2
Australia	9	1
Europe	193	21
Central and South America	15	2
North America	584	63

ORAL ABSTRACTS

1 PROGRAM COMMITTEE WORKSHOP FOR NEW INVESTIGATORS AND TRAINEES

John W. Mellors[1], **Serena S. Spudich**[2]
[1]*University of Pittsburgh, Pittsburgh, PA, USA,* [2]*Yale University, New Haven, CT, USA*

Each year, the Program Committee for the Conference for Retroviruses and Opportunistic Infections (CROI) presents a half-day workshop geared toward new investigators and trainees. The goal of the workshop is to provide a broad introduction to key topics in basic, clinical and public health research, summarizing recent advances, areas of controversy and important knowledge gaps, along with a road map to relevant abstracts and presentations at CROI 2019. Presentations at the workshop are given by members of the CROI Program Committee. This year, the program will begin with a talk by **Dr Paul Bieniasz** who will review aspects of the HIV-1 replication cycle, in particular recent developments in the understanding of virus entry, capsid function and RNA turnover. Following this, **Dr Penny Moore** will describe advances in eliciting protective HIV-1 antibodies by vaccination, highlight emerging insights at the interface between innate and adaptive immunity, and summarize new immunological findings relevant to HIV-1 to be presented at the conference. **Dr Sharon Hillier** will then describe the current landscape of biomedical HIV-1 prevention research including vaccines, broadly neutralizing antibodies, oral and injectable pre-exposure prophylaxis, vaginal and rectal microbicides, and combination approaches for prevention of HIV-1. **Dr Constance Benson** will next briefly summarize the current state-of-the-art for tuberculosis treatment and prevention, highlight recent developments in the field, including new data to be presented at CROI, and identify current knowledge gaps that need to be addressed. Finally, **Dr Katharine Bar** will review the current understanding of HIV-1 persistence, highlight major obstacles to achieving a cure for HIV-1, and discuss pre-clinical and clinical developments in HIV-1 cure research. Workshop participants are encouraged to interact with speakers during the moderated discussion after each talk. By the completion of the workshop, attendees will have achieved a head start toward maximizing the knowledge gained and research ideas arising from CROI 2019.

2 DISCOVERING THE ART IN SCIENCE (AND MEDICINE): THE HUMAN CONNECTION

Dawn Averitt, *The Well Project, Women's Research Initiative on HIV/AIDS, South Strafford, VT, USA*

The scientific frontier is vast and our ongoing exploration continues to unveil stunning revelations impacting technology, medicine, and human health. However, the complexity of a person (not just a patient) introduces both an opportunity and a challenge to translate our knowledge of science into the art of medicine. Recognizing, if not understanding, the nuanced biologic, physiologic, emotional, and societal influences impacting people of different ages, races, sex, or gender provides boundless opportunities in research and medicine to uncover possibility and challenge long held assumptions.

3 ENGINEERING THE LATENT RESERVOIR

Paula Cannon, *University of Southern California, Los Angeles, CA, USA*

HIV persists in infected individuals despite antiretroviral therapy (ART). This is because the virus inserts itself into the genomes of infected cells where it can, under certain conditions, become transcriptionally silent or latent. These latent viruses are not impacted by ART but retain the potential to be reactivated at a later timepoint. In this way, latent HIV shares many of the features of a genetic locus, including sensitivity to the cell's transcriptional or activation state. The recent development of sequence-specific genome editing tools such as CRISPR/Cas9, is suggesting new ways to consider depleting or mitigating the effects of the latent reservoir. Current genetic approaches against HIV infection include: (1) strategies to create HIV resistant cells, for example by disabling the non-essential CCR5 co-receptor gene in CD4 T cells or their precursor hematopoietic stem cells; (2) strategies to boost or artificially redirect immune responses to recognize infected cells; and (3) strategies to target integrated HIV genomes themselves for disruption, suppression or activation. The first two approaches have the advantage of being amenable to ex vivo cell engineering, the capabilities for which have greatly advanced in recent years. Strategies targeting the HIV genome itself, however, will require the development of in vivo delivery methods that can find the needle in the haystack that an integrated latent HIV genome represents.

4 NOVEL IMAGING APPROACHES TO CHARACTERIZE AND QUANTIFY VIRAL RESERVOIRS

Jake D. Estes, *Oregon Health and Sciences University, Portland, OR, USA*

Effective combination antiretroviral therapy (cART) for HIV has led to vastly improved survival when treatment is available and affordable, an outcome that relies on uninterrupted adherence to cART for life. In the quest for sustained viral remission in the absence of cART (i.e. functional cure) or the complete eradication of HIV from infected individuals, it is necessary to understand the sizes, locations and characteristics of the reservoirs throughout the body from which infection can rebound after treatment is suspended. In addition, understanding HIV reservoirs in the context of their resident immune "neighborhoods" and surrounding inflammatory "landscapes" will likely be important to determine key mechanisms of viral persistence and potentially identify opportunities or pathways to exploit for future viral remission and eradiation strategies. In this talk, I will discuss advances in approaches to image viral reservoirs at the tissue and cellular level in the infected host that have provided key insights on the phenotype, size, and characteristics of viral reservoirs and their local tissue microenvironments. Integration of unique, but complementary, imaging platforms that provide critical contextual insights into HIV reservoir biology with sensitive molecular and single cell approaches should prove instrumental in further promoting the development of new therapeutic strategies for sustained viral remission or elimination needed for an 'HIV cure' to be realized.

5 MORE COLORFUL IMMUNOLOGY: TARGETED ISOLATION OF MONOCLONAL ANTIBODIES

Mario Roederer, *NIH, Bethesda, MD, USA*

Monoclonal antibody (mAb) interventions for the prevention or treatment of HIV-1 infection have galvanized the field in the past five years. Broadly HIV-neutralizing mAbs are now being evaluated in clinical trials as therapeutics, "cure" strategies, and prophylaxis. The primary method of identification and isolation of these antibodies has been flow cytometric sorting of single cells, either based on antibody binding characteristics, or in bulk, from B cells of individuals infected or immunized with the antigens of interest. Optimization of this process has been undertaken on a wide range of fronts: probes (used to identify the B cells), immunophenotyping panels (to define particular subsets of interest), sorting speed and viability, post-sort culture or sequence identification (from single cells), highly sensitive micro-scale assays to define useful antibodies, cloning to express the antibody, and post-isolation improvements in affinity, solubility, manufacturability, and off-target effects. At the VRC, we built upon the successful isolation, optimization, and clinical development of VRC01 (now in Phase IIb testing HIV prophylaxis in 4,500 adults) to expand the repertoire of clinically-relevant antibodies for HIV, flu, malaria, and RSV, as well as testing interventions in preclinical primate models using SHIV or SIV. In this talk, I will review some of the types of screening technologies that we use to efficiently isolate novel, potentially clinical useful monoclonal antibodies.

6 FELLOW TRAVELERS: INTERPRETING THE IMPACT OF THE MICROBIOME IN CLINICAL INTERVENTION

Adam Burgener, *Public Health Agency of Canada, Winnipeg, MB, Canada*

The microbiome represents the composition of bacteria, fungi, viruses, and their products that exist within the human body. It helps us digest food, shapes our immune system, and provides essential functions for human health. Many human diseases, including diabetes, inflammatory bowel disease, and cancer

have been linked to alterations to the microbiome. There are currently >1000 registered clinical trials examining microbiome-based interventions to promote human health and its role in disease, underscoring this expanding field of research. In HIV, the microbiome has been associated with HIV transmission and infection, mucosal inflammation, immune responses to vaccines, and efficacy of topical antiretroviral-based microbicides. Therefore, integrating microbiome sub-studies in future clinical trials will be an important component for HIV prevention and treatment strategies. In this seminar I will provide an overview of the basics of the microbiome, methods to measure its different components, how to interpret data, examples of how this can be integrated it into clinical studies and provide highlights on the microbiome in HIV and human disease.

7 MISSING U: HANDLING AND AVOIDING MISSING DATA IN CLINICAL TRIALS

Heather Ribaudo, *Harvard T.H. Chan School of Public Health, Boston, MA, USA*

Randomized clinical trials are the gold standard for evaluation of interventions. However, the presence of missing data can compromise their benefits, and lead to bias and inappropriate study conclusions. While methods exist to handle missing data in analysis, these may appear intimidating to the statistician and non-statistician alike, and are generally under-utilized. Even when used, handling of missing data in analysis can only do so much, and it has long been advocated that considerations for minimizing missing data must start at trial design. At the request of the FDA, the National Research Council (NRC) recently convened a panel of experts to consider current state-of-the-art for handling missing data in clinical trials. The panel recommendations reinforced previous considerations and introduced some new ideas and concepts to be considered in the design and analysis of clinical trials to mitigate the impact of missing data. This talk will demonstrate the issues associated with inappropriate handling of missing data and attempt to demystify the associated analysis methodology. The recommendations of the NRC panel will be presented, including an introduction to the definition of estimands in study design and a discussion of appropriate sensitivity analyses. Examples from HIV clinical trials for both treatment and prevention will be used throughout to help demonstrate and solidify concepts. By the end of the talk, the audience will be familiar with terminology associated with missing data and have an understanding of the appropriate points to consider, and tools to implement, in clinical trial planning, analysis, and reporting to minimize the impact of missing data.

8 DESIGNING AND INTERPRETING HIV PREVENTION TRIALS IN THE ERA OF EFFECTIVE INTERVENTIONS

David Dunn, *University College London, London, UK*

Until recently, the design and analysis of clinical trials to evaluate HIV prevention interventions was relatively straightforward. Participants would be randomised to receive the intervention of interest or to receive no intervention (placebo under the most robust design). The analysis would compare HIV incidence rates between the groups, yielding an estimate of the effectiveness – the proportionate reduction in incidence – achieved by the intervention. This model of experimental simplicity was ended with the discovery of the remarkable effectiveness of oral pre-exposure prophylaxis (PrEP) using TDF-FTC. This meant it became ethically unacceptable to include a no intervention group in most study populations. Current studies of novel PrEP agents have instead been designed as non-inferiority trials in which the experimental arm is compared with an active-control TDF-FTC arm. The challenges in analysing and interpreting such trials will be discussed, pointing out the need to collect additional contextual information. A different perspective is required for the evaluation of other prevention interventions, including vaccines. Here, the primary interest may be in estimating biological efficacy rather than a direct comparison with oral PrEP. Nevertheless, the ethical requirement to offer PrEP complicates trial design and interpretation, as well as potentially requiring much larger studies. This session will attempt to illuminate key, basic concepts, keeping statistical detail to a bare minimum.

9 INTERACTIVE CASE-BASED WORKSHOP ON LIVER DISEASE

Marion G. Peters[1], **Andri Rauch**[2]
[1]*University of California San Francisco, San Francisco, CA, USA,* [2]*University Hospital Bern, Bern Switzerland*

This interactive case-based session is geared toward clinicians who are involved in treatment of HIV-infected patients with various liver diseases. Despite major recent breakthroughs in the treatment of viral hepatitis, there are important remaining challenges in the clinical care of those with liver diseases. This workshop will address difficult to treat HCV-coinfected patients who have failed direct-acting antiviral (DAA) therapies, highlight the important but often ignored hepatitis D and E viruses, and address the epidemiology and management of nonalcoholic fatty liver disease (NAFLD). **Dr Sven Pischke** (University Hospital Hamburg-Eppendorf) will discuss issues in diagnosis, clinical features, and treatment of Hepatitis E. He will highlight geographic differences in epidemiology and testing, and address the current management strategies. **Dr Jeffrey Glenn** (Stanford University) will provide an overview of current diagnostic tests, clinical challenges and emerging new therapies for Hepatitis D, and the varied prevalence throughout the world. **Dr Giada Sebastiani** (McGill University) will discuss NAFLD and its complex multifactorial pathogeneses, including frequent metabolic comorbidities and lifelong use of antiretroviral therapy and HIV itself, which is thought to drive this epidemic. She will highlight that early diagnosis, preventive and therapeutic strategies may help reduce the burden of NASH in people living with HIV. **Dr John Scott** (University of Washington) will describe HCV DAA failures, the scenarios in which HCV resistance testing should be performed, and the choices of therapy for patients with end-stage liver disease.

(2010) SPECIAL PRESENTATION
ENDING THE HIV EPIDEMIC: A PLAN FOR THE UNITED STATES

Anthony S. Fauci, MD, *NIAID, Bethesda, MD, USA*

This presentation will describe the newly announced U.S. Department of Health and Human Services initiative targeting the ongoing HIV epidemic in the United States with the goals of decreasing the number of HIV incident infections by 75% within 5 years, and then by 90% within 10 years. This coordinated, multi-agency initiative will focus on geographic and demographic hotspots in 48 counties, Washington D.C., and Puerto Rico where the majority of new HIV cases are reported, as well as in 7 states with a disproportionate occurrence of HIV cases in rural areas. This new initiative builds on the scientific findings over the past 4 decades in HIV prevention, treatment, and care. Under the leadership of the Assistant Secretary for Health, HHS agencies including NIH, CDC, HRSA, and IHS will coordinate their programs and resources to implement with local, regional, and state partners evidence-based strategies to diagnose, treat, prevent, and rapidly detect and respond to the continuing HIV spread in the U.S. This HHS initiative will focus on interrupting or disrupting the kinetics of HIV spread and provide a way forward to ending the epidemic in this country.

10 DISCOVERY AND DEVELOPMENT OF HIV BROADLY NEUTRALIZING ANTIBODIES

Michel Nussenzweig, *The Rockefeller University, New York, NY, USA*

Combination antiretroviral therapy (ART) has revolutionized the treatment and prevention of HIV-1 infection. Taken daily, ART prevents and suppresses the infection. However, ART interruption almost invariably leads to rebound viremia in infected individuals due to a long-lived latent reservoir of integrated proviruses. Therefore, ART must be administered on a life-long basis. The lecture will focus on emerging preclinical and clinical studies that suggest that immunotherapy may be an alternative or an adjuvant to ART because in addition to preventing new infections, anti-HIV-1 antibodies clear the virus, directly kill infected cells and produce immune complexes that can enhance host immunity to the virus.

11 THAILAND'S ACHIEVEMENTS IN HIV TREATMENT, PREVENTION, AND CURE RESEARCH

Praphan Phanuphak, *Thai Red Cross AIDS Research Center, Bangkok, Thailand*

To the external world, Thailand has achieved considerably on HIV treatment, prevention, and cure research but the reality could be different. For HIV treatment, even with Universal ART Coverage since 2006 and the Treat-All policy since 2014, the "second 90" is still far below with a median CD4 count at ART initiation of <150 cells/ML in Thailand. To close this gap, "Same-Day ART (SDART) Initiation Hub" was launched at the Thai Red Cross Anonymous Clinic (TRC-AC). In one year, 77% of 2,000 PLHIV started ART on the day of diagnosis and another 19% in a week. However, the Thai government and most ID doctors are still too afraid of SDART since even in the US it has not yet been implemented and WHO puts SDART only as a subset of Rapid ART. Only 54% of PLHIV in Thailand reached undetectable viral load. This, coupled with low 'consistent condom use' rate among key populations, dictates the urgent need of PrEP. Providers who serve MSM, transgender women, and sex workers have been

trained and qualified to provide HIV testing and dispense PrEP, the so called "key population-led health services or KPLHS", to around 50% of all Thai PrEP users. Four years after Thai Guidelines recommended PrEP, only 4% of 150,000 Thais at risk access PrEP. Government needs to de-medicalize PrEP and accept KPLHS roles in ending AIDS now. Over a decade, the world's largest cohort (RV254) of 600 acute HIV cases has been established at TRC-AC. Through available routine NAT screening, early and frequent HIV testing has formed among certain populations. Immediate ART, together with extensive virologic/immunologic studies, demonstrated very low HIV reservoir even though there is no good news so far for HIV remission/cure. Crucial data for global HIV cure research are generated from Thailand although it is still too far away to get government's attention. Achievements described is the outcome of continuing commitment of government, civil society, academics and royal family. Policy makers and politicians, who change frequently, are vital in the process since all successful pilot projects need to be scaled up. The country needs some influential 'watch dogs' to keep these strategies on track. Too much international appraisal can cause complacency among policy makers and politicians.

12 DENIAL, DOOM, OR DESTINY? RESURGENT STIs IN HIV CARE AND PREVENTION

Jeanne M. Marrazzo, *University of Alabama at Birmingham, Birmingham, AL, USA*

Antiretroviral therapy (ART) that achieves virologic suppression essentially eliminates the risk of sexual transmission to HIV-uninfected partners, informing the hope that treatment as prevention can play a major role in crippling the HIV epidemic. Moreover, persons who appropriately use preexposure prophylaxis (PrEP) can avoid HIV acquisition, and use of the currently approved agent, tenofovir-emtricitabine (TDF-FTC), is increasing globally. As uptake of these approaches has escalated, sexual behaviors have evolved on the different timelines that defined their implementation: first in people living with HIV as increasingly powerful ART reliably effected HIV suppression, then in people at risk for HIV as PrEP was rolled out. As ART enhanced quality of life and, naturally, sexual health, increases in rates of sexually transmitted infections (STIs) were reported among people living with HIV-notably syphilis, especially among men who have sex with men (MSM). This might be considered the "first new wave" of STIs in the post-ART era. As PrEP uptake has gained traction, a "second new wave" of increasing STI incidence has gathered strength, with record rates of gonorrhea and syphilis in MSM. The high efficacy of PrEP, especially in MSM, means that individuals at risk can avoid HIV acquisition in the absence of barrier methods of protection. Critically, MSM are not the only concern. In sub-Saharan Africa, PrEP is being rolled out in settings where syndromic management is still the standard approach to STI management-clearly, a suboptimal situation. Demonstration projects of PrEP in these settings have not had the capacity or intent to evaluate concomitant shifts in STI incidence at a community level. The implications of rising STI rates require reassessment of the alignment and prioritization of HIV research funding, health policy, and community engagement and inform numerous questions. Are STIs an inevitable byproduct of biomedical HIV control, and should the answer change our view of sexual health? Do we need to think differently about management of non-HIV STIs (screening, diagnosis, treatment, partner management) in those at risk for HIV? Is high STI incidence likely to undermine success of TasP or PrEP in the long term or in certain populations? Should new approaches focus on broader spectrum prevention (agents that inhibit HIV and other viruses)? What are the broad implications, including funding and trial design, for clinical STI research?

13 INFLAMMATION: TAMING THE FLAMES

Irini Sereti, *NIAID, Bethesda, MD, USA*

From the outset of the HIV epidemic it became clear that the virus capitalized on the immune defenses of the host to create an immune environment that would further foster availability of cellular targets and viral replication. Several studies in animal models of SIV and in humans at various stages of disease have concluded that immune activation represents an independent prognostic factor in HIV including treated disease with successful virologic suppression. Systemic inflammation and immune activation in HIV have been linked to excess risk for both AIDS and non-AIDS serious events in both untreated and treated people living with HIV (PLWH), and seem to accelerate the detrimental effect of other comorbidities such as smoking or diabetes or aging. In addition, inflammation and cellular activation can be critical in viral persistence contributing to the preservation, expansion or population shifts of the HIV viral reservoirs. The etiology of immune activation and inflammation in treated HIV is considered multifactorial encompassing residual viral replication, mucosal injury at effector sites that leads to innate immune activation and potentially dysbiosis, incomplete CD4 restoration, tissue fibrosis and coinfections. Inflammation and fibrosis in HIV are also accompanied by coagulopathy. Biomarkers that signify the degree of inflammation such as IL-6, CRP, sCD14 as well as D-dimer levels have been found in numerous studies to be strong independent predictors of morbidity and mortality in PLWH. It is though unclear if and to what extent, altering these biomarkers with anti-inflammatory or other therapies could alter clinical outcomes. Efforts to counteract the chronic inflammation in HIV have focused on the various facets of its etiology largely with small or moderate success. At the moment the best approach is treatment with antiretroviral therapy, preferably at diagnosis at early stages of disease when CD4 counts are still high, in combination with aggressive treatment of possible comorbidities. A better understanding of the etiologic pathways and how they intersect leading to chronic inflammation in HIV will be critical for improved, and efficacious, treatment interventions.

14 HV VACCINE WITH LEEP DID NOT PREVENT RECURRENT CERVICAL HSIL IN HIV-INFECTED WOMEN

Cindy Firnhaber[1], Avril Swarts[2], Masangu Mulongo[3], Bridgette Goeieman[3], Sophie Williams[3], Simon Levin[3], Mark Faesen[3], Pamela Michelow[4], Timothy Wilkin[5]

[1]University of Colorado, Aurora, CO, USA, [2]Clinical HIV Research Unit, Johannesburg, South Africa, [3]Right to Care, Johannesburg, South Africa, [4]National Health Laboratory Service, Johannesburg, South Africa, [5]Weill Cornell Medicine, New York, NY, USA

Background: Women living with HIV are at high risk for cervical HSIL and rates are especially high in sub-Saharan Africa. These women have high HSIL recurrence rates after loop electroexcision procedure (LEEP) requiring additional monitoring and treatment. More effective treatment for HSIL lesions in HIV infected women is needed. Some retrospective studies suggest that the Human Papillomavirus (HPV) vaccine used as adjuvant therapy with LEEP improves response to treatment of High-grade Squamous Intraepithelial lesions (HSIL) in HIV negative women. We evaluated the effectiveness of the HPV quadrivalent vaccine in preventing the recurrence of HSIL after LEEP in HIV infected women in Johannesburg South Africa.

Methods: We performed a double-blind, randomized clinical trial that enrolled 180 HIV infected women, between the ages of 18-65 years and cervical HSIL on histology in Johannesburg South Africa according to Consort criteria. The women were excluded if they were pregnant. Women received the quadrivalent HPV or placebo vaccine (1:1) at entry, week 4, and week 26. LEEP was performed at week 4. Colposcopy and directed biopsies and cervical cytology were performed at week 26 and 52. The primary endpoint was cervical HSIL by histology or cytology at either week 26 or 52, and this was compared between arms using Chi-square analysis.

Results: Participant characteristics included median age 39, median CD4 489, and 94% had HIV suppression (<200 copies/ml) on antiretroviral therapy. Of the 180 women enrolled, 179 women underwent LEEP and 174 women completed the vaccine/placebo series and had evaluable results at week 26 or 52. The proportion experiencing the primary endpoint of HSIL was similar in the vaccine and placebo groups, 53% vs. 45% (RR 1.16, 95% CI .87-1.6, P=.29). Similar results were seen when using only histologic results at 26 and 52 weeks (32% vs. 31%, RR 1.04, 95% CI .67-1.04, P=.9). HSIL recurrence was associated with a LEEP result of HSIL and positive margins on LEEP at week 4.

Conclusion: This randomized, double-blind clinical trial did not find evidence to support an adjuvant role for HPV vaccination for preventing recurrent HSIL post-LEEP in women living with HIV. Recurrent HSIL was high despite virologic suppression with antiretroviral therapy. More effective treatment strategies are needed to reduce the burden of recurrent cervical HSIL in this high risk population.

15 OPTIMAL LUNG CANCER SCREENING CRITERIA AMONG PERSONS LIVING WITH HIV

Subhashini A. Sellers[1], Andrew Edmonds[1], Catalina Ramirez[1], Sushma Cribbs[2], Igho Ofotokun[2], Laurence Huang[3], Alison Morris[4], Meredith C. McCormack[5], Ken M. Kunisaki[6], Maria P. Rivera[1], M. Brad Drummond[1], Adaora Adimora[1]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]Emory University, Atlanta, GA, USA, [3]University of California San Francisco, San Francisco, CA, USA, [4]University of Pittsburgh, Pittsburgh, PA, USA, [5]Johns Hopkins University, Baltimore, MD, USA, [6]Minneapolis VA Health Care System, Minneapolis, MN, USA

Background: Based on the National Lung Screening Trial (NLST), US Preventive Services Task Force (USPSTF) recommends screening with low-dose chest computed tomography scan for adults aged 55-80 with >30 pack-year smoking history who are current smokers or quit within the last 15 years. Persons living with HIV (PLWH) are at increased risk for lung cancer but were excluded from the NLST. This study evaluated the performance characteristics of NLST criteria in confirmed lung cancer cases and matched controls from observational cohorts of men and women with HIV. We also explored alternative thresholds to improve lung cancer detection rates.

Methods: We selected all confirmed lung cancers among PLWH who were current/former smokers and ≥40 years at diagnosis in the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS). Controls, selected from each cohort, were PLWH with no reported lung cancer during all follow-up visits, matched on 5-year age windows. Clinical and demographic characteristics, and proportions meeting NLST screening criteria, were compared. Alternative thresholds included iterative reductions in age, pack-years, and quit date.

Results: We identified 44 WIHS women and 17 MACS men with HIV and incident lung cancer (Table). Lung cancer incidence was 270 and 104 per 100,000 person-years in women and men, respectively (p<0.001). Race and income did not differ between cases and controls. Compared to controls, women with lung cancer had a significantly lower median CD4 count but no significant difference in median viral load. In men, there were no significant differences in these markers of HIV infection between cases and controls. Only 16% of women and 24% of men with lung cancer met USPSTF screening criteria. Optimal age and pack-year screening criteria in women (age 49-75, ≥16 pack-year history) yielded 52% sensitivity and 75% specificity. In men, optimal criteria (age 43-75, >19 pack-year history) yielded sensitivity (82%) and specificity (76%).

Conclusion: Current USPSTF lung cancer screening guidelines performed poorly in PLWH, as <25% of lung cancer cases met criteria. Alternative thresholds of age, smoking history, and quit date can better identify PWLH to screen for lung cancer. Among PLWH, lung cancer risk was higher in women than men. This study demonstrates the need for risk prediction modeling incorporating sex and markers of HIV infection to identify high risk individuals who would benefit from screening despite not meeting current USPSTF criteria.

Characteristic	WIHS Women			MACS Men		
	With lung cancer (n=44)	Without lung cancer (n=44)	p-value*	With lung cancer (n=17)	Without lung cancer (n=17)	p-value*
Age, years	54 (50-57)	53 (49-58)	0.98	52 (48-55)	51 (49-56)	0.95
Black race	36 (82)	29 (66)	0.09	4 (24)	5 (29)	1.00
Low annual income†	35 (80)	34 (77)	0.80	9 (60)	5 (33)	0.16
CD4 count, cells/μL	348 (182-560)	452 (276-732)	0.03	387 (150-833)	549 (472-858)	0.21
HIV RNA, copies/mL	221 (48-4100)	80 (20-720)	0.16	124 (40-22,283)	400 (40-14,146)	0.74
ART use at time of diagnosis	25 (57)	32 (73)	0.12	10 (63)	11 (65)	0.72
Current smokers	27 (61)	26 (59)	0.83	12 (71)	4 (24)	<0.01
≥30 pack-years smoked	13 (30)	9 (20)	0.33	12 (71)	4 (24)	<0.01
Quit ≤15 years ago (% of former smokers with quit data available)	14 (93)	10 (56)	0.02	5 (100)	12 (92)	1.00
Meeting screening criteria§	7 (16)	3 (7)	0.18	4 (24)	1 (6)	0.34

All values n (%) or median (interquartile range).
*Chi-Square Test for categorical variables and Wilcoxon Test for continuous variables
†Household income of ≤ $18,000 for WIHS and individual income ≤ $20,000 for MACS
§Individuals age 55-75, ≥30 pack-year smoking history, current smoker or quit within last 15 years

16 HIV IS ASSOCIATED WITH DECREASED BREAST CANCER SURVIVAL: A PROSPECTIVE COHORT STUDY

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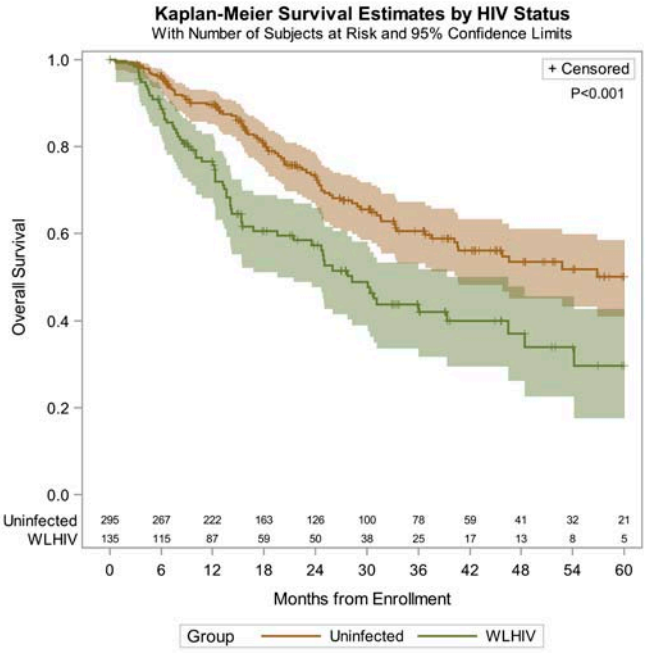
Background: Breast cancer is the second leading cause of cancer death among women living with HIV (WLHIV) with access to ART. In the context of ART coverage exceeding UNAIDS 90-90-90 targets, we sought to prospectively assess the impact of HIV on overall survival of women with breast cancer.

Methods: As part of the Thabatse Cancer Cohort, we included women presenting (October 2010 to March 2018) for initial treatment of breast cancer at one of four oncology centers in Botswana. Consenting patients were interviewed, records abstracted, and followed for up to 5 years. The association between HIV infection and all-cause mortality was assessed using a multivariable Cox proportional hazards model including covariates selected a priori: cancer stage, curative versus palliative intent, receptor status, age, and personal income.

Results: A total of 430 women with breast cancer with known HIV status were enrolled (4 women with unknown HIV status excluded), including 135 (31.4%) WLHIV and 295 (68.6%) uninfected women. WLHIV were younger than uninfected women, median 47.5 and 55.5 years, respectively (p<0.001). Among WLHIV, 110 (84%) were on ART prior to cancer diagnosis (median duration 6.8 years) and median CD4 count was 513 cells/μL. Advanced cancer stage (III/IV) was common for both WLHIV (67%) and uninfected women (66%). Immunohistochemistry results were available for 250 women (58%); 154 (62%) women were ER+ and 65 (26%) were triple-negative. Receptor status was similar by HIV status (p=0.89). The majority (69%) received multimodality treatment with curative intent and the proportion did not differ by HIV status (p=0.80). After 847 patient-years of follow-up, 156 women died, including 66 (49%) WLHIV and 90 (31%) uninfected women. Three women (0.7%) were lost to follow-up. The majority of deaths (141, 90%) were attributed to cancer and none to HIV. Two-year survival for WLHIV was lower than those without HIV, 57% and 73%, respectively (see Figure, p<0.001). Findings were similar in adjusted analyses with WLHIV experiencing higher mortality (hazard ratio 1.86, 95%CI 1.33 to 2.61, p<0.001). Cancer stage, treatment intent, and personal income less than $50/month were also inversely predictive of survival (p<0.001 for each).

Conclusion: HIV infection is associated with substantially higher non-AIDS mortality among women with breast cancer. Improved understanding of mechanisms underlying excess mortality could contribute to improved outcomes in the majority female and aging African HIV epidemic.



17 LONG-TERM OUTCOMES OF 58 PATIENTS WITH HIV AND KSHV+ MULTICENTRIC CASTLEMAN DISEASE

Ramya Ramaswami, Kathryn Lurain, Priscila H. Gonçalves, Mark Polizzotto, Anaida Widell, Matthew Lindsley, Richard F. Little, Thomas S. Uldrick, Robert Yarchoan
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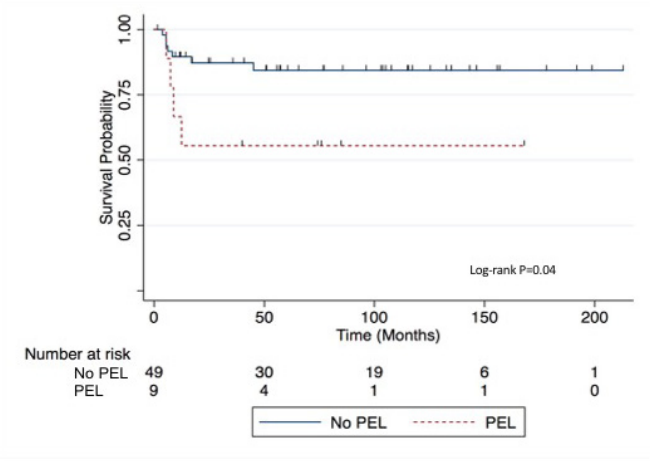
Background: Multicentric Castleman disease (MCD) is a rare systemic lymphoproliferative disease caused by Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpes virus 8 (HHV-8). Patients with HIV and KSHV-MCD may also have Kaposi sarcoma (KS) and are at increased risk of developing non-Hodgkin lymphoma, especially primary effusion lymphoma (PEL). The historical overall survival was 2.5 years, but this has improved following the use of rituximab for KSHV-MCD and antiretroviral therapy for patients with HIV. Here, we present the long-term outcomes of the largest prospective study of KSHV-MCD and HIV+ patients in North America.
Methods: We evaluated longterm outcomes and concurrent diagnoses (KS and PEL) that influenced overall survival for patients with HIV and KSHV-MCD in a natural history study with 5 optional treatment regimens for MCD flares. This included high-dose zidovudine and ganciclovir, sirolimus, rituximab (R) with liposomal doxorubicin (R-LD) followed by interferon-α or high-dose zidovudine with valganciclovir (AZT/VGC), or rituximab plus infusional chemotherapy (R-EPOCH).
Results: There were 58 participants (54 male, 4 female) with a median (range) age of 44 years (26-68), HIV VL <50 copies/mL (50 – 64100) and CD4 count 180 cells/μL (3-1319) at MCD diagnosis. All patients were on combined antiretroviral therapy at study entry, 38 patients had received prior therapy for KSHV-MCD (18 patients with R-based therapy), and 39 patients had a concurrent diagnosis of KS. Nine patients (15%) developed PEL after entry and 1 patient had been diagnosed with PEL prior to KSHV-MCD. Patients diagnosed with PEL were treated with R-EPOCH. The median duration of follow up was 4.1 years. Of the treatment options available in this study, the majority (52 patients (89%)) received R-LD, usually followed by high-dose AZT/VGC. The 5-year overall survival was 80% (95% confidence interval (CI), 66% to 88%). Eleven patients died: 4 from PEL, 4 from KSHV-MCD and associated complications, 2 from KS and sepsis, and 1 died from pancreatic cancer. A concurrent diagnosis of KS was not clearly a prognostic factor (hazard ratio (HR) 2.4; 95% CI, 0.5-11.1, P=0.3). However, a coexistent diagnosis of PEL was associated with worse survival (HR 3.4; 95% CI, 0.99-11.6, P=0.05, figure 1).
Conclusion: KSHV-MCD is an under diagnosed but highly treatable condition if recognized. Physicians need to identify and promptly treat concurrent diagnoses of PEL and KS that may contribute to morbidity and mortality.



18 REDUCTION OF KAPOSI SARCOMA–ASSOCIATED HERPESVIRUS LATENCY USING CRISPR-CAS9

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Background: Kaposi sarcoma-associated herpesvirus (KSHV) is the causative agent of Kaposi sarcoma (KS), an AIDS defining cancer in HIV-1 infected individuals or immune suppressed transplant patients. The prevalence for both KSHV and KS are highest in sub-Saharan Africa where HIV-1 infection is also epidemic. Current therapies for KS are not effective, with high reoccurrence and mortality rate. Similar to other herpesviruses, KSHV's ability to establish latency in the host presents a major challenge to KS treatment or prevention. Among KSHV genes, the latency-associated nuclear antigen (LANA) is absolutely required for latency. Hence, strategies to eliminate LANA from KSHV latently infected cells might lead to prevention or treatment of KS.
Methods: We designed a replication-incompetent adenovirus to deliver LANA-specific CRISPR-Cas9 system (Ad-CC9-LANA) at high efficiency into various KSHV latently infected cells and monitored over a period of 32 days. The effects of Ad-CC9-LANA had on KSHV episome in latently infected cells were then determined by droplet digital PCR. Real-time PCR was utilized to measure the mRNA expressions for LANA and Cas9. Immunohistochemistry (IHC) was performed to demonstrate the reduction of KSHV latently infected cells in Ad-CC9-LANA transduced cultures.
Results: Reduction in KSHV episome was evidence as early as 4 days of transduction by Ad-CC9-LANA. At 32 days post-transduction, the Ad-CC9-LANA transduced cultures demonstrated a substantial reduction in KSHV episome copy number in latently infected cells. These reductions were accompanied by decrease in the LANA mRNA expression and confirmed by IHC. These observations were not due to cell death due to adenovirus transduction as demonstrated by the similar growth kinetic between transduced and non-transduced cells. The Cas9 mRNA expression was also shown to be robust and detected throughout the study period.
Conclusion: Our study demonstrated the feasibility of using a KSHV LANA-targeted CRISPR-Cas9 system to disrupt KSHV latency in infected epithelial and endothelial cell lines. This approach to limit KSHV latency may also represent a viable strategy for against other tumorigenic viruses such as HCV, HPV and EBV. Therefore, it will have significant benefits to human health worldwide and particularly in developing countries where the viral cancer burden is high.

19 THE ROLE OF WILMS' TUMOR 1 IN KAPOSI SARCOMA HERPESVIRUS ONCOGENESIS

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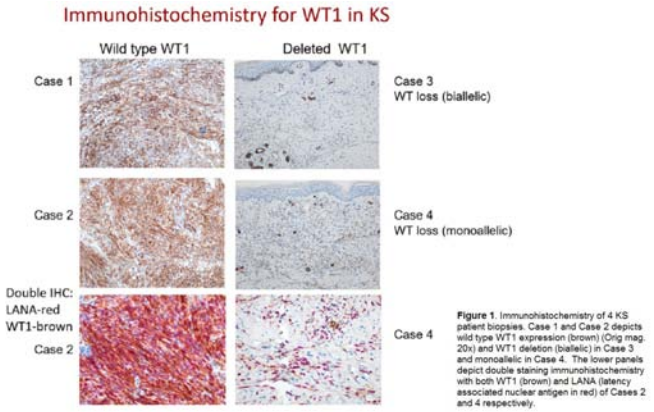
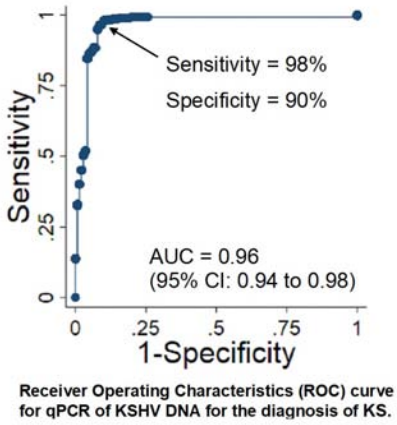
Background: Kaposi Sarcoma (KS), caused by HHV-8, is the most common HIV associated malignancy globally. It occurs predominantly in sub-Saharan Africa where it has a high mortality rate. Despite the burden of KS, it is unknown if KSHV causes a reactive proliferative process or a clonal malignancy due to oncogenic genetic alterations that occur in latent infection due to genetic instability. Discovery of recurrent genetic alterations would provide an improved understanding of KS pathogenesis and may allow for the development of prognostic biomarkers and improved treatment options. A promising cancer antigen is WT1 (Wilms' Tumor 1), for which WT1 therapeutic vaccines have demonstrated benefit in patients with leukemias and solid tumors, and has served as a prognostic marker in patients with myelodysplastic syndromes and leukemias. Different isoforms of WT1 are proposed in leukemias and in solid tumors to have both tumor suppressive and oncogenic roles. We propose that genetic alterations of WT1, a preliminary finding among a subset of KS patients play a role in KS tumorigenesis.
Methods: KS biopsy samples are obtained from Weill Cornell Medical College, Stroger Hospital in Chicago and from the HIPPOS study (Kampala, Uganda). Lentiviral transduction of WT1 shRNA of KSHV infected 293T and endothelial cells were used to explore the role of identified genetic alterations.
Results: We identified a deletion of WT1 in 2/11 patients with KS. Loss was confirmed by immunohistochemistry in these cases, while WT1 overexpression was seen in non-mutated cases. In an expanded cohort, we found additional cases that overexpress WT1 while others had no expression. In addition, the 'tumorigenic' form, cugWT1, was upregulated in endothelial and 293T cells upon infection with KSHV. Similar to the role of the oncogenic form of WT1 in other cancers in regulation of secondary target genes, knockdown of WT1 decreased BCL-2 expression, an anti-apoptotic gene.
Conclusion: Kaposi sarcoma may manifest along a spectrum, as an inflammatory lesion or as a clonal malignancy, due to transformation in the setting of chronic KSHV infection leading to genomic instability. Given the finding of WT1 deletions in a subset of cases, as well as overexpression in others, WT1 isoforms may have pro-oncogenic and tumor suppressive roles in KS. Our

data suggest that two types of KS exist, based on loss or overexpression of WT1. In KS cases that overexpress this protein, WT1 may be a promising target as a biomarker and immunotherapy.



in point-of-care format, and ultimately greatly increase access to timely and accurate KS diagnosis.



Receiver Operating Characteristics (ROC) curve for qPCR of KSHV DNA for the diagnosis of KS.

20LB QUANTIFICATION OF KSHV DNA AS A DIAGNOSTIC TEST FOR KAPOSI SARCOMA IN AFRICA

Aggrey Semeere[1], Andrea Gardner[2], Megan Wenger[3], Priscilla Namaganda[1], Ryan Snodgrass[4], Varun Kopparthy[4], Esther Freeman[5], John Ssali[6], Mwebesa Bwana[7], Toby Maurer[3], Robert Lukande[8], Miriam Laker-Oketta[1], David Erickson[4], Ethel Cesarman[2], Jeffrey Martin[3]

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Background: Histopathologic evaluation, the gold standard for diagnosis of Kaposi sarcoma (KS), has long been limited in sub-Saharan Africa by lack of personnel and materials. Even where pathology is available, accuracy of KS diagnosis is often sub-optimal. This has led to widespread delays and inaccuracies in KS diagnosis, often resulting in late or improper treatment (e.g., unwarranted chemotherapy). As an alternative to histopathology, we hypothesized that quantification of KSHV DNA in skin lesions can diagnose KS.

Methods: We evaluated consecutive patients with skin lesions, suspected by their primary care providers to be KS, who were referred for a skin biopsy at 3 HIV care centers in Uganda. Traditional histopathologic evaluation of the 5 mm skin punch biopsies, including anti-LANA staining, was performed in Africa and by up to 3 pathologists in the US. Quantitative PCR (qPCR) for KSHV ORF 26 was performed on extracted DNA from the biopsy. Using the consensus of the US pathologists as the gold standard, we determined the sensitivity & specificity of PCR (both qualitative and quantitative) for KS diagnosis. A receiver operating characteristics curve was used to assess quantitative cutpoints and area under the curve (AUC).

Results: We tested 506 participants with skin lesions. Median age was 33 years, 38% were women, and 94% were HIV-infected; 22% of lesions were macules, 64% plaques, and 14% nodules. Consensus US pathologic testing revealed that 330 biopsies were KS, 149 not KS and 27 were indeterminate. Using US pathology as gold standard, the sensitivity of African pathology was 95% and specificity was 70%. Sensitivity of qualitative detection (presence or absence) of KSHV DNA for KS diagnosis was 99% but specificity was only 78%. Evaluation of quantitative KSHV DNA content found an AUC of 0.96; at the optimal cutpoint (1412 KSHV copies per 5 µl specimen), sensitivity was 98% and specificity was 90%, with 96% of subjects correctly classified.

Conclusion: In the context of sub-Saharan Africa, where KSHV is endemic, quantification of KSHV DNA content in skin lesions by PCR has both high sensitivity and specificity for the diagnosis of KS when compared to gold standard pathology. In contrast, qualitative detection of KSHV DNA is non-specific. The findings suggest that a nucleic acid amplification-based diagnostic test for KS could largely replace the need for histopathology, be implemented

21 TWO NOVEL POTENTIAL THERAPEUTIC TARGETS IN THE KSHV LIFE CYCLE

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Twenty-five years after the discovery of KSHV our understanding of the molecular mechanisms governing its replication, persistence and pathogenicity has advanced to the point where it may become possible to identify novel therapeutic targets for pharmacological intervention. In our recent work, we have focused on the KSHV thymidine kinase and a non-structural membrane protein encoded by open reading frame (ORF) K15. Work by Gill and colleagues (EMBO J. 2014) had suggested that the KSHV thymidine kinase (TK) homologue, encoded by ORF 21, has tyrosine kinase properties. We therefore explored if tyrosine kinase inhibitors already approved for cancer chemotherapy would show activity against KSHV TK. We found that several compounds potently inhibit KSHV TK in *in vitro* and *ex cellulo* kinase assays, and also strongly inhibit KSHV productive (lytic) replication in tissue culture, as well as KSHV-dependent tumorigenesis in a xenograft model. Regarding the viral non-structural membrane protein encoded by ORF K15 (pK15), we have previously shown that is expressed in Kaposi Sarcoma tissue and that, in primary endothelial cells, it is required for KSHV-dependent angiogenic and proliferative effects, as well as for the ability of KSHV to reactivate from latency; pK15 recruits, and promotes the activation of, the cellular lipase PLCϒ1 to achieve these biological properties (Bala et al., PLoS Path. 2012; Gramolelli et al., PLoS Path 2015; Abere et al. PLoS Path. 2017; Abere et al. J. Virol. 2018). We have now studied the interaction of pK15 with PLCϒ1 at the molecular and structural level and identified first small molecule inhibitors that potently interfere with the activation of PLCϒ1 by pK15 and KSHV lytic replication. Ongoing work aims to optimize these ‹hits› to reach a starting point for hit-to-lead development.

22 TARGETING THE NONCANONICAL NF-κB PATHWAY REVERSES SIV LATENCY

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Background: The leading approach to eradicate HIV consists of the induction of latency reversal and subsequent clearance of cells reactivating the virus. Here, we tested a novel latency reversing agent (LRA) strategy that selectively activates the non-canonical NF-κB pathway (ncNF-κB) using a mimetic of the second mitochondrial-derived activator of caspases (SMACm).

Methods: We evaluated the SMACm AZD5582 in 12 SIV-infected ART-suppressed rhesus macaques (RM) compared to 9 controls. After over a year of ART, RM received 3-10 weekly doses of AZD5582 intravenously at 100 µg/kg. Plasma viral loads (PVL) were measured longitudinally and levels of cell-associated SIV-RNA and -DNA were quantified in resting CD4+ T-cells isolated from peripheral blood, lymph nodes (LN), spleen and bone marrow (BM).

We performed flow cytometric analysis of T cell activation and assessed the gene expression profile and SIV-specific T-cell responses following AZD5582 treatment.

Results: Treatment with AZD5582 resulted in efficient activation of ncNF-κB in absence of generalized T-cell activation in blood and LN. A persistent increase in PVL on ART was observed in 5/12 (42%) AZD5582-treated RM while PVL remained undetectable in 9 control animals. The episodes of viremia induced by AZD5582 started as soon as 48h after the first dose. Viremia >60 copies/ml was measured in 15/28 samples (53%) in a period of 10 weeks with levels reaching 1390 SIV-RNA copies/ml. The levels of cell-associated SIV-RNA in resting CD4+ T-cells isolated from LN were significantly higher in 10-dose AZD5582-treated animals vs. controls (p= 0.0157) and tended to also be higher in the spleen, but not blood or BM. The levels of SIV-DNA quantified in the same compartments were not significantly different between AZD5582-treated and control groups. Principal component analyses revealed a distinct impact of AZD5582 on the transcriptome of CD4+ T cells isolated from blood and LN pre- and post-treatment. SIV-specific T cell responses measured in blood and LN by ELISPOT were not negatively impacted by treatment with AZD5582.

Conclusion: Activating the ncNF-κB pathway in vivo with the SMACm AZD5582 resulted in high level and persistent induction of SIV-RNA expression in ART-suppressed RM in absence of generalized T-cell activation, indicative of latency reversal. Further studies will combine this promising LRA with immune clearance strategies to reduce viral reservoirs.

23 NONSUPPRESSIBLE VIREMIA ON ART FROM LARGE CELL CLONES CARRYING INTACT PROVIRUSES

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Background: Clinically detectable viremia on ART is generally attributed to virus replication from incomplete adherence and/or drug resistance. One case of infectious viremia from a large cell clone with an intergenic intact provirus has been reported in an individual with metastatic cancer (Simonetti, PNAS 2016). We studied individuals referred for clinically detectable viremia despite receiving potent ART, adherence counseling, and in some cases, regimen switches or intensification.

Methods: Peripheral blood mononuclear cells (PBMCs) and plasma were collected at two or more time points from donors with plasma HIV RNA >20 copies/ml occurring for >6 months on combination ART. Single-genome sequencing was performed on plasma HIV RNA, cell-associated HIV DNA (CAD), and p24+ culture supernatants from quantitative viral outgrowth assays (qVOA). The clonal cellular origin of viremia was assessed by phylogenetics and integration site analysis (ISA), and confirmed by sequencing the integrated provirus and the flanking host sequences.

Results: Across the 10 individuals referred, median plasma HIV-1 RNA was 97.5 cps/mL (range 40 to 356 cps/mL) after a median of 10 years on ART. One donor (A-04) had phylogenetic evidence of virus evolution and accumulation of resistance mutations and was not analyzed further. Each of the other 9 donors had multiple identical single-genome HIV RNA sequences in plasma that did not change over time and lacked resistance to the current ART regimen. In 6 of 9 donors, HIV sequences from plasma matched proviral sequences in PBMC. Plasma HIV RNA and proviral sequences were identical to HIV RNA in p24+ qVOA wells for 4 donors (C02, C03, R09, T13). The integration sites for the intact proviruses producing viremia were mapped to the human genome for 3 donors (4th pending). Integrations were in introns of the MATR3, ZNF268, and ABCA11P genes for C02, C03, and R09, respectively. The provirus in MATR3 and ZNF268 were in the opposite orientation to the gene, whereas the ABCA11P integrant was in the same orientation. The intact provirus comprised 4.2-15.4% of all proviruses in PBMC with amplifiable pro/pol sequences.

Conclusion: Large cell clones carrying intact proviruses can produce clinically relevant levels of viremia and should be considered in managing patients. The mechanisms involved in clonal expansion and persistence of cells with intact proviruses that produce viremia need to be understood to effectively target the HIV reservoir.

Donor	Identical Plasma HIV RNA Sequences	Matches to HIV DNA in PBMC	% of Total DNA Sequences That Match	qVOA-Derived Sequence Matches	IUPM	Cell-Associated HIV DNA (copies/ 10^6 PBMC)	Cell-Associated HIV RNA (copies/ 10^6 PBMC)	Integration Site
K01	Yes	Yes	6.9%	No	0.59	1383	74	-
C02	**Yes**	**Yes**	**9.5%**	**Yes**	**0.12**	**373**	**29**	***MATR3***
C03	**Yes**	**Yes**	**4.2%**	**Yes**	**1.36**	**2505**	**1162**	***ZNF268***
A04	No (Replication)	No		No	0.72	1047	215	-
T05	Yes	No		No	0.43	650	109	-
A06	Yes	No		No	0.24	1825	630	-
F07	Yes	Yes	4.7%	No	3.77	1603	1112	-
P08	Yes	Yes	12.5%	No	0.4	1056	382	-
R09	**Yes**	**Yes**	**14.0%**	**Yes**	**18.1**	**1533**	**139**	***ABCA11P***
T13	**Yes**	**Yes**	**15.4%**	**Yes**	**36.1**	**2049**	**126**	***Pending***
Median	-	-	9.5%	-	0.66	1458	177	-

Bold indicates intact proviruses that are the source of infectious viremia in vivo and that can be activated ex vivo to produce infectious viruses (qVOA). IUPM = infectious virus per million PBMC

24 EX VIVO AND IN VIVO EDITING OF THE SIV GENOME IN NONHUMAN PRIMATES BY CRISPR-CAS9

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Background: Antiretroviral therapy (ART) has increased survival, but is a non-curative approach as replication competent proviral DNA, with high risk for reactivation upon ART cessation, remains. As such, HIV is now a chronic disease with a broad range of co-morbidities and drug toxicity. Curative strategies to eradicate the infected cells or viral genome without further treatment are vital. Here, we develop and test the ability of the CRISPR-Cas9 gene editing method for elimination of the SIV viral genome in rhesus macaques.

Methods: We employed AAV-9 as a vector to deliver CRISPR-Cas9 designed to target sequences spanning the LTR and Gag genes and permanently inactivating proviral DNA by excising intervening DNA fragments. Adult Chinese rhesus macaques (n=8) were i.v. infected with SIVmac239. At 8 weeks post infection, animals were treated daily with a drug regimen of tenofovir, emtricitabine and dolutegravir (5.1/50/2.5mg/kg daily by s.q.). Ex vivo gene editing was performed in PBMCs by AAV9-CRISPR-Cas9 transduction, PCR amplification and Sanger sequencing of the amplicons to assess the potency and precision of viral DNA elimination. In a proof of concept in vivo study, 4 animals, 3 were given an i.v. infusion of AAV-9-CRISPR-Cas9 (10^13GC/kg), and after three weeks, animals were necropsied, blood and tissues were harvested virological and gene excision evaluations.

Results: In all SIV-infected animals, ex vivo excision of viral DNA was confirmed by the detection of distinct DNA fragments of 464bp and 358bp resulting from the removal of intervening DNA sequences between 5'LTR to Gag and 3'LTR to Gag, respectively. Results from Sanger sequencing confirmed the breakpoint of the viral DNA. Delivery was confirmed by the presence of Cas9 and expression of both gRNAs. In vivo, both 5'LTR to Gag and 3'LTR to Gag excision were confirmed in blood of animals that received AAV-9-CRISPR-Cas9 infusion. In contrast to the control animal, which displayed rapid viral outgrowth, no outgrowth was detected in PBMC/CEM co-cultures after 30 days from animals with AAV-9-CRISPR-Cas9.

Conclusion: We demonstrated, for the first time, high specificity and efficacy of the CRISPR technology for targeting SIV proviral LTR and Gag regions, which led to both ex vivo and in vivo editing of SIV DNA. These observations support the potential use of CRISPR/Cas9 technology as a curative strategy that warrants further investigation.

25 DELAYED VIRAL REBOUND DURING ATI AFTER INFUSION OF CCR5 ZFN-TREATED CD4 T CELLS

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Background: Autologous CD4 T cells modified using CCR5 specific Zinc Finger Nucleases (ZFN) have a survival advantage in the presence of HIV, but the levels of modification are insufficient to control viremia (NCT00842634). The main

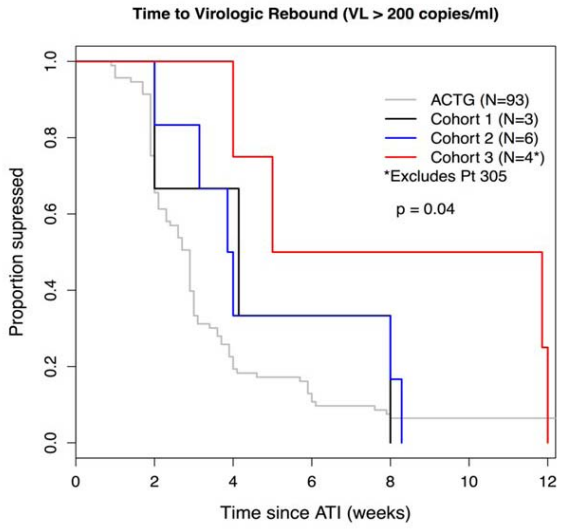
goals of this study were to evaluate: 1) if delivery of ZFN using RNA-based transfection provides similar level of CCR5 disruption as the Ad5/35 vector 2) the safety and tolerability of a single dose of this product in HIV+ subjects 3) if a single dose of cyclophosphamide (CTX) increases engraftment 4) the persistence of the disrupted cells and their impact on viral rebound during an ATI and 5) if Δ32 CCR5 heterozygotes preferentially benefit from infusion of CCR5 ZFN treated T cells.

Methods: We conducted a 3-arm open-label pilot study of the safety and antiviral activity of a single infusion of autologous CD4 T cells modified at the CCR5 gene by RNA encoding ZFN SB-728 with or without the prior administration of two different doses of CTX in well-controlled HIV+ individuals in which some were CCR5 Δ32 heterozygotes. We compared the AUC of the modified cells during the 16-week ATI between groups and time to viral rebound with ACTG historical controls.

Results: We enrolled 14 participants; 93% male, 57% AA, 7% Hispanic, median age 44. Median baseline CD4 count was 831 c/mm3 (IQR 630-1030). SB-728mR-T was safe and well tolerated. No related grade 3 or higher adverse events were observed. CCR5 disruption in the product (MiSeq) was 24% vs 23% with Ad5 vector. The median CCR5-modified T cells was 7.4% at 1 week post infusion. The engraftment of the modified cells varied between groups during the 16-week ATI (KW p=0.04) with trend to greater early engraftment in the CTX groups (p=0.08) that was significant for the Δ32 group compared to the control (p=0.04). The rebound of HIV viremia (HIV RNA > 200 copies/ml) (Fig 1) was delayed when compared to ACTG historical controls (p=0.03). A subset of Δ32 CCR5 heterozygotes had low viral load in the absence of ART for up to 40 weeks.

Conclusion: Introduction of CCR5 ZFNs via RNA transfection led to similar levels of disruption as Ad5/35 vectors. CTX led to an increase in engraftment and the administration of the product led to a modest, significant delay in viral rebound during the ATI and maintenance of low level viremia for up to 40 w in some, suggesting that a more efficient CCR5 modification could potentially benefit more individuals from this cure strategy.

Figure 1. Time to virologic rebound compared to historical ACTG controls. The Generalized Wilcoxon P-value was p=0.04. A participant that had detectable drug levels during the ATI is excluded in cohort 3.



26 MULTIDOSE IV ROMIDEPSIN: NO INCREASED HIV-1 EXPRESSION IN PERSONS ON ART, ACTG A5315

Deborah McMahon[1], Lu Zheng[2], Joshua C. Cyktor[1], Evgenia Aga[2], Bernard J. Macatangay[1], Catherine Godfrey[3], Michael Para[4], Ronald T. Mitsuyasu[5], Joseph Hesselgesser[6], Curtis Dobrowolski[7], Jonathan Karn[7], Edward P. Acosta[8], Rajesh T. Gandhi[9], John W. Mellors[1], for the A5315 Team

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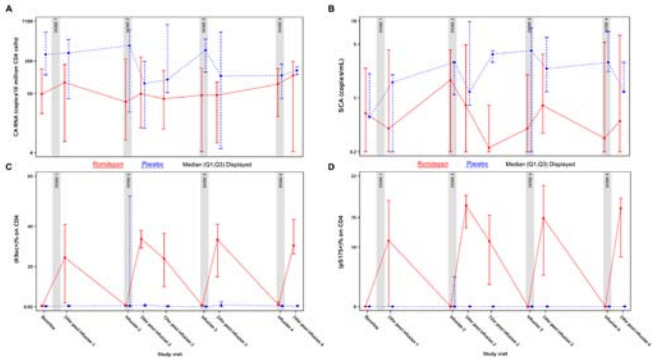
Background: Romidepsin (RMD) is a histone deacetylase inhibitor that has been reported to increase HIV-1 RNA expression in plasma and cells after single or multiple infusions of 5 mg/m2. We sought to determine if administering multiple doses of RMD would be safe and induce HIV-1 expression.

Methods: HIV-1-infected participants were enrolled in a double-blind, randomized, placebo-controlled (3:1 RMD/placebo) cohort to receive RMD 5 mg/m2 x 4 doses (at days 0, 14, 28, 42). Enrollees were receiving RAL- or DTG-containing ART with plasma HIV-1 RNA <50 cps/mL. Viremia was measured by integrase single copy assay (iSCA) before and 24hr after each RMD/placebo infusion and 72hr after the 2nd infusion. Cell-associated HIV-1 DNA (CAD) and cellular unspliced RNA (CAR) were measured by qPCR in PBMC at the same time points, as well as changes in CD4%, histone-3/4 acetylation and methylation (H3-Ac/Me), P-TEFb, and NFκb by flow. Other measures included changes in T cell activation and apoptosis from baseline to 24 hrs post 1st and 4th infusion. RMD levels were measured at hr 4 post-infusions 3 and 4. Comparisons between arms used Wilcoxon tests.

Results: 16 participants enrolled (13 RMD; 3 placebo); 11 male; median CD4 699 cells/mm3. All but two completed 4 infusions. One Grade 3 event (transient neutropenia) was deemed possibly treatment-related. Median RMD levels were 69 and 134 ng/mL, at hr 4 post-infusions 3 and 4, respectively. No significant increases in iSCA, CAR, or CAD were observed from baseline to post-baseline time points or from pre- to post-infusion for each infusion compared to placebo (Figure; all p>0.05). Evidence of host pharmacodynamic effects was demonstrated as significant decreases in CD4% at 24hr after infusions 2, 3, and 4 (median -3.5% to -4.5% vs. 1.5% to 1% in placebos, all p≤0.022). Significant increases were observed in H3-Ac/Me (pNFκB+)%, (pS175+)% on CD4+ T cells 24 and 72 hrs after 2nd infusion of RMD compared to placebo (Figure; all p≤0.02). No differences were detected in T cell activation/apoptosis changes between arms.

Conclusion: Multiple RMD doses were safe but did not induce HIV-1 expression in individuals on suppressive ART despite pharmacodynamic effects on host cells including reductions in % CD4+T-cells, increases in histone acetylation, and PTEFb activation. More effective strategies will be needed to reverse HIV-1 latency.



27 PEMBROLIZUMAB INDUCES HIV LATENCY REVERSAL IN HIV+ INDIVIDUALS ON ART WITH CANCER

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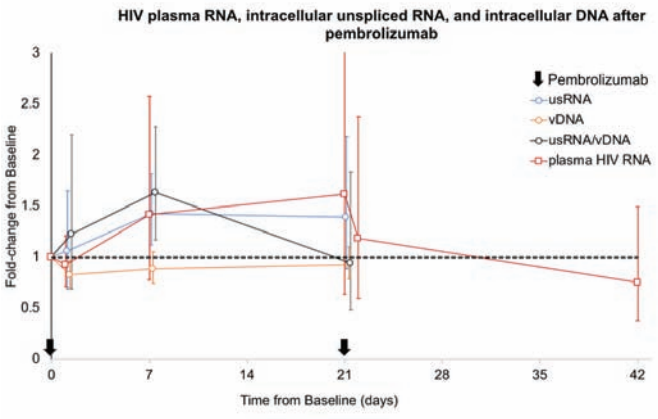
Background: Pembrolizumab is a monoclonal antibody against PD-1 approved for several cancers. In HIV-infected individuals on suppressive antiretroviral therapy (ART), HIV is enriched in CD4 T-cells that express PD-1. Within a Cancer Immunotherapy Trials Network (CITN) study, we prospectively evaluated markers of HIV persistence to test the hypothesis that pembrolizumab administration might increase HIV transcription and viral production consistent with latency reversal.

Methods: CITN-12 is a prospective multicenter phase I study of pembrolizumab 200mg IV every 3 weeks in participants with HIV on ART and advanced cancer. Participants were enrolled in cohorts with CD4 counts of: 100-199 (C1), 200-350 (C2) and >350 cells/uL (C3). Specimens were collected at baseline, 2 hours, 1 day, 7 days (cycle 1 only) and before cycles 2 and 3. Plasma HIV RNA was measured using a single copy (sc) qRT-PCR for HIV gag. Intracellular unspliced (us) HIV RNA (RNA) and viral DNA (vDNA) were measured in CD4 T-cells. Pairwise correlation between assays was assessed by Pearson's correlation coefficient. Kinetics of HIV plasma RNA, intracellular usRNA, usDNA, and usRNA/vDNA were evaluated by negative binomial regression. P<0.01 was considered statistically significant, p<0.05 a significant trend.

Results: 29 participants (C1 N= 6, C2 N=12, C3 N=11) with a range of tumors were evaluated; median age 56 years (IQR 50-61); 28 men, 1 woman. Baseline sc HIV = 1.1 copies/mL (IQR 0.3-2.4). Median baseline CD4 272 cells/uL (IQR 210-568). After pembrolizumab, mean usRNA and usRNA/DNA ratio were significantly elevated at Day 7 compared to baseline (usRNA: 1.43 fold, 95% CI 1.12 – 1.82, P=0.004; usRNA/DNA 1.63 fold, 95%CI 1.17-2.27, P=0.004) but not at day 21 (P=0.15, P=0.87 respectively). vDNA was decreased at 24 hours (0.82, 95%CI 0.70-0.97, P=0.02) but not on Day 7 (P=0.2) (Figure). No significant changes in plasma scHIV RNA were observed over 2 cycles. scHIV RNA , usRNA, and vDNA were not correlated (p>0.05).

Conclusion: Pembrolizumab leads to a transient increase in HIV transcription in CD4+ T-cells in vivo in individuals on ART consistent with latency reversal. It did not lead to increased plasma HIV RNA after administration of 2 doses. Evaluation of the long-term effects of pembrolizumab on HIV persistence and HIV specific immunity are ongoing. Further evaluation of monoclonal antibodies against PD-1 as a strategy for HIV cure is warranted.



28LB POTENT ANTIVIRAL ACTIVITY OF TRISPECIFIC BROADLY NEUTRALIZING HIV ANTIBODIES

Amarendra Pegu[1], Ling Xu[2], Megan Demouth[1], Cassandra Almasri[1], Eun S. Yang[1], Jason M. Hataye[1], Mangaiarkarasi Asokan[1], Wanwisa Promsote[1], Ronnie R. Wei[2], Dana M. Lord[2], Ercole Rao[2], Jochen Beninga[2], Zhi-yong Yang[2], John R. Mascola[1], Gary Nabel[2]

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Background: Broadly neutralizing antibodies (bnAbs) against HIV-1 have been suggested as a complementary immunotherapy to current combination small molecule anti-retroviral therapies (cART) for treatment of HIV-1 infection. Due to their monospecific nature, use of single bnAbs leads to rapid selection for escape variants in most HIV-1 infected patients and therefore use of a combination of 2 or more bnAbs is desirable to maintain durable suppression of HIV-1 replication.

Methods: We engineered trispecific antibodies (Abs) that allow a single molecule to interact with three independent HIV-1 envelope determinants: 1) the CD4 binding site, 2) the membrane proximal external region (MPER) and 3) the V1V2 glycan site. Prior studies demonstrated improved neutralization compared to parental bnAbs. These trispecific Abs have an intact IgG1 backbone and were assessed for Fc effector function and ability to suppress virus replication from activated HIV-1 infected donor T cells. One of the trispecific Abs was administered to viremic simian-human immunodeficiency virus (SHIV)-infected rhesus macaques to assess inhibition of viral replication.

Results: Each of the three combining sites of the trispecific Abs were actively bound with high affinity binding to the HIV envelope glycoprotein. In addition, trispecific Abs retained binding to Fcγ receptors via their Fc region and mediated antibody dependent cellular cytotoxicity (ADCC). In cultures of activated CD4+ T cells from HIV-1 infected patients, trispecific Abs durably suppressed viral replication compared to individual parental bnAbs. In viremic SHIV-infected macaques, treatment with trispecific Abs reduced plasma viremia up to 1000-fold that was maintained until the plasma trispecific Ab levels dropped below a value that was greater than 5-fold its IC80 titer against the SHIV.

Conclusion: Trispecific HIV antibodies demonstrate potent neutralization and ADCC in vitro, and mediate antiviral activity in vivo. Thus, trispecific Abs provide an attractive single immunotherapeutic protein for treatment of HIV-1 infection.

29LB SUSTAINED HIV-1 REMISSION FOLLOWING HOMOZYGOUS CCR5 DELTA32 ALLOGENIC HSCT

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Background: The "Berlin Patient" underwent 2 consecutive HSCTs with total body irradiation. It is unclear which aspects of treatment contributed to this only known case of HIV cure. We report an HIV-infected male diagnosed with Hodgkin's Lymphoma (HL) who underwent allogenic HSCT using a homozygous CCR5d32 donor. Nadir CD4 was 290 cells/mm and baseline VL 180,000 copies/ml. ART (TDF/FTC/EFV) was started in 2012. During episodes of ART interruption viral rebound and selection of NRTI resistance was seen. HL was refractory to 1st line chemotherapy and multiple salvage regimens. An unrelated CCR5d32 homozygous donor was identified with one allelic mismatch at HLA-B. Conditioning was initiated with Lomustine, cyclophosphamide, Ara-C and etoposide followed by 3.6 million CD34+ cells/kg. In vivo T-cell depletion employed anti–CD52 and GvHD prophylaxis was cyclosporine and methotrexate. ART was continued throughout (Rilpivirine, 3TC, dolutegravir). The patient developed mild gut GvHD. Full donor chimerism was maintained in blood. Six months post-HSCT complete remission was observed.

Methods: Co-receptor tropism was predicted with Geno2Pheno based on single genome sequencing (SGS). Post-HSCT PBMC were analysed by ddPCR and qPCR. Infectious virus was repeatedly analysed by qVOA. Isolated CD4 T cells were experimentally infected with X4 and R5 HIV.

Results: SGS from pre-transplant PBMC identified multiple envelope clones all with predicted R5 tropism. ART was stopped 17 months post-HSCT and plasma HIV VL remained undetectable (<1.4 copies/ml) at 33 months. ART drugs were not detectable in plasma by LC-MS. Total HIV DNA in CD4+ T-cells at 33 months showed 2 positive droplets in 1 out of 8 replicates (ddPCR HIV LTR, 10^6 cells tested) and no signal in qPCR (<0.69 HIV-gag and <0.65 HIV-LTR copies/million cells). At 16 months post transplant HIV-specific Western blot was positive while p24/p31 bands were absent. VITROS detuned and avidity analysis revealed low quantity and quality of HIV antibody titers. At three time points post-HSCT qVOA showed no reactivatable virus using a total of 24 million resting CD4+ T cells. Post-transplant CD4+ T cells did not express CCR5 and were susceptible in vitro to X4- but not R5-tropic virus.

Conclusion: Absence of viral rebound was observed for 16 months following ART interruption at 17 months after single allogeneic CCR5-d32 HSCT using a no

irradiation approach with only mild GvHD. To our knowledge this is the longest adult HIV remission observed since the Berlin patient.

30 BREAKING BONES IS BAD: INCIDENT FRACTURE AND MORTALITY IN THE HIV OUTPATIENT STUDY

Linda Battalora[1], Carl Armon[2], Frank J. Palella[3], Jun Li[4], Edgar T. Overton[5], John Hammer[6], Jack Fuhrer[7], Richard Novak[8], John Spear[1], Kate Buchacz[4]
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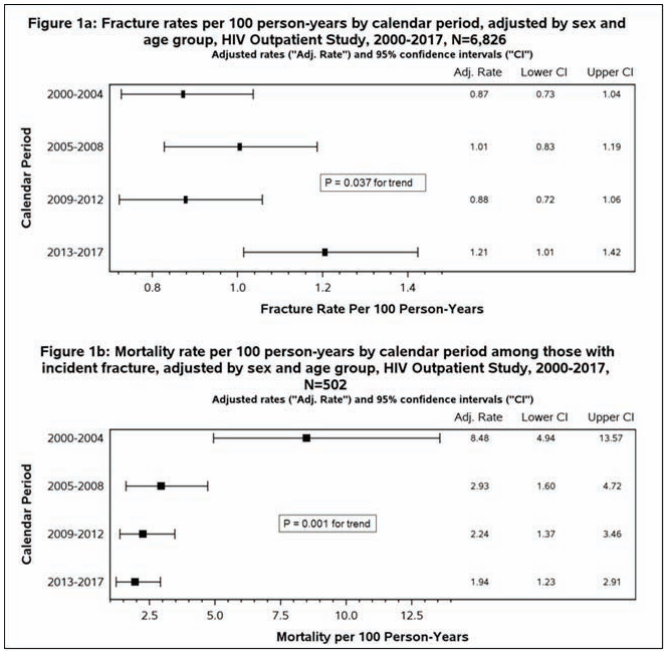
Background: Persons living with HIV (PLWH) have higher rates of low bone mineral density (BMD) and fracture than those without HIV infection, but the contribution of bone fractures to mortality among aging PLWH in care in the United States (U.S.) has not been explored. We evaluated the associations of bone fracture with mortality controlling for sociodemographic, behavioral, and clinical factors.

Methods: We analyzed data from HIV Outpatient Study (HOPS) participants seen at nine U.S. HIV clinics from January 1, 2000 to September 30, 2017, with ≥2 HOPS encounters. Incident fracture rates and mortality after fracture were compared, adjusted by age, sex, and calendar period: 2000-2004, 2005-2008, 2009-2012, and 2013-2017. We used Cox proportional hazards analyses to determine factors associated with all-cause mortality for all participants and for the subset with incident fracture.

Results: Among 6,826 HOPS participants followed for a median of 6.2 years, 502 (7%) had incident fracture recorded and 729 (10%) had died. Of 502 fractures, 97 were major osteoporotic (hip, wrist, spine, shoulder) and 405 were not (47 site unknown). Median age at fracture was 48 years (interquartile range 41-55 years). Of patients, 16.5% with major osteoporotic fractures died (crude mortality 1.5 per 100 person-years [py]), while 14.6% with fractures at other sites died (crude mortality 1.3 per 100 py). Age- and sex-adjusted fracture rates per 100 py increased from 0.9 during 2000-2004 to 1.2 during 2013-2017 (p=0.037 for trend), and all-cause mortality rates per 100 py among those with incident fracture decreased from 8.5 to 1.9 (p=0.001 for trend), (Figure 1a and 1b, respectively). In multivariable analysis, incident fracture was significantly associated with all-cause mortality (Hazard Ratio 1.5, 95% confidence interval 1.2-1.9) as were multiple other factors, notably nadir CD4+ cell count < 200 cells/mm3, non-AIDS cancer, hepatitis C infection, and chronic liver, renal, and cardiovascular disease comorbidity. Among the 502 patients followed after incident fracture, chronic renal disease and hepatitis C infection remained independently associated with all-cause mortality.

Conclusion: Incident fracture increased the risk of all-cause mortality by 50 percent among U.S. PLWH in care, underscoring the need for BMD screening and fracture prevention among at-risk patients. Although fracture rates among PLWH increased during follow-up, death rates after fracture decreased, coincident with advances in HIV care.



31 COPD AND THE RISK FOR MYOCARDIAL INFARCTION BY TYPE IN PEOPLE LIVING WITH HIV

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Background: People living with HIV (PLWH) are at increased risk for chronic obstructive pulmonary disease (COPD) compared to uninfected persons, in whom COPD is a known risk factor for cardiovascular disease such as myocardial infarction (MI). However, the relationship between COPD and MI in PLWH is less well understood. MIs have been classified into types including type 1 (T1MI, atherothrombotic coronary plaque rupture) and type 2 (T2MI, supply-demand mismatch as with sepsis), with a much higher proportion of T2MI in PLWH than the general population. We hypothesized that COPD would be associated with increased MI risk among PLWH, particularly for T2MI.

Methods: We utilized data from six sites in the CFAR Network of Integrated Clinical Systems (CNICS) cohort. MIs were centrally adjudicated by two reviewers (3 if discrepancies) and also categorized by type and cause of T2MI. COPD was defined based on an algorithm we previously validated against spirometry requiring COPD diagnosis codes and ≥90-day continuous supply of long-acting COPD controller medications. Time to MI was assessed using Cox proportional hazards models. Models were adjusted for baseline age, sex, race/ethnicity, HIV viral load, nadir CD4 count, diabetes, hypertension, statin use, and CNICS site. We subsequently examined whether associations were attenuated by adjustment for smoking status (ever vs. never), as this was potentially an important confounder.

Results: In total, 25,509 PLWH were included, of whom 423 met our definition of moderate-to-severe COPD. There were 698 PLWH who had MIs (339 T1MI [54%], 294 T2MI [46%]). COPD was associated with a significantly increased risk of MI [adjusted hazard ratio (aHR) 2.09 (95%CI 1.50-2.91)] even after adding smoking [aHR 1.88 (95%CI 1.34-2.63)]. COPD was significantly associated with T1MI and T2MI in unadjusted analyses, but only T2MI in adjusted analyses, and this was only minimally attenuated by smoking (Table); this association was particularly notable for T2MI due to sepsis/bacteremia.

Conclusion: COPD is independently associated with an increased risk for MI in PLWH, particularly T2MI in the setting of sepsis/bacteremia. COPD severity,

inadequate disease control and/or exacerbations can contribute to supply-demand mismatch, and COPD increases risk for pneumonia, a common cause of sepsis. Further investigation is required to understand mechanisms for this association and to optimize preventative and therapeutic strategies.

Table: Risk of myocardial infarction associated with COPD (N=25,509)

	Hazard ratio (95%CI)		
	Unadjusted	Adjusted[a]	Adjusted with smoking[b]
All MI	3.45 (2.49-4.78)	2.09 (1.50-2.91)	1.88 (1.34-2.63)
Type 1 MI	2.82 (1.71-4.66)	1.58 (0.95-2.63)	1.40 (0.84-2.34)
Type 2 MI	3.45 (2.49-4.78)	2.74 (1.75-4.27)	2.52 (1.61-3.95)
Type 2 MI due to sepsis/bacteremia	4.18 (1.94-9.00)	3.10 (1.41-6.82)	3.23 (1.45-7.18)
Type 2 MI due to other causes	3.02 (1.55-5.90)	2.11 (1.07-4.18)	1.90 (0.95-3.77)

[a]adjusted for age, sex, race/ethnicity, HIV viral load, nadir CD4 count, diabetes, hypertension, statin use and CNICS site.
[b]also includes ever smoking status

32 HIV POST SCD STUDY: 80% HIGHER RATE OF AUTOPSY-DEFINED SUDDEN ARRHYTHMIC DEATH IN HIV

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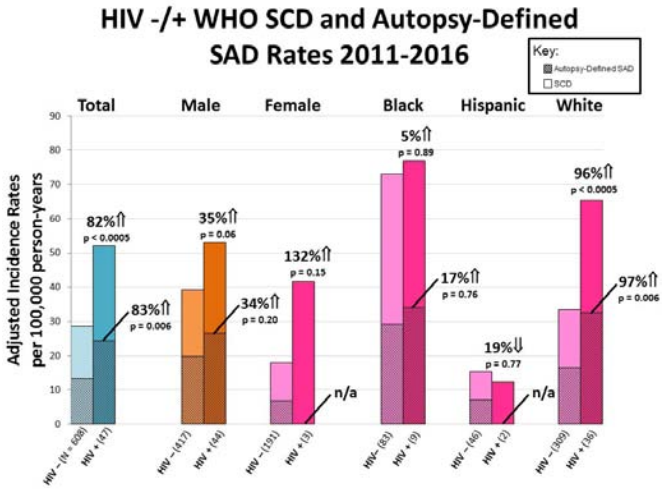
Background: Persons living with HIV have higher rates of CVD including acute MI, heart failure, and our group first reported high rates of out-of-hospital presumed sudden cardiac death (SCD) using World Health Organization (WHO) criteria. However, the precise incidence of actual sudden arrhythmic deaths (SAD) in HIV remains unknown.
Methods: Between 2011 to 2016, we prospectively identified all incident deaths attributable to out-of-hospital cardiac arrest among individuals with and without HIV aged 18-90 in SF County for medical record review and comprehensive autopsy, toxicology, and histology via medical examiner surveillance of consecutive out-of-hospital deaths. Autopsy-defined SAD had no extracardiac cause of death or acute heart failure. Final cause was adjudicated by a committee of pathologists, cardiologists, HIV clinicians, and electrophysiologists.
Results: 126 out-of-hospital HIV-infected deaths were identified, and 47 of these met WHO SCD criteria. The mean age was 65.6 years, 94% male, and 57% white. Compared to uninfected WHO-defined (presumed) SCDs (N=505), SCDs with HIV were more likely to have a history of MI, psychiatric disorder, cigarette smoking, and substance abuse. Similar to the general population, about half of WHO-defined SCDs in HIV were autopsy-defined SADs; the remainder were non-cardiac and included 16 due to occult overdose. Presumed SCDs with HIV were more likely to be due to occult overdose (13% vs 34%, p<0.0001) and renal failure (1% vs. 6%, p=0.003) as compared to uninfected presumed SCDs. Adjusted incidence ratios for WHO (presumed) SCD and autopsy-defined SAD were both significantly higher in HIV (IRR 1.82, 95%CI 1.4-2.4, p<0.0005 and IRR 1.83, 95%CI 1.2-2.8, P=0.006, see Figure). After adjustment for age, gender, heart disease and CAD, SCDs with HIV had 60% higher interstitial fibrosis by myocardial trichrome staining compared to uninfected SCDs.
Conclusion: In this countywide postmortem study, 1/3 of apparent SCDs in HIV over a 5-year period were due to occult overdose. However, adjusted rates of both presumed SCDs and autopsy-defined SAD were 82% and 83% higher respectively in HIV compared to the uninfected population. Higher levels of cardiac fibrosis in HIV, a known substrate for SAD in the general population, may underlie the mechanism by which HIV increases risk for SAD. Development of criteria and evaluation for implantable defibrillators should be carefully considered in HIV as a means to prevent SAD in this high-risk population.



33 SUDDEN CARDIAC DEATH AMONG HIV-INFECTED AND -UNINFECTED VETERANS

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Background: We have reported HIV infection as a risk factor for sudden cardiac death (SCD) in San Francisco County, but to date this association has not been examined in larger populations using chart-reviewed events. Here we examine the association between HIV infection and SCD in a large, national, cohort of HIV infected (HIV+) and uninfected veterans
Methods: We analyzed data on 144,362 Veterans (30% HIV+) from the Veterans Aging Cohort Study, a prospective study of HIV+ veterans and age, sex, race/ethnicity and clinical site matched uninfected veterans. We followed veterans from their first clinical encounter on or after 4/1/2003 until SCD, non-SCD death, or censoring on 12/31/2014. Sudden cardiac death was determined using death certificates and manual review of the VA electronic health record (EHR). To meet our SCD definition, participants had to have cardiac cause of death on their death certificate. SCD was excluded for deaths in a hospital, hospice, or nursing home, or due to accidents, overdose, suicide, or homicide. SCD was also ruled out if in the year prior to death, EHR review revealed metastatic cancer or active treatment for cancer, use of high flow oxygen or dialysis, an AIDS defining illness, CD4<50 cells/mm3 within 6 months before death, DNR/DNI, a new significant health condition one month before death, or a life altering event within one year if this event resulted in an end stage disease or severe disability. We calculated rates of SCD by HIV status and used Cox proportional hazards regression to model the association between HIV infection and SCD, adjusting for demographics, prevalent cardiovascular disease, SCD risk factors, and possible confounders. In secondary analyses we compared SCD incidence in HIV+ subgroups defined by time-updated viral load and CD4 cell count to HIV uninfected veterans.
Results: Participants had a mean age of (50±10.7 years), were mostly male (97.2%) and African American (47.3%) and were followed for a median of 9.0 years. After adjustment for demographics, prevalent cardiovascular disease, SCD risk factors, and other possible confounders, HIV+ veterans had a 14% higher risk of SCD (hazard ratio=1.14, 95% confidence interval 1.04-1.25) compared to uninfected veterans. The risk was highest among those with sustained high HIV viral loads or low CD4 cell counts (Table).
Conclusion: HIV infected people have an increased risk of sudden cardiac death compared to uninfected people when they have sustained unsuppressed HIV viremia or low CD4 cell counts.

Table: HIV infection and the risk of sudden cardiac death stratified by HIV status and HIV specific biomarkers

Group	N[a]	SCD Events[b]	Rate/1000PY [95% CI][b]	Minimally Adjusted SCD Risk [95% CI][c]	Adjusted SCD Risk [95% CI][d]	Time-updated Adjusted SCD risk [95% CI][e]
HIV exposure characterized by CD4 cell count						
HIV-	100,949	2259	2.3 [2.2, 2.5]	1.00	1.00	1.00
HIV+, CD4≥500	12,308	214	2.2 [1.9, 2.5]	0.96 [0.85, 1.10]	1.09 [0.95, 1.25]	1.02 [0.89, 1.18]
HIV+, 200≤CD4<500	14,592	256	2.2 [1.9, 2.5]	0.95 [0.84, 1.08]	1.12 [0.98, 1.27]	1.11 [0.97, 1.28]
HIV+, CD4<200	8320	145	2.6 [2.2, 3.1]	1.15 [0.97, 1.36]	1.32 [1.10, 1.57]	1.59 [1.30, 1.94]
HIV+, Missing CD4[f]	8193	163	2.5 [2.1, 2.9]	---	---	--
HIV exposure characterized by HIV viral load						
HIV-	100,949	2259	2.3 [2.2, 2.5]	1.00	1.00	1.00
HIV+, VL<500	16,147	304	2.2 [2.0, 2.5]	0.95 [0.85, 1.06]	1.10 [0.98, 1.24]	0.98 [0.87, 1.10]
HIV+, VL ≥500	19,031	312	2.4 [2.1, 2.7]	1.05 [0.94, 1.17]	1.19 [1.06, 1.34]	1.70 [1.45, 1.98]
HIV+, Missing VL[f]	8235	162	2.4 [2.1, 2.8]	---	---	--

a CI = confidence interval; HIV = human immunodeficiency virus; SCD = sudden cardiac death; PY = person years; VL=viral load
b Values correspond to the analysis using baseline values of CD4 and HIV viral load, not the time-updated analysis
c adjusted for age, sex, race/ethnicity, and prevalent CVD
d adjusted for age, sex, race/ethnicity, hypertension, diabetes, LDL and HDL cholesterol, triglycerides, HCV infection, smoking status, renal disease, body mass index, anemia, cocaine dependence or abuse, alcohol dependence or abuse, COPD, and prevalent CVD.
e adjusted for all factors in (*d*) but CD4 and Viral load are time updated
f missing category used only for calculation of incidence rates. For models, missing CD4 cell counts and HIV viral loads were imputed using multivariate imputation by chained equations (MICE).

34LB CABOTEGRAVIR IS NOT ASSOCIATED WITH WEIGHT GAIN IN HIV-NEGATIVE INDIVIDUALS: HPTN 077

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Background: In people living with HIV, ART treatment with regimens containing integrase inhibitors (INIs) has been associated with weight gain and increased waist circumference, raising concerns about possible future risk for metabolic and cardiovascular disease. These changes have been associated with female sex, non-white individuals, and those with higher baseline BMI. HPTN 077, a Phase 2a randomized placebo-controlled study of two dose/dose-interval regimens of cabotegravir, enrolled HIV-uninfected participants from 8 sites in the US (4), Brazil (1), and sub-Saharan Africa (3). 199 participants were enrolled and randomized 3:1 to active CAB or placebo and received oral CAB 30mg or placebo (PBO) QD x 4 weeks, a one-week washout, and then sequential injections of CAB LA or 0.9% saline PBO from Week (W) 5 through W41.

Methods: We measured weight at study entry (W0), during oral study product administration (W2, W4) and during injectable study product administration (W5, 17, 19, 29/33, and 41). Age, race/ethnicity, sex at birth, injectable dosing cohort, smoking status, and BMI were assessed at baseline. Longitudinal models fitted via generalized estimating equations (GEE) were used to assess marginal effects of study arm on weight over time. Wilcoxon rank sum tests were used to compare medians of numeric variables and chi-square tests were used to compare frequencies of categorical variables.

Results: The Table shows median weights at W0 and W41 overall, and changes from baseline (W0-W41) by covariates of interest. Median weight change over 41 weeks was +1.1 kg (IQR -0.9, 3.0) in the CAB arm and +1.0 kg (IQR -1.2, 3.2) in the PBO arm (p=.66). In longitudinal statistical analyses, no statistically significant differences were found in change in weight from W0 to 41 in CAB vs. PBO treated participants in aggregate, by sex, dosing cohort, age, race/ethnicity, smoking status, BMI, nor by baseline BMI category. No differences in weight change for CAB vs. PBO were seen for W0-4 and W5-41 separately.

Conclusion: In this moderately sized global cohort of 199 HIV-uninfected males and females, there was no difference in weight change for participants receiving CAB compared to PBO-treated participants. Although structurally similar to dolutegravir, CAB may have different effects on weight/weight gain, or the interaction between HIV-infection and INI treatment may be an important contributor to observed weight gain as part of ART.

Table: Demographics and Weight/Weight Change for HPTN 077 participants who had at least one injection

Parameter	Overall	CAB	PBO	p-value
Age, *median (IQR)*	31.5 (24.0, 39.0)	29 (24, 38)	34 (27, 40)	0.04
Sex at birth, *n (%)*				0.88
Female	117 (66%)	89 (66%)	28 (65%)	
Male	60 (34%)	45 (34%)	15 (35%)	
Race/Ethnicity, *n (%)*				0.40
Non-Hispanic white	47 (26%)	36 (27%)	11 (26%)	
Non-Hispanic Black	71 (40%)	55 (41%)	16 (37%)	
Latino/Latina	46 (26%)	36 (27%)	10 (23%)	
Asian	3 (2%)	2 (1%)	1 (2%)	
Mixed/Other	10 (6%)	5 (4%)	5 (12%)	
BMI, *median (IQR)*	26.6 (23.4, 32.7)	26.6 (23.1, 32.8)	26.5 (23.7, 32.5)	0.48
Cigarette Smoking, *n (%)*				0.73
Yes	18 (10%)	13 (9%)	5 (12%)	
No	158 (89%)	120 (90%)	38 (88%)	
Missing	1 (1%)	1 (1%)	0 (0%)	
Weight (kg), *median (IQR)*				
Baseline	74.7 (62.4, 91.2)	74.8 (61.3, 91.4)	74.0 (64.7, 90.5)	0.80
Change over entire observation period (W0-41)	1.1 (-0.9,3.0)	1.1 (-0.9, 3.0)	1.0 (-1.2, 3.2)	0.66
Change during oral product administration (W0-4)	0.2 (-0.4, 1.0)	0.4 (-0.4, 1.0)	0.1 (-0.6, 1.0)	0.60
Change during injectable product administration (W5-41)	0.9 (-1.4, 2.6)	0.9 (-1.2, 2.8)	0.7 (-1.5, 2.0)	0.65
Cohort 1 (all)	0.5 (-0.8, 1.7)	0.5 (-0.7, 1.7)	0.5 (-0.8, 1.7)	0.98
Cohort 2 (all)	0.5 (-0.5, 1.8)	0.6 (-0.4, 1.9)	0 (-1.1, 1.5)	0.51
Male (both cohorts)	1.7 (-0.7, 3.8)	1.4 (-1.1, 3.0)	3.2 (-0.6, 4.6)	0.21
Female (both cohorts)	1.0 (-1.0, 2.8)	1.1 (-0.9, 3.0)	0 (-2.1, 1.7)	0.12
Baseline BMI, *median (IQR)*				
BMI > 26.6 (median)	0.9 (-1.2, 3.5)	0.9 (-1.2, 3.7)	1.1 (-1.6, 2.5)	0.54
BMI ≤ 26.6 (median)	1.1 (-0.9, 2.7)	1.2 (-0.5, 2.5)	1.0 (-1.2, 3.8)	0.96
Baseline Smoking, *median (IQR)*				
Yes	2.5 (-0.1, 4.6)	1.9 (-0.1, 3.0)	3.8 (3.2, 4.6)	0.25
No	1.0 (-1.0, 2.9)	1.1 (-0.9, 3.0)	0.6 (-1.5, 2.5)	0.32
Race/Ethnicity, *median (IQR)*				
Non-Hispanic white	0.9 (-0.8, 3.2)	1.3 (-0.7, 3.2)	-0.1 (-1.4, 2.9)	0.59
Non-Hispanic black	1.2 (-1.3, 3.2)	1.2 (-1.1, 3.1)	1.1 (-2.5, 3.6)	0.80
Latino/Latina	0.7 (-1.1, 2.4)	0.7 (-1.6, 2.5)	0.7 (0, 1.5)	0.88

35 ASSESSING THE PROBIOTIC EFFECT IN TREATED HIV: RESULTS OF ACTG A5350

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Background: HIV alters gastrointestinal (GI) tract permeability, GI lymphoid tissue structure and function, contributing to systemic inflammation. In inflammatory bowel diseases, probiotics can resolve gastrointestinal symptoms and reduce local and systemic inflammation. In this trial, we evaluated whether the probiotic Visbiome Extra Strength (ES) reduced measures of systemic inflammation in persons with HIV (PWH).

Methods: A5350, a phase II, randomized, double-blind, two-arm, placebo-controlled study, evaluated changes in soluble inflammatory markers after 24 weeks of probiotic Visbiome ES, and the safety/ tolerability in PWH on antiretroviral therapy (ART). Primary endpoint was change in sCD14 levels; secondary measures included D-dimer, Kynurenine to Tryptophan (KT) ratio, CD4 count, & CD4/CD8 ratio. Mean changes were compared between arms with a 2-sample t-test. Per-protocol analysis included all randomized participants with baseline & week 25/26 sCD14 measurements, remained on study product through week 26 with >50% adherence, no use of prohibited medications, without confirmed virologic failure, and did not experience inflammatory conditions, receive vaccines, or have concurrent illness.

Results: Overall, 93 participants (46 placebo, 47 Visbiome ES) enrolled; 86% men, 55% white, 42% black, 20% Hispanic/Latino; median (Q1, Q3) age was 51 (45, 56) years, BMI was 27.1 (24.2, 30.7) kg/m2, CD4 count was 712 (542, 893) cells/mm3 and 99% had HIV-1 RNA <40 copies/mL; one participant had 48 copies/mL. Overall, 25 participants reported adverse events: (8 [19%] placebo; 17 [36%] Visbiome ES) (p=0.098). Excluding 19 participants who did not complete study treatment and one virologic failure, 73 participants (31 placebo; 42 Visbiome ES) remained in the per-protocol population. The mean change (95% CI) in sCD14 from baseline to week 25/26 was 92.3 (-48.5, 233)

ug/L in the placebo arm and 41.0 (-94.1, 176.2) ug/L in the Visbiome ES arm, but these changes were not statistically different (p=0.60). Similarly, there were no significant differences in changes in D-dimer, KT ratio, CD4 cell counts, CD4/CD8 ratio between the arms.

Conclusion: Visbiome ES was safe and well tolerated among this cohort. No significant effect of Visbiome ES on systemic inflammatory markers was identified. While high loss to follow up in the placebo arm limits the strength of our conclusions, these results do not support Visbiome ES as a viable strategy to reduce systemic inflammation in suppressed PWH with preserved CD4 counts.

36 FACTOR X INHIBITION REDUCES COAGULATION BUT NOT INFLAMMATION IN PERSONS WITH HIV

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Background: Activation of coagulation among persons with HIV is associated with a broad spectrum of end-organ disease risk, but the underlying pathogenesis is not well characterized. We hypothesized that hypercoagulation contributes to disease, in part, via upregulation of inflammatory pathways, in addition to direct effects from thrombogenesis.

Methods: Treatment effects of oral edoxaban (30mg), a direct factor Xa inhibitor, versus placebo were investigated in a randomized, double-blind, cross-over clinical trial, among participants with HIV receiving ART with plasma HIV RNA <200 copies/mL and D-dimer levels ≥100 ng/mL. Blood specimens were collected twice prior to receiving study drug and then monthly during each 4-month cross-over treatment period. Soluble biomarkers (Table) were measured using ELISA, electrochemiluminescence, and immunoturbidmetric methods. The treatment effect, defined as change on edoxaban versus change on placebo, was calculated with linear mixed models for biomarkers (ln-transformed) and clinical labs (untransformed).

Results: Forty-four participants were randomized among 83 screened; 40 completed the first period and 37 completed the second period. Mean age was 49 years and CD4+ count was 739 cells/mm3; 91% were male, 70% white, 36% current smokers, 34% with prior AIDS, and 70% had an integrase inhibitor-based ART regimen. Table 1 reports the treatment effect of edoxaban versus placebo on soluble biomarkers. Edoxaban treatment demonstrated a consistent reduction in coagulation activity; relative changes were -42% for D-dimer, -26% for TAT, and 7% for INR. There was no evidence of a significant treatment effect on the inflammatory biomarkers evaluated. Adherence was quantified as percent of days adherent (among the 92% that returned study drug) and did not differ between edoxaban (94%) and placebo (97%) periods. More non-laceration bruising or bleeding events occurred during edoxaban (28 among 17 persons) than during placebo or no drug periods (15 among 13 persons). All non-laceration bleeding events were either grade 1 (93%) or grade 2 (7%), and the most common were bruising (28%), epistaxis (23%), and bleeding gums (30%).

Conclusion: The oral direct factor Xa inhibitor edoxaban substantially reduced coagulation activity among persons with HIV receiving ART with viral suppression. In this study, no effect on soluble systemic inflammatory markers was observed and there was an increased risk for minor bruising and bleeding events.

TABLE 1:	Receiving Edoxaban ('E', n=40)		Receiving Placebo ('P', n=41)		
Biomarkers	Pre-Treatment, Mean (SD)	Change, Mean (SD)	Pre-Treatment, Mean (SD)	Change, Mean (SD)	*p*-value[a] (E vs. P)
IL-6 (pg/mL)[b]	0.69 (0.36)	0.10 (0.29)	0.83 (0.61)	-0.04 (0.55)	0.26
IL-1β (pg/mL)[b]	0.04 (0.02)	0.01 (0.03)	0.04 (0.02)	0.01 (0.03)	0.34
sTNFR-1 (pg/mL)[b]	1369 (248)	-15 (201)	1377 (299)	-8 (173)	0.57
sCD163 (ng/mL)[b]	686 (243)	-3 (108)	685 (240)	-5 (106)	0.81
TAT (μg/L)[b]	12.1 (20.0)	-7.9 (18.2)	9.0 (14.7)	-3.5 (15.3)	<0.001
D-dimer (μg/mL)[b]	0.21 (0.13)	-0.06 (0.12)	0.22 (0.16)	-0.03 (0.13)	0.002
INR	1.06 (0.09)	0.11 (0.11)	1.05 (0.08)	0.02 (0.06)	<0.001
Hemoglobin (g/dL)	14.70 (1.42)	-0.15 (0.65)	14.29 (1.56)	0.19 (0.70)	0.05
Platelets (10^3/μL)	238.1 (58.0)	-1.93(26.1)	238.9 (54.9)	4.9 (24.7)	0.18

[a]p-value is for comparison of change on Edoxaban versus change on Placebo considering all follow-up measures during the 4-month study drug period, controlled for assigned treatment sequence and pre-treatment biomarker level; [b]Comparison of change analyzed on natural log scale, but mean biomarker levels presented as untransformed values in table; TNFR-1 = tumor necrosis factor receptor-1; TAT = thrombin anti-thrombin complex; INR = international normalized ratio for prothrombin time

37LB SAFETY, TOLERABILITY AND IMMUNOLOGIC ACTIVITY OF RUXOLITINIB ADDED TO SUPPRESSIVE ART

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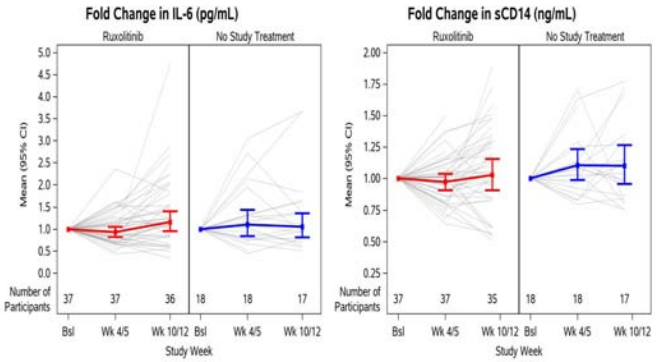
Background: Chronic inflammation is associated with end-organ disease and mortality for people living with HIV (PLWH). Ruxolitinib (RUX) is a Janus kinase (Jak) 1/2 inhibitor that reduced biomarkers of systemic inflammation in HIV-uninfected individuals, and HIV reservoir and persistence markers ex vivo. The goal of this trial was to determine the safety and efficacy of RUX in treated HIV disease.

Methods: ACTG 5336 was an open-label, multi-site, randomized controlled trial of RUX (10 mg BID) for 5 weeks plus continuing ART versus ART alone. Eligible participants were suppressed on ART for > 2 years, CD4+ T cells >350 cells/μL, and had no current diagnosis or history of significant medical comorbidities. Primary tolerability and safety outcomes were premature RUX discontinuation and occurrence of any pre-defined safety event. Mean changes in plasma levels of IL6 (primary efficacy outcome), sCD14, and circulating CD4 and CD8 counts were compared between arms with t-tests. Plasma HIV-1 RNA levels were measured by integrase single copy assay (iSCA) with a limit of detection of 0.4 cpm. GEE models for binary data compared changes between arms.

Results: Sixty participants enrolled (80% men, median age 44 yrs and CD4 count 737 cells/ μL; n=40 RUX and n=20 ART alone). Primary safety events occurred in 2.5% in RUX arm and 0% in control arm (Fisher's, p=0.67). Three participants prematurely discontinued RUX due to participant request, unrelated syncope, and a grade 3 increased AST. At week 4/5, there was a non-significant decrease in IL6 in the RUX arm compared to control arm (mean fold change (FC) 0.93 vs 1.10, p=0.18), but a significant decrease in sCD14 in the RUX vs control arm (mean FC 0.97 vs 1.10, p=0.03). Those on RUX had a similar likelihood of iSCA < 0.4 cpm compared to control (relative risk = 0.98, p=0.94). In the RUX arm, CD4 and CD8 cell counts increased significantly at week 2 (mean Δ 131 and 162 cells/μL) and compared to control arm (p=0.01); at week 5, CD8 counts returned to baseline while CD4 counts remained elevated in the RUX arm.

Conclusion: In a highly selected cohort of HIV-positive adults on suppressive ART, RUX was safe and well tolerated but did not significantly reduce IL6 levels. On RUX treatment there was a modest decrease in sCD14 with an increase in circulating T cells through mechanisms undefined. This proof-of-concept trial provides a rationale for future studies of Jak inhibitors in PLWH who have residual inflammation or immune dysfunction despite long-term suppressive ART.



38LB WITHDRAWN / INTENTIONALLY UNASSIGNED

39LB RANDOMIZED TRIAL OF RALTEGRAVIR-ART VS EFAVIRENZ-ART WHEN INITIATED DURING PREGNANCY

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Background: There are no randomized trial data comparing the efficacy and safety of antiretroviral therapy (ART) containing an integrase inhibitor with efavirenz (EFV) when initiated during pregnancy.
Methods: NICHD P1081 is a Phase IV multicenter, randomized, open-label trial comparing HIV virologic response (plasma HIV viral load <200 copies/ml near delivery), tolerability (remaining on study drug through delivery), and safety (maternal and infant adverse event (AE) ≥grade 3) of ART when initiated during pregnancy. ART-naïve pregnant women with HIV were randomized to raltegravir (RAL)- or EFV-based ART through delivery. Enrollment began in Sept 2013 for women 28 to <37 weeks (wks) gestation (gest), was expanded to 20 to <37 wks gest after 22% were enrolled, and was completed in Feb 2018. Women and their infants were followed through 24 wks post-delivery. The randomization and primary statistical comparisons were stratified by gest age at entry.
Results: 408 pregnant women (206 RAL arm, 202 EFV arm) were enrolled at 19 sites in South America (n=210), Africa (n=144), Thailand (n=47) and the US (n=7), 205 (50%) at 20 to <28 wks and 203 (50%) at 28 to <37 wks. In the primary efficacy subgroup (n=307 with no HIV genotypic resistance to study ART at entry), a larger proportion of women in the RAL arm vs. EFV arm had delivery viral load <200 copies/mL (94% vs. 84%; p=.001), mainly among those enrolled at ≥28 wks gest (interaction p=.04); results were similar after including women with HIV genotypic resistance to study ART at entry (n=362, Table, interaction p=.06). Viral load decline was greater in RAL arm at study wks 2, 4 and 6 (Wilcoxon p<.05). Both regimens were well tolerated (Table). A larger proportion of RAL arm women achieved a rapid, sustained viral load reduction while staying on study drug until delivery, mainly by achieving a rapid viral load decline by study wk 2 (Table). There were no significant differences in occurrence of AE ≥grade 3 among women or infants, stillbirth, or preterm birth (Table). One RAL infant and 4 EFV infants were HIV infected (Fisher exact p>.05).
Conclusion: Both regimens were well tolerated in women initiating ART during pregnancy. Viral load reduction with RAL-ART was faster leading to more women with delivery viral load <200 copies/mL. These data from the first large randomized trial comparing an integrase inhibitor with EFV-ART initiated during pregnancy support the use of RAL-ART during pregnancy, especially for women starting ART late in gestation.

	RAL arm	EFV arm	P-value*
Delivery viral load <200 copies/mL[a]	174/183 (95%)	151/179 (84%)	<.001
Enrolled 20 to <28 weeks	85/88 (97%)	87/90 (97%)	
Enrolled 28 to <37 weeks	89/95 (94%)	64/89 (72%)	
Remained on study drug through delivery[b]	199/200 (>99%)	188/194 (97%)	.05
Rapid, sustained virologic response AND remained on study drug through delivery[c] (combines the next 3 rows)	151/162 (93%)	98/156 (63%)	<.001
Viral load ≥2.0 log decline or <200 copies/mL by wk 2	153/162 (94%)	105/156 (67%)	
Viral load <1,000 copies/mL at all time points after wk 4	144/149 (97%)	140/147 (95%)	
Remained on study drug through delivery	161/162 (99%)	151/156 (97%)	
Maternal adverse event ≥grade 3 until wk 24 after delivery[d]	61/206 (30%)	59/197 (30%)	.91
Stillbirth	3/200 (2%)	1/194 (1%)	.62
Preterm birth (<37 wks gestation)	24/195 (12%)	20/190 (11%)	.63
Infant adverse event ≥grade 3 until wk 24 after delivery[d]	50/199 (25%)	48/194 (25%)	.94

*Cochran-Mantel-Haenszel test stratified by gestational age at entry (20-<28, 28-<31, 31-<34, or 34-<37 wks), except Fisher exact test for stillbirths and preterm births.
[a]For all women with screening/entry viral load (VL) > 200 copies/mL and VL result ≤21 days pre-delivery.
[b]For all women who received at least one dose of study drug and remained on-study through delivery.
[c]Secondary composite outcome for all women in the primary virologic response and tolerability analyses with a VL result at study week 2 (day 11-17) and at least one subsequent VL result after study week 4.
[d]For all women who received at least one dose of study drug; for live-born infants delivered on-study.

40LB RCT OF DOLUTEGRAVIR VS EFAVIRENZ-BASED THERAPY INITIATED IN LATE PREGNANCY: DOLPHIN-2

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Background: ART initiation late in pregnancy is associated with failure to achieve viral suppression by delivery and increased MTCT.
Methods: DolPHIN-2 (NCT03249181) is an open label trial, randomising (1:1) pregnant women from Uganda and South Africa initiating ART from 28w gestation to dolutegravir (DTG) vs efavirenz (EFV) plus 2NRTIs. Viral load (VL) was measured at baseline, 1w and 4w after initiation, then at 36w gestation and delivery, and 6w post-partum (PP). The primary endpoint was VL<50 cps/mL at delivery (measured up to 14d PP) for efficacy, and occurrence of drug toxicity in mothers and infants. Here we report on all primary trial endpoints through delivery.
Results: All 268 mothers randomised were included in safety, and 237 (122 DTG, 115 EFV) in efficacy analyses by ITT. At enrolment there were no differences between DTG vs EFV in median gestation (31w), VL (log_{10} 4.4 vs 4.5 cps/mL), CD4 count (464 vs 412 cells/μL) or other characteristics. The median duration of ART at delivery was 52 vs 59 days (range 0 – 133 days). VL<50 cps/mL at delivery was significantly higher with DTG (90/122, 74%) vs EFV (49/115, 43%); adjusted risk ratio (RR) and 95% CI, 1.66 (1.32-2.09) (Figure). This trend was consistent across subgroups of baseline VL; CD4 cell count; gestation at initiation; and other characteristics. VL<1000 cps/mL at delivery was also more likely in women on DTG vs EFV (93% vs 83%); RR, 1.11 (1.00-1.23). DTG was well-tolerated in pregnancy with no differences with EFV in frequency or organ class of severe adverse events. There were no significant differences between DTG and EFV arms in median gestational age at delivery (39.9w for both arms), or births at <34w (4.76% vs 5.13%) and <37w (16.67% vs 15.38%) gestation respectively. There were 4 stillbirths (aetiological factors under investigation), all in the DTG arm. Of 270 live births, congenital anomalies (excluding umbilical hernias and birthmarks) were reported in 17 infants (DTG 8, EFV 9) up to 6w of age; no neural tube defects were observed. There were 7 infant deaths (DTG 4, EFV 3). Three cases of MTCT were detected at birth, all from the DTG arm, and considered likely to be in-utero transmissions.
Conclusion: DTG is well-tolerated and achieves more rapid virological suppression before delivery compared to EFV when initiated in late pregnancy. Late presentation in pregnancy is associated with poor outcomes despite ART and regardless of arm.

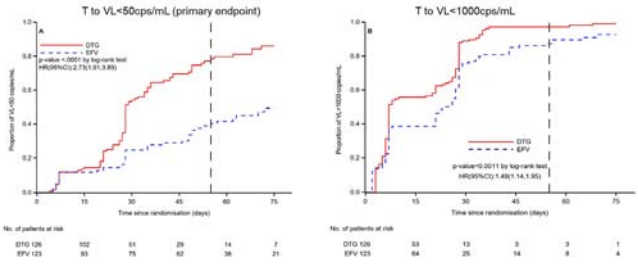

Figure. Kaplan-Meier plots of time from randomization to viral load (a) <50 (primary endpoint) and (b) <1000 cps/mL. Dashed vertical line in each plot represents the median time from randomization to delivery in the total trial population

41 MATERNAL HBV VIREMIA IS ASSOCIATED WITH ADVERSE INFANT OUTCOMES IN HIV/HBV WOMEN

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Background: HIV/HBV coinfection is common, yet there is little information on maternal and infant clinical outcomes. We assessed the prevalence of

HBV coinfection and its impact on HIV transmission and infant and maternal outcomes in HPTN 046, a HIV mother-to-child (MTCT) transmission study.
Methods: HPTN 046 was a randomized controlled clinical trial of HIV MTCT which evaluated 6 months of infant nevirapine vs placebo for HIV prevention. Mother-infant pairs were enrolled in sub-Saharan Africa from 2007-2010; 1579 women (78%) also received ART. Maternal samples were retrospectively tested for hepatitis B surface antigen (HBsAg), and if positive, were tested for hepatitis B e antigen (HBeAg) at study entry and HBV viral load (VL) at delivery. Women who were HBsAg positive were classified as HIV-HBV co-infected (HIV-HBV). High HBV VL was defined as $>10^6$ IU/ml. The impact of HIV/HBV coinfection on HIV MTCT, low birth weight (LBW), infant mortality and maternal premature rupture of membranes and C-section was assessed using multivariate (MV) logistic and Cox regression.
Results: Among 2025 HIV-infected (HIV) women, 88 (4.3%) were HIV-HBV. HIV-HBV women with high HBV VL had lower median CD4 T-cell count at study entry, when compared to HIV+/HBV- women or HIV-HBV women with HBV VL < 10^6 IU/ml (320, 490, and 434 cells/mm^3, respectively ($p<0.007$)). In MV analysis, adjusted for maternal CD4, age, and maternal ART, infants born to women with high HBV VL were more likely to be low birth weight (LBW), compared to HIV+/HBV- and HBV low VL women: [30% (3/10) vs 10% (194/1953) vs 6% (5/78), respectively, $p=0.03$)]. In a dose response analysis, HBV VL greater than 102 IU/ML was associated with LBW [RR=6.1 (95% CI 1.31 - 28.39)]. HIV MTCT occurred in 2/10, 0/78, and 53/1953 high HBV VL, low HBV VL, and HIV+/HBV – women, respectively. High HBV VL was associated with HIV MTCT [(HR 6.75 (95% CI 1.86 – 24.50)]. There was no impact on infant mortality or maternal outcomes at 18 months.
Conclusion: In HIV/HBV coinfected women, HBV replication increases the risk for poor infant outcomes including LBW and potentially HIV MTCT. Reduction of antepartum HBV viremia may have beneficial effects beyond the prevention of HBV MTCT in HIV/HBV coinfection.

42 IMPACT OF IMPROVED NUTRITION/SANITATION ON NEURODEVELOPMENT OF HIV-EXPOSED CHILDREN

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Background: HIV-exposed children may be at risk of impaired early child development (ECD), but preventive interventions are currently limited.
Methods: We conducted a 2x2 factorial cluster-randomized trial of improved infant and young child feeding (IYCF) and improved water, sanitation and hygiene (WASH) in rural Zimbabwe (ClinicalTrials.gov NCT01824940). Pregnant women were eligible if they lived in study clusters randomized to standard-of-care (SOC; 52 clusters); IYCF (20g Nutributter®/day for infants from 6-18mo, complementary feeding counseling; 53 clusters); WASH (pit latrine, 2 hand-washing stations, liquid soap, chlorine, play space, hygiene counseling; 53 clusters); or (IYCF+WASH; 53 clusters). A sub-study evaluated ECD outcomes at 2 years of age among HIV-exposed children using the Malawi Developmental Assessment Tool (MDAT; assessing motor, cognitive, language and social development); MacArthur-Bates Communication Development Inventory (CDI) (assessing vocabulary and grammar); A-not-B test (assessing object permanence); and a self-control task. Masking of participants/fieldworkers was not possible. Analysis was by intention-to-treat using unadjusted and adjusted generalized estimating equations.
Results: 726 HIV-positive pregnant women were recruited. Mean (SD) CD4 count was 473 (221) cells/μL. Among 738 HIV-exposed live births (additional 12 from twin pregnancies), 323 children from 142 clusters had ECD assessments (68 from 31 SOC clusters; 68 from 40 IYCF clusters; 83 from 33 WASH clusters; 104 from 38 IYCF+WASH clusters). 300 children were HIV-exposed uninfected, 6 were HIV-positive and 17 had an unknown HIV status. Compared to SOC, children randomized to combined ICYF+WASH had higher MDAT scores (+4.6; 95%CI 1.9, 7.2), but there was no evidence of impact of IYCF or WASH alone (Table). The increase was accompanied by higher gross motor (+1.5; 95%CI 0.5, 2.5), fine motor (+0.7; 0.0, 1.5), language (+1.5; 95%CI 0.2, 2.8) and social components (+1.0; 95%CI 0.5, 1.5). Children randomized to combined IYCF+WASH also had higher MacArthur-Bates CDI vocabulary scores (+8.5 words; 95%CI 3.7, 13.3), but we found no evidence of an impact of IYCF or WASH alone. There was no evidence of an impact of either intervention on object permanence or self-control.
Conclusion: Combining IYCF and WASH interventions significantly improved motor and cognitive development in HIV-exposed children at 2 years of age.

ECD assessment tool	Trial arm	Mean score (SD)	Unadjusted difference (95% CI)	P	Adjusted difference (95% CI)*	P
MDAT total score	SOC	90.9 (8.2)	Reference	-	Reference	-
	IYCF	91.7 (8.8)	0.81 (-1.99, 3.61)	0.572	-0.91 (-3.40, 1.58)	0.476
	WASH	89.6 (9.2)	-1.26 (-3.80, 1.28)	0.330	-1.63 (-4.26, 0.99)	0.222
	IYCF+WASH	95.3 (9.0)	4.57 (1.91, 7.23)	0.001	3.05 (0.86, 5.25)	0.006
MacArthur-Bates CDI vocabulary score	SOC	56.6 (18.5)	Reference	-	Reference	-
	IYCF	57.6 (21.3)	1.00 (-5.74, 7.55)	0.771	-2.47 (-8.60, 3.67)	0.431
	WASH	58.2 (20.1)	1.58 (-4.12, 7.29)	0.586	-2.27 (-8.14, 3.60)	0.448
	IYCF+WASH	65.1 (17.0)	8.50 (3.66, 13.33)	0.001	6.01 (1.14, 10.88)	0.015

Table: Effect of infant and young child feeding (IYCF) and water, sanitation and hygiene (WASH) interventions. MDAT: Malawi Developmental Assessment Tool; CDI: Communication Development Inventory; SOC: standard-of-care; IYCF: infant and young child feeding; WASH: water, sanitation and hygiene.

*Models were adjusted for baseline variables: maternal nutrition status (mid-upper arm circumference), maternal education, maternal employment, maternal capabilities, maternal CD4 count, presence of latrine, low birthweight, prematurity, gencer, child age at assessment, study nurse, birth season.

43 UNIQUE IMMUNOLOGICAL AND VIROLOGICAL FEATURES OF EARLY TREATED HIV-INFECTED NEWBORNS

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Background: Studying HIV-1 infection in neonates with a developing immune system may offer unique opportunities for understanding viral reservoir establishment and exploring eradication strategies. The Early Infant Treatment (EIT) project in Botswana provides antiretroviral therapy (ART) to newborn HIV-1-infected infants, and longitudinally evaluates virological and immunologic parameters.
Methods: Serial PBMCs were collected from 10 infants with neonatal HIV-1 infection who started ART within 72 hours (n=9) or 31 days (n=1) after birth, and were followed for 84-96 weeks (w). PBMCs collected cross-sectionally in 10 infants after a median of 93w (range: 65-127) of ART started at a median of 119 days (range: 79-350) after birth were used as controls; PBMCs from HIV-1-negative infants (n=22) at 12w of life from Botswana were also analyzed. HIV-1 DNA was analyzed by near full-length single-genome sequencing, paired with corresponding chromosomal integration site analysis. Multiparametric flow cytometry was used to quantify phenotypic characteristics of innate and adaptive immune cells.
Results: Compared with control children, EIT infants had lower total (5.3 vs 981.4, $p<0.0001$), intact (0.35 vs 2.4, $p=0.006$), and defective (1.9 vs 25.6, $p=0.003$) HIV-1 DNA copies/million PBMCs after 84-96w on ART. Intact proviral full-genomes represented an average of 54.3% of all sequences at baseline, compared with 5.9% at 84-96w on ART among EIT infants. Integration sites of 24 intact proviruses (determined at w0) were predominantly (71%) located in genes, with a preference for a configuration in the same orientation as host transcripts (65%); a similar distribution was noted for integration sites of defective proviruses. Proportions of mature CD56+CD16+ NK cells were significantly increased in EIT infants at 12w on ART relative to healthy infants ($p=0.035$); by contrast, the more immature CD56-CD16+ NK cells were notably reduced compared to controls ($p=0.0031$) and healthy infants ($p=0.0006$). HIV-1-specific CD8 T cells in EIT infants were weak in magnitude but displayed a polyfunctional profile. In a longitudinal analysis among EIT infants, positive correlations were found between total HIV-1 DNA copies and activated CD38+HLADR+ effector memory and terminally-differentiated CD8 T cells.
Conclusion: Immediate initiation of ART during neonatal HIV-1 infection is associated with a remarkably reduced viral reservoir, a prematurely-expanded

CD56+CD16+ NK subset and a weak but polyfunctional HIV-1-specific CD8 T cell response.

44 NEONATAL ART < 7 DAYS VS 7-28 DAYS REDUCED TIME TO SUPPRESSION

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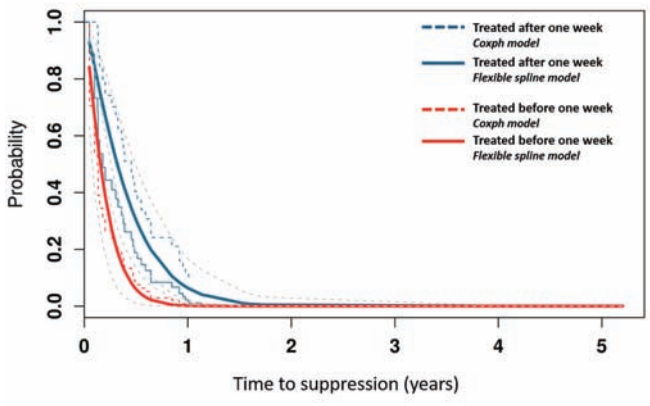
Background: Early antiretroviral therapy (ART) in children is associated with better clinical and virological outcome. Few data are available about long-term outcome of children starting ART in the neonatal period. Our hypothesis is that HIV-perinatally infected neonates initiating ART within <7 days of life have a better long-term clinical and virological response than neonates treated ≥7 days and ≤28 days of life.

Methods: 44 children with perinatal HIV aged ≤28 days at start of ART were included from 4 cohorts (11%UK, 52% Spain, 7% Italy, and 29% Thailand). Primary endpoints were clinical - mortality, and progression to AIDS – and virological: time to suppression, time to virological failure, and proportion of time suppressed. Data were collected up to 15-years of follow-up. Those subjects who received triple postpartum prophylaxis and subsequently transitioned to ART within <15 days were considered as starting ART from date of prophylaxis initiation. A flexible spline interval censored survival model was applied adjusting for CD4 and viral load (VL) at the start of ART.

Results: 57% were female and 35% preterm. Median follow-up was 11.5[IQR 8.2-15.6] years. No patient died. 84% received postpartum prophylaxis. At ART initiation, children were aged 15.5 [0.00;24.2] days, with CD4 total 2766[2126;3368], CD4:CD8 2.5[1.6;3.1], and log10VL 4.2[2.9;5.2] copies/ml. 36/44 (83%) ever suppressed (VL≤50). Time to viral suppression was 0.57[0.25;1.04] years. 12/44 (34%) had subsequent virological failure after suppression (median time to failure, 2.40 [1.01;9.61] years). Participants had 2.9 ±1.8 ART regimen switches, 26% progressed to AIDS. 19/44 (43%) patients started ART <7 days of age. Viral load was higher in children treated <7 days (log10VL 4.4 [4.2;5.4] vs 3.3 [2.9;4.4], p=0.018). Time to suppression was shorter in those treated in the first 7 days of life (18.9[7;41.7] y 44.1[24.6;61.0] weeks, p = 0.038). The probability of suppression decreased by 24% for each week the ART initiation was delayed (aHR=0.76 [0.6;0.97], p=0.035, Figure 1). No differences were observed in progression to AIDS, ART switches, time to immunological recovery (CD4:CD8>1), time to virological failure or proportion of time suppressed.

Conclusion: Even among children initiating ART<28 days of age, children starting ART in the first week of life suppress earlier. There was similar long-term clinical, virological and immunological outcomes in children treated <7 days vs. 7 to 28 days.



45 SAFETY AND PHARMACOKINETICS OF MONOCLONAL ANTIBODY, VRC01LS, IN HIV-EXPOSED NEWBORNS

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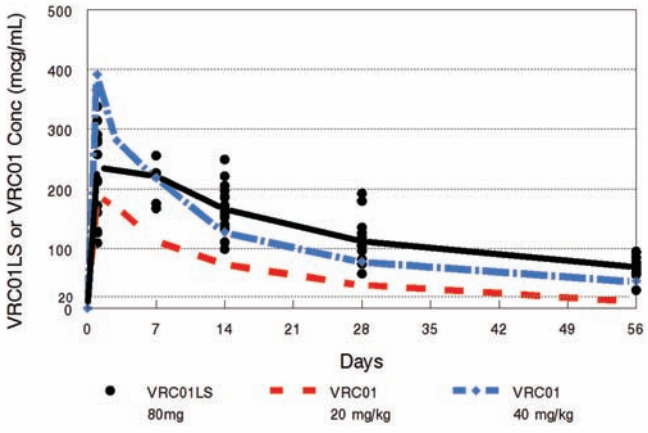
Background: Vertical HIV transmission occurs despite use of antiretroviral therapy (ART). A broadly neutralizing monoclonal antibody, administered to HIV-exposed infants might further prevent transmission. VRC01LS, modified from VRC01, has an extended half-life and may be a feasible adjunct to ART prophylaxis.

Methods: This is an open label safety and pharmacokinetic study of VRC01LS administered to HIV-exposed infants. Cohort 1 infants (non-breastfeeding) receive subcutaneous (SC) Dose 1 (80mg for birth weights 2.0 to <4.5kg) within 72 hours of birth. Cohort 2 (breastfeeding) receive Dose 1 within 5 days of birth and Dose 2 (100mg SC) at Week 12, if still breastfeeding. All infants and their mothers receive ART to prevent HIV transmission. Safety is assessed post vaccination at 4 hours, Day 1, 14, 28, 56, Week 12, and then every 12 weeks through Week 96. Cohort 2 also has safety assessments at Week 14 and 16. Preliminary VRC01 pharmacokinetic parameters are determined through Week 12.

Results: Cohort 1 (n=10) and 2 (n=11) fully accrued from 8 sites (6 in the US, 1 site each in Zimbabwe and South Africa) with no HIV transmissions. All infants received Dose 1. Ten in Cohort 2 received Dose 2, as of the April 2018 safety analysis. Birth weight ranged from 2.5-4.1kg. VRC01LS was well tolerated with no treatment related toxicities >grade 2. Local reactions (all grade 1 or 2; 95% resolved by 24 hr) were common after Dose 1, occurring in 5/10 (50%) and 9/11 (82%) infants in Cohort 1 and 2, respectively, but less frequent after Dose 2, occurring in 2/10 (20%) infants. Plasma VRC01LS levels for Dose 1 (Cohorts combined) are available at Days 1 (n=14), 7 (n=5), 14 (n=20), 28 (n=20), 56 (n=17), and Week 12 (n=12) and compared to previously reported levels at Day 28 (n=13) and Day 56 (n=12) for 20mg/kg and 40mg/kg VRC01 given SC at birth (Figure). VRC01LS was rapidly absorbed following SC administration, with all Day 1 levels >100mcg/mL. VRC01LS levels were significantly greater than VRC01 levels at Day 28 (p=0.0018) and Day 56 (p=0.0019) despite the lower weight-band dosing (VRC01LS 20-32mg/kg vs. VRC01 40mg/kg). At Week 12, the median VRC01LS level was 39.1mcg/mL and all infants' levels were >20mcg/mL.

Conclusion: Preliminary results indicate that VRC01LS administered to neonates via the SC route at birth and age 12 weeks is well tolerated with mild-moderate transient local reactions. VRC01LS with its extended half-life could achieve target levels for the duration of breastfeeding with infrequent dosing.



46 BICTEGRAVIR/FTC/TAF SINGLE-TABLET REGIMEN IN ADOLESCENTS AND CHILDREN: WEEK 48 RESULTS

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Background: B/F/TAF, approved for adults living with HIV-1, is a single-tablet regimen (STR) containing the novel integrase strand transfer inhibitor (INSTI) bictegravir (B) 50 mg, emtricitabine (FTC) 200 mg, and tenofovir alafenamide (TAF) 25 mg. B/F/TAF has a high barrier to resistance and no food restriction. Short-term safety and pharmacokinetics (PK) of B/F/TAF in children and adolescents, reported previously, support the use of the full adult strength tablet in this population. The 48-week (W) safety and efficacy data for 6- to <18-year-olds receiving B/F/TAF are reported.

Methods: Virologically suppressed adolescents (12 to <18 yrs) weighing ≥35 kg (Cohort 1) and children (6 to <12 yrs) weighing ≥25 kg (Cohort 2) with HIV-1 RNA <50 c/mL for ≥6 months before screening and CD4 ≥200 cells/µL received B/F/TAF once daily, in a prospective, 48-week, single-arm, open-label trial. Adverse events (AEs), laboratory results, and HIV-1 RNA <50 c/mL were assessed.

Results: Fifty adolescents and fifty children (total n=100) were enrolled. At baseline for Cohort 1, median age was 15 yrs (range 12-17 yrs), weight 44.7 kg (range 35-123 kg), 64% female, 65% Black, median CD4 count 751 cells/µL, 90% vertically infected. For Cohort 2, median age was 10 yrs (range 6-11 yrs), median weight 29 kg (range 25-69 kg), 54% female, 72% Black, median CD4 count 930 cells/µL, and 96% vertically infected. All 100 participants (100%, 100/100) had HIV-1 RNA <50 c/mL at W24 and 98% (74/75) at W48 by US FDA Snapshot Algorithm; no participant had treatment-emergent resistance. CD4 count remained stable to W48. With a 50-week (range 20-93 wks) median duration of exposure to study drug, the only study drug-related AE reported with greater than single participant incidence was abdominal discomfort (2%, 2 participants; grade 1). One participant discontinued after W16 due to an AE (grade 2 insomnia and anxiety). All participants reported B/F/TAF size and shape as acceptable and taste as palatable; median percent adherence (pill counts) to study drug was high at 99% (range 80-100%).

Conclusion: This 48-week efficacy, safety, acceptability, and palatability data, combined with the previously reported PK data, support the use of the first, unboosted, INSTI-based STR of B/F/TAF 50/200/25 mg for the treatment of adolescents and children (6 to <18 years of age and weighing ≥25 kg) living with HIV-1 and prompts further pediatric studies of appropriate formulations of B/F/TAF for children weighing <25 kg.

47 INCIDENT SYPHILIS RATES AND PREDICTORS IN US WOMEN WITH HIV, 2005-2016

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Background: Early syphilis rates in the US have increased 76% since 2013 and congenital syphilis rates are at a 20-year peak. Although defined as high-risk for STI screening, rates and predictors of syphilis in US women with HIV are not well described. We aimed to determine unique predictors of incident syphilis in a longitudinal US cohort of women living with HIV.

Methods: This retrospective study included women enrolled in the US CFAR Clinical Network of Integrated Clinical Systems (CNICS) Cohort with at least one HIV clinic visit between 2005 and 2016. Data were extracted from the electronic medical record and patient reported outcomes (PRO) were collected every 6 months. Incident syphilis was defined as a newly positive nontreponemal serologic test after a previously negative test or a 4-fold increase in titer, both with positive confirmatory testing. Each year in care was analyzed separately and more than one incident syphilis infection was allowed. Univariate (UV) and multivariable (MV) logistic regression with auto-regressive correlation structure and generalized estimating equations (GEE) were used to model the incident syphilis outcome. Variables were chosen for the MV model based on prior studies, statistical significance in the UV model ($p<0.05$), and data completeness.

Results: A total of 4,795 women in the CNICS cohort were included with 27,249 woman-years in care. Median age was 47, 63% of women were Black and 75% had acquired HIV from heterosexual sex. Overall, 4219 (88%) were tested for syphilis and 119 women (2.8%) had 125 incident infections (7.6 cases per 1000 person-years). In the unadjusted model, active drug abuse, prior IVDA, hepatitis C (HCV Ab+), HIV viral load >1000 copies/mL, black race and later year of entry to care predicted incident syphilis. In the adjusted model, independent predictors were prior IVDA (aOR 2.3, 95% CI 1.3-3.9), HCV Ab+ (aOR 2.1, CI 1.3-3.7), later year of entry to care (aOR 2.3, CI 1.4-3.9 for 2011-2016 compared to 1994-2004), and black race (aOR 2.3, CI 1.4-3.9 compared to white). Age and HIV VL were not predictors. (see Table)

Conclusion: In a large national cohort of US women with HIV, history of IV drug use and hepatitis C infection were the best predictors of incident syphilis infection. Further studies are needed to determine if this association is mediated via transactional sex or high-risk sex partners. Guidelines should prioritize women with HIV and IVDA for syphilis screening and the prevention of congenital syphilis.

Table – Predictors of Incident Syphilis Infection in 4795 US Women in HIV Care; 2005-2016*

Variable**	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Demographics and Clinical		
Age		
18-29	1.4 (0.8-2.5)	1.8 (0.9-3.4)
30-39	0.7 (0.4-1.2)	0.9 (0.5-1.6)
40-49	1.0 (0.7-1.5)	1.1 (0.7-1.7)
50+	REF	REF
Race		
White	REF	REF
Black	**1.8 (1.1-3.0)**	**2.3 (1.4-3.9)**
Other	1.0 (0.4-2.5)	1.1 (0.4-2.8)
IVDA HIV Risk Factor	**3.2 (2.2-4.7)**	**2.3 (1.3-3.9)**
HIV Viral Load >1000 copies/mL	**1.7 (1.2-2.4)**	1.4 (1-2.1)
CD4 Count (cells/mm^3)		
<200	1.1 (0.7-1.9)	Not included
200-350	1.2 (0.8-2.0)	
>350	REF	
Hepatitis C Infection (HCV Ab+)	**3.0 (2.1-4.4)**	**2.1 (1.3-3.7)**
Hepatitis B Infection (HbSAg+)	1.2 (0.5-2.8)	Not included
Initial HIV Visit at CNICS Site		
1994-2004	REF	REF
2005-2010	**1.9 (1.3-2.9)**	**2.0 (1.3-3.1)**
2011-2016	**1.8 (1.1-2.9)**	**2.3 (1.4-3.9)**
Patient Reported Outcomes in the Past 3-6 Months		
Drug Abuse		
Never	REF	Not included
Prior Use	2.2 (1.0-4.8)	
Active Use	**3.3 (1.3-8.6)**	
Alcohol Intake		
Not at risk	REF	Not included
Low risk	0.3 (0.0-2.3)	
High risk	0.5 (0.2-1.5)	
Number of sex partners		
0	REF	Not included
1	1.3 (0.7-2.7)	
2+	2.6 (1.0-7.1)	

* GEE models with auto-regressive covariance structure. Values highlighted are statistically significant at p<0.05.
**Missing data: 11 for age, 151 for HIV risk factor, 420 CD4, 433 HIV VL, 2920 for alcohol abuse, 2963 for substance abuse, 2961 sex partner #.

48 PREPARING FOR PrEP IN ENGLAND: PREVALENCE AND INCIDENCE OF HIV AND BACTERIAL STIs

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Background: In England, the recent decline in new HIV diagnoses among men who have sex with men (MSM) attending sexual health clinics (SHCs) has been attributed to HIV combination prevention including HIV pre-exposure prophylaxis (PrEP). To evaluate recent trends in HIV and STI diagnoses, we determined the prevalence of bacterial sexually transmitted infections (STIs) and annual incidence of HIV in MSM attending SHCs in England.

Methods: Using GUMCAD, England's national STI surveillance system, we extracted data on HIV (from 2012 to 2017) and bacterial STI (from 2017: chlamydia, gonorrhoea, and primary, secondary, early latent syphilis) diagnoses

in MSM aged ≥16 years attending SHCs. Period prevalence and 95% confidence intervals (CIs) for HIV among all attendees and bacterial STIs (at least one diagnosis in calendar period) among HIV negative attendees in 2017 were calculated. Annual HIV incidence per 100 person-years (PY) and 95% CIs in MSM who tested for HIV at least twice in the same SHC from 2012 to 2016 were determined. As a proxy measure of high risk, HIV incidence in a subset of MSM with a history of a negative HIV test and an ano-genital bacterial STI in the preceding year was also examined.

Results: In the 159,368 MSM attending SHCs in 2017, HIV period prevalence was 20.0% (95% CI 19.8-20.2%). In MSM not known to be HIV positive (n=128,772), gonorrhoea, chlamydia, and syphilis period prevalence in 2017 was 12.1% (11.9-12.2%), 9.0% (8.9-9.2%), and 2.7% (2.6-2.8%), respectively. The number of MSM not known to be HIV positive (% tested for HIV at least twice) increased from 85,500 (31.0%) in 2012 to 120,606 (36.2%) in 2016. The annual incidence of HIV in MSM decreased 60.5% from 2.0 per 100 PY (95% CI: 1.8-2.2) in 2012 to 0.79 per 100 PY (0.69-0.89) in 2016; compared to the latter, MSM meeting proxy high risk criteria in 2016 had a two-fold higher HIV incidence [1.58 (1.25-1.99) per 100 PY].

Conclusion: While there is a high prevalence of bacterial STIs, there has been a sharp decrease in the incidence of HIV in MSM regularly attending SHCs. The fall in HIV incidence coincides with further intensification of HIV testing, especially repeat testing, and earlier initiation of HIV treatment and, more recently, the scale up of privately purchased generic PrEP in England from late 2017. The PrEP Impact trial, which aims to enrol 13,000 participants from communities most affected by HIV, is likely to have an additional effect on the incidence of HIV.

49 EXPANDING TESTING STRATEGIES IN PARIS: A FREE POSTAL COMPREHENSIVE STI TEST KIT

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Background: Testing is critical to HIV and other sexually transmitted infections (STI) treatment and prevention. The MemoDepistages multicenter study is a novel French government-based comprehensive STI testing program, providing free postal self-sampling kits to high-risk MSM. We present here the baseline results from the Paris area, accounting for 60% of all participants.

Methods: The program was advertised by dating apps and social media. Inclusion criteria were: MSM aged over 18, ≥2 male sex partners in the last year, HIV-seronegative without PrEP. Test kits included 1 Microtainer Serum Separator Tube, lancets for the collection of 600µl capillary blood, 1 UriSwab collection tube, 2 PCR Dual Swab kits and pre-paid packaging to return samples. Serum was tested for HIV-1/2 EIA 4G serology, anti-HCV antibodies, HBs antigen (Architect, Abbott) and syphilis Tp and RPR (Bioplex, Biorad). Urine, throat and anal swabs were tested for Chlamydiae trachomatis (CT) and Neisseria gonorrhoeae (NG) DNA (Cobas 6800, Roche). Results were provided to the participants, as they chose, by community-based workers following text, phone or e-mail contact or by their family physician.

Results: From April, 10th to June, 11th 2018, 4419 applicant men from the Paris area were eligible. Median age was 30 years, 13.0% had never been tested for HIV, they reported a median of 10 partners/year. 48.5% confirmed their inclusion and ordered the kit. As of August, 31st 2018, 1238 kits were returned to the core lab. 1.3% (13) of tested samples were positive for HIV, 0.5% (6) for anti-HCV antibodies, 0.3% (3) for HBs antigen and 1.8% (11) for active syphilis. Full serology testing was hindered by hemolysis and low blood volume (Table 1). Six HIV-positive participants were unaware of their infection (0.6%) and one sample revealed an acute primary infection, as confirmed by further sampling. NG was found in 11.2% of participants and CT in 9.4%. The most common bacterial STI was throat NG (8.2%). Community-based linkage to care was excellent and newly diagnosed participants sought counseling and treatment.

Conclusion: This is the first study of a postal viral and bacterial STI test in France. Enrollment was fast, highlighting the need for access to testing in the target population. Blood collection was feasible in most participants and laboratory-based serology allowed for the detection of acute and chronic HIV infections, HCV, HBV and syphilis. CT and NG were frequent and would not have been detected by a typical urine-only strategy.

	Performed Test (%) (tested samples / total samples)	Positivity rate (%) (reactive tests / performed tests)
HIV	81%	1.3%
HCV	81%	0.5%
HBV	70%	0.3%
Syphilis	49%	1.8%
CT – Throat	100%	1.8%
CT – Anal	99%	7.2%
CT - Urine	99%	1.6%
NG –Throat	100%	8.2%
NG – Anal	99%	4.8%
NG – Urine	99%	0.6%

50 RANDOMIZED CONTROLLED TRIAL OF INTRAUTERINE DEVICE SAFETY IN WOMEN LIVING WITH HIV

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Background: Few data exist regarding impact of exogenous progestins on genital tract HIV viral load (gVL) in women living with HIV (WLHIV). We compared safety via gVL and plasma HIV VL (pVL) and acceptability via continuation of copper (C-IUD) compared to levonorgestrel (LNG IUD) intrauterine devices among WLHIV stratified by ART use in Cape Town, South Africa.

Methods: This double-blind trial allocated consenting WLHIV to C-IUD or LNG IUD 1:1 between October 2015 and December 2016. Eligibility included screening and treatment for reproductive tract infections (RTIs) within the past 1m, not desiring pregnancy within 2y, and either viral suppression (pVL<1000 c/mL) in the last 6m (on ART) or CD4 count above ART initiation threshold (non-ART). We tested genital tract menstrual cup samples for gVL and swabs for RTIs, and pVL at enrollment and 3, 6, 12, 18, and 24m follow-up visits. We compared detectable gVL at 6m (primary outcome) and 24m by arm with intent-to-treat (IT) and as-treated (AT) Mantel-Haenszel Odds Ratios (OR), stratified by baseline gVL and ART use. We reported serious adverse events (SAEs) related to IUD use and compared acceptability via IUD removal rates over 24 months by arm using proportional hazards models.

Results: We enrolled 199 WLHIV (134 on ART/65 non-ART users; median age of 31y and 95% had >1 prior pregnancy). 62% of non-ART users and 15% of ART users had detectable gVL at enrollment with no differences by IUD arm. There were no significant differences in detectable gVL between arms adjusting for baseline gVL and ART group at 6m (IT OR=1.03, 95%CI 0.53-2.02, p=0.92; AT OR=1.01, 95%CI 0.51-2.01, p=0.98) and 24m (Table). Over 24m, there were 39 SAEs (18%, n=7 related to IUD). IUD continuation was 75% overall, with 3 partial and 7 complete expulsions and 34 elective and 5 non-elective (for PID, colposcopy and pregnancy) removals by 24m. Expulsion (8% vs. 2%, p<0.001) and elective discontinuation (7.1m vs. 10.9m median time to removal, Hazard Ratio=9.00, 95% CI 3.17-25.5) were higher for C-IUD users. Common elective discontinuation reasons were dysmenorrhea/pain (40%, C-IUD and 75%, LNG IUD) and heavy bleeding (33%, C-IUD).

Conclusion: This first randomized study comparing local progestin effect (LNG IUD) to a non-hormonal method (C-IUD) indicates no increase in gVL shedding, a proxy for sexual transmission risk, or pVL between IUDs, with or without ART use. The LNG IUD had low discontinuation rates, reflecting its value in broadening the contraceptive method mix for WLHIV.

Randomized controlled trial comparing levonorgestrel to copper IUD outcomes over 24 months, stratified by ART use (n=199).						
	ART users (n=132)		*Non ART users (n=67)*		*Total (n=199)*	
(n; p-y)	LNG IUD (65; 109.9)	C-IUD (67; 116.9)	LNG IUD (36; 67.9)	C-IUD (31; 61.2)	LNG IUD (101; 177.8)	C-IUD (98; 178.1)
Baseline characteristics						
Median age (IQR; years)	32 (28, 36)	32 (29, 36)	30 (25, 34)	31 (27, 34)	31 (28, 35)	32 (28, 35)
Median CD4 at screening (IQR)	N/A	N/A	568 (472, 794)	684 (551, 832)	N/A	N/A
Detectable (>40 copies/mL) gVL, n (%)	7 (10.8%)	10/66 (15.2%)	23/35 (65.7%)	17/30 (56.7%)	30/100 (30.0%)	27/96 (28.1%)
Detectable (>40 copies/mL) pVL, n (%)	12 (18.5%)	14 (20.9%)	34 (94.4%)	30 (96.8%)	46 (45.5%)	44 (44.9%)
Median $\log_{10}$ pVL (IQR; copies/mL) among those with detectable pVL	2.2 (1.9, 3.1)	3.0 (2.1, 3.6)	3.8 (3.1, 4.3)	4.0 (3.3, 4.5)	3.5 (2.9, 4.2)	3.6 (2.7, 4.5)
Outcomes over 24 months using GEE logit models; OR (95% CIs)						
Detectable pVL as treated*	1.0	1.13 (0.59, 2.18)	1.0	0.79 (0.38, 1.66)	1.0	1.03 (0.65, 1.64)
Detectable gVL as treated*	1.0	1.38 (0.83, 2.29)	1.0	0.73 (0.36, 1.49)	1.0	0.99 (0.65, 1.52)
Adjusted detectable gVL as treated **	1.0	1.29 (0.82, 2.06)	1.0	0.87 (0.42, 1.82)	1.0	1.02 (0.70, 1.48)
Pelvic inflammatory disease (n)	1	0	1	1	2	1
Pregnancy with IUD in place (n)	1	1‡,†	0	1†	1	3

ART: antiretroviral therapy; CI: confidence interval; C-IUD: copper IUD; gVL: genital viral load; IQR: interquartile range; IUD: intrauterine device; LNG IUD: levonorgestrel IUD; OR: odds ratio; pVL: plasma viral load; p-y: person-years
*adjusted for baseline gVL or pVL; total also adjusted for ART use; **adjusted for baseline & concurrent pVL, concurrent RTI, & age.
† Tubal ectopic pregnancies; ‡ Spontaneous abortion after probable unrecognized complete expulsion.

51 DOUBLE-DOSE LEVONORGESTREL IMPLANT DOES NOT FULLY OVERCOME INTERACTION WITH EFAVIRENZ

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Background: We previously described 57% lower levonorgestrel (LNG) exposure in women receiving the LNG subdermal implant (standard dose, 150mg) with efavirenz (EFV)-based antiretroviral therapy (ART) compared to ART-naïve women. Three of 20 women (15%) had an unintended pregnancy within 48 weeks of LNG-EFV combined use, with observed LNG concentrations ≤303 pg/mL at the visit prior to pregnancy. Among women receiving LNG-EFV, 18 (90%) had any LNG concentration ≤303 pg/mL during the study. We hypothesized this interaction could be overcome by doubling the LNG implant dose; specifically, LNG 300mg exposure over 48 weeks in women receiving EFV-based ART would be similar to ART-naïve women receiving LNG 150mg.
Methods: This was a pharmacokinetic evaluation of double-dose (300mg) LNG implants in Ugandan women receiving EFV-based ART with an undetectable HIV-RNA (DoubLNG group; n=28). LNG implants, one in each arm, and a copper intrauterine device were placed at entry. Historical controls were ART-naïve Ugandan women (n=17) who received a standard-dose (150mg) LNG implant at entry. Plasma was collected at 1, 4, 12, 24, 36, and 48 weeks. LNG concentrations were analyzed by a validated LC-MS/MS method (range 50-1500 pg/mL), summarized as median (IQR), and compared between groups by geometric mean ratio (GMR) with 90% CI. The proportion with LNG ≤303 pg/mL were compared by Fisher's Exact test.
Results: All women were Black African. The DoubLNG group had a median age of 33 years and median weight of 58 kg; the control group was 29 years and 69 kg, respectively. The Table summarizes LNG results by visit. After 48 weeks, LNG concentrations were 373 (319, 540) pg/mL in the DoubLNG group versus 651 (469, 879) pg/mL in the control group [GMR (90% CI) 0.66 (0.61, 0.72)]. During the study, 18% (n=3) in the control group and 46% (n=13) in the DoubLNG group had any LNG value ≤303 pg/mL (p=0.06).
Conclusion: We observed 33-44% lower LNG concentrations over 48 weeks in women receiving EFV-based ART plus LNG 300mg implants compared to ART-naïve women on LNG 150mg implants. Relative to our prior study, the magnitude of the interaction with EFV at week 48 was smaller with double-dose LNG (34% lower) vs standard-dose LNG (57% lower). Also, fewer women receiving EFV-based ART had an LNG ≤303 pg/mL in the double- vs standard-dose group (46% vs 90%, respectively; p=0.002). Doubling the dose of LNG implants does not fully overcome the interaction with EFV, and the contraceptive effectiveness of this approach remains uncertain.

Table: Levonorgestrel Plasma Concentrations Over 48 Weeks; Median (IQR)

Study Week	DoubLNG: LNG 300 mg + EFV n=28 (pg/mL)	Control: LNG 150 mg ART-naïve, n=17 (pg/mL)	DoubLNG: Control GMR (90% CI)	P-value[a]
1	571 (466, 894)	1073 (744, 1586)	0.56 (0.52, 0.61)	<0.001
4	441 (369, 658)	741 (472, 787)	0.67 (0.67, 0.68)	0.005
12	404 (329, 512)	598 (417, 816)	0.67 (0.64, 0.67)	0.014
24	313 (251, 530)	501 (366, 706)	0.63 (0.61, 0.64)	0.003
36[b]	376 (320, 520)	630 (487, 715)	0.61 (0.60, 0.61)	<0.001
48[b,c]	373 (319, 540)	651 (469, 879)	0.66 (0.61, 0.72)	0.003

[a] All values were statistically compared using the Wilcoxon rank sum test.
[b] DoubLNG group week 36 and 48, n=27.
[c] Control group week 48, n=15.

52 PHARMACOGENETICS WORSENS AN ADVERSE ANTIRETROVIRAL-HORMONAL CONTRACEPTIVE INTERACTION

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Background: In ACTG A5316 women receiving efavirenz (EFV)-containing ART had 79% and 59% lower etonogestrel (ENG) and ethinyl estradiol (EE) concentrations, respectively, after 21 days of ENG/EE given as a vaginal ring (VR). Women receiving atazanavir/ritonavir (ATV/RTV)-containing ART had 71% higher ENG and 38% lower EE. These results are likely related to ART modulation of pathways responsible for hormone metabolism. We studied genetic associations with ART and hormone pharmacokinetics (PK) in A5316.
Methods: A5316 enrolled women living with HIV in Africa, Asia, South America and the US into one of three groups: controls (not on ART), EFV group (600mg daily with nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), and ATV/RTV group (300/100mg daily with NRTIs). On day 0, a VR was inserted, releasing ENG/EE 120/15 mcg/day. On days 0 (pre-VR) and 21 (during VR), intensive PK sampling for EFV, ATV and RTV was done. On days 7, 14 and 21, single plasma samples for ENG and EE analysis were obtained. We genotyped 27 single nucleotide polymorphisms (SNPs), including 3 that define CYP2B6 normal, intermediate and slow metabolizers, CYP3A4/5, UGT1A1 and CYP1A1/2 SNPs, and estrogen trait-associated SNPs.
Results: Of the 74 evaluable participants in A5316, 72 (97%) had both PK and SNP data (n=25 controls; n=24 EFV; n=23 ATV/RTV). Of these, 35 (49%) identified as Black, 26 (36%) as Hispanic, 8 (11%) as Asian/Pacific Islander and 3 (4%) as White, with 22 (31%) CYP2B6 normal, 32 (44%) intermediate and 18 (25%) slow metabolizers. On both days 0 and 21, CYP2B6 genotype predicted EFV PK (e.g., p=4.5E-5 for day 0 log10 EFV AUC0-8h). In the EFV group, CYP2B6 genotype predicted lower day 21 ENG (p=1.7E-3) and EE (p=6.7E-4) concentrations (Figure), which persisted after adjusting for weight and/or age. Compared to controls, EFV reduced median day 21 ENG concentrations by ~75% in CYP2B6 normal and intermediate metabolizers yet by at least 93% in slow metabolizers. EFV reduced median day 21 EE concentrations by 41% in CYP2B6 normal and intermediate metabolizers, but by 75% in slow metabolizers. No other SNPs were associated with hormone or ART PK after correcting for multiple testing.
Conclusion: CYP2B6 slow metabolizer genotype worsens the adverse PK interaction of EFV with ENG and EE administered by VR, likely due to enhanced

cytochrome P450 induction by higher EFV concentrations. Lower EFV dosing based on CYP2B6 genotype may reduce, but likely not eliminate, the impact of EFV on ENG and EE PK.

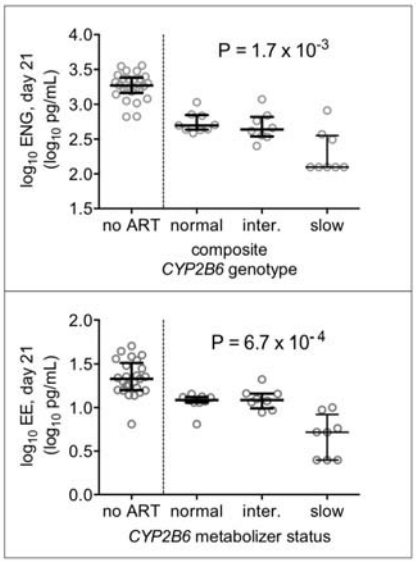

Figure: *CYP2B6* genotype and day 21 log_{10} ENG (top) and EE (bottom) concentrations in the EFV group. At left is the control group regardless of *CYP2B6* genotype. Error bars are medians and IQRs. Linear regression model P-values are shown.

53LB POINT-OF-CARE VIRAL LOAD TESTING IMPROVES HIV VIRAL SUPPRESSION AND RETENTION IN CARE

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Background: Achieving the 90-90-90 targets will require efficient methods to monitor people living with HIV (PLHIV) on antiretroviral therapy (ART) in resource-limited settings. We compared point-of-care (POC) viral load (VL) testing to standard laboratory VL testing for achieving VL suppression and retention in care for PLHIV in Durban, South Africa.

Methods: We conducted an open-label, randomized controlled trial among adults (≥18 years) enrolled 6 months after ART initiation at an urban public clinic. Participants were randomized to receive either POC VL testing (Xpert® HIV-1 VL, Cepheid) and same day counseling or standard-of-care (SOC) laboratory VL testing. All participants were followed for 12 months and received HIV care according to South African guidelines, including clinic visits every 2 months, VL testing at month 6 and 12 after ART initiation, and consideration for decentralized ART delivery at community pharmacies 1 year after ART initiation. The primary outcome was retained with VL suppression (<200 copies/mL) after 12 months, with retained defined as collecting ART at the study clinic between 44-56 weeks after enrollment. Those not retained were contacted for follow-up VL testing.

Results: Among 390 participants, mean age was 33 years, 235 (60%) were female, and median CD4 count at enrollment was 468 [IQR 309-666] cells/mm3. After 12 months, 175 (89.7%) participants in the POC arm and 148 (75.9%) in the SOC arm were retained with VL suppression, an increase of 13.9% (95% CI 6.4-21.2, p=0.0004) among participants who received POC VL testing compared to those who received laboratory VL testing (Table). When disaggregated, POC VL testing increased VL suppression by 10.3% from 83.1% to 93.3% (p=0.003) and increased retention by 7.7% from 84.6% to 92.3% (p=0.03). When restricted to those with a VL result at exit, the proportion with VL suppression increased by 5.3% from 91.0% to 96.3% (p=0.05) in the POC arm. During the study, 99.5% of POC arm participants received the VL result on the same day, while 74.7% of SOC participants received a VL result a median of 41 [IQR 28-69] days after blood draw. Participants in the POC arm had a 3.4-fold (95% CI 2.5-4.8) higher rate of entry into decentralized ART delivery.

Conclusion: POC VL testing significantly improved HIV viral suppression and retention in care in South Africa, partly by ensuring rapid receipt of VL results to PLHIV and their providers. Increasing access to POC VL testing could help to achieve the 90-90-90 targets.

Table. Composite primary outcome and secondary endpoints in the STREAM study.

	Standard-of-Care (SOC) arm	Point-of-care viral load (VL) testing (Intervention arm)	Absolute Risk Difference [a] (Intervention - SOC) [2-sided 95% CI]	p-value [b]
Primary outcome				
VL suppression <200 copies/mL and retention in care [c]	75.9% (148/195)	89.7% (175/195)	13.9% [6.4, 21.2]	0.0004
Secondary endpoints				
VL suppression <50 copies/mL and retention in care [c]	71.3% (139/195)	85.6% (167/195)	14.4% [6.2, 22.3]	0.001
VL suppression <200 copies/mL	83.1% (162/195)	93.3% (182/195)	10.3% [3.9, 16.8]	0.003
Retention in care [c]	84.6% (165/195)	92.3% (180/195)	7.7% [1.3, 14.2]	0.03
VL suppression <200 copies/mL, among those with a 12-month VL test result	91.0% (162/178)	96.3% (182/189)	5.3% [0.2, 10.7]	0.05
VL test result communicated to participant, among those with a mid-study blood draw	74.7% (127/170)	99.5% (191/192)	24.8% [18.4, 31.8]	<0.0001
Secondary endpoints as time to event	**Median days to event [IQR]**		**Cox Hazard Ratio [2-sided 95% CI]**	**p-value**
Appropriate switch to second-line ART following virologic failure	4/9 76 [20, 134]	6/7 0.5 [0, 7]	4.7 [1.3, 17.3]	0.02
First referral into the CCMDD decentralized ART delivery program [d]	52/195 261 [231, 281]	116/195 168 [168, 175]	3.4 [2.5, 4.8]	<0.0001

a. We used Newcombe-Wilson score to calculate 2-sided 95% confidence intervals.
b. We used Fisher's exact test to calculate 2-sided p-values.
c. Retention in care was defined as collecting ART from the study clinic or a community pharmacy at 44-56 weeks after enrollment.
d. The Central Chronic Medicine Dispensing and Distribution (CCMDD) program is a decentralized ART delivery at community pharmacies.

54LB EFFECT OF THE HITS INTERVENTION ON HIV TESTING UPTAKE AMONG MEN IN SOUTH AFRICA

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Background: The uptake of HIV testing and linkage to care remains low among men, contributing to continued high HIV incidence in women and HIV-related mortality in men in South Africa.

Methods: The "Home-Based Trial to Test and Start" (HITS) is a cluster-randomized controlled trial of 45 communities (clusters) in the Umkhanyakude district of KwaZulu-Natal (ClinicalTrials.gov # NCT03757104). It is based in the Africa Health Research Institute (AHRI)'s population-based HIV testing platform, which offers home-based rapid HIV testing to all adults. In a 2x2 factorial design, we randomly assigned all men aged ≥15 years living in the 45 clusters to one of four arms: (i) a financial micro-incentive for HIV testing (R50 [$3] food voucher) (n=8), (ii) male-targeted counseling (n=8), (iii) both the micro-incentive and male-targeted counseling (n=8), and (iv) standard of care (SoC). The male-targeted counseling application, called EPIC-HIV, was a tablet-delivered theoretically-informed application, developed iteratively, to encourage HIV testing and individually offered to men. Here we report the effect of the interventions on the first registered primary endpoint of the HITS trial: uptake of home-based HIV testing among men. Intention-to-treat (ITT) analysis was performed using modified Poisson regression with adjustment for clustering of standard errors at the cluster level.

Results: Among all men ≥15 years living in the 45 communities who were eligible for HIV testing based on registration in AHRI's population-based HIV testing in 2018 (n=13,838), HIV testing uptake was 28% (683/2481) in the micro-incentive arm, 17% (433/2534) in the EPIC arm, 27% (568/2120) in the arm receiving both interventions, and 18% in the SoC arm. The HIV testing uptake among those men who could be located and approached for testing was 68% (micro-incentive), 56% (EPIC-HIV), 70% (both interventions), and 52% (SoC). In ITT analysis, compared to men in the SoC arm, the probability of HIV testing was 55% higher in the micro-incentive only arm (risk ratio (RR)=1.55, 95% CI: 1.31-1.82, p<0.001) and 50% higher in the arm with both interventions (RR=1.50, 95% CI: 1.21-1.87, p<0.001). The probability of HIV testing was not

significantly different in the EPIC-HIV only arm (RR=0.96, 95% CI: 0.76-1.21, p=0.72).

Conclusion: Micro-incentives significantly increased the uptake of home-based HIV testing among men in rural South Africa and should thus be considered as a policy option where HIV testing rates are low.

55 MODULATION OF HOST INNATE IMMUNITY BY KSHV

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Host cells sense viral infection through pattern recognition receptors (PRRs), which detect pathogen-associated molecular patterns (PAMPs) and stimulate an innate immune response. PRR activation initiates signal transduction events that ultimately result in interferon and inflammatory responses. Human tumor viruses, including Kaposi sarcoma-associated herpesvirus (KSHV), are detected by several different PRRs. KSHV, also known as human herpesvirus (HHV8), is associated with three different cancers in the human population and evasion of host immunity is intimately linked to viral pathogenesis and oncogenesis. We will discuss host immune pathways that are activated upon KSHV infection and we will describe how KSHV viral genes engage a variety of mechanisms to evade the host innate immune response.

56 EBV: IMMUNOPATHOGENESIS AND THE PATH TO AN EBV VACCINE

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EBV is the principal cause of infectious mononucleosis and is associated with about 2,000 new cases of cancer worldwide each year, including epithelial cell malignancies such as gastric and nasopharyngeal carcinoma, and B cell lymphomas. EBV is associated with several malignancies in patients with HIV including Burkitt lymphoma, Hodgkin's lymphoma, diffuse large B cell lymphoma, primary CNS lymphoma, primary effusion lymphoma, plasmablastic lymphoma, and smooth muscle tumors. No vaccine has been licensed to prevent EBV infection or disease. We have developed two EBV self-assembling nanoparticle-based vaccines that present viral glycoproteins in a symmetrical array. The first contains a bacterial ferritin conjugated to a portion of EBV glycoprotein gp350, the major target for B cell neutralizing antibody in human plasma. The second nanoparticle vaccine consists of EBV gH/gL/gp42 which are viral glycoproteins important for fusion of the EBV envelope to host cell plasma membranes and entry of the virus into cells. Nanoparticles containing gp350 induced high titers of antibodies in mice and nonhuman primates that neutralized virus infection of B cells. Most of the antibody elicited in nonhuman primates targeted the host cell receptor (CD21) binding site on gp350. Nanoparticles containing gH/gL/gp42 induced potent neutralizing antibody in mice and nonhuman primates that inhibited infection of both B cells and epithelial cells. These antibodies also blocked EBV glycoprotein-mediated fusion of epithelial cells and B cells. These EBV vaccines are promising candidates to prevent EBV infection and/or disease.

57 HPV: NEW INSIGHTS INTO ONCOGENESIS AND OPPORTUNITIES FOR IMMUNE CONTROL

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A group of ~ 15 high risk human papillomaviruses (HPVs) cause nearly all cervical cancers and the majority of anal, vulvar, vaginal, penile, and oropharyngeal cancers. These cancers all express the two viral oncoproteins, E6 and E7. The E6 protein binds to the ubiquitin ligase E6AP, and targets the tumor suppressor p53, the proapoptotic Bak protein and a repressor of hTERT transcription for degradation. Through a C-terminal motif E6 binds various PDZ proteins that affect epithelial polarity. The E7 proteins bind and degrade pRb and p130, as well as histone remodeling and modifying enzymes, and CDK inhibitors. Together these activities promote genetic instability. We have been investigating additional mechanisms by which E6 and E7 cause genetic instability by impairing the response to DNA damage. Both oncogenes, but particularly E6, impair the Homology dependent repair pathway and the Fanconi Anemia/ BRCA pathway. Understanding the precise mechanisms provides new mechanisms for therapies to treat HPV associated cancers.

58 HBV: FROM VIRAL INTEGRATION TO LIVER CANCER, IMPACT ON CURE STRATEGIES

Fabien Zoulim, *INSERM, Strasbourg, France*

Chronic HBV infections represent a major public health problem as they are the main cause of hepatocellular carcinoma (HCC) worldwide. Viral suppression is achieved in the majority of treated patients with current antiviral approaches and is associated with a decreased risk of disease progression towards cirrhosis and HCC. However, the later risk is not eliminated. The development of HBV-induced HCC relies on multiple mechanism: i) random integration of HBV genome into host chromosomes leading to insertional mutagenesis, ii) expression of viral proteins interfering with cellular gene expression and signaling pathways, or to chronic oxidative stress, iii) chronic liver inflammation, iv) hepatocyte death and regeneration, that may lead to clonal expansion and selection of transformed hepatocytes. Deep sequencing of HBV associated tumors have shown telomer shortening, mutations in TERT promoter and TP53. It was shown in hepatocyte culture that viral genome integration can occur very early after infection. In patients, in the so called "immune tolerance" phase, major integration events occur and are associated with clonal expansion of hepatocytes. This suggests that molecular damage of the host genome occurs even in this phase that is generally recognized as clinically benign, and that hepatocyte death and turn over occurs leading to clonal expansion. This is a strong argument for early treatment intervention to prevent integration events. Integration has also other impact on the novel cure strategies. HBsAg loss is used as a clinical endpoint of functional cure. Recent studies showed that the expression of HBsAg is mainly driven by cccDNA in HBeAg(+) patients, but mainly by integrated viral sequences in HBeAg(-) patients. Thus, this endpoint might be more difficult to reach in patients where HBsAg is mainly expressed from integrated sequences. It was also shown, that siRNA approaches targeting the extreme 3'end of the viral transcripts may be limited by truncation of these RNAs resulting from viral genome rearrangements during the integration process. It will be also important to understand the impact of integration on circulating viral RNAs, a newly described biomarker of HBV infection, that could serve to track the pool of cccDNA and/or of integration events. In conclusion, HBV integration is a molecular event involved in liver oncogenesis which may have an impact on the development of novel cure strategies and monitoring of patients.

59 UPDATE ON ANTIRETROVIRAL DRUGS AND BIRTH DEFECTS

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While there are >30 antiretroviral (ARV) drugs approved for HIV therapy, there are only limited data on ARVs in pregnancy. The mean lag time from ARV approval to data availability in pregnancy is 5 years; most ARVs receive regulatory approval with only animal data to evaluate potential fetal effects. For low incidence outcomes such as birth defects, data are often only collected post-approval. To determine if a birth defect is associated with a drug or simply reflects the baseline population rate of a defect, the number of required exposures will vary based on the defect population prevalence. To rule-out >2-fold increased risk in overall defects, with 3% population prevalence, 200 early pregnancy exposures are needed, but to rule out >3-fold increased risk in a rare defect like neural tube defects (NTD), with 0.1% population prevalence, 2000 early exposures are needed. Exposure timing is critical, as teratogenic risk is highest very early in pregnancy, before most women recognize they are pregnant, but most reports do not distinguish pre-conception from first-trimester exposure. Post-pregnancy defect reports to pharmacovigilance databases have limitations including reporting bias, case duplication, and lack of denominators. Prospective reports during pregnancy, with follow-up for birth outcome, such as the Antiretroviral Pregnancy Registry, has fewer biases. In 1998, efavirenz (EFV) was approved with a warning on use in pregnancy due to animal data showing central nervous system defects with in utero exposure in primates. Retrospective reports of NTDs in humans increased concern, leading to FDA classification of "positive fetal risk" in 2005; collection of prospective cases over the subsequent 13 years has now shown no increased NTD risk. In contrast, with dolutegravir (DTG), animal data did not raise concerns, but a well-designed prospective active surveillance study in Botswana detected a potential signal of concern for NTD with preconception DTG exposure. In contrast to the delay experienced with EFV, due to active surveillance, significant numbers of already-exposed pregnancies will be collected prospectively over the next 12 months, and with coordinated global efforts to combine additional exposures with denominator data, this signal should be able to be confirmed or refuted within a year. Continuing prospective active birth outcome surveillance is required as new ARVs are introduced into populations including women of childbearing potential.

60 ART OPTIONS AND TREATMENT DECISIONS FOR WOMEN OF REPRODUCTIVE POTENTIAL

Monica Gandhi, *University of California San Francisco, San Francisco, CA, USA*

In light of recent data on the safety of antiretrovirals in pregnancy, a review of what is known and what is not known about ART options and treatment decisions for women of reproductive potential will be undertaken. This talk will summarize guidelines for the use of ART for women of childbearing potential desiring pregnancy and during pregnancy and the data (or lack of data) behind these recommendations. Pharmacokinetic, safety, tolerability, and efficacy considerations for various ART regimens during pregnancy will be covered. The importance of involving women in decision-making around treatment options pre-conception and during pregnancy will be emphasized. Moreover, the talk will touch upon ART considerations for women of reproductive potential not desiring pregnancy and on contraception. The talk will conclude with recommendations to researchers and policy-makers on how to increase the participation of women of child-bearing potential and pregnant women in clinical trials and observational cohorts.

61 POLICY AND PROGRAM DECISIONS FOR ART IN WOMEN OF REPRODUCTIVE POTENTIAL

Irene Mukui, *Ministry of Health, Nairobi, Kenya*

Women represent 51% of persons living with HIV globally. In sub-Saharan Africa, women account for close to 60% of HIV-infected persons, a large proportion of whom are in their reproductive years. Women living with HIV have changing fertility desires and reproductive health needs and frequently become pregnant particularly with increasing access to antiretroviral therapy (ART). Making programmatic, public health, and clinical management decisions for HIV infected women requires consideration of factors that influence women, maternal and fetal health safety. HIV care and treatment programs are uniquely placed to address child bearing desires of women, provide an opportunity to prevent unwanted pregnancies by availing effective contraception, make choices for use of antiretroviral agents that minimize risk of maternal transmission of HIV, and provide optimal maternal outcomes and have minimal or no potential fetal teratogenic effects. This presentation will provide insight into public health and programmatic considerations that middle and lower income countries that manage large HIV treatment programs have to make while developing policy guidance for ART use among women of reproductive potential. These considerations include safety and efficacy of ARV agents, availability of and access to comprehensive reproductive and family planning services, the need for understanding of women's fertility desires and reproductive health choices and the balance between individualized care versus a public health approach to program implementation. Recent safety concerns on use of dolutegravir (DTG) suggesting possible increased risk of neural tube defects in infants born to women who were taking DTG at the time of conception have brought into sharp focus and reinvigorated the discussion on the need for safety data among women of reproductive potential. In addition, many large public health programs are now faced with the realities of individualized care and choice versus public policy directives, which can present significant implementation challenges based on how sophisticated health systems are. The talk will include case studies from middle and lower income countries' adaptation of DTG following the release of the WHO interim guidance recommending use of DTG based regimes as preferred first-line with caution on DTG use at periconception period . The presentation will also explore the involvement and role of women in policy decision making and lessons learnt.

62 CHALLENGES IN ANTIRETROVIRAL RESEARCH IN WOMEN OF REPRODUCTIVE POTENTIAL

Anne D. Lyerly, *University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

The HIV research agenda has historically been characterized as having a "vessels and vectors" orientation toward woman – in other words, when included in research, women have been studied primarily in terms of their capacity to infect partners and fetuses. While progress has been made, significant evidence gaps remain due to under-representation of women, including women who become pregnant while on ARVs (and their interests) in the HIV research agenda. These evidence gaps lead to uncertainty about safety and dosing of drugs in women of reproductive potential, suboptimal or adverse outcomes for women and offspring, as well as issues of access to effective treatments and preventives. Advancing the evidence base will require addressing a range of ethical, legal and cultural challenges around research with women of childbearing potential. This presentation will highlight the importance of and ethics around conducting such research, and attend to four (of several) pressing challenges facing researchers designing research with women of childbearing potential, including: 1) assessing and managing risks and benefits to a fetus that does not yet and may never exist; 2) deciding when it is appropriate to require and/or offer access to contraception; 3) managing unexpected (or incident) pregnancies, including decisions about data collection and continuation of study drug; and 4) appropriate communication of study results, including development of guidance that is responsive to the interests and priorities of those most affected. Finally, current or evolving international consensus recommendations regarding these specific challenges will be described.

63 CHASING THE DRAGON: OPIATES AND HIV

Ricky N. Bluthenthal, *University of Southern California, Los Angeles, CA, USA*

The opioid crisis is the first truly national drug epidemic in US history. Unlike prior drug use epidemics, the opioid crisis has reached all groups regardless of demographic characteristics, economic status, or geography. HIV-related consequences of the opioid crisis include increased injection drug use (still a key risk factor for HIV transmission), increased mixing of drug using subgroups (e.g., opioid and methamphetamine use), and HIV outbreaks in remote and poorly served locales (e.g., Scott County, Indiana). In addition, increases in acute HCV are also likely to lead to elevated susceptibility to HIV transmission among people who inject drugs. Research aimed at identifying "hot spot" for HIV outbreaks and consideration of policy responses for addressing the multiple consequences of the opioid crisis on HIV epidemiology, prevention, and care will be presented.

64 CHEMSEX AND IMPLICATIONS FOR HIV TRANSMISSION AND MANAGEMENT

Mark R. Pakianathan, *St. George's University of London, London, UK*

Chemsex refers to the use of psychoactive substances in sexual settings by gay, bisexual, and other men who have sex with men (GBMSM). Chemsex is a socially constructed phenomenon and as such there is no specific case definition for it and substances used and social contexts vary between countries. Chemsex is often facilitated by smartphone geospatial networking applications and the substances linked to chemsex include methamphetamine, GHB/GBL (Gamma hydroxybutyrate/Gamma butyrolactone), mephedrone, other cathinones, cocaine, ketamine, and other amphetamines. The presentation will review published data on chemsex across the globe. In particular it will explore its relationships with STIs, shigellosis, hepatitis C and HIV. Additionally it will explore implications for PrEP use in this population. Potential drug-drug interactions between the psychoactive substances and antiretrovirals will be explored and data on antiretroviral adherence in HIV-positive men disclosing chemsex will also be presented. Finally there will be practical suggestions for clinicians on effective clinical communication around chemsex and how to address harm minimization. Implications for health policy and research gaps will also be highlighted.

65 HIDDEN IN PLAIN SIGHT: THE ALCOHOL EPIDEMIC

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Alcohol is widely used for pleasure by many cultures throughout the world except in Muslim-majority countries. Although it has also been credited with having some protective effect for some health outcomes, its abuse is highly problematic as it causes a large social and economic burden, both to individuals who consume it and other people close to them such as family members, friends, co-workers and strangers. Most importantly, causal relationships have now been established between harmful alcohol drinking and the risk of HIV acquisition. Alcohol abuse also has some impact on the engagement in care and adherence with antiretroviral therapy among people living with HIV. This presentation will present an update on the global epidemic of alcohol especially harmful drinking, followed by the global epidemic of HIV, and then a brief discussion of how the two epidemics converge with each other especially in sub-Saharan Africa. It will then posit about the mechanisms that explain the link between alcohol and HIV/AIDS as well as provide some relevant research evidence in support thereof. Finally, the implications of convergence of the two epidemics for both policies and intervention programmes will be presented.

66 TOBACCO SMOKING: THE SILENT KILLER

Lene Ryom, *Centre of Excellence for Health, Immunity and Infections, Copenhagen, Denmark*

The smoking epidemic in people living with HIV (PLWHV) differs significantly from that in the HIV-negative general population (GP). Firstly, smoking rates in PLWHV are disproportionally high (2-3 times higher than in the GP) with a roughly even distribution of smoking men and women. Smoking further impacts the health of PLWHV much more severely than that of the GP. As such, the excess risk of mortality in smoking PLWHV is three times higher compared to the GP with up to twelve life years lost due to smoking. Tobacco smoke contains several thousand substances of which multiple are considered poisonous or carcinogenic. Nicotine may enhance viral replication and several studies suggest a lower proportion of smoking PLWHV are virally suppressed. Smoking also changes the innate and adaptive immune response by causing inflammation and immune suppression- effects similar to that of HIV itself causing a state of double trouble for smoking PLWHV. Smoking further increases risks of several AIDS-defining conditions including esophageal candidiasis and tuberculosis, thereby directly counteracting the effects of antiretroviral treatment. For non-AIDS conditions the risk of bacterial pneumonia is 73% higher among smoking PLWHV compared to never-smokers. An estimated 70% of all myocardial infarctions in PLWHV are attributed to smoking, making smoking a more important individual risk factor than hypertension and HIV itself. In NA-ACCORD almost 20% of all cancers and over 90% of lung cancers were directly attributed to smoking. While smoking cessation in PLWHV may already after one-year lower risks of cardiovascular events, lung cancer risks remain elevated even several years after cessation in the DAD study. PLWHV are almost 20% less likely to quit smoking than the GP, possibly related to greater sociodemographic challenges. HIV guidelines recommend regular assessment of smoking status and motivation to quit, followed by cessation advice and combined behavioral counselling and pharmaceutical substitution therapy. As smoking is a leading cause of preventable morbidity and mortality in PLWHV it is imperative to design studies to clarify the complex needs of different groups of smoking PLWHV. Such studies should address effectiveness of different smoking cessation interventions and safety profiles of pharmaceutical substitutions. Smoking cessation should further become a top priority in the clinical management of PLWHV to break the silence of the killing smoke.

67 RAISING THE WALL IN MATERNAL/FETAL IMMUNITY

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Despite the highly-successful use of antiretroviral (ART)-based prevention for reduction of mother to child transmission (MTCT), as of 2017, 180,000 children continue to become infected with HIV-1 annually. Moreover, the fetal toxicities and prematurity associated with combination ART use in pregnancy are continuing to come to light. Pregnancy and the postpartum period are high risk for acute HIV acquisition, which translates into to high risk for HIV transmission to the developing fetus and breastfeeding infant. HIV variants transmitted perinatally have been demonstrated to be resistant to neutralization by concurrently circulating maternal antibodies, Thus, strategies that could synergize with ART to further reduce HIV MTCT during pregnancy may include temporary enhancement of autologous virus neutralization and targeted induction of functional antibodies that efficiently cross the placental barrier, which may be achievable with currently available HIV-1 vaccines. Furthermore, the pediatric HIV epidemic is bi-modal, with a peak in the neonatal period and a renewed high-risk period in adolescence following sexual debut. Therefore, vaccines that will eliminate the HIV epidemic will require administration during childhood. The early life immune system represents a unique immune landscape that could potentially be harnessed for qualities that are needed for the elicitation of protective immunity. In fact, recent reports have demonstrated that HIV-infected children develop broadly-neutralizing antibodies at a higher frequency and faster pace than that of HIV-infected adults. Intriguingly, the broadly-neutralizing antibodies identified in HIV-infected children have lower levels of somatic mutation than that of adults. Moreover, immunization strategies that aim for long-term development of protective immunity are well-suited for integration with the pediatric vaccine schedule, while immediate protection in the breastfeeding period can be achieved through concurrent passive administration of a potent broadly-neutralizing antibody. Therefore, enhancing and leveraging maternal and infant HIV immunity through novel passive and active immunization strategies provide renewed hope for ending the HIV-1 epidemic at the earliest stages of life.

68 HUGGING PHYLOGENETIC TREES: USE OF MOLECULAR ANALYSIS FOR PUBLIC HEALTH INTERVENTION

Alexandra M. Oster, *CDC, Atlanta, GA, USA*

New tools have made it possible to identify clusters of ongoing HIV transmission through the analysis of HIV molecular data. Although analysis of molecular data to understand transmission clusters has become more widespread in recent years, such analysis has typically been retrospective. Now, public health agencies are beginning to use data routinely collected through surveillance to prospectively identify clusters for public health response aimed at strengthening prevention efforts and ensuring that people with and at risk for HIV have access to the services they need. Cluster detection efforts can be used to prompt public health action, but this work must be done in a way that maximizes benefit and minimizes potential harms. This presentation will describe this new strategy and the promise it holds for HIV prevention.

69 A VIRUS-PACKAGEABLE CRISPR SCREEN IDENTIFIES HIV RESTRICTION AND DEPENDENCY FACTORS

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Background: HIV relies on host-encoded factors to complete its life cycle inside the host cell but also must evade recognition by host-encoded factors that have evolved to defend cells against viral invasion. We developed a powerful screening technology to identify HIV restriction and dependency factors in a system that is flexible to cell type and HIV strains.
Methods: HIV-CRISPR screening is a novel CRISPR/Cas9-mediated functional screening method to find HIV restriction factors. The HIV-CRISPR approach takes advantage of the packaging system of HIV to rescue HIV-CRISPR vectors encoding Cas9 and single-guideRNAs (sgRNAs) from cells. sgRNA-encoding HIV-CRISPR genomes are packaged in trans into budding HIV-1 particles. Release of HIV-CRISPR genomes into the supernatant is dependent on the extent of HIV replication within each cell in the population, thus revealing genes that restrict HIV replication within cells. We assembled an sgRNA library specific for Interferon Stimulated Genes (ISGs) into HIV-CRISPR to create PIKAHIV, the HIV-Packageable ISG Knockout Assembly. We then screened PIKAHIV-transduced THP-1 cells to find HIV-1 restriction and dependency factors.
Results: We find that the antiviral effects of a small panel of genes, including MxB, IFITM1, Tetherin and TRIM5, together account for the 8-fold inhibition of HIV-1LAI replication by IFN in THP-1 cells. Many, but not all of these same factors were identified in a parallel screen with an R5-tropic, clade A primary isolate. However, Tetherin does restrict the primary isolate, suggesting that Vpu-mediated antagonism of Tetherin varies significantly across viral strains. Further we find that potent IFITM-mediated inhibition of VSV-G pseudotyped HIV-1 is a major block to infection and masks the effects of other antiviral effectors. We also identify novel factors, including SEC62 and TLR2/MYD88, to be important dependency factors for replication for both viruses. Screens with viral mutants reveal additional restriction factors that may be masked by binding of host cell factors to wildtype HIV.
Conclusion: Highlighting the strength of the HIV-CRISPR approach, we have identified in one screen in one cell type with one virus, many key players in genetic resistance to HIV including TRIM5, Tetherin, IFITM, and MxB. The ability of IFN-induced restriction factors to inhibit HIV replication in human cells suggests that these human restriction factors are incompletely antagonized and that this antagonism varies from virus to virus.

70 A FUNCTIONAL MAP OF HIV-HOST INTERACTIONS IN PRIMARY HUMAN CD4+ T CELLS

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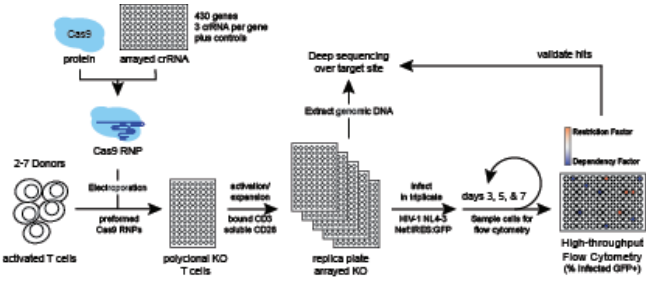
Background: The limited coding capacity of the HIV genome necessitates a heavy reliance on the host molecular architecture for optimal replication. Attempts to biochemically identify host factors that physically interact with HIV proteins have yielded hundreds of candidates, but it is unknown which

of these are essential for virus replication. Here, we report a proteomics-to-genetics approach to assess the functional roles of HIV-human protein-protein interactions in primary CD4+ T cells.
Methods: Leveraging a high-throughput CRISPR-Cas9 platform for primary T cell genome engineering, we targeted 435 host factors previously identified to physically interact with HIV proteins for knock-out in CD4+ T cells from multiple donors. Each population was subject to deep sequencing to quantify editing efficiency and concurrently challenged with replication-competent HIV-1 to assess the impact on HIV infection.
Results: Using this platform, we achieved robust editing efficiencies with high donor-to-donor concordance, averaging 75% allelic knock-out at the population level. The repair outcomes at each edited site demonstrated remarkable predictability based on the target site sequence and surrounding chromatin structure. Of the 435 targeted genes, we identified 86 HIV host factors, 47 of which have not been previously reported. While most host factors were conserved between donors, several displayed notable donor variation. These factors were temporally separated into early and late-acting genes and physically segregated by HIV interacting protein, greatly facilitating and expediting functional analyses. Mechanistic interrogation revealed critical roles for these new HIV host factors in viral entry, transcription, budding, and maturation.
Conclusion: These findings reveal several new host factors underlying HIV replication in primary CD4+ T cells and model an interdisciplinary approach to systems biology as a means to streamline experimental discovery. Donor-to-donor and cell type-to-cell type variations in host factor dependency suggest the virus employs substantial functional plasticity to achieve robust infection, complicating host-based therapeutic strategies. The continued extension of this technology to resting memory T cells and for the targeted insertion of single nucleotide variants will ultimately unveil new insight into the host determinants underlying HIV replication, latency, and pathogenesis.



71 HIV-1 COMPLEXES TRAFFIC WITH HOST CPSF6 ON MICROTUBULES PRIOR TO NUCLEAR ENTRY

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Background: HIV-1 DNA nuclear entry is required for infection and is mediated by viral capsid. The host protein CPSF6 has been shown to bind HIV-1 capsid, to facilitate nuclear import of viral pre-integration complexes, and to mediate integration of viral DNA into actively transcribed genes. While CPSF6 has predominantly nuclear expression as a result of binding to host transportin TNPO3 via its RS domain, a small fraction of CPSF6 is localized outside of the nucleus, leading us to study its interaction with HIV-1 in the cytoplasm.
Methods: In this study, we conducted high speed live-cell confocal imaging to investigate intracellular trafficking of WT or mutant HIV-1 containing functional, fluorescently tagged integrase (IN). Infection was performed in cells with fluorescently labeled microtubules, TNPO3, and full-length or mutant CPSF6. In addition, HIV-1 capsid uncoating kinetics were measured in infected cells using an imaging-based assay.
Results: CPSF6 was expressed as puncta in the perinuclear region of the cytoplasm, which trafficked on microtubules with TNPO3. Upon infection, WT HIV-1 complexes associated with perinuclear CPSF6 and TNPO3, trafficking together on microtubules. However, a mutation in capsid that abolishes binding to CPSF6, N74D, rendered the virus unable to associate with cytoplasmic CPSF6. Disruption of microtubule polymerization resulted in diminished virus and CPSF6 movement. Truncation or mutation of the RS domain of CPSF6 led to reduced binding to TNPO3 and increased cytoplasmic expression at the cell periphery, resulting in restriction of HIV-1 infection. This CPSF6 mislocalization resulted in the formation of higher-order complexes around HIV-1 IN-containing complexes, premature capsid uncoating, and altered microtubule trafficking of IN complexes after infection with WT HIV-1 but not N74D HIV-1. In addition, CRISPR-mediated knockout of the CPSF6 gene in cells altered microtubule-mediated trafficking towards the nucleus of WT HIV-1 but not the capsid mutant.
Conclusion: These data suggest that after WT HIV-1 entry into the cell, viral complexes interact with CPSF6 and TNPO3 on microtubules near the nucleus, which is required for efficient capsid uncoating and nuclear entry of pre-integration complexes.

72 HIV-1 CAPSID DETERMINANTS THAT INFLUENCE NUCLEAR ENVELOPE DOCKING AND NUCLEAR IMPORT

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Background: An essential step of HIV-1 infection is to transfer the replication complex into the nucleus. An HIV-1 intact viral core is approximately 61-nm wide must get translocated through 39-nm-diameter nuclear pores, suggesting that the viral core undergoes uncoating and/or conformational changes before entering the nucleus. While HIV-1 capsid (CA) protein plays a critical role in nuclear import, the CA determinants that influence nuclear envelope (NE) docking and viral complex translocation through the nuclear pore have not been defined. To study these events, we developed a quantitative imaging assay for association of single viral complexes with the NE and for their nuclear import. Using this system, we evaluated several CA mutants in which core surface-associated amino acids were substituted and determined their ability to dock at the NE and/or enter the nucleus.
Methods: HIV-1 CA mutants, including hyperstable (E45A) and hypostable (P38A) mutants, were generated in envelope-deficient genomes. VSV-G pseudotyped virions were produced and used to determine their infectivity in HeLa, CEM-SS, and MT4 cells. For imaging assays, HIV-1 virions were labeled with HIV-1 integrase-superfolder green fluorescent protein (sfGFP) and used to study NE docking and nuclear import in both fixed-cell and live-cell assays. A high-throughput live-cell imaging assay was developed to study NE-docking and residence time of CA mutants. HIV-1 CA amounts were determined using a quantitative immunostaining assay.
Results: We identified CA mutants that exhibited a longer NE residence time compared to wild-type viral complexes, indicating that these CA determinants can influence the kinetics of association of viral complexes with the nuclear pore. These CA mutants did not show infectivity defects in Hela cells, but were defective in T cell lines (CEM-SS and MT4 cells). Interestingly, viral complexes of these mutants docked at the NE exhibited lower CA signals in immunofluorescence assays, suggesting alterations in the viral core structures. Live-cell imaging experiments are being performed to determine whether the CA mutants increased the NE residence time of those viral complexes that enter the nucleus.
Conclusion: We have identified CA mutants that exhibit long NE residence times, indicating defects in NE association, a phenotype which has not been previously reported. Further characterization of these CA mutants may provide valuable insights into the essential steps of NE docking.

73 SINGLE HIV-1 VIRUS IMAGING WITH CA-EGFP QUESTIONS A ROLE OF NUCLEAR CA IN INTEGRATION

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Background: The role of HIV-1 capsid protein (CA) in early HIV replication is known to extend beyond uncoating. Still, a consensus model on the relationship between HIV-1 uncoating, nuclear import and integration is lacking, mostly due to conflicting results on intracellular capsid distribution. Resolving the dynamics of capsid uncoating thus necessitates a robust method of imaging functional viruses containing labeled CA.

Methods: We fluorescently labeled CA and evaluated replication of the resulting labeled viruses. We generated dually labeled VSV-G pseudotyped particles containing eGFP-tagged CA (CA-eGFP) and mCherry-tagged, Vpr-transincorporated integrase (IN-mCherry). Since CA-eGFP by itself did not allow viral particle release, we co-transfected plasmids coding for CA-eGFP with a WT CA plasmid at a 1:10 ratio during virus production. At discrete time points after infection, we analyzed the cellular localization of both CA-eGFP and IN-mCherry by confocal microscopy in the absence and the presence of inhibitors of the early HIV replication steps.
Results: We investigated the cellular distribution and intensity of fluorescent, CA and IN in HeLa P4 cells. CA and IN colocalized in 20-30% of all cytosolic complexes. Importantly, the intracellular distribution and fluorescence intensity of IN-mCherry complexes were unaffected by CA-eGFP labeling. CA-eGFP complexes accumulated in the perinuclear area, but only 10-15% of these also contained IN-mCherry. Using both CA-eGFP and immunocytochemistry, we confirmed the presence of CA in the nucleus, which rarely (<5%) colocalized with IN-mCherry. Under PF74 treatment, the number of nuclear complexes containing labeled IN decreased 15-fold while CA-eGFP decreased 5-fold, consistent with a PF74-mediated nuclear import block. The inhibition of CA-eGFP labeled viruses with PF74 suggests that at least some of the dually labeled particles undergo bona fide uncoating and nuclear import. When using Ral to block integration, we observe a 25% accumulation of fluorescent IN, but not CA-containing complexes in the nucleus. These data question the role of nuclear CA in integration and urge investigation of other nuclear roles of this protein.
Conclusion: Directly labeled CA allows single virus imaging of HIV-1 pre-integration steps and provides insights in the cytosolic and nuclear distribution of CA. Therefore, virions carrying labeled IN and CA represent a suitable system to address HIV-1 entry following both the viral PIC and the fate of the associated capsid.

74 DISRUPTION OF HIV-1 LTR SEQUENCE BY A NUCLEOCAPSID MUTATION LEADS TO DTG RESISTANCE

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Background: Dolutegravir (DTG), a key component of ART, tightly binds to the catalytic site of integrase (IN) and to the canonical '-CA_{OH}' dinucleotide sequence of the LTR at the viral DNA (vDNA) ends. Resistance to DTG is poorly understood.
Methods: DTG-resistant viruses were selected using in vitro serial passage experiments under DTG pressure. We monitored the viral dynamics of early steps of HIV-1 replication using multiplex immunofluorescent cell-based detection of viral DNA, RNA and protein (MICDDRP) and qPCR. To elucidate the resistance mechanism, we used next-generation sequencing and analyzed the sequence of the LTR termini of HIV-1 that is integrated into host DNA.
Results: Through in vitro passage experiments we discovered that a mutation at the zinc-fingers of HIV nucleocapsid (HIV_{NC}) enhances DTG resistance ~4-fold, by itself, or ~7-fold in the presence of an E157Q polymorphism in the IN region ($HIV_{NC/IN}$). We demonstrate that in the absence of DTG, both HIV_{NC} and $HIV_{NC/IN}$ replicate more slowly than wild-type HIV-1 (HIV_{WT}) without reducing integrated vDNA. MICDDRP and qPCR revealed that HIV_{NC} and $HIV_{NC/IN}$ significantly increase the amount of vDNA during reverse transcription and subsequently integrated them into host genome even at 8h post-infection. Analysis of the virus termini sequences after integration revealed that amount of «normal» '-CA_{OH}' dinucleotide sequences at the LTR ends was significantly affected: whereas '-CA_{OH}' was present in HIV_{WT} at 99% and 98% of the 5'- and 3'-LTRs, it was found in 97% and 43% for those of HIV_{NC}, and 79% and 46% for those of $HIV_{NC/IN}$. Notably, the virus termini sequences formed by HIV_{NC} or $HIV_{NC/IN}$ contained more frequent insertions, deletions, and abnormal LTR ends, which are the substrates of IN and part of the DTG binding site.
Conclusion: We report an example of a remarkable epistatic drug resistance mechanism, whereby a mutation in the NC viral gene affects the function of 3 viral proteins, (NC, RT, and IN) resulting in resistance to DTG. We propose that NC changes to affect vDNA formation, which in turn affects the selectivity of DTG binding and its exclusion from the active sites of HIV_{NC} and $HIV_{NC/IN}$. DTG resistance is further enhanced by an IN polymorphism, thus highlighting an important role of polymorphisms in IN drug resistance and therapies.

75 INTEGRASE (IN) TETRAMERS ARE THE AUTHENTIC TARGETS FOR ALLOSTERIC HIV-1 IN INHIBITORS

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Background: Allosteric HIV-1 integrase (IN) inhibitors (ALLINIs) are a new, promising class of antiretroviral agents that disrupt the proper viral maturation by inducing hyper-multimerization of IN and consequently inhibiting its binding to the viral RNA genome. Previous biochemical and crystallographic studies have emphasized the importance of IN catalytic core domain and C-terminal domain for ALLINI induced hyper-multimerization of the protein. Here, we have elucidated a crucial role of the N-terminal domain (NTD) for the ALLINI activity. Specifically, we show the importance of NTD mediated tetramerization of IN for the inhibitor induced hyper-multimerization of the protein.
Methods: The separation of different oligomeric states (tetramers, dimers and monomers) of WT IN allowed us to delineate striking selectivity of ALLINI for IN tetramers versus the lower order oligomers. In addition, trans-complementation assays, which allowed us to reconstitute IN tetramers using two dimeric IN mutants, further confirmed the selectivity of ALLINIs for IN tetramers. Based on these findings we have created molecular models of ALLINI mediated tetramer-tetramer interactions.
Results: Consistent with the experimental results, the docking scores and free energy calculations indicate that tetramers are preferred over dimers for the formation of ALLINI induced IN polymers. Interestingly, our lead pyridine-based ALLINI KF116 exhibited ~10-fold higher activity (EC50~0.7 nM) against a clinically relevant Dolutegravir (DTG) resistant mutant HIV-1NL4-3(IN N155H/K156N/K211R/E212T) virus compared with its wild type counterpart. Complementary in vitro experiments with recombinant WT and mutant INs revealed that WT IN was a mixture of tetramers, dimers and monomers; whereas under identical conditions the DTG resistant IN (N155H/K156N/K211R/E212T) predominantly formed tetramers.
Conclusion: These observations indicate that ALLINI KF116 is highly complementary to DTG and raise possibilities for the synergetic combination of ALLINIs and INSTIs to further increase the genetic barrier to resistance by limiting HIV-1 options for drug resistant substitutions. Taken together, our biochemical findings coupled with virology experiments show that ALLINIs are highly active during virion maturation and suggests that IN tetramers are formed in virions that are selectively targeted by ALLINIs.

76LB TARGETING VIRUS ENV AND CD44 IMPROVES bNAb AVIDITY AND NEUTRALIZATION POTENCY

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Background: Broadly neutralizing antibodies (bnAbs) hold great promise for the prevention and treatment of HIV infection, but this virus has evolved elaborate ways to evade effective neutralizing antibodies. One of these is the evasion of antibody avidity: Low Env density with spike distances surpassing the average "wingspan" of an IgG impedes inter-spike crosslinking and Env structural constraints hamper intra-spike crosslinking; these limitations of bivalent binding may restrain bnAb potency. Here we hypothesized that bnAb neutralizing activity could be increased through a strategy that overcomes the evasion of Ab avidity by using bispecific Abs (BiAbs) targeting both Env and a host molecule known to be present on the viral surface, CD44.
Methods: BiAbs were engineered using the CrossMAb Technology. Neutralizing activity was assessed using the Tzm-bl assay for infectious viruses, including the deCamp global panel.
Results: We engineered a prototype BiAb that combines the bnAb PGDM1400 (anti-V2 apex) with the anti-CD44 Ab RG7356 and assessed its neutralizing activity against diverse HIV-1 strains, including primary isolates and the deCamp global panel. As expected, RG7356 had no neutralizing activity. PGDM1400/

RG7356 neutralized more potently than the parental bnAb, PGDM1400, for 14/16 of HIV-1 strains tested. The mean level of neutralization enhancement (defined as IC_{50} ratio of parental and bispecific Ab) was 8.6 (range 0.6 to 75.5). Mechanistically, the potency enhancement occurred irrespective of target cell CD44 expression but was critically dependent on presence of CD44 on the virion surface. Similar enhancement of virus neutralization was observed when PGDM1400 was replaced by other bnAbs (e.g., 10-074 and N6).
Conclusion: Our data provide strong evidence that bnAbs neutralize most HIV-1 strains through predominantly monovalent binding and increasing avidity via binding to a host protein on the virion surface could substantially enhance virus neutralization.

77 IPT AND PREGNANCY OUTCOMES IN HIV-POSITIVE WOMEN: THE TSHEPISO COHORT

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Background: Pregnancy and HIV both increase the risk of tuberculosis (TB) disease which results in poor maternal and infant outcomes. IMPAACT study P1078 found that isoniazid preventive therapy (IPT) during pregnancy resulted in a higher risk of adverse maternal and neonatal outcomes compared to IPT post-delivery, questioning the safety of IPT in pregnant women living with HIV (PWLHIV).
Methods: Tshepiso was a prospective cohort study evaluating maternal and infant outcomes among PWLHIV with and without active TB disease from January 2011 through January 2014 in Soweto, South Africa. Mother-infant pairs were followed through one year of life. Here we report the outcomes among PWLHIV without TB disease who reported initiating vs not initiating IPT during pregnancy. This was an observational study; IPT was initiated by public antenatal and HIV clinics and not by the study.
Results: The Tshepiso study enrolled 155 PWLHIV without TB disease. This analysis includes 151 women with known pregnancy outcomes; 69 (46%) reported initiating IPT during pregnancy. The median age and CD4 T-cell count at enrollment was 30 years (IQR 27,31) and 364 cells/mm3 (IQR 252,464) for women on IPT vs 29 years (IQR 26,32) and 372 cells/mm3 (IQR 275,477) for women not on IPT. 63 (78%) and 43 (65%) women were on cART, 52 (83%) and 37 (86%) with EFV, respectively. Viral load during pregnancy was <400copies/mL in 60 (75%) women on IPT and 35 (52%) women not on IPT (p=0.004). The proportion of neonates born prematurely was lower in those exposed to IPT during pregnancy compared to unexposed (10% vs 22%; p=0.06). There was no difference in fetal demise (1% vs 1%; p=1.0), low birth weight (9% vs 12%; p=0.51), or congenital anomalies (1% vs 2%; p=1.0). A composite of the four outcomes (16% vs 28%; p=0.08) showed fewer events among infants exposed to IPT. Stratified analyses by viral load suppression did not demonstrate differences in pregnancy outcomes.
Conclusion: In this study, IPT use during pregnancy was not associated with a higher rate of poor maternal or infant outcomes. Though this study had well characterized exposures and outcomes, it was not designed to study the effect of IPT on pregnancy outcomes. IPT exposed and non-exposed PWLHIV may differ in factors associated with adverse outcomes in PWLHIV. More research is needed to evaluate the safety of IPT for PWLHIV given their high risk of TB disease and the poor maternal and infant outcomes associated with maternal TB/HIV co-infection, despite appropriate therapy.

Table: Maternal and Infant Outcomes

	IPT N=69	No IPT N=82	p-value
Composite Outcome* N(%)	11 (16%)	23 (28%)	0.08
Fetal Demise N(%)	1(1%)	1 (1%)	1.0
Gestational Age at Birth (weeks) Median(IQR)	39 (38,40)	39 (37,40)	0.90
Preterm N(%)	7 (10%)	18 (22%)	0.06
34-36 weeks	5	17	
28-33 weeks	2	1	
<28 weeks	0	0	
Low Birth Weight (<2500g) N(%)	6 (9%)	10 (12%)	0.51
SGA (<10th%) N(%)	8(12%)	14 (17%)	0.36
Congenital Anomaly N(%)	1 (1%)	2 (2%)	1.0
Maternal Mortality (<42 days) N(%)	0 (0%)	1 (1%)	1.00
Neonatal Deaths N(%)	1 (1%)	0 (0%)	0.45
Infant Deaths N(%)	1 (1%)	0 (0%)	0.45
TB Mother N(%)	2 (3%)	2 (2%)	1.0
TB Infant N(%)	0	0	

*Composite outcome includes fetal demise, low birth weight, prematurity and congenital anomaly

78 POTENTIAL CONCERN FOR TIMING OF DMPA INJECTION AMONG WOMEN TREATED FOR HIV AND TB

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Background: Effective contraception is of upmost importance for young women with HIV-associated TB, as unintended pregnancy among such women is associated with increased maternal and infant morbidity and mortality. Rifampicin (RIF) and Efavirenz (EFV) are both inducers of metabolizing enzymes and can reduce concentrations of contraceptive medications. Effects of these drugs on the pharmacokinetics (PK) of depot medroxyprogesterone acetate (DMPA), the most commonly used contraceptive in sub-Saharan Africa (SSA) and globally, are unknown. Safety of concurrent use of these 3 drugs is also unknown. We hypothesized that clearance of MPA would be increased when given with RIF and EFV, potentially resulting in levels of MPA <0.1 ng/mL (levels associated with escape ovulation) prior to 12 weeks post-DMPA dose.
Methods: ACTG A5338 was a multicentre, single arm, PK study among women in SSA stable on EFV-based antiretroviral therapy (ART) and RIF-based TB treatment. We determined plasma MPA concentrations pre-dose and 2, 4, 6, 8, 10 and 12 weeks after DMPA 150 mg injection and measured plasma progesterone levels from week 2 onwards. The primary outcome measure was the proportion of women with sub-therapeutic MPA levels (<0.1 ng/mL) at week 12. MPA PK parameters were calculated using non-compartmental methods and compared with historical ART-naïve controls without TB who received DMPA.
Results: Baseline characteristics of the 42 evaluable participants are shown in Table 1. Five women [11.9% (95% CI 4.0-25.6%)] had MPA <0.1 ng/mL at week 12 with one of the five having MPA <0.1 ng/ml at week 10 compared to one of 16 (6,3%) at week 12 among the historical controls. No participant had progesterone levels >5 ng/mL (suggesting ovulation) throughout the study including at week 12. Compared to historical controls, median area under the concentration-time curve over 12 weeks (AUC0-12) was lower (7.63 vs. 12.38 ng*wk/mL, p=0.004) and apparent clearance was higher (19,681 vs. 12,117 L/

wk, p=0.004). There were no grade 3 or higher adverse effects attributed to DMPA.

Conclusion: DMPA, when given with EFV-based ART and RIF-based TB therapy, was safe and well tolerated. MPA clearance was higher than in controls, leading to sub-therapeutic concentrations of MPA in some women at 10 and 12 weeks post-dose, though progesterone levels typically associated with ovulation were not observed. It may be prudent to dose DMPA more frequently than every 12 weeks in women on EFV with HIV-associated TB taking RIF.

TABLE 1: **PARTICIPANTS BASELINE CHARACTERISTICS**

Baseline Characteristics	N=42 [N (%) or median (IQR)]
Age (years)	32 (27, 35)
20-29	17 (40%)
30-39	19 (45%)
40-49	6 (14%)
African Race	42 (100%)
Weight (kg)	53.8 (47.8, 61.0)
Body Mass Index (kg/m²)	20.4 (18.7, 24.4)
HIV RNA < 400 copies/mL	36 (86%)
CD4 (cells/mm³)	414 (226, 638)
<50	1 (2%)
50-199	8 (19%)
200-349	7 (17%)
=350	26 (62%)
Enrollment by country	
South Africa	20 (48%)
Kenya	10 (24%)
Botswana	6 (14%)
Zimbabwe	6 (14%)

79 IMPROVING CHILD TUBERCULOSIS CONTACT MANAGEMENT IN LESOTHO

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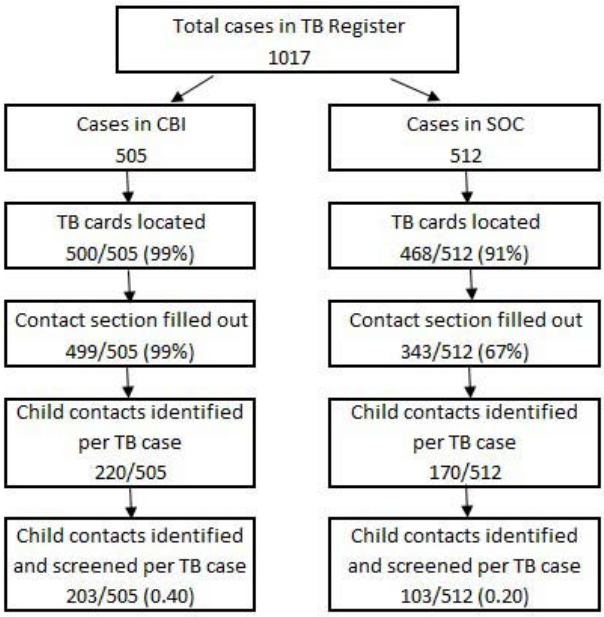
Background: Child TB contact management (CCM), including identification and screening of HIV-negative children <5 years and HIV-positive children regardless of age, who live in households with adult TB patients, is a proven strategy for preventing progression to TB and TB case finding. However, CCM implementation is suboptimal in high TB/HIV burden settings, such as Lesotho. The PREVENT Study was a cluster randomized trial to evaluate the effectiveness of a community-based intervention (CBI) to improve CCM in Lesotho.

Methods: Ten clinics were randomized to CBI or standard of care (SOC). CBI addressed the complex provider-, patient-, and caregiver-related barriers to childhood TB prevention through several interventions: nurse training and mentorship; health education for caregivers and patients by village health workers (VHW); adherence support with weekly messages and facility-based VHW who supervised community-based VHW; and multidisciplinary team meetings, where programmatic data were reviewed. Routine program data were abstracted from TB registers and cards for all adult TB cases >18 years registered during the study period, and their child contacts. The primary outcome was the yield (number) of child contacts identified and screened per adult TB case. Generalized linear mixed models were used to test for differences between study arms.

Results: From 01/17-06/18, 1017 new adult TB patients were recorded in the TB register, 505 at CBI and 512 at SOC sites; >70% were HIV co-infected. At CBI, 99% of TB cards were located and contact section was completed for 99% of TB cases compared with 91% and 67%, respectively, at SOC sites (Figure). Overall, per adult TB cases, 220/505 child contacts were identified at CBI and 170/512 child contacts at SOC sites (p=0.16). Fewer identified children were screened for TB at SOC than CBI sites (61% vs 92%, p=0.07). The yield of child contacts per adult TB case was higher at CBI than SOC sites (0.40 vs. 0.20, p=0.06).

Conclusion: The number of child contacts identified was similar across study arms, but more child contacts per adult TB case were identified and subsequently screened at CBI compared with SOC sites. However, the yield of child TB contacts requires further optimization as there are many missed opportunities to diagnose or prevent TB. Additional research is needed to enhance the definition of child household contacts and overcome barriers to CCM that impede identification and screening of child TB contacts in high TB/HIV burden settings.



80LB SAFETY & PK OF WEEKLY RIFAPENTINE/ISONIAZID (3HP) IN ADULTS WITH HIV ON DOLUTEGRAVIR

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Background: Short-course preventive therapy with 12 once-weekly rifapentine/isoniazid doses (3HP) could transform TB control, but drug interactions with antiretrovirals may pose implementation challenges. In a previous trial, 3HP administered with dolutegravir (DTG) resulted in serious adverse events (AE) in 2/4 healthy subjects (fever, hypotension, elevated transaminases); the study was halted. We conducted a Phase I/II study of 3HP and DTG in adults with HIV to characterize safety, drug interactions, and viral suppression.

Methods: HIV infected adults with undetectable viral load on efavirenz (EFV)-based regimens were recruited into 3 groups. All received DTG in place of EFV for 8 weeks, then began 3HP; after 3HP completion, all participants were followed 4 more weeks. Viral loads were measured at baseline and weeks 11 and 24. Groups 1A (n=12) and 1B (n=18) had intensive DTG PK sampling performed at week 8 (pre-HP), then weeks 11 and 16 following the 3rd and 8th doses of HP. Group 2 (n=30) were treated with the same schedule and had sparse DTG PK sampling at weeks 8, 11 and 16. Primary endpoints were 1) grade >3 AE and 2) population PK parameters of DTG with or without HP. An independent Study Monitoring Committee recommended release of results following its second review.

Results: Of the 60 participants who received 3HP, 43 (70%) were female, median (IQR) age was 40 (35-48) years, all were black African, median (IQR) CD4 was 683 (447-935) cells/mm3, and median (IQR) BMI was 28.9 (24.0-32.9) kg/m2. All participants received ≥6 HP doses at the time of this report. Three

Grade 3 AE occurred (2 elevated creatinine, 1 hypertension). HIV viral loads at baseline, day 58 (pre-HP), day 72 (3rd HP dose) and day 168 (post-HP) were all <40 c/mL. Table 1 shows Group 1A and 1B PK results. The geometric mean (GM) trough concentration of DTG on Day 58 (pre-HP) was 1003 ug/mL (5th-95th %ile: 500-2080), and during HP treatment 546 (134-1616) with all trough levels but one above DTG IC90 of 64 ug/mL; Table). Overall, HP administration decreased DTG bioavailability by 29% (RSE 13%) (+18%, -37% and -35% for week 1, 3 and 8), while clearance remained unchanged.

Conclusion: Co-administration of DTG and HP was well-tolerated, with no HP-related Grade >3 AEs. Although HP decreased DTG bioavailability, which was associated with a modest decrease in trough levels, all trough levels but one were above the DTG IC90. All viral loads were suppressed. DTG may be co-administered with 3HP without dose adjustment.

Table. Dolutegravir trough concentrations, alone and with once-weekly rifapentine plus isoniazid

Study Day	N	Day Post HP Dose	Geometric mean	Median	5th and 95th percentile	Ratio Geometric mean	Ratio Median	5th and 95th percentile	Regimen
57/58	60	0	1003	1002	500-2080	1	1	-	DTG alone
59	30	1	1053	1140	412 - 1834	1.04	1.02	0.72 -1.55	DTG+HP
72	30	7	492	553	200-1063	0.49	0.47	0.29-0.87	DTG+HP
73	30	1	663	688	225 - 1283	0.66	0.72	0.31-1.09	DTG+HP
74	30	2	359	388	92 - 813	0.36	0.42	0.16-0.68	DTG+HP
78	12	6	403	495	145 - 802	0.45	0.49	0.20-0.98	DTG+HP
108	12	1	580	749	183 - 1589	0.65	0.84	0.18-1.27	DTG+HP
109	12	2	306	424	83 - 803	0.34	0.42	0.14-0.62	DTG+HP

*HP doses were given on Days 58, 65, 72, 79, 86, 93, 100, 107, 114, 121, 128, 135

81LB PHARMACOKINETICS AND SAFETY OF ADJUSTED DARUNAVIR/RITONAVIR WITH RIFAMPIN IN PLWH

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Background: Darunavir (DRV)/ritonavir(r) is better tolerated than lopinavir (LPV)/r and has a higher genetic barrier to resistance. Co-administration of DRV/r with rifampin (RIF), the key component of first-line TB treatment, is currently contraindicated as significant reductions in DRV exposures are expected; this has been a barrier to the use of DRV/r in resource-limited settings where TB is endemic. We aimed to evaluate the safety and pharmacokinetics (PK) of adjusted doses of DRV/r in PLWH.

Methods: We enrolled virologically suppressed participants on a second-line DRV/r regimen without TB. Based on data from a Physiologically-Based PK model, we selected two adjusted doses of DRV/r (1600/200 mg daily and 800/100 mg 12 hourly) with RIF for comparison to plasma exposures with DRV/r 800/100 mg daily without RIF, in a cross-over design. Baseline DRV steady state PK was determined and RIF added for 7 days, then the dose of r was increased to 200 mg; 7 days later the dose of DRV was increased; after another 7 days participants were crossed over to the alternative adjusted DRV dose. DRV was measured in plasma samples after observed doses at baseline and after each dose adjustment. Non-compartmental analysis was used to estimate the PK measures. Clinical adverse events, ALT, and bilirubin were monitored every 2 to 3 days during treatment with RIF.

Results: Seventeen of a planned 28 PLWH were enrolled and started on study treatment before the study was stopped due to high rates of hepatotoxicity. Only 4 participants completed the study. Six (35%) of the participants were withdrawn for DAIDS grade 3 (n=3) or 4 (n=3) ALT elevations developing after 9-12 days of RIF; 3 participants were symptomatic. Hepatotoxicity resolved in all cases after withdrawal of study treatment and participants were successfully re-established on their standard of care ART regimen. The PK parameters are shown in table 1. Trough concentrations were below the protein-adjusted EC50 of 200 ng/mL in 2 participants in the QD group adjusted dose group on RIF.

Conclusion: Adjusted doses of DRV/r with RIF were associated with unacceptable risk of hepatotoxicity and there was a marked reduction in DRV trough concentrations with the QD adjusted dose in our study.

Table 1: Geometric mean (range) darunavir pharmacokinetic parameters.

	DRV/r 800/100 daily (n=17)	DRV/r 1600/200 + RIF (n=4)	DRV/r 800/100 bid + RIF (n=4)
C_0, ng/mL	2497 (631-8560	134 (15-1600)	642 (40-5680)
C_{24}, ng/mL	2719 (615-7550)	209 (58-1040)	1176 (641-3670) ng/mL
AUC_{24}, ng.h/mL	261184 (46744-830798)	39074 (21412-89785)	59751 (25259-219927; AUC_{12}*2)
C_{MAX}, ng/mL	6855 (3610-12400)	4368 (3010-7750)	3928 (2060-7930)
T_{MAX}, h	3 (2-4)	3 (2-4)	2 (1-2)

82 EARLY BACTERICIDAL ACTIVITY OF HIGH-DOSE ISONIAZID AGAINST MULTIDRUG-RESISTANT TB

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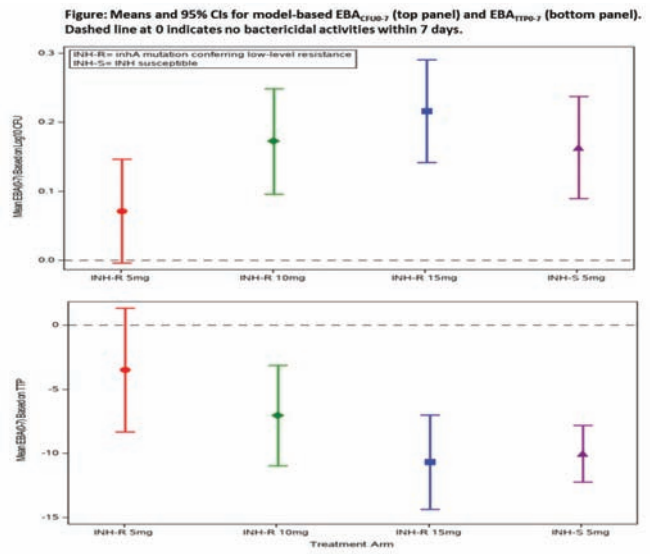
Background: High-dose isoniazid (INH) may be useful in treating multidrug-resistant tuberculosis (MDR-TB), particularly when INH resistance is mediated by inhA mutations. Although the World Health Organization (WHO) recommends 'high-dose' INH as part of the new shorter MDR-TB regimen, the optimal dose and its efficacy are not established.

Methods: AIDS Clinical Trials Group (ACTG) A5312 is a Phase 2A randomized, open-label trial in which individuals with smear-positive pulmonary MDR-TB with INH resistance mediated by an inhA mutation (Group 1) were randomized to receive INH doses of 5, 10 or 15 mg/kg daily for 7 days. Controls with drug-sensitive TB (Group 2) received the standard INH dose of 5 mg/kg/day. Sputum cultures were collected daily, beginning at baseline. The early bactericidal activity of INH, estimated as the average daily change in log10 colony forming units (CFU) on solid media (EBACFU0-7) or average daily change in time to positivity (TTP) in hours on liquid media (EBATTP0-7) over 7 days of treatment was estimated using nonlinear mixed effects models. Safety data were collected from study entry through Day 21.

Results: 59 participants (43 in Group 1, 16 in Group 2) were enrolled, all in South Africa. The majority (73%) were men, median age was 32 years, 20% were HIV co-infected, and 88% had cavitary lung disease. 58/59 (98%) completed study treatment (one withdrew consent in the 15 mg/kg arm). Eight participants had 9 grade 3 (and no grade 4) adverse events (fever, pain, dyspnea, pneumothorax (2), anemia (4)), all unrelated or unlikely to be related to study drugs. Mean EBACFU0-7 in Group 1 at doses of 5, 10 and 15 mg/kg was 0.07, 0.17 and 0.22 log10CFU/mL/day, respectively; and in Group 2 was 0.16 log10CFU/mL/day (Figure). Mean EBATTP0-7 in Group 1 (5, 10, 15 mg/kg doses) was 3, 7, 11 hours/day, and in Group 2 was 10 hours/day (Figure). Median minimal inhibitory concentrations in 90 patients screened for study participation were 1 mg/L for inhA-mutated and 0.2 mg/L for drug-sensitive strains.

Conclusion: INH had substantial EBA against Mycobacterium tuberculosis strains with inhA mutations among patients with MDR-TB, provided it was dosed at 10-15 mg/kg, supporting WHO recommendations for high-dose INH in this population. Activity at these doses was similar to the standard 5 mg/kg dose in drug-sensitive TB. Longer-term tolerability, plus efficacy of high-dose INH against strains with katG mutations require further study.



83 LONG-TERM MORTALITY AFTER TUBERCULOSIS CURE IN THE CIPRA HT-001 TRIAL

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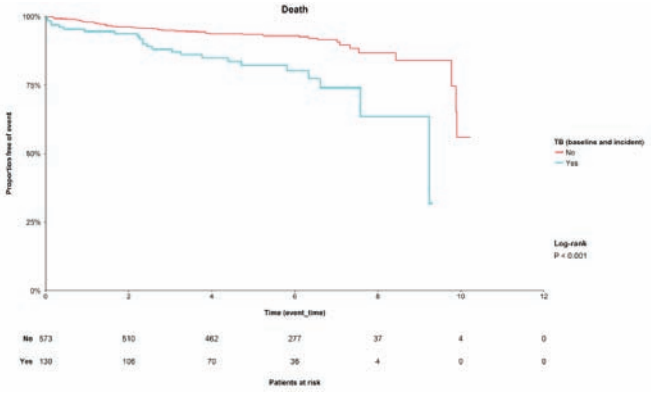
Background: Although TB is a curable disease, studies from industrialized settings suggest an elevated risk of long-term mortality after TB recovery. Long-term outcomes data for individuals co-infected with TB and HIV from the developing world are limited.
Methods: We conducted a retrospective analysis of 14-year follow-up data (2005-2018) for 703 adult HIV positive patients enrolled in the CIPRA HT-001 study at Les Centres GHESKIO, Haïti. Demographic and clinical data, including TB diagnosis, TB and HIV treatments were recorded in the study database and electronic medical records. The TB cohort was defined as patients with active TB at enrollment or incident TB during follow-up (cases). Time to death was estimated and cases and controls with no history of TB using Kaplan-Meier analysis and the log-rank test. We used univariate and multivariate Cox proportional hazards models to estimate hazard ratios for mortality. Time-varying ART status and CD4 count were included in the multivariate models. A period of 8-months post TB diagnosis was used to define the start of follow-up and exclude acute mortality from TB; additional sensitivity analyses using a longer period of 2-years were conducted.
Results: 703 patients were included; 151 cases, and 573 controls. Baseline characteristics were similar in cases and controls. After exclusion of acute mortality on TB treatment, TB cases had lower survival rates, 5-year 82.3% vs 93.5%; 9-year 63.5% vs 83.9%, and lower median time to death (9.2 months vs median not reached, p<0.001) compared to controls (Figure 1). In univariate Cox models, the risk of death was higher for cases than controls (HR 2.9, 95% CI 1.8, 4.8, p<0.001). After adjusting for time-varying ART status and CD4 count, the risk of mortality remained significantly higher for cases (HR 3.6, 95% CI 2.1, 6.3, p<0.0001) however, time-varying ART and CD4 values were not independent predictors of mortality in that model. Mortality trends were similar in all sensitivity analyses.
Conclusion: Patients with HIV who had TB coinfection had a higher risk for long-term mortality after TB-recovery compared to patients with no history of TB. CD4 count and time of ART initiation were not independently associated with risk of mortality in this model. Long-term mortality risk after TB treatment among HIV positive patients should be thoroughly documented to elucidate the mechanisms and assess its impact on mortality.



84LB QT EFFECTS OF BEDAQUILINE, DELAMANID OR BOTH IN MDR-TB PATIENTS: THE DELIBERATE TRIAL

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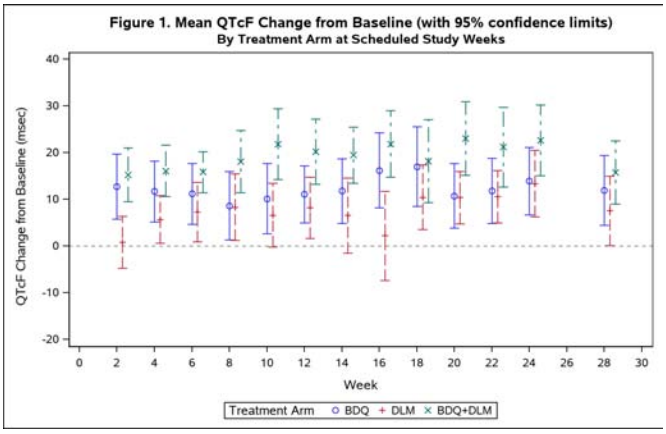
Background: Bedaquiline and delamanid are the first drugs of new classes approved for tuberculosis (TB) in 40 years. Both are oral, well-tolerated, and recommended for treatment of multidrug resistant (MDR) TB by WHO. However, these drugs and/or their metabolites have long half-lives, and each prolongs the QT interval with maximum effects weeks after drug initiation. The cardiac safety of these drugs given together as part of multidrug therapy has not been established.
Methods: AIDS Clinical Trials Group (ACTG) A5343 is a phase 2, open-label trial randomizing adults with MDR-TB receiving multidrug background treatment (MBT) 1:1:1 to receive bedaquiline (BDQ arm), delamanid (DLM arm) or both (BDQ+DLM arm) for 24 weeks. Patients with QTcF >450ms or CD4 count < 100 cells/mm3 were excluded. HIV-infected participants received dolutegravir-based ART. Clofazimine was not allowed, and levofloxacin was given in place of moxifloxacin. Three electrocardiograms (ECG) were performed at baseline, every two weeks for 24 weeks, then week 28. QTcF (in ms) was calculated by a core laboratory blinded to treatment. The mean QTcF change from baseline (averaged over weeks 8-24) was defined in each arm, and the QTcF change in the BDQ+DLM arm was compared to QTcF changes in the BDQ and the DLM arms. Grade 3 QTcF prolongation was defined as >500ms or >480ms with increase from baseline >60ms. Grade 4 was life-threatening dysrhythmia.
Results: Eighty-four participants were enrolled in South Africa and Peru. The majority (75%) were men; median age was 34 years; 37% were HIV-positive. Changes in QTcF from baseline, by week, including 4 weeks after stopping study drugs, are shown in the Figure. There were no Grade 3 or 4 QT interval prolongation events. Among 74 participants with QTc data (2062 unique ECGs, 688 visits, 69 participants with data through week 20, 64 with data through week 24), preliminary mean (95.1% CI) on-treatment QTcF value (in ms) was 410.3 (403.0, 417.7)(BDQ arm), 413.5 (406.1, 420.8)(DLM arm) and 412.5 (405.0, 420.0)(BDQ+DLM arm). Mean (95.1% CI) change (ms) in QTcF from baseline was 11.9 (7.4, 16.5) in the BDQ arm, 8.6 (4.0, 13.2) in the DLM arm, and 20.7 (16.1, 25.4) in the BDQ+DLM arm.
Conclusion: The combined effect on the QTcF interval of co-administration of bedaquiline and delamanid is clinically modest and no more than additive. This study demonstrates the cardiac safety of the combined use of these drugs in patients with MDR-TB taking MBT with normal baseline QTcF values.



85 FALL IN HCV INCIDENCE IN HIV+ MSM IN LONDON FOLLOWING WIDER ACCESS TO DAA THERAPY

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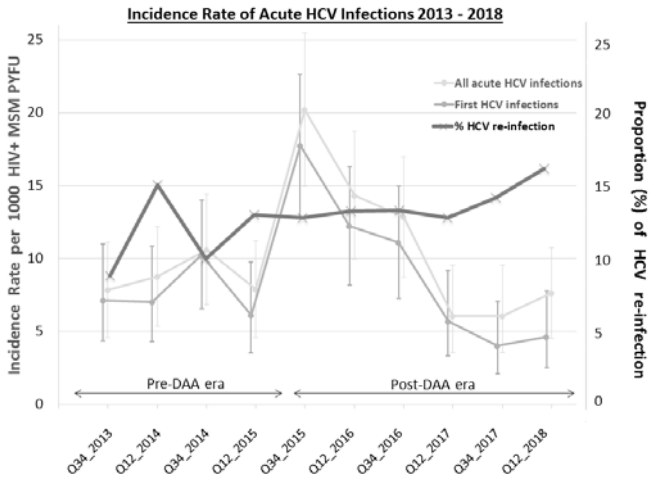
Background: Modelling of the London HCV epidemic in HIV+ MSM suggested early access to DAA treatment plus risk-behaviour modification may reduce incidence. With high rates of linkage to care and treatment access, micro-elimination of HCV within HIV+ MSM may be realistic, ahead of 2030 WHO targets. Data from European cohorts have shown a reduction in HCV incidence amongst HIV+ MSM. We examine the effect of HCV treatment access (in the pre- and post-DAA era) and risk-behaviour modification upon incidence of HCV first and re-infections in HIV+ MSM in three large London clinics.

Methods: A retrospective cohort study was conducted at 3 London HIV clinics (Royal Free and St Mary's Hospitals, Mortimer Market) between July 2013 and June 2018. During each 6-month period the following data were collected [1] number of first acute HCV diagnoses [2] number of subsequent acute HCV diagnoses (re-infections) [3] denominator of HIV+MSM under active follow up [4] number of PEG IFN/RBV or DAA-based HCV treatments for acute/early HCV (<12m since diagnosis) [5] number of PEG IFN/RBV or DAA-based HCV therapies for chronic HCV (>12m since diagnosis). Incidence rates (acute HCV diagnoses/HIV+ MSM 1000 PYFU) and re-infection rates (re-infections/all incident infections x 100) were calculated for each time-period.

Results: 293 acute HCV infections were identified (246 first infections and 47 re-infections). DAA treatment became widely available in late 2015. All centres adopted risk-reduction behaviour intervention with counselling/psychology. Incidence of first HCV episode peaked at 17.72/1000 HIV+MSM PYFU [95%CI 12.81–22.64] in 2015. Rates fell to 4.64 [95%CI 2.53–7.78] by 2018. Re-infection rates increased from 9% to 16% during the study period. Supervised early HCV treatments (<12m of diagnosis) increased from 22% to 61% between 2013 and 2018. Supervised chronic HCV/HIV treatment rates increased from 2.8/month in pre-DAA era to 15.6/month in post-DAA era. Time from diagnosis to starting any HCV treatment reduced from average of 40.9 months (2013) to 3.1 months (2018).

Conclusion: There has been a 74% reduction in incidence of first HCV infection and 62% reduction of overall HCV incidence in HIV+MSM since the epidemic peak of 2015 which coincides with wider access to DAA-based therapy across London. However re-infection rates remain high and maybe increasing. Further interventions to reduce ongoing transmission including access to treatment for reinfection are likely needed if micro-elimination is to be achieved.



86 HCV REINFECTION AMONG HIV-INFECTED MSM IN NEW YORK CITY

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Background: High HCV re-infection rates of 3-15% have been reported after IFN treatment in HIV-infected MSM in Europe. There are no data on HCV re-infection from similar cohorts in the United States, or among those cured with all-oral direct-acting antiviral (DAA) therapy.

Methods: We assessed all HIV-infected MSM from our cohort in New York City (NYC) for clearance of HCV. Clearance was defined as SVR 12 if by treatment; or undetectable HCV VL for ≥12 weeks if by spontaneous clearance (SC). Re-infection was defined as new HCV viremia after clearance. Clinical onset of re-infection was defined as the date of the 1st-noted ALT elevation or HCV viremia. Observation time was defined as the period between 12 weeks after completion of therapy or SC, and either the clinical onset of HCV re-infection or the last undetectable HCV VL in those not re-infected.

Results: We identified 267 HIV-infected MSM with documented clearance of primary HCV infection and ≥4 weeks follow-up. Median age was 45; 170 (64%) were white, 40 (15%) black, 55 (21%) Hispanic; genotypes (n=258) were 1a in 206 (80%), 1b in 23 (9%), and other in 29 (11%). Median CD4 count was 579 cells/uL; median HIV VL was <50 copies/mL. We found 44 re-infections among 38 (14%) men, onset between 2006 to 2018, a median of 1.5 (IQR 0.8,2.9; range 0.3-11.4) years after clearance; genotypes (n=41) were 1a in 31 (76%), 1b in 3 (7%), and other in 7 (17%). Including the re-infections, follow-up was available for a total of 300 episodes of HCV clearance, with a median follow-up time of 1.8 (IQR 0.8,3.3; range 0.1-11.4) years, and a total of 734 person-years (PY). The overall re-infection rate was 5.7/100PY (95% CI 4.2,7.7), with no significant difference among the 112 (37%), 160 (53%), or 28 (9%) infections cleared with IFN, DAA, or SC, respectively (p=0.52, Fisher exact). Further, time to re-infection did not differ among the groups (p=0.82, log-rank test) (Figure).

Conclusion: The high HCV re-infection rate in our large cohort of HIV-infected MSM in NYC was independent of whether clearance was by IFN or DAA treatments, or by SC, and comparable to Europe rates. Most re-infections occurred within the first 2 years, but infections continued to occur for more than 11 years after clearance. These data suggest that long-term surveillance is warranted for all HIV-infected MSM after clearance of HCV infection. Further, strategies to reduce HCV re-infections are needed to meet the goal of eliminating HCV in these men who are at significant risk for HCV infection.

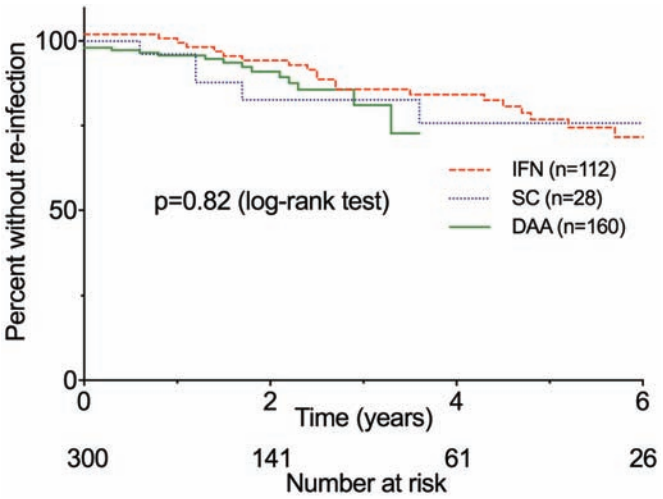

Table: HCV virologic response to LDV/SOF during pregnancy by participant (copies/mL)

Study visit	Participant number						
	1	2	3	4	5	6	7
Screening (14-21 weeks' gestation)	5.6×10^5	2.3×10^5	4.9×10^5	2.5×10^5	10.4×10^5	1.7×10^5	23.1×10^5
Enrollment (23-24 weeks' gestation)	16.9×10^5	2.6×10^5	5.2×10^5	1.5×10^5	17.4×10^5	1.0×10^5	37.6×10^5
13-21 days on LDV/SOF	<12	<12	0	0	<12	14	49
5-6 weeks on LDV/SOF	0	0	0	0	<12	0	<12
1-7 days after LDV/SOF completion	0	0	0	0	0	0	0
Delivery	0	0	0	0	0	0	NC*
12 weeks after LDV/SOF completion	0	0	0	0	0	0	0

*NC = not collected (participant delivered off site)

87 A PHASE 1 STUDY OF LEDIPASVIR/SOFOSBUVIR IN PREGNANT WOMEN WITH HEPATITIS C VIRUS

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Background: Hepatitis C virus (HCV) infection is increasing among pregnant women in the United States, increasing the risk of perinatal transmission. Pregnancy is a window of opportunity for health care interventions, including HCV treatment that could improve maternal health and prevent perinatal HCV transmission. There are no published data on the safety or efficacy of HCV direct-acting antivirals in pregnancy. Therefore, the primary objective of this pilot study was to define the safety of and virologic response to ledipasvir 90mg-sofosbuvir 200mg (LDV/SOF) therapy in pregnancy.

Methods: In this open-label, phase 1 study, HIV-negative pregnant women with chronic genotype 1 HCV infection were enrolled between 23-24 weeks of gestation and began a 12-week course of LDV/SOF. Participants had to take at least 73 (87%) planned doses to be evaluable. Viral load testing was performed at 7 visits: screening, enrollment, 13-21 days and 5-6 weeks after LDV/SOF initiation, 1-7 days and 12 weeks after LDV/SOF completion, and at delivery. Maternal adverse events, delivery outcomes and the sustained virologic response 12 weeks after therapy (SVR12), defined as undetectable HCV viral load, are reported.

Results: Of 28 pregnant women with chronic HCV who screened, 20 were excluded because of genotype 2 or 3 infection (n=10), ongoing illicit drug use (n=4), declining study participation (n=3), intensions to delivery off-site (n=2), and an APRI score of >1 (n=1). Eight women were enrolled, all of whom were white, with a median age of 32 (range 25-38) years. Seven of the women were HCV infected due to intravenous drug use, 4 of whom were receiving opioid pharmacotherapy, and one was perinatally infected. Of 7 evaluable patients, the median HCV viral load at enrollment was 518,173 (range 103,457-3,757,923) copies/mL. All had a rapid response to therapy and all achieved SVR12 (Table). All adverse events related to LDV/SOF were ≤ grade 2. All seven participants delivered at term with undetectable HCV viral loads at delivery. One-year follow-up of infants is ongoing.

Conclusion: In this first study of HCV treatment in pregnant women, response to LDV/SOF was similar to the viral response observed in nonpregnant individuals without any safety concerns identified. Larger studies are needed before this strategy can be recommended. A substantial proportion of women screened out due to genotypes 2 or 3 infection, highlighting the importance of further research to expand HCV treatment options in pregnancy.

88 INCIDENT DIABETES AND GLUCOSE CONTROL AFTER HCV TREATMENT WITH DAAs IN ERCHIVES

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Background: HCV is associated with an increased risk of diabetes. How treatment with newer directly acting antiviral agents (DAA) affects this risk is unknown. Our objective was to determine the effect of DAA treatment upon the risk and incidence of diabetes.

Methods: We identified chronic HCV-infected persons treated with pegylated interferon/ribavirin (PEG/RBV) or DAA regimens and propensity-score matched untreated controls. We excluded persons with prevalent diabetes, HIV or HBV coinfection, those treated with both PEG/RBV and DAA regimens. Diabetes was defined using a combination of blood glucose values, prescription of hypoglycemics and ICD-9/10 codes.

Results: We identified 4,764 PEG/RBV treated, 21,279 DAA treated, and same number of untreated controls. Diabetes incidence rate [95% CI]/1,000 person-years of follow up were 19.8[18.3,21.4] among PEG/RBV and 9.89[8.7,11.1] among DAA treated persons (P<0.001). Among the treated, rates were 13.3[12.2,14.5] for those with SVR and 19.2[17.4,21.1] for those without SVR (P<0.0001). Treatment was associated with a larger reduction in incident diabetes rate in persons with more advanced fibrosis/cirrhosis (absolute difference 2.9 for FIB-4<1.25; 5.7 for FIB-4 1.26-3.25; 9.8 for FIB-4>3.25). DAA treatment (HR 0.48, 95%CI 0.42,0.56) and SVR (HR 0.81, 95%CI 0.70,0.93) were associated with a significantly reduced risk of diabetes. DAA treated persons had longer diabetes free survival compared to untreated and PEG/RBV treated persons. There was no significant difference in diabetes free survival between untreated and PEG/RBV treated persons.

Conclusion: HCV treatment significantly reduces the incidence and risk of subsequent diabetes, driven largely by DAA regimens. Treatment benefit is more pronounced in persons with more advanced liver fibrosis.

Table. Incidence rate for diabetes among various subgroups.

	Number of events	Incidence rate (95% CI) per 1,000 patient years of follow up	p-value[1]
By treatment status			
Untreated	1679	20.6 (19.6,21.6)	--
Treated overall	888	15.4 (14.4,16.4)	<.0001
By treatment regimen			
Untreated	1679	20.6 (19.6,21.6)	--
Treated with PEG/RBV	633	19.8 (18.3,21.4)	<.0001
Treated with DAA	255	9.89 (8.7,11.1)	<.0001
By SVR, among those treated			
SVR	500	13.3 (12.2,14.5)	--
No SVR	388	19.2 (17.4,21.1)	<.0001
By FIB-4 at baseline			
FIB-4 < 1.25			
Treated	280	16.7 (14.8,18.6)	--
Untreated	661	19.6 (18.1,21.1)	0.02
FIB-4 1.26 – 3.25			
Treated	458	14.7 (13.4,16.0)	--
Untreated	793	20.4 (19,21.9)	<.0001
FIB-4 > 3.25			
Treated	150	15.5 (13.1,17.9)	--
Untreated	225	25.3 (22.1,28.6)	<.0001

PEG, pegylated interferon; RBV, ribavirin; DAA, directly acting antiviral agent based regimen; SVR, sustained virologic response

89 INTRAHEPATIC HEPATITIS C KINETICS WITH DIRECT-ACTING ANTIVIRALS IN HIV COINFECTION

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Background: Direct-acting antivirals (DAA) target hepatitis C virus (HCV) proteins, dramatically improving treatment in HIV/HCV co-infection. The DAA effect in liver, however, is not well understood. We examined intrahepatic clearance of HCV.

Methods: A5335S, a substudy of trial A5329 (Paritaprevir/Ritonavir, Ombitasvir, Dasabuvir, with Ribavirin) enrolled persons co-infected with HIV, suppressed HIV RNA on antiretrovirals, and chronic genotype 1 HCV without cirrhosis. Core liver biopsies were performed before and 7 days after DAA initiation, with frequent blood sampling to measure plasma HCV RNA and plasma IP-10. In liver, single-cell laser capture microdissection was used to estimate HCV-infected cells and interferon-stimulated genes (ISG) expressing cells in percentages. Plasma and liver concentrations were assessed at 2nd biopsy for all DAAs.

Results: Five (3 men, 2 women; ages 40-61, 3 black, 2 Hispanic; all from US) of six enrollees completed A5335S; all were HCV treatment-naïve. Due to anemia, participant 5 delayed 2nd biopsy until treatment day 50. Mean baseline plasma HCV RNA = 6.7 log10 IU/mL; mean decrease in plasma HCV RNA after starting DAAs was -3.0 log10 IU/mL in 24 hours and -4.1 log10 IU/mL in 7 days. At 1st biopsy, HCV-infected cells were mean (range) = 27% (13-51%), and positively correlated with baseline plasma HCV RNA (Spearman rank correlation r=0.9, p<0.05; Table). At 2nd biopsy HCV-infected cells had mean (range) = 0.9% (0.4-1.7%). The mean (range) absolute decline was 26.6% (12.4-50.1%), representing clearance of >93% of infected hepatocytes. Hepatocyte ISG expression was abundant pre-DAA [means: ISG15 22%; IFITM3 46%; IFI27 24%; IFI6 27%]: IFI27 and IFI6 decreased after DAA initiation in all participants; IFITM3 increased in 2 participants, and ISG15 increased in 1 participant. Plasma IP-10 levels rapidly declined from mean baseline = 427 pg/mL thru day 4; mean 1-week change from baseline was -296 pg/mL. Pre-dose paritaprevir concentrations from liver and plasma ranged from 1788–4228 ng/g and 6–194 ng/mL, respectively (other DAAs not shown).

Conclusion: In this intensive substudy, the burden of HCV-infected hepatocytes declined rapidly, and within the first week of DAA therapy fewer than 2% were infected. Hepatocyte innate immune signals did not diminish uniformly after DAA initiation. Given assumptions of adherence, we extrapolate that HCV could theoretically be eradicated from the liver in this study sample within 63 days.

	HCV+ Hepatocytes (%)			Plasma HCV RNA (Log_{10} IU/mL)			Pre-Dose Paritaprevir Concentration	
Participant [Sex]	1st Biopsy	2nd Biopsy	Absolute Δ	Baseline	1 Day Δ	1 Week Δ	Liver (ng/g)	Plasma (ng/mL)
1 [M]	13.0% (35/270)	0.6% (2/347)	-12.4%	6.0	-3.5	-4.0	2414	6.3
2 [F]	15.9% (63/396)	0.4% (1/260)	-15.5%	6.3	-3.0	-3.9	4228	16.0
3 [M]	18.3% (67/366)	1.1% (3/270)	-17.2%	7.0	-3.5	-4.2	963	24.7
4 [F]	39.3% (112/285)	1.7% (5/294)	-37.6%	6.9	-3.5	-4.5	1788	46.5
5 [M]	50.9% (180/354)	0.7% (2/277)	-50.1%	7.5	-1.8	-4.0	-	194.0
Overall mean	27.5%	0.9%	-26.6%	6.7	-3.0	-4.1	2348.3	57.5

90 HIV VIREMIA AND LOW CD4+ INCREASE HCC RISK IN THOSE WITHOUT ADVANCED LIVER FIBROSIS

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Background: Despite rising incidence of hepatocellular carcinoma (HCC) in HIV+ patients, few studies have evaluated determinants of HCC during the antiretroviral therapy era. We evaluated HIV-related and traditional risk factors for HCC in a large cohort of HIV+ patients.

Methods: We conducted a retrospective cohort study among HIV+ patients in the Veterans Aging Cohort Study from 1999-2015. Patients had HIV RNA and CD4+ cell count simultaneously assessed in the Veterans Affairs (VA) system, and follow-up began on this date. Incident HCC was determined using the VA Cancer Registry. We used multivariable Cox regression to determine adjusted hazard ratios (HR [95% confidence interval]) of HCC associated with cumulative unsuppressed HIV RNA (≥500 copies/mL), time-updated lower CD4+ count, older age, male sex, race/ethnicity, morbid obesity (body mass index ≥35 kg/m^2), time-updated diabetes status, alcohol use disorder, hepatitis B virus (HBV), and hepatitis C virus (HCV) coinfection. The analysis was repeated substituting time-updated HIV RNA for cumulative unsuppressed HIV RNA. Since advanced hepatic fibrosis/cirrhosis is the strongest determinant of HCC and may overwhelm other risk factors, we stratified analyses by low and high baseline FIB-4 (<3.25 versus ≥3.25, respectively), a commonly used fibrosis index.

Results: Among 36,525 HIV+ patients, 275 (0.8%) developed incident HCC. Overall, baseline FIB-4 ≥3.25 was the strongest factor associated with HCC (HR 15.1 [9.7-23.5]). However, 36.4% of HCC events occurred among those with FIB-4 <3.25. Among these patients, older age (HR 1.4 [1.2-1.7] per 10 years), morbid obesity (HR 2.6 [1.2-5.3]), diabetes (HR 1.5 [1.1-2.1]), ≥12 months of unsuppressed HIV RNA (HR 2.0 [1.4-2.9]), lower CD4+ count (200-349 cells/mm^3: HR 1.5 [1.1-2.2]; <200 cells/mm^3: HR 1.6 [1.0-2.4] versus ≥500 cells/mm^3), HBV coinfection (HR 5.2 [3.7-7.3]), and HCV coinfection (HR 6.1 [4.1-9.0]) were independently associated with incident HCC. The risk of HCC was also increased with higher HIV RNA level (HR 1.3 [1.1-1.4] per 1.0 log_{10} copies/mL).

Conclusion: Among HIV+ patients without advanced liver fibrosis, higher HIV RNA and longer duration of HIV viremia, greater immunosuppression, morbid obesity, and diabetes, in addition to HBV and HCV coinfection, increased the risk of HCC. Addressing these factors before development of advanced fibrosis could help reduce the incidence of HCC in HIV+ patients.

91LB SINGLE HEPATOCYTE ANALYSIS IN HIV-HBV COINFECTION SHOWS HBV TRANSCRIPTION SILENCING

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Background: Hepatitis B virus (HBV) is a leading cause of liver failure and hepatocellular carcinoma worldwide. Due to shared modes of transmission, ~10% of people living with HIV also have chronic HBV infection. HBV cannot be cured because the long-lived covalently closed circular DNA (cccDNA) resides in every infected hepatocyte. However, little is known about HBV replication in human livers.

Methods: Here, we used single-cell laser capture microdissection (scLCM) and droplet digital PCR (ddPCR) to characterize the HBV replication landscape in situ in humans. We quantified cccDNA, total HBV DNA, and pre-genomic RNA (pgRNA) in each hepatocyte, adjusting for intracellular cytoplasmic RNA 7SL.

Results: We examined a median (range; total) 255 (52 – 290; 1100) hepatocytes that were individually isolated from five HIV/HBV co-infected persons with increasing exposure to dually-active antiretroviral therapy (DAART) against HIV and HBV (HB1-5; no exposure to >7 years of exposure). Total HBV DNA, cccDNA, and pgRNA were quantified in each cell. The proportion of infected hepatocytes (cccDNA positive) decreased with longer DAART exposure from 100% (HB1) to 33% (HB5)(Table). The median (range) total HBV DNA per cell was 1 cp/cell (0-112 cp/cell); of cccDNA was 1 cp/cell, (0-31 cp/cell); and of pgRNA was 38 cp/cell, (0-1919 cp/cell). The amounts of cccDNA, total HBV DNA, and pgRNA significantly decreased in infected cells with longer DAART

duration (p<0.005 for all targets). HBV transcription (pgRNA) did not correspond with cccDNA levels in the same cells (p>0.05). Additionally, we identified cells that contained cccDNA but not pgRNA, defined here as transcriptionally silent, that accumulated with longer DAART from 0% (HB1) to 46.1% (HB5) of infected hepatocytes (Table).

Conclusion: Our results indicate that the HBV viral landscape is highly dynamic, and that there is heterogeneity in transcription of cccDNA including complete silencing. Understanding transcriptional silencing in HBV-infected hepatocytes may be critical to emerging immunotherapy and could be exploited to develop a functional cure.

	Participant (DAART Duration)				
	HB1 (0 months)	HB2 (discontinued 8 months prior)	HB3 (1.5 months)	HB4 (11.5 months)	HB5 (>84 months)
No. (%) infected hepatocytes	52/52 (100%)	249/255 (97.6%)	289/290 (99.7%)	73/255 (28.4%)	26/79 (32.9%)
No. (%) of all hepatocytes with transcriptional silencing (cccDNA+/pgRNA-)	0/52 (0%)	7/255 (2.7%)	0/290 (0%)	9/255 (3.5%)	12/79 (15.2%)
No. (%) of infected hepatocytes with transcriptional silencing	0/52 (0%)	7/249 (2.8%)	0/289 (0%)	9/75 (12.0%)	12/26 (46.1%)

92LB IMPACT OF UNIVERSAL TESTING AND TREATMENT IN ZAMBIA AND SOUTH AFRICA: HPTN071(POPART)

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Background: Universal testing and treatment was proposed as a strategy to achieve steep reductions in HIV incidence in generalized epidemics, yet prior trials showed inconsistent results. We report the results of HPTN071(PopART), the largest HIV prevention trial ever conducted.

Methods: In this community-randomized trial (2013-18), 21 urban communities in Zambia and South Africa were arranged in 7 matched triplets and randomized within triplets to: Arm A (full PopART intervention including universal ART), B (PopART intervention with ART per local guidelines) and C (standard of care). Local guidelines adopted universal ART in 2016. The PopART combination prevention intervention comprised annual rounds of home-based HIV testing by Community HIV-care Providers (CHiPs) who supported linkage to care, ART adherence and other HIV services. Impact was measured in a Population Cohort (PC) comprising one randomly selected adult (aged 18-44y) from a random sample of ~2,000 households per community, surveyed at baseline, 12m, 24m and 36m. Viral load (VL) was measured in all HIV+ PC participants at 24m. The primary outcome was HIV incidence between 12-36m compared between arms. Intervention data on HIV testing and ART uptake were collected by CHiPs in Arm A and B communities.

Results: A total of 48,301 adults were enrolled in the PC. Baseline HIV prevalence was similar across arms (A:21.2%; B:21.1%; C:22.4%). Between 12-36m, 553 incident HIV infections were observed in 39,733 person-years (1.4/100py). The adjusted HIV incidence rate ratio for Arm A compared with C was 0.93 (95%CI:0.74-1.18, p=0.51, Table) and for Arm B compared with C was 0.70 (95%CI:0.55-0.88, p=0.006). Intervention data indicated that the first two 90s were achieved in Arms A and B after three annual rounds. Viral suppression (VS: VL<400 copies/mL) at 24m was 72.1% in Arm A, 67.9% in Arm B and 62.5% in Arm C, with lower rates in men and younger adults (<25y).

Conclusion: The PopART intervention achieved the 90-90-90 targets and high rates of VS (~70%). The intervention, with ART delivered according to local guidelines (Arm B), reduced HIV incidence by 30%. The lack of effect in the full intervention arm (Arm A), where universal treatment was delivered prior to change in guidelines, was surprising and not explained by observed rates of VS. Phylogenetic and qualitative analyses may shed light on this dissonant finding. Community-based HIV testing and linkage is a key component of combination prevention in efforts to achieve effective HIV control.

Table HIV incidence (primary outcome), viral suppression among PC participants and estimated coverage of intervention against the first two of the 90-90-90 targets: HPTN 071 (PopART)

	Arm A PopART/universal ART	Arm B PopART/local guidelines	Arm C SOC
HIV incidence (PC, 12-36m)			
Infections/PY	198/13,007	157/14,156	198/12,570
Incidence Rate (IR/100py)*	1.56%	1.14%	1.68%
Adjusted RR (95%CI)†	0.93 (0.74-1.18) p=0.51	0.70 (0.55-0.88) p=0.006	1
Men			
IR*	0.96%	0.54%	1.00%
Adj RR (95%CI)†	0.88 (0.41, 1.88)	0.52 (0.24, 1.12)	1
Women			
IR*	1.82%	1.41%	2.01%
Adj RR (95%CI)†	0.96 (0.72, 1.28)	0.73 (0.55, 0.97)	1
Younger (18-24y)			
IR*	1.95%	1.58%	1.96%
Adj RR (95%CI)†	1.05 (0.81, 1.37)	0.93 (0.72, 1.21)	1
Older (25-44y)			
IR*	1.41%	0.94%	1.58%
Adj RR (95%CI)†	0.88 (0.67, 1.17)	0.57 (0.43, 0.76)	1
Viral suppression (PC, 24m)			
VL < 400/HIV-positive	1,530/2,158	1,318/1,891	1,480/2,183
Proportion suppressed*	72.1%	67.9%	62.5%
Adjusted RR (95%CI)‡	1.16 (0.99, 1.36) p =0.07	1.08 (0.92, 1.27) p = 0.30	1
Men	183/294 64%	153/244 61%	179/330 49%
Women	1,347/1,864 73%	1,165/1,647 69%	1,301/1,853 67%
Younger (18-24y)	132/291 47%	106/217 45%	134/298 43%
Older (25-44y)	1,398/1,867 76%	1,212/1,674 71%	1,346/1,885 66%
Intervention data (Arms A/B) after 3 annual rounds**			
Know HIV+ status (First 90)*	91.3%	90.8%	Not applicable
On ART (Second 90)*	88.8%	87.9%	

*Mean across seven communities per arm, †Adjusted for age, sex and baseline HIV prevalence, ‡Adjusted for age and sex, **Coverage estimates for adults aged 15+

93 A RANDOMIZED TRIAL ON INDEX HIV SELF-TESTING FOR PARTNERS OF ART CLIENTS IN MALAWI

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Background: HIV testing of sexual partners of HIV-positive clients (index testing) is critical for case identifications and reducing transmission. Current index testing strategies have limited reach – only 20% of partners in Malawi are tested using standard partner referral slips (PRS) – a paper version of passive facility referrals for partners. Delivery of HIVST to partners at their home may address barriers to index testing. We evaluated an index HIVST intervention among partners of ART clients in Malawi.

Methods: A randomized trial was conducted at 3 district hospitals in Malawi between March28-June13, 2018. ART clients were screened during routine services. Inclusion criteria were: >15 years of age; sexual partner with unknown HIV status; no history of interpersonal violence with that partner; and partner lives in facility catchment area. Clients were randomized 1:2: (1) standard PRS or (2) HIVST (Oraquick HIV Self-Test(c) demonstration and distribution and referral for confirmation by blood-based testing). Baseline and follow-up surveys were conducted with ART clients and a subset of sexual partners willing to present at facilities for a survey. Primary outcomes (partner tested, test result, confirmatory testing) were reported by ART clients. Uni- and multivariate logistic regressions were conducted.

Results: 365 ART clients enrolled in the study, with median age 37 years and 22% male. Only 3 clients refused HIVST. 91% and 92% of clients in HIVST and PRS arms respectively reported distributing the intervention to their partners (p-value=0.70; Table). However, 81% of partners in HIVST tested compared to only 29% of partners in PRS (AOR:9.6; p-value<0.001). Positivity rates did not differ by arm (19% in HIVST versus 16% in PRS; p=0.74). Among newly diagnosed HIV-positive partners in HIVST, only 20% received a confirmatory, blood-based test within 4-weeks. 99% and 97% of ART clients reported being comfortable providing HIVST and demonstrating use to partners, respectively. Among partners who used HIVST and completed a survey (n=126; median age

39 years; 67% men), 16% reported challenges understanding HIVST instructions and 8% were unable to interpret HIVST results. Reported adverse events (psychological IPV/end of relationship) did not vary by arm (~8%).
Conclusion: Index HIVST greatly increased HIV testing without increased risk of adverse social events. Inadequate interpretation and test confirmation limits the impact of index HIVST and requires further study.

Table. Participant characteristics and outcomes across two arms of an index HIVST study targeting sexual partners of ART clients: reported by ART clients (n=365)

	Partner Referral Slip	Index HIV Self-Test	OR (95% Confidence Interval)	p-value	AOR (95% Confidence Interval)	p-value
	n(%)	n(%)				
N	107	258	-	-	-	-
Study Outcomes						
Partner received intervention	98 (92%)	234 (91%)	0.93 (0.42-2.09)	0.87	1.21 (0.46-3.20)	0.7
Partner tested	28/95 (29%)	183/225 (81%)	10.43 (5.99-18.14)	<0.001	9.62 (4.79-19.32)	<0.001
Partner tested HIV-positive	4/25 (16%)	30/160 (19%)	1.21 (0.39-3.79)	0.74	0.84 (0.21-3.38)	0.8
Partner completed confirmatory HIV test	-	6/30 (20%)	-	-	-	-
Acceptability and Adverse Events						
Comfortable giving and explaining intervention	97 (98)	238 (99)	1.64 (0.27-9.94)	0.59	1.95 (0.30-12.89)	0.49
Comfortable demonstrating HIVST	-	223 (97)	-	-	-	-
Experienced psychological IPV in the past 4 weeks*	9 (8%)	21 (8%)	0.96 (0.43-2.18)	0.93	1.89 (0.40-8.95)	0.42
End or separation of relationship	7 (7%)	19 (7%)	1.14 (0.46-2.80)	0.77	1.61 (0.50-5.18)	0.43

*adjusting for age, sex, and marital status
**measured as being humiliated, threatened, or insulted since enrolling in the study (past 4 weeks)

94 VIRAL LOAD SUPPRESSION AND YIELD OF HIV TESTS ARE SPATIALLY CORRELATED, KENYA 2015-17

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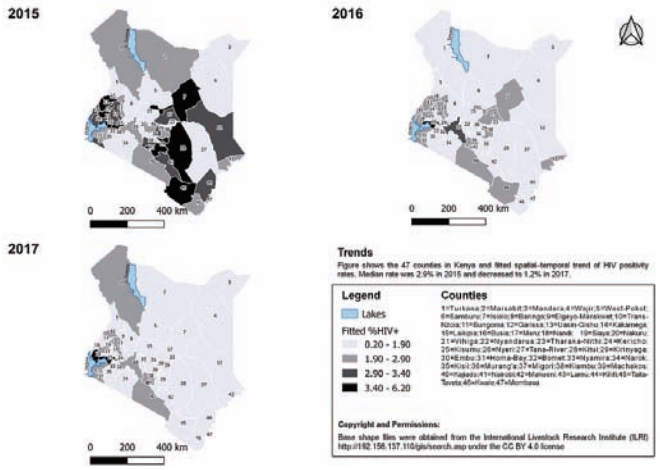
Background: High antiretroviral therapy (ART) coverage and high rates of viral load suppression (VLS) should reduce transmission of HIV, and ultimately, HIV incidence and the number of new HIV diagnoses. We used 3 years of HIV program data in Kenya to assess whether trends in the number of new HIV diagnoses were associated to ART coverage and VLS rates and spatial-temporally auto correlated at county-level [sub-National unit (SNU)].
Methods: We analyzed routine program SNU-level aggregate ART coverage and VLS (proportion of persons on ART with VL<1000 copies/mL) data for 3 years (2015-2017). We examined the association between ART coverage and VLS rates to new HIV diagnoses by fitting spatial and spatial-temporal semi-parametric Poisson regression models using R-Integrated Nested Laplace Approximation (INLA) package. We used the extended Cochran-Mantel-Haenszel stratified test of association to test for trend across years for fitted rates of new HIV diagnosis and a structural equation model to assess direct effects between the two exogenous covariates to fitted newly HIV-diagnosed as the endogenous variable adjusting for clustering by 47 SNUs. Finally, we mapped fitted HIV positivity using QGIS version 3.2.
Results: A spatial-temporal model with covariates was better in explaining geographical variation in HIV positivity (deviance information criterion (DIC) 381.2) than either a non-temporal spatial model (DIC 418.6) or temporal model without covariates (DIC 449.2). Overall, the fitted HIV positivity decreased over 3 years from median of 2.9% in 2015, [interquartile range (IQR): 1.9-3.4] to 1.5% in 2017, IQR(1.3-2.0), (Figure), stratified test of association p=0.032. VLS had a direct effect on HIV positivity rates p=0.014, but ART coverage did not, p=0.502.
Conclusion: In 3 years of widespread availability of ART, we have observed a general decline of rates of new HIV diagnoses associated with improved VLS rates. To assess the trends and impact of implementation of scaled-up care and treatment, spatial-temporal analyses help to identify geographic areas that need focused interventions.



95 HIV TESTING, TREATMENT, AND VIRAL SUPPRESSION COVERAGE IN A CLUSTER-RANDOMIZED TRIAL

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Background: In settings like Botswana with high HIV prevalence and treatment coverage, it is unknown whether uptake of HIV-prevention and treatment interventions can be further increased.
Methods: The Botswana Combination Prevention Project, a pair-matched cluster-randomized trial, compared uptake of an intervention package of intensive HIV testing/counseling(HTC) campaigns, linkage to care, expanded antiretroviral treatment(ART), and male circumcision(MC) versus standard-of-care in Botswana from 2013-2018. In mid-2016 universal ART became standard-of-care. We longitudinally followed residents aged 16-64 years of a random ~20% sample of households in 30 communities (15 intervention, 15 standard-of-care) for ~30 months to assess uptake of ART, viral suppression, and MC. HIV testing was conducted annually. To assess change in HTC coverage (documented HIV-negative test within 12 months or knowledge of HIV-positive status) by arm, we recruited an additional sample of residents not enrolled in the longitudinal cohort from six communities/three pairs at study end. For HTC, ART, and viral suppression, we estimated risk ratios(RR) and 95% confidence intervals(CI) (accounting for clustering) using log-linear Poisson regression adjusted for potential baseline coverage imbalances, stratified by time and pair. MC uptake among HIV-uninfected uncircumcised men aged 16-49 years was evaluated using pair-stratified interval-censored Cox proportional hazards.
Results: We enrolled 8,974 HIV-negative and 3,596 HIV-positive residents in the longitudinal cohort. An additional 11,767 residents were assessed for HTC uptake at study end. After accounting for baseline differences, HTC coverage was significantly higher in the intervention arm at study end (P<0.0001; Fig.1A). ART coverage and viral suppression increased in both arms, with greater increases in the intervention arm (ART P<0.0001; viral suppression P=0.004; Fig.1B-C). At study end, 98% (95%CI: 93%-100%) of HIV-positive cohort participants in intervention communities were on ART; 96% (95%CI: 92%-100%) were virally suppressed. A small number (348) of 1,873 HIV-negative uncircumcised men reported becoming circumcised, with higher uptake in the intervention arm (P<0.0001).
Conclusion: Population levels of HTC, ART, viral suppression, and MC increased in both arms over time, with significantly greater increases in the intervention arm. Remarkably, at study end, nearly all HIV-positive cohort participants in intervention communities were on ART and virally suppressed.

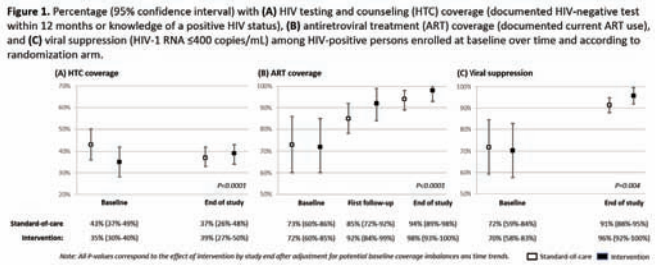

Figure 1. Percentage (95% confidence interval) with **(A)** HIV testing and counseling (HTC) coverage (documented HIV-negative test within 12 months or knowledge of a positive HIV status), **(B)** antiretroviral treatment (ART) coverage (documented current ART use), and **(C)** viral suppression (HIV-1 RNA ≤400 copies/mL) among HIV-positive persons enrolled at baseline over time and according to randomization arm.

96 FACTORS ASSOCIATED WITH PERSISTENT VIREMIA WITH UNIVERSAL "TEST & TREAT" IN UGANDA

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Background: Beginning in 2013, Uganda implemented universal "test and treat" in high-risk populations, including fishing communities along Lake Victoria. Here, we use population-based data to identify characteristics associated with persistent viremia among HIV-positive individuals in hyperendemic fishing communities during "test and treat" scale-up.

Methods: Between November 2011-February 2017, five surveys were conducted in four Ugandan fishing communities (>40% HIV prevalence) as a part of an open cohort of all consenting persons aged 15-49 years. HIV viral loads were assessed among HIV-positive participants at three surveys. The unit of analysis was a person-interval (two consecutive visits). Person-intervals were categorized into four outcomes based on a viral load cutoff of 400 copies/mL: durable suppression, new/renewed viral suppression, viral rebound, and persistent viremia. Multivariate Poisson regression with generalized estimating equations and robust variance estimators was used to estimate adjusted relative risk ratios (aRRRs) and 95%CIs of persistent HIV viremia versus durable or new/renewed viral suppression.

Results: 3,404 HIV-positive individuals participated in the cohort, including 1,346 participants with viral load data at ≥2 visits (n=1,883 person-intervals). Overall, the prevalence of durable suppression was 50.4% and becoming newly suppressed was 30.3%, while the prevalences of viral rebound and persistent viremia were 2.9% and 16.4%, respectively. Over the study period, the prevalence of population-level durable suppression increased from 29.7% to 67.9%. Younger age (15-29 vs. 40-49 years; aRRR=1.93 [95%CI: 1.27-2.93]), male sex (aRRR=1.87 [95%CI: 1.32-2.65]), and being never married (vs. currently married; aRRR=1.93 [95%CI: 1.39-2.68]) were factors significantly associated with persistent viremia. Younger age and male sex were strongly correlated with high risk sexual behaviors. These findings were consistent in sensitivity analyses restricted to the most recent survey interval.

Conclusion: In hyperendemic communities with universal "test and treat", being young (<30 years), male, and never married were associated with persistent viremia. Young people had higher levels of high-risk sexual behavior suggesting those most likely to have persistent HIV viremia are also most likely to sustain HIV transmission. Programs tailored to men and high risk youth are necessary to reduce HIV transmission in sub-Saharan Africa.

97 VIROLOGIC FAILURE, LOW-LEVEL VIREMIA, AND VIRAL BLIP AFTER HIV RNA SUPPRESSION

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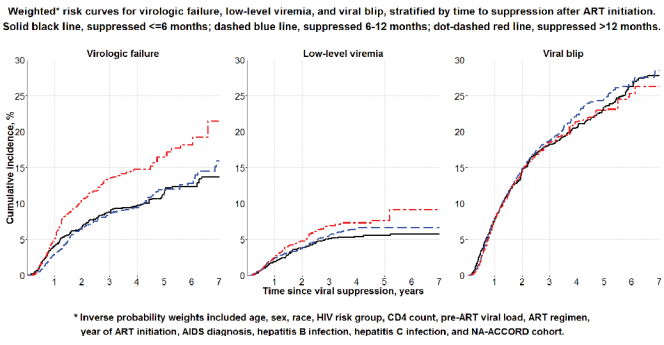
Background: Time to HIV RNA suppression after antiretroviral therapy (ART) initiation may impact durability of viral suppression. Our objective was to estimate risks of: a) virologic failure; b) low-level viremia (LLV); and c) viral blip by time to suppression among patients enrolled in NA-ACCORD clinical cohorts in 2006–2015.

Methods: We followed 14551 new ART initiators aged ≥18 years from suppression (2 consecutive viral loads [VLs] ≤50 copies/mL [cpm]) to unsuppressed VL, death, loss to follow-up, or administrative censoring. Time to suppression was categorized as ≤6, 6–12, or >12 months. Outcomes were: a) virologic failure: 2 consecutive (≤180 days) VLs ≥200 cpm; b) LLV: 2 consecutive (≤270 days) VLs 51–199 cpm; and c) viral blip: 1 VL 51–199 cpm preceded and followed by VL ≤50 cpm (≤270 days between VLs). For each outcome, we estimated cumulative incidence (risk) and risk differences (RD) by time to suppression over 7 years, accounting for death as a competing event. Unsuppressed VL other than the outcome of interest was censored. Inverse probability weights were used to account for informative censoring and confounding by ART anchor drug (NNRTI, PI, InSTI) and other factors.

Results: After starting ART, 31% (4575) of patients suppressed in ≤6 months, 41% (5912) in 6–12 months, and 28% (4064) in >12 months. Among patients who suppressed in ≤6 months, we observed 7-year weighted risks of failure, LLV, and blip of 13.7%, 5.8%, and 27.8%, respectively. Corresponding weighted risks were 15.9%, 6.6%, and 28.5% for patients who suppressed in 6–12 months, and 21.5%, 9.2%, and 26.3% for patients who suppressed in >12 months. Patients who suppressed in >12 months had a 7.8% (95% CI: 0.4%, 22.1%) higher risk of failure, 3.4% (95% CI: -1.2%, 11.1%) higher risk of LLV, and similar risk of blip (RD: -1.4%; 95% CI: -8.1%, 7.5%) compared to those who suppressed in ≤6 months. No notable differences in risks of failure, LLV, or blip were observed between patients who suppressed in 6–12 months and those who suppressed in ≤6 months.

Conclusion: Suppression >12 months after ART initiation was associated with higher long-term risks of failure and LLV compared to suppression in ≤6 months; there was no association with risk of blip. Investigating whether the relationships between time to suppression and these outcomes are modified by ART regimen is warranted. Identifying barriers to achieving rapid HIV RNA response may be needed to maximize durability of viral suppression and optimize treatment as prevention efforts.



Weighted* risk curves for virologic failure, low-level viremia, and viral blip, stratified by time to suppression after ART initiation. Solid black line, suppressed <=6 months; dashed blue line, suppressed 6-12 months; dot-dashed red line, suppressed >12 months.

* Inverse probability weights included age, sex, race, HIV risk group, CD4 count, pre-ART viral load, ART regimen, year of ART initiation, AIDS diagnosis, hepatitis B infection, hepatitis C infection, and NA-ACCORD cohort.

98 FIFTY-PERCENT REDUCTION IN HIV INCIDENCE IN CHOKWE DISTRICT, MOZAMBIQUE, 2014-2017

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Background: Reduction of HIV incidence attributed to increasing coverage of a combination of biomedical interventions (CBI) has not been evaluated in

Mozambique. We assessed in the Chokwe Health Demographic Surveillance System (CHDSS) trends in HIV incidence, and prevalence of viral load suppression (VLS, <1000 RNA copies/mL) and CBI including circumcision among men (MC), and HIV testing, diagnosis, and use of antiretroviral therapy (ART) among persons living with HIV (PLHIV). Located in Chokwe District, CHDSS includes ~95,000 residents.

Methods: Since 2014, HIV testing services (HTS) including referral for MC and follow-up linkage-to-care for PLHIV has been offered annually at all ~20,515 CHDSS households. HIV incidence and prevalence of HIV, VLS, and CBI were assessed with annual surveys of residents aged 15-59 years in 10% (2014-2015) or 20% (2016-2017) of randomly selected households. Dried blood spots of participating PLHIV were tested at CDC for VLS and recent infection (mean <161 days). Annualized HIV incidence was calculated with a standard formula; participants on ART or with VLS were defined as having longstanding infection. Census-weighted CHDSS HIV incidence, incidence rate ratios (IRR), and prevalence of HIV, VLS, and CBI were estimated for the first three survey rounds (R1-R3, April 2014–March 2017). District health facilities offered ART for all PLHIV beginning in mid-2016, R3.

Results: During R1-R3, 39,586 (72%) of 55,287 residents aged 15-59 years tested for HIV at home at least once, and 3,449 (886 men) were newly HIV diagnosed and provided linkage services. HIV prevalence decreased from 27.3% in R1 to 25.7% in R3 (p< 0.05) (Table). By R3, prevalence of MC, and prior HIV diagnosis, current ART use, and VLS among PLHIV increased 14.0%-21.6% (Table). Of 2,750 PLHIV, 30 (1.1%) had been recently infected (R1, 1.5%; R2, 1.2%; R3, 0.7%). HIV incidence decreased 53% overall (p<0.05), and 54% and 51% (p>0.05) among men and women, respectively (Table). Among persons aged 15-24 and 25-59 years, HIV incidence fell from 1.3% (0.0-2.5%) and 2.4% (0.6-4.3%) in R1 to 0.4% (0.0-1.0%) and 1.3% (0.1-2.4%) in R3, respectively.

Conclusion: In a high HIV prevalence district in Mozambique, increasing population prevalence of HIV biomedical interventions was associated with increasing prevalence of VLS and an approximate 50% reduction in HIV incidence among adults. Annual home-based HTS with referral and linkage services can help achieve rapid scale up of CBI, increased VLS, and reduced HIV incidence.

Outcomes of Annual Household Sample Surveys, Chokwe Health Demographic Surveillance System, Mozambique

Survey Round (Time Period)	Participants Total (% HIV+)	Circumcised % (95% CI)	Prior HIV Dx % (95% CI)	Current ART Use % (95% CI)	HIV VLS % (95% CI)	HIV Incidence % (95% CI)	IRR (95% CI)
Total							
Round 1 (04/2014-04/2015)	3,271 (27.3)	49.8 (46-53)	66.5 (63-70)	53.6 (50-58)	46.9 (43-51)	1.8 (0.8-2.8)	Ref
Round 2 (05/2015-01/2016)	3,263 (26.6)	56.1 (52-60)	77.8 (74-82)	63.1 (59-67)	56.9 (52-62)	1.1 (0.2-2.0)	0.63 (0.30-1.30)
Round 3 (03/2016-03/2017)	5,177 (25.7)	63.8 (61-67)	88.1 (86-90)	75.2 (72-78)	68.4 (65-72)	0.8 (0.2-1.5)	0.47 (0.23-0.96)
Male							
Round 1 (04/2014-04/2015)	1,139 (21.8)	49.8 (46-53)	58.1 (51-66)	47.2 (40-55)	36.3 (28-44)	1.7 (0.0-3.4)	Ref
Round 2 (05/2015-01/2016)	915 (21.4)	56.1 (52-60)	66.1 (58-75)	51.5 (43-60)	39.5 (29-50)	1.4 (0.0-3.4)	0.83 (0.28-2.47)
Round 3 (03/2016-03/2017)	1,423 (18.4)	63.8 (61-67)	88.0 (83-93)	67.1 (59-75)	64.8 (55-75)	0.8 (0.0-2.0)	0.46 (0.15-1.44)
Female							
Round 1 (04/2014-04/2015)	2,078 (30.8)	--	70.3 (66-74)	56.4 (52-61)	51.1 (47-55)	1.8 (0.5-3.1)	Ref
Round 2 (05/2015-01/2016)	2,348 (29.7)	--	83.0 (80-86)	68.2 (64-72)	63.6 (59-69)	0.9 (0.2-1.7)	0.50 (0.23-1.11)
Round 3 (03/2016-03/2017)	3,754 (29.9)	--	88.2 (86-90)	78.0 (75-81)	69.5 (66-73)	0.9 (0.2-1.6)	0.49 (0.22-1.08)

Dx = Diagnosis; VLS = viral load suppression; HIV Incidence = recent HIV infections per 100 person years; IRR = incidence rate ratio.

99 A MODEL IMPACT ANALYSIS OF PrEP AND TasP IN FSW DEMONSTRATION PROJECT IN BENIN

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Background: Daily pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP) can reduce HIV acquisition and transmission risk respectively. With a 2015 HIV prevalence of 19%, female sex workers (FSW) are a key group for HIV prevention in Cotonou, Benin. From 2014-2016, a demonstration project assessed the feasibility and utility of TasP and PrEP among FSW. We used mathematical modelling to project the population-level impact of the project and of extending the intervention for 20 years.

Methods: A dynamic model of HIV transmission, PrEP and treatment among FSW, clients and the general population was parameterised using PrEP, TasP and condom use data from the demonstration project and other historical demographic, sexual behaviour, epidemiological and intervention data from Cotonou. The model was calibrated within a Bayesian framework to HIV prevalence and ART coverage data by risk group pre- and post-intervention, PrEP and TasP initiations and PrEP use data from the study. The model assumed 256 PrEP initiations of HIV- FSW, 47% of whom were retained after 2 yrs, over 250 person-yrs of follow-up with average 63% detectable (>0.3 ng/mL) tenofovir (PrEP). TasP was modelled by increased testing and ART initiation among HIV+ FSW giving 107 initiations over 2 yrs, 60% of whom were retained after 2 years. We also modelled extending the intervention over 20 years reaching 21% of HIV- and 81% HIV+ FSW on PrEP and TasP respectively. We estimated the median (5th-95th percentile uncertainty range [UI]) fraction and number of incident HIV infections and DALYs averted (among FSW & whole population) over 20 yrs following the 2 or extended 20 yr interventions by comparing each PrEP and TasP intervention with its counterfactual (baseline scenario without modelled intervention).

Results: Model results suggest that the 2 yr PrEP and TasP intervention prevented 1% [0.7–1.4] and 7% [4-11] of infections in FSW over 20 yrs respectively, compared to 0.3% [0.2–0.7] and 7% [4-11] in the whole population (Table). The extended 20 yr PrEP and TasP interventions could prevent 3% [1–5] and 12% [7-19] of all infections respectively over 20 yrs. Combining TasP and PrEP has a marginal incremental impact overall (infections and DALYs averted) over TasP alone.

Conclusion: Due to suboptimal adherence to PrEP by FSW in the demonstration project, PrEP is expected to avert few HIV infections and DALYs among FSW and overall. TasP will have a greater impact and should be prioritised over PrEP to improve FSW HIV prevention in Cotonou.

Table: Median model estimates (5th-95th UI) of number and percent of HIV infections prevented and DALYs averted over a 20 year period by the PrEP, TasP and combined interventions (based on 93 model fits)

Intervention scenarios		Number of HIV infections prevented		Fraction of HIV infections prevented		DALYs averted	
		FSW	Whole adult population	FSW	Whole adult population	FSW	Whole adult population
2-year study intervention (2015–2017)†	PrEP only (10% coverage in 2017*)	3 [2 - 4]	27 [14 - 43]	1% [0.7 – 1.4]	0.3% [0.2 – 0.7]	3 [2 - 7]	70 [34 - 138]
	TasP only (83% coverage in 2017**)	20 [10 - 33]	644 [302 - 900]	7% [4 - 11]	7% [4 - 11]	106 [47 - 384]	1340 [748 - 2800]
	PrEP + TasP combined	23 [12 - 36]	565 [314 - 930]	8% [5 – 12]	7% [4 - 11]	108 [49 – 388]	1396 [768 – 2880]
20-year extended intervention (2015–2035)	PrEP only (21% coverage in 2035*)	33 [18 - 43]	224 [115 - 330]	11% [8 – 13]	3% [1 – 5]	22 [15 – 44]	346 [159 - 634]
	TasP only (81% coverage in 2035**)	35 [17 - 64]	933 [535 - 1540]	12% [7 - 19]	12% [7 - 19]	182 [80 - 631]	1950 [1130 - 4250]
	PrEP + TasP combined	64 [35 - 92]	1070 [599 - 1680]	21% [16 - 27]	14% [8 - 21]	199 [91 - 644]	2200 [1240 - 4430]

* Posterior FSW population size in 2017 of 1345 [1159 -1560]; * among HIV- FSW; ** among HIV+ FSW.

100 PROTECTION AGAINST PENILE OR INTRAVENOUS SHIV CHALLENGES BY bNAb 10-1074 OR 3BNC117

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Background: Broadly neutralizing antibodies (bNAbs) 10-1074 and 3BNC117 are in clinical development for HIV prevention and treatment. In macaque models, passively administered 10-1074 or 3BNC117 protects against repeated rectal or vaginal SHIV challenges; however, their efficacy against other HIV acquisition routes relevant to men (penile) or persons who inject drugs (intravenous, IV) has not been discerned. Here, we evaluated the protective efficacy of a single subcutaneous (SC) injection of 10-1074 alone, or in combination with 3BNC117, against repeated penile or IV SHIV challenges, respectively.

Methods: Macaques (6 rhesus, 5 cynomolgus) were injected SC once with 10-1074, or a combination of 10-1074+3BNC117, respectively (10mg each bNAb/kg). Beginning one week later, macaques were challenged repeatedly once weekly with SHIVsf162P3 (rhesus) or SHIVAD8-EO (cyno) via penile (200 $TCID_{50}$ into the prepuce pouch, 16 $TCID_{50}$ into the distal urethra) or IV (130 $TCID_{50}$) routes, respectively, until SHIV infection was confirmed via plasma viral load assay. Control macaques, which received no antibody, were challenged identically (10 penile, 2 IV). Longitudinal plasma samples were assayed via Tzmbl neutralization assay, using virions pseudotyped with 10-1074-sensitive (X2088_c9) or 3BNC117-sensitive (Q769.d22) HIV Envs to determine bNAb concentrations.

Results: Macaques administered 10-1074 and challenged via the penis were protected against a median of 15.5 weekly challenges, as compared to controls (median=2.5; P=0.0007, Log-rank test) and exhibited a median 10-1074 plasma level of 0.50µg /ml (range=0.10-0.70µg/ml) at SHIV breakthrough. Macaques administered both bNAbs and challenged IV were protected against a median of 5 weekly challenges, as compared to controls (median=1; P=0.0143, Log-rank test) and exhibited a median 10-1074 plasma level of 1.1µg/ml (range=0.6-1.6µg/ml), but undetectable 3BNC117, at SHIV breakthrough.
Conclusion: A single subcutaneous administration of 10-1074 durably protected macaques against repeated penile SHIV challenges providing the first evidence of efficacy by a bNAb against penile infection. Significant protection also was observed against repeated IV SHIV challenges following administration of 10-074+3BNC117, which was mainly due to 10-1074 that exhibited longer persistence. Our data support the continued development of 10-1074 as a long-acting PrEP candidate for men or persons who inject drugs who may not be able to adhere to daily PrEP.

101 PROTECTION AGAINST VAGINAL SHIV INFECTION WITH AN INSERT CONTAINING TAF AND EVG

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Background: On-demand topical PrEP for HIV prevention has several advantages over a daily oral PrEP regimen, including reduced costs, limited drug toxicity, decreased risk of resistance, and potential to increase adherence. Inserts containing tenofovir alafenamide fumarate (TAF) in combination with elvitegravir (EVG) are being developed by CONRAD/EVMS for flexible, on-demand vaginal or rectal pericoital use. We recently found in a dose-ranging pharmacokinetic assessment in macaques that vaginal administration of inserts containing 20 and 16 mgs of TAF and EVG, respectively, resulted in rapid accumulation of EVG and durable levels of tenofovir diphosphate (TFV-DP) in mucosal tissues at concentrations associated with in vivo protection. Here we used a macaque model of vaginal SHIV transmission to investigate the protective efficacy of TAF/EVG inserts.
Methods: Normal cycling pigtail macaques (n=14) were exposed vaginally to SHIV162P3 once a week for up to 13 weeks. Six macaques received inserts containing a fixed-dose combination of TAF/EVG (20 mg/16 mg) and 8 received matching placebo inserts. Inserts were placed in the posterior vagina near the cervix 4 hours before each SHIV exposure. Infection was monitored weekly by serology and RT-PCR amplification of SHIV RNA in plasma. A Kaplan-Meier survival analysis was used to compare the survival distribution between the two groups and efficacy was calculated as 1-(p1 / p0), where p1 and p0 denote the proportion of infections per total challenges for TAF/EVG and placebo controls, respectively.
Results: Of the 8 macaques that received placebo inserts, 7 became SHIV infected while 1 remained SHIV negative following 13 weekly challenges. The median number of challenges to infect macaques treated with placebo inserts was 3 (range 2-13). In contrast, 5 of 6 macaques that received TAF/EVG inserts remained protected after 13 challenges resulting in an estimated efficacy of 92%. Survival analysis demonstrate at least a 9-fold reduction in risk of infection in macaques that received TAF/EVG compared to placebo inserts (p=0.007; log-rank).
Conclusion: Vaginal administration of inserts containing TAF and EVG was highly effective in preventing SHIV infection in a macaque model that mimics vaginal transmission of HIV in women. The data support the clinical development and first-in-human testing of TAF/EVG inserts for on-demand topical prophylaxis against vaginally acquired HIV infection.

102 MODERATE EFFICACY OF ORAL SINGLE-AGENT TAF AGAINST VAGINAL SHIV INFECTION IN MACAQUES

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Background: Tenofovir alafenamide (TAF) is a prodrug of TFV that is under evaluation as oral PrEP in combination with emtricitabine (FTC), and as a long-acting single agent delivered from implants. We recently showed that oral TAF in combination with FTC was highly effective in preventing vaginal simian HIV (SHIV) infection in female pigtailed macaques. Here we investigated if TAF alone is sufficient for preventing vaginal SHIV infection.
Methods: The efficacy of single agent TAF in preventing vaginal infection was investigated in an established model of vaginal SHIV exposures consisting of up to 15 once-weekly virus challenges with SHIV162p3. Nine pigtail macaques received a clinically equivalent dose of TAF (1.5 mg/kg) orally 24h before and 2h after each weekly virus exposure. Infection outcome was compared with 21 placebo animals (6 real-time and 15 historical controls). TFV-diphosphate (TFV-DP) and dATP levels in PBMCs were measured once a week at the time of virus challenge. Kaplan-Meier survival analysis and a log-rank test was used to compare time to infection in TAF-treated animals relative to controls. Infection rates were compared using the fisher exact test. TFV-DP levels were measured in vaginal and rectal biopsies from a separate group of 9 macaques.
Results: Infection rates and time to SHIV RNA detection were similar in real time and historical controls (p=0.500 and p=0.319, respectively). Two of the 9 TAF-treated animals did not metabolize TAF (TFV-DP level of 15 and 16 fmols/106 cells) and were excluded from the analysis. Three of the remaining 7 TAF-treated and 19/21 control animals became infected (p=0.021). Infection in TAF-treated animals was also delayed relative to controls (p=0.036). TFV-DP levels in the 3 animals infected during TAF PrEP (median=351 fmols/106 cells; range=143-1,568) were similar to those seen in the 4 uninfected macaques (median=331; range = 236-584; p=0.359). dATP/TFV-DP ratios were also similar among infected and protected animals (median=0.685 and 1.045, respectively, p=0.982). After a single oral dose, TFV-DP was detected in 5/9 vaginal and 9/9 rectal biopsy specimens (5 and 7.9 fmols/mg, respectively).
Conclusion: A clinically equivalent dose of single agent TAF administered orally 24h before and 2h after virus exposure without FTC conferred moderate protection against vaginal SHIV infection in female macaques. These data highlight the importance of defining the PBMC TFV-DP concentrations associated with complete vaginal protection from single agent TAF.

103 LYMPHOID TISSUE PHARMACOKINETICS OF TENOFOVIR-ALAFENAMIDE VS -DISOPROXIL FUMARATE

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Background: The secondary lymphoid tissues (LT), lymph nodes (LN) and gut-associated lymphoid tissue (GALT), are the primary sites of HIV replication and where the latent pool of virus is maintained. In HIV-infected persons with undetectable plasma HIV-RNA, an association has been reported between low concentrations of antiretroviral drugs (ARVs) in LT and measures of persistent viral production. In animals, tenofovir alafenamide (TAF) has been found to have enhanced LT penetration compared with tenofovir disoproxil fumarate (TDF). No confirmatory or comparative human LT data, however, are available. The objective of this work was to compare the LT pharmacokinetics (PK) of TAF and TDF in HIV-infected persons.
Methods: Participants were HIV-infected persons enrolled in clinical studies of LT compartments and receiving TAF or TDF with other ARVs. PBMCs and mononuclear cells (MNCs) from LN, ileum and rectal tissues were obtained at steady-state. Intracellular concentrations of tenofovir-diphosphate (TFV-DP) were quantified by LC-MS/MS. Summary statistics were calculated.
Results: PK data were obtained from a total of 58 persons: TAF, n=13; TDF, n=45. The Table presents median and interquartile range values for TFV-DP in PBMCs (TAF, n=38; TDF, n=45), LN (TAF, n=9; TDF, n=43), ileum (TAF, n=9; TDF, n=22) and rectum (TAF, n=7; TDF, n=35). In PBMCs, median TFV-DP concentrations were 7-fold higher with TAF compared with TDF. In LN MNCs, TFV-DP concentrations were 4.7-fold higher with TAF vs. TDF.
Conclusion: TAF administration in HIV-infected persons produced higher TFV-DP concentrations in LN MNCs than did TDF. This finding confirms animal studies showing LN concentrations of TFV-DP were 5.7 to 15-fold higher with TAF, depending on the anatomical site of the LN. The 7-fold higher TFV-DP concentrations in PBMCs achieved with TAF vs. TDF, is consistent with other

literature and known PK characteristics of TAF and TDF. TFV-DP concentrations in the ileum and rectum were lower with TAF compared with TDF; this may be due to better bioavailability of TAF vs. TDF and thus a lower fraction of unabsorbed drug in the gastrointestinal lumen. The higher LN concentrations of TFV-DP achieved with TAF demonstrate that drug penetration into this compartment can be modified in HIV-infected persons. This finding allows pharmacodynamic evaluations to investigate whether enhanced LN concentrations elicit a different virologic response.

Matrix	Tenofovir-diphosphate (fmol/10^6 cells) Median (and Interquartile Range)	
	TAF (n=13)	TDF (n=45)
PBMC	448 (389, 622)	63 (44, 91)
LN	104 (80, 146)	22 (8, 27)
Ileum	66 (14, 246)	3056 (458, 5835)
Rectum	97 (30, 131)	441 (287, 985)

104LB THE PHASE 3 DISCOVER STUDY: DAILY F/TAF OR F/TDF FOR HIV PREEXPOSURE PROPHYLAXIS

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Background: Emtricitabine/tenofovir disoproxil fumarate (F/TDF) prevents HIV infection when used as daily pre-exposure prophylaxis (PrEP). Compared to TDF, tenofovir alafenamide (TAF) has higher intracellular tenofovir (TFV)-DP levels, lower plasma TFV levels, and improved renal and bone safety when used for HIV treatment. This study describes the efficacy and safety of F/TAF vs F/TDF for PrEP in cis-men who have sex with men (MSM) and transgender women (TGW) who are at high risk of HIV acquisition.

Methods: This randomized (1:1), double-blind, active-controlled study was conducted in North America and Europe at sites with high HIV prevalence in MSM. Entry required ≥2 episodes of condomless anal sex (CAS) in past 12W or rectal gonorrhea/chlamydia or syphilis in past 24W. Participants received daily blinded F/TAF (200/25 mg) or F/TDF (200/300 mg), with matching placebo; pill counts and blood levels were used to measure adherence. Primary endpoint was the HIV infection rate per 100 person years (PY) when 50% completed 96W. Renal safety, 3 anatomic site sexually transmitted infection (STI) testing and risk behavior were assessed every 12W. Using CDC reported HIV surveillance data we calculated the background "HIV incidence rate" in at risk individuals not on PrEP from 105 US metropolitan statistical areas (MSAs) for comparison.

Results: 5387 adults were treated at 94 sites in 11 countries, with 3226 (60%) in the US. Mean age was 36, range 18-76 years, 9% Black, 1% TGW, 23% had prior PrEP use and 41% had >3 receptive CAS partners in the 90 days before study entry. 90% of participants completed ≥48W on study, with median follow up of 84W. For this analysis, 85% remained on study drug: 6% discontinued by participant choice and 6% were lost to follow up. On-study sexual HIV risk persisted with an STI rate of 99.5/100PY. Across both arms, there were 21 HIV diagnoses-an infection rate of 0.26/100 PY-a figure significantly lower than the expected HIV infection rate for those at risk but not on PrEP in the US (Table). Both drugs were tolerated well with 1.5% AE-related discontinuations, with GI most common.

Conclusion: In a multinational population of cis-MSM and TGW at risk of sexual HIV infection, the HIV incidence rate on either F/TAF or F/TDF was very low and significantly less than the background rate in those at risk but not on PrEP in the US. In almost 2 years of follow up, both F/TAF and F/TDF, given daily, were tolerated and had low discontinuation rates.

Table: Baseline HIV risk, on-study STIs, HIV incidence rates in US (not on PrEP) and in DISCOVER

Baseline HIV sexual risk (%)	
Proportion with ≥3 CAS partners (receptive) in prior 12W	40.7
Recreational drug use in prior 12W	66.7
Rectal gonorrhea/rectal chlamydia/syphilis in prior 24W	9.9/12.5/9.1
Proportion given ≥1 post-exposure prophylaxis (PEP) in prior 12M	15.6
On-study STI rate/100 PY	
Any Gonorrhea, Chlamydia or Syphilis	99.5
Gonorrhea: any site/rectal	47.2/21.5
Chlamydia: any site/rectal	42.3/28.2
Syphilis	10.0
Background US HIV incidence rate in those not on PrEP/100 PY (95% CI)	
All 105 MSA sites in US	3.45 (3.41, 3.49)
MSA sites in US that overlap with DISCOVER	3.81 (3.76, 3.87)
Measured HIV incidence rate in DISCOVER study/100 PY (95% CI)	
All 94 sites	0.26 (0.16, 0.40)
55 US sites only	0.27 (0.14, 0.45)

105 USING EHR DATA TO IDENTIFY POTENTIAL PrEP CANDIDATES IN A LARGE HEALTH CARE SYSTEM

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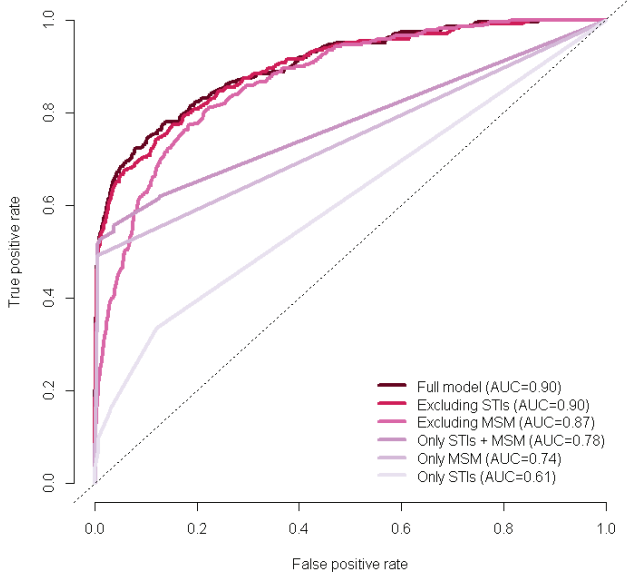
Background: HIV preexposure prophylaxis (PrEP) prevents HIV acquisition but uptake has been limited. Electronic health record (EHR) data may help identify patients who are at high risk of HIV acquisition and could benefit from PrEP.

Methods: We developed and validated a prediction model to identify potential PrEP candidates in a cohort of members of Kaiser Permanente Northern California not diagnosed with HIV and having ≥2 years of enrollment and ≥1 outpatient visit during 2007-2017. Using EHR data on 68 demographic, clinical, and behavioral variables potentially predictive of HIV risk, we applied logistic regression and machine learning methods to predict incident HIV cases in a derivation dataset of patients entering the cohort in 2007-2014. We assessed performance of candidate models by cross-validated area under the curve (AUC, range 0-1). We evaluated how the best-performing model might perform prospectively by validating it among members entering the cohort in 2015-2017, and compared this full model with simpler models using only traditional risk factor variables (i.e., men who have sex with men [MSM] and sexually transmitted infections [STIs]).

Results: Of 3,751,740 eligible patients in 2007-2017, there were 1422 incident HIV cases. The best-performing model for predicting incident HIV was least absolute shrinkage and selection operator (Lasso), with an AUC of 0.90 in 2007-2014. The final model included 41 predictors, such as Black race, home ZIP code, urine positivity for methadone, and use of medications for erectile dysfunction. The full model performed well when validated prospectively using 2015-2017 data (AUC 0.89). Model performance remained high when excluding the MSM variable (AUC 0.87) or STI variables (AUC 0.90), but was reduced when including only MSM (AUC 0.74), STIs (AUC 0.61), or both (AUC 0.78; Figure). Patients in the top 1% of HIV risk scores included 45/68 (66%) male HIV cases but 0/13 (0%) female HIV cases among those entering the cohort in 2015-2017. Using the top 1% of risk scores to define potential PrEP candidates in 2015-2017, we identified 6076 candidates, of whom 5577 (92%) were not currently on PrEP.

Conclusion: Prediction models using EHR data can identify patients who are at high risk of HIV acquisition but not using PrEP, and should be tested as a strategy to improve PrEP use. Models using rich clinical data outperform models using only traditional risk factors. Additional EHR variables or other data are needed to identify females who may benefit from PrEP.

Figure. Cross-validated area under the receiver-operating curve (AUC) for models predicting incident HIV infection, Kaiser Permanente Northern California, 2007-2014 (n=3,144,022)



106 PERSISTENCE WITH HIV PREEXPOSURE PROPHYLAXIS IN THE UNITED STATES, 2012-2016

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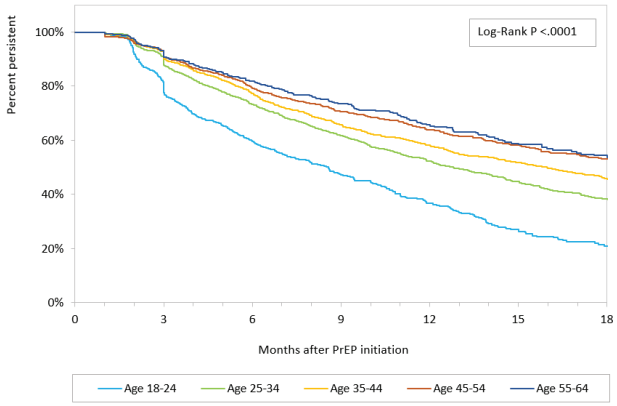
Background: Daily oral preexposure prophylaxis (PrEP) with Truvada is highly effective in preventing HIV infection with adherence to daily dosing and persistence with PrEP during periods of HIV risk. We estimated persistence and associated factors among a cohort of PrEP users with commercial health insurance.

Methods: Using data from the IBM® MarketScan® Research Databases, we created a cohort of PrEP users aged 18-64 years who initiated PrEP between 1/1/2012 and 12/31/2016. We restricted our analysis to persons continuously enrolled in their health plans for at least 6 months prior to and 6 months after their initial PrEP prescription. We monitored each person's medication fill persistence, defined as time from the initial PrEP prescription fill until there was a gap in prescription fills >30 days. Patients were considered nonpersistent if they did not refill within 30 days after exhausting PrEP medications from previous fills. We used Kaplan-Meier time-to-event methods to estimate the proportion of PrEP users who persisted with PrEP at 6 and 12 months after initiation. We censored patients if they disenrolled from insurance or were diagnosed with HIV prior to nonpersistence. We conducted Cox proportional hazards models for nonpersistence adjusting for sex, age, urbanicity, and region.

Results: In our cohort of 7,250 commercially insured PrEP users, 98.2% were male, and 10.6% were aged 18-24 years. During the study period, after initiation 74.8% of PrEP users persisted for 6 months, and 55.7% for 12 months. The median persistence was 14.5 months (95% CI=13.9-15.0), but was significantly shorter for female PrEP users (6.9 months; 95% CI=4.7-11.6) and for users aged 18-24 years (8.6 months; 95% CI=7.4-9.3). After adjusting for other factors, we found that PrEP users who were female, young, and resided in rural area were less likely to be persistent users. The Kaplan-Meier curves of PrEP persistence stratified by age group demonstrated that PrEP persistence increased with age. Only 36.6% of the users aged 18-24 years persisted for 12 months, compared to 65.3% aged 55-64 years. (Figure)

Conclusion: More than half of commercially insured persons who initiated PrEP persisted with it for 12 months. However, women and young users persisted with PrEP for shorter times than men or older adults. We were not able to assess reasons for PrEP nonpersistence. A better understanding of patient factors for nonpersistence is important to support PrEP use for persons who might benefit from it during periods of risk.

Figure: PrEP persistence by age group among commercially insured PrEP users, MarketScan commercial database, 2012-2016 (n=7,250)



Note: PrEP = preexposure prophylaxis.

107 IMPACT OF PrEP ON DRUG RESISTANCE AND ACUTE HIV INFECTION, NEW YORK CITY, 2015-2017

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Background: A major concern for PrEP use is possible induction of drug resistance by prescribing PrEP to persons with undiagnosed HIV infection. Such persons may not have been screened appropriately for HIV or may have been screened during the window period between HIV exposure and infection. However, no data are available to determine the frequency of this phenomenon.

Methods: Using data from cases assigned for partner services from November 2015 to August 2017, we examined the viral resistance profile of recently diagnosed persons (< 12 months) in New York City (NYC) with a recent history of PrEP use to determine rates of mutations to PrEP component medications: emtricitabine (3TC) (M184I/V/IV/MV) and tenofovir disoproxil fumarate (TDF) (K65R). We compared acute HIV infection (AHI), negative NAAT, and prevalence of viral resistance in pre-diagnosis PrEP users and those with no PrEP use (never-users).

Results: In this period, 95 (3%) out of 3,721 persons with a recent HIV diagnosis assigned for partner services had a report of pre-diagnosis PrEP use. Median duration of PrEP exposure before diagnosis was 3 months (IQR=7). Pre-diagnosis PrEP users were more likely than never-users to have a negative NAAT pre-diagnosis (33% vs 4%, p<0.0001), and were more likely to be diagnosed with AHI (33% vs 9%, p<0.0001). Genotypes were available for 75% of pre-diagnosis PrEP users and 62% of never-users. M184I/V/IV/MV was significantly more prevalent among pre-diagnosis PrEP users than never-users (26% vs 2%, p-value <0.0001). K65R mutations were found in 4 persons; none were pre-diagnosis PrEP users.

Conclusion: In a study of recently HIV diagnosed people from NYC, persons with a history of pre-diagnosis PrEP use were significantly more likely to have resistance mutations to 3TC. There were no signature TDF mutations (K65R) detected among pre-diagnosis PrEP users. In addition, persons with a history of PrEP were significantly more likely to have AHI leading to diagnosis. The latter may be due to an effect of the PrEP or the possibility that persons receiving PrEP are more likely to be receiving health care more regularly. Only one-third of pre-diagnosis PrEP users had evidence of a negative NAAT. Our findings stress the importance of screening regularly to reduce the likelihood of PrEP start during undetected HIV infection in order to reduce the risk of inducing drug resistance.

108 THE CURRENT STATUS OF LATENCY REVERSING AGENTS

Carine M. Van Lint, *Université Libre de Bruxelles, Brussels, Belgium*

Combination antiretroviral therapy (cART) successfully prolongs the life of HIV+ patients, prevents the development of AIDS and substantially reduces the risk of HIV-1 transmission. However, cART is not curative and patients must adhere to a life-long cART regimen, leading to a new set of complications and making of HIV a chronic disease. Indeed, cessation of cART invariably leads to a rapid rebound of the virus in most patients. HIV-1 persistence is notably due to the existence

of replication-competent, transcriptionally-silent proviruses in a latent state. Latently-infected cells, mainly resting CD4+ T cells but possibly other infected cell types, are insensitive to cART and can evade the patient immune system. However, latency is a reversible state and reactivation of HIV-1 gene expression from latently-infected cells constitutes a permanent source for virus production in cART-treated patients. One of the most explored therapeutic approach aiming at purging HIV-1 reservoirs, the shock and kill strategy, consists in reactivating HIV-1 gene expression from the latently-infected cellular reservoirs, followed by killing of the virus-producing infected cells. Several classes of latency reversing agents (LRAs), including epigenetic modifying agents, have been studied to reactivate viral gene expression, based on the understanding of the molecular mechanisms involved in HIV-1 latency. Due to the small numbers of latently-infected cells found in vivo, these molecular mechanisms have been mainly studied in in vitro cell line and primary cell models for HIV-1 latency and in ex vivo models obtained with patient-derived latently-infected cells. However, many of these studies have highlighted the major contribution of epigenetic and transcriptional mechanisms to HIV-1 silencing. Clinical trials using individual LRAs have yielded variable, but sometimes encouraging results concerning their ability to induce HIV-1 transcription. However, none of these trials have caused significant and persistent reduction in the HIV-1 reservoir size. The multiplicity of the silencing mechanisms involved in HIV-1 latency, the intrinsically dynamic and heterogeneous nature of the latent HIV-1 cellular reservoirs, the variations in patient clinical history and the lack of selectivity of LRAs constitute causes of the LRA ineffectiveness in clinical trials. These causes will need to be understood in order to rationally improve the "shock" strategy so that it could reach clinical success.

109 DISCOVERY AND CHARACTERIZATION OF A VIRUS-INTRINSIC HIV LATENCY CIRCUIT

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Over the past decade, our studies found that HIV-1 latency is driven by stochastic fluctuations in Tat transcription (Weinberger et al. *Cell* 2005), which provided the first evidence for a classic theory that transcriptional fluctuations (a.k.a., 'noise') are harnessed for cell-fate decisions. We subsequently characterized a 'hardwired' virus-intrinsic HIV circuit that regulates latency and appears optimized by evolution (Razooky et al. *Cell* 2015; Rouzine et al. *Cell* 2015). Our studies also found FDA-approved compounds that act as noise-enhancer molecules and potentiate current LRAs, dramatically increasing their potency (Dar et al. *PNAS* 2012; Dar et al. *Science* 2014). Recently, we discovered that HIV alternative splicing is post transcriptional, thereby generating a noise-attenuating circuit that regulates HIV's latency decision (Hansen et al. *Cell* 2018). Perturbing the HIV latency circuit, for example with noise-enhancer or suppressor molecules, may represent a novel strategy for HIV cure, and functional cure, approaches.

110 SILENCING OF RETROVIRAL GENE EXPRESSION BY THE HUSH COMPLEX

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Retroviral DNAs are transcriptionally silenced in a number of settings and in specific cell types, an important mechanism for the inhibition of virus replication. The HUSH complex (containing the three subunits TASOR/FAM208A, MPP8, and periphilin) was originally identified as required for the maintenance of silencing of transfected DNAs integrated into heterochromatic regions of vertebrate genomes. HUSH binds to histone H3K9me3 marks, and brings the histone methyltransferase SETDB1/ESET to sustain and likely spread this H3K9me3 silencing modification along chromatin. HUSH was found to be important for the silencing of those retroviral DNAs that have integrated into heterochromatin. This position-dependent silencing by HUSH is distinct from the more universal silencing of retroviral DNAs in embryonic stem cells, mediated by zinc finger proteins tethering TRIM28/Kap1 to specific sequence elements of the viral DNA. We have recently found that the HUSH complex is also involved in the silencing of unintegrated viral DNAs of many retroviruses in virtually all cell types. HUSH is recruited to unintegrated DNA of the mouse leukemia viruses by NP220, a large DNA-binding protein with preference for oligo(C) sequences. This silencing, involving both SETDB1/ESET and histone deacetylases (HDACs), is relieved upon integration of the DNA into euchromatic regions of permissive cell types. NP220 and HUSH thereby act to inhibit early viral gene expression and the overall rate of virus replication. The Vpx and Vpr proteins of HIV-2 and various strains of the simian immunodeficiency viruses bind HUSH and induce its proteasomal degradation, stimulating virus replication. Vpx can also induce expression of HIV-1 proviruses in various models of latency, suggesting that HUSH may help maintain repression of silent proviruses in the latent reservoir.

111 THE POWER OF THE HIV PROMOTER: IMPACT OF HIV-DRIVEN VIRAL AND HOST GENE EXPRESSION

Ya-Chi Ho, *Yale University, New Haven, CT, USA*

Antiretroviral therapy (ART) inhibits the enzymatic function of viral proteins or blocks viral entry but does not inhibit HIV-1 LTR promoter activity. The HIV-1 LTR remains functional and active despite effective ART. Around 1–64 per million $CD4^+$ T cells contain replication-competent HIV-1 proviruses. HIV-1 LTR drives the expression of intact HIV-1 proviruses, leading to viral rebound upon treatment interruptions. Around 100–1000 per million $CD4^+$ T cells contain replication-defective HIV-1 proviruses. These replication-defective HIV-1 proviruses can be transcribed and translated, leading to antigen presentation to $CD8^+$ T cells and immune distraction. Meanwhile, cells harboring intact and defective HIV-1 proviruses can both undergo clonal expansion, and the clonally expanded cells increase over time. HIV-1 integration site analysis revealed striking enrichment of HIV-1 integration at specific sites of proliferation-related genes in the clonally expanded cells, but the mechanisms remain unknown. The rarity and the lack of cellular markers of HIV-1-infected cells makes mechanistic studies challenging. Using single-cell RNAseq and high-resolution RNA landscape mapping on $CD4^+$ T cells from virally suppressed, HIV-1-infected individuals, we show that HIV-1 LTR dominates over the host promoter and drives the host gene expression at the integration sites in genes associated with in vivo clonal expansion. HIV-1 activates cryptic host gene splice sites and induces aberrant host gene transcription, while HIV-1 viral genome transcription remains intact. Overall, HIV-1 LTR drives viral and host gene expression at the same time. Strategies targeting HIV-1 LTR should be explored to disrupt HIV-1-induced immune activation and HIV-1-driven aberrant proliferation gene expression.

112 DYNAMICS OF ACUTE HCV IN WESTERN EUROPE

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The Global Health Sector Strategy GHSS calls for the elimination of viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65%). Indeed, with the advent of highly successful and well tolerated direct acting antiviral combinations, allowing HCV cure after short durations of treatment within 8-12 weeks in more than 95% of all treated patients, HCV elimination appears to be a reachable goal. Nevertheless, the WHO report from 2016 clearly describes some significant obstacles which need to be overcome in order to approach HCV elimination. The first major obstacle clearly is underdiagnoses with only 20% of people with HCV worldwide having been diagnosed so far. Equally disturbing is that while approximately 71 million people were thought to be infected with HCV in 2015, only 1.76 million people received HCV treatment in 2016 despite all praised advances in HCV therapy. Microelimination in well targeted patient groups with regular monitoring such as hemophiliacs, dialysis patients and also HIV/HCV coinfected patients therefore, appear low-hanging fruits on the pathway to global HCV elimination. First national studies from Netherlands and Switzerland suggest that indeed by increasing treatment uptake in all HIV/HCV coinfected men who have sex with men (MSM) the incidence of newly acquired acute HCV infections has been successfully reduced by over 50%. Nevertheless, increased HCV outbreaks among HIV negative MSM using PrEP as well as the high risk of HCV reinfection in MSM in general jeopardize these first encouraging reports. Clearly, earlier HCV treatment initiation and use of HCV-RNA and HCV-antigen testing rather than HCV-serology, allowing earlier acute HCV diagnosis, will be needed to impact HCV dynamics in the long-term. Under consideration of the still significantly increasing PrEP user number in Western Europe a call for action is needed to prevent a further spread of HCV into the MSM community.

113 A VACCINE TO PREVENT HCV: ARE WE GETTING THERE?

Andrea L. Cox, *Johns Hopkins University, Baltimore, MD, USA*

The World Health Organization set goals in 2016 for reductions in prevalent and incident hepatitis C infection necessary to achieve elimination of HCV as a public health problem by 2030. Modeling demonstrates that global HCV control will require annual rates of cure that are consistently and significantly higher than new HCV infection rates. However, a recent study showed that nearly 60% of surveyed countries had the opposite— more HCV infections

than cures. Therefore, control is unlikely to occur without improved focus on and success in reducing the number of new HCV infections. Risk factors for HCV infection vary globally, but together result in ~1.75 million new HCV infections annually worldwide. An effective preventative HCV vaccine could prevent transmission regardless of risk factors. While a highly effective vaccine could prevent infection altogether, a vaccine that increases the rate of HCV clearance and prevents chronic infection may be sufficient to reduce transmission and disease burden. Despite vaccine need, barriers to vaccine development remain, including limitations to HCV culture systems, viral diversity, limited models and at-risk populations for testing vaccines, and incomplete understanding of protective immune responses. On the positive side, there is evidence that protective immunity exists in populations at ongoing risk of infection. For those who have cleared initial infection and become reinfected, more rapid and effective control of viral replication with subsequent exposures compared to initial exposure supports that adaptive immunity develops and, while not sterilizing, that it protects against chronic disease. Decades of research have revealed that HCV-specific CD4+ helper T cells, CD8+ cytotoxic T cells, and antibodies are all important in mediating protection against persistent HCV infection. Vaccine strategies to induce all three adaptive immune responses are in development. Adjuvanted envelope or core protein and virally vectored non-structural antigen vaccines have advanced into healthy volunteers not at risk for HCV, with viral vectors encoding non-structural proteins the only vaccine strategy tested in at-risk individuals to date. Despite development challenges, a prophylactic vaccine is necessary for global HCV control. This talk will discuss the need for a vaccine, evidence that a vaccine to prevent chronic infection is possible, challenges to immunologic control of HCV, and the vaccine strategies tested to date.

114 CHOICES AND DILEMMAS: PREVENTING TUBERCULOSIS IN PEOPLE WITH HIV INFECTION

Amita Gupta, *Johns Hopkins University, Baltimore, MD, USA*

An estimated 23% of the world's population is infected with tuberculosis infection. Notably, an estimated 300,000 people with HIV died from tuberculosis in 2017 with the vast majority of deaths occurring in low and middle income countries. Preventing tuberculosis in people living with HIV is therefore a global priority. The most common regimen used for tuberculosis preventive therapy has been Isoniazid Preventive therapy. However this regimen requires 6-9 months of daily therapy with longer therapy needed for areas with high community exposure and incidence. Recently several trials have identified newer and shorter regimens for tuberculosis prevention: a one month daily isoniazid with rifapentine regimen; a 3 month weekly isoniazid and rifapentine regimen; and a 4 month daily isoniazid and rifampin regimen. In addition special populations such as children and pregnant women have also been more formally studied in clinical trials. Phase II vaccines trials for the prevention of tuberculosis have also had some interesting results. Lastly, expert guidance statements and new clinical trials have been launched for preventing tuberculosis in those with known exposure to multi-drug tuberculosis. This talk will summarize the data from these different studies and highlight the choices and dilemmas of preventing tuberculosis in people living with HIV infection.

115 TREATING MULTIDRUG-RESISTANT TUBERCULOSIS IN THE REAL WORLD: NEW DRUGS AND REGIMENS

Jennifer Furin, *Harvard Medical School, Boston, MA, USA*

The treatment landscape for rifampin-resistant forms of tuberculosis (RR-TB) is rapidly changing with the introduction of new drugs and shorter treatment regimens. For the first time ever, phase III trials and rigorous operational research studies are being done to support policy on the optimal management of RR-TB. This information is being used by programs and normative public health bodies to offer radically different therapeutic options for people living with the disease, including all-oral therapy. There are, however, inherent tensions between the existing RR-TB science, the WHO treatment recommendations, and what is actually being done in countries. This is driven in part by the noxious "standard of care" regimen and the long periods of time it takes to design, execute and complete RR-TB trials. This session will present the 2018 WHO recommendations for the treatment of RR-TB and the science behind those recommendations, including the STREAM-1 and delamanid phase III trials. The status of ongoing RR-TB studies will also be reviewed, with an eye toward improving the way RR-TB clinical trials are done. Finally, the state of the field will be discussed in terms of ethics, human, rights, and an alarming lack of access to novel therapies in most regions of the world, since advances in RR-TB science mean little if they cannot reach the people who need them most.

116 THE STORY OF U=U: SCIENTIFIC UNDERPINNINGS

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The story of U=U began in the 1990s when it became apparent that the risk of sexual transmission of HIV varied by sexual practice. In the beginning of this century, many physicians started to question if there was in fact any risk of HIV transmission at all during fully suppressive antiretroviral therapy. The Rakai data indicted risk of transmission to HIV negative serodifferent partners was strongly correlated with the viral load of the positive partner; and while only two small observational studies prospectively evaluated this question in the setting of fully suppressive cART, the absence of any documented case of transmission with suppressive ART gained attention. In 2008 the Swiss Federal Commission on AIDS related issues published what became rapidly known as the "Swiss statement". Based on the absence of any reported case and on additional biological data supporting the observation, the commission decided that the evidence was strong enough to claim absence of any risk of sexual transmission in the setting of optimal cART use. The statement also made reference to other similar public health messages, such as non-transmission to household contacts, where the absence of evidence was the only basis for such statements. Furthermore, the publication of the Swiss statement raised the profile of this issue and likely supported the reporting of any observed cases of transmission. The continued absence of evidence of any such cases was a further argument supporting the statement of "no-risk". The obvious weakness of the "Swiss statement" was the assumed detection and reporting of cases of transmission. Therefore, the development of prospective, well-designed studies actively looking for cases of transmission in the setting of suppressive ART provided important scientific evidence to support the statement of "no-risk". None of three large studies observed a single case of sexual transmission in the setting of fully suppressive cART. The increasing number of documented exposures without any signal of risk of transmission increases the certainty of the "no risk" statement.

117 CARING FOR U: CLINICAL CONUNDRUMS

Nneka Nwokolo, *Chelsea and Westminster Hospital, London, UK*

U=U, the concept that a person with an undetectable viral load is incapable of transmitting HIV sexually, has transformed the lives of people living with HIV worldwide and is doing much to reduce the stigma associated with this condition (although there is still a long way to go). Evidence for U=U comes from clinical trials involving thousands of couples (both homosexual and heterosexual) in serodifferent relationships in which no linked transmissions occurred from HIV-positive people with fully suppressed viral loads. Clinically, however, the practical implementation of U=U in some circumstances may pose a significant challenge; for example, - Can a clinician discussing the risk of transmission with a patient in a resource-limited setting with poor or no access to viral load monitoring, or where structural factors and competing priorities adversely impact adherence, reassure that patient with the same certainty as they could an individual who doesn't have these concerns? - Strictly speaking, U=U applies to the risk of sexual transmission; can we reliably apply this message in the context of breastfeeding, to a healthcare worker following a sharps injury or to an HIV negative individual who shares a syringe during intravenous drug use? - Should we offer postexposure prophylaxis to a patient with a sexually transmitted infection whose sexual partner informs him or her that they have an undetectable viral load? So, while at an individual level, U=U provides powerful motivation for adherence to treatment and retention in care, it is crucial that we continue to strive for answers to the many as yet unanswered questions that still remain.

118 ME AND U: COMMUNITY PERSPECTIVES

Carrie Foote, *Indiana University, Bloomington, IN, USA*

In early 2016, the Undetectable=Untransmissable (U=U) campaign began in an effort to ensure the message of U=U was shared with community; at the time there was much resistance to the science and hesitance to share the message with providers and people living with HIV. Led by people living with HIV, the campaign took off and now has become global; the U=U slogan is now universally known in the HIV arena around the world. This session provides an overview of the global campaign today, some of the main community impacts, and remaining community challenges. Key issues covered include: the impact

of U=U on dismantling HIV related stigma; importance of 'language matters' when communicating the U=U science; and the impact of U=U on the sexual and reproductive lives of PLHIV. Community concerns discussed include the continued resistance to sharing the message, limited updates to existing resources to reflect the U=U science; questions about breastfeeding and syringe sharing; concerns with unequal access to testing, treatment and care; and concerns with stigmatizing and criminalizing people living with HIV who are not virally suppressed. Personal stories of PLHIV and examples of the campaign are shared to illustrate the main points.

119 MORE THAN U: MAXIMIZING POPULATION-LEVEL EFFECTS OF U=U

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At the population level, U=U is part of HIV treatment as prevention. HIV treatment as prevention explicitly includes the goals of increasing HIV testing, HIV treatment, and undetectable viral load. In 2014, UNAIDS released its 90/90/90 goals with the dual aims of improving the health of people living with HIV and reducing HIV transmission to lead to the end of the AIDS epidemic. The 90/90/90 goals are based in part on modelling of the preventive effects of HIV treatment as prevention in an African heterosexual epidemic. Several pragmatic population-based trials of HIV treatment as prevention are underway in sub-Saharan Africa, and observational evidence provide strong evidence that treatment roll-out has been associated with reduced HIV transmission in some settings. In epidemics where transmission among men who have sex with men (MSM) predominates, transmission dynamics are substantially different, and it is likely that achieving the 90/90/90 goals may not be enough, on its own, to end the HIV epidemic. U=U is a vital part of combination prevention, and effects are maximised where it is combined with ensuring early HIV diagnosis. The treatment as prevention.

120 THE CHALLENGES OF HIV TREATMENT IN AN ERA OF POLYPHARMACY

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The prevalence of HIV-infected people aged 50 years or older is increasing rapidly and this population often exhibits a higher number of comorbidities and other age-related conditions at a younger age than in the general population. Numerous cohort studies (eg NA-Accord, EuroSIDA, DatAIDS, GEPPO, PODIVM, MACS, US Veterans Affairs, POPPY; SHCS) have highlighted the increasing burden of co-morbidities in older PLWH with some studies describing the prevalence of polypharmacy (most often described as more than 5 co-medications) to be >40%. With polypharmacy comes the inevitable consideration of drug-drug interactions (DDIs). So we need to understand i) the mechanisms of DDIs (which are not always CYP-mediated!), ii) the difference in DDI potential of the currently recommended antiretroviral agents and iii) the clinical relevance of DDIs. We always need to be aware of the unexpected! The prescribing information or label of a drug is often the primary source of DDI awareness. But the labels cover a limited number of specific DDIs and not infrequently there are differences between the US Prescribing Information and the European SmPC or country specific information which may confuse. Therefore health care professionals often rely on other sources (websites, apps) for their daily management of DDIs. With commonly used co-medications it may be necessary to: change or modify the dose of a co-medication, change the ARV, modify the dose of the ARV or take care with the timing of administration. However it is also important to take care that co-meds are not under dosed. As we look to the future, we need research programs to determine the impact of eliminating medications not essential for quality of life and survival for those aging with HIV (ie de-prescribing). We also need to face the challenge of DDI studies with long acting ARVs – currently injectable and implants. However there are other emerging technologies and with all long acting medicines there will be an important role for PBPK modelling in generating DDI data in virtual patients.

121 NEUROHIV: WHAT THE VIRUS TELLS US

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HIV-1 can be detected in the brain/CNS, and more conveniently in cerebral spinal fluid (CSF), at all times after infection. Its presence reflects a number of processes ranging from the trafficking of infected T cells through the establishment of an independently replicating population (compartmentalization) where the virus has evolved to infect a host cell with a low density of CD4 ($CD4^{low}$ phenotype). A deeper understanding of these multiple processes has come from a clearer definition of viral entry phenotypes. A common misconception in the HIV-1 field is that all viruses that use CCR5 (R5 viruses) are macrophage-tropic. In fact, macrophage-tropic/ viruses, with their ability to enter cells with a low density of CD4 (as seen on macrophages), are rarely found in the blood and have not been detected among transmitted/ founder viruses. The main form of HIV-1 found in the blood, and the form that enters the CNS by trafficking in infected T cells, uses CCR5 but requires a high density of CD4 (as is seen on CD4+ T cells) for efficient entry; this predominant form of HIV-1 is more appropriately called R5 T cell-tropic. This clearer understanding of HIV-1 entry phenotypes has allowed a reassessment of when and where macrophage-tropic/$CD4^{low}$ viruses evolve and their role in pathogenesis. Earlier studies highlighted the detection of $CD4^{low}$ viruses in the CNS and their link to severe CNS disease at late stages prior to death, such as HIV-associated dementia (HAD). The evolution of macrophage-tropic viruses can be viewed as an evolutionary path the virus follows when its target CD4+ T cells become limiting, a situation that is especially common behind the blood-brain barrier in the CNS. Persistent viral infection in the brain is likely to be very different from infection of CD4+ T cells in tissues such as lymph nodes, spleen, and GALT. The question of viral escape in the CNS during suppressive therapy, either transient or persistent, can now be addressed in the context of viruses that are adapted to replication in this environment. Similarly, rebound virus in the CSF after treatment interruption may provide insight into the presence of compartmentalized reservoirs.

122 BRAIN CONNECTIVITY IN NEUROLOGICALLY ASYMPTOMATIC PEOPLE WITH HIV SWITCHING ART

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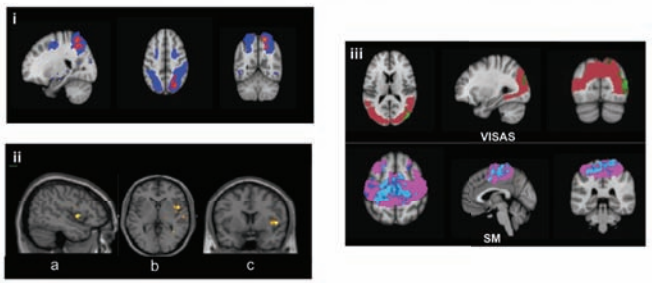
Background: Central nervous system (CNS) toxicities of antiretroviral therapies are well described. Functional MRI (fMRI) can assess brain activity and functional connectivity (FC) non-invasively, providing insights into pathogenic mechanisms. We assessed changes in fMRI patterns in neurologically asymptomatic people with HIV (PWH) participating in two studies assessing CNS parameters when switching antiretroviral therapy.

Methods: Virologically suppressed PWH switching from tenofovir-DF/ emtricitabine (TDF/F) with efavirenz to rilpivirine (n=10) and TDF/F with raltegravir to dolutegravir (n=12) were included. Changes in CNS parameters included patient-reported outcome measures (PROM) of sleep (PSQI) and depression (HADS). fMRI imaging was assessed at baseline and at least 120 days after switching therapy and included resting-state fMRI (RS-fMRI) and behavioral stop signal reaction times (SSRT) task fMRI. Resting state and SSRT fMRI were examined by independent component analyses (ICA) using the FSL's MELODIC tool.

Results: Of 22 participants, all were male, median age (range) was 49 (33-71) years, median CD4+count (range) was 700 (339-1164) cells/uL and HIV RNA was less than <20 copies/mL in all. Switching from efavirenz to rilpivirine was associated with enhanced connectivity of the Dorsal Attention Network (DAN) most pronounced in the right superior parietal lobule and a reduction in stop SSRTs (response inhibition, p=0.025, see figure) which was positively correlated with the duration of time previously on efavirenz (median 5 (range 1-10) years, p=0.02). Switching from raltegravir to dolutegravir was associated with increased connectivity in the DAN, sensory-motor (SM), and associative visual (VISAS) networks. There was a 4.8% decline in anxiety scores on HADS and a 2% decline in sleep symptoms on PSQI, with scores of 19 and 14, and 22 and 20 at baseline and follow-up, respectively, after switching from efavirenz to rilpivirine (p<0.005) and no significant changes in PROMS when switching from raltegravir to dolutegravir. No association between changes in fMRI and PROMs were observed.

Conclusion: In PWH switching antiretroviral therapy, changes in fMRI are evident. This was most pronounced in PWH switching from efavirenz to rilpivirine where improved attention and response inhibition on fMRI was evident. Whilst changes were evident on fMRI when switching integrase inhibitor, any clinical implications of these findings require further validation.

Figure 1. Functional connectivity after switching ART. i, Enhanced RS-fMRI connectivity of the DAN network after switching from efavirenz to rilpivirine. *Red: areas of enhanced connectivity; Blue DAN mask generated by MELODIC.* ii, Enhanced activation following SSRT fMRI after switching from efavirenz to rilpivirine in yellow; a. pars opercularis, b. right posterior parietal cortex c. right insula. iii Enhanced RS-fMRI connectivity of the VISAS and SM networks after switching from raltegravir to dolutegravir. *Green: areas of enhanced connectivity within the VISAS network 120 days compared to baseline; Magenta: VISAS mask; Blue: areas of enhanced connectivity within the SM network 120 days compared to baseline*



123 DEEP-LEARNING CEREBRAL BLOOD FLOW FOR COGNITIVE-IMPAIRMENT CLASSIFICATION IN HIV

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Background: Despite the use of combination antiretroviral therapy (cART), HIV-associated neurocognitive disorders (HAND) remain prevalent in people living with HIV (PLWH). A potential biomarker reflective of HAND is changes in cerebral blood flow (CBF) over time, which can be measured with Arterial Spin Labeling. We propose a method of approximating and classifying cognitive impairment (CI) in PLWH using longitudinal CBF data and deep neural networks (DNN).

Methods: Virologically controlled (viral load < 50 copies/mL) PLWH (n=63) participants and HIV- controls (n=33) with at least 2 separate imaging sessions were analyzed. The majority were male (54%) and the mean age was 48 years (+/-13.1). Free Surfer regions were combined to get an average CBF for 12 brain regions (cerebellum, thalamus, caudate, putamen, pallidum, hippocampus, amygdala, frontal, parietal, temporal, cingulate, occipital). Participants completed neuropsychological testing representing 3 cognitive domains (learning, memory, and executive). Raw scores were transformed into Z-scores using demographic-corrected norms, and Z-scores within a cognitive domain were averaged for domain Z-scores. A domain Z-score < -1 was classified as CI. Average rates of change (AROC) were calculated by subtracting the CBF of time point 1 from time point 2 and dividing by the time between the scans. A DNN was trained for each cognitive domain on the CBF and AROC using cross-validation, and evaluated based on mean squared error (MSE). A low MSE (< .2) indicates good approximation.

Results: A DNN could discriminate between PLWH and HIV- controls with AUC .94 using CBF and AROC. The best individual brain regions for discriminating these 2 groups were the thalamus, amygdala, pallidum, and hippocampus. For CI prediction in PLWH, the MSE for the DNNs across all brain regions in PLWH was .11 and AUC .86. The best predictors of impairment in the learning domain in PLWH using CBF and AROC were the caudate, thalamus, and putamen. The best predictors in the memory domain in PLWH were the putamen and amygdala. The best predictors in the executive domain in PLWH were the cerebellum cortex and cingulate. All regions showed a reduction in CBF over time in PLWH.

Conclusion: HAND persist in spite of cART. Our models indicates a decrease in CBF is associated with HIV in specific brain regions, and the rate of decrease of CBF is indicative of impairment. These changes are involved in various domains and are primarily subcortical in nature.

124 HOST GLYCOMIC DETERMINANTS OF HIV-ASSOCIATED NEUROCOGNITIVE IMPAIRMENT DURING THERAPY

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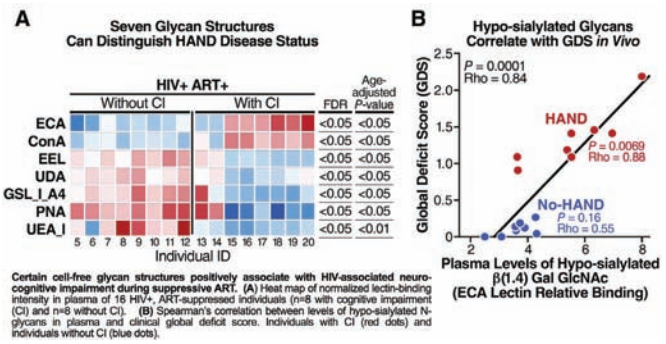
Background: A comprehensive understanding of the pathophysiological mechanisms driving HIV-associated chronic inflammation can lead to the development of strategies to delay or prevent age-associated co-morbidities that are increasingly prevalent despite suppressive antiretroviral therapy (ART). Glycans on circulating glycoproteins and immunoglobulin G (IgGs) are known to modulate systemic inflammatory responses. However, whether HIV-associated chronic inflammation, at least in part, is promoted by alterations in the host glycome remains unknown.

Methods: We profiled the glycomes of plasma and IgGs from 40 HIV+ individuals (ART-suppressed and viremic) and 10 matched HIV- controls, including a subset of ART-suppressed individuals with variation in levels of HIV-associated cognitive impairment as measured by clinical global deficit scores (GDS). We also measured levels of 16 pro- and anti-inflammatory cytokines, and markers of T-cell activation, using Luminex and flow cytometry, respectively. False discovery rates (FDR) were computed to adjust for multiple comparisons.

Results: HIV infection was associated with persistent alterations in plasma and IgG glycomes, including decreased levels of the anti-inflammatory highly-sialylated glycans when compared to HIV- controls (FDR < 0.05). Levels of IgGs highly-sialylated glycans were reduced with age in HIV+ ART+ individuals (rho = -0.72, p = 0.005). Levels of plasma highly-sialylated glycans (A4G4S3) correlated with higher CD4 count (rho=0.57, p=0.03), lower levels of CD4+ T cell activation (rho = -0.66, p = 0.004), and lower levels of the pro-inflammatory cytokine TNFα (rho = -0.8, p = 0.0009). Finally, when we compared levels of glycan structures between HIV+ ART+ individuals with and without cognitive impairment (with comparable CD4 count, nadir CD4, and age), we found that levels of seven glycan structures were statistically different between the two groups (FDR<0.05). When the levels of these seven glycan structures were correlated with GDS, we found that levels of hypo-sialylated oligosaccharides positively correlate with the degree of neurological impairment (rho = 0.84, p = 0.0001).

Conclusion: Our data show that altered glycosylation patterns persist despite suppressive ART, and suggest that lower levels of sialylated glycans, with documented anti-inflammatory roles, may contribute to immune activation, chronic inflammation, and the pathogenesis of combinatorial HIV- and age-associated co-morbidities affecting the central nervous system.



Certain cell-free glycan structures positively associate with HIV-associated neurocognitive impairment during suppressive ART. (A) Heat map of normalized lectin-binding intensity in plasma of 16 HIV+, ART-suppressed individuals (n=8 with cognitive impairment (CI) and n=8 without CI). **(B)** Spearman's correlation between levels of hypo-sialylated N-glycans in plasma and clinical global deficit score. Individuals with CI (red dots) and individuals without CI (blue dots).

125 CSF SCD30 ELEVATION DESPITE SUPPRESSIVE ART SUGGESTS CNS HIV PERSISTENCE

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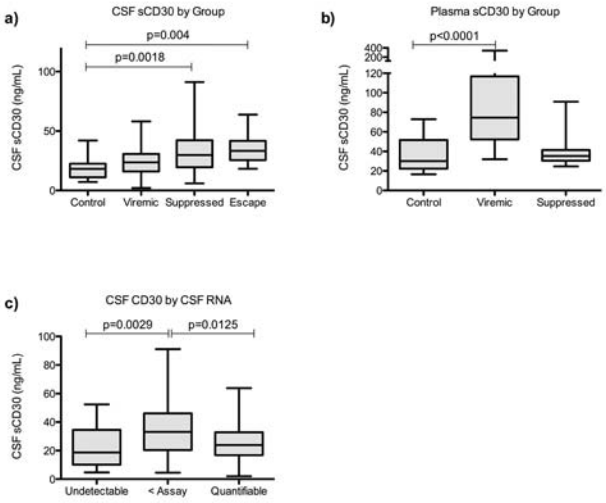
Background: HIV-1 RNA is often but variably enriched in CD30+ CD4 T cells in HIV-infected individuals on suppressive ART. ART reduces soluble CD30 (sCD30) levels in plasma, but not surface expression on T cells, and treatment with an anti-CD30 antibody-drug conjugate reduces HIV burden in cells from ART-suppressed individuals in vitro and in vivo. This study investigates sCD30 in the central nervous system (CNS), a potential HIV reservoir, as a marker of persistent HIV infection.

Methods: sCD30 levels were measured in banked cerebrospinal fluid (CSF) samples and matching plasma from healthy HIV-uninfected controls (n=18), HIV-infected viremic individuals (n=52), individuals on suppressive ART (n=40), HIV-controllers (n=10), and participants with CSF escape (plasma RNA <50 copies/mL, detectable CSF RNA; n=10). sCD30 levels (median, IQR) were compared across groups and correlated with CSF HIV RNA and markers of axonal injury and myeloid cell activation using nonparametric tests.
Results: Compared with uninfected controls (30 ng/mL, 23-50), plasma sCD30 levels were elevated in viremic participants (75 ng/mL, 53-116; p<0.001), but not in those on suppressive ART (35 ng/mL, 31-39). In contrast, CSF sCD30 levels remained elevated in ART-suppressed individuals (34 ng/mL, 19-46; p=0.002) and in those with CSF escape (33 ng/mL, 27-40; p=0.004) compared with controls (18 ng/mL, 11-23). Interestingly, individuals with very low level CSF HIV RNA (detectable but <40 copies/mL) had higher CSF sCD30 than those with higher RNA levels (quantifiable above the limit of detection) and to participants with undetectable CSF RNA (median 33 vs 24 vs 19 ng/mL, p=0.005). No association was observed between CSF sCD30 and plasma HIV RNA, concurrent or nadir CD4 T cell count, duration of infection, plasma sCD30, or CSF total protein. CSF sCD30 correlated with CSF neurofilament-light chain, a marker of axonal injury (r=0.36, p<0.001), but not with neopterin, a marker of myeloid cell activation.
Conclusion: Soluble CD30 levels remain elevated in the CSF but not plasma of HIV-infected individuals on ART. In addition, CSF sCD30 is correlated with neuronal injury markers and low-level residual CNS viremia, but not with markers of myeloid cell activation or general CNS inflammation. CSF sCD30 appears to be produced in the setting of very low, but not higher, levels of CSF HIV RNA, which may reflect virus release compared to the high burst size characteristic of productive viral infection.



126 CSF HIV RNA DETECTED AT <20 COPIES/ML ASSOCIATES WITH BLOOD-BRAIN BARRIER MEASURES

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Background: A subset of people living with HIV (PLWH) has quantifiable HIV RNA in cerebrospinal fluid (CSF) despite plasma HIV suppression; this 'CSF escape' can associate with inflammation and injury in the central nervous system. However, it is unknown whether detection of CSF HIV RNA below the limit of quantitation (LOQ) on commercially available clinical assays associates with clinical parameters or biomarkers of neuropathogenesis during antiretroviral therapy (ART).
Methods: PLWH on ART for >1 year consented to a research blood draw and lumbar puncture. HIV-1 RNA testing was performed on paired CSF and plasma samples using the Roche Ampliprep Taqman_v2.0 assay (lower LOQ 20 cps/mL). Markers of blood brain barrier dysfunction and neuroinflammation (CSF albumin, protein, and WBC) and monocyte activation (plasma and CSF neopterin) were measured in participants with plasma HIV <20 cps/mL. We compared these markers between participants with CSF HIV RNA detected below the LOQ and those with CSF HIV not detected. Mann-Whitney and Fisher's exact tests were used to determine statistical significance.
Results: Forty-one participants with plasma viral suppression had mean age 54 yrs, mean CD4 T cells 612 cells/uL, and median 20 yrs on ART. 21 of 41 participants had HIV RNA detected in CSF, with 13 having CSF HIV RNA detected below the LOQ (i.e., <20 cps/mL), and 8 with quantifiable CSF HIV (median = 47 cps/mL). Participants with CSF HIV RNA detected below the LOQ did not differ from those with CSF HIV not detected when compared for age, years on ART, nadir or current CD4 T cells, race, sex, substance use history, or current use of an integrase inhibitor. When compared to participants with CSF HIV RNA not detected, participants with CSF HIV detected below the LOQ had increased CSF albumin (median 26 vs. 20 mg/dL; p<0.04), CSF protein (median 39 vs. 30 mg/dL; p<0.05), and CSF:blood albumin ratio (median 6.5 vs. 4.5; p<0.05) (Figure 1). There were no significant differences between the two groups for CSF leukocytes (median 1-2 cells/uL) or for plasma or CSF neopterin.
Conclusion: Detection of HIV in CSF below a current commercial assay's LOQ was associated with higher CSF albumin, protein, and albumin ratio when compared to no detection of HIV in CSF, but did not associate with standard HIV metrics or treatment history. Detection at unquantifiable levels by this clinical assay may accurately differentiate low level HIV associated with changes in the blood-brain barrier, even during plasma viral suppression.

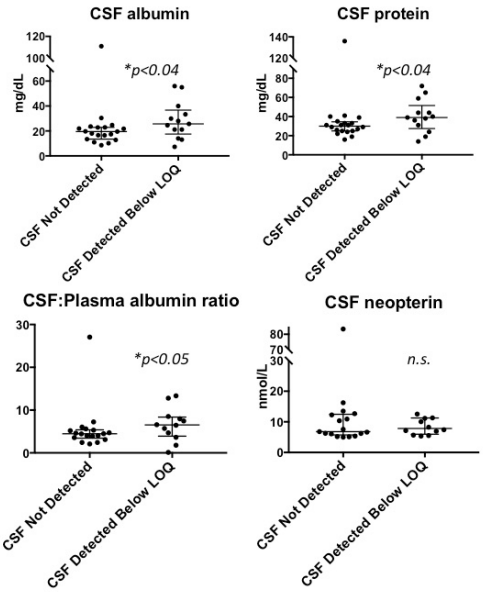

Figure 1. Shown is median +/- IQR.

127 EFFECT ON PLASMA NFL, A MARKER OF NEURONAL INJURY, AFTER SWITCHING FROM TDF TO TAF

Linn Hermansson[1], Richard W. Price[2], Aylin Yilmaz[1], Staffan Nilsson[3], Scott McCallister[4], Tariro Makadzange[4], Moupali Das[4], Henrik Zetterberg[1], Kaj Blennow[1], Magnus Gisslén[1]
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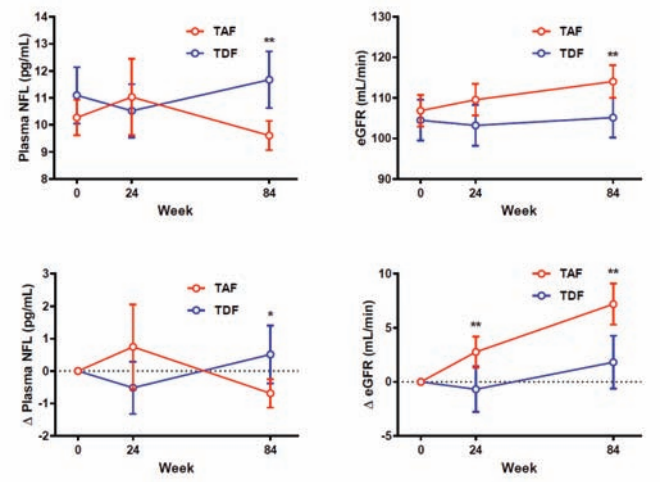
Background: Tenofovir alafenamide (TAF) is associated with significantly lower plasma tenofovir concentrations than tenofovir disoproxil fumarate (TDF), thereby decreasing bone and renal side effects. Limited data are available on TAF pharmacokinetics and effect in the central nervous system (CNS). One concern that has been raised is that because TAF is a stronger substrate for P-glycoprotein (P-gp) than TDF, it could decrease its CNS exposure, since substrates for P-gp are subject to active blood-brain barrier efflux. Plasma neurofilament light protein (NFL) is a sensitive marker of neuronal injury in a variety of neurodegenerative conditions, including neuronal injury in HIV

infection. To study whether treatment with TAF is associated with an increased risk of neuronal harm compared to TDF, we compared plasma NFL levels in patients switching from coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) to E/C/F/TAF with those who continued E/C/F/TDF.

Methods: Plasma NFL was analysed at baseline, week 24, and week 84, in stored plasma samples from 414 participants (272 switching to E/C/F/TAF and 142 continuing E/C/F/TDF) enrolled in the randomized, active-controlled, multicenter, open-label, noninferiority Gilead GS-109 trial. For quality control (QC) plasma samples with NFL concentrations of 12.1 pg/mL and 188 pg/mL, intra-assay coefficients of variation (CVs) were 7.8% and 6.7%, respectively.

Results: We found a small but statistical significant decrease in plasma NFL in the E/C/F/TAF arm after 84 weeks from 10.3 to 9.6 pg/mL, p<0.01 (Figure). The change was significantly different (p<0.01) from the E/C/F/TDF arm, in which plasma NFL increased from 11.1 to 11.7 pg/mL (ns). As expected, eGFR increased in the E/C/F/TAF arm but not in the E/C/F/TDF arm. Plasma NFL was significantly correlated with age and eGFR. Delta eGFR and treatment group were both found as independent predictors of plasma NFL changes from baseline to week 84 in a multiple linear regression analysis.

Conclusion: We found no evidence of increased risk of CNS injury when switching from TDF to TAF. It should be noted that the NFL levels in both arms were within the limits normally found in HIV-negative controls; it is unclear whether the small decrease in plasma NFL found after switch to TAF is of any clinical significance. This study indicates that switching from TDF to TAF appears safe with regard to neuronal injury.



128 CARDIOVASCULAR RISK SCORES PREDICT LONGITUDINAL COGNITIVE FUNCTION IN OLDER PLHIV

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Background: Cardiovascular (CV) disease (CVD) and associated risk factors have been linked with neurocognitive impairment (NCI) in cross-sectional studies of persons living with HIV (PLHIV), although the specific CV risk factors that correlate with NCI have varied. We examined the utility of two commonly used 10-year CV risk scores--the Atherosclerotic CVD (ASCVD) and Framingham Heart Study Global CVD risk score (FRS), which combine multiple CV risk factors--to predict longitudinal cognitive function in an observational cohort of older PLHIV.

Methods: Participants from the ongoing AIDS Clinical Trials Group A5322 study who underwent neurocognitive testing (Trailmaking A and B, Hopkins Verbal Learning Test-Revised, Digit Symbol) at entry were eligible. Raw scores are standardized using demographics-adjusted norms and combined into a summary z-score (NPZ-4). Participants undergo repeat neurocognitive testing every 48 weeks. The 10-year ASCVD risk score and FRS were calculated at entry. We first assessed how well the baseline ASCVD risk score and FRS predicted NPZ-4 at Year 4 in unadjusted linear regression models. We then performed stepwise linear regression (Table) to determine the covariate-adjusted association between baseline 10-year CV risk and NPZ-4 at Year 4.

Results: Of 988 participants, mean age was 52 years, 20% were women, and 90% had an undetectable viral load. Mean ASCVD risk score and FRS were 6.8% and 13.1%, respectively. Both risk scores were lower in women than men (ASCVD 4.1% vs. 7.5%, p<0.001; FRS 8.1% vs. 14.3%, p<0.001). For every 1% higher baseline ASCVD risk, NPZ-4 at Year 4 was lower by 1.4 SD (p=0.003). Baseline ASCVD risk predicted NPZ-4 at Year 4 overall and in both women and men (Table). In adjusted models, for every 1% higher baseline ASCVD risk, NPZ-4 at Year 4 was 1.1 SD lower, though this did not reach statistical significance (p=0.085). Baseline ASCVD risk significantly predicted NPZ-4 at Year 4 for women (-3.1 SD per 1% higher risk, p=0.010) but not for men (-0.4 SD per 1% higher risk, p=0.55), even after adjustment for NPZ-4 at entry. The associations between baseline FRS and NPZ-4 were comparable, although higher ASCVD risk had a greater effect on NPZ-4 than higher FRS (Table).

Conclusion: Higher baseline 10-year CV risk predicted worse cognitive function at Year 4 in PLHIV, though this association was attenuated in men after adjusting for covariates. A higher CV risk score may help to identify PLHIV who are at risk for worse cognitive function over time.

Table: Association between 10-year cardiovascular risk scores and cognitive function measured by NPZ-4 score

	NPZ-4 at Year 4[a]			NPZ-4 at Year 4		
Baseline 10-year cardiovascular risk score	All N=988	Women N=195	Men N=793	All[b] N=988	Women[c] N=195	Men[d] N=793
ASCVD risk score (per 1% higher risk)	-1.4 p=0.003	-3.6 p=0.007	-1.6 p=0.002	-1.1 p=0.085	-3.1 p=0.010	-0.4 p=0.55
FRS (per 1% higher risk)	-0.6 p=0.058	-1.8 p=0.059	-0.9 p=0.012	-0.5 p=0.19	-2.1 p=0.015	-0.2 p=0.72

[a]Unadjusted model evaluating association between baseline 10-year cardiovascular risk score and NPZ-4 at Year 4
[b]Model adjusted for age, sex, race/ethnicity, education, physical activity, hepatitis C infection, duration of antiretroviral therapy
[c]Model adjusted for race/ethnicity, education, physical activity
[d]Model adjusted for age, race/ethnicity, education, use of anti-depressants

Abbreviations: ASCVD, Atherosclerotic Cardiovascular Disease; FRS, Framingham Heart Study Global Cardiovascular Disease risk score

129 OBESITY IS INDEPENDENTLY ASSOCIATED WITH NEUROCOGNITIVE DECLINE IN HIV

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Background: Neurocognition may decline more with age among people living with HIV (PLWH) compared to uninfected persons. The factors related to this decline are not well understood in the current antiretroviral therapy (ART) era.

Methods: AIDS Clinical Trials Group (ACTG) A5322 (HAILO) is an observational cohort study of PLWH ≥ 40 years old, on ART. Participants undergo annual assessments for neurocognitive impairment (NCI), with NCI defined by ≥1 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. Obesity was defined as body mass index (BMI) >30 kg/m^2, overweight as 25-30 kg/m^2, normal weight as 18.5-25 kg/m^2, and underweight < 18.5 kg/m^2. Participants who developed NCI during the first 3 years were compared to persons who maintained normal neurocognition. We used logistic regression to assess the age-adjusted associations between NCI and baseline covariates including sex, race, alcohol use, BMI, waist circumference, nadir CD4, history of AIDS defining illness, hemoglobin A1C. Only covariates with a p-value < 0.1 from age-adjusted analysis were included in the multivariable models.

Results: Of 929 participants, 81% were male, 31% Black, and 20% Hispanic. Median age was 51 years (IQR 46-56). Most individuals (92%) had undetectable

plasma HIV RNA with median CD4 count 631 cells/mm^3 (IQR 458-840) at study entry. At study entry, 16% had NCI, 29% were obese, and 40% were overweight. Over 3 years, 6% of participants developed NCI while 78% remained unimpaired. In multivariable models, increasing age (OR 1.04; 95% CI 1.00, 1.08; p=0.04), and having an obese (OR 2.45; 1.05, 5.70; p=0.04) or overweight BMI (OR 2.21; 1.00, 4.91; p=0.05) vs normal BMI were associated with increasing prevalence of NCI compared to those who remained unimpaired.
Conclusion: Both greater age and obesity were independently associated with worsening cognitive function. These results extend previous work demonstrating a higher risk of NCI among obese PLWH by showing that obese individuals are also at greater risk of subsequently transitioning from unimpaired to impaired neurocognition.

130 HIGH HIV VIRAL BURDEN PERSISTS IN CXCR3+ GCTFH DESPITE VERY EARLY ART INITIATION

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Background: Early initiation of Combination Antiretroviral Therapy (cART) during acute HIV infection blunts peak viremia, reduces HIV viral reservoirs and preserves immune function, but treatment interruptions often results in rapid viral rebound. We studied persons identified and treated at the onset of plasma viremia, in many when viral load is less than 1000 RNA copies/ml to define the dynamics of HIV suppression in lymph node (LN) tissues. Additionally, we investigated the cell subset that remained persistently HIV infected.
Methods: We studied 16 hyperacute HIV-infected subjects who initiated therapy in Fiebig stage I, subdivided into three groups based on when the LN sample was obtained. Group 1 was sampled within 3 months, group 2 was sampled at one year and group 3 was sampled after two years on therapy. Immunofluorescence (IF) microscopy and RNAscope in situ hybridization (ISH) techniques were used to quantify Gag p24 protein and Gagpol RNA respectively. The Cobas AmpliPrep HIV-1 test was used to quantify LN and plasma viral loads and viral Gag, Nef and Envelope sequencing were conducted using ABI 3130xl sequencing platform. Digital droplet PCR was used to quantify HIV RNA levels in FACs sorted LN cell subsets and follicular CD4+ T cells harboring HIV antigens were extensively phenotyped by flow cytometry.
Results: Despite rapid plasma viral suppression at a median of 16.5 days, Gag p24 antigen and quantifiable RNA were readily detectable in the LN in 12 out of the 16 donors sampled in all three experimental groups. Moreover, sequencing analysis revealed viral evolution in Gag, Nef and/or Envelope sequences in 4 out of 6 LNs sampled >3 months after therapy compared to the transmitter found virus sequences obtained just before cART initiation. There was no significant reduction in Gagp24 antigen in LN samples obtained after a year on cART compared to the samples obtained within 3 months on cART (p=0.4). RNA quantification of FACs sorted TFH subsets showed significantly higher levels of Gag p24 mRNA copies in CXCR3+ follicular CD4+ T cells compared to other TFH subsets (p=0.01).
Conclusion: Our results highlight the huge difference in viral load decay kinetics between peripheral blood and LN, despite very early cART initiation. Importantly, we identify that CXCR3+ TFH contribute significantly to viral persistence in the LN during therapy. These results underscore the need for future interventions directed at eliminating residual virus in tissue sanctuaries.

131 SIROLIMUS REDUCES T-CELL CYCLING AND IMMUNE CHECKPOINT MARKER EXPRESSION, ACTG A5337

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Background: Reversing immune dysfunction and inhibiting T-cell proliferation are critical to immune-based HIV cure strategies. A prior retrospective analysis of the use of sirolimus, an mTOR inhibitor, in HIV+ renal transplant recipients suggests that it may lead to lower CD4+ T cell HIV DNA, but prospective studies are lacking. Therefore, we sought to evaluate the safety of sirolimus in ART-suppressed HIV-infected individuals and its effect on immune function and HIV-1 reservoir size.
Methods: A5337 was an open-label, single-arm, pilot study of 20 weeks of oral sirolimus treatment for HIV-infected individuals on ART with HIV RNA <40 cps/mL. Eligibility criteria included at least 24 months on ART, HIV RNA < assay limit and CD4+ cell count ≥ 350 cells/mm3. Measures of T-cell activation and cycling, immune exhuastion and CCR5 expression (secondary efficacy outcomes) were compared by paired t-tests prior to vs after continuous oral sirolimus.
Results: 32 participants enrolled in the study. Participants had a median age of 52 years, 28% were female and 56% were black non-Hispanic. The median baseline CD4+ cell count was 813 cells/mm3. Two participants did not start study drug, 14 completed less than 20 weeks of sirolimus, and 16 completed 20 weeks of therapy. Twenty weeks after initiating sirolimus, CD4+ cell counts declined by a mean of 118 cells/mm3 (p=0.04; n=16). Three participants had a grade 3 adverse event (stomatitis and perturbations of fasting glucose in a known diabetic) or a decrease in CD4+ cell count to <300 cells/mm3. Two participants stopped sirolimus because of assympomatic transient Epstein Barr viremia. Other individuals discontinued because of lower grade toxicities or minor, clinically insignificant laboratory abnormalities. Twenty weeks of sirolimus was associated with significant decreases in the percentages of cycling Ki67+ CD4+ and CD8+ T cells (mean change -0.5%, p=0.031, and -0.5%, p=0.005, respectively), PD-1+ CD8+ T cells (-2.9%, p=0.008), and CCR5+ CD8+ T cells (-3.9%, p=0.001).
Conclusion: Sirolimus use was associated with significant reductions in CCR5 expression and T-cell markers of cell cycling and immune exhaustion. There was a relatively high rate of treatment discontinuation, in part because of protocol-defined stopping criteria.

132 PD-1 AND CTLA-4 BLOCKADE IN MACAQUES INDUCES T-CELL EXPANSION AND SIV REACTIVATION

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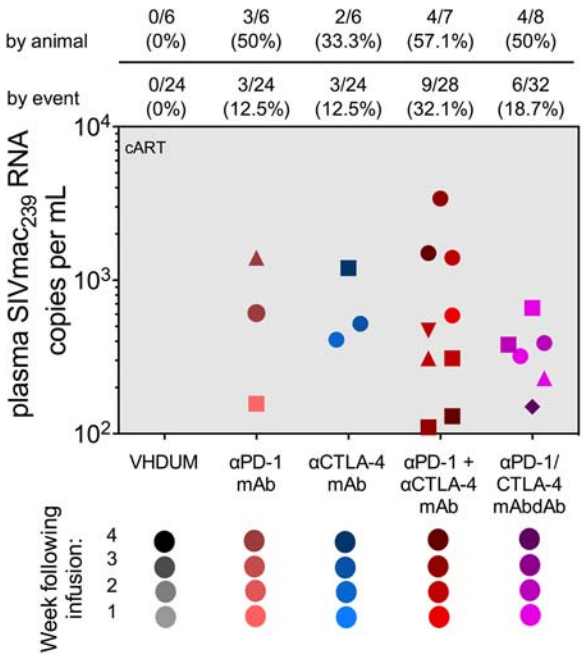
Background: The HIV reservoir is largely composed of resting memory CD4+ T-cells, a large fraction of which express the co-inhibitory receptors PD-1 and CTLA-4 that limit T-cell activation. Furthermore, PD-1 expression contributes to CD8+ T-cell dysfunction during HIV infection. We hypothesized that a dual PD-1 and CTLA-4 immune checkpoint blockade (ICB) will facilitate T-cell activation, revert latency, and restore SIV-specific T-cell responses, thus enhancing clearance of the viral reservoir.
Methods: 33 rhesus macaques (RMs) were i.v. infected with SIVmac239 and initiated ART (TDF/FTC/DTG) at day 60, which was maintained for 1 year. RMs received 4, weekly ICB infusions: control antibody (n=6); anti-PD-1 mAb (n=6); anti-CTLA-4 mAb (n=6); anti-CTLA-4 plus anti-PD-1 mAb (n=7); and bi-specific anti-CTLA-4/PD-1 (n=8). All RMs underwent analytic ART interruption (ATI). Peripheral blood (PB), lymph node (LN), and rectal biopsy (RB) were collected longitudinally.
Results: ICB treatment was well tolerated and demonstrated PD-1 receptor occupancy in PB and LN, including in T follicular helper cells. Dual PD-1/CTLA-4 ICB induced a significant increase in the number of cycling (Ki-67+) memory CD4+ and CD8+ T-cells in LN (1.96- and 1.96-fold, respectively), with significant expansion in the number of effector memory T-cells in PB (4.61- and 2.20-fold, respectively; p<0.01 for all these measures). Enhanced T-cell cycling was dependent on CTLA-4 inhibition, highlighting the synergy of the dual blockade. In addition, dual ICB increased the frequency of activated (CD38+HLA-DR+) and T-bet+ cells in LN. Notably, increased CD4+ T-cell cycling induced by dual ICB resulted in higher levels of plasma SIV RNA (indicative of viral reactivation) relative to monotherapy. Both the frequency (viremia >100 copies/mL measured in 4 out of 7 RMs and at multiple time points) and magnitude (average of 913 SIV-RNA copies/mL) of plasma SIV RNA was increased in dual vs monotherapy. Following ATI, only anti-PD-1 monotherapy produced a

significant (p=0.01), one-week delay in SIV rebound. The impact of ICB on the size of the reservoir during ART is under investigation.

Conclusion: PD-1/CTLA-4 dual blockade was well tolerated in ART-suppressed, SIV-infected RMs, and was pharmacologically active as demonstrated by the expansion of effector T-cells in PB. This effect was coupled to a synergistic and potent activity in increasing SIV RNA in plasma, suggesting checkpoint blockade may facilitate viral induction and improve T-cell function.



133 FTY720 LIMITS T FOLLICULAR HELPER CELL INFECTION IN LYMPHOID SITES OF SIV PERSISTENCE

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Background: Lymph nodes (LN) and their resident T follicular helper CD4+ T cells (Tfh) are a critical site for HIV replication and persistence. Therefore, optimizing antiviral activity in lymphoid tissues will be needed to reduce or eliminate the HIV reservoir. In this study, we treated ART-suppressed SIV-infected rhesus macaques (RM) with the lysophospholipid sphingosine-1 phosphate receptor modulator fingolimod (FTY720). With this design, we aimed at exploring the potential utility of fingolimod, approved clinically for multiple sclerosis, in retaining cytolytic lymphocytes in lymphoid sites of SIV persistence, from which they are typically excluded during ART, and to impact on the viral reservoir.

Methods: 10 RMs infected with SIVmac239 started TDF/FTC/DTG treatment at day 42 post-infection; ART was continued for 9 months. Group 1 RMs (n=5) received FTY720 at 18 µg/Kg per day and group 2 (n=5) at 500 µg/Kg per day. FTY720 was administered orally once a day during the last 28 days of ART, once viremic control was achieved for all animals. Blood (PB) and lymph node (LN) were collected longitudinally for flow cytometric, histocytometry, RNAscope and DNAscope analyses. Cell-associated SIV-DNA and -RNA were quantified in CD4 T cell subsets, including Tfh, by quantitative PCR (qPCR) and reverse transcription quantitative PCR (RT-qPCR) respectively.

Results: FTY720 treatment was safe and well tolerated, and plasma SIV levels remained undetectable (<60 RNA copies/ml) during the entire treatment. FTY720 was remarkably effective, in a dose dependent way, in reducing circulating CD4+ and CD8+ T cells (p<0.01), including those with cytolytic potential (expressing T-bet, perforin, and granzyme-B; p<0.01). FTY720 induced a transient increase in the frequencies of cycling T cells (expressing Ki-67) in blood of ART-treated, SIV-infected RMs (p<0.05). Furthermore, FTY720 promoted an increase in the number of T cells retained in LN (p=0.01), as determined directly in situ by histocytometry. Notably, the FTY720-induced inhibition of T cell egress from LN resulted in a measurable decrease of SIV-DNA and -RNA content in LN Tfh cells in most treated animals as measured by RNAscope (p=0.02; n=6) and qPCR (p=0.04; group 2).

Conclusion: By retaining cytolytic T cells in lymphoid sites of SIV persistence, FTY720 administration has the potential to limit a critical cellular reservoir of Tfh cells. As such, FTY720 should be considered in combined immune based interventions aimed at HIV remission.

134 TRANSCRIPTIONAL SIGNATURE OF LYMPH NODE CD8+ T CELLS IN HIV ELITE CONTROLLERS

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Background: Extensive evidence has indicated that peripheral blood HIV-specific CD8+ T cell cytolytic activity and effector functions are associated with the control of HIV replication in HIV elite controllers (EC). However, the majority of HIV replication in EC likely occurs in lymphoid tissue, where CD8+ T cell immune surveillance mechanisms are undefined. Here we performed single-cell RNA sequencing (scRNAseq) analyses to determine the transcriptional signature of HIV-specific CD8+ T cells that control viral replication in lymphoid tissue of EC.

Methods: We isolated human lymph node (LN) mononuclear cells from inguinal LN of HIV-infected EC and cervical LN of chronic progressors (CP) from the SCOPE cohort at UCSF and the Center for Investigation of Infectious Diseases (INER-CIENI) in Mexico City, respectively. We index sorted single HIV-specific CD8+ T cells, as identified by MHC-class I tetramers, and subjected these cells for scRNAseq using the SMARTseq-v2 platform. Functional assays were analyzed on a BD LSR II flow cytometer. The results were analyzed using RStudio, FlowJo, and GraphPad Prism.

Results: Using an unsupervised scRNAseq analysis approach, we observed distinct clustering between EC cells and CP cells driven by 2264 differentially expressed genes. Compared to CP, EC cells expressed lower levels of cytolytic genes, and heightened expression of several secreted molecules with potential anti-HIV activity, including as CCL5, TNF, and IL32. In order to determine a gene signature that could distinguish EC cells from CP cells, we next used a supervised classification approach, yielding a list of 200 genes that were enriched for immune-related and protein translation-related genes. Within this gene signature, EC cells showed a downregulation of inhibitory receptor genes and an upregulation of specific cytokines and ribosome subunits, implying that these cells are highly functional. We functionally confirmed this signature with ex vivo peptide stimulation polyfunctional cytokine and protein translation assays, finding heightened polyfunctional and protein translation capacity in lymph node CD8+ T cells from HIV EC.

Conclusion: Our findings suggest that protective HIV-specific CD8+ T cells in lymphoid tissue of EC are defined by unique non-cytolytic functional features with a high capacity to translate mRNA into protein upon antigen encounter, and call into question known correlates of protection mediated by peripheral blood CD8+ T cells.

135 CHARACTERIZING THE PROVIRAL LANDSCAPE IN HIV-1 ELITE CONTROLLERS

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Background: HIV-1 elite controllers (ECs) represent a rare group (less than 1%) of infected individuals with undetectable viral loads in the absence of

antiretroviral therapy (ART). However, the dynamics and evolution of the proviral reservoir in these individuals are largely unknown.
Methods: 68 HIV-1 ECs with undetectable viral loads (viral load <50), 38 viremic controllers (VCs, viral load 50-2000), and 34 chronically ART-treated patients were included in this study. Genomic DNA was extracted from PBMCs and diluted to single genome levels for HIV-1 near full-length next generation viral sequencing. Quantitative viral outgrowth assays (QVOA) were performed with autologous CD4+ T cells; outgrowing virus was subjected to HIV-1 near full-genome sequencing.
Results: We obtained 1066, 1385, and 1601 individual proviral sequences in ECs, VCs, and ART-treated patients, respectively. The median frequency of proviral species in ECs was significantly lower than in VCs (p=0.0009) and ART-treated patients (p<0.0001). The relative number of genome-intact sequences in ECs was also significantly lower when compared to ART-treated patients (p<0.0001), but was not different from VCs (p=0.2740). Among intact proviral genomes in ECs, 46% were clonally-expanded, a proportion considerably higher than in VCs (8%) but similar to ART-treated patients (31%). Notably, we identified 2 subgroups of ECs with markedly different intact reservoir sizes: one group of ECs had high proportions of intact proviral genomes within all detected proviral species, ranging from 13% to 100%; among these intact proviral genomes, very high proportions of clonal sequences were identified by full-genome sequencing (36%-80%) that frequently were entirely identical to sequences isolated from QVOA. In contrast, we observed 3 ECs in whom no intact proviral sequences were observed after assaying 52-76 million PBMCs for near full-genome sequencing and another 31-67.5 million PBMCs for QVOA, suggesting that these 3 patients may approximate a sterilizing cure of HIV-1 infection.
Conclusion: This detailed analysis suggests that ECs can be distinguished into 2 different subgroups - ECs with unusually high proportions of intact proviral genomes and very few defective proviral sequences, and ECs with no intact proviral genomes detectable in large numbers of cells. Exploring the reasons for differential viral reservoir dynamics in these patients may allow us to identify mechanisms enabling a drug-free remission of HIV-1 infection.

136 INTERFERON A2B REDUCES INDUCIBLE CD4-ASSOCIATED HIV IN ART-SUPPRESSED INDIVIDUALS

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Background: In prior studies treatment of ART-suppressed individuals with pegylated interferon alpha (pIFNα) resulted in a decrease in PBMC-associated integrated HIV DNA. We sought to confirm the effect of pIFNα on latent HIV by measuring inducible HIV expression from CD4 cells isolated from chronically infected, ART-suppressed individuals receiving pIFNα-2b immunotherapy in a randomized clinical trial (NCT02227277).
Methods: We enrolled 54 HIV-infected individuals receiving suppressive ART (HIV VL < 50 copies/ml) and with CD4 count > 450/µl who were randomized 1:1:1 to 3 treatment arms: 1. 1 µg/kg of pIFNα-2b (Pegintron, Merck) for 20 weeks, with ART interruption (start at week 4, resume ART upon confirmed VL > 50 copies/µl or at week 20) 2. 1 µg/kg of pIFNα-2b added to ART 3. ART only (control) All subjects were sampled at baseline and week 20. CD4+ T cells were isolated from PBMC and cultured (2-10 replicates) for 16-hour with medium or PMA + Ionomycin. HIV p24 production was measured in cell pellets using single molecule array (SIMOA) with a limit of quantification (LOQ) of 7 fg/106 cells. Analysis approach: modified intention to treat. Measurements < LOQ were censored at the LOQ; p24 levels were log-transformed. The changes in PMA-induced SIMOA HIV p24 levels at endpoint from baseline were compared between first two treatment and placebo arms, using a linear mixed-effect model, adjusted for site effect and within-subject correlation.
Results: Of 54 enrolled subjects, 46 completed the protocol for primary analysis. We observed 6 treatment-emergent AEs grade ≥ 3 (4 treatment-related). All subject in Arm 1 achieved HIV VL < 50 c/ml after resuming ART. The median baseline cell-associated p24 was 22.88 fg/10^6 CD4+ T cells for Arm 1, 12.47 for Arm 2 and 34.12 for Arm 3. At week 20, the median p24 was 0.56 for Arm 1, 7.95 for Arm 2 and 57.69 for Arm 3. Compared to Arm 3 (ART only control), that had a significant increase in p24 from baseline to week 20 (118%, $p < 0.05$), we detected a significant decrease in both treatment arm 1 (-73%) and arm 2 (-61%).
Conclusion: Consistent with pilot trial results, a 20-week course of pIFNα-2b resulted in a significant decrease in levels of CD4 T cell-associated inducible HIV compared to ART alone. This effect was independent of ART interruption. This randomized study provides a strong rationale for the use of IFNα immunotherapy as a component of cure-directed strategies.

137 NEF-STOP REPAIR DYNAMICS, BUT NOT ANTI-A4B7, INFLUENCE POSTTREATMENT VIRAL CONTROL

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Background: In contrast to published data, we have recently reported (AIDS 2018) that treatment with an antibody to α4β7 integrin in rhesus macaques infected with SIVmac239 having a stop codon in nef (SIVmac239nefstop) was not associated with prolonged significant post-treatment suppression of viremia. The only other clear difference was the rate of peripheral blood (PB) CD4 decline between the control groups of the two studies. The current analysis attempts to identify additional factors potentially responsible for the different outcomes observed
Methods: Twenty-two Mamu-A001, B008 and B017 negative Indian rhesus macaques were infected i.v. with 200 TCID50 SIVmac239nefstop. At 5 weeks post-infection (wpi), combination anti-retroviral therapy (cART) was started and 4 weeks later, animals received a total of 8 infusions every 3 weeks of α4β7 antibody (n=12) or control antibody (n=10); cART was stopped at 18 wpi and animals were followed for additional ~7 months (set-point average 45 and 48 pwi, PVL-sp). In addition to plasma SIV RNA viral loads (PVL) and PB CD4 counts, levels of cell associated SIV RNA and DNA viral load (CAVL), were measured during cART administration and ~ 3 months post cART interruption in LN and rectal gut (RAL) biopsy samples
Results: PVL peaked at week 2-5 wpi without a significant drop in PB CD4 counts by 2 wpi (~8% decline, n.s., n=22). A positive correlation was found between the frequency of nef-open restored viruses (FRV) and PVL at 2 wpi (r=0.66 P<0.001) as well as between FRV at 2 wpi and LN SIV-DNA CAVL (r=0.67, P<0.001), but not PVL or RAL SIV-DNA CAVL, at the time of cART initiation [when FRV was 100% in all animals]. PVL-sp was associated with LN SIV-DNA CAVL (r=0.62, P=0.002), but not with rectal SIV-DNA CAVL (r=0.07, n.s.) at the time of cART interruption. ~7 months following antiretroviral treatment completion mean PVL (~ 10^4 copies/ml), PB-CD4 T cell counts (~ 900 cells/ul), LN or rectal SIV CAVL were not significantly different between the two groups
Conclusion: While a lack of exactly corresponding analyses from the published study precludes direct comparison, the current analysis suggests that differential rates of repair of the nef mutation may have contributed to the observed different outcomes between the two studies. Following SIV infection, faster viral dissemination in LNs appears to be facilitated by restoration of the virus to nef-open and predicts higher virologic set-point following cART interruption

138 SEARCH INTERVENTION REDUCES MORTALITY AT A POPULATION LEVEL IN MEN WITH LOW CD4 COUNT

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Background: HIV Test-and-Treat has the potential to reduce mortality of HIV+ persons with low CD4+ counts on a population level by rapidly initiating ART among "late presenters" not previously in care and among persons disconnected from prior care. We evaluated the effect of streamlined ART delivery for HIV+ persons with CD4<350 cells/uL after population-wide HIV testing during the SEARCH study (NCT:01864603).
Methods: At baseline (2013-2014), HIV testing at multi-disease health fairs and in homes reached 91% of 143,870 adult stable residents in 32 communities

in rural Kenya and Uganda. All HIV+ persons with CD4<350 were eligible for ART. In 16 intervention communities, ART was delivered via patient-centered streamlined care including supported linkage and rapid ART start. In 16 control communities, ART was delivered via country standard of care. Mortality was ascertained after 3 years via comprehensive outreach. We evaluated (1) identification of HIV+ persons with CD4<350 at baseline, (2) among these persons, the effect of streamlined care on ART start and mortality, and (3) gender differences in mortality. Comparisons between study arms used cluster-level TMLE; survival estimates used Kaplan-Meier; estimates of ART start among ART-naïve persons treated death as a competing risk.

Results: Among 13,266 baseline HIV+ residents, 22% (N=2,956) had CD4<350. Of these, 33% (988/2,956) were new diagnoses and 10% (282/2,956) were diagnosed but ART-naive. HIV+ men (N=4,597) were twice as likely as HIV+ women (N=8,669) to have CD4<350 and untreated (18% vs. 9%, respectively). Among persons with CD4<350, streamlined care reduced mortality by 27% vs. control (RR=0.72; 95%CI:0.57, 0.93; p=0.02). Mortality was reduced substantially more among men (RR=0.60; 95%CI:0.43, 0.86; p=0.005) than women (RR=0.90; 95%CI:0.62, 1.31; p=0.56). Despite immediate ART eligibility in both arms, persons with CD4<350 started ART faster under streamlined care vs. control (76% vs. 43% by 12 months, respectively, p<0.001). Within each arm, time to ART start was similar between men and women. However, more men vs. women had baseline HIV RNA>100,000 copies/mL (29% vs. 19%, respectively), placing men at elevated risk of HIV progression/death.

Conclusion: After population-based HIV testing, SEARCH streamlined care accelerated ART start and reduced mortality at a population level among HIV+ persons with CD4<350, particularly among men. These interventions may play a key role in meeting the UNAIDS goal of eliminating AIDS deaths.

139 LONG-ACTING CABOTEGRAVIR + RILPIVIRINE AS MAINTENANCE THERAPY: ATLAS WEEK 48 RESULTS

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Background: ATLAS, a phase 3, open-label, multicenter study, was designed to establish whether switching to monthly long-acting (LA) Cabotegravir (CAB) + Rilpivirine (RPV) LA is noninferior to continuing current 3-drug oral ART in adults with virologically suppressed HIV-1 infection.

Methods: Eligible participants had HIV-1 RNA <50 c/mL for ≥6 months without virologic failure on oral regimens comprising 2 NRTI + 1 INSTI, NNRTI, or PI. Participants were randomly assigned (1:1) to continue current ART (CART arm) or switch to the LA arm. The LA arm participants received oral CAB 30mg + RPV 25mg once daily for 4 weeks for safety monitoring, then single 3 mL loading doses of CAB LA 600mg (200 mg/mL) and RPV LA 900mg (300 mg/mL) by IM injection, followed by 2 mL IM injections every 4 ± 1 weeks of CAB LA 400mg and RPV LA 600mg. The primary endpoint was HIV-1 RNA ≥50 c/mL at W48, using the FDA snapshot algorithm with a 6% noninferiority margin.

Results: 616 participants initiated treatment (308/arm; ITT-E). Median age was 42 yrs (26% ≥50 yrs); 33% were female and 68% white. Baseline regimens included 2 NRTI + 1 NNRTI (50%), INSTI (33%), or PI (17%). At W48, 5 participants (1.6%) in the LA arm and 3 (1.0%) in the CART arm had HIV-1 RNA ≥50 c/mL, meeting noninferiority criteria for the primary endpoint (Table). Similarly, the LA arm was noninferior to CART for the key secondary endpoint of HIV-1 RNA <50 c/mL (93% vs 95%). Three LA and 4 CART participants had confirmed virologic failure (CVF, HIV-1 RNA ≥200 c/mL in consecutive samples). The LA CVFs included 1 with RAM E138A, 1 with E138A+V108I (both having E138A in baseline DNA), and 1 with RT-E138E/K and IN-N155H. The 4 CART CVFs included 1 each of RAMs M184I, M184V+G190S, M230M/I, and 1 with no RAMs. In the LA arm, 231 participants (75%) had injection site pain with 4 participants (1%) withdrawing for these events. Incidences of grade 3/4 and serious AEs were similar across the LA and CART arms; there was 1 death (CART arm). Of the 275 LA arm participants completing HIVTSQc at W48, 98% were more satisfied with CAB LA + RPV LA compared with their daily oral treatment at study entry.

Conclusion: The regimen of monthly injections of CAB LA + RPV LA was noninferior to continued 3-drug oral ART at W48. The LA regimen was generally well tolerated, with low rates of serious AEs and drug- or injection-related withdrawals. Virologic failure was infrequent in both arms. Overall, these results support the therapeutic potential of once-monthly CAB LA + RPV LA.

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Table

Outcome, n (%) ITT-exposed population	CAB LA + RPV LA arm, N=308	CART arm, N=308
Primary endpoint: HIV-1 RNA ≥50 copies/mL at Week 48*	5 (1.6)	3 (1.0)
Adjusted difference (95% CI)†	0.6 (−1.2, 2.5)	
Data in window not <50 c/mL	1 (0.3)	1 (0.3)
Discontinued due to lack of efficacy	3 (1.0)	2 (0.6)
Discontinued due to other reasons while not suppressed	1 (0.3)	0
No virologic data	18 (5.8)	11 (3.6)
Discontinued study due to AE or death	11 (3.6)	5 (1.6)‡
Discontinued study for other reasons	7 (2.3)	6 (1.9)
Key secondary endpoint: HIV-1 RNA <50 copies/mL at Week 48*	285 (93)	294 (95)
Adjusted difference (95% CI)†	−3.0 (−6.7, 0.7)	
Number of injections	6978	
Number of ISR events	1460	
Grade 1 events – mild	1156 (79)	N/A
Grade 2 events – moderate	283 (19)	
Grade 3 events – severe	21 (1)	
ISR duration ≤7 days	1288 (88)	
Grade 3 or 4 AEs	35 (11)	23 (7)
Non-ISR Grade 3 or 4 drug-related AEs	4 (1)	1 (<1)
Serious AEs	13 (4)	14 (5)

*Per FDA snapshot algorithm; prespecified noninferiority margins were 6% for primary endpoint, 10% for key secondary endpoint.
†Proportion on LA minus proportion on CART,and its 95% confidence interval
‡Includes 1 participant with fatal methamphetamine overdose.
ITT, intent-to-treat.

140LB LONG-ACTING CABOTEGRAVIR + RILPIVIRINE FOR HIV MAINTENANCE: FLAIR WEEK 48 RESULTS

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Background: The 2-drug long-acting (LA) injectable regimen of the INSTI cabotegravir (CAB) and the NNRTI rilpivirine (RPV) is being developed to reduce dose frequency, pill taking and drug exposure. FLAIR, a phase 3, open-label, multicenter study is investigating whether switching to monthly CAB+RPV is noninferior to dolutegravir/abacavir/lamivudine (DTG/ABC/3TC).

Methods: ART-naïve participants received induction therapy with oral DTG/ABC/3TC (CAR[8]) for 20 weeks. Those with HIV-1 RNA <50 c/mL at 16 weeks were eligible to enter the maintenance phase and randomly assigned (1:1) to continue CAR or switch to LA. Participants in the LA arm received an oral lead-in of CAB 30mg + RPV 25mg once daily for 4 weeks to assess tolerability before receiving CAB+RPV as intramuscular monthly LA injectable therapy. The primary endpoint was viral load (VL) ≥50 c/mL at W48 by FDA snapshot algorithm (NI margin 6%). Safety, tolerability and confirmed virologic failure (CVF) were secondary endpoints.

Results: 566/629 participants who initiated induction therapy were randomly assigned to the LA or CAR arm (283/arm). The median age was 34 yr (11% ≥50 yr); 22% were female and 74% were white. At the induction phase start, median CD4 count was 444 cells/mm^3 (7% <200 cells/mm^3), median VL was 4.49 $\log_{10}$ c/mL (20% ≥100,000 c/mL). Six participants in the LA arm (2.1%) and 7 in the CAR arm (2.5%) had HIV-1 RNA ≥50 c/mL at W48, meeting noninferiority criteria for the primary endpoint (Table) and for the key secondary endpoint of HIV-1

RNA <50 c/mL (LA 93.6% vs CAR 93.3%). Four LA recipients (1.4%) had CVF; 3 had mutations in the NNRTI + INSTI domains (K101K/E/Q + G140R, E138K + Q148R, and E138E/A/K/T + Q148R, respectively) and 1 was not tested (PO only). The CAR arm had 3 CVFs with no INSTI resistance. Adverse events (AE) leading to withdrawal and serious AE were infrequent in both arms. The most common drug-related AE was injection site reactions (ISRs; 82% of participants in the LA arm); frequency decreased over time. 99% of ISRs were Grade 1 or 2; the median duration was 3 days. Of 263 LA participants completing HIVTSQc at W48, 99% were more satisfied with CAB+RPV compared with their prior daily oral CAR.
Conclusion: The regimen of monthly injections of CAB+RPV was noninferior to DTG/ABC/3TC at W48. The LA regimen was generally well tolerated with few CVFs. Overall, these results demonstrated the therapeutic potential of CAB+RPV injections, following short initial induction with oral DTG/ABC/3TC to achieve viral suppression.

Outcome, n (%) ITT-Exposed Population	CAB LA + RPV LA N = 283	DTG/ABC/3TC[&] N = 283
Primary endpoint: HIV-1 RNA ≥50 c/mL at Week 48*	6 (2.1)	7 (2.5)
Adjusted difference (95% CI)†	−0.4 (−2.8, 2.1)	
Data in window not <50 c/mL	2 (0.7)	2 (0.7)
Discontinued due to lack of efficacy	4 (1.4)	3 (1.1)
Discontinued due to other reasons while not suppressed	0	2 (0.7)‡
No virologic data in Week 48 window	12 (4.2)	12 (4.2)
Discontinued study due to AE or death[#]	8 (2.8)	2 (0.7)
Discontinued study for other reasons	4 (1.4)§	10 (3.5)‖
Key secondary endpoint: HIV-1 RNA <50 c/mL at Week 48*	265 (93.6)	264 (93.3)
Adjusted difference (95% CI)†	0.4 (-3.7, 4.5)	
Safety – all maintenance data, including dosing past Week 48		
Number of injections	7704	N/A
Number of ISR events	2203	
Grade 1 events – mild	1907 (87)	
Grade 2 events – moderate	282 (13)	
Grade 3 events – severe	13 (<1)	
ISR duration ≤7 days	1932 (88)	
Maximum Grade 3 or 4 AEs	31 (11)	11 (4)
Maximum Grade 3 or 4 AEs excluding ISRs	22 (8)	11 (4)
Non-ISR maximum Grade 3 or 4 drug-related AEs	4 (1)	0
Serious AEs	18 (6)	12 (4)
AEs leading to withdrawal	9 (3)	4 (1)

* Per FDA snapshot algorithm; 6% noninferiority margin prespecified for primary endpoint, −10% noninferiority margin prespecified for key secondary endpoint.
† Proportion on LA minus proportion on CAR. Adjusted for gender at birth and induction baseline HIV-1 RNA (<100,000 vs ≥100,000 c/mL).
‡ One relocation, 1 lost to follow-up.
# No deaths occurred during the maintenance phase. However, one non-drug-related death was reported during the induction phase.
§ One tolerability of injections, 1 incarceration, 2 lost to follow-up.
‖ Four frequency of visits (participant decision), 2 noncompliance with study treatment and protocol procedures, 1 relocation, 1 participant decision to stop treatment, 1 late to attend visits, 1 lost to follow-up.
& DTG plus 2 alternative non-ABC NRTIs (n=30 induction; n=9 randomized to CAR).

141 SAFETY AND PK OF SUBCUTANEOUS GS-6207, A NOVEL HIV-1 CAPSID INHIBITOR

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Background: GS-6207, a selective, multi-stage inhibitor of HIV-1 capsid function, is in development for the treatment of HIV-1 infection. GS-6207 is characterized by potent antiviral activity, low predicted human clearance, and low aqueous solubility, making it well suited for an extended-release parenteral formulation. This Phase 1 study evaluated the safety, tolerability and pharmacokinetics (PK) of a subcutaneous (SC) suspension of GS-6207 in healthy volunteers.
Methods: This is a randomized, blinded, placebo-controlled healthy volunteer study with staggered single dose escalation cohorts. Within each cohort, subjects were randomized (4:1) to receive single SC doses of GS-6207 (n=8/cohort) or placebo (N=2/cohort), at 30, 100, 300 or 450 mg. PK parameters will be estimated and summarized by dose and dose proportionality will be assessed. Safety, tolerability and PK will be evaluated for at least 24 weeks post-dose.
Results: 40 subjects received a single SC dose of GS-6207 (N=32) or placebo (N=8). The study is ongoing with interim safety and PK data available through at least 20 weeks (Cohort 1, 30 mg), 16 weeks (Cohort 2, 100 mg), 8 weeks (Cohort 3, 300 mg) and 4 weeks (Cohort 4, 450 mg). PK parameters for Cohorts 1 and 2 have been estimated. Analysis for Cohorts 3 and 4 is ongoing. The PK profile of SC GS-6207 is consistent with sustained delivery. T_{max} values ranged from 21 to 35 days (Cohorts 1 and 2). The median apparent terminal $t_{1/2}$ was between 30 to 38 days and concentrations are measureable for at least 16 weeks, to date (Cohorts 1 and 2). The increase in exposure (C_{max} and AUC) between 30 and 100 mg GS-6207 was approximately dose proportional. To date, there have been no deaths, serious adverse events, or Grade 3 or 4 adverse events (AEs). Most AEs were mild (Grade 1) and resolved.
Conclusion: Based on the interim data, GS-6207 was safe and well tolerated following single SC doses of up to 450 mg in healthy subjects. Sustained delivery supports a dosing interval of at least 3 months. The safety and PK of GS-6207 supports evaluation of its antiviral activity in HIV-infected participants.

142 A PHASE IIA STUDY OF NOVEL MATURATION INHIBITOR GSK2838232 IN HIV PATIENTS

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Background: GSK2838232 is a second-generation HIV maturation inhibitor with a distinct preclinical virologic profile and well-defined pharmacokinetics (PK), safety, and tolerability in non-HIV-infected subjects that suggests potential to overcome hurdles met by prior drugs in this class. This profile provided rationale for investigation of GSK2838232 co-administered with cobicistat in HIV-1-infected adults.
Methods: This proof of concept Phase IIa study assessed GSK2838232 antiviral activity, PK, safety, and tolerability in HIV infected adults currently off antiretroviral therapy. The dose-ranging two-part study evaluated 4 dose levels of once daily GSK2838232 monotherapy administered with 150 mg cobicistat for 10 days. PK samples were collected at Days 1 and 10, and safety assessments were performed throughout the study. Subjects were followed for 11 days after the end of treatment (Day 21).
Results: A total of 33 subjects were enrolled across 4 cohorts (200 mg n=8, 100 mg n=10, 50 mg n=8 and 20 mg n=7) of GSK2838232. Following completion of the 100 mg cohort, an interim safety and PK analysis was performed, then remaining cohorts enrolled. Dose-proportional increases in drug exposure were seen. There was moderate-to-high PK variability, with steady state by Day 8 and a geometric mean plasma t½ on Day 10 of 16-19 h across the dose levels. GSK2838232 monotherapy showed a reduction in plasma HIV-1 RNA from baseline to Day 11, with a mean maximum decrease of 1.70, 1.32, 1.56 and 0.67 log10 copies/mL at the 200, 100, 50 and 20 mg dose levels respectively. The population viral genotype was assessed pre- and post-GSK2838232 dosing. Of the 28 subjects with reported genotype data, 2 subjects had treatment-emergent A364A/V mixtures associated with in vitro GSK2838232 resistance. Of these 2 subjects, 1 subject had phenotypic resistance to GSK2838232. Study drug was well-tolerated with no clinically relevant trends in laboratory values, vital signs, or cardiac signals. There were no serious adverse events and all adverse events (AEs) were mild to moderate. There were 5 subjects assessed as experiencing 6 possible drug-related AEs: headache (n=2), somnolence (n=1), skin rash (n=1), abnormal dream (n=1) and pruritus (n=1).
Conclusion: GSK2838232 demonstrated short-term tolerability and antiviral activity, with the maximal response observed in the highest dose cohort. Preliminary evidence of clinical activity observed in HIV patients provides a positive proof of concept for further exploration of GSK2838232.

143 SYSTEMATIC DETERMINATION OF IN VITRO HIV-1 INTEGRASE RESISTANCE FROM CLINICAL SAMPLES

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Background: Resistance phenotype data is relatively sparse for the newest HIV integrase inhibitors, dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB). Here, we report the phenotypic susceptibility of a large panel of oligo-clonal patient-derived subtype B recombinant viruses selected to maximize in vivo sequence variation.

Methods: Using integrase sequences from the BC-CfE database (N=16,563), 27 integrase positions were identified as having amino acids that differed in prevalence between integrase-treated (primarily RAL and/or EVG) and naive individuals. All unique amino acid permutations at these positions were identified (N=288) and N=137 subtype B samples were selected as the representative samples. Extracted RNA was diluted to ~500 copies/mL and amplified in 12 independent RT-PCR reactions. Amplicons with no nucleotide mixtures at these positions were used to make recombinant viruses by co-transfection with linearized integrase-deleted pNL4.3 in CEM-GXR cells. To date, N=130 recombinant viruses were successfully harvested and sequenced to confirm the absence of mixtures at these codons and match to amplicon sequence. Titering and phenotyping were performed in MT4-LTR-EGFP cells, where infectivity data was collected using a SpectraMax i3 MiniMax 300 Imaging Cytometer. EC50s fold-change (FC) relative to a NL4.3 control were determined on day 3 or 4 post-infection.
Results: The 130 variants phenotyped to date represent 88% of the observed sequence variation among the clinical samples at these 27 relevant integrase codons. Of these, 15%, 13%, and 30% had >3-FC for DTG, BIC and CAB, respectively. As expected, variants with the highest FC had G140S and Q148R/H. R263K was the only single variant conferring >3-FC for all three drugs. However, a variant harboring G163R/D232E also had >3-FC for all three drugs. The FC values were closely correlated between all three drugs tested. The greatest exceptions were variants with N155H/G163E or L74I/T97M/F121C/V151I/E157Q/G163K, where both had >75-FC for CAB, while <3-FC for DTG and BIC. If new mutations or permutations are identified it is straightforward to select these for future phenotyping.
Conclusion: Observed sequence variation can be used to efficiently generate panels of resistant viruses for phenotype analysis. We confirm broad cross-resistance between DTG, BIC, and CAB, and identify new patterns leading to decreased susceptibility to the newest integrase inhibitors. This work should be extended to non-subtype B variants.

144 DTG VS LPV/R (DAWNING): EFFICACY BY BASELINE NRTI RESISTANCE AND SECOND-LINE NRTI USE

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Background: DAWNING is a non-inferiority study comparing dolutegravir (DTG) + 2 nucleoside reverse transcriptase inhibitors (NRTIs) with lopinavir/ritonavir (LPV/r) + 2 NRTIs in HIV-1 infected adults failing first-line therapy (HIV-1 RNA ≥400 copies [c]/mL) of a non-nucleoside reverse transcriptase inhibitor + 2 NRTIs.
Methods: Subjects were randomised (1:1, stratified by Screening HIV-1 RNA and number of fully active NRTIs) to 52 weeks of open-label treatment with DTG or LPV/r + 2 investigator-selected NRTIs, including at least one fully active NRTI based on Screening resistance testing. The primary endpoint was the proportion of subjects with HIV1 RNA <50 c/mL at Week 48 (Snapshot algorithm). Post-hoc efficacy analyses were performed based on baseline NRTI resistance profile and NRTI use in the second-line background regimen (BR).
Results: Of 624 subjects randomised and treated, 499 (80%) received <2 active NRTIs at baseline. Overall, 84% (261/312) of subjects on DTG versus 70% (219/312) on LPV/r achieved HIV-1 RNA <50 c/mL at Week 48 (adjusted difference 13.8%, 95% CI: 7.3% to 20.3%, p<0.001 for superiority). This difference was consistent regardless of the use of <2 or 2 fully active NRTIs in the BR. NRTI resistance was present in 561 subjects (90%) at baseline, M184V/I (alone or plus additional NRTI resistance-associated mutations [RAMs]) in 513 (82%), K65R in 187 (30%), and ≥1 thymidine-analogue mutations (TAMs) in 152 subjects (24%). Of subjects with M184V/I alone or plus ≥1 NRTI RAMs, 430 subjects (84%) took lamivudine (3TC) or emtricitabine (FTC) as part of their BR. Tenofovir disoproxil fumarate (TDF) was included in BR in the presence of K65R in 15 subjects while 86 subjects with 1 or more TAMs took zidovudine (AZT). Among subjects receiving 3TC or FTC in the presence of M184V/I, 85% (187/220) of subjects on DTG versus 72% (152/210) on LPV/r had HIV-1 RNA <50 c/mL at Week 48 (difference 12.6%, 95% CI: 4.9% to 20.3%). High responses were also observed in the DTG arm, when AZT or TDF were included in the BR in the presence of TAMs or K65R, respectively; however, subject numbers in these subgroups were small (Table 1).
Conclusion: In DAWNING, response rates were high in subjects receiving DTG+2NRTIs regardless of pre-existing resistance to one of the NRTIs in the BR, including in subjects using 3TC or FTC in the presence of M184V/I. In WHO interim guidance on HIV treatment, DTG+2NRTIs is now a recommended second-line treatment option for patients failing an NNRTI-based regimen.

Table 1. Proportion of subjects with HIV-1 RNA <50 c/mL (Snapshot algorithm) at Week 48 by baseline resistance and NRTI use

NRTI used	Baseline NRTI mutations	Treatment	N	Number responded/total assessed	Difference in Proportion (95% CI)
Any	M184V/I only or + ≥1 NRTI [1]	LPV/r	252	182/252 (72%)	12.1 (5.0, 19.1)
		DTG	261	220/261 (84%)	
3TC or FTC + other NRTI	M184V/I only or +≥ 1 NRTI [1]	LPV/r	210	152/210 (72%)	12.6 (4.9, 20.3)
		DTG	220	187/220 (85%)	
Any	K65R only or + ≥ 1 NRTI [2]	LPV/r	92	68/92 (74%)	10.3 (-1.3, 21.9)
		DTG	95	80/95 (84%)	
TDF + other NRTI	K65R only or + ≥1 NRTI [2]	LPV/r	8	7/8 (88%)	-1.8 (-36.4, 32.8)
		DTG	7	6/7 (86%)	
AZT + other NRTI	≥ 1 TAM	LPV/r	51	40/51 (78%)	7.3 (-8.9, 23.5)
		DTG	35	30/35 (86%)	

[1] Including K65R. [2] Including M184V/I

145LB THERAPEUTIC ACTIVITY OF PGT121 MONOCLONAL ANTIBODY IN HIV-INFECTED ADULTS

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Background: PGT121 is a recombinant human IgG1 mAb that targets a V3 glycan-dependent epitope region of HIV Env. PGT121 is a potent neutralizing antibody in vitro and has been shown to prevent and treat simian-human immunodeficiency virus in rhesus monkeys. Here we present safety, pharmacokinetic (PK) and antiviral efficacy data from the first-in-human phase 1 clinical trial of PGT121 conducted in the United States.
Methods: The first part of the study was a randomized, double blinded, dose escalation, placebo-controlled trial of PGT121 in adults who were HIV-uninfected (HIV-, N=20) and HIV-infected on ART (HIV+/ART+, N=15). PGT121 was given once at 3, 10, and 30 mg/kg IV and 3 mg/kg SC (N=5/group, 4:1 Ab/placebo). The second part of the study was an open label trial of PGT121 given once at 30 mg/kg IV in HIV-infected adults not on ART with high VL (3.3-4.8 log cp/ml, N=9) and low VL (2-2.6 log cp/ml, N=3). All participants were monitored for reactogenicity for 3 days and adverse events (AEs) for 56 days. PK and virologic assessments were performed through 6 months. The lower limit of quantification (LLOQ) of VL was 1.6 log cp/ml.
Results: PGT121 was safe and well-tolerated with no related mod/severe AEs. The elimination half-life of PGT121 was ~22 days in HIV- and HIV+/ART+ groups, with variation by dose and route. In viremic HIV+ individuals not on ART, PGT121 showed antiviral efficacy in 5/9 participants in the high VL group with a median drop in VL of 1.7 log cp/ml (1.3-2.1) by d10. These individuals showed PGT121 sensitive virus at baseline but developed rebound by d28 with emergence of resistance. In the low VL group, PGT121 decreased VL to

Table 1. Opioid overdose death rates per 100,000 persons with diagnosed HIV infection[a], United States, 2011–2015

	Year of Death					
	2011	2012	2013	2014	2015	% Change from 2011 to 2015
Total	**23.2**	**28.3**	**31.5**	**29.4**	**33.1**	**42.7%**
Age group at death (years)						
0–19	0.0*	0.0*	0.0*	0.0*	12.5*	N/A
20–29	9.7*	13.9	10.0*	12.8	20.7	113.4%
30–39	19.8	19.8	21.5	30.4	25.4	28.3%
40–49	24.7	28.3	41.8	34.1	37.4	51.4%
50–59	34.7	42.3	37.9	37.2	41.9	20.7%
≥60	8.5*	20.5	24.6	15.9	25.7	202.4%
Sex at birth						
Female	24.0	32.9	36.8	33.1	35.2	46.7%
Male	22.9	26.7	29.8	28.2	32.4	41.5%
Race/ethnicity						
Black/African American	11.4	16.6	15.6	16.2	19.7	72.8%
Hispanic/Latino	26.5	32.0	36.6	36.7	33.5	26.4%
Other	24.5	40.1	53.1	31.1	42.1	71.8%
White	36.3	39.1	45.1	41.9	49.1	35.3%
Transmission Category[b]						
Heterosexual contact	9.9	14.2	12.8	12.6	17.2	73.7%
Injection drug use	76.5	120.7	127.7	123.2	137.4	79.6%
Male-to-male sexual contact	11.6	9.9	17.6	13.8	13.7	18.1%
Male-to-male sexual contact and injection drug use	84.7	84.6	68.5	94.8	121.1	43.0%
Other	11.4	13.4	17.0	14.2	17.6	54.4%
Region of residence at death						
Northeast	38.0	49.0	49.6	47.9	60.6	59.5%
Midwest	28.5	37.8	33.1	37.5	37.5	31.6%
South	13.0	16.8	19.1	20.0	21.4	64.6%
West	23.6	21.7	35.7	22.8	23.1	-2.1%

[a] ICD-10 codes of X40–X44 for the underlying cause and ICD-10 codes of T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6 as a multiple cause of death.

[b] Data not statistically adjusted to account for unknown transmission categories.

*Interpret rate with caution; rate calculated based on numerator less than 12.

146 MORTALITY REDUCTION IN WESTERN KENYA DURING SCALE-UP OF HIV TREATMENT, 2011-2016

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Background: In the early years after ART introduction in Africa, there were marked declines in annual mortality, with reductions of 10-20% observed in various settings. There is limited information on the impact of the current rapidly expanding HIV treatment access on general population mortality in sub-Saharan Africa.

Methods: From 2011 to 2016, ART coverage in western Kenya increased from 34% to 60%. Data from a health and demographic surveillance system (HDSS) measured mortality and migration for the period; HIV home-based counselling and testing (HBCT) surveys took place in 2011, 2012, 2013, and 2016. Mortality trends were assessed in a closed cohort of residents.

Results: Seventy percent of HDSS residents in Gem, western Kenya, (22,688/32,467, aged 15-64 years) participated in the 2011 survey and comprised the cohort followed over time. All-cause mortality was 10.0 (95% confidence interval (CI) 8.4-11.7) per 1000 person-years (PY) in 2011, and declined to 7.5 (95% CI 5.8-9.1) per 1000 PY in 2016. Mortality was stable over the study period, at 5.7 per 1,000 PY among the non-HIV infected. Among HIV-infected persons, mortality declined from 30.5 per 1000 PY in 2011 to 15.9 per 1000 PY in 2016 (average decline 6% per year). Individuals on ART experienced higher mortality rates than non-HIV-infected individuals (rate ratio 2.8, 95% CI 2.2-3.4).

Conclusion: This study suggests mortality among HIV infected individuals declined substantially during ART expansion between 2011 and 2016, though less than the declines reported during early ART introduction. Mortality trends among HIV positive persons are critical to understanding epidemic dynamics. As ART use continues to expand, HDSS platforms offer a unique opportunity to monitor mortality alongside trends in HIV prevalence and incidence.

147 OPIOID OVERDOSE DEATHS AMONG PERSONS WITH HIV INFECTION, UNITED STATES, 2011-2015

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Background: The opioid epidemic is a nationwide public health emergency. Persons with HIV might be at increased risk for drug overdose deaths, including overdoses involving an opioid. We examined characteristics of unintentional drug overdose deaths involving an opioid (hereafter, opioid overdose deaths) during 2011-2015 among persons with diagnosed HIV infection in the United States.

Methods: We used National HIV Surveillance System data reported through December 2017 to summarize opioid overdose deaths between 2011 and 2015 among persons with diagnosed HIV in the 50 states and District of Columbia. Opioid overdose deaths were selected by using the *International Classification of Disease, Tenth Revision* (ICD-10). Death rates were calculated per 100,000 persons with diagnosed HIV. We examined death rates by demographic, geographic, and HIV transmission categories.

Results: There were 1,363 opioid overdose deaths among persons with diagnosed HIV during 2011-2015. Although the rate of all deaths among persons with diagnosed HIV was 12.7% less in 2015 (1630.6 per 100,000) than in 2011 (1,868.8 per 100,000), the opioid overdose death rate among persons with diagnosed HIV was 42.7% greater in 2015 (33.1 per 100,000) than in 2011 (23.2 per 100,000). Rates of opioid overdose deaths were higher in 2015 than 2011 for all subgroups examined by age, sex, race/ethnicity, transmission category, and US Census region of residence at death, with the exception of the West US Census region. In 2015, the rate of opioid overdose deaths was highest among persons aged 50–59 years at death (41.9 per 100,000), females (35.2 per 100,000), whites (49.1 per 100,000), persons who inject drugs (137.4 per 100,000), and the Northeast US Census region (60.6 per 100,000), compared to their respective counterparts.

Conclusion: Opioid overdose death rates were higher in 2015 than in 2011 among nearly all demographic, transmission, and geographic categories examined despite the decreased rate of total deaths among persons with diagnosed HIV during 2011–2015. Differences in opioid overdose deaths among subgroups of persons with diagnosed HIV call for targeted prevention efforts. Intensified overdose prevention is needed for achieving optimal care of persons with diagnosed HIV and to further decrease mortality.

148 EARLY MORTALITY IN HIV-INFECTED PATIENTS INITIATING ART WITHOUT A PRETHERAPY CD4

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Background: In the treat-all era, CD4 levels are no longer required to determine treatment eligibility, resulting in some programs phasing out CD4 tests altogether. Pre-therapy CD4, however, can play a crucial role in informing screening and prophylaxis for opportunistic infections, which are contributors to HIV-related mortality. We assessed the association between presence of a pre-therapy CD4 and early mortality among patients in Zambia starting ART.

Methods: We evaluated patients starting ART between August 1, 2013 and July 31, 2015 in Zambia. We obtained pre-therapy CD4 (most recent determination within 6 months of treatment initiation), socio-demographic and clinical data from the electronic medical record. We identified a probability sample of patients lost to follow-up for intensive tracing to determine vital status. Findings from tracing were incorporated into Kaplan-Meier estimates and multivariate proportional hazards regression through inverse probability-weights. Estimates were adjusted for potential common causes of CD4 determination and survival (e.g. WHO stage, calendar time, facility type, etc.).

Results: Of 39,556 patients starting ART (63% women, median age 35.64 (IQR 29.88 – 42.41)), 31,895 (76%) had a pre-therapy CD4 on record (median CD4 270 cells/μl (IQR 145-396)). The cumulative incidence of mortality after ART

initiation in the study population was 5.12% (95% CI 4.32, 6.10). The cumulative incidence of mortality with and without pre-therapy CD4 at 1 year was 4.54% (95% CI 3.73, 5.60) and 7.06% (95% CI 5.14, 9.98), respectively (Cox test for equality p=0.03). After adjustment for pre-therapy WHO stage, sex, age, facility type, ART initiation date, patients without a pre-therapy CD4 had 1.48 times the hazard of mortality in the first year compared to those with a pre-therapy CD4 determination (95% CI 1.00, 2.17, p=0.046). Advanced WHO stage and male sex were associated with higher probability of early mortality (WHO stage IV, HR, 7.69 (95% CI, 4.19, 14.13 p< 0.001) male sex, HR, 1.62 (95% CI, 1.13, 2.32 p< 0.008)).

Conclusion: Despite the possibility of unmeasured confounding, these results suggest that patients initiating ART without pre-therapy CD4 experience a higher risk of early mortality even after adjustment for demographic characteristics and disease stage. Even though pre-therapy CD4 are no longer required to determine eligibility, further research to evaluate the safety of discontinuing pre-therapy CD4 is needed before widespread discontinuation.

149 UTILITY OF CD4 CELL COUNT MONITORING IN BOTSWANA: ANALYSIS OF ROUTINE LABORATORY DATA

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Background: Botswana has an adult HIV prevalence of 21.9%. An estimated 317,945 patients (84% of HIV-infected individuals) are on treatment. National guidelines recommend both CD4 count and viral load monitoring. Since the country adopted universal test-and-treat in June 2016, an increasing burden has been placed on the health system. This study aims to assess the ongoing need for regular CD4 monitoring in Botswana.

Methods: Data from all HIV-infected patients having CD4 counts at the Gaborone clinics served by the Botswana Harvard reference laboratory during 2015, 2016, and 2017 were analysed. CD4 count and viral load data were assessed to determine the proportion of patients presenting with advanced disease (CD4<200 cells/µL), trends in CD4 cell counts over time, and the proportion of patients presenting without advanced disease experiencing a drop in CD4 count to below 200 cell/µL during follow up.

Results: 193,050 CD4 counts were performed on 60,899 patients, with a median frequency of monitoring of 1.48 CD4 measurements per patient per year. 76% (46,474) of patients were established clinic patients, while 24% (14,425) were new to care during the study period. 24.8% (3,571/14,425) of new patients presented with CD4 count<200 cell/µL. Age and sex were strongly associated with advanced disease, with men more likely to present with advanced disease than women (34.9% vs 18.9%, p<0.001). Increased age was associated with lower CD4 cell count. 54% of patients with baseline CD4 cell counts below 200 cell/µL attained a CD4 rise to above 200 cell/µL within 12 months of follow-up. In patients with two or more CD4 counts, a very small proportion (3.6% (180/5060)) of those with a baseline CD4 cell count ≥200 cell/µL experienced a drop in CD4 cell count to <200 cell/µL over the study period. 58.9% (106/180) of patients with a drop in CD4 count had a viral load measurement within 2 months of CD4 measurement, of these, 79.2% (84/106) were virally suppressed.

Conclusion: A significant proportion of patients in Botswana still present with advanced disease, demonstrating the ongoing importance of baseline CD4 testing to identify patients at risk of opportunistic infections and in need of interventions including cotrimoxazole prophylaxis and cryptococcal antigen screening. Very few individuals with CD4 counts above 200 cells/µL experienced a drop to below 200 cells/µL, suggesting limited utility for ongoing CD4 count monitoring in individuals without advanced disease in settings with routine viral load testing.

150 TRENDS IN CD4 AND VIRAL LOAD TESTING IN SOUTHERN AFRICA: ANALYSIS OF 6 COUNTRIES

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Background: Since 2015 the World Health Organization has recommended CD4 testing before starting antiretroviral therapy (ART) to detect advanced disease and routine viral load (VL) testing at 6 months and every 12 months thereafter to detect treatment failure. We assessed trends in CD4 and VL testing in six countries in Southern Africa.

Methods: We included adults (≥15 years old) who started ART at one of the HIV treatment programs that participate in the International epidemiology Databases to Evaluate AIDS (IeDEA) Southern Africa region between 2005 and 2017, and had ≥8 months of follow-up time from ART start. We assessed the percent of patients with a CD4 count at ART initiation, the percent with a VL test ≥6 months after ART start and, of those, the percent with virologic failure at the first test ≥6 months after ART start. Virologic failure was defined as VL ≥1000 cells/mm3. The CD4 count at ART start was defined as a CD4 count within a window of 3 months before to 1 week after ART start. Analyses were stratified by sex, age and year of ART start.

Results: Our analysis included 520,175 adults from 14 programs in six countries with a median (IQR) age of 34.4 (28.7-41.3) years, of whom 65.0% were female. Median (IQR) follow-up time was 43.6 (23.2-73.0) months and similar across countries. The percent with CD4 testing at ART start has declined over the years from a high of 76.2% in 2005 to a low of 49.4% in 2017. In recent years, the frequency of CD4 testing has also decreased, most notably in Malawi, South Africa and Lesotho (Figure). Women aged 15-24 years had the least CD4 testing (62.5%) and men aged 25-49 years the most (68.3%). Young men aged 15-24 years had the least VL testing (38.4%) and women aged 25-49 years had the most (48.0%). Of those with a VL test, 11.4% had virologic failure with young men aged 15-24 years at greatest risk (19.5%) and women 50+ years at lowest risk (6.2%). Virologic failure has been decreasing in recent years, from 13.7% in 2010 to 8.6% in 2015.

Conclusion: CD4 testing at ART start has steadily declined over the years, alongside reduced CD4 testing in general. Virologic failure has been declining; however, without expanded CD4 and VL testing, many patients with advanced disease or with treatment failure may go undetected.

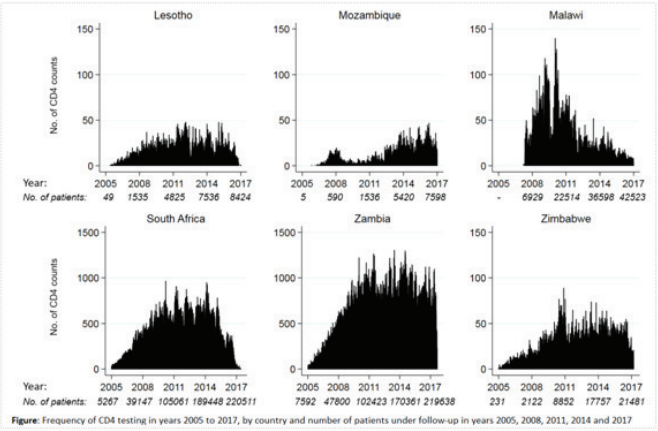

Figure: Frequency of CD4 testing in years 2005 to 2017, by country and number of patients under follow-up in years 2005, 2008, 2011, 2014 and 2017

151 HIGH LEVELS OF DRUG RESISTANCE AMONG ART-EXPERIENCED HOSPITALIZED PATIENTS

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Background: In sub-Saharan Africa, an increasing number of patients hospitalized with advanced HIV are ART-experienced and mortality among them is extremely high during and after hospitalization. In patients on first-line ART with an elevated viral load (VL≥1000 copies/ml), WHO recommends a switch to 2nd line conditional on a 2nd elevated VL three months after the 1st one and enhanced adherence counseling, regardless of CD4 level and hospitalization status. To assess if patients may benefit from a faster switch to 2nd line, we measured rates of ARV drug resistance (DR) among ART-experienced hospitalized patients. There were previously no data available on HIV DR among these patients.

Methods: A cross-sectional survey was implemented between September 2017 and April 2018 in two hospitals supported by MSF in Kinshasa (KS), Democratic Republic of Congo, and Homa Bay (HB), a rural area in Kenya. Hospitalized people living with HIV (PLWH) aged 15 years and above receiving first-line ART for at least 6 months and with CD4<350 cells/µL were invited to participate. CD4 count, VL and resistance genotype were done at inclusion. Resistance was defined as any major (intermediate/high, Stanford HIVdb) NRTI or NNRTI DR. A regimen-specific genotypic sensitivity score (sGSS) was calculated (maximum score 3, fully susceptible regimen).

Results: In total, 305 participants were included after a median time of 5.3 years [IQR:2.5-10.3] on ART in KS (77%-TDF/3TC/EFV,8%-ABC/3TC/EFV) and 4.0 years [IQR:1.8-8.9] in HB (71%-TDF/3TC/EFV,11%-AZT/3TC/NVP). 69% (KS) and 54% (HB) were female, and the median age was 38 [31-48] and 40 [32-48] years. The median CD4 was 69 cells/µL [IQR:29-134] and 135 cells/µL [IQR:46-255] in KS and HB, respectively and 70% in KS and 37% in HB had a VL≥1,000 cp/mL. Among those with CD4<50 cells/µL, 87% and 84% had a VL≥1,000 cp/mL in KS and HB. Of those with VL≥1000cp/mL, 73% had dual-class DR in both sites, with 73% on an ineffective regimen (sGSS<2) in KS, and 74% in HB. Age, low CD4 count and suboptimal self-reported adherence were associated with treatment failure (VL≥1000cp/mL and Dual-class DR) in HB and with low CD4 (CD4<50 cells/µL) in KS.

Conclusion: A high proportion of PLWH hospitalized with advanced disease and on first-line ART were resistant to their ARV treatment in each site. A fast switch to 2nd line ART after one single elevated VL or CD4<50 cells/µL should be immediately recommended to accelerate immune reconstitution and improve outcomes among those patients.

152 HIV DRUG RESISTANCE IN SOUTH AFRICA: RESULTS FROM A POPULATION-BASED HOUSEHOLD SURVEY

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Background: South Africa's antiretroviral treatment (ART) programme is the largest globally with >4 million HIV-infected persons receiving standardized treatment regimens. Monitoring levels of HIV drug resistance (HIVDR) is a priority activity for the country. HIVDR testing was included for the first time in the 5th national HIV household survey conducted in 2017.

Methods: Multi-stage stratified cross-sectional random sampling was used to select households for participation nationally. Dried blood spots were tested to determine HIV status, estimated recency of infection, exposure to antiretroviral drugs (ARVs), and HIVDR in addition to behavioral data from all household members who agreed to participate. HIVDR testing was conducted on HIV-positive samples with viral load ≥1000 copies/ml using next generation sequencing methodologies.

Results: Of 1107 HIV positive samples from virally unsuppressed participants, 697 (63%) were successfully amplified by polymerase chain reaction and sequenced. Drug resistant mutations (DRM) were identified in 27.4% (95% CI 22.8-32.6) of samples: 18.9%(95% CI 14.8-23.8) had resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) only, 7.8% (95% CI 5.6-10.9) had dual resistance to NNRTIs and nucleoside reverse transcriptase inhibitors(NRTIs), and 0.5% (95% CI 0.1-2.1) had resistance to second-line regimens that include protease inhibitors (PIs),NNRTIs, and NRTIs). Table 1 shows HIVDR by exposure to ARVs, sex, and age. NNRTI-only resistance was found in 14.3% ARV+ve and 20.0% ARV-ve samples (p=0.311), while dual NNRTI and NRTI resistance occurred in 40% ARV+ve and 2.1% ARV–ve samples (p< 0.001). Among those who were ARV-ve but self-reported daily ARV use (ARV defaulters; n=41), 75.6% had DRM; 56.4% with NNRTI-only resistance, 14.3% with dual NNRTI and NRTI resistance. There were no significant age and sex differences among either NNRTI-only resistant and dual NNRTI and NRTI resistant samples.

Conclusion: These findings demonstrate high proportions of DRM among virally unsuppressed HIV-infected persons in South Africa. While these results include treatment defaulters, potential pretreatment HIVDR levels are concerning. Programmatic implications include stronger adherence support to reduce ARV defaulting, and strengthened first line ART regimens by including integrase strand transfer inhibitors (INSTIs) as a part of first line treatment. These findings support the national transition to include Dolutegravir as part of first-line ART in South Africa.

HIVDR, South Africa, 2017

Table 1: HIV drug resistance by exposure to antiretroviral drugs, age and sex, South Africa, 2017

Variable	n	Any DRM %* (95% CI)	p value	NNRTI-only resistance %* (95% CI)	p value	Dual NNRTI & NRTI Resistance %* (95%CI)	p value
ARV +ve	102	55.7(42.6-67.9)	<0.001	14.3(7.5-25.6)	0.311	40.4(29.6-52.2)	<0.001
ARV –ve	517	22.8 (17.7-28.7)		20.0 (15.4-25.7)		2.1(0.6-6.8)	
ARV defaulters**	41	75.9 (59.2-87.3)		56.4 (34.4-76.2)		14.3(2.5-52.1)	
Male	252	29.4(22.5-37.4)	0.473	19.6(13.5-27.7)	0.772	9.7(5.8-15.7)	0.202
Female	445	25.8 (19.8-32.8)		18.3(13.2-24.8)		6.3 (4.2-9.5)	
0-14years	26	33.7(17.6-54.7)	0.684	17.7(7.2-37.4)	0.749	14.9(5.3-35.2)	0.461
15-24years	98	30.5(18.7-45.5)		22.1(12.6-35.9)		5.7 (1.7-16.8)	
25+years	573	26.6(21.7-32.2)		18.4(14.0-23.8)		7.9(5.4-11.4)	
15-49years	568	27.5(22.5-33.2)		19.2(14.8-24.4)		7.8(5.3-11.3)	
50+years	103	24.1(14.8-36.7)		17.0(8.9-30.0)		5.7 (2.5-12.8)	

%* - weighted %; **ARV defaulters - self-reported daily ARV use but tested ARV negative.

153 DURATION OF INFECTIOUSNESS AMONG PERSONS WITH HIV DIAGNOSED DURING 2012-2016

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Background: HIV treatment as prevention succeeds by reducing the duration of infectiousness (i.e., time from infection to diagnosis and from diagnosis to viral suppression). HIV testing and linkage to care efforts have been intensified over the years for promoting early HIV diagnosis and early treatment to achieve viral suppression. To evaluate the progress, we examined the time from infection to diagnosis (I-to-D) and from diagnosis to first viral suppression (D-to-VS).

Methods: We analyzed data from the National HIV Surveillance System reported through June 2018 from 27 U.S. jurisdictions with complete laboratory reporting. The analyses include persons with HIV infection (PwH) diagnosed at age => 13 years during 2012-2016, whose address at the time of HIV diagnosis was in one of the 27 jurisdictions, and had CD4 and viral load tests after HIV diagnosis. The I-to-D duration was estimated based on the CD4-depletion model. The D-to-VS duration was calculated based on viral load tests. Viral suppression was defined as <200 copies/mL. We censored viral load data at the time of death or by June 30, 2018. The median time and interquartile range for both durations were examined by year when HIV diagnosis occurred, sex, age at HIV diagnosis, race/ethnicity, and transmission category.

Results: Approximately 22,000 PwH per year met the inclusion criteria. The I-to-D duration shortened from 43 months for PwH diagnosed in 2012 to 39 months for PwH diagnosed in 2016 (9.3%). The D-to-VS duration shortened from 8 months for PwH diagnosed in 2012 to 5 months for PwH diagnosed in 2016 (37.5%). Both durations shortened in all sex, age, race/ethnicity, and transmission category. Younger age groups (13-24 and 25-34 years) had shorter I-to-D durations but had longer D-to-VS durations, compared to older groups (35 and older, see Table). Among race/ethnicity groups, Hispanics/Latinos had the longest I-to-D duration (47 months) and blacks had the longest D-to-VS duration (7 months). Among transmission categories, male heterosexuals had the longest I-to-D duration (70 months) and men who have sex with men and inject drugs had the longest D-to-VS duration (8 months).

Conclusion: Our findings show the success of promoting early HIV diagnosis and early treatment as evidenced by the shortened duration of infectiousness over time. Delayed HIV diagnoses continue to be substantial. Targeted and intensified HIV testing and care efforts are needed to address group differences in I-to-D and D-to-VS durations.

Table. ***Duration of infectiousness among persons with HIV infection diagnosed at age => 13 years or older during 2012-2016 who had CD4 and VL tests after HIV diagnosis, 27 U.S. jurisdictions***

	HIV diagnosis No.	Time from infection to diagnosis Median months (interquartile range)	Time from diagnosis to first viral suppression Median months (interquartile range)
Total	108561	41 (5-101)	6 (3-18)
Year when HIV diagnosis occurred			
2012	22562	43 (5-104)	8 (4-26)
2013	21622	43 (5-103)	7 (4-22)
2014	22093	41 (4-100)	6 (3-17)
2015	21601	39 (4-98)	5 (3-14)
2016	20683	39 (4-98)	5 (3-12)
Age at diagnosis			
13-24 years	25035	32 (4-72)	8 (4-23)
25-34 years	35375	34 (4-98)	6 (3-19)
35-44 years	21568	49 (5-125)	6 (3-16)
45-54 years	17167	57 (5-136)	5 (3-13)
55 years and older	9416	63 (6-127)	5 (2-11)

154 TISSUE-RESIDENT MEMORY CD8+ CELLS

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Recent studies have established that non-recirculating resident memory $CD4^+$ and $CD8^+$T cells can be found in virtually every human tissue. These cells bear a transcriptional profile of tissue retention and immediate effector function, suggesting a pivotal role in protective immunity. Resident memory $CD8^+$ T cells specific for HIV have been found in sites of HIV persistence (gut and LN), and have been associated with viral control. This presentation will review current knowledge on resident memory T cells in humans, in the context of HIV infection. The potential relevance of resident memory T cells to HIV cure and therapeutic and prophylactic vaccine strategies will also be highlighted.

155 MECHANISMS UNDERLYING LOSS OF ILCs IN HIV/SIV-INFECTED INDIVIDUALS

Jason Brenchley, *National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

Innate lymphoid cells (ILCs) play critical roles in mucosal barrier defense. HIV-1 infection is characterized by depletion of ILCs with decreased integrity of GI tract epithelium. Interestingly, ILC depletion is not a generalized feature of all viral infections. There is thus considerable interest in understanding the exact mechanisms of ILC loss in HIV/SIV infections. We find that in ARV naïve, SIV-infected nonhuman primates, distinct inflammatory and type I interferon gene signatures coincide with rapid loss of ILC3s in gut-draining mesenteric lymph nodes (MLN). Pharmacologic control of viremia with antiretroviral treatment was sufficient to reconstitute ILC3s in the MLN, and MLN ILCs were preserved in elite controller RMs with natural virologic control. To understand mechanisms underlying ILC3 loss in HIV-infection we created hallmarks of progressive HIV-1 infection with loss of CD4 T cells and/or GI barrier damage, and in healthy uninfected rhesus macaques. Experimental depletion of CD4+ T cells in combination with dextran sodium sulfate was sufficient to significantly reduce ILC frequencies in MLNs. Moreover, in HIV-uninfected subjects with durable CD4+ T cell deficiency, deemed idiopathic CD4+ lymphopenia, similar ILC deficiencies in blood were observed, collectively identifying determinants of ILC homeostasis in primates and potential mechanisms underlying their depletion in HIV/SIV infection.

156 MEMORY NK CELLS AS NOVEL EFFECTORS AGAINST HIV AND SIV

R. Keith Reeves, *Harvard Medical School, Boston, MA, USA*

Natural killer (NK) cells provide rapid early responses to viral infections and thus can contribute substantially to disease modulation and potentially vaccine efficacy. Traditionally, NK cells have been considered to be nonspecific components of innate immunity, but burgeoning evidence suggests that the functional repertoire of NK cells is far more diverse and can include adaptive features and memory recall. Some of the first evidence that NK cells respond in an antigen-specific fashion came from experiments revealing that subpopulations of murine NK cells could respond to a specific MCMV protein, and that in the absence of T and B cells, murine NK cells also mediated adaptive immune responses to a secondary challenge with specific haptens. These data have been followed by demonstrations of NK cell memory to viruses and viral antigens in mice, non-human primates, and most recently humans. Indeed recent work from our laboratory and others has shown that adaptive NK cells are mounted against both HIV and SIV antigens, both by infection and multiple vaccine vectors. These responses have proven to be robust, long-lived, and particularly enriched in tissues. Mechanistically, adaptive NK cell responses in humans and non-human primates largely depend on NKG2C expression and MHC-I-mediated presentation on target cells. In this presentation a current state of the field will be discussed, including multiple types of memory NK cells, how each type may mobilize against HIV and SIV infection, and how these novel phenomena could ultimately be harnessed in the context of effective vaccine and antiviral modalities.

157 HIV SUPPRESSION BY CD8+ LYMPHOCYTES

Deanna Kulpa, *Emory University, Atlanta, GA, USA*

The persistence of HIV infection under ART is due to a reservoir of latently infected cells that remain indefinitely despite full suppression of virus replication. HIV latency is triggered by several mechanisms that lead to the silencing of virus expression including epigenetic DNA modification through methylation and histone deacetylation, limited availability of critical transcription factors and inefficient elongation of the nascent viral transcripts. Defining the mechanisms responsible for the establishment and maintenance of the HIV reservoir under ART has been the focus of efforts aimed at HIV eradication. Numerous studies have demonstrated that CD8+ T cells inhibit virus replication during untreated HIV/SIV infection. However, the mechanisms responsible for this antiviral effect remain poorly understood and include the direct killing of HIV/SIV-infected cells (i.e., cytotoxic T lymphocyte activity) as well as non-cytolytic mechanisms. Several studies now have shown that depletion of CD8+ lymphocytes results in increased viremia without prolonging the average in vivo lifespan of productively infected cells, thus suggesting a key role for non-cytolytic mechanisms of virus suppression. Experiments conducted in ART-treated SIV-infected rhesus macaques have demonstrated that depletion of CD8+ lymphocytes is followed by reactivation of virus production, and increased susceptibility to the latency reversal effect of an IL-15 superagonist. These results reveal an important role of CD8+ lymphocytes in cooperating with ART to maintain virus suppression and also strongly suggest that CD8+ lymphocytes function to silence HIV expression. Indeed, our recent studies employing in vitro models of HIV latency have demonstrated a CD8+ lymphocyte mediated suppression of HIV expression in CD4+ T cells that functions to induce the establishment of latency as well as maintain latency in the presence of activation signaling. Understanding the mechanisms by which CD8+ lymphocytes suppress virus transcription and ultimately promote HIV latency and persistence in ART-treated HIV-infected individuals may provide critical insight to support the design of new approaches for HIV eradication.

158 OBESITY: A GROWING PROBLEM IN ANTIRETROVIRAL THERAPY

John R. Koethe, *Vanderbilt University, Nashville, TN, USA*

Over the past two decades, the prevalence of obesity (i.e., body mass index $\geq 30 kg/m^2$) among persons living with HIV (PLWH) has steadily risen, which is clinically important as obesity increases the risk of diabetes, cardiovascular disease, fatty liver disease, neurocognitive impairment, and other comorbidities. Among PLWH, traditional risk factors for obesity (e.g., food insecurity, lack of readily available healthy foods, insufficient physical activity, and limited knowledge of healthy lifestyle practices) intersect with HIV-specific factors. Many PLWH experience abrupt weight gain after starting antiretroviral therapy (ART). A retrospective analysis of more than 14,000 patients starting ART found that, after three years of treatment, 22% of normal-weight individuals became overweight and 18% of overweight individuals became obese. Weight gain on ART is multifactorial and may be due, in part, to reduced inflammation and catabolism following viral suppression; increased access to health education, social support services (e.g., food assistance), smoking cessation, and treatment of depression with entry into HIV care; and effects of specific ART medications. While weight gain appears to occur with all current ART regimens, between-class and within-class differences have emerged. AIDS Clinical Trials Group (ACTG) study A5257 found a higher incidence of severe (>10%) weight gain among ART-naïve participants after starting a regimen containing the integrase strand transfer inhibitor (INSTI) raltegravir versus the protease inhibitors (PI) darunavir or atazanavir, each boosted with ritonavir. In a large retrospective analysis, ART-naïve patients starting INSTI-based regimens

had higher weight gain compared to those starting non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens; among INSTIs, weight gain was greater with dolutegravir and raltegravir versus elvitegravir-containing regimens. Recent smaller analyses also report weight gain among patients with virologic suppression switched from PI- or NNRTI-containing regimens to INSTI regimens, and a minor weight increase in those switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF). In summary, weight gain is common among PLWH starting ART and may occur following regimen switches. Rigorous clinical trial data is needed to confirm findings from observational cohorts, in addition to studies of potential mechanisms linking antiretroviral agents and body weight.

159 I KEEP FORGETTING: HIV, AGING, AND COGNITIVE DISORDERS

Victor Valcour, *University of California San Francisco, San Francisco, CA, USA*

HIV infection is a leading cause of cognitive impairment in people under the age of 60, worldwide. Historically, there was little need to differentiate cognitive disorders due to HIV from that of age-associated neurodegenerative disorders, such as Alzheimer's disease, because few patients living with HIV survived into geriatric age groups where prevalence of these neurodegenerative disorders increase exponentially. This talk will provide recent evidence of persistent clinically meaningful cognitive challenges in patients aging with HIV. We will review likely neuropathogenic mechanisms and recent data on the typical clinical presentation. We will review data captured, primarily from clinical settings, that can inform potential interactions among HIV infection, vascular central nervous system damage, and Alzheimer's disease as we address facts and fiction around brain aging with HIV. Addressing one of the most challenging clinical geriatric neuroHIV issues of the current time, we will discuss current knowledge around differential diagnosis related to cognitive disorders in people living with HIV over the age of 60 years.

160 PrEP FAILURES: DIAGNOSIS, RESISTANCE, AND TREATMENT

Jean-Michel Molina, *Hôpital Saint-Louis, Paris, France*

PrEP with TDF/FTC has shown in demonstration projects and real life implementation an effectiveness that was better than in clinical trials. However, despite its high effectiveness, and because of its increased use, a number of PrEP failures have been reported highlighting that, as any preventive tool, only proper use will be associated with protection against HIV-infection. PrEP failures have many causes which need to be clearly diagnosed. System failures refer to the lack or limited access to PrEP because of unavailability, lack of awareness among people at risk and health care providers, and cost. Governments should endorse WHO guidelines and offer PrEP to those who need it. Doctors failures refer to insufficient knowledge of PrEP with the failure to rule out HIV-infection when starting or renewing PrEP, or reluctance to prescribe PrEP. People failures are mostly due to the deferred or improper use of PrEP since strict adherence to PrEP is critical for effectiveness. Assay failures refer to the challenges of HIV diagnosis due to the low sensitivity of HIV tests during the first days/weeks following HIV acquisition, the impact of TDF/FTC use on HIV antibody and viral load assays and also the challenge of ruling out HIV-infection in case of false positive serologic assays on PrEP. Drugs failures which are the most feared causes of PrEP failure remain rare with only a handful of breakthrough HIV-infections in people with good adherence to PrEP. These cases are potentially due to the acquisition of a virus with TDF and/or FTC resistance, exposure to a very high HIV inoculum, pharmacokinetic variability in blood and/or tissues, drug drug interactions, concomitant STIs or altered microbiota. PrEP failures can lead to drug resistance when started or maintained in a person with HIV-infection. In clinical trials, most cases of HIV-infection with resistance occurred when PrEP was started in someone with undiagnosed HIV-infection. In case of HIV-infection antiretroviral therapy including drugs with a high genetic barrier to resistance (boosted darunavir, dolutegravir, bictegravir) should be immediately initiated pending the results of a genotypic resistance test. Overall, true biomedical failures of PrEP remain rare, but these cases should be thoroughly investigated to understand the reasons of PrEP failures.

161 CAN TWO DRUGS TANGO: THE ROLE OF DUAL THERAPY

Laura Waters, *Mortimer Market Centre, London, UK*

In an era of largely well-tolerated antiretrovirals with high virological efficacy, the new 'battle' is that of two vs three drug regimens (2DR vs 3DR). The majority of studied 2DR have been boosted-protease inhibitor based so, despite any possible benefit of fewer drugs, hampered by the limitations of the PI class including tolerability, long-term toxicity and extensive drug-drug interactions. Additionally, several 2DR have demonstrated suboptimal efficacy with high rates of emergency drug resistance at virological failure. Unboosted integrase inhibitors with a high barrier to resistance offer the option of non-PI-based 2DR and, to date, dolutegravir/rilpivirine and dolutegravir/lamivudine have demonstrated high efficacy in stable switch and first-line therapy, respectively; these combinations, however, face the challenge proving efficacy, bu t the challenge of shifting the paradigm of 3DR that has been central to practice for over 2 decades. Current guidelines still prefer 3DR – how much evidence is required for 2DR to be elevated from 'alternative' status? Must 2DR be better than 3DR in some way or simply similar? With injectable options on the horizon we need to consider not only how to best use 2DR, but how to deliver treatment in new way. Who will want to trade daily pills for regular injections and how can we integrate that into busy clinical practice?
Many questions about 2DR remain unanswered, including the impact of baseline resistance, efficacy in suboptimal adherence and the importance of compartment penetration. The balance between embracing progress and employing caution when 3DR has delivered so much is a tricky one, but the decisions we help our patients make should be considered within a robust ethical framework. We need to ensure that future studies fill the gaps in our knowledge so we can incorporate 2DR into our practice in the safest and most appropriate manner.

162 YOUNG TRANSGENDER INDIVIDUALS

Asa Radix, *Callen–Lorde Community Health Center, New York, NY, USA*

Transgender and gender diverse youth (i.e., those whose gender identity does not align with their sex assigned at birth), especially transfeminine youth of color, face high rates of verbal and physical violence, unsafe school environments, family rejection and homelessness. Stigma and discrimination against transgender people have been linked to adverse health outcomes, such as low self-esteem, depression and substance use, which are inextricably tied to HIV vulnerability. Although data on HIV incidence and prevalence are limited for transgender youth, young transgender women of color are disproportionately impacted. Few data exist for transgender men and gender diverse individuals assigned female at birth, however trans men who have sex with cisgender men and engage in sexual risk behaviors such as condomless sex, are at heightened risk for HIV infection. Transgender youth face unmet medical needs, including access to gender-affirming care and HIV/STI testing, counseling and prevention services. Research has shown underutilization of pre-exposure prophylaxis (PrEP) among those at risk for HIV. This presentation will review recent epidemiologic data related to HIV in transgender and gender diverse youth and describe current and evolving developmentally appropriate and culturally sensitive HIV prevention interventions. To be successful clinical settings should seek to engender resilience through self-acceptance and increased sense of belonging, provide navigation of legal and other structural barriers to care and offer avenues for peer support and social activism. The Callen-Lorde Community Health Center in New York City operates one of the largest and longest-running transgender clinic programs in the United States, serving over 4000 clients (including 1,215 who are aged 24 and under) though on-site and mobile health services. The clinic illustrates best practices for HIV prevention including implementation of trauma-informed medical care, multidisciplinary teams with expertise in transgender medicine, facilitated referrals to surgeons and specialists, comprehensive sexual health education and a robust PrEP program.

163 ENGAGING YOUNG WOMEN IN SUB-SAHARAN AFRICA

Sinead Delany-Moretlwe, *Wits Reproductive Health and HIV Institute, Johannesburg, South Africa*

Adolescent girls and young women (AGYW) in sub-Saharan Africa (SSA) are at substantial risk for HIV infection. Oral PrEP has the potential to provide HIV protection if used consistently. Two blinded efficacy trials of oral PrEP in women in SSA did not show evidence of HIV protection in AGYW because of low adherence in these trials; adherence was lowest in AGYW. These findings led to concerns that AGYW did not perceive their risk or did not want to use HIV prevention products. Recent open-label demonstration studies of oral PrEP in AGYW however have shown that young women do perceive their risk and that uptake of open-label oral PrEP is high. Challenges remain, however with taking a pill a day. This presentation will present updates on findings from open-label studies about uptake and continuation of oral PrEP in AGYW, as well as strategies that have been shown to improve PrEP continuation. Progress on expanding national programmes and lessons learned from these will also be

reviewed. The implications of these findings for the development of new PrEP products and delivery approaches will be considered.

164 MAKING PREVENTION WORK FOR YMSM: BRIDGING REAL-WORLD NEEDS THROUGH DIGITAL ENGAGEMENT

Lisa Hightow-Weidman, *University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Despite evidence for the efficacy of treatment as prevention as both antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP), uptake and sustained retention in the prevention and care continuum for young men who have sex with men (YMSM) is suboptimal. Thus, both in the United States and globally, YMSM remain disproportionately impacted by HIV. The effectiveness of ART for reducing HIV transmission requires successes at multiple steps of the HIV prevention and care continuum (HIV testing, PrEP or ART treatment initiation, and treatment adherence), which may prove challenging for YMSM due to individual, structural, and societal barriers. Comprehensive, evidence-based behavioral, psychosocial, and structural interventions are needed to optimize PrEP and treatment as prevention among YMSM. Technology-delivered interventions are well-suited for YMSM given their modality, the ubiquity of technology in the population, and the platform's suitability for delivering tailored content specific to each users' unique needs. These interventions can be particularly useful for YMSM who, due to anticipated or actual stigma, are unable or unwilling to talk to providers about their same-sex attractions and behaviors, and yet are in need of prevention and care services. However, the strategies to "make prevention work" for YMSM must maximize the potential for digital tools to address gaps in the cascade, and ensure that engagement bridges the resources shared through the digital world with their real-world needs. The accessibility and anonymity of online spaces may provide a particularly powerful intervention modality for amplifying resilience and empowerment thus countering the stereotypes and social institutions that perpetuate HIV-related stigma, racism, and blame experienced by YMSM. A brief review on how the use of technology, specifically, mobile health (mHealth) has evolved as seen from the lens of researcher, provider and patient/participant will be provided. Use of mHealth to mitigate stigma, improve patient-provider communication and provide social support - all factors known to be important in prevention and care outcomes – will be discussed. Practical strategies, best practices and future innovations will be presented.

165 DON'T LEAVE THEM BEHIND: HETEROSEXUAL YOUNG AFRICAN MEN

Webster Mavhu, *Centre for Sexual Health and HIV/AIDS Research Zimbabwe, Harare, Zimbabwe*

Background: The number of young people living in Africa (15-24 years) is projected to double over the next 30 years. Africa's ability to benefit from this population growth will depend on their health and well-being. High HIV incidence among young people may drive rises in the absolute numbers of new infections. Whilst HIV prevention initiatives are focusing on specific subgroups of young people (e.g. adolescent girls and young women, young men and women selling sex, men having sex with men), young heterosexual men are being left behind. As for adult men, adolescent and young men are less likely to seek health services than their female counterparts, with research suggesting that this is at least in part due to shame or the need to "save face". Indeed, a well-recognized notion is that help-seeking can be seen as a threat to masculine identity in both adult and young males, due to masculinity-related cultural constructs which conflate help-seeking behavior with being "weak". Supply-side barriers include stigmatizing attitudes of providers about sexuality and, limited youth-friendly services. Studies conducted in sub-Saharan Africa (SSA) suggest that efforts to engage and interest male youth in HIV prevention could include: offering them free or low-cost specific sexual & reproductive health and HIV services, creating separate and confidential spaces for them, intensifying efforts to sensitize health-care workers to be more "youth friendly", in particular, respecting confidentiality, being nonjudgmental and accommodating young men's concerns of looking "weak". Conclusions: The population-level impact of youth-focused HIV prevention interventions being implemented in SSA will be diminished if young heterosexual men continue to be left behind. Lessons learned from innovative approaches to enhance voluntary medical male circumcision uptake, including use of HIV self-testing and harnessing female peers' influence, could inform design and implementation of other male youth-focused HIV prevention initiatives. Setting the pattern for healthy health-seeking behavior in adolescents will likely have benefits throughout the life course.

POSTER ABSTRACTS

166 ENTRY KINETICS OF GLOBALLY REPRESENTATIVE AND VERTICALLY TRANSMITTED HIV ENVELOPES

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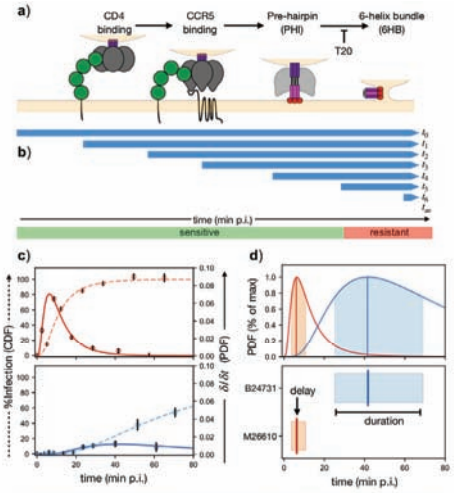
Background: Understanding HIV entry kinetics may reveal important dynamic properties relevant to transmission and vaccine design. To date, most entry kinetics studies are limited to either lab-adapted isolates or a limited selection of primary isolates and their mutational derivatives. We sought to determine the breadth of naturally occurring HIV-1 isolates.

Methods: An optimized time-of-addition assay with T20 was used to measure the kinetics of the transition between the prehairpin (PHI) and 6-helix bundle (6HB) states of HIV gp41 for more than 150 primary envelopes (Env). Env isolates included a globally representative panel (global) and vertically transmitted Envs associated with in-utero (IUT, 5 mom/baby pairs, 37 Envs) and breast milk (BMT, 6 mom/baby pairs, 50 Envs) transmission. Normalized time-dependent infectivity data were fit to a lognormal cumulative distribution. The corresponding probability distribution (PDF) was used to derive the average time it takes to reach the PHI/6HB transition (delay, time point of greatest increase in infection) and the duration of transition (width of PDF at 75% of its maximum, in minutes).

Results: Lognormal distributions fit the data with high accuracy (R^2>0.85 for 99% of experiments). The delay and duration among global Envs ranged from 3-15 minutes and 6-35 minutes, respectively. IUT Maternal/infant isolates had a uniquely confined range of delay/duration with some of the fastest kinetics (~1 min). BMT Env kinetics were highly diverse and 3/6 infants each harbored a single Env with remarkably long delays of 40–60 minutes and equally long durations. Kinetic interpretations of these metrics were supported by strong correlations to both T20 (R^2=0.87) and 10E8 sensitivity (R^2=0.79) across a 1000 and 100-fold range of EC_{50}, respectively.

Conclusion: Circulating HIV Envs exhibited a broad range of PHI kinetics that reflect their diverse nature. PHI kinetics were also significant determinants of sensitivity to both T20 and 10E8, one of the broadest neutralizing antibodies known to date. Vertically transmitted BMT isolates exhibited remarkably unique kinetic extremes suggesting a functional bottleneck in this transmission route that restricts labile Envs, while IUT isolates were highly restrained in both delay and duration. The naturally occurring, kinetically slow Envs we identify may offer unique insights into the design of highly stable and native gp41 antigens that reflect the natural diversity of Env.



HIV Entry Kinetics. Schematic of the HIV entry cascade (**a**) shows the pre-hairpin (PHI) to 6-helix bundle (6HB) transition in gp41 that drives membrane fusion, and its inhibition by T20. (**b**) Outline of time of addition assay where entry is initiated by shifting temperature from 4°C to 37°C and saturating doses of T20 are added at various time points (blue bars) post-initiation (p.i.). Entry is sensitive when T20 is added prior to PHI/6HB transition and becomes resistant once this transition is complete. (**c**) Time-dependent infectivity data fit to lognormal cumulative distribution (CDF, dashed lines) for representative fast (top) and slow (bottom) primary HIV Envs. CDF-derived probability distributions (PDF, solid lines) with the corresponding transformation of raw data provide a more intuitive representation of transition kinetics. (**d**) Normalized PDFs for fast (red) and slow (blue) Envs (top) were distilled into two metrics: the peak change in infectivity or *delay* of the transition and its *duration*, the width of the PDF at 75% of its max, summarized as bar plots (bottom).

167 CD4-DEPENDENT MODULATION OF HIV-1 ENTRY BY LY6E

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Background: The role of IFN-induced genes (ISGs) in viral infection remains incompletely understood. While most ISGs are antiviral, some ISGs have been shown to promote viral infection, including HIV-1. Indeed, we previously showed that IFN-inducible LY6E protein promotes HIV-1 infection in human PMBCs and high CD4-expressing SupT1 cells.

Methods: We examined the effect of LY6E on low- and high-CD4+ T cells, as well as human primary cells including monocyte-derived macrophages (MDMs). We used shRNAs to knock down the endogenous LY6E in these cells and determined its influence on HIV-1 entry and replication. We performed immunofluorescence microscope imaging analysis to examine the co-localization between CD4 and LY6E. We performed lipid flotation assay to dissect the biophysical and functional interplay between CD4 and LY6E on the plasma membrane and intracellular compartments.

Results: We provide evidence that LY6E inhibits HIV-1 entry and spread in low CD4-expressing Jurkat cells and human monocyte-derived macrophages (MDMs), through downregulation of the viral receptor CD4 from the plasma membrane. We found that knockdown of LY6E in Jurkat cells increases HIV-1 entry yet overexpression of LY6E in Jurkat cells inhibits HIV-1 entry and replication. LY6E is co-localized with CD4 in Jurkat cells and MDMs and enhances the CD4 internalization from the plasma membrane. We artificially manipulated the CD4 level in Jurkat and SupT1 cells and found that overexpression of CD4 in Jurkat cells overcomes the inhibitory effect of LY6E; blocking the function of CD4 in SupT1 with a neutralizing antibody eliminates the enhancement of LY6E on HIV-1 entry. The CD4-dependent inhibitory phenotype of LY6E can be recapitulated in low CD4-expressing human MDMs.

Conclusion: Our study reveals a CD4-dependent function of LY6E that distinctly modulates HIV-1 entry and replication. Given that HIV-1 targets low CD4-expressing cells during primary infection but replicates efficiently in high CD4-

expressing T cells at the late stage of diseases, our observation have implications for understanding of the diverse roles of IFN-induced proteins in different stages of HIV-1 infection and AIDS pathogenesis.

168 ELUCIDATING MECHANISMS BY WHICH MUTATIONS IN ENV CONTRIBUTE TO HIV-1 DRUG RESISTANCE

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Background: Despite the effectiveness of antiretroviral therapy (ART), virological failure can occur in HIV-1 infected individuals, often in the absence of recognized drug resistance mutations (DRMs). By performing in vitro selection experiments, we identified mutations within the HIV-1 envelope (Env) glycoprotein that broadly increase viral fitness by overcoming blocks to virus replication, including several selected in the presence of the antiretroviral (ARV) inhibitor Dolutegravir (DTG). The goal of this study was to determine the mechanism by which the Env mutations afford ARV escape.
Methods: Virus replication and quantification of viral spread in the presence of ARVs were measured by propagating Env mutant viruses in a spreading infection in T-cell lines and primary PBMCs. Cell-free and cell-to-cell virus transmission was measured using reporter viruses and cell lines. Finally, we measured the effective multiplicity of infection (MOI) of viral transmission events.
Results: We calculated the fold-change in IC_{50} of two of the DTG-insensitive Env mutants, A556T and A539V, as 4-5 fold, comparable to that of current DTG DRMs in integrase. The de novo-selected DTG-resistant Env mutant, A539V, also exhibits markedly reduced sensitivity to at least two other classes of ARVs. Using a GFP-expressing reporter virus, we determined that the A539V mutation greatly enhances the efficiency of cell-to-cell transfer and increases the effective MOI of the transmitted virus. We are currently measuring the viral DNA load per infected cell in the presence and absence of DTG. Remarkably, we selected a DTG-resistant Env mutation at the same position in a subtype C transmitter founder virus. Finally, we observed that propagation of an ARV-resistant mutant in high concentrations of DTG forced selection of additional Env mutations, which may ultimately enable the acquisition of DRMs in integrase.
Conclusion: These results provide insights into escape from ARVs and demonstrate that mutations in Env can contribute to broad HIV drug resistance in vitro. The study of Env mutants that result in a decreased sensitivity to DTG is of particular interest as resistance mutations in integrase have been challenging to characterize to date. We speculate that these Env mutations may provide a "stepping stone" on the path to high-level drug resistance in vivo.We are currently investigating the implications of these findings for HIV drug resistance in nonhuman primate models and in patients.

169 NONRANDOM GENERATION OF DELETIONS WITHIN HIV PROVIRAL SEQUENCES IN VIVO

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Background: Most latent HIV proviruses integrated into CD4+ T cells of HIV positive individuals on long-term antiretroviral therapy (ART) are defective and replication-incompetent. The most common defects are deletions in the proviral sequence which are assumed to be generated by the same mechanism as HIV recombinants: template switching by the reverse transcriptase (RT) enzyme.
Methods: To investigate whether deletions are generated by template switching, we 1) determined the distribution of deletion start and stop sites across the length of the HIV genome and compared this with known recombination sites, and 2) investigated whether the presence of nucleotide homology, a common feature of recombination sites also occurred between deletion start and stop sites. Near full-length HIV proviral sequences from CD4+ T cells from 10 participants on long-term ART (3-17 years) were obtained. Sequences containing internal deletions of ≥2 bases were identified and the position and sequence (surrounding 10 bases) of deletion start and stop sites recorded.
Results: Within the 896 proviral genomes sequenced, 539 unique deletion sites were identified. Deletion length ranged from 2-8884 bases, with 76% of deletions >4000 bases in length. Deletion start and stop sites were non-randomly distributed along the HIV genome. Most deletion start sites occurred at the 5′ end of the provirus (76% between positions 666-4000, 5′ U5 LTR to pol). Most deletion stop sites occurred at the 3′ end (80% between positions 8000-9676, env to 3′ U5 LTR). Additionally, 9.3% of deletion start sites occurred between positions 4750-4950, a region that encompasses the central polypurine tract (cPPT). Investigation of nucleotide context found a significant association ($p<0.001$) between short sequence repeats and deletion start and stop sites, indicating that nucleotide homology at deletion sites is not due to chance.
Conclusion: This study showed that deletions in HIV proviruses occur at non-random sites, indicating they are generated by a specific mechanism. The presence of short sequence repeats at deletion junctions (an important factor for the generation of recombinants) and the identification of a common deletion site at the cPPT (a known recombinant site) suggests deletions occur as a result of RT-mediated template switching. Understanding the mechanisms that generate defective proviruses will be important for developing future eradication methods that enhance their production.

170 HOST FACTORS INFLUENCE SIV AND HIV-1 INFECTION AND SENSITIVITY TO CAPSID INHIBITORS

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Background: SIVs of chimpanzees (cpz) and gorillas (gor) rarely established infections in humans in which these viruses were further transmitted from human to human. The viral capsid (CA) is the key viral determinant of primate lentiviruses that are targeted by cytoplasmic proteins such as cyclophilin A, TRIM5α, CPSF6 (mRNA processing protein cleavage and polyadenylation specificity factor 6) and MX2 that affect infection and likely regulate cross-species transmission.
Methods: In order to characterize the impact of different cell types and dependency pathways versus restriction pathways, luciferase reporter viruses for SIVcpz (for both SIVcpzPtt and SIVcpzPts), SIVgor and rare HIV-1 N, O and P were constructed. Infection experiments using VSV-G pseudotypes were performed in the presence and absence of host proteins and pharmacological inhibitors (e.g. cyclosporine A, PF74).
Results: Here we show that small inhibitors of the viral capsid (PF37, PF74) differently effect the infection of SIVcpz and HIV-1s in human and non-human cells. While SIVcpzPtt was sensitive to PF37 inhibition in human HOS and HeLa cells, SIVcpzPts were only inhibited in HOS cells. No SIVcpz were blocked in rhesus monkey cells by PF37. In contrast, HIV-1 M was sensitive to PF37 in all three cell types. We constructed a SIVcpzPtt with the capsid of the Pts virus. The chimeric SIVcpz lost only partially the sensitivity to the capsid inhibitor.
Conclusion: Manipulation of the viral infection by inhibitors for capsid is strikingly dependent on the cell-type. PF37 and related capsid inhibitors can inhibit non-HIV-1 primate lentiviruses. This inhibition, however, requires unidentified cellular host factors that differentially interact with HIV-1 M, and SIVcpz. PF37/PF74-sensitivity of SIVcpz is only partially regulated by the viral capsid.

171 VPX INDUCES AN IFN-RELATED INNATE IMMUNE RESPONSE DISTINCT FROM SAMHD1 ABROGATION

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Background: SAMHD1 is an HIV restriction factor that acts by depleting the intracellular pool of nucleotides, a process that is counteracted by the virion-packaged accessory protein Vpx, through SAMHD1 proteosomal degradation. SAMHD1 mutations lead to Aircardi-Goutieres syndrome characterized by increased IFN production. SAMHD1 depletion has also been associated to aberrant DNA production and production and innate immune activation. Here, we investigate the interplay between SAMHD1 depletion, innate immune activation and susceptibility to HIV-1 infection.
Methods: CD14+ human monocytes were differentiated to macrophages. Knockdown of SAMHD1 was achieved by RNA interference or by transducing macrophages with VLP-containing HIV-2 Vpx. A SAMHD1 knockout TZM-bl

cell line was generated by CRISPR/Cas9. Susceptibility to HIV-1 infection was examined by flow cytometry after infection with a VSV-pseudotyped NL4-3 GFP-expressing virus. Gene expression was assessed by quantitative PCR. Protein expression and phosphorylation were analyzed by immunoblotting. Whole transciptome was assessed by RNA-seq.
Results: Vpx-induced degradation of SAMHD1 significantly increased HIV-1 infection in primary macrophages. However, no significant change in infection was seen when SAMHD1 expression was inhibited by either siRNA in macrophages or in the CRISPR/Cas9 knockout cell line model. To assay the role of Vpx, whole transcriptome profiling of macrophages untreated or Vpx transduced was performed. 41 genes were differentially expressed: 14 downregulated and 27 significantly upregulated after Vpx-induced SAMHD1 degradation. Interestingly, 14 out of 27 upregulated genes (52%) were IFN-stimulated genes (ISG), including IFNB1, IRF7 and CXCL10, suggesting a relationship between Vpx and activation of the innate immune system. Identified ISG expression was confirmed and extended in additional donor cell samples. Further evaluation of the pathway underlying innate immune activation after Vpx treatment in macrophages showed enhanced expression of the RNA sensors RIG-I and MDA5 without involvement of DNA sensors. On the contrary, when SAMHD1 expression is downregulated by siRNA or by CRISPR/Cas9, increased expression of DNA sensors cGAS and STING was found, without any significant effect on RNA sensors.
Conclusion: Vpx-mediated degradation enhances innate immune activation that is distinct and independent of SAMHD1 expression. These differences may help explain variability in the pathogenicity and immune control of HIV infections.

172 EVOLUTION-GUIDED STUDIES TO UNDERSTAND THE ANTIVIRAL MECHANISM OF IFITM3

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Background: The interferon-induced transmembrane (IFITM) proteins are a group of antiviral factors that inhibit the replication of diverse viruses, including HIV-1, at two stages: restriction of incoming viruses in target cells and inhibition of virion infectivity in producer cells. Evidence points to inhibition of virus-cell fusion as the basis for both antiviral functions, but the precise molecular mechanism is unknown. Recent studies suggest that IFITM genes belong to a family of transmembrane proteins known as Dispanins, which are characterized by two transmembrane domains separated by a conserved intracellular loop (CIL). Whereas IFITM proteins inhibit viral and host membrane fusion, another member of the Dispanin family known as PRRT2 inhibits synaptic vesicle fusion in neurons. Therefore, a comparative evolutionary and biochemical analysis between IFITM proteins and other Dispanin members, such as PRRT2, will uncover the mechanistic basis behind membrane fusion regulation.
Methods: Multiple sequence alignments of Dispanin family members were performed to identify regions of conservation and divergence. Residues in IFITM3 that are analogous to functionally important sites in PRRT2 were mutated and tested for impact on antiviral functions. 293T cell lines stably expressing IFITM3 variants were generated and challenged with Influenza A and retroviral pseudotypes to study the inhibition of virus entry, while 293T cells co-transfected with IFITM3 variants and retroviral plasmids were used to study the inhibition of virion infectivity.
Results: A single residue change in the CIL of IFITM3, never before studied in the context of its function, resulted in a substantial loss of antiviral activity. Importantly, the analogous residue in PRRT2 is critical for its regulation of synaptic vesicle fusion. Western blot and immunofluorescence analysis indicate that the single mutation disrupts protein function without affecting protein expression or turnover.
Conclusion: The identification of a single amino acid residue critical to the function of IFITM3 provides an important tool in the search for the molecular mechanism driving antiviral function. The finding that analogous mutations in IFITM3 in PRRT2 disrupt their respective functions suggests that both proteins similarly remodel host membranes and/or operate via the same downstream effectors. We are currently addressing whether the two proteins contain overlapping interaction partners which coordinate vesicular trafficking and fusion.

173 ERAP2 ADMINISTRATION REDUCES IN VITRO PBMC SUSCEPTIBILITY TO HIV-1-INFECTION

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Background: Haplotype-specific alternative splicing of the endoplasmic reticulum (ER) aminopeptidase type 2 (ERAP2) gene results in either full-length (FL, haplotype A) or alternatively spliced (AS, haplotype B) mRNA. HapA/HapA homozygous (homoA) subjects show a reduced susceptibility to HIV-1 infection, probably secondary to the modulation of antigen processing/presenting machinery. As recently it was reported that ERAP2 can be secreted from plasma membrane in response to activation, we investigated if, once released, ERAP2 still retains its antiviral function
Methods: Peripheral blood mononuclear cells (PBMCs) isolated from 30 healthy controls (15 homoA and 15 homoB) were in vitro HIV-infected with or without adding different doses of recombinant human protein ERAP2-FL (rhERAP2-FL) and p24 viral antigen quantification was used to assess viral replication. Seven-days post in vitro HIV-1-infection the percentage of perforin and granzyme-producing CD8+ T Lymphocytes and HLA-ABC-expressing cells were analyzed as well; these two parameters were shown to correlate with endogenous ERAP2 activity.
Results: As previously shown homoA subjects were less susceptible to in vitro HIV-1 infection ($p< 0,01$). Addition of rhERAP2-FL to in vitro HIV-infected cells did not affect cell viability and resulted in a reduction of viral replication in both homoA and homoB individuals with a peak effect observed using 100 ng/ml of the protein ($p<0.01$ in both cases). This protective effect was independent from an increase of HLA-ABC expression and/or of perforin and granzyme expression by CD8+ lymphocytes
Conclusion: The role and the targets of ERAP2-FL in the extracellular milieu are still undisclosed and need further investigation. However, data herein suggest that once added to cell culture ERAP2-FL preserves its protective function against HIV-1 infection, even in homoB subjects who do not genetically produce it. Presumably this defensive feature is mediated through an unconventional mechanism, distinct from immune system modulation.

174 INCREASED SAMHD1 CORRELATES WITH ISGS IN HIV-1–INFECTED PATIENTS

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Background: SAMHD1 is an inducible host innate immunity restriction factor that inhibits HIV-1 replication. The underlying mechanisms of SAMHD1 transcriptional regulation remains elusive and considerable controversy exists over whether type I IFN can support SAMHD1 production. In order to gain new insights into the role played by SAMHD1 in regulating the natural course of HIV-1 infection, we evaluated SAMHD1 expression and its relationship with the IFN response in vivo.
Methods: Peripheral blood mononuclear cells (PBMC) from 335 HIV-1-infected patients, both therapy naïve (n=92) and virological suppressed long-term HAART-treated (n=243), and from 100 gender and age-matched healthy individuals were examined. Demographical and clinical characteristics of patients are reported in Table 1. CD4+ T cells, CD14+ monocytes and gut biopsies were also analysed in a subgroup of HIV-1-infected patients on suppressive antiretroviral therapy. Gene expression levels of SAMDH1 and ISGs (MxB, HERC5, IRF7) were evaluated by real-time RT-PCR assays.
Results: SAMHD1 levels in HIV-1-positive patients were significantly increased compared to those in healthy donors ($p=0.04$). Virologically suppressed treated patients exhibited higher SAMHD1 levels than healthy donors ($p=0.0008$), and naïve patients ($p<0.0001$). SAMHD1 levels were higher in CD4+ T cells than in CD14+ monocytes paired samples (treated patients: $p=0.038$; healthy donors: $p<0.0001$). By comparing SAMHD1 expression in CD4+ T cells and CD14+ monocytes between HIV-1 infected patients and healthy donors, an increased SAMHD1 expression in these cell subsets was recorded in treated HIV-1 positive patients (patients vs healthy donors, CD4+ T cells: $p<0.0001$; CD14+ monocytes: $p<0.0001$). We selected a subgroup of 7 out of treated HIV-1-positive patients with relatively low PBMC SAMHD1 mRNA expression in order

to explore SAMHD1 levels in GALT. We found twofold higher median values of SAMHD1-mRNAs in PBMC compared to those measured in GALT paired samples (p=0.04). Moreover, SAMHD1 was expressed more strongly than MxB, HERC5, and IRF7 in virologically suppressed HIV-1-infected patients (p<0.0001 for all the analyses), and positive correlations were found between SAMHD1, MxB, HERC5, and IRF7, levels.
Conclusion: Taken together these findings indicate that SAMHD1 is more strongly expressed than the classical IFN-related genes, increased during antiretroviral therapy and correlated with several ISGs in HIV-1-infected patients on HAART.

Table 1 Demographic and clinical characteristics of naïve and antiretroviral-treated HIV-1 infected patients and HIV-seronegative healthy subjects.

Item*	Healthy subjects	Naïve HIV-1 positive patients	Treated virologically suppressed HIV-1 patients	A vs B p values	A vs D p values	B vs D p value
	n=100 (A)	n=92 (B)	n=243 (D)			
Age (years)	48±16.6	38±11.81	50±14.02	0.07	0.3	0.05
Male [n (%)]	60 (60)	71 (77)	170 (70)	0.06	0.1	0.22
HIV-1 RNA (copies/mL)[b]	NA[c]	34925 (143-1405000)	<37	NA	NA	<0.000
CD4+ T cells/mm[3]	NA	445 (15-1200)	560 (60-1882)	NA	NA	0.000
Duration of HAART (years)	NA	NA	12 (2-27)	NA	NA	NA
Therapy class[d] (number)	NA	NA	PI (100) NRTI (142) NNRTI (51) INSTI (34)	NA	NA	NA
SAMHD1 mRNA expression in PBMC[e] (median/range)	5.24 (0.02-83.28)	4.90 (0.01-53.44)	9.64 (0.001-76.10)	0.3	0.0008	<0.000
SAMHD1 mRNA expression in CD4+ lymphocytes[f] (median/range)	5.50 (2.63-15.03)	NA	12.38 (3.55-38.05)	NA	p<0.0001	NA
SAMHD1 mRNA expression in CD14+ monocytes[f] (median/range)	2.34 (1.29-4.65)	NA	10.85 (0.24-19.29)	NA	p<0.0001	NA

175 SCHLAFEN 14 (SLFN14) INHIBITS TRANSCRIPTION OF HIV-1 BY TARGETING P-TEFB

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Background: SLFN14 belongs to Schlafen (SLFN) family involved in important functions, such as the control of cell proliferation, induction of immune responses, and the regulation of viral replication. Positive transcription elongation factor b (P-TEFb), which comprises cyclin-dependent kinase 9 (CDK9) kinase and cyclin T subunits, is an essential kinase complex for productive elongation of transcription of HIV genomes.We recently identified Schlafen 14 (SLFN14) that interacts with HIV-1 essential host cellular proteins complex P-TEFb and inhibits HIV-1 transcription.
Methods: In our study, western blot, RT-PCR, Co-IP and ChIP-qPCR were performed to examine the effect of SLFN14 upon viral replication and transcription, and investigate its interaction with P-TEFb.
Results: We found that over-expression of SLFN14 significantly reduced Gag expression and viral mRNA level, while silencing endogenous SLFN14 promoted viral replication. Using a HIV LTR reporter assay, we demonstrated that SLFN14 significantly impaired tat-mediated transcription activity of viral promoter, resulting in an inhibitory effect on productive elongation of viral mRNA transcription. Further mechanistic studies revealed that SLFN14 interact with P-TEFb dependent of N-terminus region of SLFN14. Furthermore, overexpression of SLFN14 reduced the phosphorylation of Ser2 (Ser2P) of RNA polymerase II (Pol II) CTD on HIV-1 promoter.
Conclusion: This work provided evidence for the first time showing that SLFN14 interacts with P-TEFb and inhibits HIV-1 transcription. The study sheds a light on the role of SLFN14 in negative regulation of HIV-1 transcription, and may provide a novel strategy for treatment of HIV-1 infection.

176 FLOW VIROMETRY REVEALS PATIENT VARIATIONS IN HIV PROTEASE THAT CORRELATE WITH FITNESS

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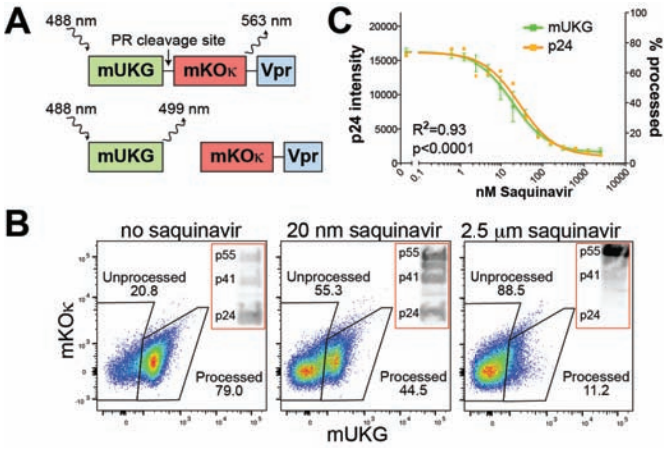
Background: Nearly all current methods for analyzing viruses interrogate large numbers of viruses, obscuring viral heterogeneity that may play a critical role in infection, immunity, and pathogenesis. Direct flow cytometric detection of viruses ("flow virometry") enables high-throughput analysis of individual viruses. In this study, we wanted to evaluate HIV-1 protease activity within individual viruses and under physiological conditions of assembly and budding.
Methods: We developed a Förster resonance energy transfer (FRET) construct consisting of the mUKG and mKOk fluorescent pair, separated by a protease cleavage site and linked to the viral accessory protein Vpr that is incorporated into virions via a non-covalent interaction with the Gag p6 protein. Viruses were monitored using a FACSAria II flow cytometer.
Results: The FRET protease (PR) substrate is incorporated into viruses and undergoes cleavage in the presence of active protease, resulting in a colorimetric change that can be detected by flow virometry. Processing of the FRET PR substrate correlated extremely well (R2=0.93, p<0.0001) with processing of Gag by western blot over a wide range of protease inhibitor (PI) concentrations, indicating it is an accurate surrogate of protease activity within virions. Next, we generated viruses from patient-derived infectious molecular clones (IMCs) that incorporated the FRET PR reporter. We found that processing of the FRET PR reporter varies significantly in patients, with 35.0-59.8% of viruses demonstrating processing. Importantly, the extent of processing observed by flow virometry correlated with the infectivity of the viruses on JLTRG reporter cell lines (R2=0.29, p<0.0001). The FRET PR reporter also correctly identified PI drug resistance in 2 of 13 IMCs and was able to detect differences in budding efficiency for several Gag and PR mutant viruses. The assay is highly reproducible (Z-factor of 0.88) indicating it has robust sensitivity to probe mutant phenotypes or screen for drugs affecting the precursor or mature protease.
Conclusion: Flow virometry represents a powerful technique for monitoring viral heterogeneity with important implications for immunity and pathogenesis. This study is the first demonstration that flow virometry can (1) monitor functional viral activities such as protease processing, (2) detect interpatient viral heterogeneity that correlates with fitness, (3) identify drug-resistant viruses, and (4) identify mutants resulting in alterations in viral budding or maturation.



177 THE HIV-1 ANTISENSE PROTEIN ASP IS A NOVEL STRUCTURAL PROTEIN OF THE VIRAL ENVELOPE

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Background: The negative strand of the HIV-1 genome encodes a 189-aa, highly hydrophobic antisense protein (ASP) with no known homologs. Humoral and cellular immune responses against ASP in HIV-1 patients demonstrate that it is expressed in vivo, but its role in viral replication remains unknown. We

studied ASP expression in chronically infected myeloid and lymphoid cell lines, and its impact on viral fitness.
Methods: For intracellular and nuclear staining, we used BD Cytofix/Cytoperm and eBioscience FoxP3 kits. Data were acquired on Millipore Guava flow cytometer and analyzed with FlowJo, or Zeiss LSM 800 confocal microscope and analyzed with Zen Blue. Virion-capture assays used antibodies immobilized on Protein G Dynabeads. For Fluorescence Correlation Spectroscopy (FCS) we used ISS Q2 confocal microscope and ISS VistaVision.
Results: We analyzed two myeloid and seven lymphoid HIV-1 infected cell lines using a monoclonal antibody (324.6) against an epitope mapping between two putative transmembrane domains of ASP, and we detected ASP in the nucleus of all infected cell lines. Confocal microscopy evidenced a polarized nuclear distribution of ASP, preferentially in areas with low content of suppressive epigenetic marks. Reactivation of HIV-1 with PMA led to translocation of ASP to the cytoplasm and cell membrane. Cell surface detection of ASP without cell permeabilization shows extracellular exposure of the ASP epitope recognized by 324.6. Surface staining with antibodies to ASP and gp120 showed that the two proteins co-localize (Manders overlap coefficient 76%), suggesting that ASP might be incorporated in the membrane of budding virions. Indeed, 324.6 captured HIV-1 particles with efficiency similar to anti-gp120 VRC01. Also, FCS showed that the binding efficiency of 324.6 to single virions in solution was ~28%. Thus, these two assays demonstrate the presence of ASP on the surface of mature HIV-1 virions. Finally, we produced HIV-1NL4-3-derived viruses with single-nucleotide mutations that introduce early stop codons in the ASP open reading frame without changing the amino acid sequence of Env on the opposite strand. ASP-deficient viruses displayed a ~50% reduction in replication rate compared to wildtype virus.
Conclusion: ASP is expressed on the surface of productively infected cells, and is a structural protein found in the envelope of mature HIV-1 virions. Further, ASP expression promotes viral replication. Thus, ASP may represent a new target for therapeutic or preventive vaccines.

178 UNPAIRED GUANOSINES IN THE HIV LEADER RNA DIRECT HIV GENOMIC RNA PACKAGING

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Background: HIV-1 and HIV-2, the causative agents of AIDS, package two copies of their RNA genome into one viral particle. It remains unclear how the viral protein Gag specifically selects viral RNA from a large pool of cellular mRNAs. HIV-1 Gag protein has been shown to bind exposed guanosines in the leader region of its RNA and these interactions are thought to be important for packaging. Currently, little is known about HIV-2 RNA packaging mechanisms. To test the hypothesis that exposed guanosines in the HIV-2 leader RNA play a key role in RNA packaging, we mutated guanosines predicted to be exposed in nine regions of the leader RNA and examined the effects of these mutations on genome packaging.
Methods: We visualized HIV-2 RNA in individual viral particles using single-virion analysis, an assay developed in our lab that can detect viral genomes at single RNA sensitivity. In this system, viral particles are visualized by tagging Gag proteins with cerulean fluorescent protein (CeFP), whereas RNA is visualized based on specific interactions between bacterial protein BglG tagged with yellow fluorescent protein (YFP) and RNA stem loop sequences (BSL) engineered into the HIV-2 constructs. RNA packaging efficiency is determined by quantifying the proportion of Gag particles (CeFP signal) that contain HIV RNA (YFP signal).
Results: HIV-2 RNA with wild-type sequences were packaged efficiently: ~95% of viral particles contained viral RNA. In contrast, mutating guanosines in all nine regions of the HIV-2 leader RNA resulted in loss of RNA packaging: only ~10% of viral particles contained viral RNA. Thus, exposed guanosines are critical for HIV-2 RNA packaging. To identify specific regions crucial for RNA packaging, we examined additional mutants in which individual regions or multiple regions were mutated. We identified one primary region and three secondary regions that are important for RNA packaging. Mutation of any individual region did not significantly affect genome packaging. However, mutating the primary region together with any of the secondary regions caused defects in genome packaging and we identified the specific set of guanosines that were responsible for the most severe defect.
Conclusion: Our results demonstrate that exposed guanosines in the HIV-2 RNA leader are critical for genome packaging. Furthermore, not all guanosines in the RNA leader are equal; cumulative interactions between Gag and multiple specific sites direct genome packaging.

179 DETECTION AND SEQUENCING OF ASP TRANSCRIPTS DURING EARLY HIV-1 INFECTION

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Background: The asp gene is an antisense ORF encoding for the putative HIV-1 AntiSense protein Asp. The existence of an asp gene product in HIV-infected individuals is still controversial. Detection of asp antisense RNA by conventional RT-PCR is hampered by RT non-specific priming, which does not allow to assess whether amplified products are from asp transcripts, env transcripts, or env genomic RNA. Thus, no information is yet available on the expression of this gene in patients. Using a modified RT-PCR methodology, we detected asp RNA in CD4+ T cells from patients during early infection, with high viremia and naïve to suppressive ART. We hereby report the first nucleotide sequences of asp transcripts in HIV-infected individuals.
Methods: CD4+ T cells isolated from three patients infected with subtype B were stimulated with anti-CD3/CD28. Reverse transcription was performed using the biotinylated specific antisense primer, followed by cDNA purification by streptavidin-coated magnetic beads, PCR amplification with patient-specific asp primers, cloning and sequencing.
Results: Expression of asp RNA was detected in CD4 + T cells from three HIV-infected individuals during early infection following stimulation with anti-CD3/CD28. In contrast, no expression was detected in unfractionated PBMCs, either resting or stimulated, or in unstimulated CD4+ T cells. Sequence analysis of asp transcripts from cells (26 clones) and of the corresponding env on the plus strand in serum (30 clones) indicate that the dominant length variants in the asp RNA pool in cells are the same as those found in genomic env in serum. In asp RNA transcripts from cells, the complete canonical (i.e. as in HXB2) asp ORF was identified in 20% of the clones, in two of three patients. Clones carrying shorter or longer ORFs (non-canonical stop codons) were also identified, in regions that were either hypervariable or characterized by a variability to some extent in the corresponding env sequence on the plus strand.
Conclusion: Our results show that asp RNA is easily detectable in stimulated CD4+ T cells isolated from untreated patients during early infection. Our data also represent the first nucleotide sequences obtained in patients for asp, demonstrating that it may well be expressed in those HIV-1 lineages in which the asp ORF is present. The finding of a new HIV antigen would represent an important step in our understanding of HIV pathogenesis and perhaps open new perspectives in the development of novel anti-HIV drugs and vaccines.

180 IDENTIFICATION OF HIV-1 ENV MUTATIONS THAT ENHANCE ENTRY INTO MACAQUE CELLS

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Background: Although rhesus macaques are a central animal model for HIV-1 vaccine development research, most transmission/founder (T/F) HIV-1 strains replicate poorly in macaque cells. This species-specific restriction has been attributed to the activity of host specific restriction factors, as well as a single nonsynonymous mutation in macaque CD4 that inhibits binding by HIV-1 Envelope (Env). Recent research efforts employing either laboratory evolution or structure guided design strategies have discovered several Env mutations in gp120 that enhance binding of macaque CD4 by T/F HIV-1 viruses. Additional screens have the potential to reveal mutations that further enhance HIV-1 infection of macaque cells, thereby facilitating the use of macaques for vaccine development.
Methods: In order to identify additional Env mutations that promote infection of macaque cells, we utilized deep mutational scanning to screen thousands of Env point mutants for those that enhance usage of macaque receptors.
Results: We identified many uncharacterized amino acid mutations in both the HR1 and HR2 regions of gp41 that enhance infection of macaque cells by up to 30-fold over wild type residues. These mutations also increased infection of cells bearing human CD4 and CCR5, suggesting a mechanism of action involving a general enhancement of infection kinetics, rather than a specific

accommodation of macaque CD4. Surprisingly, mutations had minimal effect on neutralization properties.
Conclusion: Identification of this set of mutations may be of use in the development of clinically relevant vaccine design strategies, and additionally may provide insights into mechanisms underlying cross species viral transmission.

181 STRUCTURAL AND DYNAMIC CHARACTERIZATION OF MCD4-BINDING HIV-1 ENVELOPE GLYCOPROTEINS

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Background: SHIVs are valuable tools that combine SIV and HIV genes in order to replicate within non-human primates. An ideal SHIV would be capable of infecting non-human primates while retaining antigenicity associated with a wild-type HIV. Since HIV-1 envelope glycoprotein (Env) confers cell tropism, it is necessary to utilize an Env that can infect non-human primate CD4+ T cells. Mutations have been found that allow Env to use macaque CD4 (mCD4) for infection. Two of these mutations, A204E and S375W, enable Env isolates to utilize mCD4, but differ in their antigenicity. As Env is a dynamic protein that can shift between closed/unbound and open/CD4-bound states, this suggests that there may be differences in the mechanisms that allow the two mutations to bind mCD4. Using a combination of structural and biophysical approaches, we aim to correlate Env structure with its interaction with mCD4 and neutralizing antibodies (nAbs).
Methods: A204E and S375W mutations were introduced into BG505 SOSIP.664 constructs. Negative stain electron microscopy (ns-EM) was used to characterize the structure of both constructs and will be used to image the trimers bound to antibody Fabs and mCD4. The structural nature of these Envs was also probed using hydrogen/deuterium-exchange mass spectrometry (HDX-MS) to provide insight into dynamic conformational differences between the mutants. HDX-MS will be used to characterize structural changes in response to CD4 binding. Lastly, biolayer interferometry (BLI) has been used to measure the binding affinities to nAbs and profile their antigenicity.
Results: There were no obvious dynamic conformational shifts apparent using HDX-MS with both A204E and S375W. However, BLI and ns-EM suggest that A204E samples both an open and closed conformation in contrast to WT and S375W BG505 that maintain a closed conformation. The nAb 17b, which binds the open conformation, binds to A204E trimers but not to wild-type BG505 or S375W. Surprisingly, A204E also binds PGT145, which recognizes the closed structure, suggesting that it does in part adopt a closed conformation.
Conclusion: HIV Env variants encoding A204E and S375W differ in their dynamics and their antigenicity. While S375W maintains a closed conformation when unbound to CD4, A204E exhibits the ability to switch conformations without being CD4-bound. Thus, the antigenicity profile of A204E is altered compared to the wild type, while S375W is unchanged. Ongoing studies will define structural changes in response to CD4 binding.

182 MUTATIONS IN THE GP41 ECTODOMAIN CAN CONTRIBUTE TO HIV-1 RESISTANCE TO SMFIS

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Background: Small-molecule fusion inhibitors (smFIs) such as IC9564 can inhibit human immunodeficiency virus type 1 (HIV-1) entry into the cells. Recently, we have developed novel IC9564-derived smFIs as a new class of HIV entry inhibitor. In the present study, we investigated HIV-1 variants selected under smFI pressure to get a better understanding of the smFI-virus interaction.
Methods: Resistant variants were induced by culture of HIV-1 89.6-infected PM1 cells in the presence of smFIs. We then constructed infectious 89.6 clones carrying mutations selected in the resistant variants. The susceptibility of the infectious clones to smFIs and other class of entry inhibitors was tested by TZM-bl assay.
Results: Selection of 89.6 variants under gradually-increased concentrations of IC9564, OKS3-019 and NAT-078 revealed the sequential selection of 4 mutations (H769P (CT), F522V (FP), M26I (SP) and H72Y (C1)), 3 mutations (R838K (CT), R588K (HR1) and V68I (C1)) and 2 mutations (G594R (DSL) and G600E (DSL)), respectively. Studies with engineered smFI-resistant env variants indicate contribution of amino acid changes in the gp41 ectodomain to smFI resistance. Unexpectedly, these variants were not only highly resistant to smFIs, but also critically dependent on smFIs for its replication. In addition, these resistant mutants exhibited higher sensitivity to BMS-378806, which preferentially recognizes the metastable closed Env conformation.
Conclusion: We found viral mutations in the gp41 ectodomain that contribute to the resistance to smFI derivatives. It can be speculated that gp41 modification by these mutations may induce structural rearrangements resulting in formation of the closed conformation, thereby rendering these viruses dependent on smFIs. These results enhance our understanding of Env complex interactions that influence both HIV-1 entry and susceptibility to smFIs.

183 HIV PROVIRAL TRANSCRIPTION RAPIDLY UPREGULATES BCL3, BIRC2, AND BIRC3 TRANSCRIPTION

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Background: ACH-2 cells usually produce low levels of HIV when unstimulated. Viral production increases dramatically with TNFα stimulation. Prior to stimulation with TNFα, surface staining of HIV Env identifies two ACH-2 populations, one which stains for Env and p24, and one which does not. With TNFα stimulation the HIV Env+ population stains more intensely for Env and produces >90% of the virus found in the supernatant; the Env- population slowly becomes Env+ but produces virus at a much lower rate. We have used the ability to separate Env+ and Env- population using flow cytometry to describe the effect of HIV proviral transcription on the ACH-2 transcriptome immediately prior to, and 3, 6, and 9 hours after TNFα stimulation in Env- and Env+ cells.
Methods: ACH-2 cells were dual stained with PG9 and VRC07 and bulk sorted before and 3, 6, and 9 hours post-stimulation with 10U TNFα/ml (N=6 replicates). Cells were immediately spun down, lysed with RNAzol and then frozen. Total RNA was extracted, poly-adenylated RNA purified, fragmented and then reversed transcribed using random hexamers. Illumina ready libraries were generated and sequence by paired-end HiSeq 4000 2x75 reads.
Results: In the HIV Env- population the frequency of HIV RNA reads increased from 0.05±0.01% prior to stimulation to 0.53±0.15% 9 hour post-stimulation. In the HIV Env+ population the frequency of HIV RNA reads increased from 3.8±0.4% prior to stimulation to 12.9±2.0% 9 hours post stimulation. In both populations, similar increases between pre-stimulation and 3, 6, and 9 hours frequencies of NFKB2, NFKBIA, REL B and TNFAIP3 message were consistent with similar TNFα and NFκB signaling in both populations. The Env+ population showed an 8.4x increase in BCL3 ($P=7.5x10^{-12}$), a 5.6x increase in BIRC3 ($P=1.1x10^{-29}$) and 2.4x increase in BIRC2 ($P=1.x10^{-7}$) messages 3 hours post-stimulation. Except for BIRC2, these changes persisted 9 hours post -stimulation. These changes were not observed in the Env- population.
Conclusion: These data suggest that proviral transcription of HIV DNA results in a rapid increase in cellular anti-apoptotic message. Upregulation of these transcripts could stymie the cells innate antiviral responses, increase the longevity of infected cells and increase viral proliferation. Upregulation of BCL3 could also contribute to non-canonical activation of the NFκB pathway thus further increasing viral production.

184 CHARACTERIZATION OF THE EPITRANSCRIPTOMIC LANDSCAPE OF HIV-INFECTED CELLS

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Background: The study of RNA modifications, today known as epitranscriptomics, is of growing interest. The N6-methyladenosine(m^6A) and 5-methylcytosine (m^5C) RNA modifications are abundantly present on mRNA molecules, and impact RNA interactions with other proteins or molecules, thereby affecting cellular processes, such as RNA splicing, export, stability and translation. Recently m^6A marks were found to be present on HIV transcripts and affect viral replication. However, no study has been performed to date to investigate the impact of HIV replication on the transcript methylation level in the infected cell. We used a productive HIV infection model to explore the landscape of m^6A and m^5C marks on the transcriptome of HIV-infected cells over a time period of 36 hours and compared them with mock-treated cells.
Methods: The SupT1 T cell line was infected with a high dose of VSV-G pseudotyped HIVeGFP-based vector to ensure ~80% infection efficiency. Cells were collected at 12, 24 and 36h post-infection for mRNA extraction

and FACS analysis. M^{6}A RNA modifications were investigated by methylated RNA immunoprecipitation followed by sequencing (MeRIP-Seq). M^{5}C RNA modifications were investigated using a bisulfite conversion approach followed by sequencing (BS-Seq). Untouched mRNAs were used as input controls. Libraries were prepared using TruSeq stranded mRNA protocols (Illumina) and sequenced on Illumina HiSeq2500.
Results: We obtained a total of 707 million reads. Upon quality control, filtering, and genome alignment we obtained between 8.3 and 40.6 million aligned reads depending on the sample. Preliminary analyses identified transcript methylation as well as multiple genes displaying differential methylation upon HIV infection.
Conclusion: Our results highlight the presence of RNA modifications and their potential modulation by HIV, and provide a valuable resource for epitranscriptomic analyses. Therefore, RNA methylation offers a new layer of possible regulation for HIV replication, as well as an array of novel putative therapeutic opportunities to block HIV.

185LB AN HIV E-MAP REVEALS GENETIC INTERACTIONS MEDIATING HIV INFECTION

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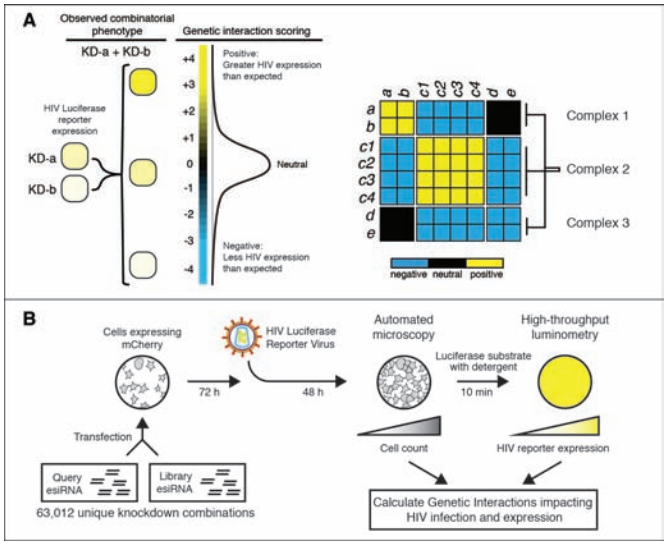
Background: Functional genetic screens using RNAi and CRISPR-Cas9 are useful for identifying host genes mediating viral infection, however individual genes identified in conventional genetic screens are sometimes difficult to place into the cellular complexes and pathways in which they function. Pairwise genetic interaction screens offer an enhanced approach to studying gene function, permitting for the quantification of functional relationships between genetic perturbations, facilitating the characterization of protein complexes and hypothesis generation regarding gene function. In this proof-of-principle study we have applied genetic interaction mapping to investigate the genes mediating HIV infection in human cells. We present a HIV viral epistasis map (vE-MAP) constructed by pairwise knockdown of 356 human genes in human cells (>63,000 unique combinations).
Methods: We generated a combinatorial knockdown matrix of 356 HIV host-dependency factors (>63,000 unique combinations) in cultured human cells and utilized high-throughput microscopy and luminometry to quantify genetic interactions impacting HIV infection. Human genes of interest identified in the vE-MAP screen were studied in primary CD4+ T-cells utilizing Cas9-RNP single and combinatorial knockouts.
Results: Hierarchical clustering of vE-MAP data highlights known human protein complexes and resolves structural submodules of the eIF3 complex. In addition to combinatorial knockdown perturbations, we also demonstrate that gene knockdowns may be combined with small molecules and viral mutants to gain insights into their function. In a novel discovery, the vE-MAP identifies numerous negative genetic interactions between the CNOT complex and known HIV host-dependency factors, several of which we validate in primary CD4+ T-cells. Finally, we observe that HIV infection in primary CD4+ T-cells requires CNOT1, 10 and 11 for suppression of type 1 interferon response.
Conclusion: This study establishes a foundation for viral genetic interaction mapping utilizing host genetic perturbations, viral mutations and small molecule treatments. We report that the CNOT complex is required for HIV infection in primary T-cells via suppression of the innate immune response.



186 ELUCIDATING THE ROLE OF THE PPIP MOTIF IN HIV-1 CAPSID IN POSTENTRY EVENTS

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Background: The HIV-1 capsid (CA) protein plays multiple roles in the viral replication cycle. As a domain in Gag, CA drives the formation of the immature Gag lattice. Upon maturation, CA reassembles to form the conical core which encompasses the viral RNA genome. During the early stages of the viral replication cycle, CA is involved in a number of processes, including uncoating, recognition by host cellular proteins and nuclear import. Recently, we demonstrated that a highly conserved proline-rich motif (PPIP122-125) in the short loop between CA helices 6 and 7 is an important element for virion assembly. In this study, we characterize the role of the CA PPIP motif in early stages of HIV-1 infection.
Methods: We selected for compensatory mutations that rescue assembly and maturation defects of the original PPIP mutants. Replication kinetics, nuclear import efficiency, and host cell restriction factor sensitivity of mutant viruses were analyzed in different cell lines and physiologically relevant cell types. Structures of mutant CA proteins were determined by X-ray crystallography. Nuclear import kinetics were characterized by light microscopy using APOBEC3F-labeled viral complexes.
Results: A set of replication-competent viruses including T58S/T107I/P122A, V11I/T58A/P122A, T58A/I124A and V11I/T58A/I124A have been analyzed in this study. Although T58A/I124A and V11I/T58A/I124A mutants are replication competent in PBMCs and parental Jurkat cells, they are highly replication defective in cyclophilin A (CypA)-deficient Jurkat cells and monocyte-derived macrophages (MDMs). We further demonstrated that V11I/T58A/I124A virions enter the nucleus faster than WT virus and are insensitive to cyclosporine A treatment. Upon propagation in CypA-deficient Jurkat cells, the V11I/T58A/I124A virus acquired a mutation, I124V, which restores its replication competency. Structural analysis by X-ray crystallography revealed that the above-described mutations alter intersubunit interactions and induce subtle changes in the PPIP- and CypA-binding loops.
Conclusion: Our findings demonstrate that the PPIP loop in CA modulates the interaction of the incoming viral core with host cell factors, including CypA and potentially nuclear import factors. These results expand our knowledge of post-entry functions of CA and the role of host proteins in productive HIV-1 infection.

187 SINGLE-CELL ANALYSIS REVEALS P2X-DEPENDENT HIV-STIMULATED CALCIUM SIGNALING

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Background: HIV-1 infection is associated with numerous comorbidities due to chronic inflammation. Purinergic (P2X) receptors are mediators of inflammatory signaling and have been increasingly implicated in HIV pathogenesis. Activation of P2X receptors can facilitate calcium influx, which then triggers downstream inflammatory signaling. Here we investigate whether HIV-1 binding or entry can activate P2X receptors and whether this receptor activation is associated with HIV-1 productive infection.

Methods: MT4 cells loaded with Fluo-4 calcium-sensitive dye and onto the Beacon (Berkeley Lights) single-cell imaging platform. Cells were exposed to HIV-1 NL-CI, a fluorescent reporter virus that expresses mCherry in place of nef and nef is expressed on an IRES. Calcium influx was measured in short time intervals up to 20 minutes after exposure to virus by measuring the Fluo-4 (green) fluorescence. The same cells were tracked over 48 hours for development of mCherry signal to indicate HIV-1 productive infection. This experimental setup was repeated in parallel in the presence of NF449, a P2X receptor antagonist.

Results: HIV-1 exposure was associated with an acute increase in intracellular calcium levels that corresponded to HIV-1 productive infection. Treatment with NF449 reduced HIV-stimulated calcium influx and HIV-1 productive infection. The higher magnitude of calcium influx was associated with higher levels of HIV-1 productive infection.

Conclusion: The Beacon single cell imaging platform is a novel and effective tool for tracking both calcium influx and HIV-1 productive infection in cells. Our findings demonstrate that HIV-1 exposure can activate calcium influx through a mechanism that is sensitive to a P2X receptor antagonist. We observe that a P2X receptor antagonist reduces calcium influx and HIV-1 productive infection. These findings demonstrate that calcium signaling correlates with productive infection and indicates importance of calcium signaling in early infection events. Further development of P2X inhibitors as drugs could prove to be effective at both suppressing viral load and preventing inflammation-associated comorbidities.

188 HOMODIMERIZATION IS REQUIRED FOR HIV-1 NEF FUNCTION IN HUMANIZED MICE

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Background: The HIV-1 Nef accessory factor is essential for efficient viral replication and immune evasion in vivo. Nef homodimer formation affects interaction with host cell effectors, including the endocytic trafficking adaptor protein, AP-2. HIV-1 virions harboring dimerization-defective Nef show reduced infectivity and replication in cell culture. Here we explored the role of Nef dimerization and AP-2 recruitment in viral replication and CD4+ T cell loss in humanized mice.

Methods: We generated mutants that are deficient for Nef dimerization (Ile 109/Leu 112/Tyr 115/Phe 121 to Asp; 4D mutant) and AP-2 binding (Asp 174/175 to Ala; DDAA mutant and Arg134 to Glu; RE mutant) based on previous X-ray crystal structures. A virus defective for Nef expression was also included (ΔNef mutant) as reference control. Effects of these mutations on viral infectivity and replication were investigated using TZM-bl reporter cells and CEM-GFP cells, respectively. BLT (bone marrow-liver-thymus) and hPBMC-NSG humanized mice were infected with each virus (2000 TCID50 equivalents/mouse), and replication measured by real-time quantitative RT-PCR targeting Gag or p24 AlphaLISA assays in plasma and tissues. Human CD4+ T cell counts were followed in peripheral blood and tissues by flow cytometry as a surrogate for HIV-1 pathogenesis.

Results: In vitro, HIV-1 infectivity and replication were both significantly reduced with the 4D, DDAA, RE and ΔNef viruses. Humanized BLT mice infected with ΔNef viruses showed significantly lower viral loads and reduced CD4 depletion compared to wild-type HIV-1 within the course of 22 weeks post infection. hPBMC-NSG mice infected with the ΔNef and 4D mutant viruses showed decreased viral loads and displayed CD4+ T cell counts comparable to uninfected mice within the course of 6 weeks post infection. Nested PCR and nucleotide sequencing did not identify reversions of the 4D mutant recovered from humanized mice. However, a possible reversion was found in one viremic mouse infected with the RE mutant.

Conclusion: Our results demonstrate that Nef homodimerization is important for HIV-1 pathogenesis in humanized mouse models of HIV/AIDS. These data support a strategy to disrupt Nef dimerization by small molecules as a new path to antiretroviral drug discovery.

189 RESTING HIV-INFECTED CD4 T CELLS EXPRESS NEF AND VPU, WHICH DOWNREGULATE MHC AND BST2

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Background: The HIV reservoir resides in resting memory CD4 T cells. These infected cells are difficult to eradicate because of their lack of virus expression. Current eradication strategies aim to reactivate virus expression in these cells, allowing them to be recognized and killed by immune CD8 T cells specific for HIV peptide/MHC-I complexes (pMHC). In addition, broadly neutralizing antibodies may bind to cell surface Env protein and elicit antibody-mediated killing. However, HIV encodes two proteins, Nef and Vpu, which allow escape from both these eradication strategies through downregulation of pMHC and tetherin (BST2). Importantly, the timing of the expression of Nef and Vpu in HIV-infected resting CD4 T cells remains unclear.

Methods: We aimed to explore this aspect of HIV infection by direct infection of resting CD4 T cells with two CCR5-tropic replication-competent GFP reporter viruses. For one virus GFP reports the expression of the Nef transcript, and for the other virus GFP reports the expression of the Vpu/Env transcript. We sorted CD4 T cells that were lacking expression of four activation markers: CD69, CD25, CD154 and HLA-DR. These resting CD4 T were infected with either reporter virus and examined daily for the expression of GFP, cell surface CD4, HLA-A02/-B07, tetherin, CD45RO, and CCR5 by antibody staining. Env expression was monitored by staining with the broadly neutralizing antibodies PG9 or VRC07.

Results: Our data show that HIV directly infects resting memory CD4 T cells expressing CCR5. GFP expression for either virus starts to appear 3 to 4 days after infection. The GFP-positive cells infected with either virus showed downregulation of CD4, HLA A02, HLA-B07, and tetherin. These resting HIV-infected cells lacked the surface expression of Env and did not express infectious virions by virus outgrowth assays from the supernatant. In addition, TCR activation of these HIV-infected CD4 T cells attenuated the upregulation of both pMHCs and BST2.

Conclusion: We conclude that HIV directly infects resting memory CD4 T cells to establish the reservoir. This direct infection of resting memory CD4 T cells confers a replicative advantage to HIV by expressing Nef to downregulate pMHC and Vpu to downregulate BST2 before activation for virion production. We therefore believe latently HIV-infected cells are cloaked from recognition by the immune system, thus providing a new strategy for persistence.

190 IMPAIRED NEF'S ABILITY TO COUNTERACT SERINC5 BY IMMUNE-DRIVEN MUTATIONS

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Background: The host proteins SERINC 3 and 5 (SERINC3/5) are inhibitors of HIV-1 infectivity that are counteracted by Nef. Introduction of mutations to the highly conserved $FPD_{121\text{-}123}$ motif in Nef resulted in disruption of Nef›s ability to counteract SERINC5 and enhance infectivity. Because this region encompasses HLA-restricted CTL epitopes, we hypothesized certain naturally arising HLA-driven mutations may impair Nef›s ability to SERINC5 and affect patients› disease progression.

Methods: Nef genes were PCR-amplified from plasma viral RNA of treatment-naïve, chronically HIV-1-infected subjects (N=375) recruited in Japan. The amplified fragments were directly sequenced and cloned in to a plasmid for functional assays of their gene products. Nef's ability to counteract SERINC3/5 was assessed by infectivity of viral particles that were produced by co-transfection of NL43 and the patient-derived nef genes to Jurkat cells expressing SV40 Large T antigen (JTAg) and JTAg cells lacking expression of SERINC3/5.

Results: The phylogenetically-informed statistical approach revealed that Y120F and Q125H mutations located close to the $FPD_{121\text{-}123}$ motif were significantly enriched in Nef sequences from subjects harboring HLA-B*51:01 that was known to present $_{120}$YFPDWQNYT$_{128}$ as a CTL epitope. Interestingly, the number of the two mutations (120F/125H) was significantly inversely correlated with the plasm viral load; whereas no other HLA-associated polymorphisms

showed similar trend. Infectivity assays revealed that the patient-derived Nef clones carrying the double 120F/125H mutations exhibited impaired ability to counteract SERINC3/5 and that the observed impairment was restored when reversion mutations (120Y/125Q) were introduced. Corroboratively, Western blot analysis of viral particles revealed that the Nef-mediated inhibition of SRINC5 incorporation to progeny viral particles was impaired in Nef clones harboring the double 120F/125H mutations, compared to those harboring the consensus 120Y/125Q. In contrast, Nef functions of CD4 and HLA class I downregulation remained unchanged regardless of the Nef genotype of 120Y/125Q or 120F/125H.

Conclusion: Taken together, these results suggested that the immune-driven Nef mutations 120F/125H located at the highly conserved $FPD_{121-123}$ motif impose fitness cost to Nef-mediated counteraction of SERINC5 and thereby viral replication in infected hosts.

191 SYNTHESIS AND EVALUATION OF TIGHT-BINDING HYDROXYPYRAZOLE INHIBITORS OF HIV-1 NEF

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Background: The HIV-1 Nef accessory factor is critical to the HIV life cycle in vivo and promotes immune escape of HIV-infected cells in part via downregulation of cell-surface MHC-I. Previously we discovered small molecules that bind directly to Nef and block many of its functions, including enhancement of viral infectivity and replication in T cell lines. These compounds, based on a hydroxypyrazole core, also rescue cell-surface MHC-I expression in patient-derived CD4+ T-cells, enabling recognition and killing by autologous CTLs. Nef inhibitors may provide a new approach to antiretroviral therapy that includes a path to eradication of HIV-infected cells. This study focused on medicinal chemistry optimization of hydroxypyrazole Nef inhibitors to improve potency and metabolic stability.

Methods: Nef inhibitor analogs in this study are based on a previous diphenylpyrazolodiazene hit compound with a hydroxypyrazole core linked to chlorophenyl, nitrophenyl, and thioamide moieties. The thioamide group was replaced with a variety of heterocyclic moieties, along with multiple substitutions of the other ring systems, for a total of 254 unique compounds. Analogs were screened for interaction with recombinant Nef proteins by surface plasmon resonance (SPR), and for antiretroviral activity in TZM-bl reporter cells infected with HIV-1. Active compounds were then evaluated for antiretroviral activity in donor PBMCs and for metabolic stability against liver microsomes in vitro.

Results: Multiple analogs bound tightly to recombinant Nef proteins by SPR, with K_D values in the nM to pM range. Several of these compounds suppressed HIV-1 replication in donor PBMCs with IC_{50} values in the 1-10 nM range without cytotoxicity, and were resistant to metabolism by mouse liver microsomes. Some analogs also reversed MHC-I downregulation in a Nef-transfected T cell line.

Conclusion: HIV-1 Nef inhibitors based on a hydroxypyrazole core are amenable to a wide range of structural modifications and retain inhibitory activity despite addition of bulky heterocyclic substituents. Several analogs displayed tight binding to recombinant Nef in vitro, potent antiretroviral activity in primary cells infected with HIV-1, and the capacity to restore cell-surface MHC-I expression. Future efforts will evaluate pharmacologic properties in vivo with the goal of identifying analogs suitable for testing in humanized mouse models of HIV-1 replication and latency.

192 ACTIVATION OF TEC KINASES BY HIV-1 NEF AT THE CELL MEMBRANE REQUIRES DIMER FORMATION

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Background: The HIV-1 Nef virulence factor supports high-titer viral replication and pathogenicity. Nef interacts with Itk and Btk, two Tec-family kinases expressed in HIV-1 target cells (CD4 T cells and macrophages). Knockdown or pharmacological inhibition of Itk suppresses HIV-1 entry, transcription and egress, suggesting that Nef-mediated Itk activation is required for efficient viral replication in vivo. Here we demonstrate that Nef activates both Itk and Btk at the cell membrane through a mechanism dependent on Nef homodimer formation.

Methods: Nef-kinase interaction and kinase activation were assessed in transfected 293T cells by combining bimolecular fluorescence complementation (BiFC) with immunofluorescence using phosphospecific antibodies for the activation loop tyrosine of Itk (pY511) and Btk (pY551). Mutants of the Nef dimerization interface, based on previous crystal structures, targeted conserved residues L112, Y115, and F121 either alone or in combination. Endogenous Itk activation was assessed by phosphoflow cytometry in HIV-1 infected Jurkat and SupT1 cells using the phosphospecific antibody for Itk.

Results: BiFC analysis showed that wild-type HIV-1 Nef interacted with both Itk and Btk at the cell membrane, resulting in enhanced kinase activation loop phosphorylation. Nef dimerization interface mutants retained interaction with both kinases, but failed to induce kinase activation, supporting a role for Nef homodimer formation in the activation mechanism. Addition of small molecule Nef inhibitors reversed Nef-dependent Itk autophosphorylation, suggesting that these compounds may interfere with Nef dimerization and Itk activation through an allosteric mechanism. HIV-1 infection upregulated endogenous Itk activity in Jurkat and SupT1 cells in a Nef-dependent manner, while HIV-1 with Nef dimerization interface mutations replicated poorly in both T cell lines and donor PBMCs.

Conclusion: Our results support a mechanism in which Nef recruits Itk and Btk to the membrane, and drives kinase activation via a dimerization-dependent mechanism. Nef dimerization interface mutants replicate poorly in T cells, and Nef inhibitors interfere with Itk activation, suggesting that suppression of the Nef-Itk pathway may account for part of their antiretroviral mechanism of action. These findings provide a strong rationale to support further antiretroviral drug development targeting Nef homodimerization and the Nef-Itk/Btk signaling pathways.

193 ACTIVATION OF TEC-FAMILY KINASES ITK AND BTK BY HIV-1 AND SIV NEF PROTEINS IN VITRO

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Background: The Nef proteins encoded by HIV-1 and SIV are critical for efficient viral replication and AIDS progression. In addition to downregulating cell-surface immune and viral receptors, Nef also induces constitutive activation of host-cell tyrosine kinases of the Src and Tec families. Nef-mediated activation of Itk, a Tec family member expressed in CD4 T cells, is essential for several stages of the HIV-1 life cycle. Nef also interacts with Btk, which is expressed in B cells and macrophages. Itk and Btk share a similar domain organization consisting of PH, SH3, SH2 and kinase domains. Here we tested whether interaction of recombinant purified Btk and Itk proteins with Nef was sufficient for kinase activation in vitro.

Methods: Full-length and 'Src-like' cores (SH3-SH2-kinase) of Itk and Btk were expressed in Sf9 insect cells and purified. A kinetic kinase assay (ADP Quest; Eurofins) was used to measure the rates of autophosphorylation and peptide substrate phosphorylation in the presence and absence of recombinant purified HIV-1 and SIV Nef. Activation loop autophosphorylation was assessed by immunoblotting with phosphospecific antibodies. Surface plasmon resonance (SPR) was used to measure the interaction of Nef with recombinant purified Itk and Btk regulatory domains.

Results: Both HIV-1 and SIV Nef strongly enhanced full-length Btk autophosphorylation and kinase activity in vitro, with autophosphorylation occurring primarily on the activation loop at Tyr551. In contrast, Nef had no effect on the Btk core protein, implying that the PH domain is important for interaction with Nef and kinase activation. Nef induced modest enhancement of full-length Itk autophosphorylation on activation loop Tyr511, but did not affect the ITK core. Interestingly, a mutant of Nef lacking the conserved motif required for SH3 domain binding (PxxP) activated Btk and Itk to the same extent as wild-type Nef. This mutant failed to activate the Src-family kinase Hck, suggesting that Nef activates Tec and Src family kinases by distinct mechanisms. This conclusion is supported by SPR data, which showed that the Itk SH3 domain alone does not bind to Nef.

Conclusion: HIV-1 and SIV Nef proteins activate Btk and to a lesser extent Itk in vitro, through an SH3 domain-independent mechanism distinct from Src-family kinases. Small molecules that interfere with this Nef-dependent kinase signaling pathway may provide a new route to antiretroviral drug development.

194 NEF DIMERIZATION REGULATES HIV-1 INFECTIVITY AND SERINC5 INCORPORATION

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Background: Nef is an HIV-1 accessory factor essential for viral pathogenesis and immune escape. Nef lacks intrinsic biochemical activity, functioning instead via interactions with multiple host cell effectors related to signaling and endocytic trafficking. Nef function also depends on self-association through conserved hydrophobic residues that form a dimer interface (L112, Y115, F121). Mutation of these residues disrupts diverse Nef functions, including enhancement of viral infectivity, replication, and receptor downregulation. Here we investigated whether Nef dimerization is linked to sensitivity to the host cell restriction factor SERINC5 (S5), a potent suppressor of infectivity that is antagonized by Nef.

Methods: Viruses were produced in 293T cells transfected with HIV-1 NL4-3 proviral DNA in the presence or absence of an expression vector for S5 with a C-terminal HA tag. Viral supernatants were harvested 48 h later and assessed for infectivity using TZM-bl reporter cells. S5 incorporation was assessed by immunoblotting of HIV-1 virions following purification by ultracentrifugation.

Results: Consistent with previous reports, co-expression of S5 in producer 293T cells severely impaired the infectivity of Nef-defective HIV-1 (ΔNef). The infectivity of wild-type HIV-1 produced in the presence of S5 was higher due to the expression of Nef, which excludes S5 from the cell membrane to prevent incorporation into the envelope of budding virions. Interestingly, the infectivity of virions produced from proviruses with Nef dimerization interface mutations showed reduced infectivity approaching that of the ΔNef virus, and infectivity was reduced even further upon co-expression of S5. Immunoblotting showed an increase in S5 incorporation into purified virions with Nef dimerization interface mutants similar to that observed with the ΔNef virus.

Conclusion: The infectivity of HIV-1 virions expressing Nef dimer interface mutants is impaired to a similar extent as the Nef-defective virus when produced in the presence of S5, suggesting that Nef homodimer formation is important for S5 antagonism. This conclusion is supported by biochemical data, where S5 incorporation is increased in newly synthesized virions in the presence of these Nef mutations. However, the infectivity of Nef mutant viruses is also impaired in the absence of S5 expression, suggesting that additional mechanisms control infectivity of viruses produced in 293T cells that are S5-independent.

195 LIPID BINDING DOMAIN IMPACT ON HIV-1 NEF AND SRC-FAMILY KINASE HCK U-SH3-SH2 COMPLEX

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Background: The HIV-1 accessory protein Nef supports high-titer viral replication, immune evasion of HIV-infected cells, and is essential for AIDS progression. Efficient replication of HIV-1 in primary human macrophages requires expression of the myeloid Src-family kinase, Hck. Nef provides a crucial link between HIV-1 and this host cell kinase, interacting with Hck through its SH3 domain and driving constitutive kinase activation. Both Nef and Hck are myristoylated at their N-termini, resulting in co-localization to the cytoplasmic face of cellular membranes. Also contributing to membrane localization are the anchor and unique domains of Nef and Hck, respectively, which are positioned N-terminal to the Nef core and Hck SH3 domain. To better understand the role of these N-terminal lipid binding domains on Nef homodimerization and Hck recruitment, we are pursuing the X-ray crystal structure of full-length Nef (FL-Nef; SF2 allele) in complex with the Hck unique-SH3-SH2 (Hck-U32) regulatory domains.

Methods: We developed an E. coli expression system for the expression and purification of soluble Hck-U32 tandem regulatory domains. Stable interaction between purified Hck-U32 and FL-Nef was then determined using analytical size-exclusion chromatography (SEC) and surface plasmon resonance (SPR). The Hck-U32 and FL-Nef expression systems were combined to co-purify the two proteins as a complex (FL-Nef:Hck-U32) by immobilized metal affinity chromatography and SEC. Crystallization trials of this purified complex are in progress using the sitting-drop vapor diffusion method.

Results: Using our expression system, the Hck-U32 protein has been successfully expressed and purified from E. coli in soluble form. Hck-U32 and FL-Nef form stable complexes in solution as demonstrated by both analytical SEC and SPR. The SPR analysis suggests a high affinity interaction between Hck-U32 and FL-Nef with a kinetic K_D value in the low μM range. In addition, the recombinant FL-Nef:Hck-U32 complex has been purified to homogeneity and is currently in crystallization trials.

Conclusion: The Hck-U32 protein is amenable to expression and purification in soluble form and stably interacts with FL-Nef in solution, enabling structural analysis of the complex by X-ray crystallography. This complex structure is anticipated to yield fresh insight into the role of these N-terminal lipid binding domains in the regulation of protein:protein interactions at biological membranes.

196 IP-10 PRODUCTION BY THE LYMPH NODES MEDIATES ENTRY OF SIV-SPECIFIC CXCR3+CD8+ T CELLS

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Background: Lymph nodes (LN) harbor cells chronically infected by HIV/SIV, especially CD4+ follicular helper lymphocytes which are located within the B cell areas. LN are characterized by low frequency of effector memory CD8 T cells that are, in general, excluded from the follicles. Using a vaccination protocol that combines intramuscular DNA delivery followed by in vivo electroporation, we have analyzed the trafficking of virus-specific CD8+ T lymphocytes.

Methods: Eight MamuA01+ rhesus macaques were immunized with plasmid DNA encoding p57gag. Two weeks after the fourth vaccination, the animals were sacrificed, and the dissemination of vaccine-induced T cell responses was monitored throughout the body by immunophenotyping combined with CM9gag tetramer staining, followed by flow cytometry. Chemokine production, including CXCL9, CXCL10 and CXCL11, by lymph node mononuclear cells (LNMC) from the vaccinated animals stimulated ex vivo with SEB and IFNγ was measured by ELISA, multiplex chemiluminescence detection assays (MSD) and intracellular staining.

Results: High magnitude (up to 15% of total CD8+ T cells) of vaccine-induced virus-specific CD8+ T cells were found in peripheral blood from all the immunized macaques. These cells were actively dividing (ki67), expressed high levels of CXCR3 and efficiently migrated into central and peripheral LN. The CM9-specific CD8+ T cells within the LN also expressed CXCR3 and had an effector phenotype (CD95+CD28lowCD45RAlowCD127-CCR6-CCR4-) with no significant CCR7 expression, suggesting that these cells could be located outside the T cell areas. LNMC from these vaccinated macaques stimulated ex vivo with IFN-γ or SEB released high levels of IP-10 (CXCL10) and CXCL11. A combination of surface and intracellular staining with anti-CXCL9 and IP-10 antibodies revealed that these chemokines were produced by HLA-DR+ B lymphocytes, CD11c+CD14- dendritic cells and a subset of cells with the phenotype (CD3-CD20-CD14-CD11c-HLA-DR-CD21+) of follicular dendritic cells (FDC).

Conclusion: Expression of CXCR3 by the vaccine-induced virus-specific CD8+ T cells indicates that these cells can migrate into areas where the chemokines CXCL9, CXCL10 and CXCL11 are produced. Because these chemokines are produced within the LN by cells located in the B cell areas (B lymphocytes and FDC) the data suggest that a CXCR3-dependent and CXCR5-independent pathway of effector cells entry into the follicles exist.

197 LYMPH NODE TREG SUBSETS ARE EXPANDED IN SOME HIV+ PEOPLE ON SUPPRESSIVE ART

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Background: Tregs including follicular regulatory T cells (TFR) are expanded in lymph nodes of untreated HIV+ people. TFR impair TFH responses and humoral immunity in untreated disease. Little is known about the impact of antiretroviral therapy (ART) on Treg and TFR populations in secondary lymphoid organs.

Methods: Frequencies of Tregs (FoxP3+CD8-) and TFR (Tregs located in CD20+ B cell follicles) were determined by immunostaining of formalin fixed paraffin embedded lymph node (LN) tissue sections and quantitative image analysis. Frequencies of HIV RNA+ cells were determined in the same tissue section using in situ hybridization (RNAscope). Data were analyzed using descriptive and nonparametric statistics.

Results: LN were evaluated from 6 HIV+ men receiving ART for a median of 20 years (range, 7-29 years) with documented plasma HIV RNA <20 copies/mL at the time of screening. For comparison, LN sections from 8 HIV+ men not receiving ART, and 6 HIV seronegative men (SN) were also evaluated. As expected, frequencies of Tregs in the tissue cross sections were significantly higher in untreated HIV+ compared to SN men (medians, 56 vs 21 cells/mm^2; p=0.008), and a similar trend was seen for TFR within follicles (medians, 59 versus 22 cells/mm^2; p=0.10). In ART treated HIV+, Tregs (median, 36 cells/mm^2) and TFR (median, 76 cells/mm^2) did not differ significantly from either group. Tregs and TFR from ART-treated HIV+ demonstrated a clear dichotomy; 3 subjects had elevated levels similar to what was seen in untreated HIV+, and 3 had low levels of TFR similar to SN. HIV RNA+ cells were detected in LN of all ART-treated HIV+ (range, 0.05 to 0.5 cells/mm^2) and were significantly fewer than those detected in untreated HIV+ (range, 0.2 to 2.6 cells/mm^2; p=0.04). Higher concentrations of HIV RNA+ cells were found in the LN follicles of all ART treated individuals (median, 0.4 cells/mm^2) compared to extrafollicular regions (median, 0.2 cells/mm^2) with median F:EF ratio of 1.8 (range, 1.5 to 3.2). Frequencies of both Tregs and TFR in LN of ART-treated individuals correlated directly with frequencies of HIV RNA+ cells (r=0.88; p=0.03 for both).
Conclusion: Persistent expansion of Tregs including TFR is seen in LN of some ART-treated individuals with plasma virus suppression and is related to tissue HIV RNA expression. Expansions in TFR may contribute to impairments in humoral immunity seen in some ART-treated individuals.

198 DENDRITIC CELLS CROSSTALK WITH FOLLICULAR CD8+ T-CELLS IN HIV-INFECTED LYMPH NODES

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Background: Plasmacytoid dendritic cells (pDCs) have been related with HIV spontaneous control. However, a deregulation mainly consisting in an aberrant IFN-I production lead to an inflammatory environment that could enhance HIV pathogenesis. It has been communicated that HIV provokes alteration in phenotype and location of CD8 T-cells within lymph nodes (LN). In a mouse model, a cooperative activity between pDCs and XCR1 dendritic cells (DCs) in order to effectively antigen cross-priming to CD8+T cells has been reported. However, the phenotype, function of pDCs and its interaction with other cell types in lymphoid tissues in relation with HIV-disease outcomes remain largely unknown.
Methods: Seven inguinal LN samples prior to antiretroviral onset were obtained from HIV-infected patients. PBMCs were obtained at the same time point of LN biopsies. A comprehensive analysis of DCs, pDCs and T-cells was performed by deep immunophenotyping using multiparametric flow cytometry.
Results: pDCs levels were inversely correlated with viral load (VL) both in PBMCs and LNs (r=-0.893; p=0.007 and r=-0.9; p=0.037, respectively). Alternatively, VL positively correlated with exhausted pDCs in LN, assessed by PDL-1 expression (r=0.829; p=0.042). Indeed, we found a strong positive correlation between the frequency of pDCs in PBMCs and pDCs in LN (r>0.9, p=0.016). Interestingly, associations between pDCs survival and CD141 mDCs and frequency of follicular CD8 (fCD8) T-cells within LN were presented. The more frequency of CD141 mDCs was present in LN, the less pDCs exhibiting an early stage of apoptosis and the less frequency of fCD8 T-cells were present (r=-0.829, p=0.042 and r=- 0.886, p=0.019, respectively). Furthermore, we found a strong correlation between the percentage of pDCs expressing pDL1 and the levels of follicular CD8+T cells PD1+ (r=0.943, p=0.005). Of note, this correlation was not present neither between the levels of pDCs PD1+ and non-follicular CD8+T cell levels nor with other myeloid dendritic cells expressing PDL1.
Conclusion: We explored a pDCs crosstalk with CD141+mDC and fCD8+T-cells, and its relation with fCD8 T-cell exhaustion in LNs of HIV-infected patients. This pathway may be a drug target that may enhance HIV-specific response within LNs, allowing the development of HIV curative strategies.

199 LONGITUDINAL DYNAMICS OF FOLLICULAR CD4+ T CELLS IN ACUTE SIV INFECTION

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Background: Follicular T helper CD4+ (Tfh) cells play a critical role in germinal center (GC) formation and B cell maturation. GCs in lymph nodes (LN), particularly within Tfh cells, are sites for preferential SIV infection and replication. Changes in Tfh phenotype and functions in early acute SIV infection may be a major determinant in the development effective antibody-mediated control of SIV infection.
Methods: Eighteen rhesus macaques were intravenously infected with SIVmac251 and underwent staggered necropsy during acute and chronic infection. Tfh cells from surface LN (sLN), mesenteric LN (mLN) and spleen were immunophenotyped. We further examined mLN to quantify and localize viral RNA (vRNA) using immunohistochemistry, and performed gene expression and pathway enrichment analyses on sorted Tfh cells from LNs in resting and stimulated conditions.
Results: The frequency of Tfh cells decreased at day 10 post-infection (p.i.) and partially rebounded after 20 days in all tissues. Using principal component analyses we found similar phenotypic profiles in Tfh from mLN and sLN; in contrast, Tfh isolated from the spleen clustered separately after 10 days p.i. Although plasma viremia (pVL) peaked day 10 p.i., vRNA in mLNs was detectable as early as day 5 p.i. within follicles and the T cell zone. While pVL decreased after 20 days, tissue vRNA was increased until 90 days p.i. but was not preferentially found within the follicles during this early period. Very early following infection, transcriptional profiling of Tfh-related genes showed profound modulation of cytokine production and inflammatory pathways. Moreover, we observed a decrease in Tfh responsiveness to stimulation as early as day 5 p.i. This functional ability was partially recovered after 20 days p.i. irrespective of the increasing vRNA found the tissue. tSNE analyses showed independent clustering pre- and post-infection, and Tfh cells from day 90 p.i. had the most similar profile to pre-infection suggesting a partial recovery in responsiveness in later stages of infection.
Conclusion: SIV infection has a profound effect in Tfh frequencies, phenotypic and genetic profiles across tissues since acute infection. This effect suggests a temporal decrease in Tfh ability to provide B cell help during early stages of infection associated with high levels of viremia in blood and tissues, that may directly impact or delay the early induction of SIV-specific antibody production.

200LB CYTOLYTIC HIV-SPECIFIC CD8+ T CELLS DO NOT RECIRCULATE THROUGH TISSUES

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Background: Cytolytic effector memory HIV- and SIV-specific CD8+ T cells are key correlates for natural and vaccine-induced viral control. While assumed, it remains unknown if these cells leave the blood to access HIV reservoirs in lymphoid and peripheral tissues. To directly address this question, we present for the first time a spatial map of the tissue egressing (recirculating) immune system by sampling blood, lymph nodes (LNs) and thoracic duct lymph (TDL) in HIV-seronegative and seropositive individuals.
Methods: We isolated LNs and matched human blood and TDL mononuclear cells through thoracic duct cannulation of HIV-seronegative and seropositive individuals on and off antiretroviral therapy. Functional and phenotypic assays on total and HIV+ lymphocytes were performed by flow cytometry and transcriptional data was collected through RNAseq using the SMARTseq2 platform. The results were analyzed using RStudio, FlowJo, and GraphPad Prism.
Results: Through transcriptional, functional and phenotypic analysis, we show that expression of cytolytic molecules by effector memory CD8+ T cells are almost entirely confined to blood, while their phenotypic counterparts in the thoracic duct, and many tissues, represent non-cytolytic T cells with a higher regenerative capacity. Unlike their blood counterparts, HIV- and CMV-specific CD8+ T cells in TDL and LNs generally lack cytolytic molecule expression and killing ability. We further demonstrate that those HIV-specific CD8+ T cells

detectable in the TDL possess an intermediate differentiation status (CCR7-CD45RA-CD27+), thereby defining the identity of HIV-specific CD8+ T cells capable of accessing HIV reservoirs in peripheral tissues.
Conclusion: Our results demonstrate that not all types of memory CD8+ T cells survey tissues and reveal that cytolytic molecule expression is mostly confined to effector memory HIV-specific CD8+ T cells in blood during steady-state and chronic HIV disease. These data also suggest that the intermediate differentiation status of peripheral blood HIV-specific CD8+ T cells is a marker of tissue recirculation rather than a dysfunctional state as previously assumed.

201 MICROBIAL TRANSLOCATION MEASURED BY CONFOCAL ENDOMICROSCOPY IN HIV-INFECTED PATIENTS

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Background: The disruption of the intestinal mucosa in HIV individuals leads to an increase of bacterial translocation, immune activation and non-AIDS events in HIV infected individuals. Confocal endomicroscopy could help to assess the changes in gut mucosa. The objective of the study was to describe morphological and dynamic findings in patients with HIV infection by direct visualization of the intestinal mucosa with confocal endomicroscopy and correlate these findings with bacterial translocation markers.
Methods: Demographic and clinical characteristics, pathological changes of rectal mucosa biopsies, confocal endomicroscopy findings (amount of intramucosal bacteria, amount of fluorescein in the crypt lumen and in lamina propia), microbial translocation (LBP, sCD14 and EndoCAb) and inflammation (TNF-alpha, IL-6, usPCR, DD) in plasma, T-cell and myeloid subsets in rectal biopsy and peripheral blood were analyzed in 10 HIV individuals. A correlation between microbial translocation and other factors was also performed.
Results: We recruited 9 men and 1 woman with median age of 37 years, 9 homosexual and 1 heterosexual. The median CD4 nadir and current CD4 was 572 and 767 cells/mm3, respectively. Only 1 out of 10 patients showed fibrosis in rectal epithelium. In most of the biopsies analyzed, mild chronic inflammation was observed (8/10 individuals). Regarding confocal endomicroscopy, the amount of intramucosal bacteria was high and fluorescein in lamina propia was increased in most individuals, suggesting an abnormality of the mucosal barrier. Translocation markers and myeloid subsets in mucosa were associated with changes of gut mucosa assessed by confocal endomicroscopy: a) CD14s and %CD11c+ CD14- cells vs. the amount of fluorescein in lamina propia (Rho=0.73 p=0.015 and Rho= 0.81 p=0.0045, respectively); b) Endocab and %CD83+ cells vs intramucosal bacteria (Rho=0.64 p=0.04 and Rho=-0.68 p=0.029, respectively). In addition, translocation markers were also correlated with markers of inflammation [EndoCAb vs TNF-alpha (Rho=-0.76 p=0.01) and LBP vs TNF-alpha (Rho=0.65 p=0.04)] and T-cell subsets in peripheral blood [LBP vs CD4+(Rho=-0.75 p=0.01), LBP vs CD4+ CD38+ HLA-DR+ (Rho=0.70 p=0.02), and LBP vs CD8+ CD38+ HLA-DR+ (Rho=0.73 p=0.01)].
Conclusion: These data suggest that confocal endomicroscopy could be a good tool to further study gut epithelial damage and microbial translocation in HIV infected patients.

202 ISOLATION OF TRANSLOCATING BACTERIA IN PROGRESSIVE SIV INFECTION OF RHESUS MACAQUES

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Background: Microbial translocation is a significant contributor to chronic immune activation and inflammation in HIV–infected humans. In SIV–infected rhesus macaques (RM), translocation has been demonstrated to occur across the gastrointestinal barrier; however, translocating bacterial taxa are not representative of the gut microbiota, with Proteobacteria appearing to preferentially translocate. To fully characterize translocating bacterial populations, we isolated translocated bacteria from chronically SIV-infected macaques and identified them subsequent to live culture.
Methods: Liver, mesenteric lymph node, and spleen samples were taken during necropsy from one uninfected and twenty chronically SIV– or SHIV–infected RM, including some Vancomycin–treated animals. Tissue samples were homogenized and plated on: a) Brain Heart Infusion, b) TSA+Tween 80, and c) TSA+5% Sheep's Blood media under aerobic conditions, and d) Brucella Blood and e) CDC Blood media under anaerobic conditions. Isolates were grown for 1–7 days, colonies re–streaked for purity, and identified using MALDI–TOF and 16S rDNA sequencing. Shannon α–diversity was calculated for a) SIV+, b) SIV+ Vancomycin–treated and c) SIV+ or SHIV+ animals (no Vancomycin).
Results: Thirty-six species have been identified thus far, 5 Proteobacteria (Enterobacteriaceae), 4 Actinobacteria (50% Actinomycetaceae, 25% Corynebacteriaceae, 25% Coriobacteriaceae), 2 Bacteroidetes (50% Odoribacteraceae, 50% Prevotellaceae) and 25 Firmicutes (32% Lactobacillaceae, 16% Streptococcaceae, 12% Enterococcaceae, 8% Aerococcaceae, 8% Eubacteriaceae, 8% Leuconostocaceae, 4% Bacillaceae, 4% Planococcaceae, 4% Staphylococcaceae, 4% Veillonellaceae). Surprisingly, although our cohort exhibited comparable microbial translocation, α-diversity between tissue sites was significantly reduced in the Vancomycin group as compared to the infected but untreated group with higher levels of Proteobacteria having translocated in Vancomycin-treated animals (two-way paired t-test, p=0.0739).
Conclusion: While PCR has been relied upon in previous studies to show the presence of translocated bacteria, this study reveals that several translocated bacteria are replication competent and that dysbiosis could influence the types of bacteria which translocate. It remains to be seen whether reduced diversity in Vancomycin-treated animals is due to a further alteration in taxa crossing the epithelial barrier or a change in selection pressure once they've translocated.

203 SYNERGY BETWEEN TH1 AND TH22 IMPAIRS TH17 CELLS RECRUITMENT TO THE GUT ON ART

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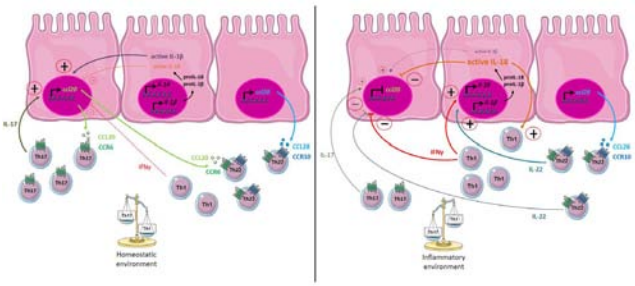
Background: During HIV-1 infection, a deep depletion of Th17 cells occurs early in the gut mucosa. Th22 cells are also initially depleted but appear to be able to efficiently recover on antiretroviral therapy (ART), while Th17 do not. A pro-inflammatory state also promotes Th1 cells recruitment to the gut on ART. Both Th17 and Th22 cells express CCR6 and could thus be recruited through the CCL20-CCR6 axis. However, we previously reported that CCL20 production by enterocytes is impaired in the duodenum on ART. But Th22 cells can alternatively use the CCL28-CCR10 axis to migrate to the gut. We hypothesized that Th1 and Th22 cells synergistically impair CCL20 production by the enterocytes thus preventing Th17 cells recruitment to the gut.
Methods: Duodenal biopsies were obtained from 10 HIV-1-infected subjects on ART and 10 healthy controls. Intestinal T cells were isolated and Th1 (CD3+CD4+CXCR3+CCR4-CCR6-), Th17 (CD3+CD4+CXCR3-CCR4+CCR6+CD161+), and Th22 (CD3+CD4+CXCR3-CCR4+CCR6+CD161-CCR10+) cell frequencies were analyzed by flow cytometry (BD Fortessa). A model of primary human intestine epithelial cell culture was used to decipher enterocyte response to cytokines and T cells in co-culture experiments. CCL20 and CCL28 expression was quantified by qRT-PCR (mRNA) and ELISA (protein).
Results: The frequency of Th17 cells in the duodenum of treated HIV-1-infected subjects remained lower than in healthy controls (4.3% vs 7.6%, P<0.05). By contrast, Th22 cells were restored to normal values (6.3% vs 5.4%, P=0.53), and Th1 cells were increased (9.0% vs 4.7%, P<0.01) in HIV-1-infected vs healthy controls. Ex-vivo, IFN-γ, the main Th1 cytokine, induced a 5-fold decrease in CCL20 mRNA expression by enterocytes. IFN-γ strongly increased IL-18 production (up to 100-fold), which in turn further decreased CCL20 expression by 2 to 3-fold. IL-22, mainly produced by Th22 cells, induced a 2 to 3-fold decreased in CCL20 expression by enterocytes, and also indirectly contributed to CCL20 inhibition by promoting IL-18 expression. Similarly, co-cultures between enterocytes and Th1 and Th22 cells showed a reduction of CCL20 production by enterocytes. By contrast, CCL28 production was preserved allowing Th22 recruitment through the CCR10 axis in this setting.
Conclusion: Th1 and Th22 synergistically blunt CCL20 production by enterocytes through IFN-γ, IL-18, and IL-22, preventing Th17 reconstitution in the gut of HIV-1-infected subjects on ART.



204 THE ROLE OF CS1 FIBRONECTIN IN HIV-1 INFECTION OF GUT-HOMING T CELLS

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Background: The intestines are the principle site of HIV replication, and are severely damaged during acute infection. Gut-homing CD4+ T lymphocytes expressing the α4β7 integrin are preferentially targeted by HIV and are implicated in intestinal pathology. Previous studies indicated that gut-homing T cells are targeted through binding of HIV envelope protein to α4β7; however, we demonstrated that purified envelope proteins do not bind to α4β7 (Plotnik et al., J. Virol. 2017). Instead, we discovered that envelope-α4β7 interactions are mediated by the extracellular matrix protein CS1 fibronectin. In the present study, we extended this observation and tested the hypothesis that CS1 fibronectins facilitate infection of α4β7+ T cells.
Methods: The recombinant CS1 fibronectin fragment RetroNectin™ (TaKaRa Inc.) was used in our studies. RetroNectin was used to capture HIV on polystyrene plates. Infection of primary α4β7+ T cells by RetroNectin-associated or free viruses was measured by p24 ELISA of culture supernatants. The effects of HIV-neutralizing antibodies and α4β7–blocking antibodies on both modes of infection were compared. Cell-to-cell virus transmission between autologous T cells was measured by flow cytometry. The effect of infection on CS1 fibronectin expression was assessed by co-culturing fibroblasts with infected or uninfected lymphocytes, and measuring CS1 fibronectin mRNA by quantitative PCR.
Results: Infection by RetroNectin-captured viruses resulted in threefold higher peak p24 output compared to infection with free viruses. RetroNectin-mediated infection was reduced by α4β7–blocking antibodies Act-1 and 2B4. Importantly, unlike infection by free viruses, infection by RetroNectin-captured viruses was resistant to neutralizing antibodies VRC01, PG16, and 2G12. Cell-to-cell virus transmission was threefold higher in the presence of RetroNectin. CS1 fibronectin mRNA levels were twofold higher in fibroblasts co-cultured with HIV-infected vs. uninfected cells.
Conclusion: Results from these studies indicate that CS1 fibronectin may have previously unrecognized roles in HIV infection. These include facilitating α4β7+ cell infection through co-localizing viruses and α4β7+ T cells, and promoting cell-to-cell virus transmission while protecting captured viruses from neutralizing antibodies. Since HIV infection also induces CS1 fibronectin expression in vitro, we hypothesize that CS1 fibronectins may amplify HIV infection in vivo through a positive feedback mechanism.

205 INFLAMMATION WITHIN THE SMALL INTESTINE IS ASSOCIATED WITH IMMUNE RECONSTITUTION

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Background: The relationship between immune reconstitution after starting cART in gut, peripheral blood and persistent systemic inflammation is poorly understood. We sought to investigate how gut immune reconstitution impacts residual systemic inflammation.
Methods: Patients with chronic HIV (pts) naïve to ART prior to start darunavir/ ritovavir/ tenofovir disoproxil fumarate/ emtricitabine underwent duodenal biopsies (gut) and phlebotomy at baseline (BL) and at 12 mo of ART. 17 age, sex and risk group (MSM) matched HIV- controls (C) underwent identical procedures one time. T-cell subsets by FACS and lamina propria density by immunohistochemistry (IHC) in gut and PBC and a panel of inflammatory biomarkers were measured by ELISA at BL and 12-mo. Values are expressed as median [interquartile range] and non-parametric were used where appropriate.
Results: 18 HIV-positive men with a median baseline CD4+ count of 431 cells/ dL[272-559] and HIV load of 40,500 copies/mL[19,750-84,250], were enrolled. HIV load became undetectable and CD4+ increased to 742 cells/mm3 [561,861] at 12-mo; p=0.001. 17 C were of similar demographics and age. Activated gut CD8+ and central memory (cm) T-cell subsets positively correlated with their peripheral counterparts (Spearman's rho (SpR)=0.721 and 0.835 respectively; p=0.001). After 48-weeks of treatment only correlation in CD8+ central memory persisted (SpR 0.628;p=0.01). However, no correlations between the total CD4+ CD8+ T-cell between both sites were found suggesting that only activated phenotypes are in equilibrium between compartments. Gut T-cell density (IHC) were lower in pts at baseline 80 CD8+ /mm2 (34-190) and 769 CD4+/mm2 (61-967) compared to C 268 CD8+/mm2 (164-408); p=0.002 and 475 CD4+/mm2 (389-627); p=0.006 respectively. Although partially recovered, differences with controls persisted after 12-months 268 CD8+ /mm2 (164-408) p=0.02 and 475 CD4+/mm2 (389-627);p=0.03. A significant correlation was found at baseline between CD8+ gut density and I-FABP (SpR 0.568;p=0.013) and Thromboplastin (SpR 0.668;p=0.002). Moreover, I-FABP levels at entry were negatively correlated with peripheral CD4+T-cell recovery after ART (SpR -0.577;p=0.012).
Conclusion: Our data suggests the potential trafficking between activation phenotypes from GALT and peripheral T-cell subpopulations, and that these drive gut integrity biomarkers. Inflammation and immune changes within the small intestine compartment are associated with immune recovery at that level.

206 ALTERED GUT IMMUNITY IN IMMUNOLOGICAL NONRESPONDERS PARTLY RESTORED BY PROBIOTICS

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Background: Immunological non-responders (INR) have increased non-AIDS morbidity. A proposed mechanism for INR's inferior prognosis is microbial translocation across gut mucosa, which promotes chronic immune activation. In-depth immune function in gut mucosa of INR has not been systematically assessed, nor have the effects of probiotics.
Methods: In a cross-sectional study, we included three groups of Caucasian age-matched men: 20 INR (ART>4 years with HIV RNA <50 copies/ml and CD4 count <400 cells/μL for >3.5 years); 20 immunological responders (IR) (ART>4 years with HIV RNA <50 copies/mL and CD4 count >600 cells/μL for >3.5 years) matched on nadir CD4 count; and 20 HIV-negative controls. Mucosal biopsies from the terminal ileum and the sigmoid colon, fecal samples and blood were collected. INR received probiotics (>1.2*1010 cfu/day with five mixed probiotic strains) for 8 weeks in an open-label phase II exploratory interventional trial (NCT02640625), followed by an end-of-study colonoscopy. Lamina propria mononuclear cells were isolated and after mitogenic stimulation, frequencies of Th17 (CD4+IL-17+), Th22 (CD4+IL-22+) and Th1 (CD4+IFNγ+) were measured by flow cytometry. Soluble CD14, IL-6, CD163, CRP, Zonulin, IL-18, intestinal fatty acid binding protein (iFABP), lipopolysaccharide binding protein (LBP), LPS and CD25 were analyzed by ELISA. The microbiome was characterized by 16S rRNA gene sequencing (V3-V4).
Results: INR had increased serum levels of iFABP and sCD14 compared with controls (p<0.05). The frequencies of gut mucosal Th17 and Th22 were not significantly different between the three groups. After stratifying INR and IR according to blood CD4/CD8 T cell ratio, INR with low (<0.5) CD4/CD8-ratio had significantly higher frequencies of gut mucosal Th17, Th22 and Th1 cells than IR with high (>1.0) CD4/CD8 T cell ratio (p<0.01). In INR, probiotics for 8 weeks significantly reduced the frequency of Th22 cells in terminal ileum (p<0.05), with a corresponding increase in mucosa-adherent bacterial diversity (Shannon Diversity Index, p<0.01 and Phylogenetic Diversity, p<0.05), whereas no significant changes were observed for the soluble markers.

Conclusion: INR had increased markers of impaired mucosal barrier function. INR with low blood CD4/CD8 T cell ratio had elevated frequencies of mucosal CD4 subsets, indicating a more pro-inflammatory tissue environment. The alterations were partially reversed by probiotics, providing a rationale for further trials of gut targeted treatment in INR.

207 INCREASED ADENOSINE SIGNALING WITH DIPYRIDAMOLE DECREASES GUT MUCOSAL TREG FREQUENCY

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Background: Adenosine (ADO) production is increased during inflammatory states to limit tissue damage. In a study evaluating the anti-inflammatory effect of dipyridamole (DP) among virally suppressed people with HIV (PWH), we evaluated how DP-induced increase in ADO signaling can affect gut mucosal T cell populations.
Methods: Virally-suppressed adults on ART were enrolled, randomized 1:1, to receive DP (100mg 4x/day) or placebo, double blinded, for 12 weeks. In a subset of participants, we obtained rectosigmoid biopsies at baseline and 12 weeks, and processed these biopsies into mucosal mononuclear cells (MMC) for flow cytometry studies. We evaluated frequencies of T cells in gut MMC, including frequencies of the regulatory T cell (Treg) and Th17 cell subset to assess changes after 12 weeks of DP vs placebo. Plasma levels of DP, inosine (initial ADO metabolite and surrogate for ADO levels), and urine cAMP (produced when ADO binds to its receptor) were measured by mass spectrometry. Linear regression models on log-transformed outcomes were used for the primary 12-week analysis.
Results: Nine DP and 9 placebo participants with data from both baseline and 12 weeks were included in the analyses. Median peripheral blood baseline CD4+ T cell counts were 718 and 666 cells/mm3 for DP and placebo, respectively (p=0.70). At visits when participants had detectable plasma DP (9/9 in DP and 0/9 in placebo), median plasma inosine and urine cAMP levels were higher compared with each participant's baseline (p=0.03 and p=0.05, respectively). Compared to placebo, DP participants had a significant decrease in absolute %Treg in gut mucosal CD4+ T cells from baseline to week 12 (5.99 to 2.09% for DP vs 2.91 to 4.76% for placebo; p=0.008). There was also a trend for increased gut mucosal %CD8+ T cells in the DP arm (36.0 to 40.9% in DP vs 40.7 to 35.3% in placebo; p=0.054). No differences were observed in the baseline to week 12 change in gut mucosal %CD4+ T cells, %Th17, and Th17:Treg ratios, or in baseline to week 12 change in peripheral blood CD4+ and CD8+ T cells and Treg.
Conclusion: Oral dipyridamole administered to PWH on ART was associated with a significant decrease in gut mucosal Treg frequencies and a trend for increased frequencies of gut CD8+ T cells. Our results suggest that modulating adenosine signaling among virally-suppressed PWH on ART could regulate gut mucosal immunity. How this regulation affects control of the gut HIV reservoir should be further studied.

208 PD-1HI CD4+ T CELLS ARE ASSOCIATED WITH REDUCED HIV-SPECIFIC RESPONSES

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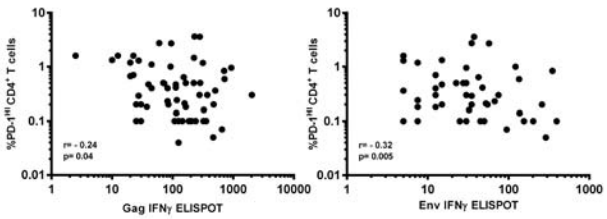
Background: T cells with high expression of PD-1 (PD-1HI), a marker of T cell exhaustion, persist among people with HIV on antiretroviral therapy (ART).To assess whether PD-1HI expression may reflect exhaustion of T cells targeting HIV, we determined whether the frequency of PD-1HI T cells is associated with reduced HIV-specific T cell responses.
Methods: Peripheral blood mononuclear cells from participants in ACTG A5321 with documented viral suppression on ART for at least 4 years (N=93) were analyzed for percentage of CD4+ and CD8+ T cells with PD-1HI expression as determined by flow cytometry. HIV-specific T cell immunity was determined by IFNγ ELISPOT in response to Gag, Pol, Env, Nef/Tat/Rev, Vpr/Vpf/Vpu peptide pools as well as CMV-pp65 and EBV BZLF-1 peptide pools.
Results: Frequencies of both CD4+ and CD8+ PD-1HI T cells pre-ART significantly correlated with levels of pre-ART HIV-1 RNA (r=0.28, p=0.01 and r=0.24, p=0.03, respectively; Spearman correlation). At 4 years of viral suppression with a median CD4+ T cell count of 681 cells/mm3, participants had the same median (Q1-Q3) frequencies of PD-1HI CD4+ (0.3%; 0.1-0.5) and CD8+ (0.3%; 0.2-0.6) T cells. Both CD4+ and CD8+ PD-1HI T cell frequencies showed negative correlations with IFNγ responses to all HIV peptides, although not all reached statistical significance. The %CD4+ PD-1HI T cells had significant negative correlations with Gag- and Env-specific responses (r= -0.24, p=0.04 and r= -0.32, p=0.005; Figure 1). A modest negative trend was observed with Pol (r= -0.2; p=0.08) and combined Vpr/Vif/Vpu (r= -0.22, p=0.07) peptide pools. The %CD8+ PD-1HI T cells showed a trend for a negative correlation with the same HIV peptide pools (Gag, r= -0.22, p=0.06; Env, r= -0.21, p=0.07). By contrast, no significant correlations were observed between PD-1HI T cell frequencies and responses to CMV or EBV peptides.
Conclusion: Peripheral blood frequencies of PD-1HI CD4+ T cells of people with HIV on ART were negatively associated with HIV-specific IFNγ responses, but not with CMV or EBV responses. These findings suggest that the PD-1HI CD4+ T cell subset contains HIV-specific cells that have decreased helper function and should be targeted to reverse immune dysfunction and improve immune control of HIV.



209 PROPORTION OF SIV-INFECTED MEMORY T HELPER SUBSETS CORRELATED TO SIZE OF POPULATION

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Background: Naïve CD4 T cells can differentiate into multiple functionally-defined memory CD4 T cell subsets. The types of memory CD4 T cells which exist in tissues of HIV/SIV-infected individuals are perturbed compared to healthy individuals. The mechanisms underlying these functional perturbations remain unclear. Here we assess whether viral infection of functionally-defined memory CD4 T cells might contribute, and how these populations of memory CD4 T cells contribute to, the total pool of infected CD4 T cells and plasma viremia.
Methods: Lymphocytes from Peripheral Blood Mononuclear Cells (PBMC), spleen, and Mesenteric Lymph Nodes (MLN) of SIV+ rhesus macaques were isolated and simulated for 6 hours with PMA and ionomycin in the presence of Brefeldin A. CD28+ memory CD4 T cells were studied and CCR6+/IL-17+ and IL-17- CD4 T cells (Th17 cells), CCR4-/IFNg+ and IFNg- CD4 T cells (Th1 cells), CCR4+/IFNg-/IL-17- CD4 T cells (Th2 cells) and FoxP3+ CD4 T cells (Tregs) were then flow cytometrically isolated, and the proportions of cells harboring SIV DNA were then assessed through qPCR.
Results: Viral DNA was detected in all subsets of memory CD4 T cells (irrespective of functionality, phenotype, or anatomic location). However, irrespective of anatomic site studied, we found that no one population of isolated memory, CD28+, CD4 T cells harbored more (or less) viral DNA than any other population of memory CD4 T cells.
Conclusion: Loss of CD4 T cells is a hallmark of progressive HIV/SIV infection and several studies have shown that Th17 cells are preferentially loss from mucosal tissues and lymph nodes that drain mucosal tissues. However, our data suggest that preferential infection of Th17 cells is unlikely to cause this immunological perturbation. Moreover, we see a positive correlation between the size of a T helper subset population and its contribution to the infected memory pool. Thus, functional differentiation of memory CD4 T cells is unlikely to influence their susceptibility to infection in vivo.

210LB NATURAL HOSTS OF SIV EMPLOY UNIQUE DNA METHYLATION PROGRAMS TO SILENCE THE CD4 GENE

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Background: African green monkeys (AGMs) downregulate CD4 to maintain a large population of CD4-CD8aa+ virus-resistant T cells which retain CD4-helper functions. AGMs can become aviremic and apparently cured of SIV by down-regulating CD4 to completion. Thus, understanding mechanisms of HIV/SIV coreceptor control in natural hosts has important implications.
Methods: To understand the mechanisms of this process, purified CD4+ T cells from four AGMs, closely-related Patas monkeys, and rhesus macaques were stimulated with SEB for 5 days and RNAseq was performed on divided cells induced to downregulate CD4 (AGM, Patas) and those that divide and maintain CD4 expression (rhesus).
Results: 1,917 differentially-expressed genes (DEGs) were revealed to be common among divided, CD4-downregulated AGM and Patas T cells, yet unique from divided rhesus CD4+ T cells. Genes well-known to be regulated in natural hosts were selectively present in this dataset, including CD4, CD8A, and CXCR6 (p= 1.27e-27, 2.68e-5, 6.72e-15, respectively). Pathway analysis of DEGs revealed proteins involved in DNA methylation to be enriched in CD4-downregulated AGM and Patas T cells (p=0.013). Gene expression of the Ten-eleven translocation protein 3 (TET3), was downregulated in AGM and Patas T cells induced to downregulate CD4, but not in divided CD4+ rhesus T cells (p=1.35e-11). Unique downregulation of TET3 in CD4-downregulated AGM T cells was confirmed independently by qPCR (p= 0.006). Methylation of cytosine is associated with gene silencing, and inhibition of the DNA methylation machinery with 5-aza-2 deoxycitidine inhibited CD4 downregulation in AGM CD4+ T cells induced to divide in vitro (p=0.005), indicating CD4 can be pharmacologically manipulated in natural hosts. Single clones of CD4-CD8aa+ AGM T cells revealed higher degrees of cytosine methylation at the CD4 gene promoter (p= 0.04) and a region well-within the gene body (p= 0.0001) when compared to these same genomic regions in CD4+ AGM T cells.
Conclusion: These results suggest AGMs uniquely employ epigenetic mechanisms to durably silence the CD4 gene. Targeting proteins involved in DNA methylation, such as TET3, could provide avenues for modulating SIV/HIV-1 coreceptor expression in hosts that become progressively HIV/SIV infected.

211 HIV-1 INFECTION IS ASSOCIATED WITH INCREASED USP18 AND DAMPENED TYPE 1 IFN RESPONSES

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Background: Although HIV-1 care has greatly advanced with antiretroviral therapy (ART), people living with HIV-1 (PLWH) still suffer from adverse outcomes. We and others have reported that immune activation contributes to unfavorable outcomes in PLWH. Type 1 interferons (IFN) are a potent and broad endogenous antiviral system that contribute to immune activation in PLWH. However, the efficacy of type 1 IFN against HIV-1 is diminished. We hypothesized that HIV-1 infection results in dampened type 1 IFN responses.
Methods: We treated peripheral blood mononuclear cells (PBMCs) from untreated PLWH (n=9), ART-suppressed PLWH (n=7), uninfected people who inject drugs (PWIDs, n=9), and healthy controls (n=3) with IFNα. We quantified by flow cytometry induction of phospho-STAT1 (pSTAT1), critical in type 1 IFN signaling, and upregulation of antiviral interferon-stimulated genes (ISG). We also stimulated purified CD4+ T cells with IFNα from the same subjects and measured the induction of several ISGs (MX2, ISG15, PKR, BST2) using quantitative RT-PCR (qPCR). In the same experiment, we quantified baseline expression of type 1 IFN regulators (USP18 and SOCS genes). We confirmed our findings in vitro by infecting primary CD4+ T cells with a GFP-tagged HIV-1, sorting GFP+ cells, and measuring baseline expression of type 1 IFN regulators. To validate our results, we interrogated an RNAseq dataset of CD4+ T cells from PLWH who were treated with pegylated-IFNα (PEG-IFN).
Results: We found that untreated PLWH had diminished induction of pSTAT1 and ISGs compared to uninfected PWID and healthy controls (p<0.05 for all); ART-suppressed PLWH had intermediate induction. Among three type 1 IFN regulators, baseline USP18 levels were best correlated with MX2 induction (r=-0.73; p<0.05; Figure) and with other ISGs. After infection of CD4 + T cells with GFP-tagged HIV-1, GFP+ CD4+ T cells had elevated levels of USP18 compared to GFP- CD4+ T cells (p<0.05). In PLWH who received PEG-IFN in vivo, baseline USP18 levels in activated CD4+ T cells were strongly associated and inversely correlated with MX2 induction (r=-0.77; p<0.05) and with the subsequent reduction in plasma HIV-1 RNA levels (r=-0.69; p<0.05).
Conclusion: Our data are the first from PLWH to support that USP18 upregulation facilitates HIV-1 evasion of endogenous antiviral control. USP18 has been reported to inhibit type 1 IFN responses in other viral infections, and could be exploited as a molecular target to control HIV-1.

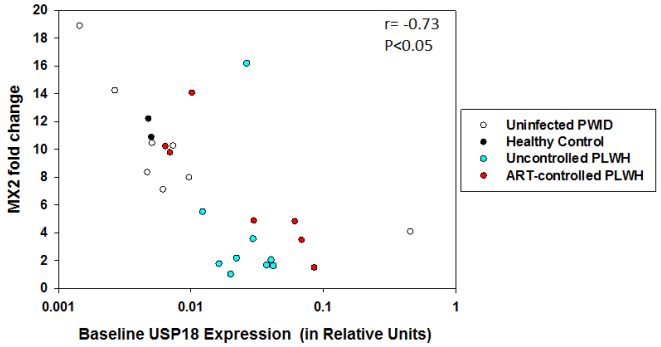

Figure. Baseline USP18 expression is inversely correlated with MX2 inducibility: Total CD4+ T cells were isolated from PBMCs from uninfected PWIDs (n=9), healthy control (n=3), uncontrolled PLWHs (n=9), and ART-controlled PLWHs (n=7), and stimulated with universal type 1 IFN for 6 hours. The level of baseline 18 expression and MX2 induction was quantified by qPCR, after normalizing to several housekeeping genes(RPLP0, YWHAZ, and SDHA). MX2 induction was calculated by computing the delta-delta Ct value of MX2 in type 1 IFN stimulated cells, normalized to unstimulated cells for each patient.

212 SINGLE HOUSING OF MACAQUES INCREASES THE IMMUNE IMPACT OF SIV INFECTION

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Background: Simian immunodeficiency virus (SIV)-infected macaques are an essential animal model for the study of HIV infection, especially in the quest for an effective cure or vaccine. Macaques are a social species, yet are often singly housed for infectious disease research studies. Singly housed uninfected macaques show signs of stress, including decline in CD4+ T cell count and other changes in their immune response. SIV also causes perturbations to the immune response, as reflected most prominently by the decline in CD4+ T cell counts that is commonly used to monitor disease progression, yet the effect of single housing on the progression of SIV infection has yet to be explored. In the context of SIV and HIV, stress has previously been demonstrated to result in lower CD4+ T cell counts, more T cell activation, higher viral loads and increased mortality. We therefore hypothesized that singly housed SIV-infected macaques would demonstrate a greater impact on the immune system and less control of viral replication compared with singly housed SIV-infected macaques.
Methods: We compared retrospective data on lymphocyte subset counts, T cell activation and viral loads from 35 singly and 41 socially housed SIV-infected pigtailed macaques (Macaca nemestrina) for three pre-infection timepoints and two post-infection timepoints during acute infection using linear mixed effects regression modeling.
Results: Singly housed macaques demonstrated a more profound decline in the number of circulating CD4+ T cells ($P = 0.0012$), CD8+ T cells ($P = 0.0003$) and total lymphocytes ($P < 0.0001$) throughout acute infection compared to socially housed macaques, with the magnitude of CD4+ T cell decline in socially housed animals more closely mirroring that seen in HIV-infected patients during acute infection. We additionally observed a greater percentage of circulating activated CD69+ CD4+ T cells ($P < 0.0001$) and CD69+ CD8+ T cells ($P < 0.0001$) in singly housed macaques. Singly housed macaques furthermore had higher viral loads in the plasma ($P < 0.001$) and cerebral spinal fluid ($P < 0.001$) throughout acute infection compared to socially housed macaques, and greater variability in plasma viral load data ($P < 0.0001$).

Conclusion: Single housing of SIV-infected macaques may provide an exogenous cause of immune modulation and introduce increased variability in data, with the potential to confound results, reduce the translational value of the model and interfere with reproducibility.

213 ORAL CYTOKINE EXPRESSION IS LINKED TO ORAL HIV-1 LEVELS IN ACTG A5254

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Background: HIV infection is known to disrupt oral mucosal immunity, but the pathogenesis of this immune dysregulation remains unknown. We determined the levels of 11 soluble immune mediators in oral washings of people with HIV (PWH) with varying levels of plasma viremia and CD4+ T cell counts. We also evaluated whether these immune mediators are associated with levels of HIV in blood and oral washings with the aim of characterizing the mucosal immune response at variable stages of HIV infection.
Methods: Oral washings were obtained from participants of ACTG A5254, a cross-sectional study of PWH to evaluate oral complications of HIV. Participants were divided into 4 strata: A (n=148; 52% on ART), CD4≤200 cells/mm3, plasma HIV-1 RNA (VL)>1000 cps/mL; B (n=82; 98% on ART), CD4≤200, VL≤1,000; C (n=29; 21% on ART), CD4>200, VL>1000; D (n=29; 100% on ART), CD4>200, VL≤1000. Levels of soluble markers were tested in oral washings using a multi-bead fluorescent platform, and were compared between strata. Associations between soluble marker levels and HIV in plasma and oral washings as well as CD4+ counts were determined.
Results: Stratum (St) A participants (CD4 <200, VL >1000) had higher levels of pro-inflammatory markers IL-6, IL-17, TNFα, IL-1β, and IFNγ compared to St B and St D which had VL<1000 and where 98-100% of participants were on ART (p=0.02 to p<0.0001; Kruskal-Wallis with Dunn's post-test, adjusted for multiple comparisons), but were not different from St C. Two pro-inflammatory markers, IL-12p70 and IL-8, and the anti-inflammatory marker IL-10 differentiated St A from the other 3 strata (p=0.046 to p<0.0001). St B and D had no differences in levels of the soluble markers except for IFNγ (p=0.04). Oral HIV levels correlated with plasma HIV (r=0.76; p<0.0001, Spearman) and with IL-6, IL-1β, IL-8, TNFα, IFNγ, and IL-10 (all r>0.4; p<0.001). Meanwhile, plasma VL only correlated with TNFα, IFNγ, and IL-10 (all r>0.4; p<0.001). No correlations were seen with IL-2, and only modest (r<0.35) correlations were seen with IL-17. No significant correlations were observed with CD4 count.
Conclusion: Our results suggest that high levels of oral HIV rather than low CD4 counts or plasma HIV are more linked to production of oral immune mediators. Despite severe immunosuppression, participants with AIDS demonstrated elevated levels of cytokines corresponding to both Th1 and Th2 T cell responses. The interplay of HIV and these immune mediators could be an important factor in the oral health of PWH.

214 HIV INFECTION AND SMOKING DEFERENTIALLY REGULATE ALVEOLAR MACROPHAGES

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Background: HIV infection impacts immune cells in the lung leading to pulmonary complications which persist with antiretroviral therapy (ART). Alveolar macrophages (AM) are principle immune cells type in bronchoalveolar compartment and as such play a pivotal role in host defense against pathogenic microorganisms and tissue remodeling. Examination of the effect of HIV on AM is complicated by the high prevalence of smoking in HIV infected subjects from the United States. Smoking increases auto-fluorescence of AMs, inhibiting the reliability and resolution of traditional flow cytometry. Cytometry by Time of Flight (CyTOF) utilizes pure metal conjugated antibodies and detection by mass cytometry, which effectively bypasses auto-fluorescence. Here, we utilize CyTOF to comprehensively evaluate the effect of HIV infection and smoking on AM.
Methods: Bronchoalveolar lavage (BAL) cells from 10 untreated HIV-infected non-smokers, 9 untreated HIV-infected smokers, 10 HIV-seronegative non-smokers and 9-HIV-seronegative smokers was subjected to traditional flow cytometry and CyTOF. Our CyTOF panel consisted of 34 unique markers and phenotypic analysis was performed using traditional methods and three unbiased clustering algorithms.
Results: Compared to those without HIV we found a decrease in CD206 (p=0.0002), CD71 (p=0.03) and CD164 (p=0.002) positive cells, indicating a loss of alternatively activated AMs (M2) caused by HIV infection. The loss of M2 macrophages indicates an increased inflammatory environment. Smoking increased AM expression of CCR2 (p=0.007) which is a marker of inflammatory macrophages. Together, compared to healthy non-smokers, smoking and HIV increased CXCR4 expression on AM (p=0.004) demonstrating increased susceptibility to X4 tropic HIV infection.
Conclusion: While the aim of characterizing alveolar macrophages during HIV infection and smoking was our primary goal, this study also demonstrates the sensitivity of mass cytometry, and its ability to detect significant differences between patient groups which would have otherwise been masked by auto-fluorescence. Overall, these findings indicate that HIV and smoking drive alveolar macrophages toward an inflammatory state, leading to an overall more inflammatory environment in the lung.

215 HUMAN INFECTION WITH ZOONOTIC SIMIAN FOAMY VIRUSES: ALTERED CD4 AND CD8 T LYMPHOCYTES

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Background: A spillover of simian foamy virus (SFV) to humans, following bites from infected nonhuman primates (NHPs), is ongoing in exposed populations. These retroviruses establish persistent infections of unknown physiological consequences to the human host. Replication-competent virus can be isolated from human blood cells, and SFV DNA has been detected in blood lymphocytes. Human infection with zoonotic SFV is thus a natural model to study the key steps of the emergence of retroviruses. Here, we aimed to assess whether SFV infection is associated with changes in the phenotype of peripheral blood mononuclear cells (PBMCs).
Methods: We performed a case-control study to compare 15 Cameroonian hunters infected with gorilla SFV and 15 controls matched for age and ethnicity. All participants were men and had been injured by a NHP. Ages ranged from 22 to 75 years. SFV infection was defined by positive results for both western blots and polymerase chain reaction assays. The duration of SFV infection ranged from 1 to 45 years. CD4 and CD8 T lymphocytes, B and NK lymphocytes, and their major subsets were quantified by flow cytometry. Wilcoxon signed-rank tests were used to compare cases and controls.
Results: The cases had significantly higher percentages of CD8 T lymphocytes and lower CD4/CD8 ratios than controls (median: 17.6% vs. 13.7%, P = 0.03 and 3.1 vs. 3.5, P = 0.04, respectively). The percentage of CD4 T lymphocytes were similar for cases and controls (47.7% vs. 46.9%, P = 0.73). Programmed cell death 1 (PD-1) expression on memory CD4 T lymphocytes was higher for cases than controls (31.7% vs. 24.7%, P = 0.001). B and NK lymphocytes showed no differences between cases and controls (8.7% vs. 9.9%, P = 0.70 and 7.5% vs. 6.0%, P = 0.78, respectively).
Conclusion: This case-control study of apparently healthy SFV-infected Cameroonian hunters showed phenotypic differences among blood T lymphocytes. Lymphocyte subsets affected in chronic untreated HIV infection were also affected in chronic SFV infection, albeit to a lower extent. The decreased CD4/CD8 ratio and increased expression of the exhaustion marker PD-1 are consistent with a T-cell response against viral infection. Although SFV has been reported to be nonpathogenic, our findings of T-lymphocyte activation may have implications for infected individuals.

216 CHARACTERIZATION OF PLASMA METABOLITE PROFILE IN HIV+ PERSONS WITH OR WITHOUT IRIS

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Background: Immune reconstitution inflammatory syndrome (IRIS) is an aberrant inflammatory response against an underlying infection after initiation of antiretroviral therapy (ART) in HIV+ persons and is associated with significant morbidity and mortality. Inflammation and T cell activation are dependent

on cell metabolism and specific metabolic pathways could regulate T cell activation. We hypothesized that differences in metabolic profile could be used as biomarkers to further elucidate pathogenesis of IRIS.
Methods: Non-targeted global metabolomic profiling was performed on plasma samples derived from a perspective longitudinal study of 30 HIV patients (17 HIV non-IRIS and 13 HIV IRIS) at pre-ART (CD4 ≤ 100 cells/mm3), 1-month post-ART, and 12-month post-ART timepoints by Metabolon, Inc. Metabolites were identified by liquid chromatography/mass spectrometry followed by comparison to a reference library. Plasma cytokines were measured using Meso Scale multiplex cytokine detection kit then correlated with metabolic pathways via Spearman correlation.
Results: A total of 832 metabolites were identified in plasma samples. Comparing HIV IRIS and HIV non-IRIS groups, more differentially expressed metabolites reaching statistically significance (($p \leq 0.05$) were identified at pre-ART and 1-month post-ART time points than the 12-month post-ART time point. Lipid and amino acid metabolites composed the majority of the compounds that achieved statistical significance. The IRIS group had significantly higher levels of select acylcarnitines, and lower levels of plasmalogen and phosphatidylcholine at pre-ART. Amino acids including tryptophan, glutamate, glycine, and tyrosine metabolism were found to be differentially expressed in IRIS and non-IRIS groups at pre-ART and 1-month post-ART. Spearman correlations revealed that glutamate metabolism was positively correlated with TNF, while tryptophan and glycine metabolism were negatively correlated with IL-10, and D-dimer respectively in the IRIS group at pre-ART.
Conclusion: HIV+ persons who develop IRIS have a distinct metabolic profile with perturbed lipid and amino acid metabolism that is associated with known inflammatory mediators of IRIS. These data suggest that evaluation of immunometabolism and its role in inflammation associated with IRIS warrants further investigation.

217 EXTRACELLULAR VESICLE–ASSOCIATED CYTOKINES IN HIV-INFECTED HUMAN EX VIVO TONSILS

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Background: Cytokines play an important role in HIV infection. Some of these cytokines are associated with extracellular vesicles (EVs) either on their surface or being encapsulated. Here, we investigated the modulation of EV-associated cytokines during HIV infection and antiretroviral therapy (ART) in human ex vivo tonsils.
Methods: Ex vivo tonsils were infected with HIV-1 strains, X4-LAI04 or R5-SF162. HIV was either allowed to replicate for 15 days, or tissues were treated with ART (3TC and AZT) at day 2 post-infection. 33 cytokines in soluble or EV-associated forms were evaluated with multiplexed bead-based assays.
Results: Early in HIV infection there was a significant increase in soluble IFNα, MCP-1, MIG, MIP-1α, MIP-1β, RANTES, and TNFα. EV-associated cytokines that significantly increased were IL-13, IP-10, and MIP-1β for X4, and MIP-1α, MIP-1β, and RANTES for R5. In addition to increased concentrations, some cytokines also shifted their distribution: MIP-1α and MIP-1β to a higher percentage in EV-associated form, and RANTES to more soluble. In cumulative analyses, in X4-infected tissues there was an increase in the release of soluble IL-2, IL-21, IFNα, MIP-1α, MIP-1β, RANTES, and TNFα, and decrease of TGF-β. R5 infection increased tissue production of MIP-1α, MIP-1β, and RANTES. X4 significantly increased total EV-associated IL-2, IL-7, IFNα, M-CSF, MIP-1α, MIP-1β, RANTES; R5 infection led to increased EV-associated IL-2 and RANTES. ART treatment halted HIV-1 replication, but most cytokine levels remained similar to those in HIV-infected controls, including MIP-1α, MIP-1β, and RANTES. In X4-infected tonsils treated with ART there was a significant decrease in only soluble IL-7, IP-10, and MIG, and an increase in IL-6; in R5-infected tissues treated with ART there was a decrease in soluble IL-1α, IL-1β, IL-16, IL-17, IL-18, MIG, and MIP-3α. ART treatment restored the levels of some soluble cytokines but did not restore EV-associated cytokines.
Conclusion: Cytokine levels increased during HIV infection in both soluble and EV associated forms. Cytokines most upregulated by HIV did not decrease even after 13 days of ART. The most affected EV-associated cytokines were chemokines, which were not restored by ART. ART-treated ex vivo infected human tissues provide a new model to study tissue activation after HIV replication is suppressed. These studies will assist in desiphering mechanisms of pathologies that develop in ART-treated patients.

218 MASSIVE RELEASE OF PLATELET-DERIVED EXTRACELLULAR VESICLES DURING HIV INFECTION

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Background: Extracellular Vesicles (EVs) derived from different cell types by ectocytosis (microvesicles) or endocytosis (exosomes) may serve as intercellular messengers in pathogenic processes. Circulating mitochondrial DNAs (mtDNA) are potent danger-associated molecular patterns (DAMPs) found in inflammatory diseases including viral infections. We evaluate the EVs profile and plasma mtDNA levels in a well-characterized cohort of HIV-infected patients and controls.
Methods: Plasma samples from HIV-infected patients from the HIV Biobank-Spanish HIV/AIDS Network and 2 hospitals in Galicia were selected. Five groups were defined: 1) treatment-ART; 2) receiving ART with non-detectable viremia (ND) > 1 year); 3) elite controllers (EC) (<50 copies/mL without ART > 1 year); 4) viremic controllers-VC (HIV-RNA >50 and < 2000 copies/mL without ART for more than 1 year); and 5) a control group of HIV negatives. EVs (<1µm, CD9+) were quantified and characterized by flow cytometry using monoclonal antibodies targeting their source CD61/CD41 for platelets; CD16/CD11b for neutrophils. MitoTrackerDeepRed identified EVs containing mitochondria. mtDNA was quantified using a quantitative real-time PCR assay.
Results: 120 HIV-infected patients (30 naïve, 30 ND, 30 EC, and 30 VC) and 30 controls were included. The table shows the main characteristics of the study population and results. EVs numbers were expanded at least 10 fold in all HIV-infected groups compared to controls' counts. Most EV had platelet markers (>79%) within the HIV groups, and few had neutrophil markers (< 2%). A minority of platelet-derived EVs contained mitochondria, but most neutrophil-derived EVs did. Mitochondria+ EV were less frequent for those on ART than in other HIV+ groups. A positive correlation was found between the number of platelet-derived mitochondria+ EVs and total plasma mtDNA levels (rho=0.727; p<0.001) but not for neutrophil-derived mitochondria+ EVs. Mitochondrial density (MFI) was greater in controls' EVs than in HIV-infected groups, lowest levels for those on ART.
Conclusion: A massive release of platelet-derived EVs occurs during HIV infection regardless of HIV status. EVs count correlates with plasma mtDNA levels. HIV infection and ART both appear to diminish mitochondrial density in EVs yet as EVs numbers are expanded, total mitochondrial levels in plasma are preserved in HIV infection or increased. The mechanisms underlying these perturbations in EVs levels and the mitochondria within them in HIV infection are not known.

	Controls (N=30)	Naïve (N=30)	ND (N=30)	EC (N=30)	VC (N=30)	p
Age (years)	36.0 [29.0-41.0]	41.5 [33.0-52.0]	52.0 [43.0-56.0]	53.0 [44.0-58.0]	51.0 [39.0-54.0]	<0.001
Sex (male)	50.0 (15)	71.0 (22)	66.7 (20)	50.0 (15)	56.7 (17)	N.S
Days since HIV diagnosis	NA	7 [0-64]	4803 [2316-7373]	5246 [2048-8249]	2347 [787-7421]	<0.001
HIV Viral load (copies/mL)	NA	27450 [9700-110000]	< 20	50 [37-50]	361 [92-758]	<0.001
CD4/CD8 ratio	1.56 [1.43-2.05]	0.36 [0.25-0.70]	1.05 [0.77-1.31]	0.92 [0.56-1.32]	0.78 [0.65-0.99]	<0.001
mtDNA copies/µL [IQR]	23.40 [11.95-41.85]	29.15 [11.10-60.50]	33.55 [14.65-83.00]	58.0 [36.05-136.0]	105.25 [53.50-169.0]	<0.001
Total EVs count	6982.3 [5185.0-8970.8]	68467.8 [27298.6-145591.2]	116385.1 [66713.0-220466.4]	120008.9 [29266.0-377810.8]	139602.2 [81729.2-259126.8]	<0.001
EVs platelet-derived (%)	40.65 [25.60-51.10]	84.85 [71.90-89.90]	91.80 [85.5-94.5]	79.70 [64.70-91.40]	81.95 [72.00-89.60]	<0.001
EVs platelet-derivedMito+ (%)	29.4 [19.3-37.2]	22.15 [16.6-25.1]	13.4 [11.1-21.7]	20.9 [10.6-36.7]	21.3 [10.8-29.6]	<0.001
EVs neutrophil-derived (%)	6.20 [2.69-24.20]	1.15 [0.35-2.45]	0.15 [0.08-0.54]	1.04 [0.31-6.62]	1.88 [0.35-4.52]	<0.001
EVs neutrophil-derivedMito+ (%)	88.9 [72.5-93.1]	88.6 [57.9-98.1]	48.2 [34.8-81.7]	65.9 [31.4-84.3]	64.1 [30.1-85.9]	<0.001
Mitochondrial MFI	1346 [1101-1799]	720 [691-1260]	628 [584-754]	764.5 [567-1038]	711 [632-796]	<0.001

219 IN VIVO MODEL FOR HBV/HIV COINFECTION STUDIES

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Background: The interplay between innate immune responses of hepatocytes to HBV in the setting of ongoing HIV-1 replication require in vivo model system, and the underlying mechanisms by which HBV-induced liver pathogenesis, and mechanisms by which HIV co-infection accelerate that process remain unknown due in large part to the lack of small animal models. Such model is crucial for the development of novel therapies, treating HBV/HIV-coinfections and associated liver diseases. There are several unresolved problems in mice co-transplanted with human hepatocytes and immune cells: transplantation of mismatched by HLA genotypes hepatocytes and hematopoietic stem cells contain a risk for allograft rejection and the low functionality of adaptive immune responses. We hypothesize that human hepatocyte transplanted mice, infected with HBV and co-transplanted with human HIV-1 infected or uninfected macrophages will reproduce the features of viral interaction.
Methods: TK-NOG mice were transplanted with human hepatocytes, and after confirmation of the human albumin concentration in peripheral blood, animals were infected with HBV 107 GE/mouse (subtype D *ayw*). Following confirmation of HBV DNA presence in peripheral blood (~1.5x10^4 copies/ml), animals were injected with human monocyte-derived macrophages (MDM) or HIV-exposed MDM (5x10^6 cells/mouse i.p.) and controls kept without MDM. Animals were observed for 51 days and levels of HIV RNA, HBV DNA, HBsAg in plasma were monitored. At end-point liver tissues were analyzed for histopathology, presence of viruses and human MDM by RT-PCR, and staining for human cells and viral proteins.
Results: Multiphasic HBV viral kinetics – increase HBV DNA by day 13 and decline by day 51 in the presence of MDM, and exponential increase in HIV viral load were observed in the blood reaching steady levels at ~10^6 copies/ml by day 38. The plasma levels of HBsAg concentration also peaked at this point. Mice with HBV+HIV-MDM had higher content of HBV DNA, HIVgag RNA and human CD45 transcripts. Human hepatocytes in HBV infected mice showed strong expression of human HLA-DR, and proliferation. The plasma albumin concentration increased two folds in coinfected animals.
Conclusion: This study utilizes a novel humanized mouse model which will fill the critical knowledge gaps on the mechanism by which HBV/HIV co-infection accelerates liver diseases and is the first model to observe changes in both viral replication pattern and tissue histopathology.

220 AN EARLY DECLINE IN HIV ANTIBODY BREADTH PREDICTS MORE RAPID DISEASE PROGRESSION

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Background: The HIV immune response evolves during infection and may be impacted by factors such as antiretroviral treatment (ART). We used a massively-multiplexed system to profile the antibody (Ab) response to HIV infection in individuals with early to late stage infection and to evaluate the relationship between Ab diversity and ART initiation.
Methods: Ab profiles were analyzed with the VirScan assay. This assay uses phage immunoprecipitation sequencing to quantify Ab binding to >3,300 HIV peptides spanning the HIV genome. The analysis included 403 samples from 57 African women with known duration of HIV infection (14 days to 8.7 years). ART was started at a CD4 count <250 cells/mm^3; 32/57 women started ART during the study period (ART group). For each sample, network graphs were used to calculate the number of unique non-overlapping epitopes that had high levels of Ab binding (Ab breadth). We measured the change in Ab breadth 9-24 months after infection and compared time to ART initiation among those with declining vs. stable or increasing Ab breadth. We also analyzed the associations between the rate of change in Ab breadth over time, ART initiation, and other factors.
Results: In most persons, Ab breadth increased during the first 6 months of infection. In the non-ART group, Ab breath reached a plateau ("Ab breadth set point") 9-12 months after infection. In the ART group, analysis using a Cox proportional hazards model showed that those who had stable or increasing Ab breadth 9-24 months after infection started ART later than those with decreasing Ab breadth (log-rank test for earlier ART initiation: p=0.009, hazards ratio: 0.29, 95% CI: 0.11, 0.78, p=0.014). A faster decline in Ab breadth was correlated with lower baseline CD4 cell count (p=0.002) and higher pre-ART viral load set point (p=0.001). Ab breadth stabilized after ART initiation at levels similar to those seen in early HIV infection.
Conclusion: Deep profiling of the antibody response to HIV infection identified a novel feature of the anti-HIV immune response, Ab breadth, that was associated with clinically-significant outcomes.

221 HIV INFECTION ALTERS DYNAMIC MACROPHAGE: T-CELL INTERACTIONS TO PROMOTE VIRAL SPREAD

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Background: Recent studies suggest that tissue macrophages and microglia represent an important, long-lived HIV reservoir in vivo. While T cells are the main target of HIV infection, antigen-presenting cells like macrophages contribute to the activation/maintenance of these cells. HIV is known to be transmitted via cell-cell contact, but the cellular and molecular dynamics of HIV spread using 3D systems recapitulating the lymphoid structures remains unclear.
Methods: We developed a model to dynamically characterize macrophage:T cell contacts within 3D collagen matrices. HIV-infected monocyte-derived macrophages (MDM) were co-cultured with autologous CD4+ T cells and changes in migration behaviors and cell-cell contact dynamics were visually characterized using live-cell microscopy. In parallel, viral spread kinetics was measured in collagen gels. The role of virus- and host-derived adhesive molecules in facilitating stable MDM:T cell contacts were assessed using blocking antibodies. The efficacy of various antiretroviral drugs was also explored during dynamic cell-cell transmission.
Results: We observed substantial changes in MDM morphology following HIV infection: the formation of long, irregular podosomal extensions were a direct result of Nef expression. While Nef-induced podosomes did not enhance T cell contacts, HIV infection of MDM led to a dramatic increase in stable conjugates. We show that such stable contacts are a pre-requisite for enhanced HIV dissemination. Antiretroviral drugs at concentrations that completely suppresses infection by cell-free HIV, only reduced infection to 43±19% (raltegravir), while tenofovir and emtricitabine reduced infection to 36±5% and 71±6%, respectively. We further show that gp120:CD4 interactions are key regulators of MDM:T cell contacts, which is further supported by LFA-1:ICAM-1 adhesive contacts. Blockade of LFA-1 led to destabilization of MDM:T cell contacts and translated into a substantial reduction (~70%) in infection. Interestingly, blocking LFA-1:ICAM-1 contacts caused long tethering events, which we interpret as a result of incomplete restraint of motile T cells.

Conclusion: This study highlights the importance of MDMs as a key contributor of persistent T cell infection through their ability to facilitate numerous cell-cell contacts in lymphoid tissues. Our 3D imaging approach allows for T cells to randomly migrate and engage HIV-infected macrophages, modeling their initial encounters and mimicking the main concepts of the same in-situ environment.

222 THE ROLE OF MIGRATORY DENDRITIC CELLS IN ESTABLISHING HIV DISSEMINATION

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Background: HIV-1 dissemination from the genital mucosal tract to the lymphoid organs is the first critical step towards systemic infection. HIV-1 can disseminate either as free-virus, or it can be transported to lymphoid tissues by migratory cells. Our previous studies strongly argued that the trafficking of cell-associated HIV-1 from the genital mucosa to lymphoid organs played a dominant role in viral spread early after sexual transmission in humanized mice. Here, we further extend these observations by addressing the role of migratory DCs in the capture, retention and transfer of HIV-1 to susceptible T cells through trans-infection, a route of viral transmission that occurs through cell-cell contact.
Methods: To characterize the molecular and cellular aspects of DC:T trans-infection, we modeled the dynamics of DC:HIV and DC:T cell interactions within a 3D collagen matrix that recapitulates the stromal networks of the lymph node. Two-photon microscopy was performed to visualize (1) the cellular dynamic of HIV capture and retention by DCs, and (2) the interaction between HIV-bearing DCs and T cells. We used blocking antibodies to dissect the molecular underpinnings of HIV capture by DCs, and the role of adhesion molecules ICAM-1 and LFA-1 in stabilizing DC:T cell contacts during trans-infection. To determine the role chemoattractant receptor-mediated DCs such as S1PR1 and CCR7 play in spreading HIV, we employed transwell chemotaxis assays and live-cell imaging studies of in situ DC migration within explanted mouse ear slices.
Results: Mature DCs captured HIV-1 on the cell surface, mediated by Siglec-1, and that captured virus rapidly formed dense clusters near the uropodia of migrating DCs. The chemotactic responses of HIV-1 bearing DCs towards lymph node homing chemokines CCL19/21 and S1P were preserved. HIV-bearing DCs engaged in progressively stable contacts with T cells in 3D collagen, which was a pre-requisite for rapid HIV transmission at the contact site. Consistent with this, HIV-bearing DCs transmitted virus was five-fold more efficient at infected T cells compared to cell-free virus, and that LFA-1:ICAM-1 adhesive contacts played a critical role in this process.
Conclusion: DCs retain their ability to migrate into lymph nodes following virus capture, and are able to engage T cells and form stable DC:T cell interactions. This suggests that blocking the movement of HIV+DCs out of the genital mucosa may be a novel approach to restrain virus dissemination and limit systemic viremia.

223 CHARACTERIZATION OF SHIV IMMUNOPATHOGENESIS IN RHESUS MACAQUES

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Background: Simian-human immunodeficiency viruses (SHIVs) have been utilized to test vaccine efficacy and characterize mechanisms of transmission and pathogenesis. However, the SHIV model has a significant limitation in that the majority of strains have been created using HIV-1 Env sequences from laboratory-adapted or multiply passaged viruses. Recently, a newly developed SHIV that incorporates the vpu-env(gp140) sequence from a transmitted/founder HIV-1 subtype C strain (CH505) was shown to retain attributes of primary HIV-1 strains. Here, we characterize the immunopathogenesis of this novel SHIV in peripheral and mucosal tissue of male rhesus macaques.
Methods: Male rhesus macaques (n=7) underwent multiple low-dose intra-rectal challenges with SHIV.C.CH505.375H.dCT. Viral challenge was halted when animals tested PCR positive for viral sequences in plasma. Blood, colon and rectum biopsies were collected pre- and post-infection and used to monitor plasma viral load and intestinal immune populations.
Results: All animals became productively infected within 6 challenges and exhibited similar acute viral replication kinetics, including a median peak viral load of $1x10^6$ RNA copies/ml plasma (range=$0.89x10^6$ – $5.5x10^6$) reached by two weeks post-infection. Set point viral loads ranged from $3.8x10^3$ – $0.99x10^6$ RNA copies/ml plasma. At week2-post-infection, CCR5+ CD4+ T cells were significantly decreased in both the colon (p=0.01) and the rectum (p=0.001) compared to pre-SHIV infection. The frequency of CCR5+CD4+ T cells remained consistently lower than pre-SHIV infection levels through week8- and week16-post-infection. In addition, by week16-post-infection, there was a significant depletion of CCR6+CD4+ T cells in both the colon (p=0.05) and rectum (p=0.01) compared to pre-SHIV infection.
Conclusion: In line with previous findings, we demonstrate that SHIV.C.CH505.375H.dCT is capable of infecting and replicating efficiently in rhesus macaques after low-dose intra-rectal challenge, resulting in peripheral viral kinetics similar to that seen in SIV/HIV infection. Furthermore, our findings indicate that this virus is capable of eliciting intestinal immunopathology typical of SIV/HIV, including decreases in the intestinal frequency of a major cellular target population, CCR5+ CD4+ T cells. These findings affirm the value of this novel SHIV as a tool to evaluate SIV/HIV vaccine efficacy and viral pathogenesis.

224 PLASMA CXCL13 AS A MARKER OF HIV DISEASE PROGRESSION AND SYSTEMIC IMMUNE ACTIVATION

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Background: CXCL13 is preferentially secreted by Follicular Helper T cells (TFH) to attract B cells to germinal centers. Plasma levels of CXCL13 have been reported to be elevated during chronic HIV-infection, however there is limited data on CXCL13 levels during early phases of infection. Moreover, the contribution of CXCL13 to disease progression and systemic immune activation have been poorly defined. Herein, we assessed the relationship between plasma CXCL13 and validated markers of disease progression.
Methods: Study samples were collected in 146 people living with HIV (PLWH) who were in early (EHI) and chronic (CHI) HIV infection and 35 elite controllers (EC) compared to 28 uninfected controls (UC). A subset of 25 progressors were followed prospectively for 2 years, 11 of whom initiated ART. Plasma levels of CXCL13 were compared with CD4 T cell count, CD4/CD8 ratio, plasma viral load (VL), markers of microbial translocation (LPS, sCD14, and LBP), markers of B cell activation (total IgG, IgM, IgA, and IgG1-4), inflammatory cytokines (TNF-α), and immune activation markers (frequency of CD8+CD38+DR+ T cells, and PD-1 expression on CD4+ T cells).
Results: Plasma levels of CXCL13 were elevated in EHI (127.9±64.9 pg/mL) and CHI (229.4±28.5 pg/mL) compared to EC (71.3±20.1 pg/mL) and UC (33.4±4.9 pg/mL). Longitudinal analysis demonstrated that CXCL13 was significantly elevated after 24 months without ART (260.5±30.4 pg/mL, p<0.001) and was reduced without normalization 24 months after ART initiation (81.5±10.3 pg/mL, p=0.002). CXCL13 correlated positively with VL (r=0.390; p<0.001), negatively with CD4 T cell count (r=-0.298; p<0.001), CD4/CD8 ratio (r=-0.359; p<0.001), positively with markers of microbial translocation LPS (r=0.225; p=0.007) and sCD14 (r=0.260; p=0.03), markers of B cell activation total IgG (r=0.422; p=0.003), IgG1 (r=0.276; p=0.05), TNF-α (r=0.280; p<0.001), frequency of CD38+HLA-DR+ CD8 T cells (r=0.543; p=0.008) but not CD38+HLA-DR+ CD4 T cells (r=0.287; p=0.366), and PD-1 expression on CD4 T cells (r=-0.460; p=0.03).
Conclusion: Plasma CXCL13 levels increased during HIV disease progression. Early initiation of ART may reduce plasma CXCL13 and B cell activation without normalization. CXCL13 represents a novel marker of HIV disease progression and inflammation at the early and chronic phases of the infection, and may be a predictor of non-AIDS events.

225 MODULATION AND PATHOGENESIS OF HIV-1 X4 EVOLUTION IN DISEASE PROGRESSION

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Background: Emergence of CXCR4-using HIV-1 (X4) expands host cell range and is associated with advanced stage disease in the absence of therapy. Yet, the developmental program modulating X4 evolution remains elusive. This study tracked X4 evolution genetically during the natural history of pediatric HIV-1 infection to develop sequence profiles associated with functional characteristics of entry and tropism.

Methods: Archived longitudinal blood samples were collected over 2-10 years from 8 untreated perinatally HIV-infected children. Disease progression was monitored by CD4 T-cell inflection point and CD4 T-cell decline to <15%. A total of 831 HIV-1 Env single genome sequences were generated. Env evolution was inferred by time-calibrated phylogenetic trees. CCR5 and CXCR4 coreceptor use was predicted by position specific scoring matrix and verified functionally using coreceptor indicator cells. Single-cycle viruses pseudotyped with Env V1-V5 were constructed to test tropism and entry efficiency into blood lymphocytes and monocyte-derived macrophages (MDM).

Results: Infection was initiated by R5 variants in 7 cases or by X4 viruses in 1 case. R5 viruses persisted over years in 2 cases, while R5X4- and X4-predicted genotypes evolved from low frequency R5 viruses in 5 individuals prior to CD4 decline. Alignment of R5 and R5X4 Env sequences identified discontinuous nonsynonymous changes that altered neutralizing antibody epitopes initially in V1V2 and subsequently in V3. Single-cycle viruses generated using R5 and R5X4 Envs displayed entry into CD4 T-cells, but only R5X4 viruses infected MDM. In contrast to R5, R5X4 Envs were more sensitive to sCD4 (CD4 antagonist) or 447-52D (V3 antibody), indicating increased access to CD4 binding site and the V3-loop, but less sensitive to Maraviroc (anti-CCR5) or T20 (fusion inhibitor), consistent with increased CCR5-use and fusion efficiency.

Conclusion: X4 evolution follows a complex developmental pathway that includes R5 ancestral strains and R5X4 intermediates, expands HIV-1 cell tropism, enhances viral entry via increased access to the CD4 binding site and the V3 loop and increase in fusion efficiency. Evolution of coreceptor preference accompanied by changes in neutralizing epitopes may reflect escape from immune response.

226 HIV+ TO HIV+ KIDNEY TRANSPLANT: TRACKING DONOR VIRUS IN RECIPIENT URINE AND BLOOD

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Background: HIV-1 positive individuals have increased risk of end-stage kidney disease due the HIV-1 infection and associated treatments, yet now live longer. The HOPE Act allows individuals living with well-controlled HIV-1 to be eligible for organ transplant from HIV-1 positive donors that would have been otherwise discarded. One concern associated with HIV+ to HIV+ transplantation is the risk of superinfection and/or viral recombination resulting from the transmission of a genetically distinct HIV-1 strain from the donor to the recipient. In this study we used analysis of viral sequences derived from donor and recipient specimens to determine the source of virus in urine and blood specimens in the transplant recipient.

Methods: Blood and urine specimens were obtained from both donor and recipient before transplantation and at different time points post-transplantation from the recipient. A renal biopsy from the donor kidney was obtained at time of procurement. We performed single genome amplification (SGA) of the full-length HIV-1 env gene with viral RNA extracted from urine, plasma and donor kidney biopsy as well as from viral DNA extracted from PBMC and urine derived renal cells. Neighbor-joining trees were constructed using the Kimura 2-parameter model.

Results: Multiple HIV-1 env sequences were obtained from the samples collected from both donor and recipient. We found that all the env sequences from the recipient's urine collected at 12 hours post-transplant were genetically similar to those in the donor while subsequent urine-derived sequences were genetically similar to the recipient virus. Furthermore, the majority of the urine derived sequences formed a separate cluster from donor-derived blood sequences, suggesting that the majority of urine-derived viruses were produced by infected cells within the donor kidney. Although the donor viruses could be readily amplified from the recipient's urine soon after transplantation, it became undetectable in the urine and plasma on the subsequent follow-up visits while the recipient was continuously maintained on ART.

Conclusion: Our study demonstrates that following HIV+ to HIV+ kidney transplantation viruses from the donor's kidney are found in the urine of the recipient immediately following transplantation, suggesting that donor's kidney as the source of these viruses. Our results warrant long term monitoring of viral populations in the recipient to fully assess any clinical and virologic implications of this finding.

227 GUT MICROBES DRIVE EXPANSION AND PREFERENTIAL HIV INFECTION OF GUT CD4 CTL EX VIVO

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Background: HIV infection is associated with disruption of gut homeostasis and changes in the gut microbiome (dysbiosis). During early infection, HIV replicates to high levels in gut CD4 T cells concurrent with epithelial barrier breakdown and onset of microbial translocation. In transcriptome profiling studies using primary human lamina propria mononuclear cells (LPMC), we identified Granzyme (GZ) B and GZA induction in microbe and microbe/HIV stimulated gut CD4 T cells ex vivo (PMID 28241075). Here, we profiled microbe-induced human gut GZB-expressing CD4 T cells (termed CD4 CTLs) to determine the specificity of this response, potential mechanisms driving expansion and relative levels of HIV infection.

Methods: Jejunum LPMC (n=13 donors), peripheral blood mononuclear cells (n=5) or tonsil cells (n=5) were cultured with or without gut commensal Escherichia coli lysate as well as enteric pathogenic, probiotic or dysbiotic bacteria altered in people living with HIV (PLWH). LPMCs were pre-treated with HLA blocking/control antibodies prior to addition of bacteria (n=7). LPMC were infected with Transmitted/Founder HIV-1 strain CH40 (n=3). Cytolytic markers (GZB, perforin, CD107a), infection (intracellular p24) and proliferation (CFSE) were measured by flow cytometry. Paired t tests were used for analyses.

Results: Percentages of gut CD4 T cells expressing GZB were low at baseline (mean, SEM 1.4±0.5%), but exposure to multiple enteric bacteria increased % of GZB+ CD4 CTLs (Table 1), with greatest increases with E. coli (733-fold) and S. typhimurium (376-fold). E. coli induced a 4-fold increase in % of blood GZB+ CD4 CTLs (p=0.008), but did not induce GZB expression in tonsil CD4 T cells. HLA-DR blockade decreased the % of E. coli-driven GZB+ CD4 CTLs by 33±10% (p=0.02), but not their proliferation. Following HIV infection of E coli-exposed LPMC, a greater fraction of GZB+ than GZB- CD4s were infected (p24+; p=0.058). GZB+ CD4 CTLs that expanded with HIV + E. coli exposure expressed perforin (23±9.5%) and of those, 25±7.7% had degranulated (CD107a+).

Conclusion: Diverse enteric bacteria induced GZB+ gut CD4 CTLs that are preferentially infected by HIV-1 ex vivo. Microbe-driven GZB induction was prominent in the gut, but not blood and lymphoid tissue CD4 T cells and was partially MHC Class II dependent. Gut cytotoxic CD4 T cells may have evolved for antimicrobial defense, but in the setting of HIV infection, these cells may accelerate gut pathogenesis by enhancing overall HIV infection and CD4 T cell death.

Table 1. Induction of Granzyme B-expressing gut CD4 T cells in response to exposure of lamina propria mononuclear cells to enteric bacteria *ex vivo*.

	Bacteria description#	Fold change *
Escherichia coli	GN commensal	733±369 p=0.008
Salmonella typhimurium	GN pathogen	376±208 p=0.034
Bifidobacterium infantis	GP probiotic	45±33 p=0.067
Acinetobacter junii	GN commensal increased in PLWH‡	45±26 p=0.076
Bacteroides thetaiotaomicron	GP commensal decreased in PLWH‡	35±21 p=0.080
Ruminococcus bromii	GP commensal decreased in PLWH‡	18±11 p=0.082

#GN: Gram-negative, GP: Gram-positive. *Values reflect the fold change in percentage of CD4 CTLs in response to bacteria compared to unstimulated conditions and are shown as mean±SEM (N=5). P values reflect paired t tests between percentages of Granzyme B-expressing CD4 T cells in bacteria-stimulated versus no stimulation cultures. ‡Bacteria selection based on identification of mucosa-associated bacteria that were altered in PLWH who were not receiving anti-retroviral drugs versus uninfected controls (PMID 26762145).

228 MODULATION OF GUT MICROBIOTA IMPROVES MUCOSAL PERMEABILITY IN HIV+ PATIENTS

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Background: Intestinal dysbiosis and the disruption of enterocytes tight junctions play a major role in the pathogenesis of HIV infection. Recent findings support the role of probiotics in restoring intestinal microbiota in HIV+ patients.
Methods: 15 Caucasian HIV-1 positive patients on long-term suppressive combined antiretroviral therapy (cART) and 30 healthy control individuals matched by age and gender were recruited at the Department of Public Health and Infectious Diseases, "Sapienza" University of Rome (Italy). HIV+ participants received two sachets of Vivomixx®, containing 450 × 109 billion bacteria each, twice a day for a period of six month. All patients underwent pancolonoscopy and fecal sample collection before (T0) and after 6 months of probiotic supplementation (T6). Mucosal biopsies taken from distal ileum and different colonic tracts of intestine were evaluated before and after the probiotics treatment. Occludin, Zonulin, E-cadherin and Claudin-2 expression was detected in biopsies at T0 and T6. Metabolomics investigation were performed by 1H-NMR (X).
Results: Occludin and Zonulin were significantly lower in the T0 samples compared to the T6 biopses (T0 vs T6 $p<0.0001$). No significant differences were observed for E-cadherin and Claudin-2 expression before and after the treatment, while, in the large intestine, Claudin-2 was significantly higher amongst the pre-treated HIV infected patients compared to the same patients after probiotic therapy (T0 vs T6 $P<0.0001$).Ultrastructural examination of biopsies revealed the morphological conformation of the tight junctions: open, for the structures near the basolateral pole of enterocytes, or for those detected at the intercellular contact sites, near the apical surface of the colonic cells, before the treatment (T0). By contrast, the junctional complex exhibited a closed conformation after 6 months of supplementation (T6). Although no difference was observed at baseline in fecal concentration of phenylalanine and tryptophan between HIV+ subjects and controls, metabolomics investigation resulted in lower levels of tyrosine and a higher phe/tyr in HIV+ participants at baseline. At T6, HIV+ individuals showed a significant decrease of fecal tryptophan concentration and a lower phe/tyr.
Conclusion: Our data show evidence that supplementation with oral probiotics drives a beneficial functional modulation of intestinal microbiota with the recovery of mucosal integrity.

229 RECTAL MICROBIOME ALTERATIONS ASSOCIATED WITH TDF/FTC FOR PREEXPOSURE PROPHYLAXIS

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Background: Oral daily tenofovir (TFV) disoproxil fumarate/emtricitabine (TDF/FTC) for HIV pre-exposure prophylaxis (PrEP) is highly effective at preventing HIV infection, yet long-term adverse effects are not fully understood. We investigated the effects of PrEP on the rectal microbiome in a cohort of men who have sex with men (MSM).
Methods: Rectal swabs were obtained from an ongoing cohort (The mSTUDY) examining the effects of substance use on HIV-1 transmission and pathogenesis in young MSM. This cross-sectional analysis included HIV-negative participants currently on PrEP based on clinician review and confirmed by self-report (n=37). HIV-negative control participants not on PrEP (n=37) were selected using 1:1 matching on a propensity score which was calculated using multiple clinical and behavioral confounding factors (including sexual activity). Hair specimens were used to quantify TFV and FTC exposure over the past 6 weeks on a subset of participants. Microbiome composition was analyzed using targeted sequencing of the V4 region of the 16S rRNA gene followed by exact sequence inference using DADA2. Associations between PrEP use and microbiota abundance were examined using zero-inflated negative binomial regression (ZINB) and binomial least absolute shrinkage and selection operator (LASSO) regression analyses.
Results: The median duration of oral TDF/FTC use in the PrEP group was 7 months (IQR 2 -13), and self-reported adherence was good to excellent among 86% of participants. Hair analyses on a subset (n=15) of PrEP participants showed median tenofovir concentrations of 0.027 ng/mg hair (IQR 0.022-0.031); consistent with adherence of 4 or more doses per week. No significant differences in rectal microbiome diversity were seen between PrEP and control participants, but changes in microbiome composition were seen. PrEP use was associated with significant increase in abundance of *Streptococcus* (adjusted $p=0.015$) using ZINB models. Similar associations were selected using LASSO regression, confirming the increase in *Streptococcus* abundance and also showing increased *Mitsuokella*, *Fusobacterium*, and decreased *Escherichia/Shigella*.
Conclusion: Oral TDF/FTC for PrEP use is associated with changes in the rectal microbiome compared to well-matched controls not taking PrEP, specifically increased *Streptococcus* abundance. This study highlights the need for future investigation of the role of microbiome changes on HIV susceptibility and effectiveness of PrEP.

230 JOINT EFFECTS OF HIV AND OBESITY ON THE MICROBIOME OF YOUNG MEN WHO HAVE SEX WITH MEN

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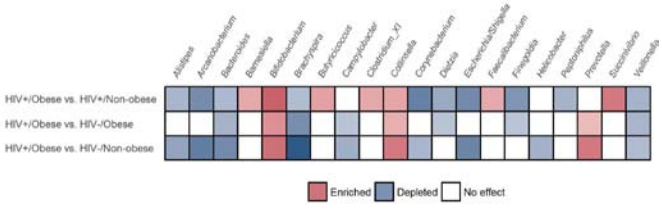
Background: The prevalence of obesity among people living with HIV continues to rise rapidly. Both obesity and chronic HIV infection are pro-inflammatory conditions which can alter the composition and function of the gastrointestinal microbiome. However, the combined effects of HIV and obesity on the microbiome have not been examined.
Methods: Participants (N=381) with archived rectal swabs collected between 2014 and 2017 were selected from an ongoing cohort of diverse young men who have sex with men (The mSTUDY). Both HIV+ (n=182) and HIV- (n=199) participants were included. Obesity was defined as BMI > 30 or waist circumference > 40 inches. Microbiome composition was assessed by targeted sequencing of the V4 region of the 16S rRNA gene followed by exact sequence inference with DADA2. For analysis, specimens were compared between HIV+ and obese (H+O+) participants and HIV+/non-obese, HIV-/obese, and HIV-/non-obese controls. Analyses included permutational multivariate ANOVA (PERMANOVA) with Bray-Curtis distance to test for differences in overall composition and zero-inflated negative binomial (ZINB) models to test for differential abundance of specific genera. All analyses utilized inverse probability of treatment weighting to control for a large set of clinical and behavioral factors including demographics, ART use, sexual behavior, positive rectal STI test by PCR, smoking, and self-reports of methamphetamine, marijuana, and alcohol use.
Results: PERMANOVA analyses showed that HIV and obesity combined explained a significant amount of between-subject variation in the microbiome over and above each factor alone (R^2 for the marginal contribution of the H+O+ group = .007, p = .002). H+O+ participants had the highest average ratio of Prevotella to Bacteroides, a pro-inflammatory enterotype that has been described in HIV and obesity separately. Using ZINB models, a number of differences in bacterial genera between H+O+ and other participants were also observed. Namely, the double positive H+O+ participants had higher levels of Bifidobacterium and Collinsella and lower levels of Bacteroides, Brachyspira, and Veillonella than all other groups.
Conclusion: Our findings indicate that microbial composition is altered by the combination of HIV and obesity over and above the contributions of each condition alone. Synergistic effects of HIV and obesity on bacterial communities may help explain the increased risk of inflammation-associated comorbidities among those living with HIV and obesity.



231 EFFECTS OF LACTOFERRIN ON IMMUNE ACTIVATION AND MICROBIOME AMONG HIV+ INDIVIDUALS

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Background: Irreversible injury to gut mucosa with loss of epithelial integrity and translocation of microbial antigens represents a potential mechanism driving immune activation, and subsequent clinical risk, among ART-treated HIV+ individuals. Lactoferrin is an endogenous iron-binding protein that binds lipopolysaccharide, improved outcomes among those with sepsis, and has immunomodulatory properties that could reduce HIV-associated inflammation.
Methods: Treatment effects of oral recombinant human rh-lactoferrin versus placebo were investigated in a randomized, double-blind, cross-over clinical trial, among participants ≥40 yrs with suppressed plasma HIV RNA receiving ART. Plasma, serum and peripheral blood mononuclear cell (PBMC) specimens were collected and cryopreserved at baseline and months 1 and 3 of each 3-month cross-over period. Soluble biomarkers were measured with ELISA, ELFA (D-dimer) or electroluminescence methods, and immune phenotyping of monocytes, T cells and Mucosal Associate Invariant T cells by LSRII flow cytometer. The treatment effect was calculated for each biomarker with longitudinal mixed models. A rectal swab specimen was collected before and after study drug exposure among a subset of participants for microbiome study. The QIIME 2.0 was used for a pairwise group comparison test.
Results: 54 participants were randomized and received study drug, with 50 completing the first period and 46 completing the second period. Median age was 51 years and CD4+ count was 651 cells/mm3; 89% were male, 72% white, and 39% with prior AIDS. Adherence and adverse events did not differ between rh-lactoferrin and placebo periods. Results for representative biomarkers and immunophenotyes are shown in Table 1, with no consistent evidence of a treatment effect demonstrated. The percent serum iron saturation significantly increased on rh-lactoferrin versus placebo by 2.6% (95%CI: 0.2, 5.0), but this effect did not reach significance for ferritin (5.8 ng/mL; 95%CI: -3.3, 15.0). Among a subset (n=12), intestinal microbiota analysis revealed stability in α and β diversity and in the abundance of Bacteroidetes and Firmicutes members over follow-up with no discernible treatment effect from rh-lactoferrin.
Conclusion: Oral rh-lactoferrin administration among HIV+ individuals receiving ART with viral suppression was safe and well tolerated, but had no effects on systemic inflammation or cellular immune activation, and exerted no changes in gut microbiome.

Table 1. Treatment Effect on Inflammatory and Immunologic Outcomes Over Three Months of Lactoferrin vs. Placebo

	Treatment Effect of Lactoferrin vs. Placebo	
Laboratory Outcomes	**Mean (95% CI)**	***P*-value**
IL-6 and D-dimer Score	0.01 (-0.07, 0.06)	0.82
Inflammation Biomarkers		
IL-6, log2 pg/mL	-0.02 (-0.20, 0.17)	0.87
IL-6 receptor, ng/mL	0.03 (-0.01, 0.06)	0.15
TNF-r1, ng/mL	-0.00 (-0.04, 0.03)	0.84
Coagulation Biomarkers		
D-dimer, log2 mg/L	-0.03 (-0.14, 0.07)	0.53
Mucosal Integrity Biomarkers		
Zonulin, log2 ng/mL	0.00 (-0.07, 0.08)	0.99
FABP, log2 ng/mL	-0.04 (-0.17, 0.10)	0.56
Monocyte Biomarkers and Immunophenotypes		
sCD14, log2 mg/L	0.01 (-0.04, 0.06)	0.67
sCD163, log2 mg/L	0.09 (0.02, 0.17)	0.02
CD14+CD16+, %	-0.36 (-1.06, 0.33)	0.30
CD14dimCD16+, %	0.35 (-0.35, 1.05)	0.32
T-cell Immunophenotypes		
Mucosal associated invariant T-cells (MAITS), %	0.01 (-0.09, 0.11)	0.86
CD8+CD38+HLADR+, %	-0.52 (-1.10, 0.06)	0.08
CD4+TREG, %	0.03 (-0.28, 0.33)	0.87

IL=interleukin, TNF=tumor necrosis factor, FABP=fatty acid binding protein.

232 COTRIMOXAZOLE MODULATES IMMUNE CELL ACTIVATION & THE GUT MICROBIOTA IN HIV INFECTION

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Background: Long-term cotrimoxazole prophylaxis reduces mortality and morbidity in HIV infection but the mechanisms underlying these sustained clinical benefits are unclear. We have previously shown that long-term continuation of cotrimoxazole reduces systemic inflammation, a driver of mortality, in HIV+ ART-treated children. Here we explore the mechanisms that underlie the anti-inflammatory benefits of cotrimoxazole.
Methods: Circulating inflammatory mediators (CRP, IL-6, TNFα and soluble CD14) were quantified in plasma samples from HIV-positive Ugandan and Zimbabwean children receiving antiretroviral therapy in the ARROW trial randomised to continue (n=149) versus stop (n=155) cotrimoxazole. Using an in vitro model of systemic inflammation, we evaluated the direct effect of cotrimoxazole on immune cell activation in blood samples from HIV-positive (n=16) and HIV-negative (n=8) UK adults who were cotrimoxazole-naive. Since HIV enteropathy can drive systemic inflammation, we quantified biomarkers of intestinal inflammation (myeloperoxidase, neopterin, alpha-1-anti-trypsin and REG1β) and microbiome composition using randomised stool samples from ARROW. In a parallel in vitro model of gut inflammation (Caco-2 gut epithelial cell transwell cultures), we assayed the effect of cotrimoxazole on epithelial barrier function and chemokine production.
Results: Inflammatory biomarkers (CRP and IL-6) were significantly lower among children continuing cotrimoxazole. This was not explained by global differences in symptomatic illness, viral suppression, CD4+ T-cell counts or activation status, or sub-clinical gut pathogen carriage. In vitro cotrimoxazole treatment reduced pro-inflammatory cytokine production in response to pathogen antigens by both HIV+ and HIV- adults. In stool samples from ARROW, myeloperoxiadse levels were significantly lower in children continuing cotrimoxazole 84 weeks post-randomisation and this was associated with suppression of viridians group Streptococci and their mevalonate metabolism. Cotrimoxazole-treated Caco-2 produced less IL-8 in vitro.
Conclusion: Cotrimoxazole reduces systemic and intestinal inflammation both through its antibiotic properties and by direct immunomodulation of leukocytes and gut epithelial cells. Synergy between these pathways may contribute to the sustained clinical benefits of long-term cotrimoxazole prophylaxis despite high antimicrobial resistance, providing a further rationale for extending coverage among people living with HIV in sub-Saharan Africa.

233 DARUNAVIR/RITONAVIR THERAPY CONTRIBUTES TO INTESTINAL DYSFUNCTION IN HEALTHY MACAQUES

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Background: HIV infection results in damage to the gastrointestinal (GI) immune system that is incompletely restored with antiretroviral (ARV) therapy. Recent findings have implicated that GI immune system competency is dependent upon signaling originating from the commensal microbiota and that the composition of the microbiome is altered in some diseased states (dysbiosis). In Asian macaque models of HIV infection, we noted that the initiation of ARV therapy - though not SIV-infection itself - was associated with dysbiosis. Similar to HIV-infected humans, this dysbiosis was characterized by an enrichment for Gammaproteobacteria at the expense of Clostridia sub-taxa. We thus postulated that ARVs might themselves contribute to dysbiosis and non-AIDS related comorbidities.
Methods: We treated 6 healthy rhesus macaques (RM; Macaca mulatta) with a Darunavir-Ritonavir (DRit) protease inhibitor regimen (400mg and 100mg b.i.d. respectively) for 90 days and evaluated immune function in intestinal lymphocytes by flow cytometry in these and 4 control animals. We further collected stool samples to evaluate changes in the intestinal microbiome by 16S Illumina sequencing.
Results: We observed that DRit-therapy was associated with increases in systemic inflammation as compared to controls - most notably, increased IFNg and TNFa expression from intestinal CD8+ memory T-cells. Among DRit-treated RM, deep sequencing of intestinal microbiota revealed a modest but prolonged expansion of Anaeroplasmataceae and Erysipelotrichaceae which were

associated with the increased inflammatory milieu we observed. Importantly, we did not observe an enrichment for Proteobacteria.
Conclusion: Our findings suggest that protease inhibitors contribute modestly to microbial dysbiosis and immune dysfunction in uninfected lentiviral infections. As such, the side effects of protease-inhibitors commonly observed in HIV-infected individuals are unlikely to be attributed solely to GI tract dysbiosis or inflammation. Further research is required to determine if other ARVs interfere with intestinal stasis and whether ARVs contribute to dysbiosis in the context of ongoing lentiviral infections.

234 THE MICROBIOME MAY MODIFY HIV INFECTION RISK ASSOCIATED WITH HORMONAL CONTRACEPTIVES

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Background: The injectable hormonal contraceptive depot medroxyprogesterone acetate (DMPA) has been associated with increased risk of HIV-1 acquisition in women, but these observations have been inconsistent. We examined whether the vaginal microbiome influences rates of HIV acquisition in women using different hormonal contraceptives in the CAPRISA 004 trial at study enrollment.
Methods: Mass spectrometry was used to characterize the bacterial metaproteome (microbiome) from cervicovaginal lavage samples collected from study participants.
Results: Among the 685 women included in this study, the majority were using hormonal contraceptives (97.7%) including DMPA (65.1%), norethisterone enanthate (NET-EN) (18.0%), and combined oral contraceptives (COC) (14.1%), and the majority did not switch contraceptives during the study (91.7%). Women belonged to two major vaginal microbiome profiles which were similarly distributed across hormonal contraceptive groups- one dominated by Lactobacillus (59.2%) and the other that was non-Lactobacillus dominant (microbial dysbiosis), where Gardnerella vaginalis predominated with other anaerobic bacteria (40.8%). Rates of HIV infection were trending higher in those using DMPA when compared to NET-EN and COC users as a single group, but this was not statistically significant (6.58 vs 4.15 infections per 100 women-years, respectively; adj. HR: 1.80, 95% CI: 0.90 to 3.59, P=0.097). In women with microbial dysbiosis, rates of HIV acquisition were similar between hormonal contraceptive types (7.13, 7.72, and 6.59 per 100 women-years in DMPA, NET-EN, and COC users, respectively), and not significantly higher in those using DMPA compared to all other hormonal contraceptives (HR: 1.16, 95% CI: 0.56 to 2.40, P=0.70). However, in Lactobacillus-dominant women, DMPA use associated with an infection rate of 6.23 per 100 women-years compared to 1.74 and 2.15 per 100 women-years with NET-EN and COC, respectively – a > 3-fold increase for DMPA users relative to women using other hormonal contraceptives (HR: 3.39; CI: 1.61 to 7.15, P=0.0152). These observations were consistent in models adjusted for study arm, study site, age, sexual behavior and other clinical variables.
Conclusion: This suggests that the association between DMPA and HIV acquisition risk may depend on the composition of the microbiome, which may have important implications for safe contraceptive design and interpretation of future studies of contraceptives and HIV acquisition risk.

235 ROLE OF FREM1 IN PRO-INFLAMMATORY RESPONSES DURING VAGINAL HIV/SIV INFECTION

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Background: A single nucleotide polymorphism in FRAS1-related extracellular matrix 1 (FREM1) is associated with resistance to HIV. A splice variant of FREM1-Toll/Interleukin 1-like receptor regulator, (TILRR)- is an IL-1R1 co-receptor capable of potentiating inflammatory responses. This study investigated the role for FREM1 in modulation of immune responses during vaginal HIV transmission.
Methods: FREM1 protein expression was examined in human and Rhesus macaque (RM) female genital tissues, and changes in its expression measured following intravaginal SIV infection in RMs. FREM1 expression in both human and RM female genital tracts (FGTs) was similar, with high expression in the epithelium and submucosa
Results: FREM1 levels increased following intravaginal SIVmac251 infection, accompanied by infiltration of SIV target cells into the genital mucosa. Different human immune cells in blood, expressed FREM1, including T cells, monocytes, and B cells to varying degrees. Notably, FREM1-expressing CD4+ and CD8+ T cells from women with the protective FREM1 allele had lower cellular activation. Only Escherichia coli LPS (TLR4 agonist), and not Imiquimod (TLR7 agonist) or ssRNA40 (TLR8 agonist) alters FREM1 expression on some T cells and monocyte subsets. Co-expression analysis of FREM1 and TLR4 in PBMCs and tissues also suggests close association between these proteins. Stimulation of human monocyte populations with a TLR4 agonist or antagonist, alone and in combination with anti-FREM1 mAbs, indicates that FREM1 modulates pro-inflammatory cytokine production and co-stimulatory factor expression.
Conclusion: These results suggest FREM1 potentially regulates innate immune responses, based on its association with TLR4. These findings add to the understanding of early HIV transmission in the context of cellular structural proteins being influenced vaginal microbiota driven inflammation.

236 CERVICOVAGINAL MICROBIAL STRAINS ARE ASSOCIATED WITH DISTINCT IMMUNOPHENOTYPES

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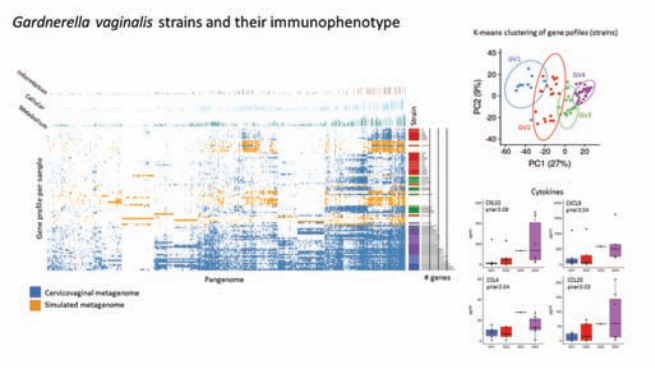
Background: Elevated inflammation in the female genital tract (FGT) is associated with an increased risk of HIV infection, and cervicovaginal bacteria have been shown to impact genital inflammation (Gosmann et al., 2017). These associations have been identified through bacterial 16S rRNA gene sequencing which has limited resolution and rarely achieves taxonomic assignment to the species-level. Within-species genetic differences can be vast, with some species-level pangenomes (all the unique genes observed for a species) exceeding the size of any single strain's genome by orders of magnitude. Furthermore, 16S sequencing provides no functional information, limiting our mechanistic understanding of disease associations.
Methods: To better characterize strain-level variation in the FGT microbiota we generated species-specific pangenomes from single culture genome sequences (1000 primary bacterial isolates and 2000 publicly available genomes). We produced sample specific gene profiles by mapping metagenomic sequences from 300 North America and South Africa women to the species-specific gene catalogues. Profiles were partitioned using centroid based clustering to form groups containing similar gene complements (strains). Local inflammation was measured using Luminex cytokine assays performed on cervicovaginal lavages from South African women with distinct strains.
Results: We show that most species possess a small core genome (~1000 genes) with an extensive pangenome (6000 to 30,000 genes). We find that Gardnerella vaginalis comprises 4 distinct strains and that some women possess enough genes to make 4 complete genomes, suggesting some women are colonised by multiple strains. Furthermore, we show that these strain complexes are associated with higher levels of cytokines in the FGT.
Conclusion: Our findings signify the importance of distinguishing microbial strains in the FGT when linking the endogenous microbiome to local inflammation influencing HIV acquisition risk.



237 GENITAL AND SYSTEMIC INFLAMMATION ASSOCIATED WITH FACTORS THAT MAY ALTER HIV RISK

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Background: Evidence suggests that epidemiologic factors modify susceptibility to HIV-1 acquisition by modulating innate inflammatory responses, and defining these changes may identify novel HIV-1 prevention interventions. However, few studies have assessed host responses to varied HIV risk altering exposures in the genital (vaginal and cervical) as well as systemic compartments. Here we compare vaginal, cervical and systemic inflammatory responses to potential HIV-1 risk modulating exposures ([depot] medroxyprogesterone acetate [MPA], bacterial vaginosis [BV], genital herpes [HSV-2], and oral HIV pre-exposure prophylaxis [PrEP]) to identify compartment-specific cytokine signatures.

Methods: We analyzed vaginal and cervical swabs and serum samples collected at 90 visits from 68 HIV-negative Kenyan and Ugandan women enrolled in the Partners PrEP Study. We measured compartment-specific concentrations of 28 cytokines using Milliplex beads, and tested for associations with PrEP use, serum MPA concentrations, BV and non-lactobacillus dominant (NLD) vaginal flora, and HSV-2 infection. We defined inflammation status as: 1) elevated IL1α or IL1β, or lowered IP10 (based on published literature), or 2) cytokine sets associated with each exposure from the 28 measured. We used logistic regression to assess associations of exposures with the IL1α/IL1β/IP10 signature and LASSO regularization to identify exposure-specific cytokine sets.

Results: In multivariable models, NLD flora (OR=13.4, 95%: CI 2.96-60.4) were associated with increased odds, and MPA (OR=0.15, 95% CI: 0.02-0.92) and PrEP exposure (OR=0.11, 95% CI: 0.02-0.59) were associated with reduced odds of the IL1α/IL1β/IP10 signature in the vagina (Table 1). No HIV risk modulators were associated with cervical or systemic inflammation. By LASSO regression, NLD flora were associated with IFNα2, IL-12 p40, IL-17A, IL1β, IL-1RA, IL-33, IL-8, IP-10, TNFα and sCD40L concentrations in the vagina. BV was associated with IP-10 concentration in the cervix. PrEP cessation was associated with concentrations of IFNα2 and IL-21 in the vagina and IL-15, IL-1β, IL-1RA, IL-2, IL-21 and MIP-1β in the cervix. No systemic exposure-specific cytokine sets were identified.

Conclusion: We identified associations between inflammatory signatures in vaginal and cervical compartments and potential HIV risk exposures that warrant further investigation. To this end, we intend to assess for similar signatures in a larger, more diverse sample of HIV-1 seronegative African women.

Table 1. Association of epidemiological exposures with candidate inflammation signature (IL-1α/β, IP10)

Exposure	# visits	Vaginal Inflammation		Cervical Inflammation		Systemic Inflammation	
	n (%)	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*
Detectable serum MPA	8 (8.9)	0.15 (0.02-0.92)	0.04	0.24 (0.04-1.45)	0.12	1.21 (0.14-10.5)	0.87
HSV-2 positive	65 (72.2)	0.42 (0.07-2.57)	0.35	0.49 (0.12-2.05)	0.33	1.91 (0.49-7.41)	0.35
NLD flora	35 (38.9)	13.4 (2.96-60.4)	<0.001	2.00 (0.63-6.38)	0.24	0.65 (0.16-2.59)	0.54
BV	15 (16.7)	3.57 (0.74-17.3)	0.11	3.90 (0.71-21.3)	0.12	1.21 (0.32-4.58)	0.78
PrEP use	32 (35.6)	0.11 (0.02-0.59)	0.01	0.46 (0.09-2.29)	0.34	3.00 (0.57-15.7)	0.19
Post-PrEP cessation	38 (42.2)	0.20 (0.03-1.42)	0.11	0.59 (0.13-2.77)	0.50	2.12 (0.43-10.3)	0.35

MPA=medroxyprogesterone acetate, HSV-2=herpes simplex virus-2, NLD=non-lactobacillus dominant, BV=positive or intermediate bacterial vaginosis status, PrEP=pre-exposure prophylaxis, OR=odds ratio, CI=confidence interval All models adjusted for other exposures presented in the table in addition to participant age, nationality, partner's most recent viral load, and any unprotected sex in the prior month; cervical models were also adjusted for whether sample is presumed to be an endocervical or ectocervical swab

238 CHLAMYDIA AND CERVICOVAGINAL MICROBIOTA MODULATE GENITAL-TRACT CD4+ T-CELL SUBSETS

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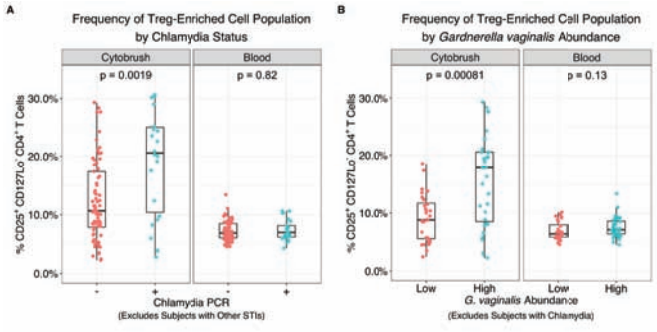
Background: Mucosal CD4+ T cells are critical to female genital tract (FGT) health, helping control bacterial, viral, and fungal infections while serving as primary targets for HIV transmission. Immune responses to FGT infections are known to depend on T helper subsets including Th17 and regulatory (Treg) cells in mouse models, but human studies have been hampered by paucicellular samples, small cohort size, and sexually transmitted infections (STIs). FGT Th17 cells (often experimentally defined by markers CCR6 and/or CD161) have been studied in context of inflammation and HIV, but FGT Tregs remain poorly characterized. Importantly, different T helper subsets are differentially permissive to HIV infection. We hypothesized that mucosal CD4+ T cell subset composition was modulated by both chlamydia and the non-STI genital tract microbiota.

Methods: We examined FGT CD4+ T cell subsets in a cohort of 119 HIV-negative South African women (ages 18-24). We used flow cytometry of cervical cytobrush samples to enrich for Th17 cells and Tregs by gating on CD161+CCR6+ and CD25+CD127Lo- cells respectively. We identified bacterial STIs via commercial laboratory testing and characterized the microbiota using bacterial 16S gene rDNA sequencing. Data were analyzed with DADA2 and custom R scripts.

Results: Median cervical CD161+CCR6+ and CD25+CD127Lo- CD4+ T cell frequencies were 48.0% and 12.4% respectively. Subjects with chlamydia had higher numbers of activated CD4+ T cells, as well as higher frequency of CD25+CD127Lo- (Fig A), lower frequency of CD161+CCR6+, and lower ratio of CD161+CCR6+ / CD25+CD127Lo- CD4+ T cells ($p < 0.002$ for each, Mann-Whitney U test). Using 16S sequencing, we classified STI-negative women into microbial cervicotypes and found significant cervicotype-related differences in T helper subsets, attributable in large part to *Gardnerella vaginalis*. Subjects with *G. vaginalis*-high communities (defined as exceeding median *G. vaginalis* abundance of 6.7%) had higher CD25+CD127Lo- CD4+ T cell frequency ($p < 0.001$; Fig B) and lower CD161+CCR6+ / CD25+CD127Lo- ratio ($p = 0.012$). We saw no differences in paired peripheral blood samples, confirming the effects were due to local rather than systemic factors.

Conclusion: We characterized FGT CD4+ T cell subsets and showed they were associated with both chlamydia and the non-STI microbiota. Future work will investigate the mechanistic basis for these findings and implications for adaptive immunity and HIV.



239 PENILE BACTERIAL SPECIES ASSOCIATED WITH INCREASED HIV RISK IN HETEROSEXUAL MEN

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Background: Anaerobic genera that are decreased in abundance after male circumcision have been associated with increased risk for HIV seroconversion. It is hypothesized that only a subset of species within these genera are specifically associated with HIV risk, but they have yet to be identified. Additional penile bacteria that remain abundant after male circumcision could also play a role, which may explain the residual HIV risk after male circumcision. Identifying such novel bacteria requires a broad, discovery-based study of penile bacterial species and associations with HIV acquisition risk.

Methods: We conducted a case-control study of uncircumcised men enrolled in a randomized trial of male circumcision in Rakai, Uganda. Cases (n=68) were men who acquired HIV during the 24-month follow-up and controls (n=199) were persistently HIV-uninfected men. Cases and controls were matched by randomization arm. Using DNA extracted from eluent of sub-preputial swabs, bacterial absolute abundance was estimated by pan-bacterial real-time PCR and sequencing of the 16S rRNA V3V6 region. Species-level classification was performed using a custom in-house Bayesian Classifier. Logistic regression was used to assess the adjusted odds ratio (adjOR) of HIV seroconversion associated with anaerobe abundance. Using a step-wise approach, genera, and subsequently species associated with HIV seroconversion were identified if they met three of four following criteria: a) above 1st quantile in absolute abundance, b) indicator value > 0.7 from indicator analysis, c) significant univariate association with seroconversion, and d) a priori evidence of association with seroconversion (genera only).

Results: We identified 14 penile genera associated with increased seroconversion risk, which included nine of the 10 anaerobic genera reduced by male circumcision, plus Atopobium, Gardnerella, Lactobacillus, Parvimonas, and Sneathia. Analyses using species-level data from the 14 genera identified 21 penile bacterial species associated with increased HIV risk (Table 1). Each 10-fold increase of penile bacterial species was associated with 22-57% increase in the odds of seroconversion after adjusting for known HIV risk factors.

Conclusion: This open-ended analysis demonstrated that men acquiring HIV had a higher density of anaerobic penile bacteria and a higher density of bacteria associated with vaginal inflammation (G. vaginalis) and health (L. crispatus).

Table 1. Species-level Associaiton with HIV Seroconversion (SC) Risk

Species	OR SC (95% CI)	aOR_1 SC (95% CI)
Candidatus Peptoniphilus massiliensis	1.12 (1.02-1.23)*	1.49 (1.11-1.98)*
Dialister micraerophilus	1.14 (1.06-1.23)*	1.43 (1.09-1.86)*
Dialister propionicifaciens	1.11 (1.02-1.19)*	1.36 (1.09-1.69)*
Dialister succinatiphilus <0.97	1.14 (1.07-1.22)*	1.23 (1.00-1.52)*
Finegoldia magna	1.14 (1.02-1.29)*	1.52 (1.09-2.13)*
Lactobacillus crispatus	1.14 (1.03-1.27)*	1.47 (1.09-1.97)*
Murdochiella spS5-A16 <0.97	1.09 (1.01-1.18)*	1.29 (1.03-1.61)*
Peptoniphilus duerdenii <0.97	1.11 (1.03-1.2)*	1.39 (1.10-1.75)*
Peptoniphilus lacrimalis	1.08 (1.01-1.16)*	1.28 (1.03-1.58)*
Peptostreptococcus anaerobius	1.12 (1.04-1.2)*	1.22 (1.00-1.50)*
Porphyromonas asaccharolytica	1.07 (1.01-1.15)*	1.34 (1.09-1.66)*
Prevotella bivia	1.1 (1.03-1.19)*	1.26 (1.02-1.57)*
Prevotella buccalis	1.09 (1.01-1.17)*	1.32 (1.05-1.66)*
Prevotella corporis	1.12 (1.05-1.21)*	1.38 (1.13-1.70)*
Prevotella disiens	1.14 (1.06-1.22)*	1.41 (1.14-1.74)*
Prevotella disiens <0.97	1.15 (1.08-1.23)*	1.43 (1.13-1.80)*
Prevotella genera_<0.97	1.08 (1.01-1.15)*	1.22 (0.99-1.50)*
Prevotella timonensis	1.11 (1.03-1.2)*	1.43 (1.14-1.80)*
uncultured Prevotella_sp<0.97	1.1 (1.03-1.18)*	1.30 (1.05-1.60)*
Gardnerella vaginalis	1.30 (1.06-1.59)*	1.31 (1.03-1.68)*
Sneathia sp-Sn35	1.26 (1.05-1.51)*	1.27 (1.01-1.59)*

Primary outcome was seroconversion (SC) within two years. Odds ratios (OR) and 95% confidence intervals (CI) were calculatd by logistic regression for tenfold increases in absolute abundance of penile bacterial species.

[1] Multivariable model included adjustment for marital status, number of non-marital sexual partners, condom use, and STI symptoms.

*p-value<0.05.

240 FORESKIN HIV TARGET CELLS AND PENILE ANAEROBES ASSOCIATED WITH HIV SEROCONVERSION

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Background: Inflammation has been associated with risk for HIV seroconversion. Specific penile anaerobes may increase HIV risk in men by triggering a cascade of soluble pro-inflammatory factors, such as IL-8, resulting in the recruitment of CD4+ cells to the foreskin. To test this hypothesis, we evaluated the association between abundance of penile anaerobes with sub-preputial soluble immune factors and target cells.

Methods: We conducted a cross-sectional study of 88 HIV-negative heterosexual uncircumcised men from the Rakai Community Cohort Study in Uganda. Sub-preputial swabs and foreskin tissues were collected. Using DNA extracted from sub-preputial swab eluent, we estimated absolute abundance of 21 penile bacterial species associated with seroconversion as the log10 16S rRNA gene copies/swab by pan-bacterial real-time PCR and sequencing of the 16S rRNA V3V6 region. Four negative control genera-Corynebacterium, Staphylococcus, Helcococcus, and Negativiococcus were also included in the analysis. We measured IL-8 concentration using multiplex mesoscale discovery platform analyzed foreskin tissue for immune cell density by immunohistochemistry and flow cytometry. We assessed association between abundance of penile anaerobes with sub-preputial IL-8 and foreskin total CD4+ (log10) T-cell densities by rank-based metrics: Spearman's correlation and quantile regression.

Results: Abundance of all 21 seroconversion-associated penile bacterial species correlated significantly with sub-preputial IL-8 (Spearman Rho range: 0.25-0.60; $p < 0.05$) while none of the negative control bacteria were significantly associated with IL-8. However, only seven species from three genera (Peptostreptococcus, Dialister, Prevotella) were correlated and associated significantly with increased CD4+ T-cell density (Table 1). The four negative control bacteria were not associated with sub-preputial IL-8 or foreskin immune cell density (Table 1).

Conclusion: The uncircumcised penis is enriched with sub-preputial anaerobes; the abundance of some of these anaerobes has been associated with HIV acquisition risk. HIV-associated anaerobes are associated with sub-preputial levels of the chemoattractant cytokine IL-8. Although collinearity of bacteria in the uncircumcised penile microbiome makes it difficult to assess independent IL-8 associations, only a subset of species were linked to the density of putative HIV target cells in the underlying foreskin tissue.

Table 1. Association between penile bacteria abundance with foreskin CD4+ cell density

		Correlation		Quantile Regression		
Species	Association with Seroconversion	Rho	p-value	coefficients	lower	upper
Peptostreptococcus anaerobius	Yes	0.396	<0.001	0.087	0.027	0.224
Dialister propionicifaciens	Yes	0.280	0.009	0.071	0.010	0.161
Dialister microaerophilus	Yes	0.276	0.010	0.046	0.007	0.094
Dialister succinatiphilus<0.97	Yes	0.227	0.035	0.058	0.005	0.132
Prevotella bivia	Yes	0.399	<0.001	0.070	0.032	0.205
Prevotella disiens	Yes	0.345	0.001	0.154	0.087	0.201
Prevotella disiens <0.97	Yes	0.220	0.042	0.063	0.011	0.101
Corynebacterium sp.	No	-0.038	0.727	-0.050	-0.204	0.107
Staphylococcus sp.	No	-0.018	0.869	0.028	-0.072	0.066
Helcococcus sp.	No	-0.112	0.303	-0.022	-0.074	0.013
Negativicoccus sp.	No	0.060	0.584	0.005	-0.040	0.044

241 HIV-SUPPRESSED PATIENTS' PLASMA AND SEMEN EXOSOMES CONTAIN PROTECTIVE LEVELS OF ART

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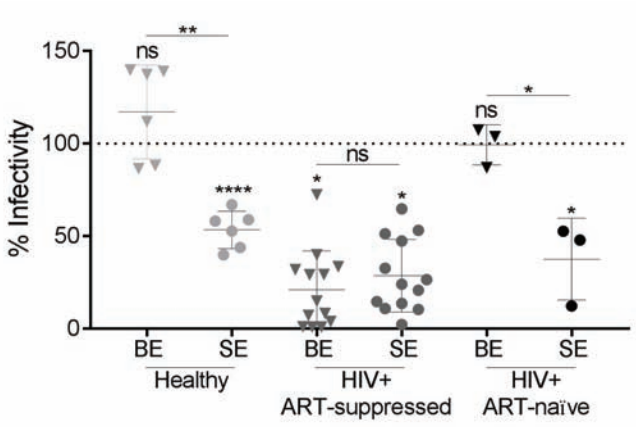
Background: Exosomes are non-viral vesicles released from cells with diverse cellular effects that may influence HIV-1 pathogenesis. In vitro, HIV-1-infected cells release exosomes that promote pathogenesis, whereas healthy-donor derived breast-milk, vaginal fluid, and semen exosomes inhibit HIV-1. Little is known regarding the effect of HIV-infected donors' body fluid exosomes. Here, we characterize the function of exosomes from HIV-infected donor plasma and semen to examine their impact on HIV-1 infection.

Methods: Exosomes were isolated from plasma and semen of HIV-positive ART-naïve persons with >50,000 HIV RNA copies/mL (n=3); HIV-positive ART-suppressed with <50 HIV RNA copies/mL (n=13), and HIV-uninfected (healthy) controls (n=6). Exosome inhibition of HIV-1 NL4.3 replication was determined in TZM-bl cells. Exosome-associated ART levels (tenofovir: TFV, TFV-diphosphate; emtricitabine: FTC, FTC-triphosphate; dolutegravir: DTG; and efavirenz: EFV) were measured by LC-MS/MS. ART was loaded onto HIV-uninfected exosomes using ExoFect™ exosome transfection.

Results: Semen exosomes (SE) but not plasma exosomes (BE) from HIV-uninfected and HIV-positive ART-naïve donors inhibited HIV-1 (47% and 62% inhibition, respectively). SE and BE prepared from HIV-infected, ART-suppressed donors reduced HIV-1 replication in TZM-bl cells (>75% inhibition), and contained concentrations of antiretroviral (ARV) medications above the IC_{50} values for all drugs measured (TFV, FTC, DTG, and EFV). TFV and FTC were more abundant in SE fractions than in BE while DTG and EFV were more abundant in the BE fractions, though this did not reach statistical significance. Loading HIV-negative BE with ART confirmed that exosome-associated ARVs mediated protection against HIV-1.

Conclusion: Although semen is the main vector in sexual transmission, it contains exosomes that inhibit HIV-1 independent of donor HIV or ART status. Thus, SE may contribute to the low rates of sexual transmission observed in vivo (1/200-1/1000 sexual events). Plasma and seminal exosome fractions from HIV-positive ART-suppressed donors inhibited HIV-1. ARVs and their active metabolites were detected in HIV-positive suppressed donors' body fluid exosomes at biologically relevant, inhibitory levels. Further, ART-loaded exosomes inhibited HIV-1 replication, indicating that exosomes could play a role in HIV-1 drug delivery.



242 BLOOD MICROBIOTA CORRELATES WITH INFLAMMATION AND ART-MEDIATED IMMUNE RESTORATION

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Background: HIV infection impairs the mucosal immunity and leads to bacterial translocation, fueling chronic inflammation and disease progression. The compositional profile of the translocated bacteria remains undefined.

Methods: A total of 80 samples from 50 individuals were studied: 30 HIV-infected individuals with <350 CD4+ T-cells/uL or AIDS at diagnosis and after 48 weeks of first-line ART, and 20 controls matched by sex and age. HIV+ subjects were categorized by the median CD4/CD8 ratio fold increase during ART (cut-off: 2.5) to classify study participants as immunological responders (IR) or non-responders (INR). Total DNA was extracted from 50 uL of blood and was analyzed by highly sensitive 16S rDNA targeted metagenomic sequencing of V3-V4 regions using MiSeq Illumina and the FROGS metagenomic workflow. LEfSe analysis was used to identify bacterial biomarkers. Their correlations which markers of inflammation, bacterial translocation and peripheral T cell activation was calculated using Spearman's regression.

Results: Alpha diversity was significantly higher in HIV+ vs. HIV- subjects, and these differences were attenuated after 48 weeks of ART. We did not detect differences in beta diversity. LEfSe analysis revealed that HIV+ subjects showed enrichment for several pathobionts, including Flavobacterium, Haemophilus, Chitinophagaceae, and Lactobacillales, and depletion of Pseudomonas and Rubrobacter. This pattern of dysbiosis was attenuated after 48 weeks of ART, yet we still found enrichment for Escherichia, Shigella, Ralstonia, Achromobacter, Pandoreae and depletion of Rubrobacter and Micrococcaceae. At baseline, enrichment for Lactobacillales, Nocardiaceae, Flavobacterium and Rhodococcus predicted greater immune recovery and depletion of Actinobacteria, Moraxellaceae and Corynebacteriacae. We selected the most enriched (Lactobacillales) and depleted (Actinobacteria) bacteria for correlation analyses. These taxa significantly correlated with changes in IL6, sCD163, LTA and CD8 T cell activation.

Conclusion: HIV infection affects the composition of the blood microbiota by increasing the abundance of pathobionts. ART appears to attenuate these compositional abnormalities. Different translocated bacteria were predictive of the extent of immune recovery after 48 weeks of ART and significantly correlated with markers of inflammation, bacterial translocation and immunoactivation. Hence, these taxa may prove functionally relevant for HIV immunopathogenesis and deserve further investigation.

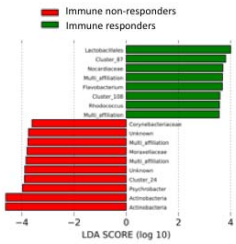
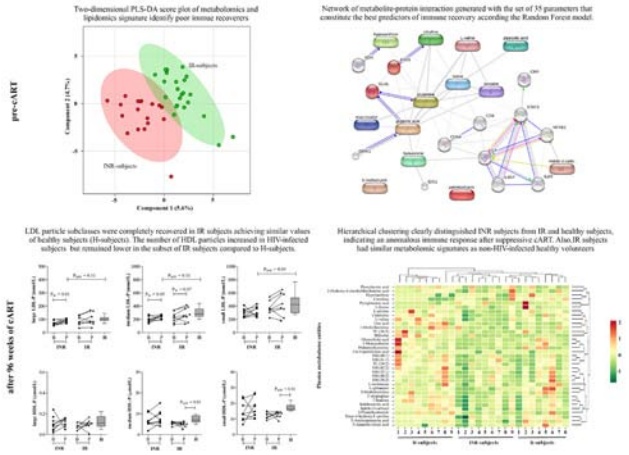


Figure 1. Taxonomic biomarker Discovery with LEfSe

Table 1. Correlations between taxa with linear discriminant analysis score ≥4 at baseline and by fold change with inflammation and immunoactivation markers.

	Most enriched - Lactobacillales		Most Depleteted- Actinobacteria	
	Week 0	Change through week 48	Week 0	Change through week 48
	Rho (p value)	Rho (p value)	Rho (p value)	Rho (p value)
IL-6	0.025 (0.913)	-0.010 (0.973)	***0.547 (0.008)***	0.126 (0.587)
sCD163	0.266 (0.230)	***0.612 (0.020)***	0.128 (0.570)	0.176 (0.445)
LTA	0.395 (0.100)	***-0.631 (0.016)***	0.146 (0.518)	0.358 (0.110)
IP-10	0.274 (0.217)	***0.631 (0.015)***	-0.198 (0.376)	-0.339 (0.132)
%CD8+ HLADR+CD38+	0.194 (0.386)	***0.612 (0.020)***	-0.218 (0.329)	0.304 (0.179)

Abbreviatures, IL-6, interleukin-6, sCD163, soluble CD163; LTA, lipoteichoic acid; IP-10, interferon-gamma induced protein 10; %CD8+HLADR+CD38+, %CD8+ T cells expression HLA-DR and CD38.



243 GLUTAMINOLYSIS AND LIPOPROTEINS KEY FACTORS IN HIV LATE IMMUNE RECOVERY

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Background: The immunological, biochemical and molecular mechanisms associated with poor immune recovery are far from known, and metabolomics profiling offers an additional value to traditional soluble markers. Here, we search for predictive markers of late immune response and disease progression in a cohort of HIV-subjects with increased CD4 T-cell turnover and inflammation preceding their poor immune recovery.

Methods: We executed a nuclear magnetic resonance (NMR) and mass spectrometry (MS)-based circulating metabolomics approach in 41 cART-naive HIV-infected patients who were initiating cART and subsequently followed up these patients for 96 weeks (n = 17). Random forest (RF) was performed to identify the variables that best partitioned the overall study population according to immune recovery predisposition. Network of metabolite-protein interaction and functional enrichment analyses were generated to identify the metabolomics pathways affected.

Results: Plasma L-tyrosine (P = 0.04), L-glutamate (P = 0.05), and phosphatidylcholine (PC) (16:1) (P = 0.01) by univariate model, and hsCRP, IL-6 and palmitoylcarnitine (PalC) by Random Forest, were identified as predictive markers of late immune recovery. After 96 weeks of cART, CD4+ T-cell counts were positively correlated to glycocholic acid (r = 0.51, P = 0.04) and citrulline (r = 0.60, P = 0.03), and inversely correlated to lipopolysaccharide (LPS) (r = -0.61, P = 0.03) and DL-pipecolic acid (r = -0.94, P < 0.01). Compositional and structural changes on HDL and decreased glutamate concentrations were associated to immune recovery during cART.

Conclusion: Metabolomics improve the value of soluble parameters and shows novel and relevant data that may contribute to a better understanding of molecular mechanisms preceding discordant response and immunological progression under suppressive stable cART. The metabolomics signature of ART-naïve HIV subjects with late immune recovery is the expression of pro-inflammatory molecules and glutaminolysis, which is probably related to their higher T-cell turnover.

244 EXPANSION OF MYELOID-DERIVED SUPPRESSOR CELLS IN ART-SUPPRESSED HIV-INFECTED PATIENTS

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Background: The existence of HIV reservoirs represents the main obstacle to cure HIV. The role of the immune system at maintaining and regulating this viral persistence remains largely unknown. Here, we studied the role of the myeloid-derived suppressor cells (MDSC), a heterogeneous population of immature myeloid cells with high immunosuppressive effects on the HIV reservoir.

Methods: Samples from n=14 ART-suppressed and n=8 heathy controls were included in this study. Frequency of two subpopulation of MDSC (CD3-, CD33+, CD11b+, HLA-DRlow), M-MDSC (CD14+) and G-MDSC (CD14-), was assessed by multiparametric flow cytometry, as well as immune activation in CD4+ and CD8+ T cells (markers CD38 and HLA-DR). The functional status of MDSC was assessed by the expression of Indoleamine 2,3-dioxygenase (IDO) and Arginase-1 (ARG-1). Total HIV-DNA and intracellular HIV-RNA were quantified by qPCR in purified CD4+ T cells. P24 expression and MDSC infiltration in B-cell follicles within lymph nodes of n=2 chronic infected patients was measured by immunohistochemistry.

Results: ART-suppressed patients presented significantly higher proportions of M-MDSC compared to healthy controls (0.24% and 0.78 in healthy and ART-suppressed donors, respectively). Importantly, this expanded M-MDSC population showed higher expression of IDO and ARG-1 (MFI of 488 and 628 for IDO, 533 and 685 for ARG-1 in healthy controls and ART-suppressed, respectively), two enzymes highly related with the immunosuppressive capacity of the MDSC. Moreover, the percentage of M-MDSC in ART-suppressed patients positively correlated with the activation of CD4+ and CD8+ T cells (rho=0.830 p=0.0008 for CD4+, and rho=0.741 p=5495 for CD8+), which in turn correlated with intracellular HIV-DNA (rho=0.742 p=0.0140 for CD4+, and rho=0.672 and p=0.0331 for CD8+) and HIV-RNA (rho=0.837 p=0.0095 for CD4+, and rho=0.877 and p=0.0042 for CD8+). Additionally, infiltration of MDSC in B-cell follicles was preferentially observed in association with the expression of p24 (rho=0.372 p=0.039).

Conclusion: Overall, in ART-suppressed patients, MDSC might be an important player in the preservation of the HIV-reservoir. Finding new therapeutic strategies to modulate the immunosuppressive actions of the MDSC might significantly impact the HIV reservoir.

245 CIRCULATING B-D-GLUCAN AND INDUCTION OF IMMUNE ACTIVATION

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Background: (1→3)-β-D-Glucan (βDG) is one of the most abundant components of fungal cell walls. People living with HIV (PLWH) without invasive fungal infection have been reported to have elevated plasma levels of circulating βDG. Such elevation is correlated with markers of gut damage, immune activation, and the occurrence of non-AIDS events. However, the mechanisms by which βDG induces immune activation and contributes to disease progression remain undefined. We aim to 1) Correlate βDG levels with CD4 and CD8 T cell activation markers as well as integrated HIV DNA, 2) Correlate plasma levels of βDG with expression of its receptors, and 3) Demonstrate a direct effect of βDG on the induction of immune activation in vitro.
Methods: We analyzed plasma and peripheral blood mononuclear cells (PBMC) from participants receiving or not ART. We assessed the frequency CD4 and CD8 T cell activation (HLADR+CD38+) in PLWH PBMC and CD4 T cell bearing integrated HIV DNA by nested qPCR. We used flow cytometry to measure the expression of the βDG receptors Dectin-1 and NKp30 on monocytes and NK cells respectively. We assessed the dynamics of βDG receptor expression up to two days after Saccharomyces-derived βDG stimulation compared to bacterial lipopolysaccharide (LPS) stimulation in vitro. We analyzed indoleamine 2,3-dioxygenase-1 (IDO-1) expression by flow cytometry and cytokine secretion in the supernatant by ELISA following stimulation with βDG and/or LPS.
Results: Higher plasma βDG levels correlated with higher frequencies of HLADR+CD38+ CD4 (r=0.69, p<0.001) and CD8 T cells (r=0.65, p<0.001, n=26), as well as HIV reservoir size in PLWH (r=0.41, p=0.04, n=24). Plasma βDG negatively correlated with the expression of its receptors Dectin-1 on monocytes (r=-0.58, p<0.01) and NKp30 on NK cells (r=-0.61, p<0.01) in 33 participants. In vitro, βDG stimulation prompted a reduction of Dectin-1 and NKp30 expression after 24 and 48 hours of stimulation. βDG stimulation predominantly induced IL-8, TNF-α and IDO-1 production over IL-1β and IL-6 in vitro.
Conclusion: βDG elevation correlated with the frequency of activated CD4 and CD8 T cells and HIV reservoir size. βDG induced immune activation independently of LPS by triggering Dectin-1 and NKp30 on monocytes and NK cells respectively, and inducing cytokine secretion mostly IL-6, IL-8 and IDO expression. Our results pave the way to new treatment strategies to reduce inflammation and prevent the development of non-AIDS events.

246 MINING FOR CD4 CELL RECOVERY PHENOTYPE REVEALS DISTINCT PATTERN FOR BLACK ETHNICITY

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Background: With ever increasing majority of HIV-infected individuals receiving suppressive antiretroviral treatment (ART), one of the key questions is understanding the factors that govern the CD4 cell recovery in this population.
Methods: We explored a range of asymptotic growth curve models to describe CD4 cell recovery after ART initiation and to capture its saturation. A well-characterized ART-naïve patient population of 2,583 individuals from the Swiss HIV Cohort Study (SHCS) receiving suppressive combination ART for at least 3 years (with >9 CD4 cell counts available) was used to establish the recovery phenotype and its population distribution, in particular the CD4 cell count plateau (ART-CD4-plateau) under suppressive ART (supp-ART). Individual ART-CD4-plateaus for a broader population of 4,089 ART-naïve SHCS patients under supp-ART (for at least 3 years with >5 CD4 observations) were inferred from the individual CD4 cell counts given the population distribution. The same approach was applied to CD4 cell percentage to obtain CD4 cell percentage plateaus (ART-CD4%-plateau).
Results: Median ART-CD4-plateau in the supp-ART population based on a Janoschek growth model was 769 cells/µL (IQR [606-945]). Among patients of white ethnicity (76.1%) the median plateau was 785 cells/µL [620-968] compared to a lower median plateau of 720 cells/µL [560-872] observed in black population (14.9%). Lower nadir CD4 cell count, male sex, lower pre-ART HIV-1 RNA, older age at ART initiation and black ethnicity were identified as significant risk factors for lower ART-CD4-plateau in the multivariable model. Although the patients of black ethnicity were, when compared to patients of white ethnicity, younger at ART start (34 [28-39] vs. 40 [33-48]) and predominantly women (64.1% vs. 16.8%) the black population was found to have 61 cells/µL lower ART-CD4-plateau (95%-confidence interval [32-91]) even after adjusting for all cofactors (Fig. 1). Moreover, this finding was consistent among all the considered growth models. Lastly, the ART-CD4%-plateau was also found to be significantly lower for black ethnicity, indicating a different pattern of CD4 cell recovery.
Conclusion: Our approach established a CD4 cell recovery phenotype based on longitudinal data and revealed black ethnicity as an important subpopulation with a distinct CD4 recovery profile. Enabling in-depth analysis of determinants of immune system recovery in treated HIV infection highlights the utility of our method as component for precision medicine.

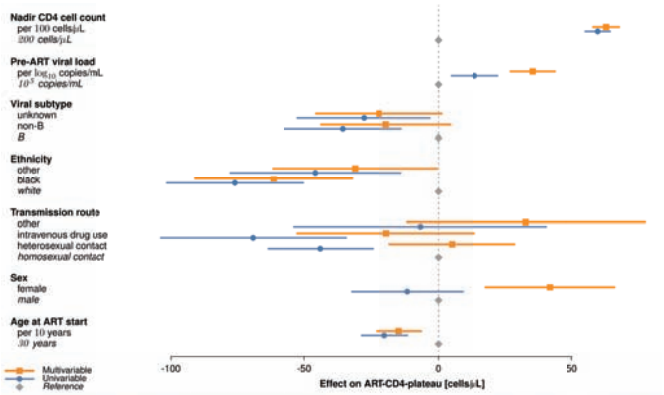

Fig. 1. Determinants of CD4 cell count plateau under suppressive ART. Absolute effect sizes on the absolute plateau and the corresponding 95%-confidence intervals (CI) are shown in blue. Orange squares and bars depict the effect sizes and 95%-CI from the multivariable model, adjusting for all the factors shown in the plot. The vertical dotted gray line refers to the reference CD4 cell count plateau.

247 SPD-L1: A POTENTIAL NOVEL IMMUNE MARKER FOR HIV-1 INFECTION AND VIROLOGIC FAILURE

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Background: Despite viremic control, basal chronic inflammation and its related comorbidities remains an unsolved problem among people living with HIV (PLWH). We explored the impact of HIV-1 infection, antiretroviral therapy (ART) exposure, viral load (VL) and sexual transmitted coinfections (STI) in soluble Programmed death-ligand 1 (sPD-L1) levels, a well-described inductor of T-cell exhaustion in other clinical contexts.
Methods: Plasma samples were collected from 69 adults under clinical follow up in Madrid, Spain. Forty-nine were HIV-1-infected (20 drug naïve and 29 under ART) and 20 HIV-1 free. Among ART treated, 13 were under virological failure and 16 had suppressed VL (<1.6log or <40 HIV-1 RNA copies/ml), with sexual transmitted coinfections (STI) in 5 of 16 cases. Plasmatic sPD-L1 levels were measured using ELISA Kit for Programmed Cell Death Protein 1 Ligand 1, Cloud Clone Corp.
Results: All 49 HIV-infected patients exhibited significant higher sPD-L1 levels than 20 uninfected adults (1.05ng/ml vs. 0.52ng/ml; p<0.001). Levels remained elevated in HIV-infection despite VL control, after comparing 16 infected with undetectable VL with 20 uninfected (0.75ng/ml vs. 0.52ng/ml; p=0.02). ART exposure seemed not to decrease sPD-L1 levels when comparing 16 treated infected with undetectable viraemia vs. 20 naïve (0.75ng/ml vs. 0.87ng/ml; p=0.199). We also found a significant impact of VL on sPDL1 values. Thirteen ART treated subjects under virological failure exhibited the highest sPDL1 levels, being significantly higher than in naive (1.68ng/ml vs 0.87ng/ml; p=0.002) or than in 16 ART treated subjects with supressed viraemia (1.68 ng/ml vs. 0.79ng/ml, p=0.002). The last could be explained by differences in mean VL (5.1log vs. 3.7log vs. <1.6log, respectively). Along these line, there was a positive correlation between VL and sPD-L1 levels in plasma in the whole cohort

(Spearman r=0.3; p=0.03). A non-significant decrease in sPDL-1 values was observed in HIV-1-infected subjects with controlled viraemia with vs. without STI (0.57ng/ml vs. 0.88 ng/ml, p= 0.29).
Conclusion: sPD-L1 levels are significantly elevated during HIV-1 infection, despite control of viraemia. This fact opens new avenues for this biomarker as a predictor factor of virological failure or VL during the clinical follow up of PLWH.

248 IMPACT OF HIV INFECTION AND ANTIRETROVIRAL THERAPY ON IMMUNE CELLULAR FUNCTIONS

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Background: Despite viral suppression by ART and restoration of CD4 T cells, immune activation and exhaustion persist in many of HIV infected individuals which might result in overall decreased cellular activity. In this study we analyze cellular metabolism, function and proliferation in context of HIV infection and immunological parameters.
Methods: Glycolysis and oxidative phosphorylation of lymphocytes from HIV infected treatment-naïve (n=12), ART-treated (n=12) and HIV negative (n=12) individuals were analyzed using extracellular flux analyzer and expression of key metabolic genes was measured by qPCR. Changes in HIF1α transcription factor were analyzed by western blot. We assessed the impact of ART regimens on proliferation capacity by CSFE staining ex vivo. We used ICS staining to determine changes in cellular function and phenotype using multicolor flow cytometry. Comparison of mitochondrial mass was done by qPCR, mitochondrial membrane potential and production of mitochondrial ROS by flow cytometry.
Results: Respiration of CD4, CD8 T cells and NK cells from HIV infected treatment-naïve individuals was significantly reduced compared to HIV negative subjects ($p<0.001$, $p<0.0001$, $p<0.05$). Both respiration and glycolysis of CD8 T cells were in strong correlation with expression of inhibitory receptor PD-1 ($p<0.0001$) and immune activation (HLA-DR+, CD38+; $p<0.0001$). While we expected ART to restore metabolic profiles, we observed that the respiration of CD4 T cells was significantly decreased ($p<0.001$). This was in particular the case for INSTI containing regimens. We observed that cells from these individuals showed significantly lower ex vivo proliferation compared to CD4 T cells from individuals receiving either PI ($p<0.05$) or NNRTI ($p<0.001$). We next assessed the impact of individual ART on CD4 T cells. Both INSTI, EVG and DLG, but not RAL, dramatically reduced respiration (EVG $p<0.05$; DLG $p<0.0001$) without having an impact on glycolysis, Glut1 and PGK1 expression or HIF1α. We also observed decreased secretion of IL-2 ($p<0.001$), MIP-1β ($p<0.001$), CD107a ($p<0.05$) and INFγ ($p<0.05$) indicating impaired function of the cells. Both INSTI increased mitochondrial mass (EVG $p<0.01$; DLG $p<0.05$) and mitochondrial reactive oxidative species (EVG $p<0.0001$; DLG $p<0.05$), but had no impact on mitochondrial membrane potential.
Conclusion: We identified significant interference of INSTI with CD4 T cell respiration, proliferation and immune responses resulting in decreased immune cellular function.

249 HIV-1 DIVERSITY IN GUT IS ASSOCIATED WITH RESIDUAL MUCOSAL VIRUS PRODUCTION ON ART

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Background: HIV-1 persists in cellular reservoirs and some anatomical compartments despite antiretroviral therapy (ART). We compared HIV-1 in gut and blood compartments on ART, regarding differences in target cells, residual HIV-1 DNA and RNA, coreceptor usage, and virus diversity.
Methods: Peripheral blood and duodenum samples were obtained from 17 HIV-1-infected subjects with sustained plasma VL <50 c/mL for 5 years. Blood and gut CD4+ T cells were phenotyped by flow cytometry (BD LSRII). HIV-1 DNA was quantified in sorted blood and gut CD4+ T cells by qPCR. HIV-1 RNA was quantified in duodenum tissue by qRT-PCR. Virus quasispecies were characterized by next-generation sequencing of C2V3C3 env (454 GS Junior), with data cleaning and coreceptor usage prediction by Pyrovir software. Viral diversity in blood and gut compartments was assessed by haplotype numbers, adjusted-Shannon entropy, and Hill numbers. Phylogenetic analyses were performed using CLUSTAL W. A non-parametric test for panmixia was used to look for compartmentalization.
Results: CD4+ T cells in the gut were mainly CD45RO+CCR7- effector memory cells (88.2% vs 13.1% in blood, $P<0.01$). CD4+ T cells were more frequently activated (HLA-DR+, 15% vs 8.2%, $P<0.05$) and proliferating (Ki67+, 2.7% vs 2%, $P<0.01$), and expressed much more CCR5 (83% vs 5.7%, $P<0.01$) in gut than in blood. HIV-1 DNA was 6.7-fold higher in gut than in blood CD4+ T cells ($P<0.01$). Low-level HIV-1 RNA was detected in duodenum tissue of 13/14 subjects (1-7 c/mg). HIV-1 quasispecies displayed compartmentalization between the gut and blood (test for panmixia, $P<0.01$). In the blood, 9 subjects harbored only R5 viruses vs 8 R5/X4 dual-mixed (DM) viruses, while in the gut 13 harbored only R5 viruses vs 4 DM viruses. Virus diversity in V3 env region was reduced in gut vs blood compartment: median haplotype numbers (7 vs 10, $P<0.01$), median adjusted-Shannon entropy (0.14 vs 0.18, $P<0.05$). Virus diversity in the gut, assessed by adjusted-Shannon entropy of C2V3C3 env, correlated with mucosal CCR5+CD4+ T cell frequency ($\rho=0.71$, $P<0.05$), and residual mucosal HIV-1 RNA level ($\rho=0.57$, $P<0.05$).
Conclusion: HIV-1 persists in the gut mucosa on ART with increased levels of infected cells compared to blood CD4+ T cells, and low-level mucosal HIV-1 RNA production. Virus diversity was reduced with enrichment in R5 viruses and compartmentalization in gut compared to blood. Virus diversity in the gut was associated with residual mucosal virus production.

250 ASSOCIATION BETWEEN HIV ANTIBODIES AND D-DIMER: ROLE OF "DEFECTIVE" PROVIRUSES

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Background: Persistent inflammation and immune activation can be seen in HIV-infected individuals who have achieved prolonged suppression of plasma viremia. The potential contributions from transcription/translation-competent yet "defective" HIV-1 proviruses ("Zombies") to sustained aberrant immune activation and inflammation has recently received attention. The purpose of the study was to identify pathway(s) that contribute to persistent immune activation by looking at associations among proviral genome burden, transcription of "defective" proviruses, levels of biomarkers for inflammation and immune activation, and magnitude of anti-HIV Ab responses.
Methods: 15 HIV-infected pts on suppressive cART with pVL<40 copies/mL for >2 yrs (range 2.1-10.8) and 5 pts with pVL≥40 copies/mL (range 2,044-26,100) were studied. HIV genomes were assessed by 5'LTR-to-3'LTR PCR single-genome amplification and direct amplicon sequencing. Levels of proviral DNA and cell-associated HIV-RNA were determined by a semiquantitative PCR. Levels of D-dimer, IL-6 and hsCRP were measured on plasma by ELISA assays. Western blots (WB) were performed using the Cambridge Biotech HIV-1 Western Blot kit. A WB score, reflecting the magnitude of anti-HIV Ab responses, was assigned to each patient.
Results: Persistence of HIV antibodies was seen in all pts, irrespective of virological status or duration of viral suppression. A positive correlation was observed between WB scores and D-dimer levels ($p=0.0083$), indicating that the magnitude of the anti-HIV Ab responses could serve as a biomarker for identifying a state of immune activation. WB scores were also associated with proviral copy numbers ($p=0.0087$). Incomplete WB banding profiles, involving the absence of p31 and p17 bands, were found exclusively in pts with pVL<40 and were associated with the presence of "defective" proviruses (1.5-8 kb in length).
Conclusion: Identifying the source and the mechanism(s) that contribute to persistent immune activation and inflammation in individuals with HIV infection is of critical importance in advancing our understanding of HIV-1 pathogenesis. The close relationship found between the magnitudes of anti-HIV Ab responses and D-dimer indicates a novel interplay between antigen production and immune activation/coagulation. "Defective" proviruses that overwhelmingly persist during suppressive cART can serve as a persistent source of viral antigen productions and stimulate the adaptive and innate immune systems.

251 ANTI-CD4 AUTOANTIBODIES ARE ASSOCIATED WITH DISCORDANT IMMUNOLOGICAL RESPONSES TO ART

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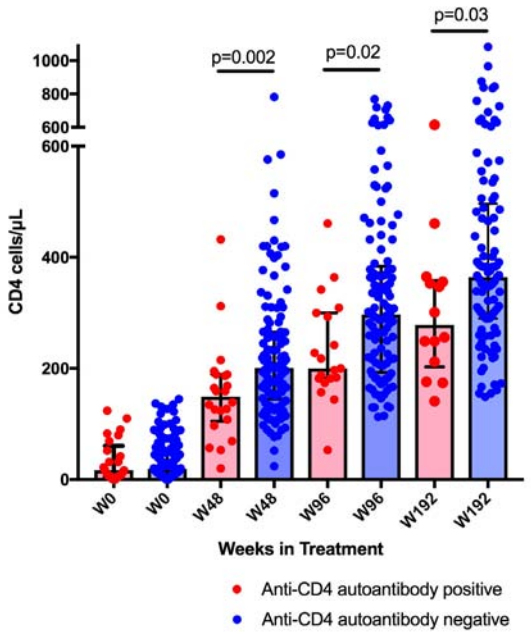
Background: A discordant immunological response to ART with poor CD4 T cells reconstitution is associated with increased inflammation, morbidity and mortality. We hypothesized that anti-CD4 autoantibodies could limit CD4 T cell recovery despite suppressed HIV-1 replication.

Methods: 204 HIV+ART naïve patients with CD4<100 at baseline were included in this prospective study and followed longitudinally for 192 weeks after ART initiation. Demographic, virologic and clinical data were analyzed. Luciferase Immunoprecipitation Systems (LIPS) was used for detection of autoantibodies against CD4, CD8α, CD8β, CD3γ, CD3ε, IFNGR1, CD127, CD25, CTLA4, CCR5, Ro52. IgG deposition and natural killer (NK) antibody-dependent cell mediated cytotoxicity (ADCC) assays in PBMCs were developed to assess the binding of anti-lymphocyte antibodies and their possible biological effects. Mann-Whitney U test and Wilcoxon matched pair tests were used to compare groups.

Results: Out of the 204 patients tested with LIPS, 36 had (17.6%) CD4 autoantibodies (aCD4-Ab) and no other immunoreactive protein was detected. Patients with aCD4-Ab had significantly lower CD4 reconstitution at week 48 compared to those without with median CD4 of 162 CD4/µl vs 199 CD4/µl in (p=0.02). Median Δ for CD4 reconstitution for the aCD4-Ab group was 117.5 vs 162 in the group without (p=0.0037). After excluding patients who received immunomodulant treatment that could have affected CD4 T cells reconstitution (i.e. corticosteroids, rituximab, chemotherapy), patients with aCD4-Ab, had lower CD4 reconstitution at all timepoints (weeks 48, 96 and 192) with median CD4 at 192 weeks 278 CD4/µl for the aCD4-Ab group vs 364 CD4/µl for the anti-CD4 negative group (p=0.03) with median Δ of 247 CD4/µl vs 338 CD4/µl (p=0.057). The aCD4-Ab binding site was mapped to the D3-D4 domain of CD4 by mutation analysis. No evidence of IgG deposition or ADCC was identified in any of the tested subjects with aCD4-Ab.

Conclusion: aCD4-Ab are associated with discordant immunological response to ART in patients with advanced HIV/AIDS. In this cohort, aCD4-Ab effects on CD4 T cell homeostasis was not explained by ADCC suggesting other potential mechanisms that may adversely affect T cell homeostasis.



252 SEX DIFFERENCES IN CMV REPLICATION AND HIV PERSISTENCE DURING SUPPRESSIVE ART

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Background: CMV replication is common in men living with HIV (MLWH), and is associated with increased immune activation, T cell proliferation and larger HIV reservoirs. The prevalence of CMV shedding and its relationship to HIV persistence have not been investigated in women (W)LWH.

Methods: Fifty virologically suppressed WLWH were enrolled in New York City (between 07/2014 thru 09/ 2016). Participants provided oral, vaginal and urine samples with peripheral blood mononuclear cells (PBMCs, N=50) at one time-point. CMV DNA was quantified in each specimen by real-time PCR. Cellular HIV DNA and HIV RNA transcripts (unspliced and multiply spliced [ms] encoding tat-rev) were quantified by droplet digital (dd)PCR. Historical data generated from 49 CMV-seropositive MLWH (blood and semen) were used as controls (Gianella et al, PMID: 26842469).

Results: Median age was 53 years for women and 46 years for men; 28 (56%) women were post-menopausal and 43 (86%) acquired HIV through heterosexual contact. All men reported sex with men as risk factor. Both groups were chronically infected with HIV and had undetectable HIV RNA in blood. Median CD4+ were 721 cells/ml (490-930) for women and 625 (538-744) for men. Levels of cellular HIV DNA and unpliced HIV RNA were not different between sexes, but women were less likely to have detectable msHIV RNA (54% versus 100% in men, Fisher <0.01). Of the 49 CMV-seropositive WLWH, 16/49 (33%) had detectable CMV DNA in at least one specimen type, compared to 26/49 (53%) men (P<0.01), Table 1. CMV DNA was most frequenty detected in vaginal swabs (16%) and PBMCs (14%) for women and in semen (40%) for men. Unlike previously shown in men, the presence of CMV DNA was not associated with increased HIV DNA in women. Among women, pre-menopausal status was associated with significantly lower HIV DNA compared to post-menopause, after adjusting for age and duration of HIV infection (42 versus 150 HIV DNA copies/106 cells, P<0.01. Men: 90 copies/106 cells). There was no difference in cellular HIV RNA transcription and CMV shedding between pre- and post-menopausal women.

Conclusion: WLWH co-infected with CMV presented reduced cellular HIV transcription and less subclinical CMV replication compared to men, but similar HIV DNA levels. Interestingly, post-menopausal status was independently associated with increased HIV DNA reservoir, even after adjusting for age and duration of HIV infection. The exact mechanism is unclear and should be evaluated in future longitudinal studies.

Table 1: Sex differences in Demographics, CMV and HIV Reservoir Data

Demographics		Women (N=50)	Men (N=49)
Ethnicity, n (%)	Hispanic	7 (14%)	19 (39%)
	Non-Hispanic	43 (86%)	30 (61%)
Race, n (%)	Asian	1 (2%)	2 (4%)
	Black	37 (74%)	11 (22%)
	Native-American	1 (2%)	0
	Other	3 (6%)	0
	White	8 (16%)	36 (74%)
HIV transmission, n (%)	IVDU	3 (6%)	0
	Sex with men	43 (86%)	48 (98%)
	Both	2 (4%)	0
	Other	2 (4%)	1 (2%)
Menopausal status, n (%)	Pre-menopausal	24 (48%)	
	Post-menopausal	26 (52%)	
Age (years), median (IQR)		53 (47-57)	46 (38-51)
Current CD4$^+$ cells (cells/mm^3), median (IQR)		721 (490-930)	625 (538-774)
Nadir CD4$^+$ cells (cells/mm^3), median (IQR)		172 [56-265]	215 (68-350)
CMV Data			
CMV IgG seropositive		49 (98%)	48 (98%)
CMV IgG levels		37 (33-41)	34 (26-43)
Detectable CMV DNA (any samples)		16 (33%)	26 (53%)
HIV Reservoir Data			
HIV DNA levels (copies/10^6 cells), median (IQR)		89 (19-209)	90 (18-148)
Unspliced cellular HIV RNA levels (per 200ng DNA Input), median (IQR)		7 (3-15)	7 (4-15)
Detectable multiply spliced cellular HIV RNA		27 (54%)	41 (100%)*

Legend: n (%): number (percent), IVDU: IV drug users, IQR: inter quartile range, CMV: cytomegalovirus. * Cellular HIV RNA data for men only available on a subset of n=41.

253 EBV AND CMV LEVELS IN BLOOD ARE ASSOCIATED WITH NON-AIDS EVENTS DURING ART

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Background: Despite antiretroviral therapy (ART), HIV infection remains associated with higher morbidity/mortality, driven in part by increased inflammation. We sought to identify associations between cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) DNA in peripheral blood mononuclear cells (PBMC) with occurrence of non-AIDS events and mortality during ART.
Methods: Participants (140 cases, 305 controls, 929 samples) were selected from the ACTG ALLRT trial; all were HIV suppressed on ART at year 1 and thereafter. Blood was collected: pre-ART (baseline), 1-year post-ART, and immediately pre-event (for cases). Cases included myocardial infaction/stroke, malignancy, serious bacterial infection or death. Controls had an event-free follow-up equal or greater than the relevant case. Participants were matched on age (within 10 years), sex, pre-ART CD4+ count (within 50 cells/mm3), ART regimen, and parent study. At each time-point, levels of CMV and EBV DNA were measured in PBMC by ddPCR. Levels of CMV and EBV IgG were measured at year 1 in plasma by ELISA. Other cellular and soluble biomarkers were obtained from previous projects (see table). Conditional logistic regression analysis assessed associations of the biomarkers with events, adjusted for relevant covariates. Correlation between biomarker levels were assessed with Spearman's correlations among controls.
Results: Cellular CMV DNA was detected in 25% of all time-points, while EBV was detected in >90%. Higher levels of EBV were associated with an increased risk of events at all time points (OR per one IQR = 1.5-1.7, all p<0.009), with the strongest associations at baseline. Associations remained unchanged when adjusting for relevant clinical factors. At year 1 (but not other timepoints), having detectable CMV DNA (yes/no) was associated with increased risk of events in most adjusted models (OR per one IQR = 1.4-1.8, p ranging 0.03-0.17). CMV and EBV levels were correlated only at the pre-event time point (r=0.18, p<0.0001). Levels of EBV DNA were associated with EBV IgG (r=0.37, p<0.0001), while CMV DNA was not associated with CMV IgG. Levels of CMV were correlated with all soluble markers at baseline, while EBV DNA was correlated with some biomarkers at each time point (see table).
Conclusion: Subclinical replication of EBV and (to lesser extent) CMV in blood were associated with increased inflammation and were predictive of non-AIDS events and mortality in ART suppressed HIV-infection.

Table 1. Spearman's correlations comparing CMV and EBV DNA with inflammatory biomarkers at each time point among the controls.

	CMV			EBV		
	Baseline	Year 1	Pre-Event*	Baseline	Year 1	Pre-Event*
I-FABP	0.18	-0.05	-0.09	-0.01	0.06	0.18
LBP	0.31	0.02	-0.04	-0.01	0.11	0.02
sCD163	0.17	-0.07	-0.03	0.14	0.18	0.09
suPAR	0.29	0.05	0.01	0.09	0.13	0.09
BDG	0.27	0.04	-0.02	-0.09	0.11	0.04
IL-6	0.26	-0.05	0.03	0.06	0.13	0.14
IP-10	0.30	-0.08	-0.06	0.20	0.23	0.28
sTNFR-I	0.31	-0.08	-0.06	0.16	0.23	0.08
sTNFR-II	0.31	-0.10	-0.08	0.19	0.20	0.15
sCD14	0.38	-0.02	0.07	0.03	0.18	0.11
D-dimer	0.26	0.07	-0.09	0.14	0.09	0.18

Legend: Cells in gray have p<0.05 based on Spearman's correlation, I-FABP: Intestinal fatty-acid binding protein, LBP: Lipopolysaccharide binding protein, sCD163/14: Cluster of Differentiation 163/14, suPAR: soluble urokinase-type plasminogen activator receptor, BDG: (1-3)-β-d-glucan, IL-6/10: Interleukin-6/10, sTNFR-I/II: Soluble tumor necrosis factor receptor I/II. * Since control had no event, this column refers to the time-point matched to the events in the case group. Biormarkers were generated as part of Tenorio et al, PMID: 24795473 and Hoenigl et all, CROI 2018 abstract Nr. 529.

254 GAMMA DELTA T-CELL IR SIGNATURES REVEAL DIVERGENCE OF HEALTHY AND AVIREMIC HIV+ AGING

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Background: Even with effective viral control, HIV-infected individuals are at a higher risk for morbidities associated with older age than the general population, and these serious non-AIDS events (SNAEs) track with plasma inflammatory and coagulation markers. The cell subsets driving inflammation in aviremic HIV infection are not yet elucidated. Also, whether ART-suppressed HIV infection causes premature induction of the inflammatory events found in uninfected elderly or if a novel inflammatory network ensues when HIV and older age co-exist is unclear.
Methods: In this study we measured combinational expression of five inhibitory receptors (IRs) on seven immune cell subsets and 16 plasma markers from peripheral blood mononuclear cells (PBMC) and plasma samples, respectively, from a HIV and Aging cohort comprised of ART-suppressed HIV-infected and uninfected controls stratified by age (≤35 or ≥50 years old). For data analysis, multiple multivariate computational algorithms (cluster identification, characterization, and regression (CITRUS), partial least squares regression (PLSR), and partial least squares-discriminant analysis (PLS-DA)) were used to determine if immune parameter disparities can distinguish the subject groups and to investigate if there is a cross-impact of aviremic HIV and age on immune signatures.
Results: IR expression on gamma delta (γδ) T cells exclusively separated HIV+ subjects from controls in CITRUS analyses and secretion of inflammatory cytokines and cytotoxic mediators from γδ T cells tracked with TIGIT expression among HIV+ subjects. Also, plasma markers predicted the percentages of TIGIT+ γδ T cells in subjects with and without HIV in PSLR models, and a PLS-DA model of γδ T cell IR signatures and plasma markers significantly stratified all four of the subject groups (uninfected younger, uninfected older, HIV+ younger, and HIV+ older).
Conclusion: These data implicate γδ T cells as an inflammatory driver in ART-suppressed HIV infection and provide evidence of distinct 'inflamm-aging' processes with and without ART-suppressed HIV.

255 SENESCENCE & EXHAUSTION OF T-CELL MEMORY SUBSETS INCREASED IN AGING PERSONS WITH HIV

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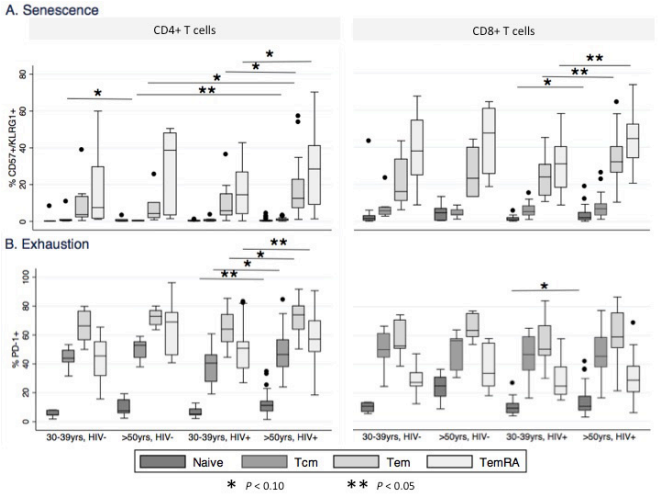
Background: Changes in adaptive immunity including activation, senescence, and exhaustion have been observed in aging and in HIV infection and have been associated with aging-related co-morbidities. We designed a prospective cohort study to examine the HIV- and aging-related changes of T lymphocytes among aging persons living with HIV (PLWH).
Methods: We recruited adults aged 30-39 years and ≥50 years with and without HIV infection in Nashville, TN. PLWH must have had HIV-1 RNA <40 copies/mL ≥1 year. We collected demographic, social, health, and aging-related data on all persons. PMBCs were analyzed with flow cytometry to evaluate the frequency and phenotypes of CD4 and CD8 T cell memory populations (naïve [Tn],central memory [Tcm], effector memory [Tem], and effector memory RA+ [TemRA] cells) and expression of markers of activation (HLA-DR+CD38+), senescence (CD57+KLRG1+), and exhaustion (PD-1+). We used linear regression and Fisher exact tests to assess age- and HIV-infection related differences in T cell phenotypes.
Results: Our baseline data of 80 persons includes 17 adults without HIV (10 aged 30-39 years, 7 aged ≥50 years) and 63 PLWH (19 aged 30-39 years, 44 aged ≥50 years). In all, 23% were women and 34% were African American; 59% of HIV-negative and 95% of PLWH were seropositive for CMV; and the median CD4 cell count of PLWH was 779 [interquartile range: 507, 938]). In general, increasing age was associated with decreased CD4 and CD8 naïve T cell populations in both HIV-negative persons and PLWH (PLWH CD4 Tn β=-0.58% per year of age, p=0.002; HIV-negative CD4 Tn β= -0.85%, p=0.007) and increasing proportions of CD8 Tem and TemRA in PLWH (β= 0.19% [p=0.050] and 0.29% [p=0.055], respectively). T cell activation was generally very

low and did not significantly differ by HIV status or age. Increasing age was associated with increased senescence in CD4 and CD8 memory subsets (Figure 1a) and with increased exhaustion in CD4 subpopulations (Figure 1b). Overall, aging-related changes were similar between HIV-negative persons and PLWH. T cell phenotypes were not statistically associated with frailty in HIV-negative persons or PLWH.

Conclusion: Among PLWH with virologic suppression, increasing age was associated with loss of naïve T cells and increasing proportions of highly differentiated, exhausted and senescent memory T cells. Further research into the mechanisms and effects of aging-associated adaptive senescence and exhaustion in PLWH is needed.



256 CLONAL HEMATOPOIESIS AMONG OLDER TREATED HIV+ PERSONS ENROLLED IN COCOMO

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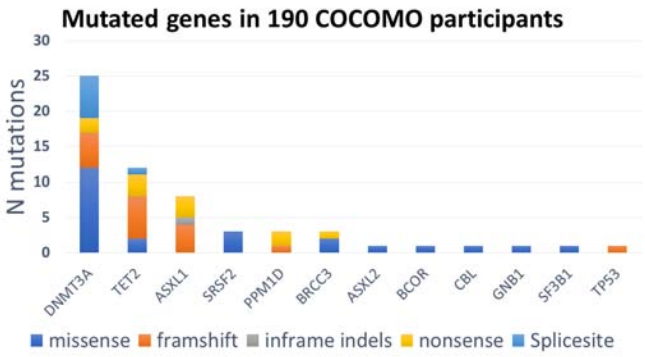
Background: Clonal hematopoiesis (CH) is the expansion of blood cell subpopulations containing somatic mutations. CH increases with age and has been associated with death, cancer and cardiovascular disease in the general population. Here, we set out to investigate CH prevalence and its association with inflammation, T cell subpopulations and coronary calcium among older treated HIV+ persons enrolled in the COCOMO cohort.

Methods: Targeted error-corrected sequencing of 21 CH-associated genes was performed in stored buffy coats of COCOMO participants older than 55y. IL-1β, IL-2, IL-4, IL-6, IL-10, IL-17A, IFNγ and TNFα levels were measured in plasma using a multiplex assay. Flow cytometry identified T cell subpopulations. Agatston score was used to quantify coronary artery calcification among those participants undergoing a cardiac CT. Cytokine levels, T cell subpopulations and Agatston score were compared between participants with ad without CH. Multivariate logistic/linear regression identified independent associations.

Results: Out of 190 participants (median [IQR] age: 66y [61-70], 87% male, mean CD4+ cell count 678, 99.5% virologically suppressed), 49 (25.8%) had at least one mutation. In line with reports from general population, the most frequent mutations (n/%) were: DNMT3A (25/13.2), TET2 (12/6.3) and ASXL1 (8/4.2) (Figure). Those with any mutation were older (68 [60-76] vs. 65 [57-73], p=0.009) and more likely to be male (98 vs. 83%, p=0.006). No differences were observed in terms of HIV-related factors. Participants with CH had lower IL-10 levels (0.51 [0.29-0.69] vs. 0.58 [0.36-0.89]pg/mL, p=0.049) and tended to have a higher proportion of detectable IL-4 levels (48.5 vs 25.9%, p=0.09); other cytokine levels were similar. With adjustment for age and sex, CH remained associated with lower IL-10 (adjusted β [95%CI]: -0.10 [-0.20, -0.01], p= 0.03). Participants with and without CH had similar proportions of T cell subpopulations (p>0.10 for all subpopulations investigated). Participants with and without CH had similar median Agatston scores (111 [5-357] vs. 76 [0-279], p=0.68). When compared to participants with no mutations, those with TET2 tended to have higher Agatston scores: 232[46-874], p=0.07, but after adjustment for age and sex, TET2 was no longer associated with coronary calcium: β=-0.04 [-0.19, 0.10]; p=0.57.

Conclusion: CH is common among older treated HIV+ persons. Albeit limited by sample size, our analyses suggest that CH may be associated with dysregulated inflammation.



257 IMMUNOSENESCENCE IN HIV IS ASSOCIATED WITH CMV STATUS AND LOWER CD4:CD8 RATIO

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Background: It remains unclear whether increased immunosenescence observed in people living with HIV (PLWH) is driven by high rates of cytomegalovirus (CMV) co-infection or underlying immune dysfunction. We investigate relationships between immune function, CMV IgG positive status (CMV+) and immunosenescence in PLWH and HIV- control subjects.

Methods: Using cryopreserved PBMC from subjects in HIV UPBEAT, a cohort of PLWH and HIV- controls from similar demographic backgrounds, we measured CD4 and CD8 T-cell immunosenescence by flow cytometry, defined as CD4+/CD8+, CD28- CD57+ T-cells. We used linear regression to explore associations between immunosenescence, HIV status, demographics, CMV+, CMV IgG titres and CD4:CD8 ratio. Data are median (interquartile range) or model estimate (ME) [95% confidence interval (CI)] unless stated.

Results: Of 219 subjects, 107 (48.8%) were PLWH (68% male, 34% African, age 47 [39-53] years, 30% smokers) and 112 were HIV- (48% male, 17% African, age 50 [44-56] years, 15% smokers). PLWH had lower CD4:CD8 ratios (0.89 [0.65-1.19] vs 2.3 [1.63-3.18], P<0.001), higher % of senescent CD4+ and CD8+ T-cells (4.2 [1.4-7.6] vs 0.5 [0.1-2.1] and 34 [21.0-45.4] vs 22.6 [14.4-35.0] respectively, both P<0.001) and were more likely to be CMV+ (89% v 40%, P<0.001). In univariate analyses, HIV status, lower CD4:CD8 ratio and CMV+ were associated with higher CD4+ and CD8+ senescence. In analyses adjusted for age, gender, ethnicity and smoking, HIV infection remained significantly associated with higher CD4+ (ME [95%CI) 1.668 [1.168-2.168], P<0.001) and CD8+ (0.306 [0.115-0.497], P=0.002) T-cell senescence. Additional adjustment for CD4:CD8 ratio or CMV+ attenuated this association (table1), with both lower CD4:CD8 ratio and CMV+ associated with increased CD4+ and CD8+ senescence. When both were included in the model, CD4:CD8 ratio and CMV+ remained independently associated with increased T-cell senescence. CMV+ was similarly associated with CD4+ and CD8+ senescence in PLWH and HIV- subjects (interaction p=0.27 for each) but associations with CD4:CD8 ratio were slightly weaker among PLWH (interaction p=0.002 and p=0.001, respectively). Replacing CMV+ with CMV IgG titres did not alter these findings.

Conclusion: Increased CD4+ and CD8+ senescence in PLWH can be attributed to both immune dysfunction, reflected in lower CD4:CD8 ratios, and CMV status. Future research should focus on immunosenescence and its impact on clinical outcomes in PLWH.

Table 1: Association between HIV, log CD4:CD8 ratio and CMV positivity with CD4+ and CD8+ T-cell senescence*

*All models adjusted for age, gender, ethnicity and smoking status.

Effect on log CD4+ T-cell senescence	Model (i)			Model (ii)			Model (iii)		
	ME	95% CI	*P*	ME	95% CI	*P*	ME	95% CI	*P*
HIV+ vs HIV -	0.665	0.075; 1.256	0.03	0.422	-0.022; 0.866	0.062	-0.206	-0.698; 0.287	0.41
log CD4:CD8 ratio	-0.999	-1.357; -0.642	<0.001	-	-	-	-0.713	-1.001; -0.425	<0.001
CMV IgG: Positive vs Negative				2.786	2.317; 3.254	<0.001	2.591	2.139; 3.043	<0.001
Effect on CD8+ T-cell senescence	ME	95% CI	*P*	ME	95% CI	*P*	ME	95% CI	*P*
HIV+ vs HIV -	-0.087	-0.312; 0.138	0.45	-0.053	-0.245; 0.139	0.59	-0.328	-0.541; -0.116	0.003
log CD4:CD8 ratio	-0.392	-0.529; -0.256	<0.001	-	-	-	-0.313	-0.437; -0.189	<0.001
CMV IgG: Positive vs Negative	-	-	-	0.803	0.6; 1.005	<0.001	0.717	0.522; 0.913	<0.001

258 TELOMERE LENGTH, TELOMERASE ACTIVITY, AND AGE-RELATED DISEASE: ACTG NWCS 422

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Background: Telomere length (TL) and telomerase activity (TA) require further study as biomarkers of age-related disease among persons with HIV (PWH). We assessed factors associated with short TL and associations between TL, TA and age-related co-morbidities among PWH on suppressive ART.
Methods: A nested case-control study using clinical data and banked PBMCs from ACTG Longitudinal Linked Randomized Trials (ALLRT). Cases had: (1) sustained plasma HIV RNA (VL) suppression to <200 copies/mL within 24 weeks of ART initiation and for ≥96 weeks; (2) non-accidental death or confirmed diagnosis of cancer, cardiovascular, liver, renal, neurocognitive, or pulmonary disease, bone fractures or diabetes; (3) banked PBMC pre-ART, week 48 and pre-event. For each case, there were 2 controls matched for sex, age and duration of NRTI. TL was determined using qPCR with relative TL measured by quantifying a telomere repeat copy versus single copy reference gene ratio (T/S ratio). TA was determined using a real-time quantitative telomerase repeats amplification protocol (RQ-TRAP). TA data were $\log_{10}$ transformed. Univariable and multivariable conditional logistic regression evaluated associations between TL, TA and disease.
Results: We studied 351 participants (117 cases, 234 controls); 23% female, 53% non-white, 8% IDU and 56% smokers. Pre-ART, median age was 42 years, CD4 cells/µl 253, CD8 cells/µl 766, CD4/CD8 ratio 0.25, VL 4.7 $\log_{10}$ copies/mL, TL 0.41 and TA 1.9 $\log_{10}$. Among incident cases, 14 (35%) were diabetes, 33 (28%) renal disease, 18 (15%) cancer, 14 (12%) CVD, 7 (6%) death and 4 (4%) bone fractures. Short pre-ART TL (<0.4 T/S ratio) was associated with pre-ART VL $>10^5$ copies/mL (OR=1.9; 95% CI 1.2-3.0) and pre-ART TA in the lowest quartile (OR 1.8; 95% CI 1.0-3.2). We found no associations between short pre-ART TL and age, smoking, CD4 or CD4/CD8 ratio. Factors positively associated with age-related disease were earlier calendar study entry year, pre-ART CD4<200 cells/µl, higher pre-ART VL, initial ART regimen without TDF, lower CD4/CD8 ratio at 96 weeks and smoking. Neither pre-ART TL nor TA were associated with age-related disease in univariable or multivariable analyses.
Conclusion: Pre-ART telomeres were significantly shorter among PWH with higher VL levels; however, pre-ART TL and TA were not associated with age-related disease. Longitudinal data of changes in TL and TA during ART and associations with disease events are forthcoming.

259 HEU HAVE INCREASED PROPORTIONS OF TREG ASSOCIATED WITH DECREASED T-CELL FUNCTIONALITY

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Background: HIV-exposed uninfected infants (HEU) are at higher risk of lower respiratory tract infections (LRTI) that result in hospitalization and death compared with HIV-unexposed infants (HU). We have previously shown that antibody titers against respiratory pathogens do not differentiate HEU with and without LRTI, suggesting that decreased T cell responses may be responsible for the increased morbidity and mortality of LRTI in HEU. To start addressing this question, we compared functional T cell responses, proportions of regulatory T cells (Treg), T cell differentiation and antigen presenting cell (APC) phenotypes in HEU and HU and assessed correlations between function and phenotypes.
Methods: Peripheral blood mononuclear cells (PBMC) collected at 1-2 days of age from 59 HEU and cord blood PBMC from 17 HU were stimulated with Staphylococcal Enterotoxin B (SEB) or mock for 72h, and tested by flow cytometry for proliferation and expression of IFNϒ, IL4, IL10, TGFβ, CD39 and CD107a. Treg, T cell differentiation and APC phenotypes were measured in unstimulated PBMC. Data were analyzed by univariate and multivariate linear regression adjusting for HIV exposure status. P-values were adjusted using false discovery rate.
Results: HEU had significantly lower IFNϒ, IL4, IL10, TGFβ and CD39 CD4+ T cell functional responses (SEB/mock) and similar CD8+ T cell responses. Phenotypic characterization of unstimulated PBMC revealed higher CD4+/CD8+FOXP3+, CD4+/CD8+FOXP3+CD25+ and CD8+IL10+ Treg and CD27- and/or CD28- differentiated conventional T cells and Treg in HEU vs HU. CD4+TGFβ+ and CD8+FOXP3+CD27+CD28+ naïve Treg were lower in HEU vs HU. HEU also had higher proportions of CD16+ intermediate monocytes; more CD16+ and CD16- conventional dendritic cells type 1 (cDC1); and higher expression of the CD103 inhibitory ligand on CD16- cDC1. Regression analyses adjusted for HIV exposure showed that higher CD8+IL10+ and CD8+FOXP3+ Treg in unstimulated PBMC were significantly associated with lower CD8+IFNϒ+, CD8+CD107a+, CD8+CD39+ and/or CD8+IL4+ responses to SEB stimulation. There were no associations between T cell function and proportions of Treg in stimulated PBMC or between T cell function and T cell differentiation or APC phenotypes in PBMC .
Conclusion: T cell responses to SEB were lower in HEU vs HU. Although HEU and HU had multiple T cell and APC phenotypic differences in SEB-stimulated and unstimulated PBMC, only high proportions of Treg in unstimulated PBMC were associated with decreased T cell function.

260 RNAPOL III CONNECTS RIG-I AND CGAS HIV-SENSING PATHWAYS IN DC FROM ELITE CONTROLLERS

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Background: HIV-1 elite controllers (EC) represent a small proportion of HIV-1-infected individuals capable of naturally controlling HIV-1 replication in the absence of therapy, likely as a result of complex interactions between innate and HIV-1 specific immune responses. Recent data suggest that enhanced detection of cytosolic HIV-1 nucleic acids in conventional dendritic cells (cDC) from EC may depend on the activation of specific intracellular nucleic acid sensors and may trigger potent antiviral effector cell responses in these patients. Here, we investigated molecular mechanisms of effective detection of intracellular HIV-1 DNA in cDC from EC.
Methods: Maturation of circulating cDC from n=22 EC and n=9 HIV negative individuals in response to nanoparticles loaded with HIV-1 Gag dsDNA probes was tested by flow cytometry. Subsequently, RNAseq characterization of transcriptional patterns in cDC from n=8 EC with different levels of response to in vitro stimulation was performed. Subsequent RNAseq analysis was also included using cDC from a larger cohort of HIV-1 controllers (n=23) and Progressors (n=14) was performed. siRNA-mediated gene silencing and Small inhibitors were used to validate the potential candidates predicted by our transcriptional study. Finally, analysis of single nucleotide polymorphisms (SNP) of selected candidate molecules was performed using public GWAS data.
Results: Frequencies of activated cDCs responding to intracellular HIV-1 dsDNA were significantly higher in EC patients compared to healthy individuals ($p<0.01$), thanks to a subgroup of EC with markedly superior responses (good responders). Interestingly, transcriptional profiles of cDC from good DNA responders were characterized by differential upregulation of pathways associated with both DNA and RNA sensors. Surprisingly, cytoplasmic immune recognition of HIV-1 dsDNA was impaired after inhibition of RIG-I and RNA polymerase III (RNA pol III) to similar levels observed after cGAS knock down, suggesting that RNA pol III-dependent transcription of HIV-1 DNA allows simultaneous sensing of HIV-1 through cGAS and RIG-I pathways. Defined SNPs in transcripts encoding for RNA pol III and RIG-I were associated with improved innate immune recognition and immune control of HIV-1.

Conclusion: The data suggest previously unnoticed synergistic interactions between intracellular DNA and RNA sensing pathways in cDC in some EC, probably affected by genetic polymorphisms in molecules involved in nucleic acid sensing in these individuals.

261 PROTEOMIC PROFILE ASSOCIATED WITH LOSS OF SPONTANEOUS HIV-1 ELITE CONTROL

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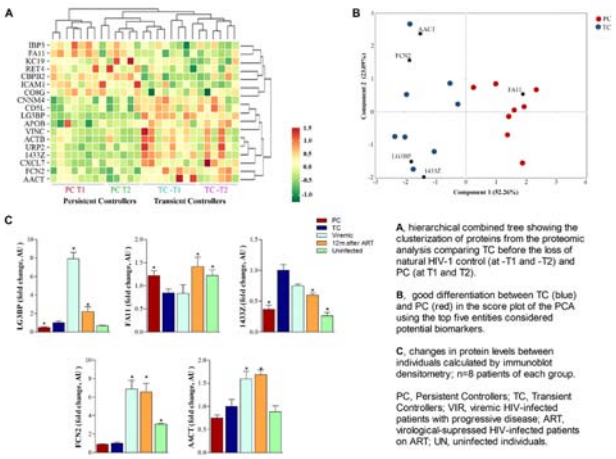
Background: Elite Controllers (EC) spontaneously control plasma HIV-1-RNA without antiretroviral therapy (cART). However, 25% lose virological control over time. Recent findings have identified Transient Controllers (TC) as subjects with low Gag-specific T-cell polyfunctionality, high viral diversity and high proinflammatory cytokine levels. The aim of this work was to study the proteomic profile that preceded this loss of virological control to identify potential biomarkers.

Methods: Plasma samples from TC (EC who spontaneously lost virological control, n=8) at two and one year before the loss of control, were compared with a control group of EC who persistently maintained virological control during the same follow-up period (Persistent Controllers, PC, n=8). Comparative plasma shotgun proteomics was performed with TMT isobaric tag labeling and nanoflow liquid chromatography coupled to Orbitrap mass spectrometry.

Results: Eighteen proteins exhibited differences comparing PC and pre-loss TC time points (Figure A). These proteins were involved in proinflammatory mechanisms and some of them play a role in HIV-1 replication and pathogenesis and interact with structural viral proteins. A good differentiation between groups was observed with the proteins Coagulation factor XI (FA11), Alpha-1-antichymotrypsin (AACT), Ficolin-2 (FCN2), 14-3-3 zeta/delta protein (1433Z) and Galectin-3-binding protein (LG3BP) (Figure B), considered potential biomarkers. We compared the levels of those five proteins by western blot in non-infected healthy donors, viremic HIV-infected patients with progressive disease and HIV-1-infected patients on supresive cART (n=8 of each group). TC and viremic HIV-infected patients showed a similar trend in most of the protein levels, while protein profile in PC were comparable to uninfected patients and somehow to patients on supresive cART (Figure C).

Conclusion: The proteomic profile associated with the loss of virological control was characterized by higher levels of inflammation, transendothelial migration and coagulation. These proteins, especially Galectin-3-binding protein, could be considered as potential biomarker for the prediction of virological progression as well as members of this mechanistic pathways can be considered good candidates for potential drug targets for achieving persistent control. This finding enhances the recent idea that suggests that HIV controllers is a heterogeneous group of subjects being persistent controllers a good model of functional cure.



262 ANTI-GP120 ANTIBODY TITRES CORRELATE WITH AB-DEPENDENT FUNCTIONS IN HIV CONTROLLERS

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Background: Post-antigen (Ag) recognition, the Fc portion of antibodies (Abs) activates the complement cascade and also binds to Fc receptors (FcRs) on innate immune cells such as monocytes, triggering phagocytosis and natural killer (NK) cells inducing target cell lysis. Elite controllers (EC) and viremic controllers (VC) are treatment-naïve HIV+ individuals who maintain viral loads (VL) <50 copies/ml plasma (c/mlp) and <3000 c/mlp, respectively. Ab-dependent (AD) functions have been implicated in playing a role in HIV control. Thus, EC & VC would differ from HIV+ untreated progressors (UTP, VL>2000c/mlp), antiretroviral therapy (ART) treated individuals (TP, VL<50c/mlp) in terms of anti-HIV envelope (gp120)-specific IgG functionality. Here, we compared Abs in plasma from these groups that mediate AD complement deposition (ADCD), AD cellular phagocytosis (ADCP) and AD cellular cytotoxicity (ADCC).

Methods: Total IgG and anti-gp120 IgG concentrations in plasma from 18 UTP, 24 TP, 36 EC and 16 VC were quantified by ELISA. ADCD and ADCC assays assessed the frequency of HIV-infected CEM.NKr.CCR5 (iCEM) target cells (T) positive for the cell surface C3b complement component and annexin V (AnV), respectively. The ADCP assay measured the phagocytosis of gp120-coated fluorescent beads by THP-1 (E) monocyte-like cells. Activity was expressed as the area under the curve (AUC) of the ADCD and ADCP score (% fluorescent T/E x mean fluorescence intensity (MFI) of T/E), respectively for 2 plasma IgG concentrations. The ADCC readout was expressed as the AUC of the frequency AnV+ T for 2 plasma IgG concentrations. Pooled plasma from HIV+ and HIV- individuals were used as positive and negative controls, respectively.

Results: UTP, EC and VC had significantly higher concentrations of anti-gp120 specific Abs than TP ($p<0.0001$, Kruskal-Wallis tests with Dunn's post tests). No statistically significant differences were found between UTP, EC and VC groups for the 3 AD assays, but each was significantly higher than results for plasma from TP ($p<0.001$ for all, Dunn's). When ADCD, ADCC and ADCP results were normalized to the concentration of each sample's anti-gp120 Ab, between group differences disappeared.

Conclusion: High concentrations of anti-gp120 Abs resulted in higher AD functions in UTP, EC and VC compared to TP. Therefore, between group differences in these AD functions are attributed to the between-group differences anti-gp120 Ab concentrations rather that AD function potency.

263 RAPID DECLINE OF IMMUNE ACTIVATION WITH ART IN HIV CONTROLLERS WITH LOW CD4 COUNTS

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Background: The benefits of antiretroviral therapy (ART) for HIV controllers (HCs) remain unclear, but studies have shown that HCs with low CD4+ T cell counts have very high levels of immune activation. Immune activation is classically measured by the dual expression of HLA-DR and CD38 on T cells, but a subset of activated cells, HLA-DR+CD38- CD8+ T cells, are thought to play a role in elite control. Here, we measured HLA-DR and CD38 expression pre and post ART initiation in 3 HCs with low CD4 cell counts to assess the contribution of low level viremia to immune activation.

Methods: HLA-DR and CD38 expression on CD4+ and CD8+ T cells and NK cells was determined by flow cytometry in 2 VCs (VC19 and VC20) and a post treatment controller (PTC2) with low CD4+ T cell counts. Results at baseline and after 2 weeks of ART were compared to historical controls: elite controllers (EC) n=8, chronic progressors (CP) n=11 and HIV negative subjects (HN) n=16. Pre and post therapy viral loads (VL) were measured and compared to changes in immune activation.

Results: All data is presented in the order of VC19, VC20 and PTC2, respectively. Despite low baseline VL (509, 395 and 1073 copies/ml), CD4+ T cell counts in all 3 HCs were low (254, 154, and 77 cells/ul). Two weeks of ART dropped VL in all 3 HCs to < 50 copies/ml. The median percentage of HLA-DR/CD38 co-expression on CD4+ T cells, CD8+ T cells and NK cells was < 5 in ES, CP and HN controls. It was however elevated in all 3 HCs (5, 37 and 12% of CD4+ T cells, 26, 47 and 11% of CD8+ T cells, and 17, 31 and 7% of NK cells). There was a marked decline (>

67% reduction) in the frequency of these activation markers on all 3 lineages after ART that was associated with the degree of decline in viremia. There was no significant decline in the percentage of HLA-DR+CD38- CD8+ T cells in the first two weeks of ART.
Conclusion: While a prior study showed no effect of ART on the frequency of HLA-DR+CD38+ CD8+ T cells in HCs after 4 weeks of treatment, we show here that there is a substantial decline in these cells in HCs with low CD4+ T cells as early as 2 weeks after the initiation of ART. This is not associated with a decline in the percentage of HLA-DR+CD38- CD8+ T cells that are thought to contribute to the control of viral replication. Given the association of T cell activation with HIV associated morbidity, this study offers an immunologic rationale for initiating ART in HCs with low CD4+ T cell counts.

264 ELITE CONTROL OF HIV-1 INFECTION IS ASSOCIATED WITH REDUCED TRAILSHORT EXPRESSION

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Background: Decline of CD4 T-cells in untreated HIV-1 infection is mainly due to apoptosis. TNF-related apoptosis inducing ligand (TRAIL) contributes to this CD4 T-cell decline but does not kill all infected cells. A novel protein, TRAILshort, which is expressed by HIV infected and uninfected cells, prevents the pro-apoptotic TRAIL from killing TRAIL receptor expressing cells and may promote HIV persistence. We hypothesized that HIV-1 elite controllers express less TRAILshort compared to viremic persons, leading to increased killing of HIV-1 infected cells, higher CD4 counts and lower HIV-1 reservoir size.
Methods: Two independent cohorts were studied. Elite controllers (ECs) had undetectable HIV-1 RNA viral load for >1 year in the absence of ART (N=40 and 19 in discovery and validation cohorts). Viremic persons (VPs) had HIV-1 RNA viral loads >10,000 copies/ml off therapy (N=42 and 17). Expression of TRAILshort and full length TRAIL in PBMCs was assessed by RNAseq and flow cytometry. Plasma concentration of TRAILshort was assessed by antibody bead array and full length TRAIL by ELISA. Reservoir size was estimated by ddPCR for total HIV-1 DNA in PBMCs.
Results: ECs were significantly older (51 yrs vs. 41 yrs, P<0.001) and had higher baseline CD4 T cell counts (991 cells/mm3 vs. 479 cells/mm3, P<0.001) compared to VPs. ECs had significantly lower total HIV-1 DNA content in PBMCs than VPs (82 copies/106 cells vs. 1572 copies/106 cells, P<0.001). In the discovery cohort, ECs had lower TRAILshort (P=0.002) and full length TRAIL (P=0.001) gene expression in PBMCs compared to VPs. TRAILshort surface expression on CD4 and CD8 T cells and monocytes was lower in ECs relative to VPs but not statistically significant. In the validation cohort, TRAILshort (P=0.06) and full length TRAIL (P=0.004) gene expression was lower in PBMCs of ECs vs. VPs. ECs had statistically significant lower plasma TRAILshort concentration (normalized to CD4 count) than patients with chronic HIV infection (P<0.001), primary HIV infection (P=0.002) and patients on long term ART (P=0.002).
Conclusion: ECs have lower TRAILshort expression, higher CD4 T cell counts and lower HIV-1 reservoir size than VPs. Reduced TRAILshort expression may facilitate TRAIL-mediated killing of HIV-1 infected cells by the innate and adaptive immune system in ECs. TRAILshort may be an attractive novel target for immunomodulatory therapy to enhance immunologic control of HIV-1 infection.

265 HIV-DNA CONTENT IN PTFH CELLS IS ASSOCIATED WITH RESIDUAL VIREMIA IN ELITE CONTROLLERS

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Background: Low levels of HIV plasma viremia below the limits of detection of commercial assays (residual viremia) has been demonstrated in patients with cART-induced control as well as in those with spontaneous control of HIV replication. The source of residual viremia is highly debated and its potential relationship with levels of cell-associated HIV DNA has not been clarified to date. Herein, we have analyzed the HIV-DNA content in different CD4-T cell subsets and its potential association with residual viremia in elite controllers and in patients with cART-mediated suppression of HIV replication.
Methods: Chronically HIV-infected patients maintaining undetectable pVL were included: 7 with spontaneous viral control (EC) and 9 with cART-mediated HIV replication control (cART-treated). Cell-associated HIV-DNA content was measured by ddPCR in purified resting T memory (rTm) and peripheral T follicular helper (pTfh) cell subsets as important compartments of HIV reservoir. Residual HIV viremia was quantified using a PCR single-copy assay (SCA) with a sensitivity of 0.3 copies/ml. Differences between groups were tested by non-parametric tests and associations by Spearman´s rho coefficient.
Results: Lower levels of cell-associated HIV-DNA (median[IQR] Log copies/million cells) was found in EC compared to cART patients in rTm (2.5[1.9–2.9] vs. 3.1[2.8–3.2]; p=0.059) and in pTfh (1.9[1.9–2.5] vs. 2.9[2.6–3.0]; p=0.025). In 3 of 7 EC (43%) and in 5 of 9 cART patients (56%) HIV could not be detected (<0.3 copies/ml). No significant differences (p=0.468) were found in median values of HIV-RNA between EC (9.5[1.5-16.8]) and cART patients (3[1.3-10.8]) in the subgroup of patients having detectable residual viremia (>0.3 copies/mL). Interestingly, we found a significant and positive correlation between the HIV-DNA levels in pTfh cells and the residual HIV viremia (rho coefficient=0.928, p=0.008) in EC, and this was not observed in cART patients.
Conclusion: Our results suggest that pTfh cells could be an important source of residual plasma viremia in EC patients. This could be the consequence of higher transcriptional activity of HIV in pTfh cells of EC compared to that in cART patients, what could explain the similar levels of residual viremia in both groups in spite of the lower HIV-DNA content in pTfh cells of EC compared to cART patients. Further studies are warranted to check if administration of cART to EC patients could help to reduce HIV-DNA in pTfh cell compartment and/or residual plasma viremia.

266 CXCR3+ FOLLICULAR HELPER TC ARE ASSOCIATED WITH HIV CONTROL DURING CHRONIC INFECTION

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Background: Follicular Helper CD4+ (TFh) are antigen experienced T cells found in secondary lymphoid organs such as lymph nodes (LN). Recently, different TFh subsets has been described during chronic SIV infection based on chemokine receptors expression including CXCR3-Tfh1, CCR4-Tfh2 and CCR6-Tfh17. We characterized TFh subsets proportions and activation patterns during chronic HIV infection and its association with disease progression and viral control.
Methods: Cervical LN mononuclear cells (LNMC) from 22 chronic-untreated (CHR) and 7 treated-undetectable (ART) patients were characterized by flow cytometry including CXCR5hiPD-1hi (TFh), chemokine receptors (R5, R4, R6, X3, X5) and activation markers (CD38, HLA-DR, CD69). LNMC and PBMC HIV CA-DNA were measured by qPCR. T cell counts were assessed by BD True count kit. pVL was determined by m2000 system. Analysis were performed on Cytobank and Prism6 using non-parametric tests.
Results: CHR participants had an average CD4+Tc count of 454 cells/ul. CD4+Tc represented 21.43% of LNMC. TFh were 3.11% of total LN CD4+Tc. Significant negative correlation was detected between TFh% and CD8+Tc count (Spearman r=-0.56, P=0.006). We found low beta chemokine receptors expression on TFh (Tfh2=2.6%, Tfh17=0.7%). CCR5 expression on TFh was 5.2% on CHR and 11.6% on ART, p=0.005. Of note, CXCR3+ Tfh1 are a prevalent population on both CHR (45.8%) and TAR (44.1%). Interestingly, Tfh1% from CHR negatively correlates with pVL (r=-0.55, P=0.007), PB CA-DNA (r=-0.58, P=0.004) and LN CA-DNA (r=-0.47, P=0.02). Tfh1 clustered as separated population on viSNE analysis. Furthermore, Tfh1 expressed significantly higher levels of CCR5, HLA-DR, CD38, CD69 when compared to CXCR3 negative TFh (p<0.0001 in all markers). Finally, CCR5 expressing Tfh1 were significantly higher on treated participants (9.5% CHR vs 26% ART; p<0.0001).
Conclusion: Our study defined preferential chemokine receptors expression patterns on TFh during HIV infection including higher proportions of CXCR3+ Tfh1 cells. Tfh1 levels were associated with lower pVL and CA-DNA on LN and PB. Likewise, Tfh1 were found to be highly activated. These results suggest that Tfh1

have a role controlling HIV during chronic infection. Furthermore, we showed that Tfh1 express higher CCR5 levels compared to other TFh populations. CCR5 expressing Tfh1 are increased in treated individuals suggesting preferential infection on this subset. Our results encourage further Tfh1 studies to detail their role on HIV control and persistence

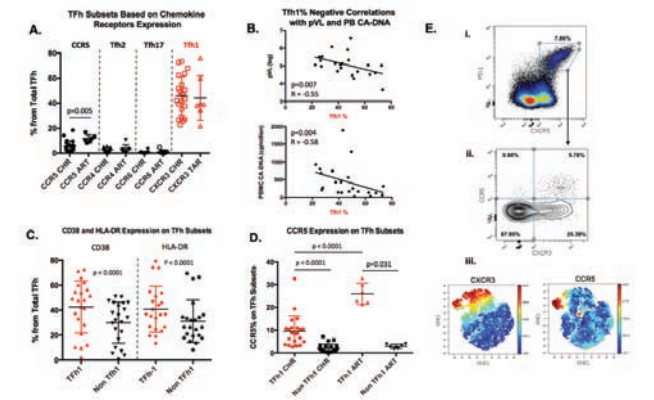

Figure 1. Chemokine Receptors Expression on TFh During Chronic (CHR) and Treated (ART) HIV Infection
A. Identification of CCR6, CCR4 (TFh2), CCR6 (TFh17) and CXCR3 (TFh1) expressing T Follicular helper CD4+ Tc.
B. Negative correlation between Tfh1% and plasma viral load (pVL) and PBMC HIV CA-DNA
C. CD38 and HLA-DR expression on TFh1 and Non TFh1 follicular helper CD4+ Tc in chronic infection.
D. CCR5 expression on TFh1 and Non TFh1 follicular helper CD4+ Tc in chronic and treated infection
E. Flow cytometry analysis showing i. CXCR5/inPD-1hi, ii. CXCR3, CCR5 expression on TFh and iii. viSNE analysis on total TFh showing CXCR3 and CCR5 clustering.

267 METABOLOMIC PROFILE ASSOCIATED WITH LOSS OF SPONTANEOUS HIV-1 ELITE CONTROL

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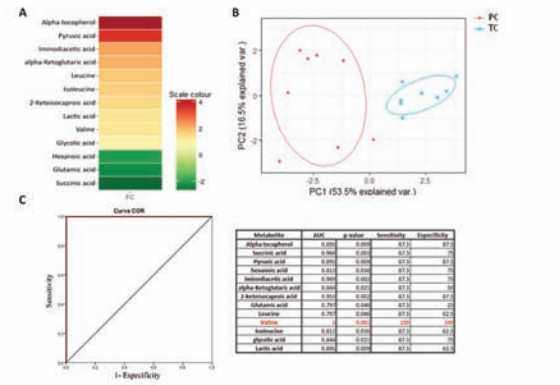
Background: Although Elite Controllers (EC) spontaneously control HIV-1 replication without antiretroviral therapy, approximately 25% of them lose virological control over time. Recently, it has been demonstrated that immunolovirological factors characterized the loss of spontaneous control. To date, no longitudinal study elucidating the metabolomic profile associated with the loss of spontaneous HIV-1 elite control has been performed. In this sense, the aim of this work was to perform a metabolomic approach to identify the underlying mechanistic pathways and potential predictive biomarkers associated with the virological loss of control.

Methods: Plasma samples from EC who spontaneously lost virological control (Transient Controllers,TC, n=8), at two and one year before the loss of control, were compared with a control group of EC who persistently maintained virological control during the same follow-up period (Persistent Controllers, PC, n=8), up to two determinations were performed at one-year interval. The determination of metabolites and plasma lipids was performed by GC-qTOF and LC-qTOF using targeted and untargeted approaches. Metabolite levels were associated with the polifunctionality of HIV-specific CD8-T cell response. A multivariate analysis was performed in order to select and evaluate the performance of the potential biomarkers.

Results: We were able to identify and quantify a total of 70 metabolites and 334 lipids in plasma samples. Before the loss of control, TC showed a metabolomic profile characterized by alterations in glycolysis, Krebs cycle, branched amino acid catabolism and lipid metabolism. Besides, CD8+ T-cell polyfunctionality from PC and TC before the loss of control was strongly associated with these metabolites and lipid levels ($p<0.05$ and $r>\pm0.6$). Finally, the aminoacid valine showed the highest discriminatory power between TC and PC (100% of sensitivity and specificity).

Conclusion: Our study determined a specific metabolomic profile associated with the spontaneous loss of virological control in EC. This profile was characterized by higher immunological activation, oxidative stress and mitochondrial dysfunction. Metabolites and lipid plasma levels were strongly correlated with immunological parameters. These key metabolites, mainly the aminoacid valine, could not only be used as biomarkers for a rapid screening of future loss of virological control but also can be suggested as therapeutic targets in EC.



Metabolomic analysis comparing TC before the loss of natural HIV-1 control and PC. Multivariate analysis were performed in order to select and evaluate the performance of the potential biomarkers. **A)** Heatmap representation of statistically significant metabolites. **B)** Score plot of the PCA using the statistically significant entities showed good differentiation between TC (cyan, n=8) and PC (red, n=8). **C)** Logistic regression and receiver operator characteristic (ROC) curves elucidated valine as the most reliable biomarker for the prediction of the spontaneous loss of virological control in EC

268 KSHV-ASSOCIATED MORTALITY IN HIV-INFECTED SOUTH AFRICANS WITH SUSPECTED TUBERCULOSIS

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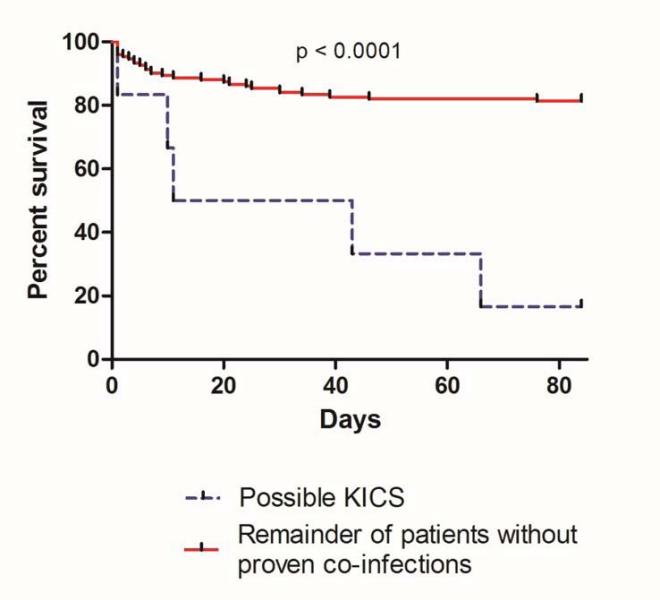
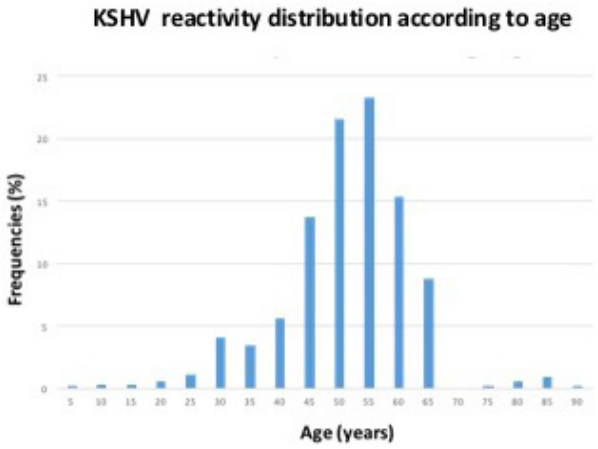
Background: Despite increasing numbers of HIV-infected South Africans receiving antiretroviral therapy, tuberculosis remains the leading cause of mortality. Approximately 25% of suspected tuberculosis is not confirmed microbiologically. We assessed whether co-infection with Kaposi Sarcoma-associated Herpes Virus (KSHV), and particularly the newly described KSHV inflammatory cytokine syndrome (KICS) contributes to mortality in HIV-infected patients with suspected tuberculosis.

Methods: We conducted a cohort study of HIV-infected patients presenting to Khayelitsha Hospital, Cape Town, South Africa, with suspected tuberculosis and followed for 12 weeks. KSHV serostatus was evaluated using ELISA for KSHV K8.1 and LANA. KSHV DNA was measured in blood cells. Clinical correlatives of KSHV lytic activation were evaluated. KSHV viral load and clinical criteria for KICS were evaluated for prognostic value.

Results: 682 participants were accrued, 47% men, 53% women. Median age 36 years (range: 18-80), median CD4 count 62 cells/µl (range: 0-526). 30.7% (95% CI: 27-34%) were KSHV seropositive. 10 (1.5%) had clinical Kaposi sarcoma, 5% had elevated cell-associated KSHV DNA (>100 copies/10^6 cells). Anemia was associated with antibodies against KSHV lytic antigen K8.1 (p=0.003). Overall, 22% died. In patients without tuberculosis or other microbiologically confirmed co-infections, elevated KSHV viral load was associated with mortality after adjusting for age, sex, CD4 count and ART (p=0.023, OR=6.467 [95% CI: 1.290, 32.406]). Applying KICS working case criteria, we identified six «possible KICS» patients. Five died, a significantly worse survival ($p<0.0001$) than other patients without microbiologically confirmed co-infections.

Conclusion: Due to high mortality associated with KICS, contribution of lytically active KSHV in critically ill patients presenting with tuberculosis should be considered to avoid misdiagnosis and to determine appropriate treatment strategies. KSHV viral load testing and application of KICS criteria is warranted to identify HIV-infected South African patients with suspected tuberculosis but no microbiologically identified infection at high risk of death.





269 KAPOSI SARCOMA–ASSOCIATED HERPESVIRUS IN AN HIV-INFECTED COHORT, SOUTH AFRICA

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Background: Kaposi sarcoma associated herpesvirus (KSHV), is an oncogenic virus and a key determinant for Kaposi sarcoma development, particularly in individuals with prolonged immune suppression, for example HIV infected individuals. South Africa is highly endemic with HIV, with the potential for an epidemic of Kaposi sarcoma. For a better understanding of the consequence of KSHV and HIV co-infection, it is important to establish the burden of KSHV infection in South Africa, particularly in regions such as northern South Africa (Limpopo Province) which has a relatively high prevalence of HIV but where data on KSHV in the HIV population does not exist. We aimed at determining the sero-prevalence of KSHV K8.1 lytic and KSHV ORF73 latent antibodies in northern South Africa.
Methods: A multi-district, cross sectional study was carried out in three thousand, five hundred and one plasma samples were retrospectively collected between September 2015 to February 2016, from HIV infected individuals from the five main districts comprising the Limpopo Province. Plasma samples were tested for antibodies to K8.1 and ORF73 antigens of KSHV by ELISA, using an in-house protocol developed by the Viral Oncology Section of the National Cancer Unit, USA. A sample was considered positive if antibodies to either of the antigens was detected. Distribution of infection was analyzed based on demographic, socioeconomic, and immunological parameters. Statistical inferences for significant differences were determined by Chi-square, at a confidence interval of 95%. P-values less than 0.05 were considered significant.
Results: An overall prevalence of 18.9% was observed. Antibodies to both antigens were detected in 8.2% of the subjects. Prevalence of antibodies to the lytic antigen was significantly higher than prevalence of antibodies to the latent antigen (p=0.0001). Significant differences were observed for ORF73 antibody prevalence by ethnicity and year of sample collection (p=0.0001 and p=0.013 respectively). Although the prevalence of KSHV seropositivity in women was high for both antigens as compared to men, no significant difference was observed (p=0.921). No association was found between both antigens in comparison with the different variables (R2=0.1).
Conclusion: This data has for the first time demonstrated a high seroprevalence of KSHV among the HIV infected population in northern South Africa. Infection with KSHV was observed to be associated with ethnicity. More findings are needed to conclude our findings.

270 PRIMARY ROLE OF KSHV IN PATHOGENESIS OF ENDEMIC AND EPIDEMIC KAPOSI SARCOMA

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Background: Kaposi sarcoma (KS)-associated herpesvirus (KSHV) is etiologically linked to all KS forms but mechanisms underlying KS development are unclear. The high incidence of KS in HIV-1+ individuals, epidemic-KS (EpKS), implicates immune dysregulation in co-infection; however, the lack of in-depth comparison with KSHV immune responses in African endemic-KS (EnKS) and the continued incidence of KS despite ART-mediated immune reconstitution make the pathogenetic role of HIV-1 in KS unclear.
Methods: We have utilized cohorts of Zambian and Tanzanian KS patients to compare immune responses and expression patterns between EpKS and EnKS patients or asymptomatic controls. Antibody and cytokine responses were investigated in histologically and PCR confirmed EpKS and EnKS patients, versus asymptomatic controls with and without KSHV infection. KSHV-vDNA, total anti-KSHV antibody, KSHV-neutralizing antibody and cytokines were quantified. RNASeq and bioinformatics analyses were used to compare transcriptomes from biopsied KS and normal skin in both KS groups versus asymptomatic controls using DESeq2 algorithm, and FDR<5% results were considered significant. Two-tailed Mann-Whitney U-test was used to assess median differences between groups where P-value <0.05 was considered significant.
Results: KSHV was consistently detected in tumors but variably detected in plasma and PBMCs from EpKS and EnKS patients. Consistent with elevated antibody-associated cytokines (IL-6, IL-5 and IL-10), total anti-KSHV and neutralizing antibody titers were higher in EpKS and EnKS patients than in controls (P<0.05). Also, titers of anti-KSHV antibody correlated with neutralizing antibody titers in KS patients (r=0.7384, P<0.0001). Despite HIV-1 co-infection in EpKS, total and neutralizing antibody titers were similar between EpKS and EnKS patients (P=0.3067). Likewise, analyses of transcriptomes from KS tissues with and without HIV-1 co-infection revealed remarkable similarities in gene expression patterns and dysregulated pathways.
Conclusion: The detection of similar antibody and cytokine responses as well as transcriptomes in EpKS and EnKS patients suggest that KS results not due to co-infections like HIV-1, but rather primarily due to KSHV-induced pathogenesis, wherein HIV-1 co-infection accelerates and exacerbates disease progression.

271 METABOLIC ABNORMALITIES IN CD8 T CELLS FROM HIV+ INDIVIDUALS WITH KAPOSI SARCOMA

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Background: A subset of HIV-infected individuals suffer from Kaposi Sarcoma (KS) despite viral suppression and CD4 recovery under anti-retroviral therapy

(ART). CD8 T cells are important for control of KSHV, the etiologic agent of KS. Upon activation, CD8 T cells upregulate glycolysis, enabling rapid generation of ATP and biosynthetic precursors. However, CD8 T cells infiltrating the tumor microenvironment must operate under conditions of glucose restriction. We hypothesized that CD8 T cells from individuals with persistent KS under ART exhibit functional and metabolic abnormalities.

Methods: Specimens were obtained from HIV-infected participants on ART with biopsy-confirmed KS (HIV KS; obtained from the AIDS and Cancer Specimen Resource; n = 8) and HIV-infected participants on ART with no known history of KS (HIV controls; n = 8). CD8 T cell differentiation (CD45RO, T-bet, Eomesodermin), metabolic phenotype (glucose transporter Glut1, mitochondrial master regulator PGC-1α), and senescence (CD57) were assessed by flow cytometry. Proliferation in response to PHA was measured by CFSE dilution, and mitochondrial activity using MitoTracker® Deep Red.

Results: Relative to HIV controls, memory (CD45RO+) CD8 T cells from HIV KS participants were skewed toward a more terminally differentiated phenotype, with a lower frequency of T-bet^{low} Eomes^{low} CD57^{low} cells (p = 0.01). HIV KS participants displayed an expanded population of CD8^{dim} T cells (median 9.3% of CD3+ T cells vs 3.1% in controls; p = 0.001). This population exhibited reduced expression of Glut1 (p = 0.008) and PGC-1α (p = 0.04) and increased CD57 expression (p = 0.02) compared with CD8^{bright} T cells, suggesting impaired capacity to utilize glycolysis and proliferate. CD8 T cell proliferation and mitochondrial activity were compared in 10 mM and 5 mM glucose. Proliferation and mitochondrial activity were lower in 5 mM glucose in 2/4 HIV KS participants tested (replication index in 10 mM vs 5 mM glucose 11 vs 6.5 and 19 vs 16, respectively), indicating reduced metabolic flexibility when glucose is limiting. CD8 T cell proliferation and mitochondrial polarization were correlated (r = 0.73; p = 0.02).

Conclusion: Our data suggest that metabolic and functional abnormalities in CD8 T cells may contribute to KS persistence in HIV-infected individuals receiving ART. Therapeutic strategies to normalize CD8 T cell metabolism represent a novel approach to the treatment of persistent KS under ART.

272 SINGLE CELL EVALUATION OF KAPOSI SARCOMA TUMORS REVEALS COMPLEX IMMUNE INFILTRATE

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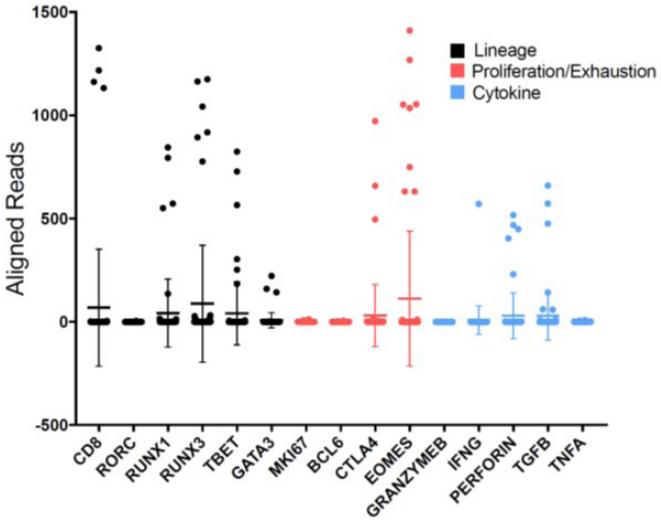
Background: Kaposi sarcoma (KS) is highly associated with immunosuppression, and evidence suggests that KS oncogenesis is associated with loss of T-cell mediated control of human herpesvirus-8 (HHV-8). KS is a complex tumor, characterized histologically by spindle-like tumor cells infected with HHV-8 and marked inflammatory infiltrate. Identifying the elements that comprise the KS tumor, the phenotypic and translational state of these cell types, and how these cellular components interact in vivo will advance our understanding of KS tumorigenesis and guide the development of new targeted therapies.

Methods: We evaluated KS tumor and normal skin samples obtained from treatment-naïve HIV-positive and HIV-negative adults with KS enrolled in an ongoing study at the Uganda Cancer Institute in Kampala, Uganda. RNA was extracted from tissue that had been snap frozen or preserved in RNALater, and sequencing was performed on Illumina HiSeq 2500. Leukocyte composition within each biopsy was estimated using CIBERSORT, an analytic platform used to characterize cellular gene expression profiles. Single-cell suspensions of a subset of KS tumors were sorted and evaluated using targeted multiplex RT-PCR with primers specific for 24 genes relevant to immune cell lineage, function, proliferation, and exhaustion.

Results: CIBERSORT analysis of 39 KS tumors revealed that CD4 and CD8 T cells, monocytes, and macrophages represent the majority of intratumoral hematopoietic cells. To date, 2 cryopreserved single-cell suspensions have been analyzed. Candidate KS tumor cells with a CD34+/VEGFR3+/LYVE-1+ surface phenotype comprised 1.54% and 0.35% of cells from HIV+KS and HIV-KS subjects, respectively. Flow cytometric sorting showed populations of immune cells, including CD4/CD8, monocytes, and macrophages. Targeted transcriptional profiling of the single CD8+ T cells revealed significant heterogeneity in the expression of various genes, but uniformly low expression of genes associated with proliferation and functional activation, such as Ki-67, granzyme B, and TNFa (Figure). Analysis of additional KS tumor single cell suspensions is ongoing.

Conclusion: Our findings to date indicate that the immune infiltrate in KS tumors is dominated by T-cells and macrophages. Initial analyses suggest that the transcriptional profile of immune cells in KS tumors is consistent with an "exhausted" profile, which may have implications for the use of anti-PD1 or other immunotherapies targeting T-cell exhaustion in the treatment of KS.



273 NEW VARIANT OF KAPOSI SARCOMA–ASSOCIATED HERPESVIRUS IN MEN WHO HAVE SEX WITH MEN

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Background: Kaposi sarcoma-associated herpesvirus (KSHV) is involved in the development of Kaposi sarcoma (KS) and lymphoid malignancies: primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD). Molecular epidemiology led to the identification of 7 distinct subtypes whose worldwide distribution was mainly related to geographic region and more rarely to the clinical presentation severity. To assess KSHV diversity, we conducted a retrospective study including 57 HIV-infected men who have sex with men (MSM) with KSHV-associated diseases and 8 MSM KSHV-seropositive on HIV preexposure prophylaxis (PrEP).

Methods: Whole blood sample of 41 KS, 12 MCM and 4 PEL patients and 8 oral swabs (PrEP users) were analyzed for (i) KSHV-DNA quantification, (ii) KSHV typing by ORF-K1 (or VR1) Sanger sequencing. A maximum of likelihood phylogenetic tree (PhyML) was reconstructed; pairwise genetic distances (GD) between amino-acid ORF-K1 sequences were calculated (Mega) and GraphPad was used to perform non-parametric tests.

Results: KSHV typing was contributive in 34/57 patients (19 KS, 11 MCD and 4 PEL) and 5/8 PrEP users. All pathologies combined, subtype C was the most prevalent (18/34) followed by subtype A (11/34). Most of subtype C fell in genotype variant C3 (15/18). Among KS patients, variant C3 was more associated with cutaneous and/or oral mucosa lesions than others subtypes (Odd ratio=11.7, IC95% 1.1-214.2, p=0.023) regardless of the immuno-virological status (CD4 count cells p=0.97; HIV VL p=0.89) and KSHV-DNA viral load (VL) in subtype A tend to be higher than those of subtype C(p=0.055). Among PrEP users, 2 fell in variant C3 and 2 others in variant A4. Viruses of 5 patients (2 visceral KS, 1 MCD, 1 PEL and 1 PrEP user) were identified as "subtype F". However, phylogenetic analysis showed that theirs sequences differed from 11% at amino-acid level of subtype F already described in Uganda (AY953882) as well as epidemiological context (MSM Caucasian versus African subtype). Moreover, ORF-K1 sequence was closed (GD=10-6) to that of KSHV described in a French MSM HIV+ patient with PEL in 2000 (AF178810).

Conclusion: Our study showed that subtype C, and specifically variant C3, was the most prevalent in MSM living in France and tend to be associated with less severe epidemic KS clinical form. We also reported 5 "subtype F" isolated in MSM and associated with severe diseases. We suggest that, in view of phylogenic and epidemiological finding, subtype F could be subdivided in 2 genotypes variants.

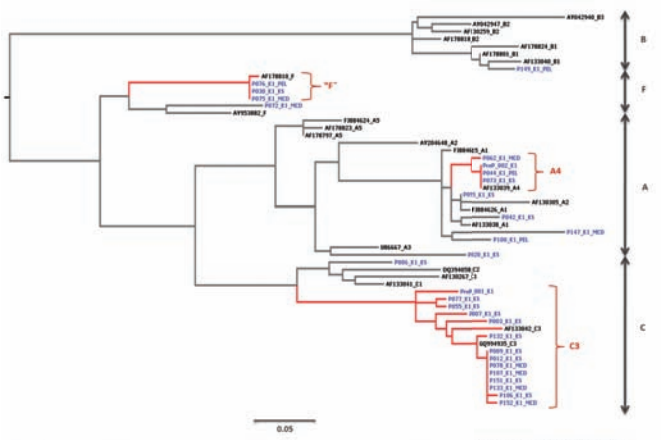

Figure 1 : Amino-acid maximum-likelihood phylogenetic tree (PhyML 3.0) of ORF-K1 patients and references sequences for subtypes A (A1, A2, A3, A4, A5), B (B1, B2, B3), C (C1, C2, C3) and "F African" available on NCBI database. *Patients sequences are represented in blue, references sequences in black and the 3 clusters found in red on the tree.*

274 ANTIRETROVIRAL THERAPY AND KAPOSI SARCOMA TRENDS AND OUTCOMES IN LATIN AMERICA

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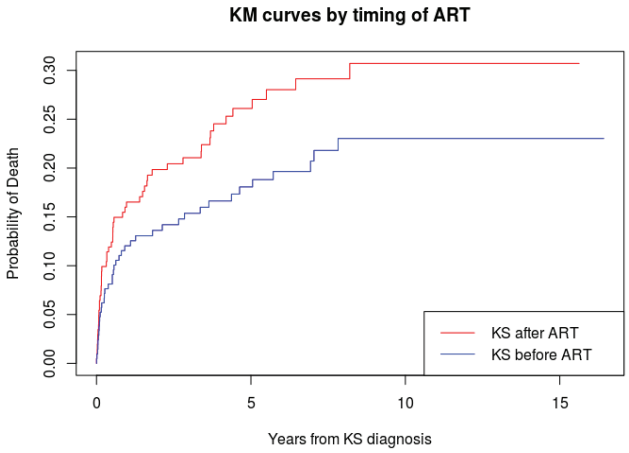
Background: Kaposi sarcoma (KS) remains the most frequent malignancy in persons living with HIV (PLWH) in Latin America, though little is known of KS epidemiology in the region. We examined KS trends and outcomes from Latin American clinical sites in the era of increased access to antiretroviral therapy (ART).
Methods: Cohorts in Brazil, Peru, Mexico, Honduras, and Chile contributed clinical data of PLWH ≥16 years old and KS outcomes from 2000-2017. As KS is often an HIV-presenting diagnosis, we included diagnoses ≤60 days before or at any time after clinic entry. KS incidence by calendar year and cumulative incidence, accounting for death and loss to follow-up as competing risks, were calculated. Patient characteristics associated with KS diagnosis before/at or after ART initiation and the association of mortality after KS with timing of ART relative to KS diagnosis were examined using stratified Cox regression.
Results: Of 22,166 PLWH, 414 had incident KS, including 202 diagnoses in ART-naïve and 212 diagnoses in ART-experienced patients. In total, 45% of PLWH and 50% of KS cases were from Brazil. From 2000-2017, the incidence of KS significantly decreased from 78.1 to 0.3 per 1,000 person-years. Among those who developed KS before ART, the median time from clinic entry to KS was 29 days (interquartile range [IQR]: 1-162) and the median time from KS to ART was 20 days [10-36]. Among those who developed KS after ART, the median time to KS was 4.6 years [2.3-8.3] from ART. Risk of KS was significantly increased in persons with low CD4 cell counts and among men who reported sex with men (MSM) for both pre- and post-ART cohorts (p trend <0.05, each). Among PLWH with KS, those with KS before ART initiation had decreased risk of mortality (Figure, logrank test p=0.08). In analyses accounting for country, HIV sexual risk factor, age, CD4 cell count, viral load, and calendar year, KS diagnosis before ART was associated with a 38% decreased risk of mortality (adjusted hazard ratio [aHR] = 0.62 [95% confidence interval: 0.38-1.02]). Low CD4 cell count (p trend =0.01) and heterosexual HIV risk among women (aHR =2.62 [1.27-5.39] vs. MSM) were also associated with mortality risk after KS.
Conclusion: With increasing ART access, KS incidence in Latin America has decreased in PLWH. However, mortality risk was increased among patients who developed KS after ART initiation. Further research into the determinants of HIV and KS outcomes in Latin America is needed.



275 KAPOSI SARCOMA INCIDENCE BETWEEN 2010 AND 2015 IN THE FRENCH DAT'AIDS COHORT

Isabelle Poizot-Martin[1], Alain Makinson[2], Camelia Protopopescu[3], Antoine Chéret[4], Marc-Antoine Valantin[5], David Rey[6], Claudine Duvivier[7], Christine Jacomet[8], Tristan Ferry[9], Clotilde Allavena[10], Thomas Huleux[11], Firouze Bani-Sadr[12], Véronique Obry-Roguet[1], Patricia Carrieri[3], for the Dat'AIDS study group
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Background: Antiretroviral therapy (ART) has reduced the risk of Kaposi Sarcoma (KS). However, the current incidence of KS remains under reported in HIV-infected people. We analyzed the data of a large French multicenter cohort to estimate KS incidence between 2010 and 2015 and to describe patient's characteristics at diagnosis.
Methods: We performed a retrospective study using longitudinal data from the DAT'AIDS cohort from 01/2010 to 12/2015. KS cases were identified using ICD-10 codes. For incidence assessment, prevalent KS cases (occurring within 30 days after cohort enrollment) were excluded. Demographic, immunologic, and therapeutic characteristics were collected at the time of KS diagnosis.
Results: Among the 44 642 HIV infected people followed-up in the DAT'AIDS cohort during the study period (median age 43 [36-50] years, 69.7% male), 209 patients developed KS, of which 130 were incident KS cases. The KS incidence [95%CI] among 41 744 patients without history of cancer accounting for 167 848.7 person-years (PY) was 77.5 [65.2-92.0]/105 PY, 106.1 [88.8- 126.8]/105 PY in males and 16.7 [8.7-32.1]/105 PY in females. At the time of KS diagnosis, 48 (23%) patients were receiving ART for less than 6 months (median CD4: 227[79; 290]), 55 (26%) for at least 6 months (median CD4: 252 [53; 469]) and 105 (50%) were not receiving ART (median CD4: 112 [36 ; 219]) of which 41 patients had a concomitant HIV diagnosis (median CD4: 41 [25 ; 160]). Patients' characteristics are presented in table according to both ART exposure for at least 6 months and HIV viral load (VL).
Conclusion: In a resource-rich setting with high ART coverage, KS incidence remained high in recent years. Though such rates usually reflected a late HIV diagnosis and/or care access, KS also occurred despite prolonged ART exposure and/or controlled of HIV viremia in a quarter of cases. Multiplying the opportunity of HIV screening among the key populations to avoid useless delays to care should result in substantial reduction of KS incidence. We need to better define factors associated of KS in patients under ART and controlled viremia.

Median (IQR)/N (%)	All KS cases n= 209	KS without ART n= 105 (a)	KS on ART* with HIV VL>50 cp/mL n= 30 (b)	KS on ART* with HIV VL<50 cp/mL n= 24 (c)	p (a)vs(b)vs(c) (b) vs (c)
Age (Y)	43.0 (35.7 ; 49.9)	42.5 (35.1 ; 49.9)	43.5 (36 ; 51.2)	48.2 (39 ; 54.7)	0.133
M / F	192 (91.9) / 17 (8.1)	98 (93.3) / 7 (6.7)	26 (86.7) / 4 (13.3)	21 (87.5) / 3 (12.5)	0.339**
Transmission group MSM Heterosexual IVDU Others/unknown	 133 (63.6) 48 (23) 6 (2.9) 22 (10.6)	 68 (64.8) 25 (23.8) 2 (1.9) 10 (9.5)	 16 (53.3) 7 (23.3) 2 (6.7) 5 (16.7)	 14 (58.3) 8 (33.3) 1 (4.2) 1 (4.2)	0.420**
HIV Time follow up (y)	2.1 (0.1 ; 9.4)	0.52 (0.03 ; 6.37)	12.8 (6.4 ; 15.8)	7.4 (2.8 ; 20.7)	<0.001; *0.210*
ART Time exposure (y)	5.7 (1.5 ; 12.8)	-	8 (3.9 ; 13.1)	4.1 (1 ; 10.3)	*0.169*
Stage C at KS Yes No	 58 (27.8) 148 (70.8)	 16 (15.4) 88 (84.6)	 12 (42.9) 16 (57.1)	 7 (29.2) 17 (70.8)	0.006; *0.307*
Nadir CD4/mm3 <200/mm3	123 (30 ; 264) 121 (57.9)	130 (46 ; 304) 58 (55.2)	13 (5 ; 154) 22 (75.9)	242 (120 ; 363) 9 (37.5)	<0.001; *<0.001* 0.013; *0.005*
CD4/mm3 CD4 >500/mm3	188 (49 ; 360) 27 (12.9)	112 (36 ; 219) 6 (6.7)	68 (12 ; 301) 1 (3.3)	467 (255 ; 819) 9 (37.5)	<0.001; *<0.001* 0.002** ; *0.003***
CD8/mm3 CD8≥ 831/mm3	761 (463 ; 1247) 85 (40.7)	676 (413 ; 986) 32 (38.1)	665 (507 ; 1321) 10 (41.7)	960 (662 ; 1360) 14 (58.3)	0.189;*0.303* 0.409; *0.248*
Ratio CD4:CD8 Ratio<1	0.2 (0.1 ; 0.4) 175 (83.7)	0.1 (0.1 ; 0.3) 82 (98.8)	0.2 (0 ; 0.3) 24 (100)	0.5 (0.2 ; 0.9) 18 (75)	<0.001; *<0.001* <0.001**;*0.022***

*Since at least 6 months ** Fisher's exact test

276 EXPLORING THE MICROBIOTA FOR THE DIAGNOSIS OF ANAL PRECANCEROUS LESIONS IN MSM

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Background: Anal cancer is a leading neoplasia in HIV-infected MSM. The current screening strategy is based on the detection of high-degree squamous intraepithelial lesions (HSIL), using anal cytology. While this approach shows good sensitivity, the specificity is poor. We aimed to identify in MSM a set of anal-associated bacterial biomarkers for the diagnosis of biopsy-proven HSIL (bHSIL).

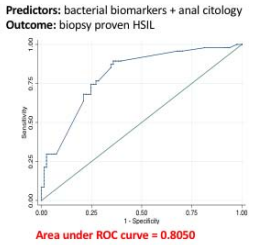
Methods: Cross-sectional prospective study performed in HIV+ and HIV- MSM referred to a high-resolution anoscopy clinic. The primary outcome was the presence of bHSIL at the inclusion or during the previous year. We analyzed fecal and mucosal microbiota to search for biomarkers predictive of the presence of bHSIL. We collected fecal samples in specific containers and obtained anal mucosa specimens with an anal cytobrush. The V3-V4 region of the 16S rRNA gene was sequenced using the Illumina platform. We selected the biomarkers based on their LDA scores, AUC-ROC in logistic regression models and concomitant predictive value in feces.

Results: We included 118 HIV+ and 33 HIV- MSM: 47 had bHSIL during the previous year and 12 at the moment of the inclusion. Differences in alpha and bacterial diversity were significant between mucosa and feces, but non-significant in the comparison by presence of bHSIL or HIV status. Linear discriminant analysis (LDA) effect size (LEfSe) revealed 40 biomarkers in mucosa and 53 in stools. After exploring the predictive value of the 15 taxa with greater LDA scores, we selected four taxa in anal samples. Each 25% increase in the abundance of the Ruminococcaceae NK4A214 group and Alloprevotella genus were associated with a 17% (p=0.041) and 8% (p=0.016) increased risk of bHSIL, respectively. The absence of Prevotella melanonigenica and Ruminococcaceae UCG-014 were predictive of bHSIL (OR 6.1, P=0.018 and OR 3.2, P=0.026, respectively). From 35 (94%) of false positive cytologic results, the combination of these four biomarkers reclassified to true negative 33 (94%), significantly improving the predictive performance of anal cytology alone to AUC 0.805.

Conclusion: We found anal-associated bacteria indicative of higher risk of precancerous anal lesions, which combination was highly specific. The microbiota could be exploited as a complementary diagnostic tool for anal cytology to overcome the low specificity and high rate of false positive results of the current screening strategy for anal cancer screening.

Diagnostic test	Sensitivity (%)	Specificity (%)	AUC ROC	P value
Anal citology[1]	72 (59-85)	57 (46-68)	-	0.002
Bacterial biomarkers[2]	37 (23-51)	90 (84-96)	0.737	0.002
Bacterial biomarkers[2] + anal citology	65 (51-79)	83 (74-90)	0.805	0.0006

[1]High or low intraepithelial squamous lesions = positive
[2]Abundance of Ruminococcaceae NK4A214 and Alloprevotella, absence of Prevotella melanonigenica and Ruminococcaceae UCG-014



277 TRANSCRIPTOME ANALYSIS IN HPV+/HIV+ TISSUE REVEALS MARKERS OF HPV-DEPENDENT DYSPLASIA

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Background: HPV is accepted today as the necessary but not sufficient etiological agent for anal and cervical neoplasia and HIV appears to be a cofactor in the association between HPV and cervical neoplasia. The objective of our study is the identification of a distinct transcriptomic signature that may serve as predictive markers of dysplasia and/or malignancy in HIV+/+HPV patients.

Methods: The study includes a unique cohort of 25 HIV-1 infected individuals co-infected with HPV with a clinical follow-up for more than 20 years. Tissue samples from individuals with signs of a high degree of anal dysplasia were chirurgical collected, together with samples from normal tissue from the same individual as control. After RNA extraction and quality control, RNA library was constructed (Illumina TruSeq RNA stranded) and sequencing was performed (Novaseq, 30M reads/sample). Data analysis was performed as implemented in the computational workflow for the detection of differentially expressed genes and pathways from RNA-seq data. Read alignment and count quantification was conducted using the Rsubread package and the statistical analysis was performed using the edgeR package. The differential expression analysis uses the quasi-likelihood functionality of edgeR.

Results: Whole transcriptome sequencing was performed to examine differential gene expression profiles, and to perform gene annotation based on gene ontology pathway information. Analyses were successfully performed on all 25 paired-ends samples with overall read mapping ratio above 95%. Thirty genes showed significant changes between biopsies showing a high degree of dysplasia and apparently healthy control biopsies. Hierarchic clustering of data demonstrated a clear discrimination between healthy and dysplasic tissues, indicating a common pattern of gene expression changes between individuals. The identified differentially expressed genes include chemokines, potential restriction factors, a miRNA and genes associated to cell proliferation and cell transformation. After filtering the results based on functionality, we selected for further validation a group of 15 genes that fulfill the criteria for becoming a biomarker.

Conclusion: Our analysis allowed the identification of at least 15 potential predictive markers of anal dysplasia in co-infected HIV/HPV individuals. Characterization of the selected genes may result in the development of new therapeutic approaches to treat HIV/HPV induced malignancies.

278 HPV CLEARANCE AND REINFECTION IN 2 YEARS AFTER RANDOMIZATION TO CRYOTHERAPY OR LEEP

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Background: Women with HIV are at increased risk of high-risk human papillomavirus (hrHPV) infection. We compared hrHPV clearance and reinfection in HIV-infected women randomized to cryotherapy or loop

electrosurgical excisional procedure (LEEP) for treatment of cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3).
Methods: From June 2011 to July 2014, HIV-infected women enrolled at the Coptic Hope Center in Nairobi, Kenya with CIN2/3 were randomized to receive cryotherapy or LEEP and followed for 2 years with a Pap smear and HPV cervical swab every 6 months. hrHPV was defined as a positive result on at least one of 13 types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) identified by the Roche Linear Array Genotyping Test. Clearance was defined as testing negative for the same hrHPV type/s detected at baseline on ≥2 consecutive visits ≥6 months apart. Time to clearance or duration of hrHPV infection was defined as the time elapsed from intervention to the date of the first negative hrHPV test. Reinfection was defined as new hrHPV infection after clearance. Outcomes were compared between arms using Chi-square tests and log-binomial regression.
Results: Of 400 women randomized to cryotherapy or LEEP, 95% (189 per arm) had baseline hrHPV results. Median age was 37 years [interquartile range (IQR): 31-43], median CD4 count was 380 cells/μl (IQR: 211-525), and median plasma HIV RNA viral load was 1.5 log10/mL (IQR: 1.5-2.8). The majority (88%) of women were on antiretroviral treatment (ART) at baseline, of whom 40% were on ART for ≥2 years. Baseline hrHPV prevalence was 93% in the cryotherapy arm and 92% in the LEEP arm (P=0.83). Clearance of hrHPV was significantly higher in LEEP than cryotherapy both at 6 months following intervention (36% vs 24%; P=0.015) and over two-year follow up (50% vs 39%; P=0.040). Median time to clearance was 6 months in each arm (P=0.16). Those who underwent LEEP were 50% (95% confidence interval (CI), 1.1-2.1; P=0.017) more likely to clear hrHPV than those receiving cryotherapy. The difference in reinfection with hrHPV following clearance of hrHPV in women with LEEP vs cryotherapy was not statistically significant (Relative risk=0.67, 95% CI, 0.4-1.1; P=0.089).
Conclusion: Clearance of hrHPV in HIV-infected women after cervical treatment was limited; 40% experienced hrHPV reinfection within 2 years. However, women receiving LEEP were more likely to clear hrHPV than those receiving cryotherapy adding a reason to consider expanding LEEP in resource-limited settings.

279 HPV DNA TESTS FOR CERVICAL CANCER SCREENING OF HIV-INFECTED WOMEN

Louise Kuhn[1], Rakiya Saidu[2], Ana I. Tergas[1], Rosalind Boa[2], Jennifer Moodley[2], Cecilia Svanholm-Barrie[3], David Persing[4], Scott Campbell[4], Thomas C. Wright[1], Lynette Denny[2]
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Background: HPV DNA testing has excellent sensitivity but poor specificity for cervical cancer screening among HIV-infected women. We evaluated whether the point-of-care test, Xpert™ HPV, could be adapted to improve performance characteristics for screening HIV-infected women.
Methods: A clinical study of 586 HIV-uninfected and 535 HIV-infected women, aged 30-65 years, was conducted in Cape Town, South Africa. All women had a cervical sample collected that was tested on-site with Xpert HPV which is a cartridge-based PCR assay that detects HPV DNA in 5 channels: HPV 16, HPV 18,45, HPV 31,33,35,52,58, HPV 51,59, and HPV 39,56,66,68. For each channel a cycle threshold (CT) value is generated and values below pre-determined CT cut-offs are defined as positive. All women underwent colposcopy with histological sampling. Cervical intraepithelial neoplasia grade 2,3 or cancer (CIN2+) was diagnosed based on consensus pathology review. Sensitivity, specificity, positive and negative predictive values were calculated based on logistic regression and receiver operating characteristic curves.
Results: Almost half (49.2%) of HIV-infected women tested positive for HPV DNA whereas 16.2% of uninfected women did (p<0.001). The prevalence of histology-confirmed CIN2+ was higher in HIV-infected women (17.0%) than in uninfected women (5.3%) (p<0.001). Sensitivity of detecting CIN2+ at the manufacturer-defined CT cut-off was 93.6% in HIV-infected women with a specificity of 59.9%. If screen-positive was limited to the 3 channels detecting HPV 16, HPV 18,45 and HPV 31,33,35,52,58, sensitivity remained high (90.7%) and specificity improved (67.5%). Shifting the CT values from these 3 channels such that sensitivity was set at 85%, resulted in improvements in specificity (77.0%). If sensitivity was set at 80%, specificity improved further (83.2%). At these CT cut-offs, positive predictive value was 49.4% and the proportion screen-positive was 27.4%.
Conclusion: Adapting Xpert HPV by restricting the definition of screen-positive to a limited number of high risk HPV types and making CT cut-offs more stringent (i.e. requiring higher levels of HPV DNA) can greatly improve performance characteristics of HPV DNA testing for cervical cancer screening in HIV-positive women. Making these adaptations limits the number of HIV-infected women who require further follow-up or treatment for cancer precursor lesions.

Table: Performance characteristics of Xpert HPV to detect CIN2+ in 535 HIV-infected women

	Sensitivity	Specificity	PPV	NPV	Screen positive
Manufacturer-determined cut-offs	93.6	59.9	32.3	97.8	49.2
Limiting to channels HPV 16,18,45,31,33,35,52,58	90.7	67.5	36.4	97.3	42.4
Changing CT cut-offs on channels HPV 16,18,45,31,33,35,52,58					
Least stringent	85.0	77.0	43.1	96.2	33.5
More stringent	80.0	83.2	49.4	95.3	27.5

280 RELATION OF CIN2 PROGRESSION WITH SERIAL CERVICOVAGINAL CYTOKINE/CHEMOKINE LEVELS

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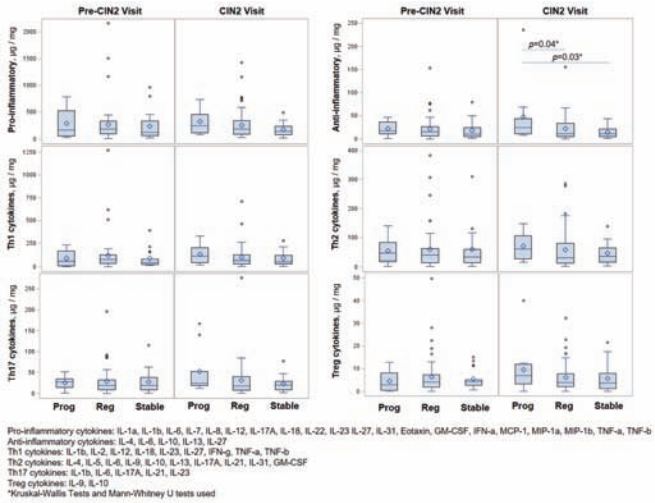
Background: Women living with HIV are high-risk for cervical intraepithelial neoplasia-2 (CIN2), a potentially pre-cancerous diagnosis. We characterized longitudinal variations in cervicovaginal lavage (CVL) chemokine/cytokine levels and their temporal relation with CIN2 and its progression.
Methods: N=104 HIV-positive women (age < 46) were selected from the Women's Interagency HIV Study (WIHS). To avoid misclassification, we excluded women CIN3+ found within 6 months post-CIN2 diagnosis. CVLs were analyzed at 4 time points: (1) 0.5-1 year prior to CIN2, (2) at CIN2 diagnosis, (3) at progression/regression event, and (4) visit between CIN2 and progression/regression. We used Luminex assays to measure 34 cytokines/chemokines (normalized by total protein and log transformed). We used Bonferoni-adjusted T tests and logistic regression for analysis; multivariate analysis included adjustment for cervical treatment, smoking status, CD4 and HIV viral load.
Results: Of the 104 women, 12 progressed to CIN3 (median 2.7 years), 63 regressed to CIN1/normal (median 1.5 years), and 29 had a subsequent CIN2 diagnosis (median 1.5 years). CIN2 treatment was received by 7 (58%) of CIN2 progressors, 20 (32%) of CIN2 regressors, and 13 (45%) of CIN2 stable women. The majority of women were African American (55%), current smokers at baseline (53%), with a median age of 34 years (no significant differences between groups). Anti-inflammatory cytokines were significantly lower in CIN2 regressors and CIN2 stable women at the CIN2 visit compared to CIN2 progressors (Figure 1). IL-27 was significantly elevated at the pre-CIN2 visit in progressors vs. regressors (p=0.03), no difference in IL-27 at visit where CIN2 was diagnosed. At CIN2 visit, IL-6 (p=0.05), IL-1a (p=0.03) and IL-10 (p=0.05) were elevated in progressors vs. regressors. Controlling for CIN2 treatment, smoking status, CD4 count, and HIV viral load, the odds of CIN2 progression was associated with higher IL-27 (aOR 1.41, 95% CI 1.23, 1.60), and IL-9 (aOR 1.39, 95% CI 1.08, 1.79), along with lowered IL-10 (aOR 0.53, 95% CI 0.34, 0.83) and IL-21 (aOR 0.83, 95% CI 0.71, 0.97), compared to CIN2 regressors.
Conclusion: We identified a group of cytokines, present at the time of CIN2 diagnosis, which may influence risk of CIN2 progression in HIV+ women. While IL-1a is strongly pro-inflammatory, IL-6, IL-9, IL-10, and IL-27 have inflammatory and anti-inflammatory activity-suggesting that a nuanced immune response to CIN2 may be key to its progression in HIV+ women.



281 IMMUNE GENE EXPRESSION IN ANAL DYSPLASTIC LESIONS BY HIV STATUS AND ABLATION OUTCOMES

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Background: The incidence of anal squamous cell carcinoma (SCCA) is 50-fold higher in HIV-infected persons and is a leading cause of morbidity among HIV patients. Anal high-grade squamous intraepithelial lesions (HSIL) are the precursors to SCCA. There has been limited study on the interactions between HIV infection, the immune microenvironment of HSIL and their natural history. In this study we compared immune gene expression profiles in HSIL lesions by HIV status and identified genes associated with post-ablation recurrence.

Methods: From the Mount Sinai anal cancer screening program we identified 44 persons (24 HIV+ and 20 uninfected persons) with HSIL and 4 with benign anal mucosal tissue as controls. All HSIL lesions were treated with electrocautery ablation and reassessed within 12 months for recurrence or regression. A targeted gene expression assay (Nanostring) was performed on the initial lesions consisting of 730 genes (including both an immuno-oncology panel and HIV and HPV related genes). After normalization we identified differentially expressed genes by HIV status and HSIL treatment outcome. All significance tests (q-values) were corrected for multiple testing.

Results: There was no difference in age by HIV status or lesional outcomes after treatment (median age 46 years); the cohort was largely men who have sex with men (93%). HIV+ subjects were virally suppressed in 71% of the cases, with a median CD4 count of 749 per mm3. We identified a single gene (CCL27) that was expressed significantly more in HIV-infected than in uninfected patients (Fold change=38.6; q=1.1E-4). CCL27 is a cutaneous cytokine associated with the attraction of T-cells to squamous epithelium during inflammatory responses. In contrast, we found 27 genes (Table 1) with significant differential expression between cured and recurrent lesions. Genes associated with recurrence were involved with T cell proliferation, localization and antigen presentation.

Conclusion: We found a significant overlap in the genes involved in host immune response, with only one gene with differential expression in HSIL lesions by HIV status. In contrast, 27 genes were associated with recurrent lesions. These findings may be useful for risk stratification of lesions. Further studies will expand on these findings by localizing the tissue compartments and cells expressing these gene products.

Table 1: Differentially expressed genes between cured versus recurrent lesions

Gene	Fold Change (Recurrent/Cure)	q-Value
ADA	3.66	0.030
ARG1	249.18	<0.001
CAMP	3.38	0.019
CCL2	2.00	0.042
CD1A	10.07	0.034
CD1B	50.47	0.011
CD1E	5.56	0.016
CD207	252.25	0.043
CD3EAP	1.97	0.019
CREBBP	2.54	0.011
FADD	14.57	0.022
FUT7	21.83	0.029
GATA3	12.90	0.001
HAMP	0.13	0.034
IFI35	0.37	0.019
IFNL1	5.10	0.0003
IL4	0.66	0.034
IRF5	1.76	0.037
MAP3K5	10.03	0.034
MAPK11	19.05	0.025
MR1	1.27	0.034
PASD1	0.59	0.035
PLA2G1B	0.47	0.0002
PRAME	36.91	0.012
PRKCE	0.58	0.019
TRAF3	3.78	0.001
ZNF205	1.22	0.011

282 HPV GENOTYPING IN 1,088 ANAL HSIL CASES: EXPECTED AND UNEXPECTED RESULTS

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Background: High-grade squamous intraepithelial lesions (HSIL), the anal cancer precursors, are caused by high-risk human papillomavirus (hrHPV). HrHPV-negative HSILs occur occasionally in clinical practice and constitute an unexpected departure from that rule leading to diagnostic and therapeutic challenges. Using 1,088 simultaneously collected anal swab and histologic HSIL specimens, we aimed to determine the distribution of hrHPV types associated with anal HSIL and to further evaluate hrHPV-negative cases using tissue HPV genotyping.

Methods: Anal swab and high-resolution anoscopy-guided biopsy were performed contemporaneously. Anal swabs were used for cytological diagnosis as well as Cobas® HPV DNA testing for HPV16, 18, and 12 other hrHPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Cobas®-negative HSIL biopsy specimens were tested for HPV DNA using real-time PCR.

Results: 1,088 anal swabs were collected from 742 patients (median age 46 years, range 20-76) with biopsy-proven HSIL. Most subjects were HIV-infected (94%), 91% were men who have sex with men and 9% women. Cytological diagnoses were unsatisfactory (5%), benign (12%), ASCUS (36%), LSIL (34%), ASC-H (5%), and HSIL (8%). Cobas® HPV cotesting revealed that 4% of swabs were negative for hrHPV, 55% positive for HPV16/18, and 41% positive for other hrHPV types. HPV16/18-positivity correlated with a higher degree of cytological abnormalities ($p<0.001$). Significantly more HPV16/18-positive subjects had ≥3 concurrent HSILs compared with subjects who either tested positive for non-16/18 or negative for hrHPV types ($p<0.001$). There was no significant difference regarding age, gender, smoking history, HIV status, CD4+ T cell count, and HIV-1 viral load between hrHPV groups. Among Cobas®-negative HSIL cases, PCR detected hrHPV types in 65% of biopsy specimens, half of which were not included in the Cobas® HPV assay (HPV53, 67, 69, 73, and 82).

Conclusion: We assessed the performance of cytological and hrHPV cotesting in anal swab samples from a large cohort of patients with biopsy-proven anal HSIL. HPV16/18-positivity was associated with a greater number of concurrent HSILs presumably explaining the improved performance of anal cytology in these patients. HPV-negative HSILs were primarily caused by rare hrHPV types not included in routine screens; these outliers must be interpreted with caution and warrant further investigation.

Table 1. HPV genotypes detected by Cobas® HPV test using anal swabs (n=1,088)

HPV Genotype	N (%)
Negative	43 (4)
Positive	1,045 (96)
16	46 (4)
18	6 (0.6)
16, 18	2 (0.2)
16, others*	321 (30)
18, others	112 (10)
16, 18, others	107 (10)
Others	451 (41)

* Others: 31/33/35/39/45/51/52/56/58/59/66/68

283 PRIMARY HPV SCREENING IN WOMEN LIVING WITH HIV

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Background: Primary HPV Screening (PHS) utilizes an oncogenic human papillomavirus (oncHPV) assay as the initial cervical cancer screening test (instead of a Pap test). Recent US guidelines support PHS in women in the general population (30-65 years of age), and suggest oncHPV- women should be retested in 5 years. For oncHPV+ women, reflex HPV genotyping is recommended and possibly an additional test (e.g., Pap test) in order to determine appropriate follow-up or triage to colposcopy. However, the current study is, to our knowledge, the first to assess PHS in WLWH. Cervical cancer screening strategies for WLWH need improvement as these women have elevated risk of cervical cancer relative to the general population, but current strategies result in a high rate of colposcopy that does not reflect clinically relevant cervical disease.

Methods: The study enrolled 865 WLWH comprised of 323 new enrollees in the Women's Interagency HIV Study (WIHS) and 542 WLWH enrolled through colposcopy clinics affiliated with WIHS. Newly enrolled WIHS women represented WLWH undergoing routine screening. Colposcopy patients represented WLWH who had a recent abnormal screening test (e.g., ASC-US+). WIHS participants underwent routine screening using liquid-based Pap tests (ThinPrep) and were tested for oncHPV by the FDA-approved Cobas test. WIHS enrollees with a positive oncHPV or ASC-US+ received colposcopy, as did 15% of women with negative oncHPV and Pap results. Like WIHS enrollees, the WLWH enrolled at colposcopy had oncHPV and Pap tests. All Pap/histology was centrally reviewed by two expert pathologists.

Results: Mean age was 47 years for both WIHS enrollees and colposcopy patients, and most were Hispanic or non-Hispanic African American. Median (IQR) CD4 count was 560 (342-843) and 631 (362-849), respectively, with 97% and 83% reporting cART use. There was a total of 70 CIN2+ of which 23 were CIN3+ (precancer). The Table shows sensitivity, specificity, and positive predictive value (PPV) to detect CIN3+, as well as the % of WLWH who would be triaged to colposcopy following several strategies. Results for PHS, as estimated by oncHPV with reflex Pap, had the highest PPV and lowest colposcopy rate; Co-Testing had moderately higher sensitivity and colposcopy triage rates.

Conclusion: The results show that PHS with reflex Pap testing is a potentially useful cervical cancer screening strategy in WLWH, but may sacrifice a moderate level of sensitivity for a moderate reduction in the rate of triage to colposcopy.

Strategy	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	Colpo. Rates (95% CI)
Pap test only (ASC-US+)	93% (75%, 98%)	71% (67%, 74%)	11% (8%, 16%)	32% (22%, 27%)
oncHPV test only	88% (68%, 95%)	66% (75%, 81%)	9% (6%, 13%)	36% (33%, 39%)
oncHPV test with reflex Pap	84% (68%, 93%)	82% (79%, 84%)	16% (11%, 22%)	21% (18%, 24%)
oncHPV Co-Testing*	91% (75%, 99%)	77% (74%, 79%)	14% (10%, 19%)	26% (23%, 29%)

*prospective WIHS data were used to estimate persistent oncHPV+ in WLWH with normal Pap tests

284LB REDUCED COVERAGE OF HPV VACCINE TYPES IN CERVICAL PRECANCER IN HIV INFECTION

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Background: Our aim was to study to which extent cervical precancer in women living with HIV (WLWH) is associated with HPV types targeted by vaccination. The Swedish National HIV registry (InfCareHIV) includes all WLWH in Sweden and the women in this cohort were found to have an increased risk of cervical precancer (Carlander et al. IJC 2016) and an increased risk of treatment failure of cervical precancer (Carlander et al. AIDS 2018). We requested all tissue blocks from cervical precancer in this cohort and subjected them to HPV genotyping.

Methods: By linking InfCareHIV, the Swedish Population Registry and the Swedish National Cervical Screening Registry we identified all WLWH, mainly migrants (70%), living in Stockholm or Gothenburg sometime between 1983 and 2014, with high-grade cervical precancer (CIN2+). For each WLWH we randomly selected two HIV-negative control women (HNW), living in the same counties and also diagnosed with CIN2+, matched for country of birth. We retrieved and HPV genotyped the archived cervical tissue blocks. Type-specific HPV prevalence was compared using prevalence ratios (PR), calculated with Poisson regression analysis. All models were adjusted for age, grade of cervical lesion and region of birth.

Results: 108 WLWH and 183 HNW had valid HPV genotype results (100 [93%] WLWH and 164 [90%] HNW were HPV-positive). WLWH were less likely to be infected with HPV16 (PR: 0.6, 95% CI: 0.4-0.9) than HNW. HPV35 (not included in the 9-valent HPV vaccine) was the second most common HPV type in WLWH and three times more common than in HNW (PR: 3.1, 95% CI 1.3-7.4). WLWH were more likely to be infected with multiple HPVs (30 vs. 20%; PR: 1.5, 95% CI: 1.0-2.4). HPV types targeted by the 9-valent HPV vaccine were significantly less common in WLWH (57%) compared to HNW (80%) (PR = 0.7, 95% CI 0.6-0.9).

Conclusion: This national population-based cohort study, controlled for country of birth of migrants, found that cervical precancer in WLWH contained HPV types targeted by vaccination to a lower extent than in HNW, implying that cervical screening remains highly important in WLWH, even if HPV vaccinated.

Table 1. Comparison of HPV genotypes detected in HPV-positive women diagnosed with CIN2/CIN3/AIS/ICC stratified by HIV status

	WLWH	HNW	Prevalence ratio[1] (95% CI)
Any positive HPV	100	164	
HR HPV single (group 1/2A[2])			
HPV 16	25 (25)	70 (43)	0.6 (0.4-0.9)
HPV 35	14 (14)	7 (4)	3.1 (1.3-7.4)
HPV 31	8 (8)	12 (7)	1.1 (0.5-2.6)
HPV 45	5 (5)	4 (2)	2.0 (0.5-7.5)
HPV 52	4 (4)	10 (6)	0.7 (0.2-2.2)
HPV 33	3 (3)	9 (5)	0.6 (0.2-2.0)
HPV 18	2 (2)	5 (3)	0.7 (0.1-3.9)
HPV 58	2 (2)	1 (1)	3.2 (0.3-35.1)
HPV 51	2 (2)	1 (1)	3.0 (0.2-47.4)
HPV 56	1 (1)	-	-
HPV 39	-	1	-
HPV 59	-	-	-
HPV 68	-	-	-
Multiple HPV			
Multiple HPV including ≥ 1 HR HPV	30 (30)	33 (20)	1.5 (1.0-2.4)
Single or multiple HPV			
Single or multiple, including HPV 16[4]	35 (35)	90 (55)	0.7 (0.5-0.9)
Potential HPV vaccine coverage			
HPV 16/18 alone[5] (bivalent vaccine)	28 (28)	77 (47)	0.6 (0.4-0.9)
HPV 16/18/31/33/45/52/58 alone[5] (9-valent vaccine)	57 (57)	131 (80)	0.7 (0.6-0.9)

Numbers are n (% of any positive HPV). Percentages do not always add up to a hundred due to rounding. [1]Prevalence ratio (PR) (HIV-infected versus HIV-negative women) calculated using Poisson regression analysis, adjusted for age, grade of lesion and region of birth. [2] 1/2A including HPV 16/18/31/33/35/39/45/56/58/59/68. [3] 2B including 26, 30, 53, 66, 67, 69, 70, 73, 82. Single or multiple infections, all including HPV 16. [5]Single or multiple infections with specified genotypes only. WLWH: women living with HIV, HNW: HIV-negative women

285 CD4/CD8 RATIO AS A PREDICTOR OF HIV-ASSOCIATED CANCERS IN CNICS

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Background: CD4/CD8 ratio is available in routine HIV practice and has been associated with immunoscenece, aging and cancer. We aimed to evaluate associations between low CD4/CD8 ratio, prior to and on ART, and individual cancer types.
Methods: We studied persons with HIV (PWH) in care 1996-2014 at 8 CNICS sites across the US, who initiated ART and had a pre-ART CD4/CD8 ratio value and at least 6 months of follow up. We assessed quartiles of the lowest CD4/CD8 ratio prior to and the highest CD4/CD8 ratio on ART as predictors of cancer overall and individual types from ART initiation to cancer event or last clinic visit using Cox regression models adjusted for age, sex, race, time on ART, HCV co-infection, tobacco and alcohol use.
Results: Among 10,817 PWH with 63,514 person-years on ART, 80% were male, 51% non-white race, 61% MSM, 17% IDU and 21% had HCV co-infection. Prior to ART, median nadir CD4 count was 229 cells/µl (IQR 89, 361), max CD8 count was 980 cells/µl (IQR 680, 1380), lowest CD4/CD8 ratio 0.29 (IQR 0.14, 0.47) and HIV RNA 4.9 $\log_{10}$ copies/mL (IQR 4.3, 5.4). On ART, 91% achieved HIV RNA suppression <200 copies/mL and median highest CD4/CD8 ratio achieved was 0.76 (IQR 0.47, 1.11). 529 PWH developed invasive cancer: 93 NHL, 86 KS, 53 lung, 43 anal, 38 prostate, 33 Hodgkin lymphoma, 20 liver, 19 breast, 18 colorectal, 16 oropharynx, 11 melanoma and 99 others. After adjustment, pre-ART CD4/CD8 ratio <0.14 (lowest quartile) was significantly associated with greater risk of cancer overall (HR 1.8; 95%CI 1.4-2.3), anal cancer (HR 4.7; 95%CI 1.5-13.0) and NHL (HR 3.9; 95%CI 1.7-8.8) compared to ratio ≥0.47 (highest quartile). On ART, CD4/CD8 ratio <0.47 (lowest quartile) was also associated with KS, lung cancer and Hodgkin lymphoma compared to ratio ≥1.11 (highest quartile)(Table). We did not find statistically significant associations between CD4/CD8 ratio prior to or on ART and melanoma, colorectal, breast, kidney, prostate or liver cancer.
Conclusion: As has been observed with other age-related diseases, CD4/CD8 ratio is a potential biomarker routinely obtained in HIV care that could be used for prediction of certain cancers and risk stratification for HIV-associated cancer screening strategies.

CD4/CD8 On ART	All cancers aHR(95%CI)	Anal aHR(95%CI)	NHL aHR(95%CI)	KS aHR(95%CI)	Lung aHR(95%CI)	Hodgkin aHR(95%CI)
<0.47	**4.5 (3.3-6.2)**	**15.3 (3.5-65.8)**	**3.9 (1.7-8.8)**	**13.6 (4.1-45.3)**	**2.9 (1.2-7.0)**	**6.4 (1.8-22.6)**
0.47–0.75	**2.0 (1.4-2.8)**	2.8 (0.5-14.7)	**3.1 (1.4-7.2)**	**3.6 (1.0-13.3)**	2.1 (0.9-5.3)	2.3 (0.6-9.2)
0.76-1.10	1.3 (0.9-1.8)	3.6 (0.8-17.6)	1.9 (0.8-4.6)	2.1 (0.5-8.4)	0.9 (0.3-2.8)	1.4 (0.3-6.1)
≥1.11	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)

286 CAUSES OF DEATH AFTER CANCER DIAGNOSIS AMONG PLHIV ON ART: COHORT COLLABORATION

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Background: People living with HIV (PLHIV) are more likely to develop AIDS-defining malignancies (ADMs) and several non-ADMs (NADMs) than the general population. However, there is a lack of information on cause-specific mortality after diagnosis of cancer among PLHIV.
Methods: We investigated causes of death within 5 years of first cancer diagnosis in PLHIV enrolled in 10 European and North American HIV cohorts that are part of the Antiretroviral Cohort Collaboration (ART-CC). Eligible adults were aged ≥16 years, started ART between 1996-2015 and were subsequently diagnosed with cancer. We used CoDe classifications of cause of death https://chip.dk/Tools-Standards/CoDe/About. We calculated cause-specific mortality rates (MR) per 1000 years following diagnosis of specific cancers and compared all-cause MR during 2006-15 with 1996-2005, for ADMs and NADMs.
Results: After 4209 cancer diagnoses (ADM=2162, NADM=2047) among 84167 PLHIV, there were 1451 deaths within 5 years. Of 604 PLHIV who died after diagnosis of ADM, 292(48%) deaths were due to an ADM while 467/847 (55%) deaths after diagnosis of NADM were due to an NADM. MR were higher for diagnoses between 1996-2005 compared with 2006-15: ADMs 102 (95% CI 92-113) vs 88 (78-100) and NADMs 213 (191-239) vs 184 (169-200). The table shows mortality rates for the 7 most commonly diagnosed cancers: these were higher after diagnoses of NADMs than ADMs and were very high for lung, liver, non-Hodgkin's lymphoma, and head and neck cancers. Patterns of cause-specific mortality suggest that cause of death was likely to have been from the diagnosed cancer for head and neck and lung cancer. A substantial proportion of deaths from liver cancer had been classified as due to viral hepatitis by our process for assigning CoDe cause of death classifications.
Conclusion: Among ART-treated PLHIV diagnosed with cancer, mortality rates and causes of death varied according to the type of cancer, with highest mortality for the NADMS liver cancer and lung cancer. Among those who died within 5 years of a diagnosis of an NADM there was a high chance that death was from cancer and not from AIDS.

Table: Rates per 1000 years (95% CI) of all-cause and cause-specific mortality during the 5-years after specific cancer diagnoses

	Cancer diagnosed (number of deaths/number of diagnoses)						
	ADMs			NADMs			
Cause of death	Cervical cancer (24/142)	Kaposi's sarcoma (208/1163)	Non-Hodgkin's lymphoma (307/701)	Head and Neck (54/138)	Hodgkin's Lymphoma (63/305)	Liver cancer (86/137)	Lung cancer (276/371)
All causes	51 (34-76)	52 (46-60)	196 (176-219)	177 (136-231)	68 (53-87)	456 (369-563)	824 (733-927)
AIDS	15 (7-31)	16 (13-21)	25 (18-34)	7 (2-26)	11 (6-20)	11 (3-42)	15 (6-36)
ADM	21 (11-40)	17 (13-21)	117 (102-136)	3 (0.5-23)	12 (7-21)	5 (1-38)	9 (3-28)
NADM	4 (1-17)	2 (1-3)	3 (1-8)	118 (85-164)	25 (17-37)	148 (102-215)	588 (511-676)
Viral hepatitis	0 (0-0)	1 (0-2)	2 (1-6)	0 (0-0)	1 (0-7)	207 (151-283)	3 (0-21)
Other	6 (2-20)	9 (6-12)	15 (10-22)	23 (11-48)	12 (7-21)	27 (11-64)	66 (43-100)
Unknown	4 (1-17)	8 (6-12)	34 (26-44)	26 (13-52)	8 (4-16)	58 (32-105)	143 (108-190)

287 AIDS PROGRESSION AND NON-AIDS DEATH IN PEOPLE WITH HIV FOLLOWING CANCER TREATMENT

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Background: CD4 and HIV viral load trajectories following cancer treatment in people with HIV (PWH) may influence both AIDS and cancer progression. We estimate the association between longitudinal CD4 and viral load and the competing events of incident AIDS-defining illness/AIDS-death (ADI) and non-AIDS death (NAD) after cancer diagnosis in PWH.
Methods: We analyzed data from 204 PWH in the Johns Hopkins HIV Clinical Cohort diagnosed with an incident cancer from 1997-2014. Initial cancer treatment was categorized into chemotherapy/radiation and surgery without chemotherapy/radiation based on their observed immunosuppressive effects. We used shared parameter joint longitudinal survival models to estimate the cause-specific hazard ratios (csHR) and subdistribution hazard ratios (sdHR) for the associations between longitudinal CD4 and viral load with ADI and NAD. Models adjusted for confounders, including SEER estimates of 5-year mortality based on cancer type and stage and ART use.
Results: PWH were on average 50 years old at cancer treatment (IQR=43-55); 59% received chemotherapy/radiation. When compared to surgery, chemotherapy/radiation was associated with a rapid initial decline of 149 CD4 cells/µL (95% CI=87,211) among patients initiating treatment with CD4≥350, and 64 cells/µL for those with CD4<350. A 100-cell increase in longitudinal CD4 resulted in a csHR of 0.84 (95% CI 0.60-1.13) and an sdHR of 0.91 (95% CI= 0.69-1.18) for ADI, adjusted for longitudinal viral load. Although not statistically significant, this implies that higher CD4 was protective against ADI. A 100-cell increase in longitudinal CD4 was associated with a lower hazard of NAD (csHR=0.77, 95%CI= 0.64-0.91; sdHR=0.73, 95%CI= 0.61-0.85), adjusted for longitudinal viral load. Increased longitudinal viral load after cancer treatment in PWH was not significantly associated with an increased hazard of ADI or NAD when accounting for changes in longitudinal CD4 after cancer treatment.

Conclusion: Chemotherapy/radiation resulted in loss of CD4 that was associated with increased risk of non-AIDS death, independent of demographic characteristics, viral load, cancer type, and stage. There was some indication that the loss of CD4 was also related to increased hazard of new ADI but results were impacted by increased risk of death (i.e., competing risk analysis). This study illustrates the importance of evaluating specific therapies in this population with respect to immunosuppression so that the most appropriate option can be recommended.

Table 1. Summary of adjusted[a] hazard ratios (HR) for longitudinal measures (CD4 scaled by 100 cells/mm^3 and $\log_{10}$ HIV viral load) and survival outcomes (incident AIDS defining illness [ADI] and non-AIDS death [NAD]) in the total population.

Longitudinal Measure	Survival Outcome	Hazard Ratio Type	HR	95% CI
CD4	AIDS Defining Illness	Cause-Specific	0.84	(0.60, 1.13)
		Subdistribution	0.91	(0.69, 1.18)
	Non-AIDS Death	Cause-Specific	**0.77**	**(0.64, 0.91)**
		Subdistribution	**0.73**	**(0.61, 0.85)**
Viral Load	AIDS Defining Illness	Cause-Specific	1.08	(0.59, 1.92)
		Subdistribution	0.99	(0.59, 1.65)
	Non-AIDS Death	Cause-Specific	1.27	(0.99, 1.63)
		Subdistribution	1.22	(0.94, 1.58)

[a] Adjusted for age, female sex, white race, injection drug use as an HIV acquisition risk, receipt of no cancer treatment (for NAD), no ART at baseline, ever hepatitis C, baseline CD4 category, and receipt of immunosuppressive cancer treatment and either longitudinal CD4 or viral load

288 VACS INDEX BETTER PREDICTOR OF MORTALITY AFTER CANCER IN HIV+ AND HIV- THAN CHARLSON

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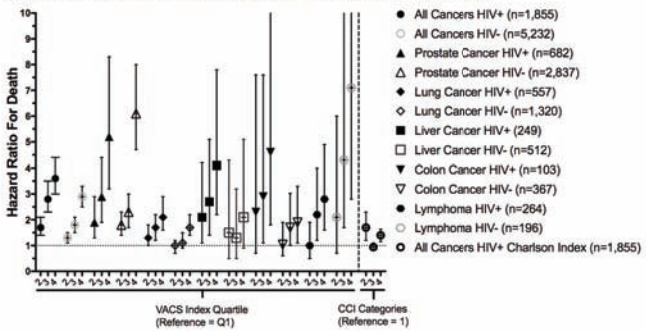
Background: Cancer is a leading cause of morbidity and mortality for people living with HIV (PWH). Mortality risk indices, like Veterans Aging Cohort Study (VACS) Index 2.0, that incorporate routine laboratory and diagnostic data may be useful for supporting clinical decision-making and assessment of prognosis. We evaluated VACS Index 2.0, a well-validated index among PWH, as a predictor of long-term survival for cancer patients, both with and without HIV infection.
Methods: We linked VACS data to Veterans Affairs Cancer Registry data, identifying 7,087 patients (1,855 PWH and 5,232 uninfected) with primary prostate, lung, colorectal, liver cancer or lymphoma. For all subjects we collected demographic data, tumor staging and VACS index 2.0 values and calculated Charlson comorbidity index (CCI) scores at time of cancer diagnosis. We fit multivariable survival models for the cohort of all, and for individual, cancers with VACS Index 2.0 alone (adjusting for tumor stage and demographics) and then fit alternate models including tumor stage and CCI to determine the relative predictive value of these indices.
Results: Patients did not differ by HIV status in age (median 52 years), sex (>99% male). PWH had higher median VACS index score at cancer diagnosis (61 vs. 37; p<0.001). For the cohort combining all cancer types in PWH and uninfected, the VACS index predicted overall survival in adjusted models with significant hazard ratios (HRs) for mortality for each quartile (Figure 1; all p<0.001) of the index, whereas the CCI had more limited predictive value. Adjusted models including the VACS index also had the best discrimination (c=0.82 versus c=0.73 for CCI model) and in models including both risk scores the VACS index was a strong independent predictor (p<0.001) CCI was of borderline significance (p=0.05). In models stratified by tumor stage, VACS index discriminated risk of mortality more effectively for early stage (I-II) than advanced cancers; in stage IV cases it was not associated with survival (all p>0.2). For individual cancers, the VACS index also predicted survival for both PWH and uninfected persons.
Conclusion: The VACS index 2.0, a prognostic index accurately predicted cancer survival after accounting for cancer stage, outperforming a traditional comorbidity index for both PWH and uninfected Veterans with cancer.

Figure 1. Adjusted Associations of VACS Index Quartiles with Survival in Cancer Patients by HIV Status



289 AIDS- AND NON–AIDS-DEFINING CANCER INCIDENCE, 2010-2015, IN THE DAT'AIDS COHORT

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Background: Although antiretroviral therapy has reduced the risk of developing AIDS-defining cancers, people living with HIV (PLWH) still have a high risk for some cancers, in particular virus-related. Given the increased life expectancy of PLWH, incidence of age and behavioral related cancers are expected to increase. However, data concerning recent incidence trends are scarce. We analyzed the data of a large French multicenter cohort to estimate incidences of AIDS defining cancers (ADC) and non-ADC (N-ADC) between 2010 and 2015.
Methods: We performed a retrospective study using longitudinal data from the DAT'AIDS cohort from 01/2010 to 12/2015. Cases were identified using ICD-10 codes. For incidence assessment, prevalent cases, occurring within 30 days after enrollment in the cohort, were excluded. If more than one cancer occurred in the same patient during the study period, only the first case was considered in the analysis. We performed a focus on some N-ADC (breast, colorectal, prostate, anal, liver, lung, Hodgkin lymphoma (HL), bladder, head and neck).
Results: Among the 44 642 HIV-infected people followed-up in the DAT'AIDS cohort during the study period (median age 43 [36-50] years, 69.7% male), 1440 cancer cases were diagnosed, including 358 ADC of which 345 were first cases (non-Hodgkin lymphoma: n= 194, Kaposi sarcoma: n= 135, and cervical cancer: n= 16). Among the 1082 N-ADC, 989 were first cases (76 patients were diagnosed with two different N-ADC during the study period, 7 with 3 and one with 4). Prostate cancer (n=111) was the most frequent N-ADC followed by liver (n=96), lung (n=90) and HL (n=82). Of note, head and neck cancer (n=66) was more frequent than anal cancer (n=53). Breast, colorectal and bladder cancer accounted for 54, 38 and 23 cases, respectively. The cancer incidence [95% CI] among the 44 642 patients accounting for 180 216.4 person-years (PY) between 2010 and 2015 was 191.4 [172.3-212.7] per 105 PY for ADC and 548.8 [515.6-584.1] per 105 PY for N-ADC. Incidence rates by calendar year and sex are reported in the table.
Conclusion: The incidence of N-ADC remained relatively stable over the 2010-2015 period overall and for both sexes, whereas ADC incidence decreased. This study highlights the growing importance of prostate, and head and neck cancers.

	ADC					
	Females		Males		All	
	N	Incidence rate [95% CI]/10^5 PA	N	Incidence rate [95% CI]/10^5 PA	N	Incidence rate [95% CI]/10^5 PA
Year of follow-up						
01/2010-12/2010	12	127.0 [72.1-223.6]	69	333.1 [263.1-421.7]	81	268.5 [216.0-333.8]
01/2011-12/2011	13	136.0 [79.0-234.3]	46	219.0 [164.0-292.4]	59	193.1 [149.6-249.2]
01/2012-12/2012	13	133.9 [77.7-230.6]	61	289.8 [225.9-371.7]	75	241.1 [192.3-302.3]
01/2013-12/2013	5	51.1 [21.3-122.7]	42	192.6 [142.3-260.6]	47	148.7 [111.7-198.0]
01/2014-12/2014	6	61.1 [27.5-136.1]	42	192.0 [141.9-259.7]	48	151.4 [114.1-201.0]
01/2015-12/2015	7	91.0 [43.4-191.0]	28	165.0 [114.0-239.0]	35	142.0 [101.9-197.7]
Study period 2010-2015	56	99.7 [76.8-129.6]	289	232.9 [207.6-261.4]	345	191.4 [172.3-212.7]
	N-ADC					
Year of follow-up						
01/2010-12/2010	32	338.6 [239.4-478.7]	139	671.0 [568.2-792.3]	171	566.8 [487.9-658.5]
01/2011-12/2011	47	491.8 [369.5-654.6]	118	561.8 [469.0-672.9]	165	539.8 [463.5-628.9]
01/2012-12/2012	40	411.9 [302.1-561.6]	134	626.3 [528.7-741.8]	174	559.4 [482.1-649.0]
01/2013-12/2013	40	408.4 [299.6-556.8]	123	564.0 [472.7-673.0]	163	515.8 [442.4-601.4]
01/2014-12/2014	45	458.4 [342.3-614.0]	128	585.0 [491.9-695.6]	173	545.8 [470.2-633.5]
01/2015-12/2015	39	507.2 [370.6-694.2]	104	613.0 [505.8-742.9]	143	580.0 [492.3-683.3]
Study period 2010-2015	234	432.8 [381.6-490.7]	746	601.3 [559.7-646.0]	989	548.8 [515.6-584.1]

290 CANCER INCIDENCE AMONG A COHORT OF PERSONS RECEIVING HIV CARE IN WASHINGTON, DC

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Background: The incidence of AIDS-related cancers (ADCs) has declined in this era of effective combination antiretroviral therapy with increases in certain non-AIDS related cancers (NADCs). We examined the incidence of ADCs and specific NADCs as well as eligibility for age-related cancer screening among persons living with HIV (PLWH) in the District of Columbia (DC).

Methods: Participants actively enrolled in the DC Cohort, a longitudinal study of PLWH which enrolled patients starting in 2011, through 12/2017 were included. Cancer diagnoses were determined through ICD-9/10 coding, and incidence was calculated among patients at risk using total person-time at risk through the observation period. Eligibility for cancer screening was determined based on age, sex, smoking history, and co-morbidity data available through the cohort and IDSA, USPSTF, or AASLD guidelines.

Results: Among 7912 participants, 72.4% were male, 77.8% black, and median age was 50 (IQR39-58) with 13.2 median years since HIV diagnosis. Fifty-six percent of participants had smoking history and 12.7% chronic Hepatitis C Virus (HCV). Median CD4+ count was 592 cells/mL(IQR 390-809.5) and 84.4% had HIV RNA <200 c/mL at most recent testing. In this cohort, cancer screening eligibility based on recommended guidelines was as follows: colorectal 4010 (51%), anal 3,301 (42%), breast 2144 (49.2%), and lung cancer 1250 (15.9%) with 264 (3.3%) eligible for hepatocellular carcinoma (HCC) screening. The incidence rate of NADCs was 12.1 (95% CI 10.7,13.8) and ADCs 1.6 (95% CI 0.6,4.6) per 1000 person-years. The most common incident NADCs were prostate 2.3 (95% CI 1.2,4.3), breast 2.6 (95% CI 0.5,12.1), skin 1.3 (95% CI 0.7,2.6), head/neck 1.1 (95% CI 0.7,1.9), anal 1.1 (95% CI 0.4,2.9), lung 1.0 (95% CI 0.5,1.9), and colorectal 0.9 (95% CI 0.4,1.9) incident diagnoses/cases per 1000 person-years. The incidence of ADCs were: non-Hodgkin's lymphoma (NHL) 0.9 (95% CI 0.3,2.5), cervical cancer 0.7 (95% CI 0.1,4.4), and Kaposi sarcoma (KS) 0.5 (95% CI 0,7.1) diagnoses/cases per 1000 person-years.

Conclusion: In this aging cohort of PLWH, there were more incident NADCs versus ADCs in contrast to older cohort studies where ADC predominated and reflective of newer data showing higher incident rates of NADCs. A large proportion of this cohort is eligible for age-related cancer screening for NADCs. Implementation of preventative measures and age-related cancer screening is an important component of care in this aging population.

291 HIGH CD20 LEVELS IN LUNG CANCER TISSUE FROM PLWH ASSOCIATED WITH IMPROVED SURVIVAL

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Background: Non-small cell lung cancer (NSCLC) is the most common non-AIDS defining cancer among people living with HIV (PLWH) and is associated with increased mortality. This study used quantitative immunofluorescence (QIF) to evaluate differences in the NSCLC tumor microenvironment between HIV+ and HIV- patients.

Methods: Paraffin-embedded tumor tissue from patients with NSCLC at Yale New Haven Hospital between 2001-2016 were retrieved. 18 HIV+ cases and 19 HIV- controls (matched for age, sex, histologic subtype, cancer stage, and year of cancer diagnosis). Clinical grade chromogenic assay was used to calculate whether the tumor expressed PDL1 (> 5% cut-off for positivity). In addition, QIF was used to measure expression of PDL1, CD4, CD8, and CD20 both within the tumor and surrounding stroma. Early stage cancer was defined as Stages I-II while late stage was defined as Stages III-IV. t-tests and chi-square tests were used to compare continuous and categorical variables, respectively.

Results: Median age was 53 and 59 among HIV+ and HIV- patients. Median CD4 count and viral load among HIV+ were 440 cells/μL and 78 copies/ml respectively, with 77% of patients on ART at time of NSCLC diagnosis. No difference in mortality was observed in early stage NSCLC between HIV+ and HIV- groups [HR 1.59 (95% CI 0.36-7.04)]. However, among late stage NSCLC, HIV+ patients had higher mortality rate [HR 5.52 (95% CI 1.87-16.46)]. Tumor cells from 44% of HIV+ compared to 21% of HIV- patients were positive for PDL1 by chromogenic assay (p= 0.14). QIF analysis revealed no statistical differences in CD4 or CD8 infiltrate between HIV+ and HIV- tissues. Cox regression analysis found higher intra-tumor CD20 expression was associated with improved survival [HR 0.775 (95% CI 0.614-0.978)]. This effect was greater in HIV- (HR 0.603) compared with HIV+ cases (HR 0.894), though this difference did not reach statistical significance (p = 0.18).

Conclusion: After controlling for age, date of diagnosis, histology, and stage in a well-matched cohort of NSCLC, we found that PLWH have a worse prognosis with late stage NSCLC. Tumors from HIV+ patients are more likely to express PDL1 compared to HIV- cases. High CD20 signal was associated with improved survival in NSCLC and HIV status may be a moderator of this interaction. Further characterization of specific T cell inhibitory and regulatory pathways within the tumor immune microenvironment is critical to understand how immune dysfunction in HIV impacts outcomes of disease.

292 BURKITT LYMPHOMA IN THE ART ERA: STABLE INCIDENCE AND POOR SURVIVAL

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Background: Despite advances in diagnosis and treatment of both HIV and Burkitt lymphoma (BL), persons living with HIV (PLWH) remain at high risk for BL. We conducted this study to determine if there have been any changes in risk or survival among patients with HIV and BL during the anti-retroviral era.

Methods: HIV positive male veterans receiving care between 10/01/1999 and 12/31/2016 in the Veterans Administration Medical Center (VAMC) were retrospectively identified using electronic medical records (EMR). Incident BL diagnosis was identified through VA Cancer Registry review and ICD-9/10 codes. Patients with a minimum of 30 days between HIV and BL diagnosis or death, their last recorded health care encounter, or study end were included in the analysis. Demographic, lifestyle, and clinical variables were extracted from EMR for analysis. Hazard ratios (HR) and 95% confidence intervals (CI) for BL risk and survival were estimated in univariate (p<0.25) and multivariate (p<0.10) time-varying Cox proportional models.

Results: We identified 46,778 HIV positive veterans, of whom 76 developed BL during follow-up (incidence rate [IR] = 2.79 per 100,000 person years, 95% CI: 2.23-3.49). The IR for HIV positive veterans did not decrease over the study period. Table 1 demonstrates results of a Cox proportional hazards model describing characteristics associated with BL diagnosis in HIV positive veterans. Median CD4 count at BL diagnosis was 274, (SD: 344.78) and was noted to increase over time (median CD4 for individuals diagnosed with BL before 1999 was 211 [SD: 195.78], 265 [SD: 354.95] for those diagnosed between 2000-2009, and 450 [SD: 516.89] for those diagnosed between 2010-2016). Survival was significantly decreased in HIV positive veterans with BL as compared to HIV negative controls (p<0.05). An undetectable viral load for at least 40% of the

follow up period was associated with higher survival (HR: 0.141, 95% CI 0.058-0.348, p<0001).

Conclusion: Although therapies for both BL and HIV have improved over time, BL incidence among HIV positive veterans did not improve between 2000 and 2016. Survival after BL diagnosis in HIV positive male veterans remains dismal as compared to their HIV negative counterparts, although veterans with prolonged periods of undetectable viral load showed better survival. Further research is needed to improve treatment and outcomes for this aggressive lymphoma in PLWH.

Table 1. Characteristics associated with incident Burkitt Lymphoma Diagnosis in HIV+ Veterans (1999-2016; N=46,778)

HIV variables		With Burkitt Lymphoma (BL) (N=76)	Without BL (N=46,702)	Hazard Ratio	95% Hazard Ratio Confidence Limits		Pr > ChiSq
Age* in years (ref=40; HR=1)	40-59	55 (72.37)	30,223 (64.82)	0.936	0.890	0.985	0.0112
	60 and above	6 (7.89)	5,815 (12.47)	1.348	1.245	1.459	<.0001
Race (ref= white; HR=1)	Black	36 (47.37)	24,519 (52.59)	0.725	0.693	0.760	<.0001
	Hispanic	5 (6.58)	2,586 (5.55)	1.695	1.576	1.823	<.0001
	Other	3 (3.95)	2,052 (4.40)	0.151	0.106	0.214	<.0001
History of smoking (Ref= Never smoker; HR=1)	Current or	63 (82.89)	37,484 (80.39)	2.145	2.002	2.299	<.0001
Body mass index	25-29.9	27 (36.00)	15,246 (34.08)	0.949	0.904	0.995	0.0318
	> 30	11 (14.67)	6,976 (15.59)	1.505	1.421	1.594	<.0001
CD4 count (ref>350; HR=1)	200-350	13 (17.33)	6,950 (15.50)	1.901	1.785	2.024	<.0001
	< 200	28 (37.33)	9,525 (21.25)	1.184	1.094	1.281	<.0001
Viral load (ref<200; HR=1)	201-400	4 (5.71)	2,167 (5.44)	1.298	1.200	1.405	<.0001
	400+	21 (30.00)	9,002 (22.61)	1.824	1.708	1.948	<.0001
Substance abuse	Yes	3 (3.95)	2,533 (5.43)	0.749	0.716	0.785	<.0001
Hepatitis C positive	Yes	16 (21.05)	10,287 (22.06)	0.864	0.821	0.910	<.0001
Hepatitis B positive	Yes	4 (5.26)	3,046 (6.53)	0.744	0.680	0.815	<.0001

*At study entry

293 LONG BOOST INTERVALS OF ALVAC-HIV/AIDSVAX B/E INCREASED GENITAL HIV ENV IGG RESPONSES

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Background: Anogenital mucosae are the primary sites of HIV acquisition. Boost with AIDSVAX B/E, with or without ALVAC-HIV, after receiving the RV144 vaccine regimen in the RV305 and RV306 trials induced HIV Env-specific IgG in cervico-vaginal mucus (CVM) and seminal plasma (SP). Here, we evaluated the effect of boosting intervals to magnitude and persistence of antibody responses in CVM and SP.

Methods: IgG and IgA to gp120 and gp70V1V2 scaffold proteins two weeks post vaccination in CVM and SP were quantified by ELISA. The effect of boosting interval was assessed by comparing peak responses after receiving the RV144 vaccine series with peak responses following a late vaccine boost of AIDSVAX B/E, with or without ALVAC-HIV, at varying boosting intervals.

Results: IgG to gp120 A244gD- and gp70V1V2 scaffold proteins in CVM significantly increased with late ALVAC-HIV/AIDSVAX B/E boost at 15 months and 18 months compared to peak responses post received RV144 series (A244gD-/gp70V1V2 titer range=800-1600/38-300), p<0.03. IgG to gp70V1V2 CaseA2 in CVM increased after the additional boost of AIDSVAX B/E in participants who received boost of ALVAC-HIV/AIDSVAX B/E or AIDSVAX B/E alone 3-4 years earlier (titer=50), p<0.05. In SP, boosting with ALVAC-HIV/AIDSVAX B/E at 18 months led to significantly higher IgG to gp120 A244gD- (titer=100) and gp70V1V2 92TH023 (titer=25) compared to peak responses post RV144 series, p<0.05. Boosting with AIDSVAX B/E at 9-12 years significantly increased IgG to gp120 MNgD- in SP (titer=150) compared to peak responses post received RV144 series (titer=50), p=0.02. Fold decrease of IgG to all proteins tested over 24 weeks post final vaccination in CVM was not significantly different among boosting groups. In SP, fold decrease of IgG to 92TH023 over 24 weeks post late AIDSVAX B/E boost in participants who received boost of ALVAC-HIV/AIDSVAX B/E or AIDSVAX B/E alone 3-4 years earlier was significantly lower than those who received late boost of ALVAC-HIV/AIDSVAX B/E at 18 months (p<0.03). HIV Env-specific IgA was not detected in any samples tested by ELISA.

Conclusion: Late boosts with AIDSVAX B/E, with or without ALVAC-HIV, produced higher peak HIV Env-specific IgG in CVM and SP at longer boosting intervals. Additional boosting with AIDSVAX B/E improved persistence of IgG to gp70V1V2 92TH023 in SP (measured by fold decrease over 24 weeks). Optimization of functional antibody responses hypothesized to correlate with protection in mucosal compartments may increase vaccine efficacy.

294 A VACCINE TARGETING HIV MATURATION PROTECTS AGAINST VAGINAL SIVMAC251 ACQUISITION

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Background: After over three decades of research, an effective vaccine against HIV-1 remains elusive. Great genetic diversity, rapid mutation and targeting CD4+ T cells are major challenges for developing an effective HIV vaccine. Studies have shown that inflammation activates CD4+ T cells and enhances susceptibility to HIV-1. Current candidate HIV vaccines focus on generating strong, broad and durable immune responses to deal with genetic diversity and rapid mutation of HIV-1. None of them have addressed the challenges to develop a vaccine for a virus targeting the immune system itself. Learning from Natural immunity observed from a group of HIV resistant Kenyan sex workers we developed a novel HIV vaccine approach, targeting the sequences surrounding the 12 protease cleavage sites (PCS vaccine). In this study we evaluated the efficacy of protection of this novel vaccine using a Macaque/SIV model.

Methods: Thirty-Two female Mauritian Cynomolgus macaques were immunized with VSV vector, PCS vaccine (rVSVpcs and NANOpcs), Gag/Env vaccine (rVSVgag/env and NANPgag/env), or NANOpcs vaccine (3 PCS peptides). Mucosal and systemic antibodies, as well as CVL inflammatory cytokines were analyzed with an in-house developed multiplexed Bead array assay using BioPLex200, and Western blot. T cell responses were analyzed using INF-gamma ELISPOT assay and FACS analysis. After immunization and boosts the vaccinated macaques and controls were challenged intravaginally with SIVmac251 (250 TCID50) every two weeks until majority of controls were infected. Keplan-Meier survival analysis and Cox regression model were used to compare vaccine efficacy.

Results: Both PCS vaccine and Gag/Env vaccine significantly protected macaques from pathogenic SIVmac251 infection (p=0.04) after 6 intravaginal challenges. Per-exposure risk reduction was >80%. The magnitude of mucosal neutralizing antibody level and the magnitude of antigen specific INF-gamma ELISPOT response after the last boost do not correlate with protection. The higher magnitude of mucosal MIP-1β/CCL4 (after the last boost) is correlated with an increased risk of SIVmac251 infection.

Conclusion: Our study showed for the first time that a candidate HIV vaccine targeting sequences surrounding the 12 protease cleavage sites, other than full Gag and Env can provide significant protection against pathogenic SIVmac251 intravaginal challenges. Generating immune response while modulating mucosal inflammatory environment may be the key for an effective prophylactic HIV vaccine.

	Hazard Ratio (95% CI)	Per-exposure risk reduction	P-Value[1]	P-Value[2]
PCS vaccine	0.105 (0.013– 0.882)	89.50%	0.038*	0.022*
Gag/Env vaccine	0.193 (0.038 – 0.971)	80.70%	0.046*	0.024*
Control	1 (Control)	N/A	N/A	N/A
	[1] Wald test of Cox model regression coefficients; [2] Log-rank test			

295 SIV- AND HIV-SPECIFIC IMMUNE RESPONSES ELICITED BY PIV5 PRIME/VLP BOOST VACCINATION

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Background: An ideal preventive HIV vaccine may be expected to generate immune protection at mucosal ports of entry and systemically. Parainfluenza virus type 5 (PIV5) is a paramyxovirus that is non-pathogenic in humans and

readily generates mucosal and systemic immune responses in animal models. We developed a series of PIV5 vectors expressing SIVgag and HIV gp140 and administered them intranasally to rhesus macaques, in order to evaluate the potential of this mucosal vaccine vector as an HIV vaccine.
Methods: HIV-1 JR-FL Env and SIVmac239 Gag were inserted individually into the PIV5 genome, and replication and expression of gene products validated in cell lines. Virus-like particles (VLPs) consisting of SIVmac239 Gag core and HIV-1 JR-FL Env were produced in stable, inducible manner from mammalian cells and purified. Macaques received four doses of PIV5-SIVgag + PIV5-HIVgp140 by intranasal administration, followed by boosting with SHIV virus-like particles (VLPs). Humoral and cellular immune responses to SIV and HIV antigens and to the PIV5 vector were measured over time.
Results: Monkeys immunized with PIV5 constructs developed HIV Env and SIV Gag-specific binding Ab titers in a dose-dependent manner. VLP boosting further enhanced SIV/HIV-specific responses, including when the VLP boost followed priming with the lowest intranasal dose of PIV5. Gp120 binding titers correlated to the magnitude of antigen specific plasmablasts measured in blood on days 5 post boost, except for a peak plasmablast response after the initial VLP boost. Presensitization with a heterologous PIV5 vector decreased the frequencies of gp120-specific plasmablasts detected following PIV5-delivered immunizations. CD4+ and CD8+ T cell responses were elicited by PIV5 vectors and boosted following VLP administration. HIV and SIV-specific IgG and weak IgA responses were detected at mucosal sites. Neutralizing antibodies and ADCC responses remain under evaluation at the time of submission of this abstract.
Conclusion: We demonstrate here for the first time that intranasal administration of PIV5-SIV/HIV vectors are well-tolerated and immunogenic. VLP boosting enhanced HIV- and SIV-specific humoral and cellular immune responses. This prime-boost approach may provide a novel approach to the development of systemic and mucosal protective responses against HIV.

296 NOVEL ANTIGEN ELICITS BROADLY NEUTRALIZING ANTI-HIV MONOCLONAL ANTIBODIES IN MICE

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Background: Although broadly neutralizing HIV antibodies are detected in infected (and sometimes uninfected) humans, immunization with HIV-1 antigens generally do not elicit broadly neutralizing antibodies. Clinical studies found that GBV-C E2 antibody is associated with improved survival in HIV and GBV-C co-infected individuals, and E2 antibody neutralizes HIV-1 infectivity by reducing virus entry in vitro. To determine if GBV-C E2 elicits broadly neutralizing HIV monoclonal antibodies (MAbs), we immunized mice with either E2 (lacking C-terminal transmembrane domain) or a synthetic peptide we previously demonstrated is involved in HIV entry and generated anti-E2 MAbs against both antigens. Here, we examined the interactions of both MAbs for their ability to inhibit HIV-1 infectivity, precipitate HIV-1 particles, and bind HIV-specific structural protein antigens.
Methods: GBV-C E2 protein was expressed in CHO cells, and a synthetic peptide generated of the 17 amino acid E2 region involved in HIV entry. Mice were immunized with 25 ug E2 protein or peptide in IFA four times prior to sacrifice, and hybridomas generated. One anti-E2 and one anti-peptide hybridoma cell line (8H2 and 1C4 respectively) were identified from more than 2,000 independent cultures using a capture E2 ELISA. HIV-1 envelope proteins (gp120, gp140 and gp41), gp41 peptides (MPER and T-20), and X4- and R5-tropic HIV-1 isolates representing clades A, B, and D were studied.
Results: Both GBV-C anti-E2 MAbs precipitated HIV-1 particles and neutralized X4 and R5-tropic HIV isolates from diverse geographic regions representing three clades (IC50 ranging from 2.5 to 7.5 ug/mL). These antibodies did not neutralize mumps or yellow fever viruses, demonstrating specificity. 8H2 reacted with HIV-1 gp140 and gp41 proteins, but not gp120 using two types of ELISA methods. Both 8H2 and 1C4 recognized the HIV-1 gp41 fusion (MPER) peptide in immunoblot assays.
Conclusion: Although HIV-1 antigens do not elicit broadly neutralizing HIV-1 antibodies, GBV-C E2 and an E2 peptide elicited HIV-1 neutralizing MAbs in mice. Since GBV-C E2 antibodies are associated with prolonged survival in three clinical studies, these data illustrate the potential for a novel antigen to incorporate into HIV-1 vaccine strategies.

297LB TRANSCRIPTOMIC HOST RESPONSES TO RHCMV/SIV VACCINATION IN RHESUS MACAQUES

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Background: The rhesus cytomegalovirus (RhCMV) strain 68-1 vaccine against simian immunodeficiency virus (SIV) induces a T cell response that protects over 50% of vaccinated rhesus macaques (RM) to clear infection against multiple SIV challenge including distinct challenge routes. To define the molecular features of the host response to vaccination and the underlying gene signature of vaccine protection we assessed the transcriptional responses of protected and non-protected RMs following vaccination prior to challenge.
Methods: Two groups of 15 RMs were administered 68-1 RhCMV/SIV vaccine via oral or subcutaneous delivery. Following vaccination, RMs were subjected to repeated limiting dose intrarectal SIVmac239 challenge until infected as detected as plasma virus or the de novo development of SIV Vif-specific T cell response. During the vaccination phase, blood samples were collected at time points near prime, boost, and before challenge. mRNA-seq was performed followed by bioinformatics analysis including differential gene expression, co-expression clustering, and functional enrichment analyses.
Results: In the subcutaneous and orally-vaccinated groups, 53% and 60% of RMs cleared SIV infection after virus challenge, respectively. Protected RMs showed both an acute and sustained increase in gene expression indicative of myeloid cell responses, including genes and gene networks involved in Toll-like receptor signaling, inflammasome induction, and monocyte activation. We identified a noncanonical T-cell signaling signature in protected animals that was characterized by a decrease in of Zap70 and Tbx21 with concomitant increase in Ido1 expression. Importantly, we identified an interleukin (IL)-15/STAT5 signaling module that links with immune cell trafficking and protection from SIV infection. A rule-based machine learning analysis confirmed that gene expression signatures controlling TLR activation of macrophages and myeloid cell activation, could predict vaccine protection. Assessment of an independent cohort of naive RM treated with IL-15 revealed gene networks of the IL-15 response. Integration analyses were conducted to identify a subset of IL-15 response genes in vaccinated animals whose induced expression tracks with vaccine protection. This gene expression signature was maintained post-virus challenge.
Conclusion: Our results define noncanonical T cell activation, inflammatory signaling, myeloid cell activation, and IL-15 response as features of RhCMV-SIV vaccine protection.

298 EARLY ART PARTLY REDUCES HIV-INDUCED MUCOSAL B-CELL HYPERACTIVATION

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Background: HIV-induced immune activation is a hallmark of HIV pathogenesis and disease progression. This includes hyperactivation of B cells with increased differentiation of B cells to plasmablasts (PB) and a decrease in memory B cells (BMem). We evaluated the effects of antiretroviral therapy (ART) initiated during acute HIV infection (AHI) on mucosal B cells.
Methods: Individuals at Fiebig stages I to III of AHI, underwent sigmoid biopsy at the time of HIV diagnosis (AHI; n=14) and 24 months post ART initiation (n=18). Matched HIV-uninfected (HIV-; n=33) and individuals who had initiated ART during chronic HIV infection (CHI - 12 to 36 months post ART initiation; n=6) served as controls. Mucosal mononuclear cells were isolated and multiparameter flow cytometry was performed to determine the frequency of B cell subsets (PB: Lin-CD20+/-CD19+CD27hiCD38hi; BMem: Lin-CD20+CD19+CD27+CD38-IgD-IgM-).
Results: Median gut HIV RNA was 3.8 log10 [copies/mg tissue] at AHI diagnosis and undetectable after 24 months of ART in 17/18 participants ($p \leq 0.001$). There

was no difference observed in the frequency of PB and BMem between the time of AHI diagnosis and HIV- individuals (PB: 6.3% vs 8.2%, BMem: 58.0% vs 53.7%, respectively). However, 24 months post ART initiation a significant increase in the frequency of PB to 17.1% was observed compared to time of AHI diagnosis (6.3%, p≤0.01) and compared to HIV- (8.2%, p≤0.0001), which was similar to the frequency of PB in CHI (14.8%, p=0.24). The frequency of BMem decreased from 58.0% during AHI diagnosis to 50.1% at 24 months post ART initiation (p≤0.01). Following 24 months of ART the frequency of BMem (50.1%) was lower compared to HIV- (53.7%, p=0.03), but remained significantly higher compared to CHI (35.0%, p≤0.05). Interestingly, the expression of IgA, the most abundant isotype produced by mucosal PB, was higher in CHI compared to AHI following 24 months of ART (10.8% vs 4.7%, p=0.03), with no increase observed between AHI diagnosis and 24 months post ART initiation (6.1% vs 4.7%, p=0.43).

Conclusion: HIV-related hyperactivation of mucosal B cells was observed despite early ART initiation. However, early ART appears to limit the loss of BMem compared to CHI as well as prevent increased IgA production by PB. These results provide further insights on mucosal B cell dynamics in HIV infection and another potential mechanism how early ART may limit immune system damage at the mucosal barrier.

299 IMPROVED CD4 T CELLS RESPONSES WITH EARLY TREATMENT DURING PRIMARY HIV INFECTION

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Background: Treatment as soon as possible, limiting viral replication, has been shown to reduce the expansion of the HIV reservoir (Laanani et al., CID, 2015). We investigated the impact of early control of HIV replication on CD4 and CD8 T cell functions. We studied the kinetics of CD4 and CD8 T cell responses during PHI and investigated the relationship between the control of viral load (VL) after 3 months of treatment (M03) and the quality of CD4 and CD8 T cell responses at month 24 of treatment (M24).

Methods: In 50 subjects included in the ARNS-147 OPTIPRIM study, cytokine production (IL-2, MIP-1β and IFN-γ) was measured on peripheral blood mononuclear cells by flow cytometry after a 15-hour stimulation with relevant optimal peptide pools according to the subjects' HLA-A and B alleles or p24 for CD8 and CD4 T cells, respectively at inclusion and at M24. In parallel, the capacity of CD8 T cells to suppress p24 production by autologous CD4 T cells in coculture was measured and expressed as Log10 of p24 decrease. Cytokine production at inclusion was explored according to the time after the estimated date of contamination by the Loess curve.

Results: Analysis of cytokine production kinetics during PHI highlights the existence of a peak of CD8 T cells responses around 30 days after the estimated date of contamination. CD8+ T cell-mediated HIV suppression which was weak during PHI (median 0.092 Log10 of p24 decrease, IQR [0.019-0.305]) did not improve after 24 months of treatment (0.144 Log10 of p24 decrease [0.047-0.359], p=0.62). At M24, the proportion of CD4 T cells producing at least one cytokine in response to p24 stimulation tended to be higher in subjects with undetectable viral load at M03 compared with subjects that still had a detectable plasma viral load at M03 (threshold = 50 HIV-RNA copies/mL) (0.068% [0.035-0.340] vs 0.028% [0.008-0.044] of CD4 T cells, respectively; p=0.06). IFN-γ production contributed greatly to the difference, with 0.016% [0.008-0.096] of IFN-γ producing CD4 T cells in subjects with undetectable VL at M03 vs 0.003% [0.002-0.007] in subjects with detectable VL at M03, p<0.0001.

Conclusion: Achieving a control of viral replication during the first 3 months of treatment initiated at PHI is crucial to protect the CD4 T cell function at long term. This is an additional argument for not delaying treatment initiation in PHI.

300 EFFECT OF TELMISARTAN GIVEN AT ART INITIATION IN AHI ON IMMUNE CELLS IN LYMPH NODES

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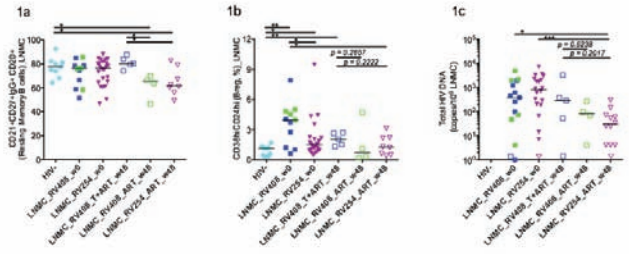
Background: HIV infection induces lymph node fibrosis and persistent inflammation even during successful ART. Telmisartan, an angiotensin II receptor blocker, could prevent fibrosis and inflammation in individuals with HIV when administered at time of ART initiation in acute HIV infection (AHI). We assessed telmisartan effect on preventing HIV-mediated damage and on HIV reservoirs in tissues in people randomized during AHI to telmisartan+ART (T+ART) versus ART alone.

Methods: Cryopreserved LN cells at time of AHI and 48 weeks after were included from RV408 participants randomized to T+ART (n=7) versus ART alone (n=4). Additionally, LN samples from other RV254 participants at AHI (n=26) and post-ART at wk48 (n=13), to compare the RV408 randomized group to a larger group. Nine uninfected individuals were also included. B cells, CD4 and CD8 T cells were characterized by flow cytometry when sufficient cells permitted. Total HIV DNA levels in CD4 T cells were quantified by ultrasensitive PCR; collagen, TGFβ and TNFα were measured by immunohistochemistry.

Results: In AHI, no differences were observed between the groups. At wk48, in LN, the frequencies of resting memory (RM) B cells (CD21+CD27+IgG+CD20+) were decreased in ART group in the RV408 and RV254 but maintained at similar levels as controls in the T+ART group (Fig.1a). Conversely, frequencies of tissue-like memory B cells and intermediate memory B cells were lower in LN in the T+ART group compared to the RV408 ART group (p=0.015 and p=0.039, respectively) as well as the RV254 group. In addition, in LN, frequencies of regulatory B cells (CD38hiCD24hiCD19+) were higher in the T+ART group compared to uninfected controls and trending to be higher compared to the ART groups (Fig.1b). No difference was observed between the two groups in activated CD4 and CD8 T cells (CD38+HLA-DR+ and Ki67+Bcl-2lo) in LN. The LN HIV DNA levels were not different between the T+ART and the ART groups (Fig.1c). No differences were observed in collagen deposition, TGFβ and TNFα between the two RV408 groups.

Conclusion: Although the number of studied samples in the T+ART group in our study limits definitive conclusions, addition of telmisartan to ART during AHI did not reduce T cell activation, HIV reservoir or collagen deposition in LN. However, we observed higher RM B cells and Bregs in LN after T+ART versus ART alone. These data suggest that adjunctive therapy in AHI with telmisartan over 48 weeks may preserve immune cells in LN especially the B cell compartment.



301 METFORMIN TREATMENT IN NONDIABETIC HIV-INFECTED INDIVIDUALS ON ART

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Background: The mechanistic target of rapamycin (mTOR) promotes HIV transcription. In line, we demonstrated that HIV preferentially targets gut-homing CCR6+Th17 cells for replication/persistence via mTOR-dependent mechanisms. Thus, mTOR inhibitors may limit residual HIV transcription during ART and subsequently reduce immune activation/inflammation. Here, we

report results from a clinical trial conceived to evaluate the effect of 12 weeks of metformin (mTOR inhibitor) therapy on the size of HIV reservoirs (primary objective) and immune activation (secondary objective) in ART-treated HIV-infected adults (HIV+ART).

Methods: Metformin (850 mg bid) was administered orally for 12 weeks in n=22 HIV+ART. Participants were non-diabetic, on ART for >3 years, with <40 HIV-RNA copies/ml plasma for >3 months, and CD4/CD8 ratios ≤0.7. Blood was collected at baseline (Visit 1), after 12 weeks of metformin (Visit 2), and 12 weeks after metformin discontinuation (Visit 3). Sigmoid colon biopsies (≈32 biopsies/participant) were collected at Visits 1-2 from n=13 participants. HIV-DNA was quantified by real-time nested PCR. Replication-competent HIV was quantified by viral outgrowth assay (VOA). Matched blood/colon memory CD4+ T-cells were analyzed for surface/intracellular molecule expression and simultaneously sorted by flow cytometry (BD AriaIII). Plasma soluble factors were quantified using R&D Systems Multiplex Assay and ELISA.

Results: Metformin was well tolerated. Total HIV-DNA levels in blood/colon CD4+ T-cells and the frequency of blood CD4+ T-cells carrying replication-competent HIV was stable between Visits 1-3. However, investigations on matched blood/colon samples revealed a positive effect of metformin as reflected by i) decreased infiltration of CD4+ T-cells in the colon (median: 7.3% vs. 4.7%, Visit 1 vs. 2; p=0.019), indicative of reduced colon inflammation; ii) decreased mTOR phosphorylation in colon CCR6+CD4+ T-cells (median: 13.0% vs. 7.9%, Visit 1 vs. 2; p=0.0087); iii) a tendency for decreased expression of the HIV co-receptors CCR5 and integrin β7, and increased expression of the HIV restriction factor SAMHD1 in colon CCR6+CD4+ T-cells; and iv) decreased sCD14 plasma levels (mean: 1,893 vs. 1,519 ng/ml; Visit 1 vs. 3; p=0.02).

Conclusion: This pilot study reveals metformin-mediated benefits in controlling inflammation, in part via mTOR regulation, and prompts us to further investigate the immunological/virological benefits of long-term metformin supplementation in HIV+ART individuals.

302 METFORMIN THERAPY WITH IMMUNE CHECKPOINT INHIBITORS IMPACTS ANTI-HIV T-CELL RESPONSES

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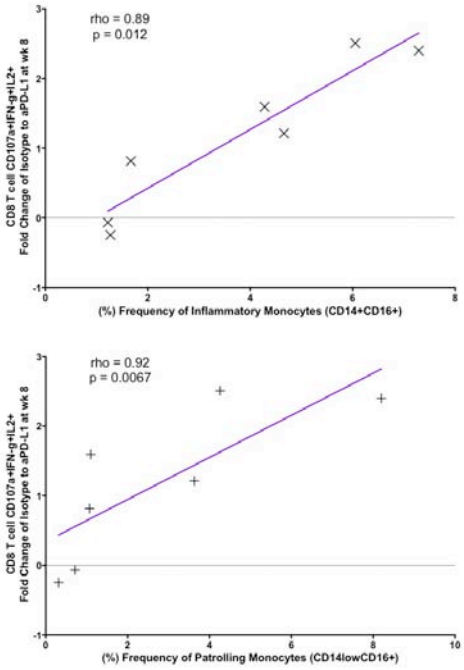
Background: Despite suppressive antiretroviral therapy (ART), chronic HIV is associated with T cell exhaustion, defined by the overexpression of negative immune checkpoint receptors. The efficacy of immune checkpoint blockade (ICB) in reversing T cell dysfunction and improving cancer survival is variable. Metformin (MET) is an oral hypoglycemic therapy for type II diabetes and has previously unrecognized therapeutic effects against age-related conditions. Recently, ICB in combination with MET has yielded favorable clinical outcomes in oncology (MZ. Afzal et.al. 2018). We assessed the ex vivo anti-HIV T cell responses to ICB during adjunctive MET therapy in banked blood from a clinical trial of MET conducted in HIV+ adults.

Methods: We conducted an open label, 8-week (wk) pilot study in seven euglycemic adults on ART, stable for >1 year with plasma HIV RNA <50 copies/ml, median age of 60.5 years and all male. MET dosing was 500mg at entry increasing to 1000mg at wk4. In cryopreserved PBMCs, we measured ex-vivo HIV-specific T cell responses (CD107a, IFN-γ, IL-2) to an HIV Gag peptide pool in the presence of blocking anti-TIGIT and/or anti-PD-L1 monoclonal antibodies and an isotype control (IgG1). Since monocyte frequencies (%) at entry have been shown to be associated with melanoma survival in response to anti-PD-1 blockade (C. Krieg et.al. 2018), we also quantified monocyte subsets by flow cytometry. Statistical analysis included non-parametric Wilcoxon rank-sum test and Spearman's rho for correlations.

Results: MET did not improve HIV-specific CD8 T cell responses in the absence of blockade. In the presence of anti-PD-L1, MET improved HIV-specific CD8 T cell responses (CD107a+IFN-γ+IL-2+) (Fold Change between IgG1 and anti-PD-L1; (entry: 0.19 (-0.28, 0.41), wk 8; 1.21 (-0.06, 2.39) p=0.04). Monocyte frequencies (%) remained unchanged. Baseline % of inflammatory (CD14+CD16+) and patrolling (CD14lowCD16+) monocytes positively correlated with wk8 HIV-specific T cell responses (CD107a+IFN-γ+IL-2+) to anti-PD-L1 blockade (r=0.89, p=0.01 and r=0.92, p=0.006, respectively), whereas classical monocytes inversely associated with these responses (r=0.78, p=0.04).

Conclusion: MET in combination with ICB may improve poly-functional HIV-specific CD8 T cell effector function. The presence of certain monocyte subsets correlated with favorable T cell responses, suggesting that monocytes may play an important role in ICB efficacy. MET may have value as an adjunctive therapy in "Shock and Kill" HIV remission studies.



303 ZINC SUPPLEMENTATION AND INFLAMMATION IN TREATED HIV

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Background: In HIV, the prevalence of zinc deficiency appears to be high and low plasma zinc levels have been linked with disease progression and an increased risk of death. In this study, we explored the effect of zinc supplementation on the heightened state of inflammation and monocyte activation observed in ART-treated HIV infection.

Methods: This is a pilot open labeled randomized double arm study, studying the efficacy and safety of zinc therapy on inflammation in ≥ 18 years old HIV-infected patients , on stable ART (for at least 12 weeks) and with zinc levels ≤75 µg/dL in the last 60 days. Patients were randomized 1:1 to zinc gluconate capsules at a dose of 45mg (low-dose), or 90mg (high-dose) elemental zinc daily for 16 weeks. We assessed the following markers at baseline and 16 weeks: high sensitivity C reactive protein (hsCRP), soluble CD14 (sCD14), soluble tumor necrosis alpha receptor I and II (sTNFR-I and II), lipopolysaccharide binding protein (LBP) and intestinal fatty acid binding protein (IFABP). We performed significance tests for the shift of distributions using Kolmogorov –Smironow test. Effect size was reported as Cohen's d.

Results: Overall, a total of 52 participants were enrolled (25 participants in the low-dose arm and 27 participants in the high-dose arm). Mean age was 49 years, 77% were males and 73% were African Americans. At baseline, mean zinc levels were 75 µg/dL. After 16 weeks, loss to follow up was minimal with 92% retention. One patient developed nausea possibly related to the zinc capsules, there were no other study related adverse events. Mean circulating zinc levels increased to 91 µg/dL in the low-dose arm and to 105 µg/dL in the high-dose arm. In addition, 88% of participants in the low-dose arm and 96% in the high-dose arm reached zinc levels >75 µg/dL. Overall, biomarkers decreased with a margin of reduction ranging between 8 and 33% (figure 1). There was a larger

margin of change in sCD14 and IFABP in the participants in the low-dose arm, however the reductions were greater for hsCRP and LBP in the high-dose arm. This change was meaningful with large effect size (Cohen's ranging from 5-19).
Conclusion: In this pilot study we found that zinc supplementation is safe and effective at increasing circulating zinc levels. In addition our findings provide novel data that zinc can impact a biological signature in patients with HIV and modulate biomarkers that have been associated with clinical comorbidities.

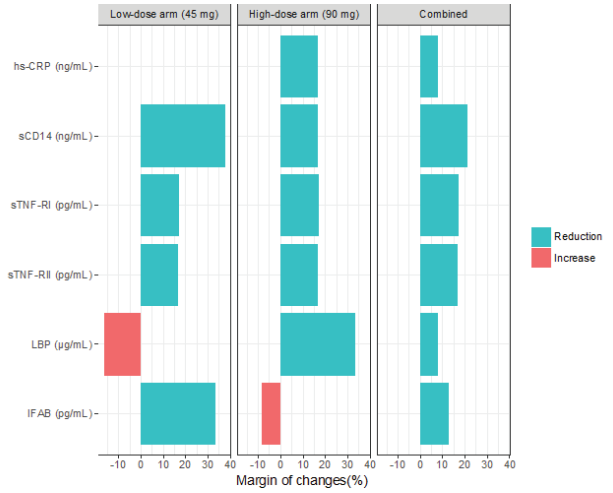

Figure: The margin of changes (effect sizes) for the low-dose arm (45 mg) and the high-dose (90 mg) zinc treatment over the 16 weeks study period. Margin of changes calculated as percent of positive change – percent of negative change. Reductions in biomarkers are shown in blue, increases in red.

304 GLYCOMIC DETERMINANTS OF INTERFERON-a MEDIATED REDUCTION OF HIV PERSISTENCE IN VIVO

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Background: Interferon-α (IFNα) therapy was associated with significant suppression of HIV viremia and reduction in levels of HIV DNA during suppressive antiretroviral therapy (ART). Cytokines modulate host glycosylation, and glycosylation plays a critical role in mediating several antibody (mainly immunoglobulin G; IgG) immunological functions, including antibody-dependent cell-mediated cytotoxicity (ADCC), and anti-inflammatory activities. Nevertheless, the impact of IFNα on host glycosylation machinery remains unknown.
Methods: We assessed the impact of pegylated IFNα2a (Peg-IFNα2a) immunotherapy on isolated IgG glycomes of 18 HIV-mono-infected individuals on suppressive ART, using capillary electrophoresis. We also examined the plasma levels of 1) the immunomodulatory lectins, galectin-1, -3, -9, E-selectin, P-selectin, and L-selectin; and 2) 16 pro- and anti-inflammatory markers and cytokines, using Luminex. ADCC activity was measured using the Chromium-51 (51Cr) release assay. Last, levels of integrated HIV DNA in CD4+ T cells were examined using qPCR. Wilcoxon signed-rank test and Spearman's correlations were used for statistical analysis. The Bonferroni method was used to correct for multiple comparisons.
Results: Peg-IFNα2a treatment was associated with a significant increase in the proportion of the pro-inflammatory, bisected GlcNAc glycan structures (such as G0FB; Bonferroni-corrected p<0.05). Fold induction of G0FB glycan trait correlated positively with the IFN-α-mediated induction of the pro-inflammatory soluble markers (sCD14 and sCD163; rho>0.56, p<0.016). Peg-IFNα2a also induced the plasma levels of the inflammatory mediators galectin-9 (p=0.0001), L-Selectin (p=0.027), and E-Selectin (p<0.008). IFNα2a-mediated reduction of the anti-ADCC total fucosylated glycans (p<0.05) correlated negatively with fold change in ADCC activity (rho= - 0.52, p=0.026). Last, IFNα-mediated reduction of A2G2S1 glycan trait (p=0.04) correlated positively with change in ADCC activity (rho=0.62, p=0.006), and with IFNα-mediated reduction of integrated HIV DNA levels (rho=0.76, p=0.037).
Conclusion: IFNα immunotherapy in HIV-infected individuals on suppressive ART is associated with glycomic alterations, that are known to mediate higher inflammatory responses and higher innate effector functions. Our data suggest that host glycan-lectin interactions may mediate signals that inform and/or determine host immune responses to HIV persistence during IFN-α treatment.

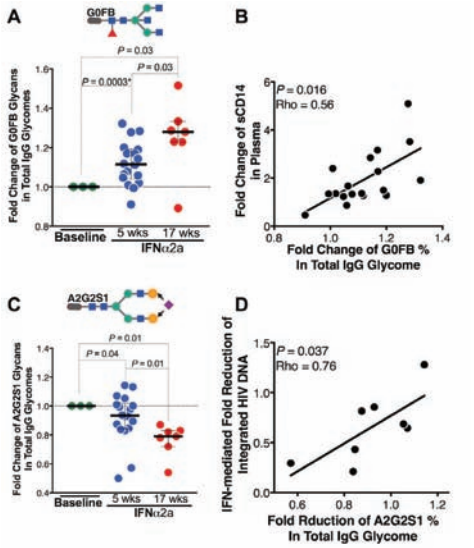

Figure 1. (A-B) IFNα immunotherapy induces levels of the proinflammatory bisected GlcNac glycan structure (G0FB) in the total gG glycome. **(C-D)** IFNα-mediated reduction of the levels of the A2G2S1 glycan trait correlates with reduction of integrated HIV DNA levels.

305 SUSCEPTIBILITY TO BNABs IS CONCORDANT IN PRE-ART PLASMA AND ON-ART PBMCs: ACTG NWC413

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Background: Pre-existing resistance is a barrier to the efficacy of broadly neutralizing antibodies (bnAbs) for treatment and cure of HIV infection. Here, we determine the range of baseline susceptibilities to bnAbs in clinical development and assess the PhenoSense HIV nAb Assay's predictive capacity in plasma virus and proviral DNA samples.
Methods: HIV envelopes derived from pre-ART plasma and PBMCs from 1 and 3 years of ART from each of 65 chronically HIV-infected participants of the ART naïve trial A5257 were tested for neutralization susceptibility to seven bnAbs (VRC01, VRC07.523LS, 3BNC117, N6, 10-1074, CAP256-VRC26.25, 10E8) using the PhenoSense nAb assay, which generates pseudovirions from plasma vRNA or PBMC proviral DNA-derived HIV envelopes. PBMCs from 9 participants at entry to A5340, which evaluated VRC01 during ART interruption, were also tested. Rank-based Spearman Correlation and Fisher's exact tests were used for statistical analyses.
Results: Participants' median CD4 count was 350 cells/mm3 and 40% had a baseline VL >100,000 copies/ml. IC50s varied more than 3 logs for each bnAb, but pre-ART plasma, year 1 and 3 PBMC values were highly correlated (Spearman r= 0.62-0.95, P<0.001 for all), with modestly lower IC50s in PBMC samples. Correlations for titers against VRC01 in the 3 samples are shown in Figure 1. Susceptibilities within the CD4 binding site bnAbs were correlated (r=0.71-0.86, P<0.001 for pre-ART plasma). No significant relationships were found between bnAb classes, except a modest correlation between CD4bs bnAbs and 10-1074 (r= 0.29-0.4, P=0.002-0.023). Among the A5340 samples, VRC01 IC50s from entry PBMCs correlated with published pre-ART plasma IC50s

available for 5 participants (Spearman r=0.9, P=0.04). In 9 participants with entry PBMCs, VRC01 IC50s did not significantly correlate with time to rebound (Spearman r=-0.35, P=0.37), but IC50<0.5 µg/mL was associated with delayed time to rebound (>8 weeks) (P=0.0278).
Conclusion: We found a wide range in baseline neutralization susceptibilities to clinically relevant bnAbs with highly correlated values across plasma and PBMC-derived samples over 3 years of ART. In A5340, PhenoSense nAb susceptibilities on entry PBMCs were similar to published pre-ART values and IC50<0.5 µg/mL was associated with delayed rebound after ATI. Results support the utility of screening for neutralization susceptibility prior to therapeutic bnAb use and suggest PhenoSense nAb PBMC testing may be a valid approach in suppressed individuals.

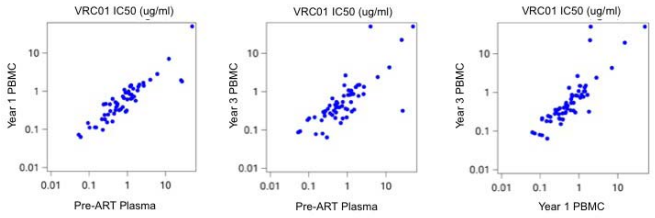

Figure 1. VRCO1 susceptibilities for Pre-ART Plasma, Year 1, and Year 3 PBMC are highly correlated (Spearman r = 0.78-0.91; P<0.001)

306 HIGH-THROUGHPUT ASSAY TO ASSESS ADCC ACTIVITY AGAINST CLINICAL ISOLATES OF HIV-1

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Background: High throughput infection based antibody dependent cellular cytotoxicity (ADCC) assays are needed to gain insights into the role of ADCC in preventing transmission. Current infection based assays often use a natural killer (NK) cell resistant CD4 T cell that expresses the CCR5 receptor (CEM-NKr-CCR5) as target cells, but transmitted viruses, such as those circulating in infected individuals, often cannot replicate in these cells. Furthermore, primary cells demonstrate highly variable susceptibility to primary HIV-1 strains.
Methods: Two different CD4 T cell lines, PM1 and MT4, were transduced with a CCR5 and a tat-inducible luciferase expression plasmid. Target cells were exposed to primary and lab-adapted HIV-1 strains and cultured with the NK cell line, KHYG-1, in the presence and absence of antibody. Percent ADCC was calculated as the loss of luciferase expression in the presence as compared to the absence of antibodies.
Results: Incubation with NK cells, without HIV-1 antibodies, decreased luciferase in infected PM1-CCR5-Luc (43.87%, range=31.5-56.7) and MT4-CCR5-Luc (1.09%, range=-1.9-4.1), suggesting PM1 but not MT4 cells were highly susceptible to background NK cell killing. Thus, PM1-CCR5-Luc cells were not examined further and MT4-CCR5-Luc cells were deemed NK cell resistant. NL4-3 infected CEM-NKr-CCR5-Luc (68.2%, range=55.4-83.8) and MT4-CCR5-Luc (70.6%, range=60.8-78.0) yielded similar ADCC estimates in the presence of 500ug/ml HIV-1 IgG (p=0.79). While NL4-3 replicated in both CEM-NKr-CCR5-Luc and MT4-CCR5-Luc cells, fold luciferase expression over background was only elevated in the MT4-CCR5-Luc cells after infection with primary CCR5-using variants, such as CH058 (4.54 fold), CH077 (2 fold), ZM247Fv2 (29.53 fold), and BJOX2000 (42.53 fold). In MT4-CCR5-Luc cells, similar ADCC estimates were obtained in the presence of heat inactivated plasma compared to isolated IgG (p=0.31). Breast milk isolated IgG, heat inactivated infant and maternal plasmas, but not breast milk supernatant, demonstrated ADCC activity against maternal strains and reference envelope panel viruses.
Conclusion: Our MT4-CCR5-Luc cell line can be used to estimate ADCC activity present in plasma, breast milk and among immunoglobulins against both primary and T/F strains. The high throughput reliable assay will be used to compare mother-infant pairs where transmission did and did not occur in order to determine if ADCC is a correlate of protection in MTCT.

307 IMPACT OF ATI ON B-CELL REGULATION BY IGG3 IN CHRONICALLY HIV-INFECTED INDIVIDUALS

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Background: Numerous immunologic abnormalities have been described in HIV infection, especially in the absence of antiretroviral therapy (ART). B-cell abnormalities include loss of classical memory B cells and gain of activated, exhausted and differentiated B cells. We recently reported a role for IgG3 in regulating B-cell activation in certain individuals with chronic HIV viremia. Here, we investigated the dynamics of IgG3 regulation in a longitudinal cohort of HIV-infected individuals undergoing analytical treatment interruption (ATI).
Methods: Longitudinal immunologic and virologic analyses were conducted on specimens obtained from seven individuals prior to receiving ART, after several years of ART, during ATI, and following re-initiation of ART. The dynamics of HIV plasma viremia, changes in B-cell populations and IgG3 binding in the peripheral blood were evaluated longitudinally. The immunologic assays were performed by multiparameter flow cytometry.
Results: In the absence of ART (pre-ART), four of seven individuals had IgG3 bound to their IgM+ B cells. After a median of ten years on ART (pre-ATI), none of the individuals had IgG3+IgM+ B cells. Following ATI, varying degrees of IgG3 binding to B cells was observed at peak viremia in the same four individuals who had the profile pre-ART. The IgG3+IgM+ B-cell profile was again extinguished following re-initiation of ART. During ATI, for all seven HIV-infected individuals studied, total B-cell percentages decreased significantly and contained a higher percentage of plasmablasts compared to ART-naïve, pre- and post-ATI time-points. During ATI, the percentage of activated memory B cells also increased significantly compared to the pre-ATI period, while the percentage of tissue-like memory B cells did not change, remaining significantly lower compared to the pre-ART period. The percentage of classical memory B cells decreased significantly during ATI compared to pre- and post-ATI periods, but remained higher compared to the pre-ART period.
Conclusion: We provide evidence that ATI elicits significant changes in B cells of HIV-infected individuals as a result of rebounding plasma viremia. The presence of circulating IgG3+IgM+ B cells is a property consistently observed in certain HIV-infected individuals during chronic plasma viremia and closely associated with active viral replication. The profile is present pre-ART, extinguishing itself during effective ART and gradually returns when individuals undergo ATI and plasma viremia rebounds.

308 PTEN OVEREXPRESSION IN ANTIGEN-SPECIFIC B CELLS FROM HIV-INFECTED INDIVIDUALS ON ART

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Background: Memory B cells (MBC) respond to secondary antigen challenge to protect against infection and to boost immunity following vaccinations. Despite effective treatment, chronic HIV infection disturbs MBCs by reducing numbers and altering functionality due to hyper-activation and increased apoptosis leading to suboptimal antibody responses against common infectious agents such as Influenza. We and others have shown that influenza-specific responses in B cells are impaired in HIV-infected individuals in both young and old (>60 years) individuals. However, these studies have largely been performed using bulk cell analysis from in vitro antigen-stimulated culture experiments and technological advances in single cell analysis now allow for deeper interrogation of cellular states in cell populations with diverse functions, such as MBC.
Methods: We used single cell gene expression analysis to evaluate post-vaccination antigen-specific memory B cells isolated from peripheral blood of virally-suppressed HIV-infected individuals and healthy controls stratified by serum H1N1 antibody response 3 weeks post-administration of the seasonal trivalent inactivated influenza vaccine. We used a fluorescent probe to isolate influenza H1N1-specific B cells and a multiplexed and targeted RT-PCR approach (Fluidigm BioMark) to measure expression levels of 96 genes involved in B cell activation and function. H1N1-specific B cells were also analyzed for memory phenotype and Ig isotype by flow cytometry to integrate with gene profiles.
Results: Single cell gene profiling revealed a 4-gene predictive signature containing IL10RA, APOBEC3G, TLR7 and the phosphoinositide-3 kinase

(PI3K) inhibitor, PTEN, for identifying antigen-specific MBC from HIV-infected individuals compared to healthy controls. Gene co-expression analysis showed that in addition to overexpression of PTEN, there was increased co-expression of type I interferon-associated genes with PTEN on single cell level in HIV compared to controls.
Conclusion: Overall, this signature reinforces the concept of an imbalance in the interferon pathway leading toward an impairment of the ability of B cells to mature where PTEN seems to play a central role. Further, this study provides a framework for analysis of antigen-specific cells using single cell gene expression analysis and provides insight into persistent defects in B cell-mediated immunity in the context of treated HIV infection and introduce potential targets of intervention to improve vaccine responses.

309 AUTOLOGOUS NEUTRALIZING ANTIBODIES DRIVE VIRUS EVOLUTION DURING REBOUND AFTER ATI

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Background: Characterization of the viral dynamics and host immune pressures present during HIV-1 rebound after analytical treatment interruption (ATI) provides insight into the environment in which therapeutic and curative strategies must act.
Methods: We studied plasma samples from a previously conducted clinical trial (NCT00051818) in which chronically-ART initiated participants underwent a single or multiple sequential ATIs. Single genome sequencing of env genes was performed on plasma vRNA from first detectable rebound through up to 1 year of ATI. Select envs were cloned and tested as pseudoviruses for sensitivity to autologous plasma neutralizing antibody (nAb) responses in the TZM.bl assay.
Results: Phylogenetic analysis of env sequences from first detectable plasma rebound in 11 participants undergoing a single ATI revealed multiple genetically distinct lineages replicating in each participant (median=5, range 2 to >10). Over time, total env diversity and the number of genetically distinct lineages expanded, with evidence of virus evolution, recombination, and reactivation of new populations. In 6 of 7 participants with adequate sampling, however, all or many of the initial rebounding lineages were not sampled in subsequent timepoints. Virus lineages that were cleared were significantly more sensitive to autologous plasma nAbs than those that persisted (median reciprocal IC50 titers of 906 vs. 153, p=0.0286, by Wilcoxon). IgG from plasma at the time of ART interruption had modest activity against cleared viruses; IgG from week 4 and 8 of ATI increased its potency against rebound viruses by 100 to 10,000-fold (p=0.0079, by Wilcoxon). In 2 participants from the multiple ATI arm of the study, initial rebound was comprised of multiple distinct lineages (6-7 lineages). Over 3 subsequent ATIs, a substantial number of initial lineages were no longer sampled, with autologous nAbs showing a non-significant trend towards greater potency against cleared viruses.
Conclusion: In ART suppressed individuals undergoing ATI, we found that multiple virus populations arise from latency and diversify rapidly over ATI, with selective sweeps of initial rebound virus populations observed in most participants. Autologous nAbs are modest initially, but quickly expand to drive virus selection over subsequent weeks. Results suggest that autologous nAbs are an important component of the immune dynamics of rebound and should be considered in immunotherapeutic approaches to virus suppression and cure.

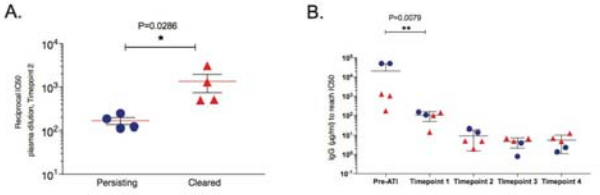

Figure 1. Autologous nAb responses drive selective virus clearance. A) Reciprocal IC50 titers against presisting or cleared viruses from 3 participants. B) IgG concentrations required to inhibit virus infectivity by 50% over ATI timepoints.

310 A NOVEL PHAGE-DISPLAY APPROACH MAPS LINEAR EPITOPES OF GP41-SPECIFIC MABS

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Background: Antibodies targeting the HIV Envelope (Env) protein can limit viral infection and provide immunity. However, the field has yet to generate a vaccine capable of producing protective antibodies in humans. With epitope-based vaccine design we can engineer immunogens to elicit antibodies against specific regions of Env, but we are limited in part by the low throughput nature of current epitope mapping methods. Here we developed and tested a high-throughput, comprehensive approach to map the epitopes of recently identified HIV-specific monoclonal antibodies (mAbs) that mediate ADCC.
Methods: We applied a phage display method that used deep sequencing, Phage Immunoprecipitation-Sequencing (PhIP-seq), to identify the linear epitopes of four newly identified gp41-specific monoclonal antibodies (mAbs): QA255.006, QA255.016, QA255.067, and QA255.072 as well as 240-D, a gp41-specific antibody previously mapped using peptide arrays. We first generated a synthesized oligonucleotide library encoding for 39 amino acid long peptides that tile along the entire length of several Env and full-length HIV sequences from different clades. This library was cloned into a T7 bacteriophage display vector. To perform a PhIP-seq experiment, mAbs were coated on beads and incubated with the phage library, samples were sequenced in parallel, and then peptides specifically enriched by the mAb were computationally identified. Competition ELISAs were performed to compare epitope mapping results using a more traditional approach.
Results: We mapped the linear epitope of QA255.067 and QA255.072 to Env amino acids 592-606 and 596-609 (HXB2 numbering), a region corresponding to the immunodominant C-C loop region of gp41. Competition ELISAs confirmed these results. We also more finely mapped the epitope of 240-D to amino acids 596-605, which is consistent with findings from structural studies. We were unable to see specific enrichment of any peptides in PhIP-seq with QA255.006 and QA25.016, but competition ELISA results indicated these mAbs target a discontinuous epitope on gp41.
Conclusion: PhIP-seq mapped overlapping but distinct epitopes of two newly identified gp41 mAbs and 240-D. This method may be useful for mapping HIV antibodies that target linear epitopes, and particularly, antibodies that recognize the gp41 protein, which is an attractive vaccine target because it is relatively conserved.

311 RAPID DEVELOPMENT OF AN INFANT-DERIVED HIV-1 BROADLY NEUTRALIZING ANTIBODY

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Background: HIV-infected infants develop broadly neutralizing plasma responses with more rapid kinetics and lower somatic hypermutation than adults, suggesting the ontogeny of infant responses could inform a better path to achievable vaccine targets. We previously isolated BF520.1, the first and only infant-derived broadly HIV-neutralizing antibody (bnAb). A thorough investigation of how BF520.1 developed will highlight possible pathways of rapid bnAb development that may be useful in vaccine design. Furthermore, resolving the structural basis of BF520.1's interaction with HIV envelope will inform the design of effective vaccine immunogens.
Methods: We sequenced antibody genes from a blood sample collected midway between HIV infection and the isolation of BF520.1. We developed robust computational methods to reconstruct the developmental lineage of BF520.1 that include using personalized germline gene sets to infer the antibody sequences of BF520.1's naïve ancestor, identifying midpoint sequences that were clonally-related to BF520.1, and phylogenetically determining likely mutational pathways that generated the mature bnAb. We compared our Bayesian lineage reconstruction approach to lineage inference by maximum likelihood, a common approach in the field. Lastly, we used single particle cryo-electron microscopy to explore the structural interaction of BF520.1 with the HIV envelope trimer BG505.SOSIP.664.

Results: We computationally validated that our method of lineage reconstruction was more accurate than maximum likelihood at identifying ancestral sequences for simulated antibody lineages similar to BF520.1. Our inferred naïve precursor bound HIV Env with a KD of 46μM. A bnAb evolved within six months of infection and required only 3% somatic hypermutation. Kappa chain substitutions were critical for bnAb functionality, validated by the observation of extensive contacts between the CDRL1 loop and the N332 glycan in our 4.8Å cryo-EM map. For the heavy chain, CDRH1 and CDRH2 mutations were important for developing breadth and potency.
Conclusion: Overall, the developmental pathway of this infant antibody includes features distinct from adult antibodies, including several that may be amenable to better vaccine responses. Our analysis highlights the importance of considering both the heavy and light chain in the development of HIV-specific bnAbs and the fact that light chain specificity can potentially be harnessed to develop vaccine approaches that elicit such bnAbs with relatively little mutation.

312 PROFILING ANTIBODY CROSS-REACTIVITY AMONG SIV ISOLATES USING A PEPTIDE MICROARRAY

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Background: In the past decade, a number of broadly neutralizing human immunodeficiency virus (HIV) antibodies have been identified; however, tools for assessing antibody cross-reactivity are still relatively low throughput. Ultradense linear peptide arrays enable the determination of antibody reactivity to as many as six million peptides in a single assay. Identification of antibodies capable of binding a wide variety of HIV strains has potential to help guide the development of vaccines and therapeutics. Here we prototyped the use of an ultradense peptide microarray to assess antibody cross-reactivity from cynomolgus macaques infected with SIVmac239 against a panel of simian immunodeficiency virus (SIV) species used to infect macaques.
Methods: Proteins represented on the array included the complete Env proteins of 21 strains of SIV and the complete proteome of SIVmac239, tiled in peptides 16 amino acids in length which overlapped by 12 amino acids. We assessed serum and plasma samples taken prior to infection and 125 days to 1 year after infection with SIVmac239 and compared pre-infection and post-infection antibody binding to proteins represented on the array. Fluorescence intensity from the application of a secondary antibody indicated regions in which primary antibodies had bound peptides representing the SIV proteins.
Results: No or minimal binding against SIV viral peptides was observed prior to infection. Following infection, evidence of antibody binding was consistently observed in peptides representing the Gag, Pol, and Env proteins of SIVmac239, with the highest levels of binding in Env. Antibody binding against other SIVmac239 proteins was also observed, though these results were less consistent between animals. We observed variable levels of antibody binding to peptides from other SIV strains, though all animals assessed showed some degree of cross-reactive binding to some number of SIV strains other than the infecting strain.
Conclusion: Serum profiling of antibody binding throughout the proteome of SIVmac239 and throughout the the Env proteins of multiple strains of SIV reveals cross-reactive antibody binding and highlights the potential of ultradense peptide arrays for high-throughput assessment of antibody binding specificity to diverse viruses.

313 REGULATION OF HIV-SPECIFIC CD8+ T-CELL FUNCTIONAL CAPACITY

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Background: Many HIV cure strategies propose to elicit HIV-specific CD8+ T cell responses to control and/or eradicate the virus. We previously reported that the T cell memory- and stem cell-associated Wnt signaling transcription factor, TCF-1, is expressed at significantly higher levels in HIV-specific CD8+ T cells from individuals who naturally control HIV infection. Moreover, its expression correlates with the proliferative capacity of these cells. Here, we explored the relationship between HIV-specific CD8+ T cell functional capacity and other molecular pathways associated with CD8+ T cell memory.
Methods: HIV-specific CD8+ T cells were identified in the peripheral blood from Viremic (VL>8,000 copies/mL; n=14), ART-suppressed (VL<40 copies/mL on stable ART for a median of 2 years; n=10), and Controller (VL<40 copies/mL not on ART; n=12) HIV-infected individuals by staining with MHC Class I multimers. The expression of transcription factors, effector molecules, and surface proteins was measured in multimer+ CD8+ T cells and proliferation was evaluated after 6-day in vitro peptide stimulation. Whole-genome RNA sequencing and DNA methylation analysis were performed on sorted multimer+ cells from a subset of participants.
Results: In addition to mounting greater proliferative responses and expressing higher levels of TCF-1 in all memory T cell subsets, multimer+ HIV-specific CD8+ T cells from Controllers (compared to Viremic or ART-suppressed individuals) were more likely to express CD127 and less likely to express PD-1, Granzyme B, and Tbet. Unstimulated multimer+ cells from Controllers (compared to ART-suppressed) were enriched for the expression of genes in the Fatty Acid metabolism pathway, which is associated with a quiescent metabolic profile ($p<0.05$). They also had a higher level of expression of "stem-ness" associated genes, including HOXB7, lower expression of the gene encoding the exhaustion-associated transcription factor Tox, and a distinct DNA methylation pattern in the WNT3 gene body (59% vs 29% methylation, $p<0.01$).
Conclusion: HIV-specific CD8+ T cells from Controllers share several molecular features with long-lived memory CD8+ T cells. The mechanisms by which these pathways may support the persistence of functional HIV-specific T cells remains to be investigated. However, our data provide a rationale for future studies to evaluate Wnt signaling and other programs that control long-lived memory T cells as a target to enhance the efficacy of CD8+ T cell-based HIV cure strategies.

314 PRESERVED TELOMERASE ACTIVITY AND TELOMERE LENGTH IN CD28- CD8 T CELLS IN TREATED HIV

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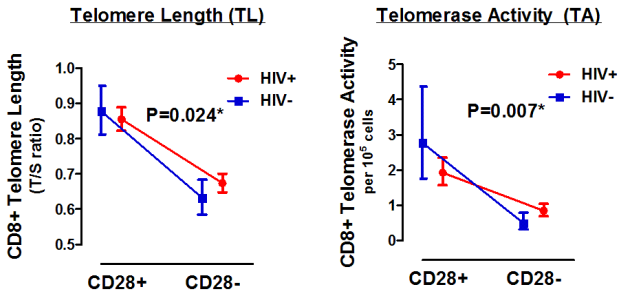
Background: HIV has been proposed as a model of "accelerated immunosenescence," but short telomere length (TL) and other T cell senescence markers fail to predict clinical outcomes in this setting. We hypothesized that the impaired effector CD8+ T cell maturation observed in treated HIV infection by our group and others might be associated with paradoxically preserved telomerase activity (TA) and TL in these cells.
Methods: HIV-infected adults maintaining antiretroviral therapy (ART)-mediated viral suppression (<40 copies/ml) for at least 2 years and age/gender-matched HIV-uninfected participants, all CMV seropositive, were sampled from the SCOPE cohort as part of a study addressing the determinants of influenza vaccine responsiveness. Active viral hepatitis and injection drug use were exclusionary. PBMC were isolated from a large-volume blood draw, sorted into CD8+CD28- and CD8+CD28+ T cell fractions, and assessed for both TL (T/S ratio) and TA (per 10^5 cells). Comparisons between groups and by CD28 status were assessed with linear mixed models, log-transforming biomarkers to satisfy model assumptions.
Results: Of 148 HIV–infected ART-suppressed participants and 37 HIV-uninfected controls, most were men (90%) and median age was 54 years (IQR: 49 to 60). Among HIV-infected participants, median current CD4 count was 662 and nadir CD4 count was 299 cells/mm^3. HIV-infected participants were less likely to be current smokers (12% vs. 33%, $P<0.01$). In both HIV-infected and –uninfected individuals, older age was strongly associated with shorter TL in both CD28- and CD28+ CD8+ T cells (rho: -0.38 for both, $P<0.001$) and women had longer TL in CD28+ CD8+ T cells than men ($P=0.01$). There was no evidence for an association between current smoking and TL in either CD28- or CD28+ CD8+ T cell fractions ($P>0.31$ for both). After adjustment for age and gender, HIV-infected participants had less of a decline in TL and TA in CD8+ T cells with the loss of CD28 than HIV-uninfected participants ($P\leq0.031$ for all, see figure).
Conclusion: Effector CD28- CD8+ T cells exhibit less of a decline in telomere length and telomerase activity in HIV-infected individuals with ART-mediated

viral suppression than HIV-uninfected individuals, consistent with a defect in maturation and proliferation of these cells in vivo. These results may offer a mechanistic explanation for the relatively poor ability of whole blood telomere length to predict morbidity and mortality in the setting of treated HIV infection.



*P value tests whether the extent of decline with loss of CD28 differs between groups after adjustment for age and gender.

315 IMPACT OF INTEGRASE INHIBITORS ON CD8 T-CELL FUNCTION AND ACTIVITY

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Background: HIV-specific CD8 T cells play a crucial role in controlling HIV replication. Although they have efficient effector function, CD8 T cells fail to clear HIV infection even in the presence of ART. Here we describe how ART can impact CD8 T cell effector function and therefore interfere -among other factors- with clearance of HIV infected cells.

Methods: PBMCs from HIV+ (n=44) and healthy (n=32) individuals were analyzed via flow cytometry to determine phenotype and functional properties of HIV-specific CD8 T cells in the presence of ART drugs and performed ex vivo proliferation assays of PBMCs from treated HIV+ individuals. We used a viral inhibition assay to determine CD8 T cells clear HIV infected cells and analyzed metabolic profiles using extracellular flux analyzer.

Results: We assessed CD8 T cell functions in HIV+ ART-treated individuals ex vivo and observed a reduction in cellular function compared to CD8 T cells of HIV+ treatment naïve individuals ($p<0.01$). We next assessed the proliferation index ex vivo and found a reduction in CD8 T cells of individuals treated with INSTI-based ART regimen (2.43 ± 0.36) compared to both PI (2.79 ± 0.35;$p<0.05$) and NNRTI (2.92 ± 0.28;$p<0.01$) based regimens. As we saw a significant impact of INSTI-based regimens on CD8 T cell function, we cultured CD8 T cells with individual ART drugs and determined the impact on CD8 T cell function of each drug individually. CD8 T cells had reduced functional properties with significantly lower expression of IFNγ ($p<0.01$), IL-2 ($p<0.01$) as well as TNFα ($p<0.01$) after treatment with INSTI, but not with other ART drugs. Due to the observed decrease in cytokine expression we decided to examine the killing ability of HIV-specific CD8 T cells in presence of individual ART regimens. Previously INSTI-treated CD8 T cells demonstrated reduced viral inhibitory activity against HIV-infected CD4 T cells compared to PI or NNRTI treated cells. We used a live cell imaging assay to determine the migratory capacity of CD8 T cells treated with different ART regimens. DLG-treated cells showed less migration activity after SDF1α stimulation compared to NRTI regimens ($p=0.07$). Next, we investigated the respiration of CD8 T cells treated with individual ART regimens and observed a significant reduction ($p<0.05$) in INSTI-treated cells compared to NRTI-treated cells.

Conclusion: Our data shows that the choice of ART can have a significant impact on CD8 T cell effector function. This may have important implications for HIV eradication strategies.

316 CD8 T-CELL INHIBITORY RECEPTOR EXPRESSION IS ASSOCIATED WITH CANCER AMONG PLWH ON ART

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Background: After controlling for traditional risk factors and viral suppression, people living with HIV (PLWH) have increased incidence of some cancers. Perturbations of the immune system persist despite virologic control on ART. This study explores the role of T cell subsets on incidence of HIV-associated cancer among ART-treated virally suppressed patients.

Methods: The United States Military HIV Natural History Study (NHS) is a well-characterized longitudinal cohort of Department of Defense beneficiaries. The NHS repository was used to identify cell samples from 25 cases and 87 controls. Cases had lung cancer, lymphoma, and HPV-associated cancers diagnosed after durable HIV-suppression. Cases and controls were matched for CD4+ T cell count, duration of HIV infection and viral suppression, and sample availability. Cryopreserved PBMCs from cases were obtained at least 6 months prior to cancer diagnosis. Using flow cytometry, PBMCs were measured for expression of markers of maturation (CD27,CD28,CCR7,CD45RA), inhibitory receptors (PD-1,LAG-3,TIGIT,2B4,CD160), immune activation (CD38,HLADR,Ki-67) and transcription factors (T-bet and Eomesodermin). Mann-Whitney U test was performed for comparison between groups.

Results: Cases and controls were well-matched (Table 1). All patients were virally suppressed. Expression of individual immune inhibitory receptors on total CD8+ T cells were not significantly different between the groups, though there was a trend towards higher PD-1 expression in cases compared to controls (25.8%vs21.8 %,p=0.067). The frequency of CD8+ T cells co-expressing three inhibitory receptors (PD-1+CD160+2B4+) was significantly higher among compared to control patients (11.3% vs 7.8%,p=0.03). In addition, among cases, expression of the transcription factor T-bet was higher on effector memory CD8+ T cells in cases compared to controls (24.1%vs15.6%,p=0.0001). There was no difference in the frequency of naïve/memory subsets (using CD27,CD28,CD45RA,CCR7) or activation (CD38+HLADR+) among CD8+ T cells between the two groups.

Conclusion: Co-expression of inhibitory markers has been associated with significant impairment of antigen-specific responses in both HIV infection and the tumor microenvironment. Our study shows that in a well-controlled sample set, the co-expression of multiple T cell inhibitory markers (PD-1,CD160+ 2B4+), is associated with a subsequent diagnosis of cancer, supporting the importance of studying the role persistent immune dysfunction on cancer incidence among PLWH.

Table 1 Baseline table by characteristics of patients in the study

Variables	Control N =87	Case N =25	P value
Age at HIV diagnosis	33.0 (28.0,36.0)	32.0 (26.0,40.0)	0.8175
Age at cancer dx or sample collection	48.0 (40.0,54.0)	48.0 (42.0,54.0)	0.8365
Duration of HIV infection at cancer diagnosis or sample collection in years	15.0 (9.0,18.0)	14.0 (8.0,20.0)	0.5661
CD4 at cancer dx or sample collection	389.0 (238.0,509.0)	459.0 (279.0,675.0)	0.1775
Race			0.0680
Caucasian	35 (40.2%)	12 (48.0%)	
African-American	36 (41.4%)	13 (52.0%)	
Other	16 (18.4%)	0 (0.0%)	
Gender			0.8502
Male	81 (93.1%)	23 (92.0%)	
PI based ART			0.7824
Yes	46 (52.9)	14 (56.0)	

317 IMPACT OF ART ON T-CELL REPERTOIRES OF HIV-INFECTED ADULTS WITH AND WITHOUT CANCER

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Background: Response to treatment of HIV-associated malignancies is likely influenced by the restoration of the T-cell repertoire and immune function after initiation of antiretroviral therapy (ART). To understand the impact of immune reconstitution on HIV-associated lymphoma outcomes, we compared the T-cell repertoire in 2 cohorts of HIV-infected adults initiating ART - one without cancer and one with pathologically confirmed diffuse large B cell lymphoma (DLBCL).

We hypothesize that one-year survival after a diagnosis of DLBCL in ART-naïve HIV+ adults will be associated with superior immune reconstitution of the T-cell repertoire.

Methods: For cohort 1, serial peripheral blood mononuclear cell (PBMC) samples and clinical data were collected from 30 HIV+ adult subjects enrolled on prospective studies conducted by the Center for AIDS Research (CFAR) at the University of Washington, Seattle, WA. 1-4 PBMC samples were collected pre-ART and 2-6 PBMC samples post-ART from each subject. PBMC samples were also collected from 16 HIV- adult control subjects. For cohort 2, serial PBMC samples and clinical data are being collected from HIV+ adult subjects presenting to the Uganda Cancer Institute – Fred Hutchinson Cancer Centre in Kampala, Uganda for treatment of pathologically confirmed DLBCL. To date, PBMC samples have been collected from 50 subjects. High-throughput T-cell receptor β chain (TRB) sequencing has been performed on all 168 samples from the HIV+ cohort; analysis of the HIV+ lymphoma cohort is ongoing.

Results: The TRB repertoire in the HIV+ cohort prior to ART initiation was significantly more "clonal" (less diverse) than that observed in the HIV- controls. Following initiation of ART, an increase in repertoire diversity was observed, accompanied by a substantial improvement in CD4+ T-cell count. Increased repertoire diversity was associated with an increase in the number and frequency of "public" TRB sequences, many which are associated with CD8+ T-cell responses to HIV epitopes.

Conclusion: Initiation of ART in HIV+ adults was associated with changes in the global and pathogen-specific T-cell repertoires. ART initiation was also associated with increases in the frequency of "public" TRB sequences associated with immunodominant CD8+ T-cell responses to HIV and other viral pathogens, suggesting that recovery of CD4+ T-cells may enable expansion of pathogen-specific and tumor-specific CD8+ T-cells.

318 FINDING THE CELLS AMIDST THE DATA

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Background: Flow and mass (CyTOF) cytometry are high-throughput technologies quantifying multiple surface and intracellular markers at the level of a single cell. Improvements of these technologies allow to describe millions of individual cells from a single blood sample according to several dozens of markers (up to 2^30 cell populations with 30 markers). This generate high-dimensional datasets, whose manual analysis, called manual gating, is highly time-consuming and poorly reproducible. We have developed 2 machine learning approaches to perform automatic gating without human intervention.

Methods: The first method is a new Bayesian nonparametric approach (NPflow) with Dirichlet process mixture (DPM) of multivariate skew t-distributions to perform model-based clustering of flow-cytometry data. DPM models directly estimate the number of cell populations from the data, avoiding model selection issues, and skew t-distributions provides robustness to outliers and non-elliptical shape of cell populations. To accommodate repeated flow-cytometry measurements, such as in a clinical trial, a sequential strategy relying on a parametric approximation of the posterior is also proposed (NPflow seq). The second one (cytometree) is based on the construction of a binary tree, whose nodes represents cellular sub-populations. At each node, a binary split between different cellular populations is done according to the normalized difference of Akaike Information Criteria (AIC) between the two normal mixture models considering either one or two possible sub-populations. Post-processing of the tree structure and derived populations allows us to automatically provide a complete annotation of the derived populations.

Results: The good performance of the methods are shown on simulated data and on an experimental benchmark datasets (FLOWCAP1) as shown in Table 1, as well as in a real dataset from an HIV vaccine trial. Compared to other available approaches the new methods, especially cytometree, performed at the top position with the shortest runtime. Also, the F-measures>0.90 demonstrate the validity of the new methods in comparison with the gold standard (consensus of 8 experimentalists).

Conclusion: The constant increase of the number of markers available to characterize cell populations leads to an untractable situation with manual gating. However, improvements of machine learning approaches allow for the automatic analysis of cytometry samples, yielding the relative count for all possible cell populations.

Method	Dataset					Mean	Runtime per sample
	GvHD	HSCT	DLBCL	WND	ND		
cytometree	**0.94**	**0.95**	**0.93**	**0.90**	0.89	**0.92**	00:01:06
NPflow	0.85	0.89	-	-	-	-	12:00:00
NPflow seq	0.89	0.77	-	-	-	-	12:00:00
ADICyt	0.81	0.93	**0.93**	0.86	**0.92**	0.89	04:50:37
flowMeans	0.88	0.92	0.92	0.88	0.85	0.89	00:02:18
FLAME	0.85	0.94	0.91	0.80	0.90	0.88	00:04:20
Flock	0.84	0.86	0.88	0.83	0.91	0.86	00:00:20

Table 1: Average F-measures (between 0 and 1, the closer to 1 the better agreement) comparing automated gating results with consensus manual gating over several benchmark datasets.

319 MACHINE LEARNING REVEALS T-CELL ACTIVATION PATHWAYS INDUCED BY INFLUENZA VACCINE

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Background: Seasonal influenza vaccine responsiveness is dependent on a specialised subset of CD4+ T-cells that are susceptible to infection with HIV. The role of CXCR5+ circulating T-follicular helper cells (cTFH) in this response is unclear in individuals with treated suppressed HIV infection. Investigations of potential biomarkers for HIV integration have identified rare CD4+ T-cells highly expressing the FC gamma receptor CD32, but with unknown function. We hypothesised that CD32 is upregulated on cTFH in response to seasonal influenza vaccine and used unsupervised computer algorithms to explore the cellular relationships arising.

Methods: 16 men with treated, suppressed HIV infection and 14 healthy control subjects receiving quadrivalent influenza vaccine (QIV) during the 2017-18 Northern Hemisphere influenza season were studied. Peripheral blood mononuclear cells (PBMCs) were collected prior to and after vaccination. Thawed PBMCs were stained with a pre-optimised cocktail of flurochrome-conjugated antibodies, before acquisition on a BD Fortessa flow cytometer. The data were analysed using T-stochastic neighbour embedding analysis (t-SNE) and Spanning-tree progression analysis of density-normalized events in FlowJo v10.4.2 and FCS express v6plus.

Results: cTFH more frequently expressed CD32 at Day 7 post QIV ($p=0.0009$) and returned to baseline at Day 28 ($p<0.0001$) with no difference in those with and without HIV infection. t-SNE identified three populations (P1, P2 and P3) of CD4+ T-cells that were defined by their expression of CXCR5 and CD32. P1 (CXCR5hiCD32hi) and P3 (CXCR5midCD32lo/mid) frequency was constant but P2 (CXCR5lo/midCD32lo/mid) was more frequent at Day 7 ($p=0.0261$) and expressed the cTFH activation markers programmed cell death 1 (PD-1) and inducible T-cell co-stimulator (ICOS). SPADE indicated a branched hierarchy of clustered nodes corresponding to P1, 2 and 3. Consistently, a central memory CXCR5mid node gave rise to a CXCR5hiCD32hi node that was unaffected by QIV and two vaccine-inducible activated ICOS+PD-1+CD38+CXCR3+CXCR5+CD32mid/hi nodes.

Conclusion: Circulating CXCR5+CD4+ T-cells fall into three major related populations. A parent population of cTFH-like cells gives rise to a vaccine-responsive cTFH population that upregulates CD32 and a vaccine-unresponsive population persistently expressing CD32 and CXCR5. These relationships were present irrespective of HIV infection in individuals receiving QIV and could be used to inform vaccine design.

320 COMPARATIVE ANALYSIS OF THE MAGNITUDE AND QUALITY OF VACCINE-ELICITED T-CELL RESPONSE

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Background: CD4 T cell responses that provide efficient help for B cells to generate a long-lived, high-affinity antibody response are considered to be an important component of an HIV vaccine. However, it is unknown how to elicit effective HIV-specific CD4 T cell responses and which vaccination strategy induces optimal T follicular helper (Tfh) cell responses. Here we evaluated and

compared the Tfh responses from chronic HIV infection to several phase one and phase II clinical trials, which differed in the immunogen, adjuvant and route of delivery.

Methods: We characterized the functional profiles of CD4 T cells using multicolor flow cytometry on cryporeserved PBMC isolated from chronically infected patients or vaccination study participants. The phase one and phase II clinical vaccination trials included in this analysis were RV138, RV172, RV114, RV132, RV135, RV158, and RV144.

Results: The HIV-specific CD4 T cell response in chronic natural HIV infection and the response to different vaccine modalities differed markedly. While chronic HIV infection provoked a higher frequency of HIV-specific CD4 T cells than vaccination ($p<0.001$, $n=6$ for chronic HIV infection, $n=97$ for vaccination), the functional profiles between the responses induced in natural HIV infection versus after vaccination were also significantly different. Chronic natural HIV infection showed an HIV-specific CD4 response dominated by TNFα. In contrast, vaccination induced mostly CD40L-positive CD4 T cell responses. In addition, when we compared the effect of different vaccination modalities (route of delivery, prime/boost strategies) on the T cell functional profile, we found that vaccine delivery via antigen-loaded dendritic cells induced a stronger Th1 polarization than intramuscular injection. Additionally, the choice of prime and boost influenced the degree of polyfunctionality induced in T cells: The prime/boost combination ALVAC-HIV/o-gp160 (RV132) led to the highest frequency of HIV-specific CD4 memory T cells with a polyfunctional profile ($p=0.028$ for the frequency of IFNγ, and $p=0.035$ for TNFα expressing cells compared to the other vaccine modalities).

Conclusion: Overall, we describe the varying functional T cell response to different vaccination strategies and the differences in responses to chronic HIV-1 infection vs. vaccination. Future approaches to vaccine design will be informed by this and further studies with the goal to induce polyfunctional T cell responses, which support the production of protective antibodies.

321 REGULATORY T CELLS IN HIV-INFECTED PREGNANT WOMEN

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Background: Maternal HIV infection and its treatment are associated with increased risk of preterm birth (PTB). Conventional wisdom holds that an expansion of regulatory T cells (Tregs) during the 2nd trimester plays an integral role in maternal tolerance of the fetal allograft. However, recent studies (in HIV-uninfected populations) using updated immunophenotyping methods specific for viable, suppressive Tregs have not shown an expansion of these cells in the peripheral circulation during pregnancy. We sought to determine whether HIV infected (HIV+) pregnant women have decreased peripheral Treg frequencies compared to their HIV uninfected (HIV-) counterparts.

Methods: Between May 2017 and January 2018, we immunophenotyped 64 1st trimester (HIV-: 53; HIV+: 11) and 270 2nd trimester (HIV-: 222; HIV+: 48) peripheral blood specimens collected from women enrolled in the Zambian Preterm Birth Prevention Study (ZAPPS), a prospective cohort ongoing in Lusaka. We quantified Treg frequencies by flow cytometry (CD4+CD25+CD127low & CD4+CD25+CD127lowFoxP3+). T test was used to compare log-transformed Treg frequencies by HIV serostatus at study enrollment. ANOVA was used for sub-group analyses by preconceptional ART and viral load at enrollment. For patients with repeat 1st and 2nd trimester specimens (HIV-: 33; HIV+: 7), changes in Treg frequency were assessed by T test of log-transformed fold changes.

Results: No significant differences in CD4+CD25+CD127low nor CD4+CD25+CD127lowFoxP3+ phenotypes were observed between HIV serostatus groups in either 1st or 2nd trimesters (figure). Additionally, individuals on preconceptional ART and with suppressed viral load were not found to differ significantly from their non-preconceptional ART and unsuppressed viral load counterparts, respectively. In individuals with repeat specimens, there were no statistically significant differences between groups for both CD4+CD25+CD127low ($p = 0.67$) and CD4+CD25+CD127lowFoxP3+ ($p = 0.42$) phenotypes.

Conclusion: Exploratory data from this African cohort established specifically to study PTB do not demonstrate significant aberrations in peripheral Treg frequencies in HIV infected pregnant women. Although Tregs may play a role in HIV-associated PTB at the maternal-fetal interface, this finding indicates that their role is unlikely to be systemic.

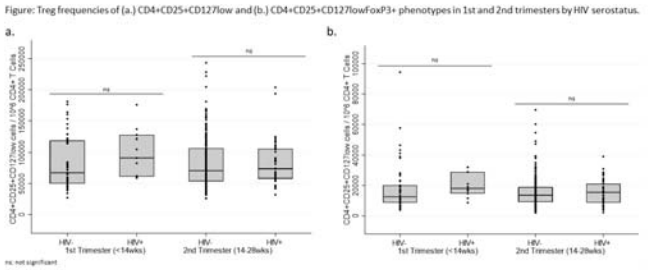

Figure: Treg frequencies of (a.) CD4+CD25+CD127low and (b.) CD4+CD25+CD127lowFoxP3+ phenotypes in 1st and 2nd trimesters by HIV serostatus.

322 THE IMPACT OF HIV EXPOSURE ON PLACENTAL PATHOLOGY AND TREG CELLS

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Background: One of the main roles of the placenta is to maintain fetal-maternal (FM) tolerance. HIV and/or antiretroviral (ARV) exposure may interfere with this tolerance but data are sparse. We characterized placental decidua T regulatory cells (Treg) from HIV-infected women who initiated ART late in pregnancy compared to uninfected controls.

Methods: Placentas of HIV-infected women were drawn from an ongoing study in which women commence antiretroviral therapy (ART) at or after 28 weeks' gestation (n=14) and HIV-uninfected controls (n=6). The maternal decidua and villous tissue were dissected and enzymatically digested to obtain lymphocytes which were characterised using 15 colour multiparametric flow cytometry. Placenta tissue sections were formalin-fixed and wax embedded for Treg cell characterisation using immunofluorescence and pathology scoring based on the Amsterdam placental workshop group consensus statement.

Results: A higher incidence of preterm deliveries was reported in the HIV infected mothers, 75% were very preterm (28+0-31+6 weeks), 18% moderate or late preterm (32+0-36+6 weeks) and 12% term (>37 weeks). The frequency of decidual CD4+ T cells was lower in placentas from HIV infected women when compared with HIV uninfected controls ($p=0.005$) and similarly, total CD8+ T cells were significantly higher in the HIV infected group ($p=0.006$). The variable expression of TIGIT (T cell Ig and ITIM domain) and CD45RA, expression on CD4+ T cells within decidual membranes was higher in HIV infected women vs uninfected. We identified a series of Treg subsets within the decidua that were all CD3+CD4+CD127-CD25HiFoxP3++ with variable expression of CD39, CTLA4 and TIGIT. Highly suppressive Treg cells, co-expressing all three markers more enriched in placentas from very preterm placentas in HIV infected women (Figure 1). Pathology indices including prolonged meconium exposure, cord vessel vasculitis and plasmacytic deciduitis were also reported in higher frequency in placentas from HIV infected women, specifically in very preterm deliveries in comparison to controls.

Conclusion: The T cell phenotype in the maternal decidua appears to have a predominantly adult systemic footprint while the villous tissue mirrors foetal cells; an increased influx of naïve cells. There are unique and multiple Treg signatures in the placenta which appear to be associated with pre-term birth and may be influenced by HIV exposure and ARV that warrant further investigation.

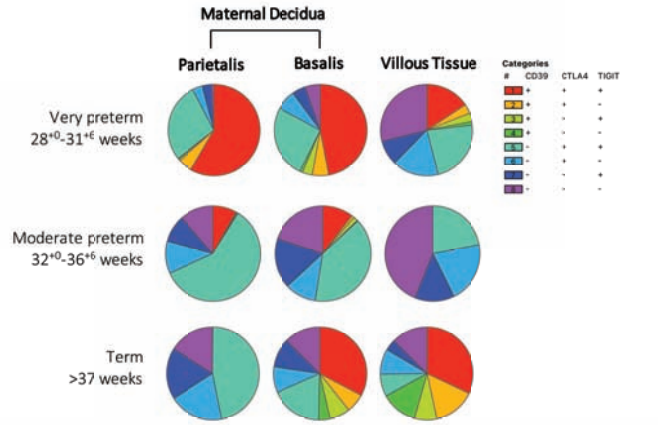

Figure 1: Boolean gate analyses using Simplified Presentation of Incredibly Complex Evaluations (SPICE) on CD4+CD25HiFoxP3++CD127lo Treg cells. Highly suppressive Treg cells, co-expressing all three markers more enriched in placentas from very preterm placentas in HIV infected women.

323 HIV RESERVOIR SIZE IS CORRELATED TO NK-MEDIATED KILLING OF EFFECTOR MEMORY CD4 CELLS

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Background: The identification of immune control mechanisms of the viral reservoir might help to develop new strategies to cure HIV. Antibody-dependent cell-mediated cytotoxicity (ADCC), largely mediated by natural killer (NK) cells, has been reported highly relevant to control HIV. However, the role of ADCC-NK at controlling the cells that compose the viral reservoir is currently unknown.
Methods: The intrinsic susceptibility of Naïve (NA), Stem Cell Memory (SCM), Central Memory (CM), Effector Memory (EM) and CD20dim CD4 T cells, to ADCC NK-mediated killing was measured by a novel flow cytometry-based assay. n=10 ART-suppressed and 5 elite controllers (EC) patients were included. Isolated CD4 T cells were stained with the markers eF670 and PKH67 and coated with the gp120Bal protein. Cells were incubated with plasma from an HIV positive patient and autologous NK cells at ratio 1:1 for 3 hours. Then, cells were stained with CD3, CCR7, CD45RO, CD95, CD20 and HLA DR antibodies. NK-mediated killing was calculated as the disappearance of cells measured with the addition of flow cytometry particles. Total HIV-DNA and HIV-RNA was quantified by qPCR.
Results: Results from all analyzed patients showed that each subset had a different susceptibility to killing, being CD20dim>CM>NA>EM>SCM more prone to be killed (ANOVA Friedman test p<0.0001). Moreover, whereas no differences in the killing of the whole CD3 population were observed between cohorts (Mann-Whitney test, p=0.5122), EC showed higher potency to kill CD20dim and EM (median 61.6, 52.0, 48.0, 33.6 and 33.4% for CD20dim, EM, CM, NA, SCM, respectively) (ANOVA Friedman test p=0.0081), while ART-suppressed patients were more efficient at killing CM and CD20dim cells (median 48.5, 38.7 ,37.6, 35.7 and 28.9% for CM, CD20dim, NA, EM, SCM, respectively) (ANOVA Friedman test p=0.0005). A more efficient killing of CD20dim cells was detected in EC compared to ART-suppressed patients (Mann-Whitney test, p=0.0383). Importantly, an inverse correlation between the capacity of NK cells to kill the EM subset and the viral reservoir was observed (rho=-0.6000 p=0.0261 for viral DNA and rho=-0.8857 p=0.0333 for viral RNA).
Conclusion: The susceptibility of different CD4 T subsets to ADCC-NK killing differs. The ADCC activity against EM cells, one of the most HIV-transcriptionally active cell subsets, was highly correlated to the size of the persistent HIV-reservoir. Inducing the specific killing of EM cells might significantly help to diminish the persistent reservoir.

324 LIGATION OF KIR3DS1 BY HLA-F ON ICD4 ACTIVATES PRIMARY NK CELLS FOR ANTI-HIV ACTIVITY

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Background: KIR3DS1 (3DS1) is an activating NK cell receptor (NKR) implicated in several viral infections, cancer outcomes and autoimmune diseases. In the context of HIV, co-carriage of 3DS1 and HLA-Bw4*80I alleles is associated with slower time to AIDS while 3DS1 homozygotes (hmz) have a reduced risk of HIV infection. The ligand for 3DS1 is HLA-F, a non-classical MHC-1b antigen expressed on infected CD4+ T cells (iCD4).
Methods: Purified NK cells from 5 3DS1hmz were stimulated with autologous iCD4 cells in duplicate. The frequency of 3DS1+/-CD3-CD56dim NK cells positive for IFN-, CD107a or CCL4 function and the sum of these functions was assessed using gating strategies that included and excluded NK cell subsets co-expressing other NKRs that may contribute to 3DS1+ NK cell function. We assessed the effect of blocking the interaction of 3DS1 and HLA-F on the function of 3DS1+ NK cells by using KIR3DS1-Fc chimeric protein and the anti-HLA-F specific mAb (3D11).
Results: We confirmed that HLA-F is expressed on iCD4 cells. HIV infection partially downmodulates HLA-F expression, though sufficient HLA-F remains on iCD4 to bind 3DS1+NK cells and activate them. The frequency of cells exhibiting the sum of all functions tested, total CCL4 and IFN-γ secretion and total CD107a expression was higher among 3DS1+ than 3DS1- NK cells (p<0.002, for all, Wilcoxon matched-pairs test). After excluding NK cells co-expressing other NKRs such as KIR2DL1/L2/L3, KIR3DL2, KIR2DS1/S2/S3/S5, NKG2A and ILT-2, a higher frequency of 3DS1+ than 3DS1- NK cells were positive for total function, total CCL4, total IFN-γ and total CD107a (p<0.002, for all, Wilcoxon matched-pairs test). Blocking 3DS1-HLA-F interactions reduced the frequency of exclusively gated functional 3DS1+ NK cells to levels close to those observed for unstimulated NK cells.
Conclusion: The interaction of 3DS1 on NK cells with HLA-F on iCD4 cells activates a higher frequency of 3DS1+NK cells. The exclusive gating strategy confirmed that the higher frequency of functional 3DS1+ NK cells was not due to co-expression of other NKRs. HLA-F levels on iCD4 are sufficient to activate 3DS1+ NK cells for anti-viral functions such as CCL4, which blocks HIV infection of new target cells, IFN-γ secretion, an important antiviral cytokine and CD107a expression, a marker of NK cell degranulation. These findings provide a mechanism explaining the association of the 3DS1hmz genotype with HIV protection.

325 IMPACT OF A NOVEL NATURAL KILLER CELL SUBSET ON IMMUNE RECONSTITUTION

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Background: We have identified a novel subset of NK cells, called 'g-NK cells', which display adaptive immune features, including clonal-like expansion and long-term persistence. The presence of g-NK cells is associated with previous infection by cytomegalovirus and have enhanced response to broad range of viral-infected cells in the presence of virus-specific antibodies. We hypothesize that g-NK cells contribute to low CD4 counts in HIV patients and CD4 recovery during ART.
Methods: In a cohort of 18 MSM chronically infected HIV patients naïve to treatment before and 12 months after starting a PI-based cART, the presence of g-NK cells, as well as their frequencies and phenotypic characteristics, were measured by flow cytometry after intracellular staining of FcR-gamma signaling protein following cell surface marker staining. 17 HIV-negative control underwent identical procedures. Plasma biomarkers of inflammation were measured by ELISA and cytokine production by g-NK cells and conventional NK cells after stimulation with HIV-infected cells in the presence or absence of HIV-seropositive plasma.
Results: We observed that (1) HIV patients possessed higher frequencies of g-NK cells compared to HIV-negative control groups [39.9% and 10.33%, p=0.0320], (2) HIV patients with readily detectable g-NK cells show a trend toward lower CD4+ T cell count before [p<0.08] and 1 yr after cART [p<0.01]. g-NK cells did not change levels before and after the treatment, and (3) compared to conventional NK cells, g-NK cells produced greater amount of IFN- and TNF- in response to HIV-infected cells in the presence of HIV-seropositive plasma.

Conclusion: g-NK cells are more frequent in HIV-infected patients compared to controls and may contribute to low CD4 counts in HIV patients and poor recovery during ART. g-NK cells may be a useful biomarker for predicting how the CD4+ T cell population may recover during HIV treatment.

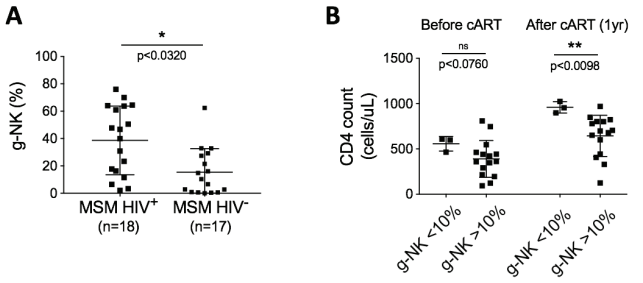

Figure 1. Higher frequencies of g-NK cells present in HIV-infected individuals and are associated with lower CD4 counts and recovery during ART. (A) The frequency of g-NK cells is presented for individual MSM donors, which are grouped according to their HIV status. (B) HIV+ patients are grouped according to their frequencies of g-NK cells and CD4+ cell counts before and after cART.

326 LIPIDOMIC FINGERPRINTING TO IDENTIFY HIV RESERVOIRS IN VITRO AND IN VIVO

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Background: One of the most important questions in designing cure-based strategies in HIV research is the origin(s) of the reservoir. It is well established that HIV rebounds upon withdrawal of Highly Active Antiretroviral Therapy (HAART) leading to viral breakthrough and HIV envelopes contain lipids originating from the membrane of the virus producing cells. Thus, an innovative highly sensitive, clinical sample-validated Virus Lipidomic Mapping (VLM) assay was developed to accurately quantify lipid compositions of HIV-1 virions (< 5 copies/mL) and host cells, allowing virus to be mapped to host cell origin.
Methods: Primary human CD4+ T cells or monocytes were isolated (healthy buffy coats; magnetic sorting; n = 12). HIV-1BaL was used to infect CD4+ T cells or differentiated macrophages (MΦ). HIV from CD4+ T cell or MΦ origin (n = 4) was captured from viremic plasma of HIV+ individuals with magnetic nanoparticles (MNP) coupled to Ab against T cell or MΦ-specific proteins incorporated into virions followed by virus purification and exosome removal. Lipids were extracted from cells; profiles, abundance and ratios (cells and virus) were determined by LC-MS/MS (Q-Exactive Plus).
Results: For all donors, the cellular lipid profiles for CD4+ T cells were distinct from MΦ lipid profiles. Virions grown in each cell type contained unique lipids that match unique lipids on host cell origin. Distinctive profiles for MΦ cellular and virion lipids included monoetherphosphatidylcholine (MePc), ceramides (Cer), glucosylceramide (CerG1), diacylglycerol (DG), phosphatidylinositol (PI), phosphatidylcholine (PC, phosphatidylethanolamine (PE), sphingomyelins (SM), and triglyceride (TG); unique profiles for T-cell virion and cellular lipids include subspecies SM(d35) and CerG1(d18). For all donor samples, virions that carried specific T-cell proteins showed unique lipid profiles compared to virions that carried MΦ-specific proteins; Cer (d17, G1d18), DG(53.1), MePC(31), PC(34), PE(42), PI(18), SM(d35), and ChE(18).
Conclusion: Conclusions: For the first time, the VLM method 1) identified host cell origin of persistent HIV-1 in vivo, even with low-prevalence populations of mixed virions, and 2) determined unique lipid profiles for virions from T-cells versus MΦ, which match cellular lipid profiles on host cell origin. This information provides a foundation for cure-based strategies to identify and eliminate key cells harboring persistent HIV not eliminated by HAART.

327 CHARACTERIZING THE HIV DNA RESERVOIRS IN WHOLE-BODY TISSUES IN THE "LAST GIFT" COHORT

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Background: HIV persistence in cellular reservoirs is the main barrier to a cure. The size and composition of HIV DNA populations in solid tissues during suppressive antiretroviral therapy (ART) is not well characterized.
Methods: We examined the distribution and genotypic composition of the HIV DNA populations across paired post-mortem tissues from one virally suppressed person living with HIV (PLWH) from the Last Gift (LG) Cohort. The LG cohort enrolls altruistic, terminally-ill PLWH, who are closely followed until the time of death and donate their "whole-body" for HIV research. Blood and tissues are collected by rapid-autopsy and cryopreserved within 6h from death. From each sample, we extracted total DNA and quantified HIV DNA (gag) levels by droplet-digital PCR. The genotypic composition of the HIV DNA in tissues was evaluated using a high-throughput single genome amplification and the PacBio platform to deeply sequence full-length HIV envelope (FL HIV-env).
Results: The participant was a 72-year-old man with chronic HIV infection and metastatic pancreatic cancer. He enrolled in the LG study 5 months prior death. He was on ART and had undetectable HIV RNA in blood plasma, up to 7 hours before death (<20 copies/ml). From 26 paired post-mortem tissues, HIV DNA was detected in 24 samples, including brain (3-11 cps HIV/106 cells), gastrointestinal (45-211), urogenital tract (46-377), lymphoid (22-243) and adipose (13-874) tissues. HIV DNA was undetectable in parietal and motor cortex. We obtained 107 individual FL HIV-env sequences across 10 tissues (median 10.7 sequences/tissue), of which 60 were unique. The maximum likelihood phylogeny (figure) showed a deep divergence, segregating the tree into two lineages, which differed by co-receptor tropism, based on in silico tropism prediction (geno2pheno). Interestingly, 100 FL HIV-env sequences were genetically intact, while 7 sequences were non-functional, with major deletions, frameshifts, and stop codon mutations. HIV-env migration appeared to be extensive, with many identical sequences sampled in multiple body tissues.
Conclusion: HIV DNA was detected in most body tissues despite long-term ART and confirmed undetectable HIV RNA at the time of death. Based on the FL HIV-env sequencing, most HIV reservoirs appeared to be intact provirus and may present different viral tropisms. The LG cohort poses a unique opportunity to characterize the HIV reservoirs in anatomic compartments, which is crucial to provide insights for future HIV cure strategies.

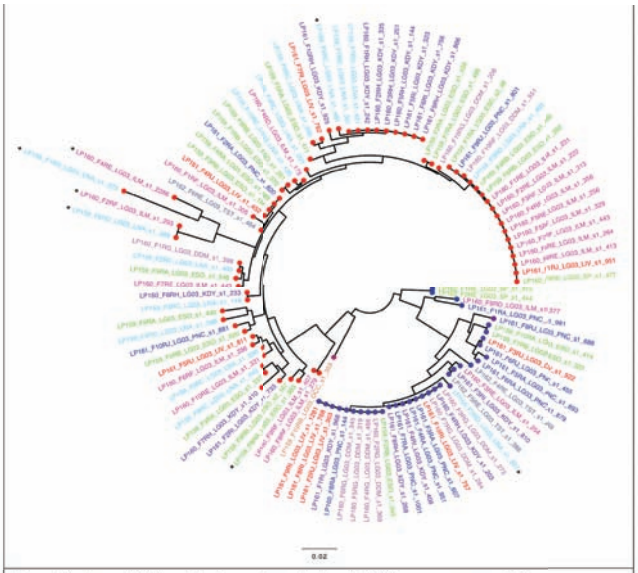

Figure: Maximum likelihood phylogeny tree showing FL HIV-*env* sequences obtained from post-mortem body tissues from one participant from the LG cohort. Colors represent different body tissues. Colored dots indicate *in silico* inferred viral tropism (red = X4-tropic viruses and blue = R5-tropic viruses). Asterisks indicate non-intact *env* sequences containing major deletions, hyper-mutation, stop-codon mutations or frameshift mutations.

328 CD4 T-CELL SUBSETS RESPOND DIFFERENTLY TO LATENCY REVERSAL AGENTS

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Background: Several pharmaceutical compounds as the Latency reversal agents (LRAs) can reactivate HIV expression from infected cells and might help to reduce the pool of latently infected CD4 T cells. However, the capacity of the LRAs to reactivate all infected CD4 T subpopulations is currently unknown.
Methods: Viral reactivation assays were performed using freshly-isolated CD4+T cells obtained from whole blood donations of n=9 ART-suppressed patients. A total of 13 conditions, including controls, Ingenol (ING) and Bryostatin-1 (BRY) (PKC agonists), Romidepsin (RMD) and Panobinostat (PNB) (HDAC inhibitors) and JQ1 (Bromodomain inhibitor), and the combinations of LRAs from different families, were set up per patient. Intracellular HIV-RNA and p24 production were evaluated by the flow-RNA/FISH technology within different CD4+T cell subsets (Naïve-NA; Stem Cell Memory-SCM; Central Memory-CM, Effector memory-EM; Transitional Memory-TM and Terminally Differentiated-TD) after 22h in culture. Synergies and antagonisms between compounds were calculated using the Bliss independence model.
Results: In general, a median of 10.74% of the whole HIV-reservoir in CD4+T cells induced HIV-RNA after viral reactivation but only 10.1% of these reactivated cells produced p24. The highest levels of HIV-RNA and the viral protein p24 were induced by ING, RMD and PNB followed by BRY and JQ1. Moreover, the combination of RMD+ING induced a reactivation of 3.50-fold compared to negative control. Regarding CD4+T subpopulations, most memory subsets were reactivated by Romidepsin and the highest susceptibility was observed in the TEM cells (FC=4.24). PNB was more efficient at reactivating TCM (FC=2.11) and TEM cells (FC=2.32), and ING was performing better in TCM (FC=4.05) and TTM (FC=5.27) but not in TEM cells. For combinations of LRAs, RMD+ING became the most effective condition in all tested CD4+T cell subsets, primarily in TTM (FC=6.72), but with no effect in TSCM. Contrarily, an antagonistic effect in terms of HIV transcription was observed when PNB+ING were added.
Conclusion: Our results validate the use of the flow-RNA/FISH protocol to assess the potency of LRAs in different CD4+T cell subsets. Although important synergies are identified when RMD and ING are combined, existing LRAs present limited capacity to induce HIV transcription in the most important reservoir cells. This study emphasizes the need to generate new drugs with wide reactivation ability in all CD4+T cells for future clinical trials.

329 HIV-TRANSCRIPTION INDUCES CD20 EXPRESSION AND RENDERS CELLS SUSCEPTIBLE TO RITUXIMAB

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Background: One of the main obstacles to cure HIV is the existence of persistent HIV reservoirs in ART-suppressed patients. New markers with which to identify and target these reservoirs will definitely advance the search for an HIV cure. Here, we studied the expression of CD20 in HIV-infected cells and the use of this molecule to target the persistent viral reservoir.
Methods: Phenotypic characterization of CD20 expression in different CD4+T cell subsets was measured by flow cytometry in n=10 ART-suppressed, n=13 viremic and n=6 healthy controls. Intracellular levels of HIV-RNA were measured by the novel FISH/RNA flow cytometry assay, and quantification of HIV-DNA in sorted CD20+ T cells by qPCR. Expression of CD20 and p24 in lymph nodes of HIV+ patients was measured by immunohistochemistry. Moreover, the dynamics of CD20 expression upon HIV infection was examined by ex vivo infection. Finally, the susceptibility of CD20+ T cells to therapy with rituximab (anti-CD20 monoclonal antibody) was examined after ex vivo viral reactivation of CD4+T cells from ART-suppressed patients.
Results: We systematically found CD4+T lymphocytes in blood with dim expression of the CD20 receptor, in both healthy and HIV-infected individuals (2.47% in healthy, 1.82% in ART-suppressed and 2.11% in viremics). These cells had a memory phenotype (mainly central memory) and an increased activation state (values of 22 and 27.6% for CD20dim CD4+T cells, and 16.4 and 20.7% for CD20- CD4+ T cells in ART and viremics, respectively). In patients on ART, CD4+T cells expressing CD20 contained viral DNA and were enriched in HIV-RNA compared to cells not expressing this receptor (p=0.001). This population represented the 20% of the total cells expressing HIV transcripts. In lymph node tissues, we observed that a proportion of p24-expressing cells were also positive for the CD20 marker. Moreover, ex vivo infection of unstimulated PBMCs showed that viral replication induced the expression of CD20 (from 4.74% to 8.31% of CD20dim in CD4+ T cells). Notably, rituximab was able to target CD20dim CD4+T cells of ART-suppressed patients by the induction of apoptosis and antibody-mediated cell cytotoxicity, and the combination of rituximab and latency reversal agent
Conclusion: CD20dim CD4+T cells harbored transcriptionally active HIV. Anti-CD20 treatment after induction of viral reactivation might represent a novel tool to target the active HIV-reservoir.

330 HIV-INFECTED CD4 T-CELL ISOLATION USING A MICROFLUIDIC MAGNETIC LEVITATION SYSTEM

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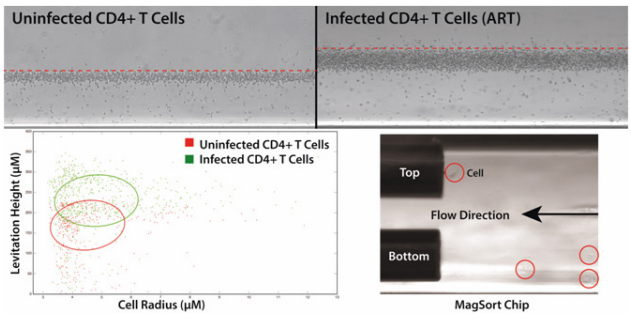
Background: Strategies to identify and isolate HIV infected cells at various states of latency or transcriptional activation are urgently needed. We developed and implemented a novel microfluidic system that is able to sort untouched CD4+ T cells from HIV-infected individuals based on levitation heights within a magnetic field (i.e. magnetic density). We compared HIV DNA and unspliced RNA burden and immune phenotypes in cells from high and low density populations.
Methods: Untouched CD4+ T cells from 15 ART-suppressed individuals were sorted based on magnetic density using our novel micirofluidic magnetic cell levitation and sorting system (Figure). A microfluidic chip-based platform incorporates collection channels for high-throughput isolation of cells levitating at different heights in a biocompatible paramagnetic medium for downstream characterization of HIV burden and immune phenotype.
Results: Overall, CD4+ T cells from infected participants on ART levitated higher than cells from uninfected controls (229.6 vs 169 µM), but cell radii were similar. Two subpopulations of CD4+ T cells from ART-suppressed individuals were then isolated based on levitation height (the higher density populations contained 2.3-fold more cells). Markers of CD4+ T activation, immune checkpoint, and naive/memory phenotype (CD69, HLA-DR, CD38, PD1, CCR5, CD45RA, CCR7, CD4, CD3), as well as cell viability, were similar in both high and low density layers by flow cytometric analysis. Interestingly, HIV RNA levels from ART-suppressed individuals were significantly lower in the lower density subpopulation (0.81 log10 fewer copies/10^6 CD4+ T cells, P=0.007). Although there were no overall significant differences in HIV DNA levels between high and low density subpopulations, HIV DNA from three participant samples was highly enriched in lower density CD4+ T cells (>3 log10 copies/10^6 cells higher than in the higher density layer).
Conclusion: We demonstrate that HIV infected CD4+ T cells of various transcriptionally active states have unique magnetic levitation/density characteristics that may be unrelated to expression of commonly tested surface protein markers, cellular activation state, and cell size. In addition, HIV DNA was observed almost exclusively in lower density CD4+ T cells in three samples, suggesting that isolating cells based on magnetic levitation has the potential to be refined and applied to various HIV reactivation, latency or eradication studies.



331 A NEW PUBLIC DATABASE FOR NEAR FULL-LENGTH HIV SINGLE-GENOME SEQUENCES

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Background: Despite the success of ART, HIV persists in reservoirs and viremia rebounds if treatment is interrupted. To facilitate understanding of the genetic structure and dynamics of the HIV reservoir, we developed a public database for the storage and meta-analyses of near full-length (NFL) HIV genomic RNA and proviral sequences that persist in donors on ART or that rebound after ART is interrupted.
Methods: The database was constructed with MySql, an open source relational database management system. Built-in sequence analysis and annotation tools were programmed in multiple programming languages. We collected HIV-1 NFL proviral sequences from published papers. Patient demographics information is also available where provided.
Results: The HIV NFL sequence database is a regularly-updated MySql-based relational database. HIV NFL DNA and RNA sequences obtained by single-genome amplification and sequencing from donors are available for meta-analyses. Sequences can be queried by host characteristics (e.g. gender, duration of infection prior to ART, duration of ART suppression) if provided by the original paper, sample type (e.g. PBMC, lymph node, or CSF), sequence type (DNA or RNA from persistent viremia), or sequence characteristics (e.g. intact, hypermutant, or large internal deletion). Tools for characterizing NFL are available including annotating the sequences, determining intactness, identifying indels, pre-mature stop codons, drug resistance mutations and more. Host integration sites of NFL proviruses are included when available. Users can query the database and analyze the data dynamically through a robust website.
Conclusion: Conclusions: This public HIV NFL sequence database and accompanying tools provide easy querying and analyses of HIV DNA and RNA genomes that persist on ART. Meta-analyses of HIV NFL genetics will contribute to our understanding of HIV persistence and may reveal targets for potential future curative interventions. The database will be extended to include other retroviruses as sequences are available.

332 TRANSCRIPTOMIC CORRELATES OF HIV RESERVOIR SIZE DURING ANTIRETROVIRAL THERAPY

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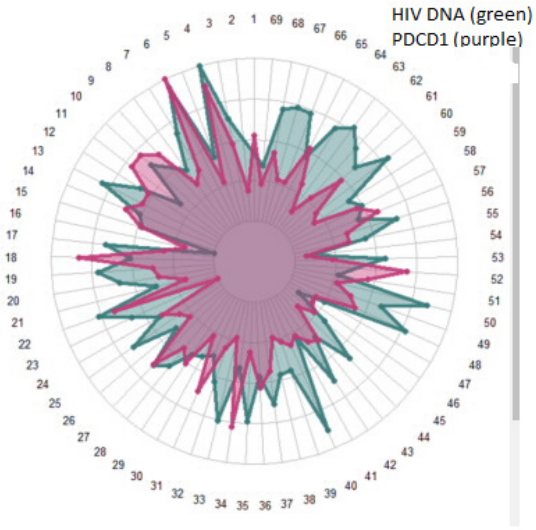
[1]Ghent University, Ghent, Belgium, [2]Wistar Institute, Philadelphia, PA, USA, [3]Blood Systems Research Institute, San Francisco, CA, USA, [4]University of California San Francisco, San Francisco, CA, USA

Background: HIV is an obligate intracellular pathogen that depends on the cellular machinery of the host to complete its life cycle. Therefore, examining the relationships between the transcriptomes of CD4+ T cells from ART-suppressed HIV-infected individuals and latent reservoir markers can reveal valuable host signatures involved in HIV persistence.
Methods: Global transcriptome profiling of blood-derived CD4+ T cells from 69 HIV-infected individuals on suppressive ART for 1-2 years was performed by RNAseq. Genes with counts above 10 Reads Per Kilobase Million (RPKM) across samples were analyzed. Levels of HIV markers were assessed via qPCR assays for cell-associated HIV RNA, total (pol) HIV DNA and 2LTR circles. CD4+ T cell transcriptomes were correlated with reservoir markers and ART initiation timing in a guilt-by-association manner and involved the construction of correlation matrices (Pearson) with subsequent gene set enrichment analysis if a large enough signal was present (>10 genes). Significance was determined using a False Discovery Rate adjusted p-value (q-value) cutoff of 0.05. Gene sets were retrieved from the molecular signature database and include BIOCARTA, KEGG and REACTOME pathways.
Results: HIV DNA, RNA and 2LTR markers were significantly correlated with expression levels of 5, 141 and 15 genes, respectively. The top correlated genes with total HIV DNA levels were ST3GAL5 ($q<0.0022$), and PDCD1 ($q<0.0031$), both showing a positive correlation. A larger signature was identified for HIV RNA levels, and associated pathways included: NFAT signaling, P53, NOTCH signaling, RIG-I and EDG1-induced T cell impairment. HIV 2LTR levels were correlated with MAD2L2 expression ($q<0.0041$). ART initiation timing was correlated with 469 genes and pathways included: mTOR, p53, IL2-induced STAT5 and MYC signaling.
Conclusion: Our study revealed biologically intuitive associations between host genetic pathways and HIV persistence. The strong positive correlation between HIV DNA and expression of the PDCD1 gene encoding PD-1 affirms T cell exhaustion as a mechanism underlying HIV persistence. The ST3GAL5 gene product catalyzes the production of GM3 which is a key regulator of cellular proliferation, trafficking, and survival; this finding is consistent with clonal proliferation as a key factor determining reservoir size. These data also demonstrate the profound and sustained effect of early versus late ART on CD4+ T cell function, and identifies several potential targets for immunotherapy.



Spider Plot: PDCD1 expression and total HIV DNA levels in 69 HIV-1 treated patients

333 EX VIVO CD4+ T-CELL DIFFERENTIATION IMPROVES HIV RESERVOIR QUANTIFICATION

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Background: Quantifying the number of cells harboring latent, replication-competent HIV provirus is critical in evaluating the efficacy of interventions aimed at reducing the viral reservoir. However, the low frequency of these cells makes this measurement extremely challenging. The quantitative viral outgrowth assay (QVOA) is based on ex vivo activation of resting CD4+ T cells to measure HIV persistence during anti-retroviral therapy (ART). Recent studies have shown that QVOA does not detect all latently infected cells assayed, potentially due to sub-optimal virus reactivation under standard culture and activation conditions. Here, we applied our observation that differentiation into effector CD4+ T cells more effectively promotes HIV latency reversal to improve proviral reactivation in the QVOA, termed differentiation QVOA (dQVOA).
Methods: Peripheral blood samples from virally suppressed donors (n=12) were enriched for resting CD4+ T cells and plated in replicate limiting dilution. Cells were then either activated according to the standard QVOA procedure, or induced to differentiate into effector lineages prior to activation. CD4+ T cell phenotypes were assessed by flow cytometry and culture supernatants were evaluated for p24 via ELISA. The frequency of infected cells was calculated using the maximum likelihood method. Single-genome sequencing (SGS) was performed on supernatants to characterize expressed and replicating viral sequences and to compare them to the integrated proviral population.
Results: Coupling CD4+ T cell differentiation with activation in dQVOA induced a 14-fold average increase (95% CI 4- to 24-fold) in the estimated frequency of cells with replication competent HIV compared to standard QVOA, indicating that promoting effector lineage differentiation significantly increases

expression of latent HIV. Viral kinetics and SGS analyses demonstrated the replication competence of reactivated virus. dQVOA reservoir measurements demonstrated a correlation with clinical markers in addition to a large reduction in the coefficient of variation, suggesting that understanding the key mechanisms of latency reversal will reduce the reliance upon stochastic HIV reactivation, which improves assay reproducibility.
Conclusion: Differentiation into an effector phenotype supports more effective latency reversal of replication competent HIV in resting CD4+ T cells and offers key insights into mechanisms of HIV latency reversal that may offer potential targets for therapeutic interventions.

334 CYTOF CHARACTERIZATION OF THE IN VIVO LATENT HIV RESERVOIR IN BLOOD AND TISSUES

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Background: One of the major hurdles for directly phenotyping the in vivo latent HIV reservoir is the need to stimulate these cells ex vivo. As the cells are stimulated, they change expression of many cell surface markers making precise phenotyping of the latent cells difficult. We recently established an approach called PP-SLIDE (Predicted Precursor as determined by SLIDE) that can effectively backtrack in time to establish the cell surface phenotype of a cell before infection (Cavrois et al 2017) using high-dimensional datasets generated by CyTOF phenotyping. This approach was implemented to chart the in vivo latent HIV reservoir and identify biomarkers of these cells.
Methods: The ability of PP-SLIDE to trace the phenotype of a reactivated cell to its precursor (non-stimulated) state was first confirmed in an in vitro model of HIV latency. Then, freshly isolated blood and lymph node cells from ART-suppressed, HIV-infected individuals from the SCOPE cohort were stimulated with PMA/ionomycin, and reactivated cells (expressing Gag) were deep-phenotyped using a 39-parameter latency-focused CyTOF panel. PP-SLIDE was used to map the reactivated cells onto a T cell atlas of unstimulated cells created for each patient sample analyzed.
Results: Comparison of latent to non-latent cells revealed unique signatures associated with latency. Receptors preferentially expressed on latently-infected T cells from blood include previously described markers such as PD1, TIGIT, and OX40, as well as novel ones including homing integrin α4β1. Latent cells from lymph nodes also preferentially expressed PD1, TIGIT, and OX40, and differed from latent cells in blood in that they exhibited features of resident memory cells and preferentially expressed the T follicular helper marker CXCR5 and the costimulatory molecules CD28 and ICOS.
Conclusion: By simultaneously detecting the expression of 39 proteins in individual reactivated cells and mapping this information onto an atlas of unstimulated cells, we have begun to establish a high-resolution view of the types of latent cells that persist in HIV-infected individuals. Applying this method to chart the reservoir in blood and tissues of additional donors will provide a more complete picture of the nature of the persistent reservoir. Our findings thus far reveal that latent cells exhibit unique features, some of which differ between blood and tissues consistent with the notion that unique mechanisms of persistence are present in tissues.

335 TREASURE HUNT: HIV DNA IN DISTINCT SUBSETS IN THE BLOOD, TERMINAL ILEUM, AND RECTUM

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Background: The gut associated lymphatic tissue (GALT) shows major differences in immune cell composition along the intestine. The largest part of the GALT is located in the terminal ileum (TI), and the HIV reservoir has been associated with CXCR3 and PD1 expression on CD4+ T-cells, and the chemokine IP-10. However, in contrast to the rectum (R), studies of the TI are scarce due to the difficulty in obtaining biopsies. The aim of this study was to compare the interplay of IP-10, CXCR3, PD-1 and the size of the viral reservoir between peripheral blood (PB), R and TI in HIV+ patients on ART.
Methods: Paired PB, TI and R samples from 20 HIV+ patients (HIV-RNA < 20 cop/ml) and 11 healthy controls were studied (median CD4+ T cells of HIV+ [cells/µl]: 696 [495-955]; time on ART [years]: 8 [5.5-10]). Expression of CXCR3 and PD-1 on sorted CD4+CD45RO+ T-cells memory subsets (T central memory (TCMCD27+CCR7+), T transitional memory (TTMCD27+CCR7-), and effector memory cells (TEMCD27-CCR7-)) was assessed. Cell associated total HIV DNA was quantified by qPCR within memory subsets (expression as cop/CD4*10^6). IP-10 in serum and tissue supernatant was measured by ultrasensitive digital ELISA (Simoa; Quanterix, pg/mL). Data were analyzed using Mann-Whitney and Spearman rank (correlation) tests.
Results: HIV+ patients had significantly higher HIV-DNA levels in the TI compared to PB and R. Distribution of memory subsets in PB, TI and R was similar between HIV+ and controls. However, in HIV+ in all compartments PD1 and CXCR3 expression was significantly higher. HIV+ had increased expression of CXCR3 and PD-1 on memory subsets in the TI+R as opposed to PB: TI showed highest PD1 expression in TTM, whereas CXCR3 was highly expressed on TCM in R. A positive correlation was observed between CXCR3 expression in PB and HIV- DNA in TCM of TI (r=0.84 p=0.0021). IP-10 levels were increased in PB and TI of HIV+ [B: 32(23-54), TI: 21(8-28)], compared to controls [B: 17(7-25) p=0.04, TI: 0.75(0.75-16) p=0.04]. In HIV+ the highest IP-10 levels were found in PB compared to TI and R [B: 32(23-54)> TI: 21(8-28) = R: 25(12-42); p=0.03; p>0.05)]. Finally, serum IP-10 levels positively correlated to total HIV-DNA in TI (r=0.89 p=0.03).
Conclusion: Highest levels of HIV-DNA are found in TI. Increased IP-10 levels as well as PD1 and CXCR3 expression in HIV+ TI correlate with total HIV DNA. Different anatomical compartments of the intestinal immune system contribute to maintain the HIV-reservoir.

Distribution of HIV-DNA in distinct CD4 memory subsets in peripheral blood, terminal ileum and rectum.

HIV-DNA/WBC [*10^6]			
	Blood	Terminal Ileum	Rectum
T-cell memory (T_{CM} + T_{TM} + T_{TM} +R)	3621 (2147-11410)	↗ 10980 (4020-74870)	5150 (1110-33280)
T-central memory T_{CM}	849 (171-1720)	37 (0-5763)	0 (0-17700)
T-effector memory T_{EM}	1660 (756-2840)	2340 (26-17275)	0 (0-2790)
T-transitional memory T_{TM}	633 (0-2210)	↗ 4510 (512-28525)	1510 (0-6080)
Rest R	0 (0-0)	0 (0-0.4)	0 (0-339)

WBC, white blood cells; ↗, significant increase when compared to peripheral blood (p <0.05). P values <0.05 are used to describe statistical significance. Data are expressed as median (IQR).

336 PROPORTION OF INDUCIBLE AND INTACT HIV-1 IN BLOOD IS REFLECTIVE OF LYMPH NODES

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Background: The latent reservoir (LR) for HIV-1 persists in CD4$^+$ T cells and is a barrier to cure. The LR has been well characterized in peripheral blood, but lymph nodes have been proposed as a unique sanctuary with concerns that they harbor a greater proportion of latently infected cells, and that measurements of the LR in peripheral blood would not be representative of other tissue sites. Measuring the LR is complicated by an excess of defective virus that is detected by many assays but is not of concern in cure strategies. Additionally, only a subset of intact proviruses are readily activated in vitro. To resolve these issues we characterized total intact, defective, and inducible virus in paired blood and lymph node samples.
Methods: Peripheral blood and lymph node samples were collected from 8 HIV-infected, virally suppressed participants immediately prior to solid organ transplantation. Purified CD4$^+$ T cell populations were analyzed using the intact proviral DNA assay (IPDA) to determine the number of intact and defective proviral genomes by ddPCR, and by a novel quantitative viral induction assay (QVIA) to determine the number of inducible proviruses in each sample by quantification of cell-associated RNA at limiting dilution.
Results: No difference in inducible virus was detected between lymph node and blood samples (median= 4.3, 7.9 inducible proviruses per million, respectively). The median number of intact provirus per million CD4$^+$ T cells was 104 (IQR 48-591) in lymph nodes and 61 (IQR=43-440) in blood; this difference did not reach statistical significance (P=0.109). There was also no difference

in defective virus per million between these sites (median=789, IQR=357-3642; median=584, IQR=299-1530; P=0.95) The ratio of intact to total virus was median=9.9%. Only a small proportion of the intact provirus population was inducible (median=5.7%, IQR=3.3-10.8%) with an even smaller subset of inducible defective provirus (median=1.3%, IQR=0.9-2.3%). Intact and inducible provirus correlated (r=0.779, P=0.0006).
Conclusion: Using two novel assays to analyze different properties of the HIV-1 LR we found no quantitative differences between the peripheral blood and lymph nodes. Taken together with previously reported data showing no difference in the distribution of HIV-1 proviral sequence variants between these sites, we conclude that levels of intact and inducible HIV-1 in blood provide a reasonable approximation of frequencies in the lymph nodes.

337LB GENUINE HIV-1 RESERVOIRS FORM IN URETHRAL MACROPHAGES OF ART-SUPPRESSED PATIENTS

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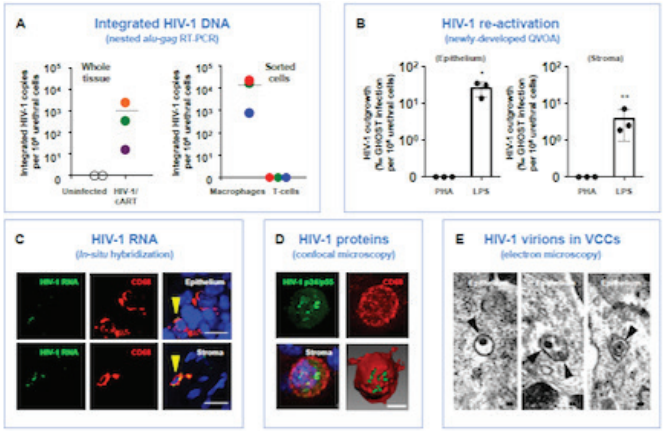
Background: HIV-1 eradication requires the elimination/reduction of the HIV-1 reservoir pool mainly characterized until now within T-cells. Yet, residual viremia in HIV-1-infected cART-suppressed individuals originates not only from T-cells but also from macrophages that posses all required characteristics to form an additional long-lived HIV-1 reservoir. Hence, macrophages, a initial target of HIV-1 infection in the genital mucosa, are tissues-resident cells that resist the cytopathic effects of HIV-1 infection, are long-lived, can self-renew, accumulate infectious virus in intracellular virus-containing compartments (VCC), and produce infectious virus upon stimulation in-vitro.
Methods: We used whole penile tissues from HIV-1-infected cART-suppressed individuals with undetectable plasma viral loads obtained upon transgender surgery and searched by PCR, FISH and microscopy for HIV-1 DNA, RNA, p24 and intact virions. Tissue viral outgrowth was used to detect infectious reactivation-competent virus.
Results: We show that urethral macrophages contain integrated HIV-1 DNA (Fig1A), RNA (Fig1C), proteins (Fig1D) and intact virions in virus-containing compartments (VCCs)(Fig1E), whereas viral components remain undetectable in urethral T-cells. Moreover, urethral cells specifically release replication-competent infectious HIV-1 following re-activation with the macrophage activator lipopolysaccharide (LPS), while the T-cell activator phytohaemagglutinin (PHA) is ineffective (Fig1B). HIV-1 urethral reservoirs localize preferentially in a newly identified subset of transitional M1/M2 urethral macrophages, highly expressing IL-1-receptor, CD206 and IL-4-receptor, but not CD163. Finally, macrophage reservoirs form longlasting conjugates with CD8+T-cells resisting killing suggestive of a mechanism of enhanced inflammation that participates in reservoir persistence.
Conclusion: Altogether, by demonstrating that replication-competent HIV reservoirs form in tissue macrophages, these results challenge the dogma is that HIV reservoirs principally reside in T-cells. Systematic investigation of the presence of HIV reservoirs in other human tissues is now clearly necessary and would be crucial for shock and kill strategies aimed at reservoir elimination.



338 A METHOD TO DETERMINE BOTH THE INTEGRATION SITES AND SEQUENCES OF HIV-1 PROVIRUSES

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Background: Most of the HIV-1 reservoir on ART is likely contained within clonally-expanded cells carrying intact proviruses. Current methods used to characterize the reservoir include near full-length single-genome sequencing (NFL-SGS) and integration site analysis. However, new technologies are needed to link proviruses to their integration sites. We describe a method, called full-length integrated proviral single-genome sequencing (FLIP-SGS), to solve this problem.
Methods: Genomic DNA from PBMC or lymph node mononuclear cell samples (LNMC) from 4 donors was diluted to much less than one provirus per well. An in-house optimized multiple-displacement amplification (MDA) method was performed on each of the wells, generating multiple copies of genomic DNA in each well. Aliquots of the MDA products were then used to obtain the integration sites and to PCR amplify and sequence the corresponding proviruses. The near full length (NFL) sequences were compared to the sequences of viruses obtained in quantitative viral outgrowth assays (qVOA) to identify clones with replication-competent proviruses.
Results: FLIP-SGS was applied to evaluate identical P6-PR-RT sequences identified by standard SGS in PBMC or LNMC. We obtained the integration sites and NFL sequences from several clones that contained defective proviruses and one clone with an intact provirus that matched the NFL sequence of an infectious virus identified by qVOA. In 3 donors, identical sequences identified by P6-PR-RT SGS were confirmed to be of clonal origin by FLIP-SGS (identical integration sites) but we also found proviruses with identical P6-PR-RT sequences that had different integration sites, i.e. "false clones." Such false clones were more common in donors with low proviral diversity or with drug resistant variants.
Conclusion: We describe a new method that can link the sequence of a provirus with its integration site. This method can differentiate 1) identical proviral sequences that are within a cell clone from those that are not; and 2) intact from defective proviruses in cell clones. We identified a second in vivo clone that contains a replication-competent provirus, providing additional evidence that the HIV-1 reservoir is comprised, at least in part, of infectious proviruses in clonally expanded cells. In donors with low proviral diversity or other genetic bottlenecks (e.g. selection of drug resistant variants), identical proviral sequences may or may not be in clones of cells.

339 DISTINCT CHROMOSOMAL POSITIONS OF INTACT HIV-1 PROVIRUSES

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Background: CD4+ T cells harboring integrated HIV-1 DNA represent a long-lasting viral reservoir that can persist for decades in infected individuals despite effective antiretroviral therapy (ART). A small minority of these proviral sequences are genetically intact yet transcriptionally silent during ART, though the mechanisms that maintain this viral latency remain unclear. Chromosomal positions of intact proviruses may critically influence viral transcriptional activity, but have been insufficiently characterized in the past, primarily due to the lack of experimental techniques enabling simultaneous analysis of proviral sequences and corresponding integration sites.
Methods: Proviral HIV-1 sequences from CD4+ T cells of 3 long-term ART-treated participants were diluted to single genomes and subjected to whole-genome amplification using phi29 polymerase. Products containing 1,000-10,000 copies of an identical proviral sequence were split and separately used for near full-length viral sequencing and for integration site analysis using integration-site loop amplification or ligation-mediated PCR. Chromatin

accessibility and gene expression in autologous CD4+ T cells were analyzed by ATAC-Seq and RNA-Seq.
Results: We identified paired proviral sequences and integration sites for 100 intact and 84 defective proviruses. Among these, we detected several clusters of clonally-expanded proviruses exhibiting identical viral sequences and integration sites (8 intact clusters, 6 defective clusters). Relative to defective proviruses, intact proviruses were enriched for non-genic or pseudogenic sites (18% vs 8%, p=0.03) and more frequently displayed an opposite orientation relative to host genes (74% vs 57%, p=0.02). Additionally, intact proviruses were preferentially integrated either in relative proximity (2 participants) or with increased distance (1 participant) to active transcriptional start sites and to accessible chromatin regions, suggesting an enrichment of sites that are either more susceptible to transcriptional interference or located in genomic regions with more limited access to host transcriptional machinery, respectively.
Conclusion: Our results suggest that prolonged ART is associated with a selection of intact proviruses with multiple discrete features of deeper latency, likely due to immune-mediated selection pressure. The intact reservoir may thus be vulnerable to interventions aimed at accelerating the selection of proviruses with deeper latency and reduced ability to fuel rebound viremia.

340 RELATIONSHIP BETWEEN INTACT HIV-1 PROVIRUSES AND PLASMA REBOUND VIRUSES

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Background: Combination antiretroviral therapy controls but does not cure HIV-1 infection due to a small fraction of cells harboring latent viruses that can produce rebound viremia upon therapy interruption. The circulating intact latent reservoir has been documented by either viral outgrowth assays (VOAs), or by amplifying near full length (NFL) proviral sequences from DNA. Analysis of samples obtained in clinical studies whereby individuals underwent analytical treatment interruption (ATI), showed little overlap between latent viruses from VOAs pre-ATI, and viruses isolated from plasma during viral rebound. To determine whether intact proviruses from DNA are more closely related to rebound viruses than those obtained from VOAs, we assayed 12 individuals who underwent ATI after infusion of two broadly neutralizing anti-HIV-1 antibodies (bNAbs).
Methods: NFL proviral genomes were amplified from DNA extracted from CD4+ T cells obtained from 2 leukapheresis samples (pre- and post-bNAb infusions) from 9 individuals that maintained viral suppression for >12 weeks after ATI. A single pre-infusion sample was also available for 3 additional individuals that experienced viral rebound within 12 weeks of ATI due to pre-existing bNAbs-resistant proviruses in the latent reservoir. VOA was performed on all of these samples to determine the number the inducible replication-competent proviruses.
Results: The env sequences from 435 intact proviruses obtained by NFL sequencing were compared with 650 latent viruses from VOAs and 246 plasma rebound viruses. Although, intact NFL and outgrowth culture sequences showed similar levels of stability and diversity with 39% overlap, the size of the reservoir estimated from NFL sequencing did not correlate with that obtained by VOA. Although all of the rebound viruses in plasma were >96% identical to at least one sequence from the reservoir, we did not find a single instance of 100% env identity among intact NFL sequences and rebound viruses. Moreover, only 12 out of 246 rebound sequences could be accounted for by mutation of reservoir sequences during the ATI window. However, 48% of the rebound viruses could be derived from recombination between intact NFL and/or VOA proviruses.
Conclusion: We find that intact proviruses obtained from DNA overlap in part with those obtained by VOA, but do not overlap with rebound viruses. However, nearly half of all rebound sequences appear to be recombinants derived from circulating latent viruses characterized by VOA or NFL sequencing.

341 LANDSCAPE OF HIV-1 INTEGRATION SITES IN LYMPHOID TISSUE FROM ART-TREATED INDIVIDUALS

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Background: The integration of HIV DNA into the host genome occurs from the activity of both viral proteins and host cellular factors. Prior analyses in cell lines and peripheral blood mononuclear cells (PBMC) samples have assessed the HIV-1 integration site distribution and characterized regions such as active transcription units that favor integration. The host encoded LEDGF/p75 protein tethers HIV-1 integrase at active transcription units, accounting for this bias. To date, no studies have compared integration site distributions within tissue resident cells – namely in lymphoid tissues where HIV-1 is known to replicate and persist even after antiretroviral treatment (ART).
Methods: Tonsil samples were collected from three ART-treated and HIV-1 infected patients to sort into non-naïve $CD4^+$ cell subsets: circulating ($HLA\text{-}DR^-\ CD69^-$), tissue-resident ($HLA\text{-}DR^-\ CD69^+$), and germinal-center Tfh ($HLA\text{-}DR^-\ CXCR5^+\ PD\text{-}1^{hi}$) cells. Genomic DNA was extracted from the different cell types, sonicated, and then uniquely labeled by cell subset and patient. Libraries were created via ligation-mediated PCR and sequenced using the MiSeq platform (Illumina). Downstream analyses were done using the INSPIIRED software pipeline and R.
Results: Of the integration sites sequenced, the majority across patients were found to be enriched within transcription units. Viral-host junctions were detected in 21 of the human autosomal chromosomes as well as the X chromosome in the combined dataset. We detected an average ratio (integration sites per one thousand cells) of 0.046 ± 0.025 for circulating cells, 0.137 ± 0.106 for tissue resident cells, and 0.067 ± 0.065 for Tfh cells. Curiously, we observe little to no overlap in integration site coverage between the circulating, tissue resident, and germinal-center Tfh cells by patient.
Conclusion: Our findings agree with previous studies regarding HIV-1 integration within transcription units. However, the lack of gene overlap across cell subsets may suggest unique integration signatures in lymphoid tissue. The novelty of these results demonstrates the need for further analysis on integration sites in lymphoid resident cells as well as PBMC cells at different stages of HIV-1 progression. Analyzing the integration site signature in the lymphoid resident cells will help contribute more insight to the goal of understanding and eliminating the latent reservoir.

342 GENETIC AND AGE DISTRIBUTION OF LATENT HIV SEQUENCES IN CD4+ T-CELL SUBSETS

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Background: HIV latency is the main barrier to cure, but our understanding of within-host latent proviral landscapes, particularly in distinct CD4+ T-cell subsets, is incomplete. We characterized sequence diversity and estimated age distribution of latent HIV sequences in naïve, central memory (CM), transitional memory (TM) and effector memory (EM) CD4+ T-cells from HIV-infected individuals with long-term viremia suppression on cART.
Methods: CD4+ T-cell subsets were sorted from PBMC from 5 participants with a median 9 [IQR 9-13] years pVL suppression on cART. Proviral DNA was sequenced from these subsets using single-genome approaches (nef region); sequence compartmentalization was assessed using the Slatkin-Maddison (SM) test following maximum likelihood phylogenetic inference. For 4 participants, single-genome HIV RNA sequences were also obtained from a median 11 [IQR 6-15] pre-cART plasma samples spanning a median 8 [IQR 3-11] years; these data were used in a novel within-host phylogenetic approach to infer proviral sequence ages.
Results: 539 Nef proviral sequences were isolated; 424 (78%) were genetically intact, of which 347 (82%) were unique. Intact sequence percentage varied between hosts (68-93%) and between T-cell subsets (naïve 71%; CM 79%; EM 86%; TM 88%). EM harbored the lowest % uniqueness (56%) and CM the highest (96%). Within-host latent HIV phylogenetic diversity varied between hosts (average tip-to-tip phylogenetic distances 2.1e-2-9.6e-2 nucleotide substitutions/site), though there was no clear relationship between within-host latent HIV diversity and length of uncontrolled viremia, or length of cART suppression. In 3 participants, proviral genetic diversity differed between subsets (Kruskal-Wallis $p<0.05$). Two of these participants, plus one other showed evidence of genetic compartmentalization (SM $p<0.01$). Proviral sequence ages varied markedly between hosts (median 10.4; max 23 years) and in two cases also differed between subsets: for example, in one participant, latent HIV sequences in naive T-cells were younger than the other subsets

(p=1.3e-6) whereas in another those in the EM subset were the youngest (p=0.01).

Conclusion: The latent HIV proviral landscape differs markedly between individuals, and sometimes between different CD4+ T-cell subsets within the same individual: eradication strategies may need to take this into consideration. Inference of proviral sequence ages in different HIV T-cell subsets can yield insight into latent HIV dynamics and persistence.

343 B CELL-T CELL DOUBLETS IN GALT ARE ENRICHED FOR TFH CELLS BUT NOT FOR HIV DNA

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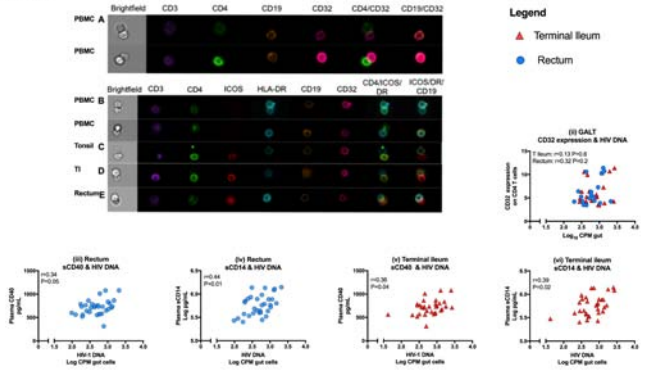
Background: Gut-associated lymphoid tissue (GALT) is a key HIV reservoir site and may play a role in HIV persistence on ART. T Follicular helper (TFH) cells and CD32+CD4+ T cells have been proposed to be enriched for HIV DNA. Here, we show that CD32+CD4+ T cells in GALT are B cell-T cell (B:T) doublets and that sCD40 (a soluble marker shed after B:T cell interaction through CD40/CD154 signaling) but not CD32 is associated with HIV DNA in GALT.

Methods: GALT from the terminal ileum (TI), rectum (R) & tonsil tissue (n=1) was obtained from consenting individuals treated during primary HIV infection (PHI). HIV DNA was quantified in GALT biopsies by qPCR. Concurrent plasma samples were used to measure IL-4, IL-5, IL-6, IL10, IL-15, MCP-1, MIP-1α, MIP-1β, IP-10, sCD163, CD40 & CD40L by Luminex (n=23). CD32 expression on GALT CD4 T cells was measured by flow cytometry (n=19) and imaging cytometry assessed CD19, CD3, CD4, ICOS, HLA-DR & CD32 expression in healthy control GALT and HIV+ tonsil. Associations between HIV DNA & CD32 were tested by Spearman's correlation. LASSO regression analyses were used to test for associations between GALT HIV DNA & plasma variables.

Results: 23 PHI individuals were studied; median (IQR) HIV DNA was significantly higher in TI compared to R [2.82 (2.58-3.05) vs 2.73 (2.42-2.96) log_{10} CPM gut T cells, p=0.03]. CD32 expression on GALT CD4 T cells was not associated with HIV DNA. Imaging cytometry analysis showed that CD32 expression on CD4 T cells in GALT (n=1) & HIV+ tonsil (n=1) was consistent with B:T cell doublets with CD32 expression primarily from B cells, while associated CD4+ T cells expressed ICOS. Plasma (n=23) sCD40 (TI: r=0.36 P=0.04, R: r=0.34 P=0.05) and sCD14 (TI: r=0.39 P=0.04, R: r=0.44 P=0.01) were the variables most strongly association with HIV DNA.

Conclusion: These data show that CD32 expression on CD4 T cells in GALT and tonsil when gated as singlets using standard methodology is due to B cell-TFH cell doublets, with CD32 expression primarily on B cells. The enrichment for TFH cells within these doublets raises the issue of whether they are artefactual or physiological. Plasma sCD40, a marker of the B:T cell interaction, & sCD14, a marker of bacterial translocation, were the factors most associated with HIV DNA, while CD32 expression was not. This suggests that the B:T cell interaction & microbial translocation in GALT may be supporting HIV persistence while CD32 is a surrogate marker of this interaction.

Figure
(i) Image stream data; showing brightfield, CD3, CD4, CD19, CD32, ICOS & HLA-DR expression on PBMCs (A & B), GALT (D &E) and Tonsil cells (C). (b) shows GALT CD4 T cell CD32 expression vs. HIV DNA. Rectal HIV DNA levels vs (c) plasma sCD40 and (d) sCD14 are shown in blue circles. Terminal ileum HIV DNA levels vs. (c) plasma sCD40 and (b) plasma sCD14 are shown in red triangles. Abbreviations: PBMC, peripheral blood mononuclear cell; TI, terminal ileum, GALT, gut-associated lymphoid tissue; s, soluble. P values calculated using spearmans correlation.



344 CD38+CXCR3+ TFH CELLS SERVE AS ACTIVE HIV RESERVOIR IN THE TOTAL TFH CELL POPULATION

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Background: T follicular helper cells (Tfhs) are a phenotypically heterogeneous cell population generally defined by the expression of CXCR5 and PD-1. Tfhs serve as a major reservoir for HIV transcription and production in both viremic and long-term ART treated subjects. In the presents study, we have dissected the phenotypic and functional heterogeneity of Tfhs and the role of the different Tfhs populations in serving as HIV reservoir and their relationship with HIV-specific B cell responses.

Methods: Lymph nodes (LN) biopsies were obtained from 17 HIV uninfected, 27 viremic untreated and 23 aviremic ART treated subjects. Definition of B and T cell populations and cytokines was performed by mass cytometry using a panel of 40 metal-conjugated antibodies. To dissect the heterogeneity of Tfh cells, we performed self-organizing map (FlowSOM) and consensus clustering. Cell-associated HIV-RNA was assessed in Tfh cells sorted on the basis of CD38 and CXCR3 expression (CD38+CXCR3+, CD38+CXCR3-, CD38-CXCR3+ and CD38-CXCR3-).

Results: Unsupervised clustering identified 20 different populations of Tfh cells within $CXCR5^{high}PD\text{-}1^{high}$ Tfh cells. CD38+CXCR3+ Tfhs significantly increased in viremics (41.18%) as compared to ART treated (17.8%) and HIV uninfected (6.9%) subjects (p<0.0001). Frequencies of CD38+CXCR3+ Tfh cells positively correlated with the percentage of total germinal center B cells (r=0.58, p<0.0001) and GC gp140+ B cells (r = 0.65, p<0.0003). CD38+CXCR3+ Tfhs expressed higher levels of expression of BCL-6, ICOS, CD57, CD40L, CCR5, HLA-DR, T-bet as compared to the CD38+CXCR3-, CD38-CXCR3+ and the CD38-CXCR3- and of production of the Tfh signature cytokine IL-21 (averages of 33%) as compared to the other three Tfh cell populations (p<0.0002). Of note, only the percentage of CD38+CXCR3+ Tfhs positively correlated with viremia (r=0.5, p=0.01) in untreated subjects. More importantly, CD38+CXCR3+ Tfhs were greatly enriched in cell-associated HIV-RNA as compared to CD38+CXCR3- (average 3.3 fold), CD38-CXCR3+ (average 6.24 fold) and CD38-CXCR3- (average 8.24 fold) Tfh cell populations (p<0.05).

Conclusion: CD38+CXCR3+ Tfhs correspond to a population of phenotypically and functionally active Tfh cells. The higher levels of expression of CCR5 may render these cells more susceptible to HIV infection and it explains why CD38+CXCR3+ Tfh cells serve as the major active HIV reservoir within the total Tfh cell population.

345 RESIDENT MEMORY T CELLS ARE A CELLULAR RESERVOIR FOR HIV IN THE CERVICAL MUCOSA

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Background: Viral reservoirs, which represent the main obstacle to cure HIV, are early established in different tissues. Target cells in peripheral tissues where HIV is acquired, such as the female genital mucosa, may express CD69 as a hallmark of their resident memory T cell (TRM) phenotype. Some of the features of TRM reported for other tissues, including long-lived and self-renewal capacities, shape them as an ideal cellular reservoir for HIV. However, the contribution of this relatively novel subset of cells to the pathogenesis and persistence of HIV remains unknown.

Methods: TRM were phenotyped in fresh cervical tissues obtained from HIV-uninfected women undergoing hysterectomy for non-neoplastic reasons (n=6-9). Activation of CD103+/-CD4+TRM subsets were compared between healthy and antiretroviral therapy (ART)-suppressed HIV+ women (n=6). The cervical explant model of HIV infection was established to determine proviral DNA (vDNA) content by qPCR and productive infection by p24 antigen expression in TRM subsets (n=7). In addition, we determined vDNA in purified cell subsets derived from blood and cervix obtained from ART-suppressed HIV+ woman (n=6). Finally, we also assessed viral HIV-RNA in cervical tissues from

suppressed HIV+ women by fluorescence in situ hybridization in combination with immunohistochemistry (n=4).
Results: Cervical CD4+ TRM cells expressed a unique repertoire of clusters of differentiation on their surface compared to non-CD4+TRM that shaped them highly susceptible to HIV infection (α4β7, CXCR4, CXCR6 and CCR6) while revealed self-renewing potential (CD122, CD132, CD127) ($p<0.032$ for all markers). CD4+TRM preferentially sustain HIV infection ex vivo and harbored more HIV protein ($p=0.003$) and DNA ($p=0.062$) than non-TRM from the same tissues. Conclusively, cervical tissue from ART-suppressed HIV+ women contained up to two logs more molecules of viral DNA per cell (median 12,929) compared to blood (median 1,092), and the CD4+TRM fraction was the principal contributor to this reservoir (median of 98.25%). Further, persistent viral RNA was detected within CD69 positive cells in cervical samples from ART-suppressed HIV+ women.
Conclusion: Here we identified first the cervical mucosa as an overlooked HIV sanctuary and second CD4+TRM as a critical cellular reservoir. Thus, the contribution of CD4+TRM to viral persistence in tissues requires major attention in order to reach a functional cure in HIV infected patients

346 CD32+CD4+ T CELLS ARE ENRICHED IN HIV DNA

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Background: CD32 was reported to mark the HIV reservoir, but several recent reports challenged this finding. We aimed to confirm or deny the role of CD32 as a marker of the viral reservoir and to further characterize the phenotype of these CD32+CD4+ T cells.
Methods: CD32 expression and co-expression of HLA-DR, PD-1, TIGIT, LAG-3 was measured by flow cytometry on PBMCs from ART-suppressed HIV-infected individuals with undetectable plasma viremia. HIV DNA was quantified in bulk PBMC samples and in CD32+ and CD32- fractions of CD4+ T cells obtained by magnetic sorting (negative selection to isolate CD4+ T cells followed by positive selection to isolate CD32+CD4+ cells).
Results: The median frequency of CD32+CD4+ T cells in HIV-infected individuals (n=19) was 0.07%. We found a positive correlation between the percentage of CD32+CD4+ T cells and total HIV DNA load in PBMCs (rho=0.58; p=0.012). CD32+CD4+ T cells demonstrated increased expression of LAG-3 (p=0.016), TIGIT (p=0.016) and HLA-DR ($p<0.0001$) compared with CD32-CD4+ T cells. CD32+CD4+ T cells were not enriched for HIV DNA (normalized to the total cell numbers) compared with CD32-CD4+ cells. However, the CD32+ fraction was found to contain many B cells, due to the abundance of CD32+ B cells in the input sample, of which some remained after one round of CD4+ T-cell purification. Remarkably, when HIV DNA was normalized to CD3G T-cell-specific mRNA, a significant positive enrichment in the CD32+ fraction was observed (p=0.0001). Therefore, we optimized the protocol to isolate a more pure fraction of CD32+CD4+ T cells from an additional set of HIV-infected individuals (n=19). An extra round of CD4+ purification resulted both in a 19-fold decrease in B-cell contribution to the CD4+CD32+ fraction ($p<0.0001$) and in an 11-fold enrichment in HIV DNA in this fraction (p=0.0007), the latter observed even when HIV DNA was normalized to the total cell numbers. In a subset of these individuals (n=8), we performed two additional rounds of CD32+ positive selection and observed a very high enrichment (mean 300-fold) for HIV DNA in the CD32+CD4+ fraction.
Conclusion: We confirm that CD32+CD4+ T cells are highly enriched in HIV DNA. Our results highlight the importance of obtaining a sufficiently pure CD32+CD4+ T-cell fraction for analysis, and provide a plausible explanation for the negative results recently obtained by others. Our data suggest that the CD32+CD4+ T cells are activated, and that they often co-express the immune checkpoint receptors TIGIT and LAG-3.

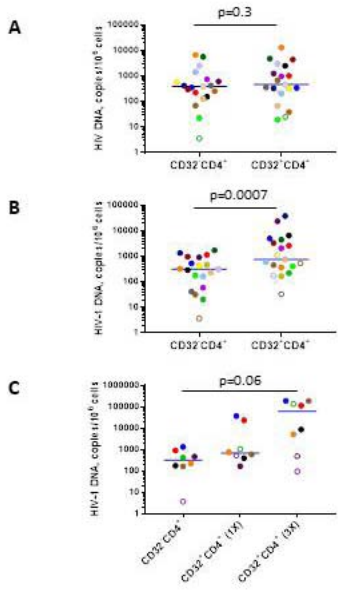

Fig. 1. Comparison of total HIV DNA levels between the CD32⁻CD4⁺ and CD32⁺CD4⁺ fractions isolated either (**A**) by one round of CD4⁺ purification and one round of CD32⁺ positive selection, (**B**) as in (A) but with one extra round of CD4⁺ purification, (**C**) as in (B) but with no or two extra rounds of CD32⁺ positive selection. HIV DNA was normalized to β-actin DNA. Undetectable values were censored to the detection limits (per 10^6 cells) and are shown by open circles. Wilcoxon tests were used to calculate statistical significance. Different colors represent ART-suppressed HIV-infected individuals.

347 DIFFERENT T-CELL SUBSETS CONTAIN INTACT PROVIRUSES IN BLOOD AND LYMPH NODE DURING ART

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Background: Understanding the distribution of genetically intact, and therefore potentially replication-competent, proviruses in different CD4+ T cell subsets and within different anatomical sites is important for identifying targets for future eradication strategies.
Methods: Naïve (NV), central (CM), transitional (TM) and effector memory (EM) cells were isolated from both the peripheral blood (PB, 13 participants) and lymph nodes (LN, paired, 5 participants) of HIV positive individuals on long-term ART (3-17 years). HIV proviral sequences were obtained using the Full-Length Individual Proviral Sequencing assay (FLIPS) which amplifies single, near full-length (92% of genome) HIV proviruses followed by Next-Generation Sequencing. Genetically intact HIV proviruses were identified as those lacking inversions, stop codons/hypermutation, insertions, deletions or frameshifts.
Results: We sequenced 1893 genomes and identified genetically intact proviruses in all cell subsets except LN EM (3 participants). The frequency of infection with any HIV genome (intact and defective) differed across the cell subsets in LN and PB ($P<0.001$). We observed the highest levels in TM and EM cells, followed by CM and then NV cells, with the trend significant in blood ($P<0.05$). The infection frequency of genetically intact proviruses also differed across the subsets in blood ($P<0.001$) and LN (P=0.02). In blood, intact genomes showed a trend of EM>NV>TM>CM with evidence for EM>CM (P=0.01). In LN, the intact genomes showed a different trend: NV>CM>TM>EM. Overall, the infection frequencies of intact proviruses within the LN and PB anatomic sites were similar (P=0.67), but this result was sensitive to 2 participants with high levels of intact proviruses in LN NV cells (10% and 26% were intact of all LN NV sequences). The intact LN sequences were genetically unique. We did not identify any identical intact sequences between PB and LN.

Conclusion: The distribution of genetically intact proviruses within T cell subsets in blood do not necessarily reflect their distribution in lymph nodes. In lymphoid tissues, the frequency of intact proviruses is highest in less differentiated cells such as NV cells, while in blood the frequency is highest in more differentiated EM cells. Tissue-based NV T cells may act as progenitors of the total reservoir during ART, whereas in the periphery this reservoir is maintained within the EM T cell population, perhaps by clonal proliferation.

348 PERSISTENT HIV LOW-LEVEL VIREMIA CAN ARISE FROM AN ACTIVE PROVIRAL CLONE

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Background: Persistent low-level viremia (LLV) is not uncommon among patients with HIV despite receiving continuous antiretroviral therapy (ART), but the mechanism behind this finding remains unclear. We describe one individual with persistent low-level viremia (200-700 copies/ml) across 16 viral load measurements over >3 years despite ART intensification to a DTG, DRV/r, TAF/FTC ART regimen. We hypothesized that the persistent LLV arose either from an expanded clone of transcriptionally-active reservoir cells or from ongoing viral replication.

Methods: Commercial ARV drug levels and resistance genotyping were performed at multiple time points. We performed plasma single-genome sequencing for the Pro-RT region at 3 different timepoints, each 1 year apart. Confirmatory near-full length plasma sequences were obtained at the first time point. We also performed a novel next-generation single-genome proviral sequencing (NG-SGS) assay from PBMCs that combines near-full length proviral amplification and integration site analysis.

Results: The LLV persisted despite detectable plasma ARV levels and the presence of at least 2 fully active ARVs by resistance genotyping. Across all 3 timepoints, 86% of all single-genome plasma sequences were comprised of one viral clone (range 67% - 100% at each time point). Intact near-full length proviruses exactly matching the majority plasma clone were identified, which constituted only 6% of all intact proviruses. Near-full length plasma HIV sequences confirmed the clonality of this population and the lack of known drug resistance mutations. Integration site analysis showed that this provirus is integrated into CD200R1, a gene encoding a transmembrane receptor expressed by CD4+ cells. Interestingly, the majority of intact proviruses consisted of one clonal proviral sequence, constituting 54% of all intact proviruses but only 9% of plasma variants. This intact provirus is integrated into the STAG2 gene, which has critical roles in regulating the chromosome structure and cell division. No evidence of viral evolution or emergence of new drug resistance mutations were detected in plasma over time.

Conclusion: Persistent LLV can arise from the integration of HIV into a transcriptionally-active region of a clonally-expanded CD4+ population without evidence of ongoing viral replication. In this setting, further intensification of the ART regimen is unlikely to be effective and suppression of the LLV will require targeting of this transcriptionally-active reservoir.

349 PREDICTING HIV REBOUND IN VIVO BASED ON EX VIVO CD4+ T CELL LATENCY DISRUPTION

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Background: Following activation of ex vivo latently-infected CD4+ T cells from HIV-infected individuals on antiretroviral therapy (ART), we reported cell-to-cell variability for HIV release, and given such virus release, the probability of establishing exponential viral growth. From these results, we fit a population dynamic model that indicated a critical initial viral population size with a rare latently-infected cell lineage breaking through this threshold and establishing exponential viral growth, attributed to stochastic emergence of superspreading.

Methods: With minimal modification, we extended our model to in vivo viral rebound following ART cessation. We assumed a latently-infected CD4+ T cell population half-life of 44 months and an initial total-body census of 1.5 million cells. To allow for potential synergy among near-simultaneous reactivations, we distributed these into 150,000 compartments of 10 cells each. We assumed virus was randomly distributed in a volume of 15 liters. We performed Gillespie simulations, to obtain an estimate for the rate of latent cell reactivation on ART and for rebound off ART.

Results: A rate of latent cell reactivation of ~ 1 x 10-6 /day resulted in simulated virus production that ranged between 0.5 and 4 HIV RNA copies /ml, consistent with in vivo ultrasensitive viral load quantitation on ART. Simulating a single HIV-infected individual for 100 days off ART, 234 viral reactivations occurred, with 26 that transitioned to exponential viral growth, 5 appearing in the first 20 days. This result was typical of 9 other simulated HIV-infected individuals. The mean time to greater than 100 HIV RNA copies /ml was 19 days (SD 3 days). The time interval between 100 HIV RNA copies /ml to 1 x 105 copies / ml was ~ 1 week. After a 1200-fold initial reservoir reduction, 5 of 10 individuals had rebound during 41 years.

Conclusion: The frequency of rebound seeding reactivations predicted here within single simulated individuals is consistent with that estimated previously in vivo. Synergy between two reactivations was very rare, however, reactivations may not be independent, particularly for in vivo expanded clonal populations. The rate of simulated viral rebound, once virus was clinically detected, was faster than that documented in vivo, perhaps because parameters were estimated from ex vivo cultures that used maximally stimulated target cells. In addition, immune responses, not considered here, could decrease the rate of viral reactivation or rebound.

350LB VRC01 EPITOPE MOTIFS PREDICTED REBOUND KINETICS AFTER VRC01/ TREATMENT INTERRUPTION

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Background: Ongoing antibody-mediated prevention clinical trials are testing infusions of the broadly neutralizing antibody VRC01 as a strategy for HIV prevention, yet the impact of VRC01 on founder viruses is unknown. We evaluated the impact of VRC01 on homogeneous HIV populations characteristic of acute infection through an Analytic Treatment Interruption (ATI) study (RV397) that enrolled 18 acutely-treated participants who had been on antiretroviral therapy (ART) for over 2 years, randomizing 13 to receive VRC01 and 5 placebo. All participants rebounded between 9 and 296 days after ATI. We investigated the impact of HIV genetic features and VRC01 neutralization sensitivity on rebound kinetics.

Methods: HIV sequencing was performed via endpoint-dilution on plasma samples in Fiebig I-III acute infection (10 genomes) and post-rebound (~15 pol and env). Env were tested for VRC01 neutralization sensitivity using the TZM-bl neutralization assay.

Results: After ATI and concurrent VRC01 infusion, viral rebound was modestly delayed in the VRC01 group (median: 29 vs 14 days, p=0.051). Post-rebound, pol and env sequences differed by 1-2 nucleotides from the founder sequence derived pre-ART and all sequences were intermingled in phylogenetic trees demonstrating no evidence of VRC01-mediated escape during the ATI. For each participant, VRC01 neutralization sensitivity did not differ between acute infection and post-rebound (p=0.875). However, viral strains differed in their sensitivity to VRC01 neutralization, with two infections with VRC01-resistant viruses. The most sensitive strains tended to rebound slower than less sensitive strains (Rho=-0.62, p=0.033). We developed an epitope similarity score that weighted sites based on their importance in the VRC01/Env interaction and compared our sequences to known VRC01-susceptible strains. Our predictor was associated with the time to rebound (Rho=-0.70, p=0.007) and with neutralization results (Rho= 0.59, p=0.045). Sequences from participants who rebounded early were enriched for D at site 279, compared to N in late rebounders, placebo and known VRC01-sensitive strains.

Conclusion: Clearing the latent reservoir to induce drug-free viral control remains a challenge, even if our findings showed that the presence of VRC01 for a few weeks, in the absence of standing HIV variation, did not select for escape. Our ability to predict how the responsiveness to VRC01 infusion varies across viral sequences could be useful to interpret results of future trials.

351 TRIFUNCTIONAL T-CELL ENGAGERS TARGETING PD-1 AND TIGIT IN CHRONIC HIV/SHIV INFECTIONS

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Background: Immune checkpoint inhibitors, such as PD-1 and TIGIT, are crucial dysregulators of CD8 T cell function during chronic HIV-1/SIV infections. Importantly, these checkpoint inhibitors are highly expressed on the surface of CD4 T cells that harbor latent HIV. We have previously demonstrated that an anti-HIV/anti-CD3 bispecific T-cell engager (BiTE) can be used to redirect functionally compromised follicular CD8 (fCD8) T cells to kill HIV infected cells in vitro. Here, we hypothesize that adding an extra specificity to target PD-1 and TIGIT to the BiTE will further enhance the functional activities of CD8 T cells and simultaneously lower the threshold for reactivation of latently infected cells in HIV infection.
Methods: We generated trifunctional anti-HIV/anti-CD3/anti-PD-1 and anti-TIGIT T-cell engagers by linking the scFvs from either anti-TIGIT and anti-PD-1 antibodies to the BiTE molecule. HIV-infected cell lines and primary cells isolated from lymph nodes (LN) of chronically SHIV-infected rhesus macaques were used as target cells in the in vitro and ex vivo killing assays to test whether trifunctional T-cell engagers could enhance the cytolytic activities of functionally compromised CD8 T cells. We also examined whether trifunctional T-cell engagers could stimulate CD8 T-cell lysis of HIV-infected CD4 T cells using a primary HIV latency model. Furthermore, multiparameter flow cytometry was used to investigate the effects of trifunctional T-cell engagers on CD8 and CD4 T cell polyfunctionality.
Results: We found that trifunctional anti-HIV/anti-CD3/anti-TIGIT and anti-PD1 increased the killing capability of CD8 T cells compared to the bifunctional anti-HIV/anti-CD3 BiTE in the in vitro and ex vivo killing assays. We also demonstrated that trifunctional anti-HIV-1/anti-CD3/anti-TIGIT and anti-PD1 enhanced the CD8 T cell lysis of latently infected cells. Furthermore, trifunctional anti-HIV-1/anti-CD3/anti-TIGIT and anti-PD1 were shown to increase antigen-specific CD107a degranulation, levels of granzyme B, cytokine and chemokine release by CD8 T cells, which could potentially underlie the observed increase in the killing capability of CD8 T cells.
Conclusion: Our results indicate that the use of trifunctional T cell engagers targeting immune checkpoints, PD1 and TIGIT, may serve as novel immunotherapeutic strategies to eliminate infected cells in HIV infected individuals.

352 IMPACT OF RAPAMYCIN ON SIV PERSISTENCE IN RHESUS MACAQUES ON ANTIRETROVIRAL THERAPY

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Background: The mammalian target of rapamycin (mTOR) is a key regulatory kinase that controls glucose metabolism and cell growth. Inhibition of mTOR has been linked with several immune regulatory functions that may limit HIV persistence, including: 1) reducing CCR5 expression, 2) limiting CD4+ T cell homeostatic proliferation, 3) reducing PD-1 expression and 4) increasing anti-viral CD8+ effector T cell responses. Here we evaluated the impact of long-term mTOR inhibition on SIV DNA and RNA in blood and tissues of SIV-infected rhesus macaques (RM) on combination antiretroviral therapy (cART). We also evaluated whether potent T cell activation can induce latent SIV reactivation in the presence of rapamycin.
Methods: A total of 14 adult male RM were intravenously infected with SIVmac239 followed by cART (tenofovir, emtricitabine and dolutegravir) 12 days later. After 219 days of cART, RM were randomized into 2 groups that received twice daily IM injections of rapamycin at 0.02mg/kg (n=7) or vehicle control for 312 days. After 464 days of cART, RM on rapamycin received 2 doses of a non-depleting anti-CD3LALA monoclonal antibody at 0.5mg/kg IV at 21-day intervals. Plasma viral loads and cell-associated SIV RNA and DNA were quantified by qRT-PCR and qPCR, respectively. Lymphocyte populations were evaluated by flow cytometry.
Results: After 24 weeks, there were significant decreases in the frequencies of Ki67+ ($p = 0.0006$), HLA-DR+ ($p = 0.0262$) and PD-1+ ($p = 0.04$) CD4+ memory T cells in blood of rapamycin-treated RM versus controls. In addition, surface expression of CCR5 ($p=0.007$) and the glucose transporter Glut1 ($p=0.007$) were also significantly reduced in rapamycin-treated RM. Despite these perturbations in CD4+ T cell homeostasis, cell-associated SIV DNA and RNA in blood and peripheral lymph nodes remained stable over time with no significant difference observed between treatment groups. However, 4 of 7 rapamycin-treated RM had blips in plasma viral loads >2 logs above threshold (1 RNA copy/ml) in response to anti-CD3LALA, suggesting T cell activation in the presence of rapamycin can induce SIV reactivation in vivo.
Conclusion: Despite profound changes in markers of immune activation, proliferation and T cell exhaustion, rapamycin had minimal effect the stability of the SIV reservoir. However, these data indicate that rapamycin used in synergy with potent T cell activation may be an effective strategy to induce viral reactivation while inhibiting global immune activation and T cell proliferation.

353 COMBINATION OF CRISPR AND LASER ART PREVENTS HIV REBOUND IN HUMANIZED MICE

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Background: Advances in CRISPR-Cas9gene editing technology and its in vivo delivery by AAV9 vectors together with cell based nanotechnology for long-acting slow effective release antiretroviral therapy (LASER-ART), were used in NSG-CD34 humanized mice to facilitate eradication of HIV-1 in vivo.
Methods: CRISPR-Cas9 proviral DNA excision followed two months of treatment with long-acting slow effective release antiretroviral therapy (LASER-ART), rilpivirine, myristolyated dolutegravir, lamivudine, and abacavir in HIV-1 infected humanized mice. A series of virological, histological, and DNA and RNA assays were used to detect HIV-1 expression and replication in the animal tissues. Ultra deep, whole genome sequencing was employed to assess in vivo off-target effects.
Results: Results from three independent sets of studies showed restorations of CD4+ T cells due to ART treatment and complete eradication of replication competent virus by CRISPR in 39% of animals. Ultrasensitive nested and digital droplet PCR and RNA scope assays failed to detect HIV-1 in blood, spleen, lung, kidney, liver, gut-associated lymphoid tissue and brain. Excision of proviral DNA fragments spanning the LTRs and the Gag gene from the integrated proviral DNA was identified, while no off target effects were observed. The absence of viral rebound following cessation of ART with no progeny virus recovery after in vivo adoptive transfer of human immunocytes from dual-treated virus-free animals to uninfected humanized mice verified HIV-1 eradication by the combined treatment strategy. In contrast, HIV-1 was readily detected in all infected animals treated with LASER ART or CRISPR-Cas9 alone.
Conclusion: CONCLUSIONS: The sequential application of LASER ART and CRISPR-Cas9 therapies administered to HIV-1 infected humanized mice provides the first proof-of-concept that viral sterilization is possible.

354 A HUMANIZED MOUSE MODEL FOR EVALUATION OF AUTOLOGOUS HIV-SPECIFIC T-CELL THERAPIES

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Background: Ex vivo expanded HIV-Specific CD8+ T-cell (HST) immunotherapy offers great promise toward achieving an HIV cure. While plans to test HST therapies in humans are currently underway, a small animal model would enable the rapid and cost-effective pre-clinical evaluation of multiple approaches. We have developed a humanized mouse model reconstituted with only the memory subset of human CD4+ T-cells, which has greatly mitigated the effects of GvHD and allows for the in vivo analysis of autologous HST therapies.
Methods: NSG mice were engrafted with 5-10x106 memory CD4+ T-cells isolated from HIV- or HIV+ donor leukapheresis samples. Autologous HSTs were generated by stimulating T-cells with pools of overlapping Clade B consensus

peptides or peptides representing only conserved viral epitopes. Four to six weeks post humanization, mice were simultaneously infected with JR-CSF and treated with autologous HSTs. Weekly blood samples were analyzed by flow cytometry to measure changes in the human CD4+/CD8+ levels as well as qRT-PCR to measure viral load. Plasma RNA was subsequently sequenced for the presence of viral escape mutations.
Results: Mice engrafted with only the memory CD4+ T-cell subset survived significantly longer than mice engrafted with total CD4+ T-cells and were able to support robust HIV infection sustained out to 20 weeks post engraftment. Daily ARV injections resulted in viral suppression and CD4+ T-cell reconstitution, followed by viral rebound and CD4+ T-cell loss upon ARV cessation. Mice that received autologous HSTs saw significant, transient decreases in plasma viral load compared to the No Treatment group ($p<0.0001$). Sequencing analysis of plasma virus revealed a dominant escape mutation in one mouse in the HST group suggesting immunological pressure. Early results from an additional in vivo experiment demonstrated similar, significant decreases in viral loads with 66% of mice receiving HST therapy reaching an undetectable viral load 4 weeks post therapy initiation.
Conclusion: We have demonstrated that our novel memory CD4+ T-cell humanized mouse model accurately recapitulates many aspects of natural HIV infection while significantly reducing the effects of GvHD. Using this model, we have observed significant decreases in viral load in mice receiving clinically relevant HST products. This platform provides opportunities to assess a variety of immunotherapeutic strategies as well as immunomodulatory approaches in an in vivo, autologous target/effector setting.

355 DIFFERENTIAL EFFECTS OF IL-15 TREATMENT DELIVERED BY DIFFERENT ROUTES IN MACAQUES

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Background: Heterodimeric interleukin-15 (hetIL-15) is a native stable form of the cytokine that activates and expands cytotoxic T and NK cells. We have reported that hetIL-15 treatment delivered subcutaneously in SHIV infected macaques results in significant decrease in viral RNA within peripheral lymph nodes (LN) and plasma viral loads. In this study, we have expanded the analysis of the hetIL-15 effects on virus-specific CD8+ T cells, as well as the general lymphocyte population, in immunized MamuA01+ rhesus macaques treated with hetIL-15 subcutaneously (sc), intraperitoneally (ip), intravenously (iv) and intramuscularly (im).
Methods: Eight DNA-immunized rhesus macaques received injections of hetIL-15 over 2 weeks using increasing doses of cytokine (step-dosing) by four different routes (sc, ip, iv and im). At the end of the treatment, hetIL-15 effects on different lymphocyte populations were monitored by multi-parametric flow cytometry.
Results: All four protocols resulted in systemic expansion of CD8+ T lymphocytes and NK cells with higher granzyme B content. These cells were found in both effector sites, such as liver, vagina and rectum, and secondary lymphoid tissues. A significant increase in cytotoxic effector memory CD8+ T cells was found in lymph nodes from all hetIL-15-treated macaques. CM9 tetramer staining demonstrated that the increase of CD8+ effector T cells in lymphoid organs included actively proliferating SIV-specific T cells with higher granzyme content. Some effects of hetIL-15 treatment were restricted to the specific delivery route. Macaques treated ip showed the highest levels of proliferation in CD8+ lymphocytes obtained from the gastrointestinal tract (duodenum, jejunum, ileum and colon), although the proliferating T cells from the gut did not show any increase in granzyme content.
Conclusion: Step-dose administration of hetIL-15 by four different routes is well-tolerated and results in systemic activation and expansion of virus-specific cytotoxic leukocytes that infiltrate LN and peripheral effector sites. The differences observed between LN and the gastrointestinal tract suggest that tissue-specific homeostatic mechanisms may modulate the response of the tissue-resident lymphocytes to hetIL-15. These results suggest that hetIL-15 could be useful in promoting the entry of cytotoxic T cells into areas of chronic HIV replication and contributing to a functional cure of the infection.

356 GS-9722: FIRST-IN-CLASS EFFECTOR-ENHANCED BROADLY NEUTRALIZING ANTIBODY FOR HIV CURE

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Background: Select broadly neutralizing anti-HIV antibodies (bNAbs) are capable of simultaneously engaging gp120/gp41 on the surface of infected CD4+ T-cells, and Fc-gamma receptors (FcγRs) on the surface of innate immune effector cells. Such bNAbs can kill HIV infected cells and may thus be capable of reducing or eliminating the HIV reservoir. PGT121 is a particularly promising bNAb in this class, having demonstrated potent in-vitro cell killing as well as in-vivo efficacy in SHIV infected monkeys (Borducchi et al. Nature, in press). Here we describe GS-9722, an engineered variant of PGT121 with enhanced effector function and improved drug-like-properties.
Methods: A panel of PGT121 crystallizable-fragment (Fc) mutations was tested in Fc-receptor (FcR) binding assays, primary cell killing assays and preclinical PK studies in order to optimize effector function and PK properties. In parallel with these efforts, in-silico and in-vitro approaches were used to guide the selection of PGT121 antibody binding fragment (Fab) mutations that reduced immunogenic risk and improved drug-like-properties.
Results: The Fc engineering campaign identified mutations that enhanced binding to activating FcγRs as well as the neonatal Fc-receptor (FcRn). The resulting antibody demonstrated significantly enhanced killing of HIV infected CD4+ T-cells by primary natural killer (NK) cells isolated from multiple human donors (mean values: Emax=71%, EC50=0.23 µg/mL) compared to PGT121 (mean values: Emax=11%, EC50=3.4 µg/mL). The Fab engineering campaign identified mutations that removed immunogenic T-cell epitopes, removed glycosylation motifs and improved thermodynamic stability. The Fab mutations had minimal impact on neutralization breadth or potency when tested on a panel of clade B patient isolates (60% at IC95≤15 µg/mL, median IC95=0.18 µg/mL,) compared to PGT121 (58% at IC95≤15 µg/mL, median IC95=0.33 µg/mL). GS-9722 incorporates all mutations identified in the Fc and Fab engineering campaigns and exhibits a pharmacokinetic profile similar to PGT121 in non-human primate studies.
Conclusion: GS-9722 is a first in class effector-enhanced bNAb for the targeted elimination of HIV infected cells and is currently in Ph1b clinical testing. Future studies will explore GS-9722 in combination with additional effector enhanced bNAbs, immune-modulatory agents (i.e. GS-9620), latency reversal agents and therapeutic vaccines in a multi-pronged approach to reduce or eliminate the HIV reservoir.

357 PASSIVE INFUSION OF FC-MODIFIED NAB DOES NOT AFFECT DYNAMICS OF PLASMA VIRUS DECAY

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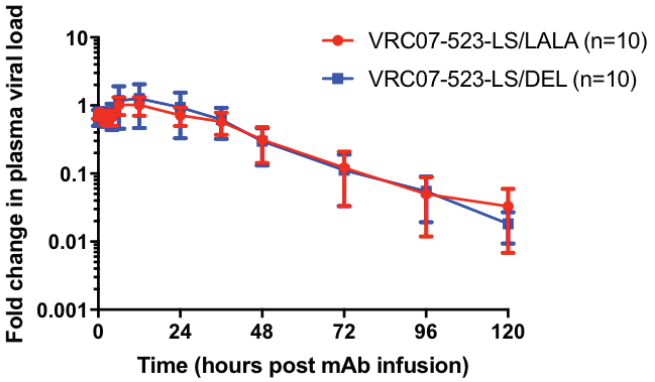
Background: Passive bNAb infusion leads to a reduction of HIV plasma viremia in infected people as well as in SHIV-infected rhesus macaques. Potential mechanisms of viral reduction include neutralization of free virus as well as Fc-dependent effector functions that can clear infected cells. Prior mathematical modeling of plasma virus decline during ART treatment can be applied to passive bNAb therapy to delineate the potential mechanism(s) of action.
Methods: We generated several Fc-variants of the human IgG1 NAb VRC07-523 and characterized them for neutralization, complement binding, ADCC, phagocytosis, and binding to rhesus FcgR and FcRn. All variants contained a two amino acid mutation termed LS, that increased affinity for FcRn. Based on these assays, we down selected two variants - LS-LALA and LS-DEL, that showed knock-out or increase in ADCC and phagocytosis respectively, with complement binding knocked out in both. These mAbs were administered at a single dose of 20 mg/kg i.v. to rhesus macaques chronically infected with SHIV-SF162P3 for 6 weeks (n=10 per group). Animals were followed for rate of plasma virus decay, antibody PK (serum and cell-bound) and viral rebound.
Results: LS-LALA and LS-DEL groups were similar in the following characteristics - 1) plasma virus decay was delayed for 24h after mAb infusion

in both groups 2) between day 2 and day 5, the rate of virus decay remained the same 3) plasma virus decay was independent of FcgRIII genotype. Pharmacokinetic analysis confirmed that during this period, both groups maintained serum antibody titers at ten-fold excess of the in vitro IC80 for SHIV SF162P3 neutralization, with higher serum concentrations for the LS-LALA antibody. Further, unlike the LA-LALA antibody, the LS-DEL antibody was able to engage natural killer cells as well as monocytes in vivo through interactions with FcgR.

Conclusion: Increased or decreased Fc-effector function did not affect the timing or rate of plasma virus decay in vivo, highlighting that initial impact on plasma viremia by passive mAb therapy with VRC07-523-LS is predominantly mediated by virus neutralization rather than ADCC or phagocytosis. Measurements of decay of infected cell load and functionality of mAb-bound cells are ongoing.



358 RELATIONSHIPS BETWEEN NEUTRALIZATION, BINDING AND ADCC OF BNABS AGAINST RESERVOIR HIV

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Background: HIV-specific broadly neutralizing antibodies (bNAbs), may contribute to the elimination of HIV reservoirs by binding to reactivated cells, targeting them for antibody dependent cell-mediated cytotoxicity or phagocytosis (ADCC/ADCP). Harnessing virus neutralization, along with these functions, will provide additional benefit. Few studies have assessed the activities of bNAbs against viruses reactivated from patient-derived reservoirs. The relationships between neutralizing activity, ADCC function and binding to reservoir virus infected primary CD4+ T cells has not been comprehensively studied.

Methods: Quantitative viral outgrowth assays (QVOAs) were performed with CD4+ T cells from participants on long-term ART from a clade B-infected cohort. A panel of 15 bNAbs were tested for binding and ADCC to cells infected with 36 reservoir isolates by flow cytometry, and for neutralizing activity against the same viruses using a TZM-bl assay. ADCC assays were performed with the same viruses, same bNAbs and a haNK cell line (a NantKwest product) as effectors.

Results: Considering all bNAbs together, we observed overall correlations between: ADCC and infected cell binding ($r=0.49$, $p<0.0001$), neutralization IC80 and binding ($r=0.56$, $p<0.0001$), and neutralization IC80 and ADCC ($r=0.46$, $p<0.0001$). At the level of individual antibodies: 7/15 bNAbs showed significant correlations between ADCC and infected cell binding, and 10/14 bNAbs showed significant correlations between neutralization and binding. Despite the overall-correlation, we did not observe statistically significant correlations between ADCC and neutralization IC80 for any individual bNAb. PGT121 and 10-1074 showed broad and potent activity for all functions with 66-67% neutralization of reservoir isolates, 42-47% binding, and >15/36 ADCC. PG9 and PGDM1400 showed 22-36% neutralization with intermediate potency, and 72-75% binding; while CD4 binding site bNAbs displayed broader activity but generally lower potencies. Combinations of CD4bs bnAbs with V3-Glycan / V1/V2 bnAbs, resulted in coverage of up to 100% reservoir isolates for infected cell binding.

Conclusion: We observed substantial heterogeneity in binding, ADCC and neutralization profiles of each bNAb to reactivated reservoir viruses. While we observed overall significant correlations between each of the functions tested, these were not always detected in terms of individual antibodies. Further study of this complexity may help guide the development of polyfunctional bNAb therapeutics.

359 MULTISPECIFIC ANTI-HIV DUOCAR-T CELLS POTENTLY ELIMINATE BNAB-RESISTANT HIV IN VIVO

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Background: Adoptive immunotherapy using chimeric antigen receptor gene-modified T cells (CAR-T) has made significant contributions to the treatment of certain B-cell malignancies. Such treatment modalities also show promise for the development of a single treatment for HIV/AIDS and obviating the need for long-term anti-retroviral drug therapy. We hypothesized that HIV-1 based lentiviral vectors encoding chimeric antigen receptors (CAR) targeting multiple highly conserved sites on the HIV-1 envelope glycoprotein (Env) using a two-molecule CAR architecture, termed duoCAR, would facilitate effectual binding of multiple targeting domains while improving CAR potency, breadth, and resistance to HIV-1 infection.

Methods: To assess CAR functionality, we adapted a previously described neutralization assay that utilizes replication-competent infectious molecular clones of HIV (IMC) encoding different env genes and a Renilla luciferase reporter (Env-IMC-LucR) to allow for sensitive detection of HIV infection in primary cells to monitor the inhibitory activity of different CARs.

Results: We show that transduction with lentiviral vectors encoding multi-specific anti-HIV duoCARs confer primary T cells with the capacity to potently suppress HIV infection in contrast to conventional CAR-T cells while simultaneously protecting them from genetically diverse Env-IMC-LucR viruses in vitro. Furthermore, the genetically modified CAR-T cells also potently suppressed broadly neutralizing antibody (bNAb)-resistant Env-IMC-LucR strains, including a VRC01/3BNC117-resistant virus. Lastly, multi-specific duoCAR-T cells effectively suppressed HIV infection in a humanized intrasplenic NOD/SCID/IL-2Rγ-/- model (hu-spl-PBMC-NSG) infected with VRC01/3BNC117-resistant virus in contrast to control-treated, HIV-infected mice.

Conclusion: We conclude that multi-specific duoCAR-T cells are superior to conventional CAR-T cells and are highly efficacious against broad and bNAb-resistant Env-IMC-LucR viruses in vitro and in vivo, respectively. Collectively, our work represents a powerful and universal multi-targeting HIV-1 immunotherapy that has strong implications for a functional cure.

					Mono	Bispecific		Trispecific		
	HIV-1 Strain	Clade	Geographic Location	VRC01 Neutralization	1944	1946	2303	2323	2329	2330
1	BaL	B	USA	Sensitive	-1.95	-2.20	-2.87	-2.64	-2.66	-2.56
2	NL4-3	B	Clone	Sensitive	-0.73	-1.62	-2.34	-1.75	-3.01	-2.70
3	SF162	B	USA	Sensitive	-1.63	-2.08	-2.77	-2.60	-2.00	-2.03
4	CAP45	C	Malawi/East Africa	Partially Resistant	-2.00	-1.79	-2.66	-1.67	-2.91	-2.49
5	C.Du172.17	C	S. Africa	Resistant	-1.14	-1.26	-1.95	-1.56	-2.05	-2.49
6	C.Du422.1	C	S. Africa	Resistant	-1.24	-1.39	-2.19	-1.46	-2.21	-2.15
7	GX1632_S2_B10	G	Spain/NW Africa	Sensitive	-1.81	-1.77	-2.10	-1.79	-2.28	-2.25
8	AC.246F3	AC	Tanzania/Africa	Sensitive	-1.35	-1.29	-1.93	-1.18	-1.96	-1.87
9	AE.CNE8	AE	S. China/Thailand	Sensitive	-0.73	-1.00	-1.88	-1.20	-1.73	-1.51
10	AE.CNE55	AE	S. China/Thailand	Sensitive	-2.02	-1.59	-2.55	-1.76	-1.71	-1.70
11	BC.CH119.1	BC	China	Partially Resistant	-1.43	-1.30	-1.93	-1.48	-2.09	-2.07

Log Inhibition
< -0.99 log
-1 to -1.49 log
-1.50 to -1.99 log
-2.00 to -2.49 log
-2.50 to -3.00 log

Figure 1. Multi-specific duoCAR-T cells broadly and potently eliminate Env-IMC-LucR infected PBMC. Summary of the *in vitro* HIV-1 killing assays expressed as log inhibition of HIV-1 infection. Log inhibition is calculated relative to HIV-infected untransduced T cells after background subtraction using uninfected PBMCs. The data represents an average of at least three independent donors.

360 LIMITATIONS OF HIV SPECIFIC CAR-T CELLS TO LYSE CELLS BEARING HIV IMMUNE COMPLEXES

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Background: Follicular dendritic cells (FDCs) reside in lymphoid follicles and preserve infectious HIV in the form of immune complexes (ICs) on their cell surface. Given the importance of FDCs in HIV-1 pathogenesis, we questioned whether the novel functional cure strategy of an HIV-specific chimeric antigen receptor (CAR) could be applied to deplete FDCs bearing HIV-ICs. In this study we evaluated the capacity of T cells expressing an anti-HIV bispecific CAR (CD4-MBL, containing extracellular human CD4 D1D2 linked to the carbohydrate binding domain of human mannose binding lectin) to recognize and lyse cells bearing HIV-ICs in vitro.

Methods: HIV-ICs were prepared using a non-neutralizing antibody to gp160 (Chessie13-39.1) and HIV_{IIIB}. HIV-ICs were used to coat FDCs and $CD45^+$ cells isolated from tonsils of HIV-negative patients. Virus infectivity was verified by co-culture with H9 cells for 3 days followed by QPCR of HIV from culture supernatants. CD4-MBL CAR-T cells were mixed with the following CFSE-labeled cells: FDCs ± HIV-IC, the B cell lines BJAB(env-) and TF228.1.16(env+) ± HIV-IC, and control or HIV-infected autologous CD4+T cells at varying effector:target (E:T) ratios. Target cell lysis was measured using a 4-hour CFSE release assay. CAR-T cell activation was quantified using intracellular flow cytometry to detect CD107a.

Results: HIV production by H9 was 14-fold higher when co-cultured with HIV-IC/FDC ($15x10^7$ virus particles/well) compared to HIV-IC/$CD45^+$ cells ($1.1x10^7$ particles/well). However no HIV-specific lysis of FDC/HIV-IC was observed in the CFSE release assay at a 3:1 E:T ratio: FDC (6.8±0.8%), FDC/HIV-IC (7.5±0.2%), while prominent specific lysis of TF228.1.16 (env+, 20.2±0.3%) occurred. Similarly in the activation assay, CD4-MBL CAR-T cells failed to respond to bead/HIV-IC (1.7% $CD107a^+$) compared to bead (1.9% $CD107a^+$), despite prominent response to bead/anti-CD4 mAb (49.1% $CD107a^+$). We also found that CAR-T cells were activated by autologous HIV-infected CD4+ T cells (43.9% $CD107a^+$) but blocked in the presence of mAb to ICAM-1 (11.8% $CD107a^+$).

Conclusion: CD4-MBL CAR-T cells were unable to lyse FDCs bearing infectious HIV-ICs. HIV-ICs failed to induce CAR-T activation. For efficient activation of CAR-T cells, ICAM-1 appeared to be required. Stabilization of cell:cell contact may be necessary for efficient lysis of target cells.

361 BCL-2 INHIBITOR ABT-199 REDUCES RESISTANCE OF HIV RESERVOIRS TO CD8+ T-CELL KILLING

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Background: We have recently reported that latently infected CD4+ T cells may resist CD8+ T cell killing through a presently unknown mechanism. Studies by Cummins et al have reported that CD4+ TCM cells from HIV-infected individuals may resist apoptosis due to increased expression levels of Bcl-2. In cancer settings, Bcl-2 antagonists can sensitize tumors overexpressing Bcl-2 to CD8+ T cell killing. Here, we investigate the ability of the Bcl-2 inhibitor 'ABT-199' to reduce the resistance of latently infected cells to CD8+ T cell killing.

Methods: Reservoir reduction was assessed by 'HIV eradication' (HIVE) assays, where resting CD4+ T cells from ART-suppressed individuals were treated with various combinations of HIV-specific CD8+ T cell effectors, LRAs (bryostatin-1, PMA/Ionomycin, or CD3/CD28 antibodies), and ABT-199. Following treatment, CD4+ T cells were assessed for remaining levels of HIV DNA by ddPCR, and infectious virus (IUPM) by quantitative viral outgrowth assay (QVOA). In "spiked" HIVE assays, a cultured TCM primary cell model of latency was generated with HIV-1 strain NL4-3 and mixed with autologous CD4+ T cells, then treated as above. In all HIVE assays, cell count and viability were monitored by flow cytometry to control for Bcl-2 related toxicity.

Results: In "spiked" HIVE assays lower proportions of QVOA wells contained NL4-3 vs patient-virus in conditions treated with HIV-specific CD8+ T cell effectors, suggesting preferential killing of latency model cells. In HIVE assays from 6 participants, combinations of LRAs and CD8+ T cell effectors led to significant decreases in HIV DNA, but not in IUPM (n=7, p=0.02, p=0.3, respectively). The addition of ABT-199 led to consistent, significant decreases in both HIV DNA (n=6, p=0.03) and IUPM (n=10, p=0.002), with no viral outgrowth observed in QVOAs following three of these HIVE assays. Lastly, combinations of LRAs and ABT-199 did not significantly decrease levels of HIV DNA or IUPM (n=10, p=0.17, p=0.18, respectively).

Conclusion: This study provides further evidence that ex vivo, latently infected CD4+ T cells exhibit a resistance to CD8+ T cell killing that is not seen in primary cell models of latency. ABT-199 is a clinical stage Bcl-2 inhibitor that, in combination with CD8+ T-cells and LRAs, enabled substantial reductions in HIV reservoirs. However, appreciable levels of ABT-199 induced bystander toxicity emphasize the need for further studies into the mechanisms underlying these observations to develop more targeted approaches.

362 BCL-2/XL ANTAGONISTS REDUCE HIV RESERVOIRS FROM IN VITRO MODELS NOT EX VIVO CD4 CELLS

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Background: HIV cure is obstructed by long-lived viral reservoirs. We previously reported that HIV reservoirs in ex vivo patient CD4+ T-cells are resistant to CTL-mediated elimination. CD4+ TCM cells from HIV-infected individuals express elevated levels of the pro-survival protein Bcl-2, which may contribute to this resistance. We tested the abilities of Bcl-2 family antagonists (also known as senolytics) in combination with the LRA bryostatin to eliminate infected cells from a primary cell model of latency and from ex vivo patient CD4+ T-cells.

Methods: Primary CD4+ cell latency models were generated with cells from HIV- donors ('cultured TCM model', Bosque lab). Ex vivo patient CD4+ T-cells were isolated from leukapheresis samples. HIV Eradication assays (HIVE) were conducted by treating cells with senolytics (ABT-199, A-1155463 or A-1331852) alone, or combined with Bryostatin. Cell viability and phenotypes were assessed by flow cytometry. HIV DNA was measured by digital droplet PCR (ddPCR). Inducible replication competent HIV reservoirs were measured by QVOA and expressed as infectious units per million cells (IUPM).

Results: Treatment of cells with the Bcl-2 inhibitor ABT-199 resulted in high levels of non-specific cell death at 1μM, and moderate levels at 100nM. The selective Bcl-xL inhibitors A-1155463 and A-1331852, showed only modest effects on cell viability. Combinations with bryostatin substantially reduced toxicity. Care was taken to standardize IUPM calculations for input of viable cells in each condition. The latency model showed substantial decreases in both HIV DNA and IUPM for both concentrations of ABT-199, and for A-1331852 as single agents (HIV DNA $p<0.0001$; IUPM $p\leq0.03$), and in combinations with bryostatin (HIV DNA $p<0.0001$; IUPM $p<0.01$). In analogous experiments using ex vivo CD4+ T-cells from 6 ARV-treated participants, we did not observe significant decreases in IUPM in any individual, nor across the sample set ($p>0.15$), with similar results for HIV DNA ($p>0.3$).

Conclusion: Our results are consistent with previous reports in demonstrating the elimination of infected cells from latency models with ABT-199, and extend this to Bcl-xL inhibitors. Unexpectedly, combination with an LRA was dispensable for these effects. These latency-model results were not recapitulated in ex vivo patient CD4+ T-cells, where elimination of reservoir-harboring cells was not detected. It is of interest to determine if the addition of CTL to these combinations may result in reservoir reductions.

363 IN VIVO ANTIVIRAL EFFECT OF DASATINIB IN HUMANIZED MICE INFECTED WITH HIV-1

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Background: Dasatinib is a tyrosine kinase inhibitor currently used for treating chronic myeloid leukemia (CML). It has also been shown to interfere with HIV-1 infection in vitro and ex vivo, mostly by the following mechanisms: 1) preserving the antiviral effect of the innate factor SAMHD1; 2) hindering HIV-1 proviral integration and NF-κB-mediated viral transcription in CD4 T cells isolated from patients with CML on treatment; 3) blocking proliferation of CD4 T cells induced by TCR-mediated stimulus or homeostatic cytokines such as IL-2 and IL-7. In this

work we assessed the in vivo antiviral effect of dasatinib using humanized mice infected with HIV-1.
Methods: Human CD34+ hematopoietic stem cell-engrafted NSG mice (hu-CD34) were treated for 5 days with dasatinib 20mg/kg/day (n=5) or with placebo (citrate buffer solution) (n=5). Then, all mice were intraperitoneally injected with purified HIV-1NL4-3 (17,500 TCID50) and treated for 21 days with dasatinib or placebo, in the absence of antiretroviral treatment (ART).
Results: 1) Viral load in hu-CD34 mice treated with dasatinib was 4.7-, 3.8- and 3.5-fold lower than the placebo group after 7, 15 and 21 days of infection, respectively. Two mice from dasatinib group persistently showed undetectable viral load. 2) Proviral load in blood of mice treated with dasatinib remained 1.6-, 4.6- and 2.2-fold lower than the placebo group after 7, 15 and 21 days post-infection, respectively. 3) Proviral load in GALT was 3.0-fold smaller at 21 days post-infection in the dasatinib-treated group. 4) Treatment with dasatinib affected the distribution of CD4 and CD8 subpopulations: CD4 and CD8 TCM cells were respectively 2.0- and 2.7-fold lower than the placebo group; CD4 and CD8 TEM cells were 4.0- and 6.3-fold lower; CD4 and CD8 TEMRA cells were 1.5- and 3.5-fold lower; whereas CD4 and CD8 naïve T cells were 1.5- and 1.4-fold higher.
Conclusion: Daily oral treatment with dasatinib in the absence of ART interfered with HIV-1 acute infection in hu-CD34 mice. Dasatinib reduced viral load and proviral reservoir size in blood and GALT, and modified the distribution of CD4 and CD8 subpopulations. This study is the first proof of concept that dasatinib decreases HIV-1 reservoir in vivo, supporting the use of dasatinib in combination with ART to reduce the reservoir size, particularly in patients with acute infection.

364 A BACTERIOPHAGE T4 NANOPARTICLE PLATFORM FOR TARGETED CURATIVE THERAPY AGAINST HIV-1

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Background: Persistent latent reservoir of CD4+ T cells containing stably integrated and transcriptionally silent form of HIV-1 provirus is a major barrier to cure HIV. An effective curative approach would be to activate the latent reservoir and selectively disrupt the proviral genome as well as elicit immune responses to neutralize any remaining viruses. We hypothesize that the 120 x 86 nm bacteriophage T4 capsid (head) nanoparticle carrying a combination of HIV cure molecules; proteins, DNAs, and RNAs can be targeted to CD4+ T cells for delivery and cure. About 170 kb DNA can be packaged inside the capsid and ~1025 proteins fused to the outer capsid proteins Soc (small outer capsid protein, 870 copies) and Hoc (highly antigenic outer capsid protein, 155 copies) can be displayed on the capsid surface.
Methods: Empty phage T4 capsids are purified from E.coli infected with mutant phage that lacks tail, neck, and outer capsid proteins. The DNA packaging motor (gp17) is attached to the portal vertex of the capsid. Packaging is carried out by adding plasmid DNAs containing Cas9 and/or gRNAs and ATP. The packaged heads are displayed with combinations of proteins; HIV envelope protein or the CD4 binding DARPin fused to Soc or Hoc and Soc-Cas9/gRNA complex.
Results: HIV cure T4 nanoparticles were assembled by packaging 7-8 molecules of 6-8 kb LTR-gRNA-Cas9 plasmid DNA inside and displaying ~150 gRNA-Cas9-Soc complexes and 155 molecules of CD4DARPin-Hoc or 30 envelope trimers from a transmitted founder virus. These in vitro assembled HIV Cure T4 nanoparticles bound specifically to CD4+ T cells (A3.01) and disrupted HIV-1 provirus integrated into HEK 293T cells, as determined by T7 EI assay. Unexpectedly, the T4 nanoparticles also activated J-Lat 10.6 full length cells (P value =0.0024, t-test) and the activation was dependent on the displayed targeting ligand specific to CD4 receptor. Experiments are underway to determine if the T4 nanoparticles can deliver cargo into these activated J-Lat cells and disrupt the proviral genome.
Conclusion: The phage T4 nanoparticle is a unique and powerful vehicle for delivery of complex cargos into mammalian cells. This study shows proof-of-principle data on targeting to CD4+ cells, provirus disruption, and activation of the latent J-Lat T cells. With its large capacity and engineering flexibility to deliver complex cargos, the T4 nanoparticle system has the potential to be an effective platform for targeted HIV-1 cure

365 DISTINCT VULNERABILITY OF VIRAL RESERVOIR CELLS TO NK CELL-MEDIATED IMMUNE EFFECTS

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Background: Potent antiretroviral therapy leads to suppression of HIV-1 replication but is associated with establishment of a stable reservoir of latently-infected cells that can fuel rebound viremia upon treatment discontinuation. Innate cellular immune responses mediated by NK cells have been inversely associated with reductions in viral reservoir size during antiretroviral therapy, suggesting that latently-infected CD4 T cells may be susceptible to NK cell-mediated immune effects.
Methods: Primary CD4 T cells were activated and in vitro infected with a dual-reporter virus allowing us to distinguish cells with productive or latent HIV-1 infection, followed by flow cytometry-based analysis of NK cell receptor ligands; moreover, the same analysis was performed in primary CD4 T cells from ART-treated patients. Single-cell RNA-Seq analysis of in vitro, latently infected cells was performed and compared to the transcriptome of productively infected and uninfected cells. The susceptibility of latently infected CD4 T cells to NK cell-mediated killing was analyzed using functional cytotoxicity assays.
Results: In vitro, latently infected CD4 T cells expressed significantly higher levels of the activating NK cell ligand ULBP1, and were significantly enriched for a population of cells simultaneously expressing a combination of the three NKG2D ligands ULBP1, MICA and MICB. Upregulation of these molecules was associated with transcriptional activation of the ATM DNA damage response pathway. Functional assays demonstrated an increased susceptibility of latently-infected CD4 T cells to NK cell-mediated killing; this vulnerability to cytotoxic immune effects of NK cells was most obvious in latently-infected CD4 T cells expressing ULBP1, MICA and MICB, and was abrogated by antibodies directed against NKG2D. An upregulation of NKG2D ligands was also observed in patient-derived CD4 T cells from ART-treated patients, and denoted a subset of CD4 T cells characterized by increased expression of immune checkpoint and activation markers.
Conclusion: Latently-infected CD4 T cells seem to express a distinct signature of activating NK cell receptors, likely in response to activation of DNA damage response signals that may result from viral latency. Expression of activating NK cell receptors on latently-infected CD4 T cells can increase the susceptibility to NK cell killing, and may represent a distinct vulnerability of the viral reservoir that provides novel targets for therapeutic viral eradication studies.

366 WITHDRAWN / INTENTIONALLY UNASSIGNED

367 WITHDRAWN / INTENTIONALLY UNASSIGNED

368 INDUCIBILITY OF LATENT HIV-1 IN RESTING CD4+ MEMORY T-CELL SUBSETS

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Background: The latent reservoir for HIV-1 is comprised mainly of resting memory CD4+ T cells that harbor integrated replication-competent proviruses that are not actively transcribed. Recent work indicated that the proliferation of infected cells is a major factor in the generation and stability of the latent reservoir. Several groups have shown that latently infected cells that clonally expand in vivo can be activated in vitro without producing virus. One hypothesis to explain this observation is that certain subpopulations of reservoir cells, such as particular CD4+ memory subsets, are predisposed to delay reactivation of the latent virus or promote a deeper state of latency. To evaluate this possibility, we studied resting naïve, central memory, transitional memory, and effector memory CD4+ T cells from 10 ART-suppressed HIV patients in a multiple stimulation viral outgrowth assay (MSVOA).
Methods: Culture readouts were measured by p24 ELISA. Flow cytometry was used to track CCR7 and CD27 expression throughout the culture. A droplet-digital-PCR (ddPCR)-based assay developed in our lab was performed on each

sorted subset to quantify the copy numbers of intact proviruses. Viral RNA from culture wells was sequenced to assess the clonality of the subset cells.
Results: The frequencies of viral outgrowth calculated from p24 ELISAs were compared to the frequencies of intact proviral DNA copies we calculated, allowing us to estimate that on average only 3% of intact proviruses can be induced by multiple rounds of global T-cell activation. Each memory subset contained similar numbers of copies of intact proviruses per million cells. We observed different levels of viral outgrowth from different subsets at different stimulation timepoints, indicating significant patient-to-patient variability and no trend in viral inducibility from each subset.
Conclusion: In this study, we investigated different resting CD4+ T cell subsets and their relationships with proviral integration and expression. We observed no enrichment of intact proviruses in any specific subset nor any correlation between the inducibility of intact proviruses and memory subset phenotype. Furthermore, we observed significant plasticity among the canonical defining memory subset surface markers and saw significant patient-to-patient variability that abrogated any potential trend seen between subset and inducibility and complicates the vision for a targeted cure approach based on T-cell subsets.

369 PKC AGONIST EXPOSURE SUFFICIENT TO ACTIVATE T CELLS IN VIVO ALSO CAUSES COAGULOPATHY

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Background: Activation of latent HIV reservoir is part of a strategy for HIV cure as it should enable the elimination of infected cells by immune-mediated clearance mechanisms and facilitate long-term remission or cure. Protein kinase C (PKC) agonists are highly effective at activating latent HIV. However, effective use of PKC agonists is limited by their severe toxicity, with a mechanism not clearly elucidated.
Methods: A novel small-molecule PKC agonist, C-232A, was identified and characterized in vitro and in vivo. PKC activation was assessed by fluorescent microscopy of GFP-labeled PKC in A549 cells. Resting CD4 T cells from ART-suppressed HIV-infected donors were treated with C-232A and HIV RNA in culture supernatants was assessed by qPCR. Flow cytometry was used to quantify CD62P on platelets and CD69 on T cells in whole blood. Dose escalation studies were performed in both rats and rhesus macaques. Activation markers and cytokines were measured by flow cytometry, quantitative PCR and multiplex immunoassay. Investigational toxicology endpoints were assessed, including hematology, coagulation and anatomic pathology.
Results: C-232A induced PKC translocation from the cytoplasm to cellular membranes, consistent with PKC agonist activity. HIV transcription was activated ex vivo to the same magnitude as seen with prostratin, but with 5-fold higher potency. IV infusion of C-232A in rhesus macaques induced dose dependent expression of CD69 on T cells. However, similar to other PKC agonists, dose levels sufficient to activate >50% of T cells in vivo also caused a rapid onset of moribundity in treated animals. Toxicity was mediated by platelet activation and ultimately manifested in disseminated intravascular coagulation, a lethal coagulopathy marked by consumption of clotting factors, thrombus formation and hemorrhage. Using a whole blood in vitro assay, dose-dependent platelet activation has been observed across multiple chemical series of PKC agonists at doses similar to those that activate T cells. Consistent with this data, expression of several PKC isoforms has been confirmed in platelets.
Conclusion: Platelet activation is a critical safety liability associated with PKC agonists and should be carefully monitored in any preclinical or clinical studies. In addition, the developed in vitro screening tools should facilitate structure-based design of novel PKC agonists with improved activity in T cells and minimal platelet activation.

370 ACTIVATION OF HIV-SPECIFIC CD8+ T CELLS FROM HIV+ DONORS BY VESATOLIMOD

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Background: Vesatolimod (GS-9620) is a Toll Like Receptor 7 (TLR7) agonist that directly activates human pDCs, B lymphocytes, and induces the production of cytokines such as type I interferon. GS-9620 is currently being evaluated in HIV-1 infected participants as part of an HIV remission strategy. Here we investigated the potential of GS-9620 to trigger indirect activation of HIV-specific CD8 T cells, using immune cell cultures derived from HIV+ donors.
Methods: Peripheral blood mononuclear cell (PBMC) cultures derived from HIV+ donors virologically suppressed on stable antiretroviral therapy (n=39) were profiled. PBMCs were collected by leukapheresis, separated by Ficoll centrifugation, and treated with GS-9620 (20 and 1000 nM) or vehicle alone for 24 hours. HIV pentamers (Proimmune) composed of five MHC Class I peptide-complexes were used to detect CD8 T cell HIV specificity. Pentamers were selected according to donors' HLA type(s). Cells were incubated with HIV specific pentamers, surface stained with anti-CD3, CD4, CD8, CD69 fluorescent conjugated antibodies, stained intracellularly with anti-CD107a, TNF-α, and IFN-γ fluorescent conjugated antibodies, and analyzed by flow cytometry (FACS). Donors with GS-9620 activated HIV-specific CD8 T cells were scored as positive using a cut-off of 0.5% Pentamer binding.
Results: In vitro treatment of PBMCs with GS-9620 resulted in all 39 donor cultures demonstrating an increase in CD8+ T cell activation of up to 80% as measured by CD69 expression compared to no treatment. Of these, 17/39 donors showed HIV-specific CD8+ T cell activation with 5/17 donors positive at 20 nM, and 17/17 donors positive at 1000 nM GS-9620. Intracellular staining was done in a subset of donors (n=13), resulting in 4 donors showing HIV-specificity, 2 of which were positive for degranulation (CD107a), 3 positive for TNF-α, and none positive for IFN-γ.
Conclusion: Vesatolimod treatment of HIV+ donor derived PBMCs resulted in robust activation of CD8+ T cells as demonstrated by expression of the activation marker CD69. Furthermore, HIV-specific CD8+ T cell activation was observed in approximately half of the donors tested, with 3 of the donors' CD8 T cells also up-regulating expression of CD107a and/or TNF- α. These data support the in vivo potential of Vesatolimod to induce HIV-specific CD8 mediated killing of latently infected cells as part of an HIV remission strategy.

371 DEBIO 1143 IS AN ATTRACTIVE HIV-1 LATENCY REVERSAL CANDIDATE

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Background: Antiretroviral therapy (ART) suppresses HIV replication, but does not cure the infection because replication-competent virus persists within latently infected CD4+ T cells throughout years of therapy. These reservoirs contain integrated HIV-1 genomes and can replenish active virus. Thus, the development of strategies to eliminate the reservoir of latently infected cells is a research priority of global significance.
Methods: We tested the ability of a new inhibitor of apoptosis protein antagonist (IAPa) called Debio 1143 (D1143) at reversing HIV latency and investigated its mechanisms of action.
Results: D1143 activates HIV transcription via NF-kB signaling by degrading the ubiquitin ligase baculoviral IAP repeat-containing 2 (BIRC2), a repressor of the non-canonical NF-kB pathway. D1143-induced BIRC2 degradation results in the accumulation of NF-κB-inducing kinase (NIK) and proteolytic cleavage of p100 into p52, leading to nuclear translocation of p52 and RELB. D1143 greatly enhances the binding of RELB to the HIV-1 LTR. These data indicate that D1143 activates the noncanonical NF-kB signaling pathway by promoting the binding of RELB:p52 complexes to the HIV-1 LTR, resulting in the activation of the LTR-dependent HIV-1 transcription. Importantly, D1143 reverses viral latency in HIV-1 latent T cell lines. Using knockdown (siRNA BIRC2), knockout (CRIPSR NIK) and proteasome machinery neutralization (MG132) approaches, we found that D1143-mediated HIV latency reversal is BIRC2 degradation- and NIK stabilization-dependent. D1143 also reverses HIV-1 latency in resting CD4+ T cells derived from ART-treated patients or HIV-1-infected humanized mice under ART. D1143 has been tested as cancer therapy in various human clinical trials. Interestingly, daily oral administration of D1143 in cancer patients at well-tolerated doses elicited pharmacodynamic effects on BIRC2 in PBMCs and induced a moderate increase in cytokine and chemokine that are mechanistically related to NF-kB signaling modulation.
Conclusion: We provide strong evidence that the IAPa D1143, by initially activating the noncanonical NF-kB signaling and subsequently reactivating HIV-1 transcription, represents a new and attractive viral latency reversal agent.

372 HIV-1 PROVIRAL CLONE-SPECIFIC DIFFERENCES IN RESPONSE TO LATENCY REVERSING AGENTS

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Background: Latent HIV-1 infections are a major obstacle to an HIV-1 cure, and efforts are ongoing to understand and develop strategies to eliminate this reservoir. One of these strategies is the "shock and kill" approach, where virus expression is induced by latency reversing agents (LRAs), allowing infected cells to either expose themselves for clearance. Some studies have shown inconsistency in the potency of LRAs using different models of HIV-1 latency. Since HIV-1 integrates quasi-randomly into active genes, it seems likely that proviruses might be subject to locus-specific gene regulation. Hence, different classes of LRAs may have differential effects on proviral-clones' response.
Methods: Here, we infected Jurkat cells with an Env-Vpr-PuroR virus harboring gfp in the nef ORF to generate a polyclonal proviral pool, with proviruses marked with "zipcodes"-sequence tags within viral sequences that identify clonal progeny of individual integration events. The GFP negative subpopulation was FACS-sorted and treated with different classes of LRAs. Latency reactivation was quantified by the frequency of GFP positive cells, and the total amount of virus released. We also determined the extent of reactivation per proviral clone by quantifying the zipcodes in released virion RNA by high-throughput sequencing for each LRA treatment.
Results: Our results suggest that only a fraction of the proviral clones were reactivated by any tested LRA, and clones responded to LRAs to differing extents. Some clones were unique to specific LRAs, with similar classes of LRAs reactivating similar proviral clones. Clonal analysis of the class I-specific histone deacetylase inhibitor (HDACi), entinostat and pan HDACi, SAHA treatments revealed proviral clones that were only reactivatable by SAHA but not entinostat, suggesting HDACs other than class I may play a role in HIV latency. Characterizing individual cell clones revealed differences from the total population's behavior. For example, while one LRA combination showed additive reactivation when monitored by total virion release in this pool, clonal analysis revealed that a few proviral clones were reactivated to greater extents than they were by one LRA, while other clones' expression appeared to be reduced by dual LRA
Conclusion: The total levels of reactivation can misrepresent the clonal behavior of a latent pool in response to different LRA classes, and mechanisms that act to reactivate one clone may act to silence another.

373 HIV-2 DYNAMICS DURING LATENCY REVERSAL

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Background: HIV-2 infection is associated with lower plasma virus loads and slower disease progression when compared to HIV-1 infection. Prior work has suggested that, in viremic participants, levels of total viral DNA are similar between HIV-1 and HIV-2 infection but HIV-2 cell-associated RNA (caRNA) levels may be lower. We hypothesized that this difference may extend to virus latency during treated infection and investigated the effects of latency reversal agents (LRAs) on HIV-2 reactivation.
Methods: We recruited participants with HIV-1 or HIV-2 infection and isolated PBMCs from whole blood. Blood draw volumes precluded the isolation of pure resting CD4+ T cell populations. Reversal of HIV latency was measured ex vivo following 24- or 48-hour exposures to a panel of LRAs with different mechanisms of action: bryostatin 10nM, romidepsin 20nM (RMD), the TLR7 agonist GS-9620 100nM, PMA/ionomycin, and anti-CD3/anti-CD28 beads (1:1 ratio). Total HIV DNA, cell-associated RNA (caRNA), and supernatant viremia levels were determined by validated real-time quantitative PCR (qPCR) assays. Results were normalized for input HIV DNA copy number.
Results: While HIV caRNA/DNA ratios were consistently lower for HIV-2 reactivation (3.2 – 11.6, HIV-2; 5.3 – 54.1, HIV-1) for the LRA conditions we tested after 24 and 48 hours of drug exposure, no statistically significant differences were observed in HIV caRNA levels between HIV-1 and HIV-2. Interestingly, levels of supernatant viremia were significantly lower during HIV-2 reactivation, when compared to HIV-1. HIV-2 supernatant viremia levels at 24 hours, corrected for HIV DNA input, were 39-, 77-, 10-, 152-, and 117-fold lower after bryostatin, RMD, GD-9620, PMA/ionomycin, and anti-CD3/anti-CD28 beads treatment, respectively. These differences persisted at 48 hours.
Conclusion: Latency reversal agents reactivate virus transcription in HIV-2 infection. Whereas levels of HIV-1 and -2 caRNA were similar during latency reversal, when normalized to HIV DNA copy number, statistically significantly less supernatant virus RNA was produced during HIV-2 latency reversal. This suggests that a post-transcriptional block may affect the ability of HIV-2 to produce virions during reactivation from latency.

374 VPU CONTROLS HIV-1 LATENCY THROUGH MODULATION OF THE NF-κB PATHWAY

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Background: The long-lived and persistent latent viral reservoir in memory T cells represents one of the main obstacles for an HIV-1 cure. Novel therapies that aim at purging the HIV-1 reservoir using latency reversal agents (LRAs), targeting cellular host proteins, have limited effects in vivo and can induce severe side effects, emphasizing the need for alternative approaches to reverse HIV-1 latency. Accessory HIV-1 proteins play an important role in optimizing viral replication, enabling HIV-1 to evade host restriction and immunity, but their role in regulating HIV-1 latency remains largely unknown.
Methods: CRISPR/Cas9 knockout was used to disrupt the accessory HIV-1 genes vpu, nef and vif in the latently HIV-1-infected J89 T cell line. The proportion of HIV-1-GFP+ (i.e. HIV-1 reactivated) cells was traced using flow cytometry and immunofluorescence microscopy. We re-introduced 89.6 Vpu protein and vpu/vpuR45K DNA in J89Δvpu cells using Cell Squeeze® and Amaxa® Cell Line Nucleofector® Kit V technologies, respectively. NK-κB pathway activity was quantified using a dual luciferase reporter assay and ImageStreamX Mark II Imaging Flow Cytometer technique.
Results: Our data showed that J89Δvpu cells completely lost control over viral latency, while knockout of nef and vif had no impact. Re-introduction of Vpu protein alone restored HIV-1 latency in a median of 55% of J89Δvpu cells. The proportion of latently HIV-1-infected (HIV-1-GFP-) cells significantly inversely correlated with the proportion of Vpu-FLAG+ J89Δvpu cells. Furthermore, Vpu-FLAG+ J89Δvpu cells showed reduced tetherin surface levels, demonstrating functionality of the Vpu-FLAG protein. As Vpu has been reported to suppress the NF-κB pathway, we measured NF-κB p65 nuclear translocation and observed that J89Δvpu cells showed higher NF-κB activation levels than parental J89 cells. Introduction of vpuR45K, encoding a Vpu mutant that selectively fails to inhibit NF-κB activation, did not affect HIV-1 gene expression in J89Δvpu cells, while re-introduction of wild-type vpu restored HIV-1 latency, indicating a critical role of the NF-κB pathway.
Conclusion: These data identified Vpu as a viral protein involved in the maintenance of HIV-1 latency through a modulation of the NF-κB pathway, and provides strong rationale to screen for novel Vpu inhibitors as potential HIV-1 LRAs.

375 FORMATION OF THE REPLICATION-COMPETENT HIV-1 RESERVOIR COINCIDES WITH ART INITIATION

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Background: Although antiretroviral therapy (ART) is highly effective at suppressing HIV-1 replication, the virus persists in a latent reservoir during therapy. The HIV-1 reservoir is present in all HIV-infected people, even when ART is initiated soon after infection, suggesting that it forms early and persists despite long-term viral suppression.
Methods: We investigated the temporal origins of the long-lived reservoir in 10 women from the CAPRISA 002 acute infection cohort who initiated treatment in chronic infection. After a median of 4.5 yrs of untreated infection, nine of

these women initiated ART and were well suppressed for a median of 4.9 yrs. Plasma-derived virus was sequenced on average every six months from acute/early infection to ART. These evolving sequences were compared to sequences of replication-competent reservoir viruses grown out of the latent reservoir. We used this same approach to analyse the viral reservoir in one woman for whom treatment initially failed. Illumina MiSeq with Primer ID was used to sequence partial env, gag and nef genes from pre-ART time points and PacBio sequencing was used to generate nearly full-length genome sequences of outgrowth viruses. The relatedness of reservoir and pre-ART viruses was evaluated using approximate maximum-likelihood analyses with phylogenetic placement.
Results: Reservoir viruses (mean = 16; range 6-48) were sequenced from the 10 women. In the nine individuals on long-term suppressive ART, a median of 78% of reservoir viruses were most similar genetically to viruses circulating in the year before ART. We expand on this initial result by examining reservoir formation in an individual who experienced treatment failure but was virologically suppressed after ART optimization. In this individual, the reservoir contained a high percentage of variants from the time when she initiated her first and second ART regimen.
Conclusion: In a cohort of nine well-suppressed women we observed that the vast majority of the persistent, replication-competent reservoir was established near the time of ART initiation. Analysis of one individual who experienced treatment failure suggests that variants may be seeded into the reservoir each time that an individual initiates therapy with a subsequent reduction in viral load. These observations suggest new strategies for reducing the size of the latent reservoir through viral clearance of variants circulating late in untreated infection.

376 TCR-ACTIVATED CD8+ T CELLS PROMOTE THE ESTABLISHMENT OF HIV LATENCY IN CD4+ T CELLS

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Background: Virus persistence in latently-infected CD4+ T cells despite ART is the major barrier to cure HIV infection. While HIV-specific cytotoxic T lymphocytes are known to control virus replication, recent studies showed that CD8+ T cells may also suppress SIV transcription in ART-treated macaques. Identifying the mechanisms responsible for CD8+ T cell-mediated HIV silencing might reveal molecular targets to disrupt the establishment and maintenance of the HIV reservoir.
Methods: CD4+ and CD8+ T cells were isolated from healthy donors, separately labeled with CellTrace Violet and CellTrace Red, and activated by TCR stimulation. CD4+ T cells were infected with an HIV reporter virus expressing eGFP under HIV-LTR control and CD8+ T cells were added for co-culture. Expression of activation markers (HLA-DR, HLA-ABC, and HLA-E), cell survival and cell proliferation were measured by flow cytometry. The non-productively-infected (eGFP-) CD4+ T-cell population from mono- or co-culture were sorted and the inducible HIV reservoir was quantified by measuring eGFP expression 24h post reactivation.
Results: CD8+ T cells significantly suppressed eGFP expression in infected CD4+ T cells during co-culture as compared to CD4+ T cells cultured alone, under multiple-round and single-cycle infection conditions (mean 57%, p=0.0078, n=8, and mean 14%, p=0.0001, n=14, respectively). This observation suggests that CD8+ T cells not only inhibit virus spread but also suppress LTR-dependent viral transcription. Concomitantly, the suppressor activity of CD8+ T cells resulted in a 25% reduction of cell proliferation in the eGFP-CD4+ T cell population (mean fold change in CellTrace Violet MFI compared to CD4+ T cells alone, p=0.0009, n=14). Moreover, CD8+ T cells mitigated virus-induced cell death thus increasing CD4+ T cell survival (mean 10% increase in live CD4+T cells, p=0.0078, n=8) and down-modulated the expression of activation markers on both productively infected (eGFP+) and eGFP-CD4+T cells. Finally, CD8+ T cells increased the inducible HIV reservoir in CD4+ T cells by 62%, as shown by reactivation of sorted eGFP- CD4+ T cells from co-culture with CD8+ T cells as compared to CD4+ T cells from mono-culture (p=0.0078, n=8).
Conclusion: TCR-activated CD8+ T cells from HIV uninfected donors reduce virus production by autologous in vitro HIV-infected CD4+ T cells by mitigating their level of cell activation and proliferation, and ultimately facilitate the transition of these CD4+ T cells into latent HIV infection.

377 METHYLATION PROFILES OF HIV-1 PROVIRAL DNA IN ART-SUPPRESSED INDIVIDUALS

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Background: The latent HIV-1 reservoir is populated with clones of cells infected with stably integrated, intact, but transcriptionally-silent proviruses. Previously, we described the integration site of one such clone harboring a replication-competent provirus called AMBI-1. We hypothesized that the silencing of HIV-1 gene expression from this and other clones was due to DNA methylation of the 5'LTR promoter. To address this question, we investigated methylation at the single-proviral level in known CpG islands in the HIV-1 proviral genome, including one in the 5' LTR promotor region.
Methods: Using a bisulfite-based, methylation-specific single-genome-sequencing (SGS) assay, we measured the levels of methylation in CpG islands from ART-suppressed, chronically-infected individuals with samples from PBMC and lymph node mononuclear cells (LNMC) (including the donor with the AMBI-1 clone).
Results: From 4 individuals an average of 30 (range: 13 to 91) bisulfite-treated SGS were obtained from each PBMC and LNMC sample. We found no significant difference in any provirus between the level of methylation of the CpG island in the 5' LTR promoter and the assay background of cytosines not in CpG sites (averaging 3.8% and 3.3% respectively p=0.9). Furthermore, the presumed AMBI-1 provirus (matching LTR sequence) was not found to be methylated above assay background. Interestingly, we did find a significantly higher level of methylation in the CpG island in the env-tat-rev overlapping reading frame in multiple proviruses in each of the samples [averaging 21% of all CpG sites methylated vs. an average of 6% assay background (p=0.03)]. In each PBMC and LNMC sample, 78% of genomes were methylated at >1 CpG site in the env-tat-rev island and 46% were methylated at ≥3 CpG sites.
Conclusion: Surprisingly, we did not find evidence that methylation of the 5'LTR promotor maintains HIV-1 latency in vivo, including LTRs of proviruses that are known to be intact and latent. Significant levels of methylation were found in a CpG island in env but its role, if any, in transcriptional silencing is unknown. Since it is well known that methylation of transcriptional enhancers located many kilobases from mRNA start sites can result in gene silencing, it is important to determine if the identified methylated CpG island in the env gene has any function in HIV-1 latency in vivo.

378 THE HIV ANTISENSE TRANSCRIPT AST INDUCES VIRAL LATENCY VIA SEVERAL SILENCING PATHWAYS

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Background: We have reported that an antisense transcript (Ast) expressed from a promoter located in the HIV-1 3'LTR induces the establishment and maintenance of HIV-1 latency. We have shown that Ast recruits the Polycomb Repressor Complex 2 (PRC2) to the HIV-1 5'LTR. PRC2 catalyzes trimethylation of lysine 27 on histone H3 (H3K27me3), an epigenetic mark that leads to nucleosome assembly and transcriptional silencing.
Methods: Ast mutants were tested after stable transduction in Jurkat E4 cells. To identify new binding partners, Ast was fused to a streptavidin-binding RNA aptamer, expressed in 293 cells, affinity-purified by streptavidin, and binding proteins identified by mass spectrometry (MS). To identify Ast modifications, Ast was affinity-purified via complementary biotinylated oligos and streptavidin, enzymatically digested and analyzed by MS.
Results: To identify the functional domains of Ast, we divided the transcript into 5 segments and produced substitution and deletion mutants. A 376-nt segment at the 5' end of Ast (5AST, mapping in the U3 region of the 3'LTR) mediates binding of Ast to the U3 region in the proviral 5'LTR via sequence homology. We divided the Ast sequence downstream of 5AST into four segments (A through D), and generated a substitution mutant for each of them. Mutation of segment A or B impacted significantly Ast function. Indeed,

mutation of 70nt within segment B containing a possible PRC2-binding motif greatly reduced Ast activity. Mutation of either segment C or D did not have a major effect, whereas concurrent mutation or deletion of both segments did. This suggests that segments C and D cooperatively recruit additional factors. Indeed, MS studies found that Ast interacts with additional transcription and epigenetic repressors such as NuRD, CTCF, YY1, TDP-43. Cell lysate fractionation through a sizing column showed that Ast purifies in high molecular weight fractions of ~2MDa that also contain Ast binding partners. We also found that Ast interacts with members of the C/D box and H/ACA box complexes, which catalyze RNA ribose methylation and pseudouridylation. Indeed, MS analysis of affinity-purified Ast showed that it contains these post-transcriptional modifications in vivo.

Conclusion: We identified the PRC2-binding motif of Ast, and showed that Ast binds other transcription repressors. We also found that Ast carries modifications affecting its stability and interaction with protein partners. Our studies suggest that Ast induces HIV-1 latency via multiple pathways.

379 TARGETING SPHINGOSINE-1-PHOSPHATE TO PREVENT LATENT HIV INFECTION

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Background: Sphingosine-1-phosphate (S1P) is an established modulator of cell cycle and chemotaxis and the therapeutic targeting of this pathway has been the subject of investigation for the treatment of multiple sclerosis and other autoimmune diseases. In the context of Human Immunodeficiency Virus 1 (HIV-1) infection, alterations in the expression of S1P receptor 1 in thymocytes as well as impaired S1P signaling in CD4+ T cells have been described. Recently agonists of the S1P receptor 1 have been shown to reverse HIV latency. Here, we sought to determine the role of the S1P in the establishment of latent HIV infection.

Methods: We examined whether targeting Sphingosine Kinase (SPK) would alter the establishment of the latent reservoir in memory CD4+ T cells using a primary cell model. Briefly, we isolated naïve human CD4+ T cells from HIV-negative donors, activated and expanded them, and infected them with NL4-3 virus by spin infection. Three days later, cells were treated with either N,N-dimethyl sphingosine (D.M.S.), a SPK inhibitor; or FTY720, a S1P receptor modulator. We quantified the effects of these inhibitors on latent infection by measuring the frequency of cells harboring total and integrated HIV DNA by qPCR and the ability to reactivate virus from latency following T cell receptor stimulation by intracellular HIV Gag.

Results: Treatment with D.M.S. reduced the establishment of latent HIV infection in a dose dependent manner as measured by the frequency of cells producing HIV Gag upon T cell receptor stimulation (6 µM n=9, 95% reduction, p=0.0067; 600 nM n=8, 38% reduction, p=0.0236; 60 nM n=5, 23.3% reduction, p=0.2). Moreover, FTY720, which is used in the clinical setting for the treatment of multiple sclerosis, recapitulated this effect (100nM n=7, 70% reduction, p=0.0425). These inhibitors reduced latent infection during or before reverse transcription since the treatments reduced to a similar extent both total (D.M.S. 600 nM n=4, 34% reduction; FTY720 100nM n=4, 52% reduction) and integrated HIV DNA (D.M.S. 600 nM n=4, 29.5% reduction; FTY720 100nM n=4, 57% reduction).

Conclusion: Our results show that targeting S1P has an effect on latent infection. Mechanistically, D.M.S. and FTY720 force CD4+ T cells into a G0 state of the cell cycle as measured by expression of Ki67. Our research suggests that the therapeutic targeting of this pathway early in infection may aid in the development of strategies to promote a functional cure by preventing the establishment of the latent reservoir.

380 RESIDUAL VIREMIA IS DOMINATED BY MONOTYPIC VIRUS RESULTING IN INFECTIOUS PLASMA VIRUS

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Background: During suppressive antiretroviral therapy (ART), 1-10 copies of residual viremia (RV) can often be detected per milliliter of plasma in HIV-infected individuals. Several studies have shown monotypic (clonal) viral sequences predominate in the RV of suppressed individuals. It is unclear whether specific variants are selectively maintained over time and if they are infectious. We evaluated 3 individuals who were chronically-infected at the time ART was initiated. Banked, longitudinally collected specimens were evaluated from pre-ART, during ART and post-ART-interruption and re-suppression. Quantitative viral outgrowth assay (QVOA) was performed to identify infectious variants with sequences matching the RV. We hypothesized that during long-term ART, prevalent RV will be maintained over time and contribute to infectious viremia, and thus to persistence of the reservoir.

Methods: Extracted RNA from at least 4 pre-ART, 4 on-ART (viral RNA <50copies/ml), and 2 post-ART interruption time points was subjected to endpoint-PCR of C2V5env, sequenced, and assembled into a maximum-likelihood tree. QVOA was performed on all 3 subjects from a time point with undetectable viral load (<50copies/ml). Predicted cell tropism was performed using PSSM.

Results: RV variants were often clonal in participants 1 and 2 (n=21/113, n=28/38, respectively), with clonal variants observed for at least 3yrs on ART, but included multiple variants in participant 3. RV across participants 1, 2, and 3 were predominately CCR5(R5)-tropic (57%, 99%, and 84%, respectively), with the remaining being CXCR4-tropic. In participant 1, a RV clone (n=4) had an identical C2V5 to a QVOA variant. This RV clone (R5-tropic) was observed for at least 7yrs sine pre-ART. A match between a QVOA variant and a monotypic plasma pair (n=2) in participant 3 was also observed and maintained for 3yrs on ART. R5-tropic RV monotypic variants detected during ART in participants 1 and 2 were also detected post-ART interruption and re-suppression and these variants were maintained for 7 and 2yrs, respectively.

Conclusion: These findings suggest that RV represent a non-latent part of the infectious reservoir that upon ART interruption could fuel new cycles of infection. Furthermore, persistence of certain monotypic clones over time suggests that cells harboring these virions may be resistant to immune clearance or regularly renewed.

381 PD-1/PD-L1 INTERACTION REGULATES HIV TRANSCRIPTION IN LYMPH NODES OF TREATED SUBJECTS

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Background: T follicular helper (Tfh) cells expressing high levels of PD-1 were recently shown to serve as a major site of active and persistent HIV transcription despite prolonged ART. The present study aimed to determine the potential role of immune checkpoint (IC)/IC-Ligand (IC-L) interactions on HIV transcription in lymph node (LN) microenvironment.

Methods: To address this issue, we assessed the expression of ICs and IC-Ls on LN cell populations and the impact of IC/IC-L interactions on T-cell proliferation, reactivation of HIV production and HIV transcription in LN memory CD4 T-cell populations from viremic and aviremic ART-treated HIV-infected subjects (N=47).

Results: We showed that PD-1 and TIGIT are the two major ICs expressed on Tfh cells of healthy, viremic and ART treated HIV-infected subjects ex vivo. We subsequently showed that PD-L1 and to a lower extent CD155 (TIGIT ligand) recombinant proteins significantly reduced TCR-mediated T-cell proliferation and reactivation of HIV production in vitro (P<0.05), demonstrating that PD-1 and TIGIT signaling pathways were 1) functionally active on PD-1+/Tfh cells and 2) regulate TCR-mediated HIV transcription and production. We therefore explored the phenotype, the frequency and the tissue distribution of IC-L expressing cells and showed that PD-L1 and CD155 were predominantly co-expressed on LN HLA-DRhighCD1chigh dendritic cells (DCs). The frequencies of PD-L1+ DCs in viremic HIV-infected subjects directly correlated with HIV viral load (r=0.93 P=0.0002) and significantly dropped after prolonged ART (P<0.05). Interestingly, PD-L1 expressing cells were detected in both extra-follicular and germinal center (GC) areas of viremic HIV-infected subjects, but were barely detectable in GCs of ART treated subjects, suggesting that ART initiation had a profound impact on IC-L tissue distribution and that PD-1/PD-L1 interactions might be selectively reduced in GCs of ART-treated subjects. Finally, the frequencies of LN PD-L1+ DCs inversely correlated with HIV transcription (r=-0.89; P<0.05) in LN memory CD4 T cells, indicating that PD-L1+ DCs contribute to control HIV transcription in vivo.

Conclusion: HIV exploits the IC regulatory mechanism of T cell activation and function to favor persistence of HIV transcription/production in treated aviremic HIV-infected subjects. It also indicates that an imbalance in IC/IC-L interactions is a novel mechanism contributing to HIV persistence in germinal centers.

382 CELLULAR PROLIFERATION MAINTAINS GENETICALLY INTACT AND DEFECTIVE HIV-1 OVER TIME

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Background: A thorough understanding of the cellular mechanisms maintaining replication-competent virus will be needed to design future HIV eradication therapies. We examined the relative proportions of genetically identical intact and defective proviruses within memory CD4+ T cell subsets from individuals on prolonged ART.
Methods: Naïve, central (CM), transitional (TM) and effector (EM) memory CD4+ T cells, as well as CD45RA-HLA-DR+ and CD45RA-HLA-DR- CD4+ T cells, were sorted from the peripheral blood of eight participants on long-term ART. Additional sequences from four participants were obtained four years later. We used the full-length individual proviral sequencing assay, which amplifies single HIV proviruses followed by next-generation sequencing, to characterise proviruses as intact or defective (containing insertion, deletion, stop codons or hypermutation). Duplicated sequences were classified as ≥2 identical HIV DNA sequences.
Results: At the early time-point, 1041 sequences were obtained, and only 4% were considered intact. The proportion of intact proviruses was different across cell subsets ($p<0.001$), with the highest proportion observed in EM and HLA-DR+ cells. Equivalent amounts of duplicated sequences were identified in defective and intact proviruses. However, when stratified by treatment duration, the proportion of duplicated sequences was higher in those on therapy for >14 years. Of note, no intact duplicated sequences were observed in participants on therapy for <5 years. Duplicated intact sequences were predominantly found in EM and HLA-DR+ cells; representing 24% and 17% of all intact sequences in these subsets respectively. These intact duplicated sequences were observed in two participants four years later. In one participant where no intact provirus was observed, a large expansion of defective sequences predominated (28/68 sequences; 41%). These defective sequences expanded four years later, representing 78% of all sequences isolated (167/215 sequences).
Conclusion: Cellular proliferation contributes to the expansion of both genetically intact and defective proviruses. Expansions of defective proviruses may dilute the number of intact proviruses and therefore lead to difficulty in their identification in some participants. Notably, genetically identical intact proviruses are enriched in HLA-DR+ and EM cells and these proviruses are stable over time, indicating the latent HIV reservoir is maintained in these T cell subsets in the peripheral blood by proliferation.

383 INCREASED NUMBERS OF INTACT HIV SEQUENCES IN A4B7 T CELLS DURING ACUTE SEROCONVERSION

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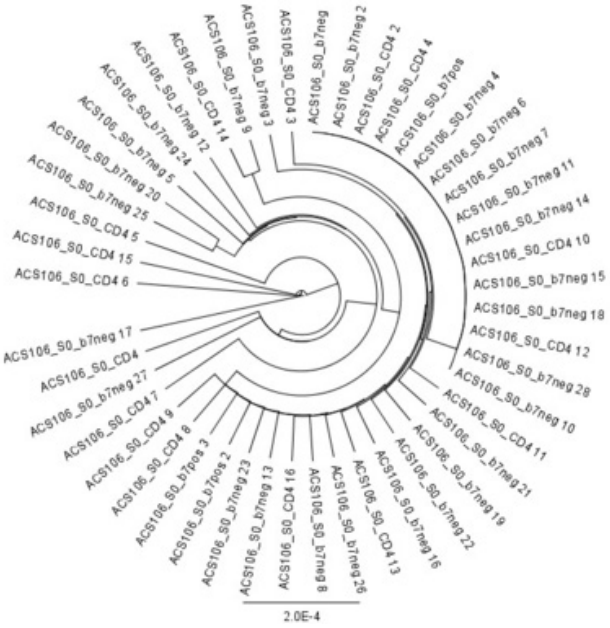
Background: Memory CD4 T cells expressing the integrin α4β7 seem highly susceptible to HIV-1 infection, and may represent a preferential site for viral infection and reservoir establishment. Recent studies suggested that when used in combination with regular antiretroviral therapy during acute SIV infection, monoclonal antibodies blocking α4β7 may enable rhesus macaques to control viremia after ART discontinuation. In contrast, a clinical trial with α4β7 blocking antibodies in humans with chronic HIV-1 infection has recently been completed, without markedly increased frequencies of individuals achieving post-treatment control.
Methods: PBMCs were isolated from HIV-1 positive patients (n=4) during acute seroconversion before ART initiation (Fiebig stage III-V). CD4 T cells were enriched by negative MACS selection, and the α4β7-positive and β7-negative memory CD4 T cell populations were sorted by FACS. Near-full-length, single-genome HIV-1 DNA sequencing of total CD4 T cells, β7-positive and β7-negative CD4 T cell subsets was performed, as described previously. Phylogenetic associations were determined using sequence alignments by MUSCLE and tree building by Unweighted Pair Group Method with Arithmetic Mean (UPGMA).
Results: In three out of four patients analyzed at acute seroconversion, the number of HIV-1 DNA copies (intact and defective combined) was higher in the β7-positive cells compared to β7-negative and total CD4 T cells (mean of 897, 186 and 117 total HIV-1 copies/million cells, respectively). The frequency of intact HIV-1 proviruses was also highest in the β7-positive compartment relative to the other two cell populations (mean of 558 versus 99 and 72 intact HIV-1 copies/million cells, respectively). The patient without an HIV-1 enrichment in the β7-positive subset presented with a very high peak viral load (> 7 log copies/mL), low CD4 nadir count below 100 cells/mm3 and CD4 T cells skewed towards a memory phenotype. Phylogenetic analysis of the intact proviral sequences showed that these viruses intermingle between the three different subsets and suggests absence of compartmentalization within the analyzed cell populations.
Conclusion: This study suggests that α4β7 memory CD4 T cells represent a primary target site for viral replication during the earliest stages of HIV-1 infection, and raise the possibility that administration of α4β7 antibodies during acute HIV-1 infection may reduce viral reservoir establishment.



384 SEX AND OBESITY ARE ASSOCIATED WITH RESIDUAL VIREMIA IN ART-SUPPRESSED INDIVIDUALS

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Background: The sex of an individual influences HIV levels prior to antiretroviral therapy (ART) and adipose tissue has been proposed to harbor part of the HIV reservoir. The effect of host characteristics, including sex and body-mass index (BMI), on HIV persistence during ART remains incompletely understood. We evaluated factors associated with HIV persistence in a cohort of people with long-term virologic suppression (ACTG A5321).
Methods: Participants who initiated ART during chronic infection with sustained virologic suppression had measurements of plasma HIV RNA by single copy assay (SCA), cell-associated HIV DNA and RNA (CA-DNA, CA-RNA). We assessed the effect of age, sex (reported at birth), BMI, waist circumference

(WC), years on ART, pre-ART HIV RNA, pre-ART CD4 count, initial ART regimen (PI, NNRTI or INSTI) on HIV persistence. Assessments were done at study entry or, for WC, at pre-study visit.

Results: 295 participants (53 females) were evaluated; median (IQR) age 48yr (41, 54); yrs on ART 7 (6, 10); BMI 27 (24, 31); WC 94cm (87, 102). CA-DNA, CA-RNA and plasma SCA were positively correlated with pre-ART HIV RNA (r=0.35, 0.29, 0.20; respectively, p-values <0.001), and negatively with pre-ART CD4 count (-0.35, -0.21, -0.12, respectively, all p <0.05). Regimen type was not associated with HIV persistence markers after controlling for ART duration. Males were more likely than females to have plasma SCA values ≥0.4 copies/mL (52% vs 29%, p=0.003) (Figure), even after adjusting for age, pre-ART HIV RNA and CD4 count, years on ART and BMI (p=0.004). Higher BMI and higher WC were each associated with higher SCA levels (r=0.12 and 0.13, p<0.04) after adjustment for age, sex, pre-ART HIV RNA and CD4 count, and years on ART. The proportion of participants with detectable residual viremia increased in a step-wise fashion by BMI category: normal/underweight 38%; overweight 50%; obese 55% (Figure). Sex, BMI and WC were not associated with CA-DNA or CA-RNA.

Conclusion: Higher BMI and obesity are associated with higher levels of residual viremia in persons on long-term ART. Adipose tissue may be an important site of HIV production due to its proinflammatory milieu or altered ARV penetration. The finding that females have lower residual viremia than males may reflect effects of estrogen on HIV expression or other biologic and immunologic differences. Studies of the mechanism by which obesity and sex affect HIV persistence are needed to inform cure strategies.

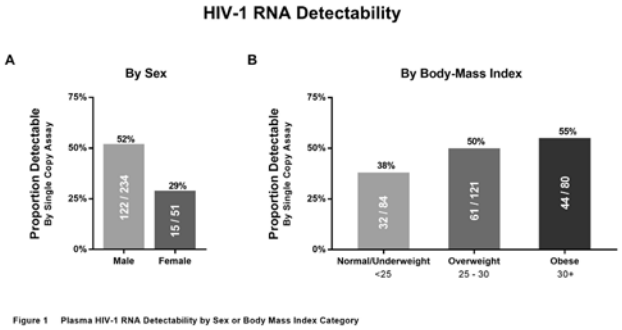

Figure 1 Plasma HIV-1 RNA Detectability by Sex or Body Mass Index Category

A5321 plasma single copy assay values from 285 of 295 total participants were grouped according to participant sex (**A**) or BMI (**B**). Illustrated are the proportions of HIV-1 RNA above 0.4 copies per mL by standard integrase single copy assay of approximately 5mL of plasma. The normal/underweight group in Panel B contains 2 underweight (<18.5) and 82 normal weight (18.5-25).

385 CD4+ T-CELL-SURFACE FUCOSYLATION DEFINES PERSISTENT HIV TRANSCRIPTION IN VIVO

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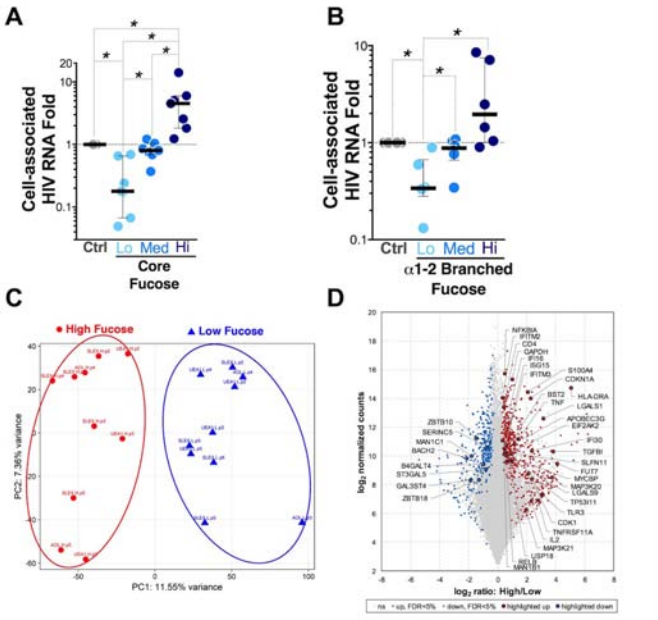
Background: Cell-surface glycosylation and glycan-lectin signaling play critical roles in modulating several immunological responses. However, the relevance of host glycosylation machinery to HIV persistence is yet to be determined. We characterized the relationship between cell-surface glycomic signatures of HIV+ cells and levels of persistent HIV transcription, in vitro and in vivo.

Methods: Primary CD4+ T cells were infected with a dual-reporter virus that enables isolation and characterization of transcriptionally inactive HIV+, transcriptionally active HIV+, or uninfected cells. Lectin microarray was used to examine the cell-surface glycomic signatures of sorted populations. We validated our in vitro analysis in vivo by sorting CD4+ T cells from 7 HIV+ individuals on suppressive antiretroviral therapy (ART) into populations with distinct glycomic profiles, using fluorescently-labeled lectins. RNA-Seq and qPCR were used in the sorted population to 1) characterize the transcriptomes, and 2) measure levels of HIV DNA and cell-associated HIV RNA, respectively. Ingenuity pathway analysis was used to evaluate the functional significance of differentially expressed genes.

Results: The glycomic signature of in-vitro sorted transcriptionally inactive HIV+ cells clustered distinctly from the other populations due to the lower binding intensity of a selective set of lectins specific for core and branched fucose. Low-fucose sorted CD4+ T cells from HIV+ ART+ individuals exhibited lower levels of cell-associated HIV RNA when compared to cells with high cell-surface fucose (P<0.05 Wilcoxon test; 17.2 fold for core fucose and 8.2 fold for branched fucose). Principal component analysis of the transcriptomic profiles showed a clear clustering between the two groups, with the activity of carbohydrate metabolism, glycolysis, T-cell trafficking, mTOR signaling, and ERK/MAPK signaling, being significantly elevated in high-fucose cells when compared to low-fucose cells (FDR<0.0001).

Conclusion: Cell-surface fucosylation and enhanced carbohydrate metabolic activity are associated with higher T cell activation and persistent HIV transcriptional activity during suppressive ART. T cell surface fucosylation is known to be critical for memory T cell activation and trafficking. Together, the role of T cell-surface fucosylation and altered carbohydrate metabolic activity in HIV persistence warrants further investigation, in order to identify glycan-based interactions that can be targeted for novel HIV immunotherapies.



Cell Surface Fucosylation Associates With Persistent HIV Transcription During ART *in vivo*. (A-B) Low-fucose CD4+ T cells isolated from HIV+ ART+ individuals exhibit low levels of cell-associated HIV RNA when compared to high-fucose cells (Lo= Low, Med = Medium, and Hi = High). **(C)** Principal component analysis of the transcriptomes of high-focuse and low-fucose cells. **(D)** Volcano plot highlighting up- and down-regulated genes when high-fucose cells compare to low-fucose CD4+ T cells.

386 GALECTIN-9 MEDIATES HIV TRANSCRIPTION BY INDUCING TCR-DEPENDENT ERK SIGNALING

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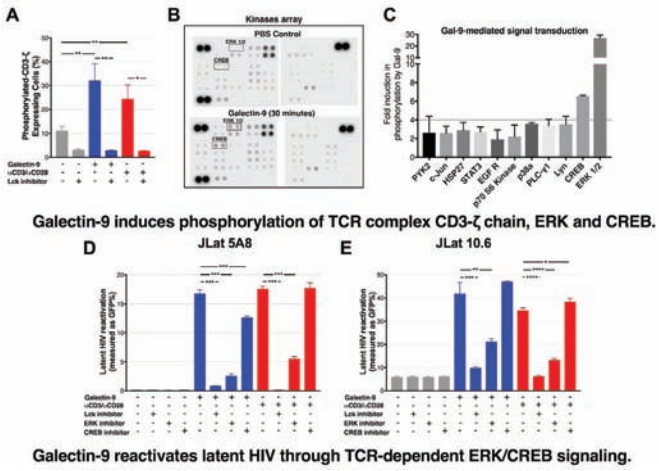
Background: Endogenous plasma levels of the immunomodulatory carbohydrate-binding protein galectin-9 (Gal-9) are elevated during HIV infection and remain elevated after antiretroviral therapy (ART) suppression. We recently reported that Gal-9 regulates HIV transcription and potently reactivates latent HIV [PMID 27253379]. Given that galectins are known to modulate TCR-signaling, we hypothesized that TCR signaling transduction contributes to the Gal-9-mediated modulation of HIV transcriptional activity.

Methods: Using an anti-phosphorylated-CD3-ζ antibody and a pharmacological inhibitor of Lck activity, we evaluated the role of TCR signaling in Gal-9-mediated 1) latent HIV reactivation, 2) T cell activation, and 3) cytokine secretion using the J-Lat 5A8 HIV latency model and CD4+ T cells from 5 HIV+ individuals on suppressive ART. Effects of Gal-9 on TCR-downstream kinase phosphorylation was examined by Phospho-Kinase antibody arrays.

Results: Gal-9 induced CD3-ζ phosphorylation (11.2% to 32.1%; P=0.008). Inhibition of Lck activity reduced Gal-9-mediated viral reactivation in the JLat 5A8 cells (15.8% to 1.5%; P<0.0001). In addition, Lck inhibitor reduced both Gal-9-mediated T cell activation (10.4% to 1.6% CD69/CD25 co-expression; P<0.0001), and IL-2/TNF secretion (P<0.001), in primary CD4+ T cells. Gal-9 increased the phosphorylation of the TCR-downstream signaling molecules

ERK1/2 (26.7 fold) and CREB (6.6 fold). ERK and CREB inhibitors reduced Gal-9-mediated viral reactivation (15.8% to 2.9% or 9.2%, respectively; P=0.0001). Given that the immunosuppressive rapamycin uncouples HIV latency reversal from cytokine-associated toxicity [PMID 28094770], we investigated whether rapamycin could uncouple Gal-9-mediated latency reactivation from its concurrent pro-inflammatory cytokine production. Rapamycin reduced Gal-9-mediated secretion of IL-2 (4.4-fold, P=0.001) and TNF (4-fold, P=0.02) without impacting viral reactivation (16.8% compared to 16.4%; P=0.2).
Conclusion: Gal-9 modulates HIV transcriptional activity through TCR/Lck-dependent ERK1/2-CREB phosphorylation pathway. Our findings could have implications for understanding the role of endogenous galectin interactions in modulating TCR signaling and maintaining chronic immune activation during HIV infection. In addition, uncoupling Gal-9-mediated viral reactivation from undesirable pro-inflammatory effects, using rapamycin, may increase the potential utility of recombinant Gal-9 within the reversal of HIV latency eradication framework.



387 TNF SURFACE RECEPTORS RELATE TO SURVIVAL PATHWAY ACTIVATION IN HIV RESERVOIR CELLS

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Background: HIV reservoir cells possess a remarkable long-term stability and represent the major obstacle to a virological cure. Understanding mechanisms that support reservoir cell survival is of great interest for developing interventions to reduce viral persistence. Previous studies suggest the selective activation of anti-apoptotic host factors in virally infected cells, but the molecular pathways involved remain unclear.
Methods: Unstimulated CD4 T cells from HIV-negative donors were infected with a dual-reporter HIV-1, allowing to distinguish productively (GFP) and latently (mKO2) infected cells. Phenotypic properties of infected cells were determined by flow cytometry. Transcriptional programs of cells with latent or productive infection were analyzed by single-cell RNA-Seq, with whole-transcriptome amplification, followed by sequencing on NextSeq 500 system.
Results: Compared to uninfected population, both productively- and latently-infected CD4 T cells showed a distinct increase in surface expression of several members of the Tumor Necrosis Factor Surface Receptor (TNFSR) family, including OX40 (p=0.008 both GFP+ and mKO2+ cells), TNFR2 (p=0.003 GFP+ cells; p=0.017 mKO2+ cells) and GITR (p=0.018 GFP+ cells only). Union gating on combinations of the TNFSRs -- OX40, HVEM and TNFR2-- allowed to distinguish mK02+ and GFP+ from uninfected cells at high levels of statistical significance (p=0.003 GFP+ cells; p=0.01 mKO2+ cells). Single-cell RNA-seq data identified several TNFSRs that distinguished transcriptional signatures of GFP+/mKO2+ cells from uninfected cells, and both latently-infected and productively-infected cells contain higher proportions (35-60%) of cells that expressed high-level OX40, TNFR2, or GITR, while frequencies of uninfected cells with high-level expression of these markers were substantially lower (18-24%). Computational analysis of single-cell transcriptomes inferred activation of survival pathways in GFP+ and mKO2+ cells, which might be driven by the TNFSRs-expressing populations.
Conclusion: Multiple TNFSR members are upregulated at the transcriptional and protein level in cells with in vitro-induced productive and latent infection. Increased expression of these markers is associated with transcriptional induction of cell survival signatures. Our data lay the foundation for future investigation on roles of TNFSRs in naturally-infected CD4 T cells to fully appreciate their impact on viral reservoir persistence.

388 HIV PROVIRAL DNA METHYLATION IN SEROCONVERTERS, CONTROLLERS, AND ART-TREATED PATIENTS

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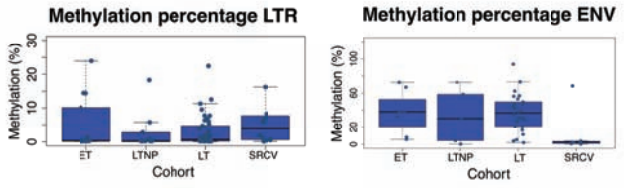
Background: DNA methylation is a well-known epigenetic modification that drives gene transcription, but its role in the HIV-1 proviral genome is largely unknown. In latency models, hypermethylation has been linked to silencing, while loss of methylation stimulates reactivation. However, due to low HIV-1 proviral DNA levels and high genomic heterogeneity, obtaining reliable and reproducible patient-derived data has been difficult. This has resulted in the past in conflicting publications. We therefore have performed an in-depth evaluation of the HIV-1 proviral methylation state in a well-characterized HIV-1 patient cohort.
Methods: To reliably measure DNA methylation in HIV-1 proviruses from clinical samples, we used a bisulfite-based deep sequencing assay to measure the methylation state of 4/5 CpG Islands (CpGIs) found in the HIV-1 genome (2 in LTR, 2 in env). This assay was used to compare methylation in PBMCs from 72 individuals, divided in four groups: early ART-treated HIV-1 seroconverters (ET, N=15), late ART-treated patients (LT, N=32), ART-naïve seroconverters (SRCV, N=8) and long-term non-progressors (LTNP, N=17). Data was mapped to a reference HIV-1 genome using Bismark (v0.10.1) and analyzed with the methylKit package (version 1.6.2).
Results: We show (i) that CpGIs inside the LTR region have low overall methylation level (median <5%) as compared to CpGIs in the env region (median up to 40%), and (ii) that LTR CpGIs are equally methylated in all 4 groups (differential methylation (DM) <5%). (iii) CpGIs in the env region show no DM between patients controlling HIV-1 replication (ET, LT, LTNP), but a decrease of 29.92% in SCRV as compared to these groups. Within the cohorts on long-term ART (median of 10 years), we found no correlation between the time of initiation of therapy and the methylation percentage (Spearman's rank correlation: p= 0.2131).
Conclusion: Our results using this sensitive assay show a paucity of DNA methylation in the HIV-1 promoter region in all patient groups with the absence of ART or different timing of ART initiation suggesting that LTR methylation is not involved in regulating latency, which contradicts the latency model results. Methylation in env on the other hand is higher, and found in all patients who are chronically viral suppressed suggesting that env DNA methylation has latency regulating effect.



389 ANALYTICAL TREATMENT INTERRUPTION (ATI) IN PATIENTS WITH VERY SMALL HIV RESERVOIR

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Background: No single parameter reliably predicts post-treatment control (PTC) among HIV infected patients. However, both total HIV-1 DNA (tDNA) and cell-associated RNA (caRNA) have been individually associated to delayed viral rebound after ATI. We evaluated the predictive value of the combination of low DNA and caRNA in the identification of PTC.

Methods: The study is a two-step single arm multi-centric non-randomized prospective trial (NCT02590354). Major inclusion criteria in step 1 were: nadir CD4+ T-cell count >350cells/µl and plasma viral load (pVL) <50 cps/ml since ≥2 years. The size of the HIV reservoir was determined by droplet digital PCR measurement of tDNA and caRNA in peripheral blood mononuclear cells (PBMCs). In step 2, consenting participants with tDNA <66 cps/10^6 PBMCs and caRNA <10 cps/10^6 PBMCs underwent a leucapheresis prior ATI. cART was re-initiated whenever pVL, measured every other week, was >1,000 cps/ml at two consecutive measurements or at pVL > 10,000 cps/ml. tDNA and caRNA were measured at every visit during ATI as well as 4 and 12 weeks after cART re-initiation. Quantitative viral outgrowth assays (qVOA), viral release assays (VRA) and ultra-sensitive pVL were performed on pre-ATI samples. Associations between clinical, virological or immunological parameters and viral rebound dynamics were assessed with Kaplan-Meier estimates and Cox proportional hazard models.

Results: Of the 114 participants, 37 (32.5%) met the viral reservoir criteria for ATI. Of them, 16 (14.0%) consented and underwent ATI. All 16 participants experienced rapid viral rebound two to eight weeks after ATI (figure), with 13/16 (81.3%) reporting an adverse event (AE) but none with serious AE. All participants suppressed viremia to levels below the limit of detection within 14 weeks of cART re-initiation. tDNA and caRNA returned to baseline levels within the 12 weeks after cART re-initiation. No correlations were observed between viral rebound dynamics and current or nadir CD4+ T-cell count, ultra-sensitive pVL, tDNA or caRNA, qVOA, VRA or any other clinical parameters.

Conclusion: We report on the first prospective study evaluating ATI in participants selected on the basis of a very small and transcriptionally silent HIV reservoir. No PTC was identified. ATI was shown to be safe, despite rapid viral rebound. The impact of ATI on the reservoir size after cART re-initiation was limited. None of the measured baseline parameters were predictive for viral rebound dynamics.

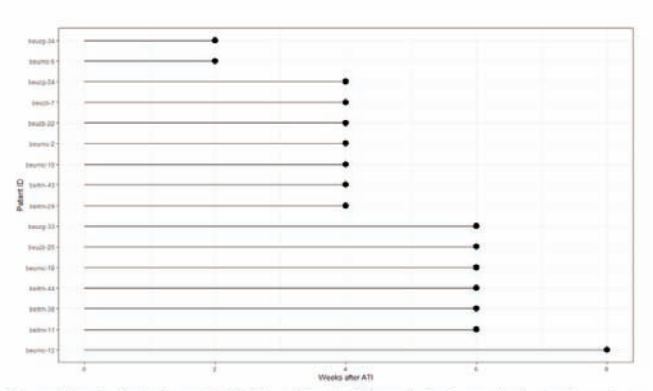

Figure. Time to viral rebound of all 16 participants with small viral reservoir that underwent an analytical treatment interruption.

390 N-803 INDUCES ROBUST SIV REACTIVATION IN ART-TREATED CD8-DEPLETED MACAQUES

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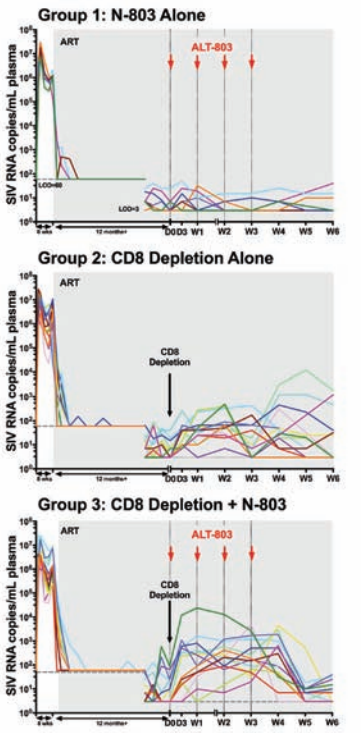
Background: The current paradigm in HIV cure research is that virus production must be reactivated in latently infected cells prior to clearance (shock and kill). Since depletion of CD8+ lymphocytes in SIV-infected ART-treated rhesus macaques (RM) results in increased plasma viremia, we propose that CD8 depletion may act synergistically with latency reversing agents (LRA) in reactivating virus production. To test this hypothesis we used the IL-15 superagonist N-803, an agent that shows LRA activity in vitro and may also boost antiviral cellular immune responses.

Methods: 35 SIV-infected RM started ART 8 weeks post-infection. After 1 year, 7 RM received four weekly doses of N-803 (100 µg/kg), 14 received 50 mg/kg of the CD8α-depleting Ab MT-807R1, and 14 RM received both treatments. All animals underwent ART interruption 3 weeks after the last N-803 dose and/or CD8 reconstitution. SIV reactivation was monitored by plasma viremia and RNAscope analysis in lymph node samples. The size of the viral reservoir was assessed by total cell-associated SIV DNA. Immunological changes were studied by flow cytometry and RNA sequencing. Diversity of the virus emerging after N-803 and/or CD8 depletion was assessed via single genome amplification.

Results: In ART-treated RM, N-803 alone did not reactivate virus production; however, its administration in CD8-depleted RM resulted in loss of virus suppression (>60 copies/ml) in 14/14 animals (100%) in 41/56 samples (73.2%) collected 1 week after each dose. In addition, viremia >1,000 copies/ml was observed in 6/14 animals (42.9%) and 13/56 (23.2%) time points, with a maximum of 21,000 SIVgag copies/mL. Preliminary virus sequence analysis indicated a diverse range of circulating virus after CD8 depletion and N-803 treatment. Despite this very robust level of virus reactivation, all groups of RM showed stable levels of cell-associated SIV DNA in CD4+ T cells following treatment and a rapid rebound of viremia after ART interruption.

Conclusion: N-803 administration in CD8-depleted, ART-treated SIV-infected RM induces the most robust and persistent reversal of latency observed to date in humans or nonhuman primates. In absence of a clearance intervention, we did not observe a significant reduction of the reservoir size. Combining N-803 and CD8 depletion with an immune-clearing component (i.e. neutralizing antibodies, CD4 mimetics or immunotoxins) may be a powerful shock and kill strategy that profoundly affects reservoir size and stability in ART-treated HIV/SIV infections.



391 REBOUND OF HIV-1 IN CEREBROSPINAL FLUID AFTER TREATMENT INTERRUPTION

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Background: HIV-1 persists in the body despite years of suppressive antiviral therapy. One well characterized viral reservoir is in resting CD4+ T cells. Under certain circumstances an independently replicating viral population can be detected in the CNS as indicated by differing viral sequences in blood and CSF. We examined rebound virus in the blood and CSF in 9 participants who chose to interrupt therapy.

Methods: Nine men interrupted therapy (TI), most in the context of early systemic failure (Price and Deeks J. Neurovirol. 2004 PMID: 14982739). Multiple blood and CSF samples were collected before and after TI over a period of up to 41 weeks, and clinical and laboratory data were recorded. Viral RNA was extracted from the plasma and CSF at each time point and viral populations examined using deep sequencing, with the sampling depth defined and sequencing errors corrected using Primer ID.

Results: In 7/8 participants with clinical laboratory data available there was a significant increase in WBCs in the CSF (i.e. pleocytosis) typically between 1-2 months after TI. The peak in WBCs in the CSF often corresponded with a peak in CSF viral load (VL), reaching viral RNA levels equivalent to those in the blood. At all analyzed time points for the 9 participants before and during the increase in VL in the CSF, the viral population in the CSF was well mixed with the viral population in the blood. Two frequently seen features of the CSF viral population were transient expansion of a single genotype (clonal amplification) of an R5 T cell-tropic virus, and differential penetration of one viral population present in the blood into the CSF relative to a second blood viral population. There was no evidence for a distinct viral population emerging from the CNS based on sampling of the CSF in these participants.

Conclusion: In this study of 9 participants we did not observe any evidence of a CNS-specific lineage in the CSF after TI in spite of extensively sampling the viral populations using deep sequencing. The large majority of the virus observed in the CSF appears to be the result of infected CD4+ T cells trafficking into the CNS from the blood rather than from 'release' from a CNS reservoir after TI. It is not clear why there is a spike in pleocytosis during virus rebound. These results do not preclude a CNS reservoir but rather point to the difficulty of observing such a reservoir in the presence of actively circulating CD4+ T cells transporting virus from the blood into other compartments.

392 COMPARTMENTALIZED HIV REBOUND IN THE MALE GENITAL TRACT AFTER ART INTERRUPTION

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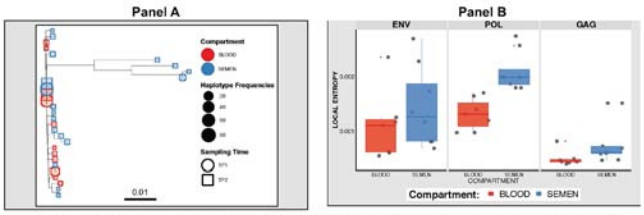
Background: If strategies currently in development succeed in eradicating HIV reservoirs in peripheral blood and lymphoid tissues, residual sources of virus may remain in anatomic compartments, including the genital tract. To design effective eradication strategies, it is crucial to determine to what extent compartmentalized HIV reservoirs contribute to viral rebound after antiretroviral therapy (ART) interruption.

Methods: Paired blood and semen samples were collected from 12 individuals enrolled in a randomized, double-blind, placebo-controlled clinical trial of HIV-MAG DNA vaccine prime, rVSVN4CT1gag booster vaccine in people living with HIV (PLWH) who began ART during acute or early infection (NCT01859325). At the first available time-points following viral rebound, we sequenced HIV-1 env (C2-V3), gag (p24), and pol (reverse transcriptase) regions amplified from cell-free HIV RNA in blood and seminal plasma using the MiSeq Illumina platform. Comprehensive sequence and phylogenetic analyses were performed to look for evidence of viral compartmentalization (Fst test), diversity (Shannon entropy measures) and unique viral subpopulations in seminal plasma as compared with blood plasma.

Results: Vaccine had no effect on kinetics and magnitude of HIV RNA rebound in blood plasma (Sneller et al, STM 2017). Compared to blood, HIV RNA rebound in semen occurred significantly later (median of 66 vs 42 days post ART interruption) and reached lower levels (164 vs 16,224 copies/ml). Paired sequence data were available for 5 participants. All presented compartmentalized viral rebound between blood and semen (Fst, $p \leq 0.05$ for all genes). Phylogenetic analysis confirmed the presence of compartment-specific monophyletic HIV RNA populations in at least one HIV region in 3 out of the 5 participants in longitudinal time-points, suggesting that rebound originated within genital compartment rather than migrating from blood (Figure 1 panel A). Interestingly, despite early ART start, genetic diversity after adjusting for variant frequency was higher in semen compared to blood in all three coding regions (Significant for gag and pol (<0.01) but not in env ($p=0.06$)), Figure 1 panel B.

Conclusion: HIV reservoirs in the genital compartment might contribute to viral rebound in PLWH interrupting ART. Higher diversity in the genital compartment illustrates viral compartmentalization and distinct evolutionary dynamics. Reservoirs in all anatomic compartments need to be actively targeted to achieve a complete functional cure.



A. Approximate maximum likelihood phylogenetic reconstruction of sequences generated from longitudinally collected HIV-1 RNA Populations in blood and semen (HIV pol region) from one participant. HIV haplotypes above a minimal frequency threshold of 0.01 were extracted from cleaned reads and were used to construct approximate maximum likelihood phylogenies using FastTree (Price et al., 2009). HIV haplotypes from blood and semen are depicted in red and blue respectively. Size of the tips is proportional to variant frequency. Scale bars are in substitutions/site. TP 1 and 2: timepoints 1 and 2 **B. Comparative genetic diversity in HIV env, pol and gag for blood and semen compartment.** Viral diversity (Shannon entropy) was assessed after adjusting for haplotype frequency for all three regions in blood (red) and semen (blue). Genetic diversity after adjusting for variant frequency was higher in semen compared to blood in all three coding regions (Significant for gag and pol (<0.01) but not in env ($p=0.06$).

393 SEEKING SUPPRESSION IN HAVARTI: VIREMIA & T CELLS AFTER VEDOLIZUMAB & ATI IN HIV/ART

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Background: HAVARTI is a dose-ranging trial of vedolizumab and analytical treatment interruption (ATI) in HIV/ART.

Methods: Eight healthy HIV+ adults on ART for 2-10 years had vedolizumab given 3 times in 6 weeks before, and 4 times in 14 weeks after ATI, at 300mg doses in 4 (Group 1) and 150mg in 4 (Group 2). Monthly follow-up for adverse events (AE), plasma viremia (pVL) and T cell count outcomes informed clinical judgement for ART retreatment.

Results: Groups had similar mean age, nadir CD4, pre-ART pVL, ART duration & baseline CD4 count. No serious clinical or severe laboratory AE occurred. One case had non-sustained pVL suppression <40 copies/mL in 2 sequential measures. CD4 T-cell count response varied, but none had sustained CD4 <350 cells/μL. Percent a4b7+ CD4 T cells in rectal mucosa decreased in Groups 1 and 2 respectively from 46.90 ±23.30 and 30.63 ±9.86 before, to 2.77 ±1.73 and 3.05 ±2.47 after vedolizumab. Group 1 pVL rebounded in 3 of 4 at 2 weeks, and all 4 at 6 weeks into ATI. pVL doubling time (T2) from ATI week 2 to 6 was 7.67 ±4.41 days, to a peak pVL level below pre-ART in each by mean 1.21 ±0.56 log10 copies/mL, sustained on average to 22 weeks, before a consistently rising pVL trajectory after 26 weeks, 12 weeks after last vedolizumab dosage. Group 2 pVL rebounded in 1 of 4 at 2 weeks, and all 4 at 6 weeks into ATI. T2 was 2.58 ±0.79 days, to week 6 peak pVL above pre-ART in 3 of 4 by mean 0.26 ±1.37, falling below mean pre-ART pVL to 14 weeks, with consistent rising trajectory onset after 18 weeks, 4 weeks after last vedolizumab dosage.

Conclusion: Viremia rebound appears attenuated in group 1 compared with group 2, supported by individual consistency of much slower T2 ($p=0.057$), and much lower pVL peak compared to pre-ART (by 1.47 log10), sustained 2 months longer after last vedolizumab dose. This difference is corroborated by

historical controls with similarly calculated T2 of 3.4 days (and from literature about 2-3 days) and pVL rebound to +0.72 log10 > pre-ART at 6 weeks, as in Group 2. Limitations include small numbers, and high variation. Strengths include coherence of a biologically large effect size on pVL rebound dynamics, on kinetics and on time to loss of activity by dosage group, suggesting dose- and exposure-related vedolizumab effects. Deeper biological study in these cases, and further data from greater numbers, doses and duration is needed to validate and confirm activity of vedolizumab in pursuit of pVL suppression after ART.

394LB ANALYTIC TREATMENT INTERRUPTION (ATI) AFTER ALLOGENEIC CCR5-D32 HSCT FOR AML IN 2013

Björn-Erik O. Jensen[1], Elena Knops[2], Nadine Lübke[1], Annemarie Wensing[3], Javier Martinez-Picado[4], Rolf Kaiser[2], Monique Nijhuis[3], Maria Salgado[4], Thomas Harrer[5], Eva Heger[2], Johanna M. Eberhard[6], Ilona Hauber[7], Carsten Münk[1], Dieter Häussinger[1], Guido Kobbe[1]

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Background: A 49y-old HIV-infected male patient received unmodified HSCT from a 10/10 CCR5-d32 donor in Feb 2013 because of acute myeloid leukemia (AML) while in 2nd complete remission (CR). At time of HSCT proviral HIV DNA load was 1.45 log10cop/Mio PBMCs. All anticipated antibodies were detected by western blot. HIV coreceptor-usage was predicted R5 (Sanger: FPR 44.5%; NGS: 0.14% X4 at 3.5% FPR, geno2pheno), confirmed by phenotypic testing (TropChase). He had a 2nd relapse of AML in Jun/13 but after 8 courses of 5-azaC and 4 donor lymphocyte infusions CR was achieved. Immunosuppression was stopped in Oct/17. During HSCT the patient remained on ART until Nov/18 with undetectable plasma viral load.

Methods: PBMC and tissues were analysed by ddPCR, qPCR and in situ hybridization in several laboratories as well as humoral and T-cell responses. Infectious virus was analysed on CD4+T-cells (qVOA, MVOA). Patient was registered to IciStem as #19.

Results: Almost all PBMC samples were negative for proviral HIV-DNA by qPCR/ddPCR at multiple time points. CSF (Jul/14), rectum (Apr/15, Mar/16), ileum (Mar/16) and bone marrow (Aug/15) were negative. Further testing with 0.1 Mio cells from ileum showed in 1/4 replicates one positive droplet with LTR-, but none with gag-primers. There was also a signal in TCM 0.2 Mio cells (ddPCR 1 positive droplet, qPCR neg) and in TEM 0.36 Mio cells (qPCR 5cop/Mio cells, ddPCR neg) while all other T-cell subsets were negative in ddPCR & qPCR. No HIV-DNA could be detected by PCR in lymph nodes of May/17, but in situ hybridization assays (RNAscope, DNAscope) detected few positive signals. Viral outgrowth assays (qVOA) in Feb/16, Mar/16 and May/16 were negative (23 Mio CD4+T-cells, IUPM<0.031/Mio cells CD4+T-cells). Mouse VOA (Apr/16: Rag2-/-γc-/-, Apr/17: NOD-SCID IL2gR-/-) were also negative. Gp160 was the only remaining band on the blot. Peptide stimulation assays revealed the presence of CCR5-negative HIV-specific CTL recognizing HLA-A2-restricted RT-epitope YV9 and HLA-B7-restricted Gag-p6 epitope YL9.

Conclusion: Despite low signals in ultrasensitive assays no virus could be detected in qVOA/mVOA in the Duesseldorf patient. Taking into account the homozygous CCR5-d32 status we consider a viral rebound to be unlikely. An ATI is the only way to find out whether HIV has been eradicated by allogeneic CCR5-d32 HSCT. Therefore ART was stopped in Nov/18 after thorough discussion with the patient. Despite all plasma samples being negative after ATI longer surveillance is essential.

395 TELMISARTAN DECREASES HIV-1 RNA IN LYMPH NODES IN TREATED HIV INFECTION

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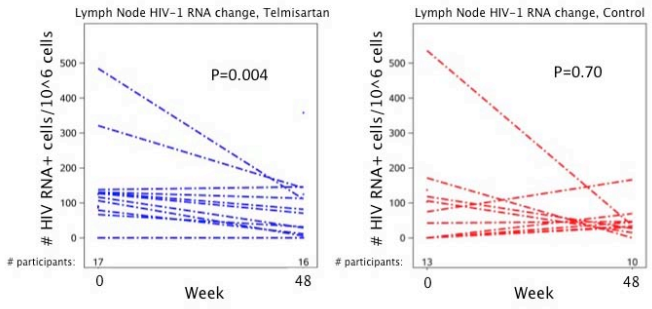
Background: Chronic inflammation in HIV infection can lead to lymph node (LN) fibrosis and limit CD4+ T-cell recovery. Telmisartan, an angiotensin receptor blocker and PPAR-γ agonist, is anti-inflammatory and anti-fibrotic. We previously reported telmisartan did not decrease LN fibrosis (i.e. collagen I by immunohistochemistry (IHC)) more than ART alone. We hypothesized telmisartan would decrease macrophage infiltration and HIV-1 RNA+ cells and increase CD4+ T-cells in LN.

Methods: In this completed, randomized-controlled trial, adults with HIV-1 RNA <50 copies/mL on ART for ≥48 weeks received telmisartan plus ART for 48 weeks or ART alone. The number of LN HIV-1 RNA+ (vRNA+) cells was measured by RNAscope and % CD4+ T cells and CD68+CD163+ macrophages by IHC at weeks 0 and 48. Statistical testing used two-sided rank-sum, signed-rank tests and Spearman correlations (α=0.05).

Results: Of 44 participants, 93% were male, 50% white non-Hispanic, median age 48 years, CD4+ T-cell count 588 cells/mm^{-3}. Week 0 median (IQR) number of vRNA+ cells/10^{-6} cells was 106 (67, 130; n=17) in the telmisartan arm and 75 (0, 118; n=13) for ART alone. By morphology, vRNA+ cells were lymphocytes. After 48 weeks, the number of vRNA+ cells/10^{-6} cells changed by -48 (-88, 0; P=0.004) in the telmisartan arm and +18 (-91, 45; P=0.70) with ART alone, with P=0.28 for the between-arm comparison. Median abundance of CD4+ T cells and macrophages in the B cell follicle (BCF) and T cell zone (TCZ) did not change significantly in either arm. With pooled treatment arms at Week 0, having less LN collagen I was associated with more CD4+ T cells in TCZ (r=-0.47, P=0.004). Having more vRNA+ cells was associated with fewer CD4+ T cells in BCF (r=-0.40, P=0.03) and fewer macrophages in BCF (r=-0.38, P=0.04) and TCZ (r=-0.35, P=0.04). While not associated at Week 0, 48-week increases in CD4+ T cells in TCZ were associated with decreases in macrophages in BCF (r=-0.60, P=0.0009) and TCZ (r=-0.60, P=0.0005) in a pooled analysis.

Conclusion: The number of LN HIV-1 RNA+ cells declined 45% with telmisartan added to suppressive ART. At Week 0, people with less LN fibrosis and fewer vRNA+ cells had more LN CD4+ T cells. Decreases in macrophages were accompanied by better LN CD4+ T cell recovery. Further characterization of these macrophages and the reservoir will clarify the interactions between HIV-1, LN immune cells, and their effects on fibrosis and the HIV reservoir.



396 DEPLETION OF BLOOD PD-1+ CD4 T CELLS BY A-PD-1 ADC SUPPRESSES HIV INFECTION IN VITRO

Patricia Jacquier[1], Craig Fenwick[1], Song Ding[2], Giuseppe Pantaleo[1]

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Background: Despite the efficacy of antiretroviral therapy (ART) at suppressing HIV-1 viral replication, treatment interruption results in viral rebound in the majority of individuals. HIV resurgence is due to the persistence of a long-lived virus reservoir that is not susceptible to ART. Recent studies have shown that PD-1+ CD4 T cells serve as a major cellular reservoir for HIV-1 replication and production, thus providing a strong rationale for developing therapeutic strategies targeting the elimination of PD-1+ CD4 T cells.

Methods: An anti-human PD-1 antibody (Ab) was conjugated with an anthracycline toxin to produce an antibody-drug conjugate (ADC) for the

targeted killing of PD-1+ CD4 T cells. Isolated CD4 T cells from eight untreated and five ART treated HIV-1 donors were incubated with either unconjugated αPD-1 Ab or ADC in a 5-day assay. Cells undergoing apoptosis and cell death were assessed by flow cytometry and culture supernatants were analyzed for viral p24 by ECL COBAS HIV Ag assay. Cells from ART treated donors were tested in a quantitative viral outgrowth assay (qVOA) to evaluate the frequency of cells harboring replication competent and infectious viruses following Ab or ADC treatment.

Results: In HIV-1 viremic donors, α-PD-1 ADC compared to α-PD-1 Ab efficiently depleted PD-1+ CD4 T cells as indicated by the increase frequency of apoptotic and dead cells in cultures treated with α-PD-1 ADC (4.4- and 5.8-fold increase in apoptotic and dead cells, P<0.0001). Of note, levels of viral p24 were strongly suppressed by 79% (P<0.0001) in culture supernatants of α-PD-1 ADC treated cultures compared to α-PD-1 Ab. In ART treated aviremic subjects, α-PD-1 ADC treatment also efficiently depleted PD-1+ CD4 T cells compared to α-PD-1 Ab (2.4/2.5 fold increase in apoptotic and dead cells, P≤0.0025). Importantly, HIV-1 p24 was undetectable in all culture supernatants from the five ART treated patients studied. Cumulative qVOA data from ART treated donors showed that α-PD-1 ADC treated CD4 T cells had a 92% reduction in the levels of HIV RNA (P<0.0001; n=4) and undetectable levels of infectious virus (p24 levels, P<0.0001; n=4) compared to α-PD-1 Ab treated cells.

Conclusion: These results indicate that depletion of PD-1+ CD4 T cells by α-PD-1 ADC represents a novel potential intervention towards functional HIV cure.

397 CHARACTERIZATION OF HIV-1 TRANSCRIPTION PROFILE AFTER ROMIDEPSIN THERAPY IN VIVO

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Background: Reversing HIV-1 latency has been suggested as a strategy to eradicate HIV-1. We investigated the effect of romidepsin on the HIV transcription profile in participants from the REDUC part B clinical trial.

Methods: Seventeen participants on suppressive antiretroviral therapy were vaccinated with six doses of the therapeutic vaccine Vacc-4x followed by treatment with three doses of romidepsin. Samples from nine study participants were available for HIV transcription profile analysis. Read-through, total (TAR), elongated (longLTR), polyadenylated (polyA) and multiply-spliced (TatRev) HIV transcripts and total HIV DNA were quantified at baseline (visit1) and 4 hours after the second (visit 10b) and third (visit 11b) romidepsin infusions, using droplet digital PCR.

Results: We observed a significant increase in read-through (1.7-fold, p=0.02), total (1.9-fold, p<0.01), elongated (2.4-fold, p<0.01) and polyadenylated (1.9-fold, p=0.03) HIV RNA/10^6 PBMCs after the second romidepsin infusion (visit 10b), and a 1.9-fold increase in elongated transcripts after the third romidepsin infusion (visit 11b) (p<0.01). No significant changes were observed in multiply-spliced HIV RNA or HIV DNA. No change was observed in the ratio of read-through/total HIV transcripts. The ratio of elongated/total HIV RNA increased after both the second and third romidepsin infusions (p=0.02), while the ratio of polyadenylated/elongated HIV decreased after the third infusion (p=0.02). A strong negative correlation was observed between HIV DNA and the time to rebound (VL>50copies/ml) at visit 1, 10b, and 11b (Rho=-0.81, -0.88, and -0.91; p=0.02, p<0.01, and p<0.01, respectively). Levels of all HIV RNAs tended to correlate negatively with the time to rebound. This association was strongest for the comparison between elongated transcripts and time to VL>1,000copies/ml after romidepsin administration (Rho=-0.78, p=0.03 at visit 10b; Rho=-0.77, p=0.03 at visit 11b).

Conclusion: In these patients, romidepsin increased early events in HIV transcription (initiation and especially elongation), but had less effect on later stages (completion, multiple splicing) that may be required for comprehensive latency reversal and cell killing. Without cell death, increased HIV transcription before or after latency reversal may hasten viral rebound after therapy interruption.

398 THE IMPACT OF VORINOSTAT AND THERAPEUTIC VACCINE ON GUT HIV DNA: THE RIVER GUT STUDY

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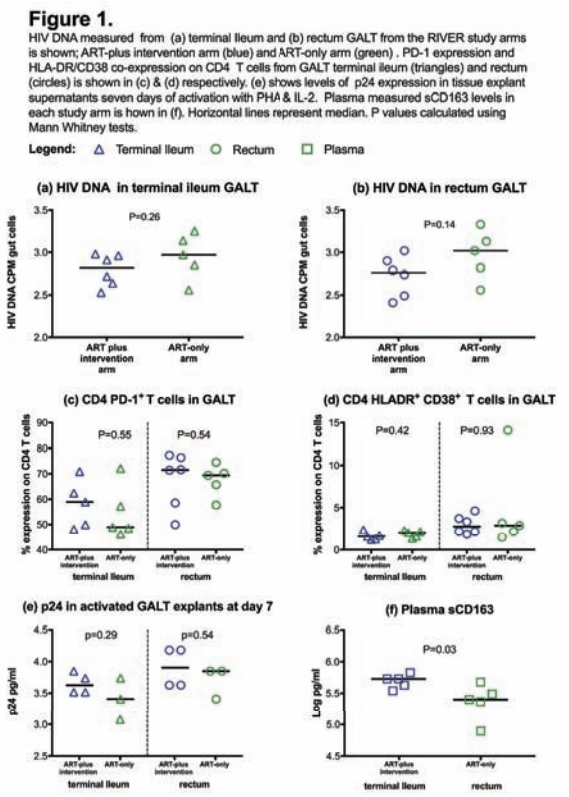
Background: The RIVER randomized trial examined the impact of a T-cell prime-boost vaccination with vorinostat plus ART (ART+V+V) compared with ART alone in treated primary HIV infection (PHI) on blood total HIV DNA. Tissue reservoirs such as the gut-associated lymphoid tissue (GALT) are important sites of HIV persistence and may be differentially affected by the intervention. This RIVER sub study compares HIV DNA, markers of immune activation & exhaustion in GALT, and microbial translocation by study arm.

Methods: ART was commenced within 4 weeks of confirmed PHI diagnosis at enrolment. At week 24, when plasma HIV-RNA was suppressed, participants were randomized (1:1) to receive either ART or ART plus a prime-boost T-cell vaccination (ChAdV63.HIVconsv and MVA.HIVconsv) followed by 10 doses of 400mg of vorinostat (ART+V+V). Following completion of the RIVER study protocol individuals (from each arm) consented to the gut sub study; individuals underwent colonoscopy, with terminal ileum and rectal biopsies taken for HIV DNA quantification (qPCR) and assessment of immune activation and exhaustion (PD-1 and HLA-DR/CD38 expression on CD4+ cells) by flow cytometry. Plasma microbial translocation markers (sCD163 & sCD14) were measured in plasma using Luminex. P24 antigen was measured in stimulated tissue explant supernatants by ELISA.

Results: Eleven men were enrolled in the RIVER gut study, five in the ART-only arm and six in the ART+V+V arm, all were male. The median total HIV DNA in the terminal ileum was 2.8 (ART+V+V) and 3.1 (ART) $\log_{10}$ copies per 10^6 gut cells (P=0.25), and in the rectum 2.8 (ART+V+V) and 3.0 (ART) $\log_{10}$ per 10^6 gut cells. (P=0.14). No significant differences in expression of PD-1 and HLA-DR/CD38 co-expression on CD4+ T-cells from GALT were observed between study arm, median p24 levels measured from explant supernatants (n=7) were similar in each arm. Significantly higher sCD163 (P=0.03) but not sCD14 (P=0.55) levels were observed in plasma from participants in the ART+V+V arm compared with ART only.

Conclusion: These data suggest that vorinostat in combination with a T-cell prime-boost-vaccine did not impact the GALT HIV reservoir, nor measures of immune exhaustion & activation on GALT CD4 T-cells in ART+V+V treated individuals compared with ART alone during PHI. Measures of bacterial translocation appear to be increased in ART+V+V over ART-only warranting further investigation.



399 RANDOMIZED TRIAL OF IMPACT OF MULTIPLE INTERVENTIONS ON HIV RESERVOIR: SPARC-7 TRIAL

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Background: Multiple interventional strategies may be required to decrease HIV-1 reservoir along with antiretroviral therapy (ART). We investigated the effect of treatment intensification with Dolutegravir (DTG) with and without Maraviroc (MVC), the HDAC inhibitor Nicotinamide (NA), and Auranofin (Au), and a dendritic cell vaccine pulsed with autologous HIV (DCv). Au had decreased viral DNA of ART treated SIV infected macaques.
Methods: 30 ART suppressed individuals for >2 years (CD4 nadir >350) were randomized to six arms of SPARC-7 TRIAL followed for 48 weeks. Patients from two arms received 3 doses of DCv after 48 weeks and were followed for additional 24 weeks. Groups: G1) continuation of ART, G2) intensified ART (ART+DTG+MVC), G3) intensified ART and HDACi (ART+DTG+MVC+NA), G4) intensified ART and Au (ART+DTG+MVC+Au), G5) partially intensified ART (DTG)+DCv, G6) partially intensified ART (DTG)+NA+Auranofin+DCv. Au was used for the first 24 weeks. DC was pulsed with autologous Gag256-367 peptides (nanomers, 3-6 peptides each patient) according to the best immunogenicity based in specific HLA of everyone. Total viral DNA was measured by qPCR in PBMCs and rectal biopsy tissues, and T cell activation by HLADR and CD38 on CD4 and CD8. In vitro immunogenicity of DCv was measured by pulsing patients' cells with autologous peptides used in DCv or S aureus enterotoxin B and brefaldine (control). IL2, TNF and interferon (IFN) were measured by flow cytometry in CD4 and CD8 collected at 1st 2nd and 3rd DCv dose and 30 days after 3rd dose (dose interval=2 weeks).
Results: There was no virologic failure or intervention-related SAE. Decrease in viral DNA was observed in G6 but not in other groups. (p=0.022; Odds ratio: 9.75, 95%CL: 1.1-72.39), and G1 showed a linear increase of proviral DNA (p<.05). One G6 patient evolved to undetectable proviral DNA during 48-week period and another after receiving the DCv. Rectal biopsy viral DNA was positive at baseline and at study end in each patient. Activation of CD4 and CD8 cells significantly decreased in G6 (p<0.05, 2-way Anova). There was a significant increase in interleukins measurement from 1st DCv dose to last dose at CD4+ T cells, and a significant increase in IL2 and TNF at CD8 from 1st to last dose (Kruskal-Wallis), with no changes in the control experiment.
Conclusion: NA+Au+antiretroviral intensification in combination with DCv reduced the viral reservoir size and cell activation markers among individuals on ART.

	Patient ID	Wk - 0	Wk - 24	W - 48	2 months after 1st DCv dose
	P26	0.62	Below LoD	Below LoD	Below LoD
	P27	33.31	4.36	34.36	63.52
G6	P28	98.30	70.37	18.09	20.37
	P29	23.43	7.65	1.65	Below LoD
	P30	0.32	0.25	0.82	15.37
	Mean	31.20	16.53	10.98	19.85

Table. Levels of viral DNA quantitation at PBMCs among patients of G6 at baseline (week zero), week 24, week 48 and 2 months after 3 doses of autologous DCv. In one patient of G6, viral DNA in PBMCs was below the limit of detection after treatment with intensified ART + NA + DTG, and, in another, viral DNA became undetectable after the DCv. One patient from G6, interrupted ART after week 48 and before DCv by his own decision, and presented a rebound in viremia, which reflected in an increase of viral DNA in PBMCs (double underline in the Table). Another patient from G5 also interrupted ART after week 48 followed by a rebound in viremia.

400 IMPACT OF EVEROLIMUS THERAPY ON HIV PERSISTENCE, IMMUNE FUNCTION, AND GENE EXPRESSION

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Background: mTOR inhibition may have beneficial effects on HIV persistence, including reducing T Cell CCR5 and PD-1 expression and promoting HIV transcriptional silencing. We previously observed lower cell-associated HIV DNA levels in renal transplant recipients that received sirolimus, an mTOR complex 1 (mTORC1) inhibitor, but prospective data are lacking. Therefore, we conducted a single-arm study of the impact of everolimus, an mTORC1/2 inhibitor on HIV persistence and immune function in ART-suppressed solid organ (SOT) recipients.
Methods: Ten HIV-infected SOT recipients on stable, suppressive antiretroviral therapy switched to or added everolimus for 6 months. Cellular and plasma HIV burden, lymphocyte immune phenotype and function, and gene expression/transcriptomic profiles were evaluated before, during and following everolimus treatment.
Results: Everolimus was well tolerated, with one participant stopping at month 2 for diarrhea. Most participants remained on long-term calcineurin inhibitors and mycophenolate anti-proliferative therapy. No overall changes in bulk measures of CD4+ T-cell-associated HIV total DNA, unspliced RNA, and residual viremia were observed, but treatment-mediated downregulation in hallmark mTOR signaling pathway gene expression at month 2 was observed in participants that experienced sustained decreases in CD4+ T-cell-associated DNA 6 months following completion of everolimus therapy. In addition, everolimus treatment was highly associated with downregulation of histone complex genes in network analyses, and the frequency of individual HIV transcriptionally active CD4+ T-cells measured directly by a single-cell encapsulation assay significantly increased from baseline to month 6 of therapy (186 to 309 RNA+ cells/10^6 CD4+ T-cells; P=0.02) across all participants. A significant decrease in PD-1 expression on terminally differentiated CD4+ TEMRA cells was observed (P<0.01), but no differences were observed in CD4+ or CD8+ T-cell intracellular cytokine responses to HIV or CMV peptide stimulations.
Conclusion: Everolimus therapy reduced mTOR gene expression in some individuals, which was associated with sustained reductions in CD4+ T cell HIV DNA levels. Everolimus also increased the frequency of individual HIV transcriptionally active cells during therapy in all participants which may have

been due, in part, to histone complex gene downregulation. These data suggest that individual genetic responses may greatly influence the efficacy of immune therapies on HIV persistence.

401 NEUROTOXICITY WITH HIGH-DOSE DISULFIRAM AND VORINOSTAT USED FOR LATENCY REVERSAL

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Background: The histone deacetylase inhibitor, vorinostat (VOR), and disulfiram (DSF), a drug used to treat alcohol dependence, reverse HIV latency in vivo by different pathways and have been safely administered to people with HIV. Three days of 2000mg DSF has been safely given as a latency reversal agent. This study aimed to determine if these two agents (i) reverse HIV latency more potently than a single agent and (ii) are safe and tolerable.

Methods: HIV-infected adults on suppressive antiretroviral therapy (ART) were enrolled in a prospective single arm study of DSF 2000mg daily for 28 days and VOR 400mg daily on days 8-10 and 22-24. The primary endpoint was plasma HIV RNA on day 11 relative to baseline. We quantified cell associated (CA) unspliced (US) and multiply spliced (MS) RNA and HIV DNA in CD4+ T-cells from blood; HIV RNA in plasma using a single copy assay; and p24 expression by SiMoA and histone acetylation by flow cytometry from PBMCs. Plasma concentrations of ART, VOR and DSF were quantified.

Results: The first two participants (P1 and P2) experienced grade 3 neurotoxicity (altered mental status possibly and probably related to DSF respectively), which led to trial suspension. P1 was a 67 year-old male on ABC/3TC/DTG with a CD4 count of 762 cells/L and VL <50 copies/mL for 16.7 years. On study day 24 (having missed DSF and VOR on day 10 and stopped DSF and all ART from day 17-24) he presented with confusion, lethargy, and ataxia. Neuroimaging revealed sagittal sinus thrombosis and chronic vertebral artery occlusion. He was admitted to hospital, anticoagulated and symptoms resolved by day 29. P2 was a 61 year-old male on TAF/FTC + RAL with a CD4 of 1085 cells/L and VL <50 copies/mL for 4.8 years. On day 11 he presented with paranoid ideation, emotional lability, lethargy and ataxia. He was admitted to hospital; brain CT scan was normal and his symptoms resolved by day 23. Both participants had increased CA-US RNA following study drugs, which persisted for weeks after drug cessation (Figure). P2 also had increased plasma viremia from day 8-37 (peak 81 copies/mL on day 21) with therapeutic ART drug levels. Low but detectable levels of VOR and histone acetylation were seen in both participants.

Conclusion: The study drug combination was not safe with significant but reversible neurotoxicity, which we suspect was related to prolonged high dose DSF. There was evidence of latency reversal in both participants. Prolonged high dose DSF, with or without VOR, should not be further pursued.

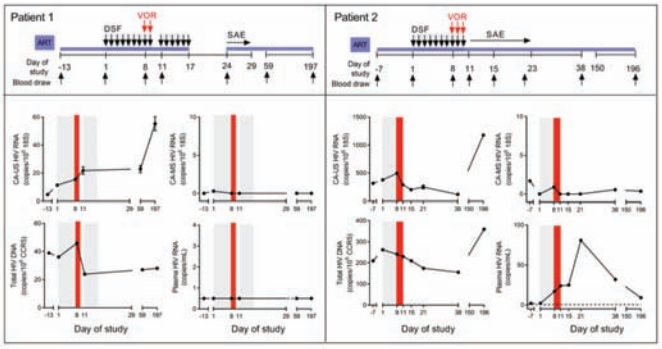

Figure. Summary of clinical course and virology (CA-US RNA, CA-MS RNA, HIV DNA, HIV RNA) for 2 participants receiving Vorinostat (red line) and high dose Disulfiram (grey) while on ART (purple). Patient 1 viral load on Day 24 was undetectable <20 copies/mL (Cobas Taqman)

402 ANOGENITAL HIV DETECTED DURING ANALYTIC TREATMENT INTERRUPTION IN REMISSION TRIALS

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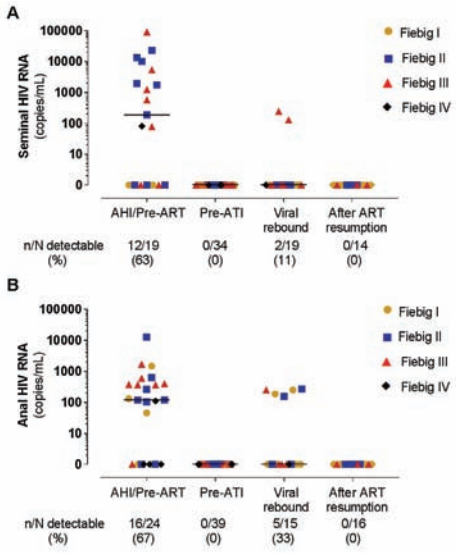
Background: Analytic treatment interruption (ATI) is a temporary and carefully monitored withdrawal of antiretroviral therapy (ART) often used to assess new interventions in early phase HIV remission trials. Rebound viremia during ATI presents a risk for HIV transmission to sexual partners.

Methods: The SEARCH 010/RV254 cohort in Thailand enrolls participants who start ART during acute HIV infection (AHI). Participants in 3 substudies that included ATI opted to provide semen and anal (lavage or sponge) samples up to 4 times: AHI prior to ART, pre-ATI, viral rebound during ATI, and after ART re-initiation. HIV-1 RNA was extracted using modified High Pure System method and quantified by Roche COBAS TaqMan HIV-1 with lower limit of detection of 1.5 (all HIV RNA values reported as log10 copies/mL).

Results: 47 male participants who underwent ATI provided anogenital samples at one or more time points. At AHI all had plasma viremia with median (range) HIV RNA 5.7 (3.3-7.2). HIV RNA was detected pre-ART in 63% of semen (median 3.3, range 1.9-5.0) and 67% of anal samples (median 2.6, range 1.7-4.1). Prior to ATI after median (range) ART duration of 136 (73-343) weeks, all participants were aviremic and all semen (n=34) and anal (n=39) samples were HIV RNA undetectable. During ATI, all but one participant experienced plasma viral rebound (median HIV RNA 3.7, range 1.7-5.4). HIV-RNA was detectable in 11% (2/19) of semen and 33% (5/15) anal samples at viral rebound; and at low level ranging from 2.1 to 2.4. HIV RNA in semen and/or the anus was predominantly detected when plasma HIV RNA was >4.0 (6/12 samples) and uncommon below this level (1/22 samples) (p=0.008 by Fisher exact). After ART re-initiation and subsequent viral suppression, at a median of 48 (range 9-52) weeks, all semen (n=14) and anal (n=16) samples were undetectable for HIV RNA.

Conclusion: Viral rebound after ATI can be associated with detectable HIV RNA in the semen and anal secretions, but at low levels and predominantly when the plasma HIV viral load is above 4.0 log10 copies/mL. This is relevant to future HIV remission trials that require longer periods and higher levels of viremia to assess intervention efficacy. ART re-initiation and suppression of plasma viremia clears HIV RNA from the semen and anus. Study participants and their sexual partners should be counseled on potential risk for HIV transmission during ATI and should employ standard HIV prevention methods such as condom use and/or preexposure prophylaxis.



403 IMPACT OF ATI ON HIV RESERVOIRS AND IMMUNE PARAMETERS IN EARLY TREATED INDIVIDUALS

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Background: Eradication of HIV from an infected individual is not feasible with current antiretroviral therapy (ART) and the vast majority of individuals experience plasma viral rebound upon cessation of therapy. Given the current requirement for life-long therapy in individuals whose virus has been successfully suppressed with ART, novel therapeutic strategies aimed at achieving drug-free HIV remission are being explored in infected individuals who began ART during the acute/early phase of infection. Such strategies would require analytical treatment interruption (ATI) for proof of concept. Thus, it is of considerable interest to investigate the impact of ATI on the HIV reservoir and immune parameters in such infected individuals.
Methods: Longitudinal immunologic and virologic analyses were conducted on specimens obtained from 22 individuals treated early in the course of infection who previously participated in a therapeutic vaccine trial. The dynamics of HIV reservoirs and immunologic parameters were examined in the study subjects prior to ATI, during ATI, and following reinitiation of ART.
Results: The median duration of the ATI phase was 124 days (range 56-242). At baseline, the frequency of CD4+ T cells carrying replication-competent HIV positively correlated with that of cells carrying HIV DNA and inducible cell-free virions. Following discontinuation of ART, all study subjects experienced plasma viral rebound and significant increases in the frequency of CD4+ T cells carrying HIV proviral DNA and cell-associated RNA, as well as the level of immune activation in the CD8+ T cell compartment (CD38+DR+). In addition, the levels of CD4+ T, B, and natural killer cells decreased following plasma viral rebound during the ATI phase. However, the size of the HIV reservoirs, including replication-competent virus and inducible cell-free virions, and all immune parameters returned to baseline (pre-ATI) levels after ART was resumed and maintained for a median of 58 months (range 30-89).
Conclusion: Our findings demonstrate that short-term ATI does not cause permanent expansion of HIV reservoirs nor irreparable damages to the immune system in individuals who initiated ART during the acute/early phase of infection. Therefore, our data support the use of ATI as a crucial component of clinical trials designed to examine the efficacy of therapeutic interventions as a substitute for ART in infected individuals who initiated ART during the early phase of infection.

404 DETECTION OF CELL-ASSOCIATED HIV-1 NUCLEIC ACID IN BLOOD AFTER EARLY ART

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Background: Initiation of HIV-1 antiretroviral drug therapy (ART) during acute infection can delay HIV seroconversion and reduce the HIV viral reservoir. The Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test v2.0 (CAP/CTM), capable of detecting both HIV RNA and DNA, was used to measure the levels of Cell Associated HIV-1 (CAH) nucleic acid in Peripheral Blood Mononuclear Cells (PBMCs) prior to and post initiation of ART during acute HIV infection.
Methods: PBMCs from 37 participants enrolled in the HIV early treatment study (RV254/SEARCH010, Bangkok, Thailand) were selected based upon Fiebig Stage (FI-VI) at time of ART initiation: FI (N=9), FII (N=6), FIII (N=7), FIV (N=7), FV (N=5), and FVI (N=3). Cell lysates of 1 million PBMCs collected at week 0 and weeks 1/2, 8 and 60 post ART initiation were tested in triplicate by CAP/CTM.
Results: Plasma HIV-1 RNA levels prior to ART initiation ranged from 2.43-5.16 and 4.17-6.9 log c/ml for individuals in F1 and FII-FVI, respectively. Initiation of ART resulted in a rapid loss of plasma HIV-1 RNA and suppression of HIV virus in all individuals by week 8. CAH levels averaged 1.44 log c/million PBMCs in FI untreated individuals, with 5/9 (55.6%) at or below Limit of Quantitation (LOQ: 1.42 log c/million PBMCs) for the assay. The average CAH log c/million PBMCs for untreated FII was 4.08 and 3.61 for untreated FIII-FVI. CAH at week 8 for F1 treated individuals was near or at the LOQ (3/9), and 6/9 (67%) were not detected. At week 60, 8/9 (88.9%) FI treated individuals were undetectable. At week 8, 4/13 (30.8%) FII/FIII treated individuals were near or below LOQ; and 6/13 (46.2%) by week 60. Only 2/13 (15.4%) were undetected. For individuals treated at FIV-FVI, 4/15 (26.7%) were near or at the LOQ by week 60 with CAH levels in 10/15 individuals ranging from 1.44-3.01 log c/million PBMCs.
Conclusion: HIV nucleic acid persists in PBMCs of infected individuals under therapy and can be readily monitored by the CAP/CTM assay in the absence of detectable plasma HIV-1 RNA. Only FI treated individuals had consistently undetectable CAH by week 8. ART resulted in a logarithmic decline in CAH with an initial rapid loss followed by a more gradual decrease. The residual HIV reservoir at 60 weeks increased when treatment was initiated at later Fiebig stages. Testing of PBMCs by the Roche CAP/CTM assay provides a convenient measure of residual HIV reservoir in blood and may be useful for monitoring patients under therapy and in HIV remission studies.

405 ALTRUISM IN END OF LIFE HIV RESEARCH: INSIGHTS FROM LAST GIFT STUDY

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Background: End-of-life (EOL) HIV cure-related research provides a novel approach to study HIV reservoirs and promising HIV cure research interventions. The Last Gift is a clinical research study at the University of California San Diego enrolling terminally ill persons living with HIV (PLWH) to contribute towards HIV cure science without personal benefits. As part of a socio-behavioral sub-study we elucidate motivations for participation and experiences while in the study.
Methods: The Last Gift study enrolled 7 participants since summer 2017 (n=7 males; aged 45–72 years). All were first-time HIV cure research participants but were not new to clinical research. Along with HIV, they had a terminal illness with a prognosis of <6 months. Ante-mortem procedures involved blood draws, baseline and follow-up interviews. Post-mortem procedures involved a rapid autopsy (<6 hours of death) to characterize the size, distribution and molecular characteristics of HIV reservoirs in various tissues. Results from the socio-behavioral interviews to Last Gift participants and their Next of Kin (NOK) were transcribed verbatim and coded using thematic analysis. Questions included (1) motivation for participation, (2) perceived benefits, (3) understanding of the study goals, (4) meaning of the Last Gift study, (5) post-mortem insights or concerns (NOK only).
Results: Deep altruism (but not monetary compensation) was the main motivator to participation. All Last Gift participants and NOK expressed psychosocial benefits and meaningfulness from being part of the Last Gift study. Participants and NOK displayed a sophisticated understanding of the study and its purpose. NOK did not perceive any risks or ethical concerns towards study participation but would like to be included earlier in the process. The post-mortem interviews were emotional and overwhelmingly positive. NOK expressed that the study benefited the grieving process and they did not report any decisional regrets from Last Gift participants.
Conclusion: Interviews identified societal and psychological benefits to participation in the Last Gift study. Terminally ill PLWH valued the altruistic benefits and the deep sense of purpose of being an integral part of HIV cure research. Thus, we are encouraged to continue the development of our EOL research model. Results emphasize the importance of incorporating perceptions of family members, as well as socio-behavioral research methodologies to understand the effects of participation on everyone involved.

406 WITHDRAWN / INTENTIONALLY UNASSIGNED

407 EARLY INFLAMMATORY PROFILES IN LONG-TERM VIRALLY SUPPRESSED WOMEN PREDICT COGNITION

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Background: Neurocognitive (NC) impairment persists even among those who are virally suppressed. Virally suppressed women living with HIV (WLWH-VS) demonstrate vulnerabilities across multiple cognitive domains. As there is strong scientific premise for immunological processes contributing to cognitive status, we examined the contribution of early neuroinflammatory profiles to future NC performance.

Methods: We selected 49 WLWH who achieved and maintained viral suppression shortly after effective antiretroviral (ARV) initiation, along with a matched sample of 56 HIV- women from the Women's Interagency HIV Study. Peripheral levels of 42 inflammatory markers were measured using stored samples from within two years of ARV initiation and 1, 7, and 12 years later. 27/49 WLWH-VS and 35/56 HIV- women completed NC testing (e.g., learning, memory, attention) following the 12 year follow-up at ≥1 time points. We searched for latent immune profiles (underlying patterns of marker changes) by adapting a dynamic matrix factorization analytic method that builds upon Tucker decomposition. We calculated the Frobenius residual to choose the number of components and named them based on the markers that contributed the most to each one. We used mixed-effects models to examine changes in immune components over time, which were subsequently correlated with domain-specific (e.g., learning, memory) and global NC performance.

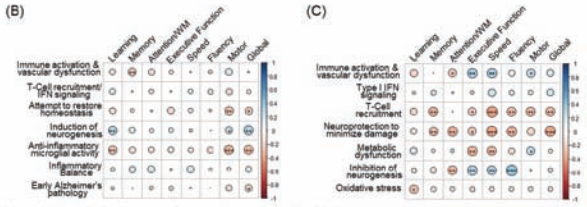
Results: Seven latent immune components emerged for WLWH-VS and HIV- women. Immune components 1-4 were common across groups (e.g., immune activation and vascular dysfunction) whereas components 5-7 were distinct (Fig 1A). Early inflammatory profiles predicted subsequent NC performance in both groups but more associations were significant in WLWH-VS (47%) versus HIV- women (20%)(Fig 1B&C). Among WLWH-VS, immune components reflecting greater T-cell recruitment and neuroprotection predicted worse global performance whereas components reflecting oxidative stress and metabolic function predicted domain-specific performance. Among HIV-, immune components predicted global versus domain-specific performance.

Conclusion: Seven latent immune components emerged for WLWH-VS and HIV- women. Immune components 1-4 were common across groups (e.g., immune activation and vascular dysfunction) whereas components 5-7 were distinct (Fig 1A). Early inflammatory profiles predicted subsequent NC performance in both groups but more associations were significant in WLWH-VS (47%) versus HIV- women (20%)(Fig 1B&C). Among WLWH-VS,

Fig 1. (A) Strongest inflammatory markers contributing to each latent component of the factor matrix by HIV-serostatus, and the mean inflammatory phenotypes associating with cognitive function among HIV-uninfected (B) and women living with HIV (C)

(A)

W-matrix Component	HIV-serostatus	
	HIV-uninfected (n=56)	Women living with HIV (n=49)
1	**Immune activation & vascular dysfunction**	**Immune activation & vascular dysfunction**
	Beta-2 microglobulin, Clusterin, Cystatin C, sCD14, sVEGFR2	*Beta-2 microglobulin, Clusterin, Cystatin C, sCD14, sVEGFR2*
2	**T cell recruitment/IFN signaling**	**Type I IFN signaling**
	TRAIL/CD253, *IL-10, FGF-2, Fractalkine/CX3CL1*, SDF-1a+b/CXCL12, ITAC/CXCL11	TRAIL/CD253, IL-10, BCA-1/CXCL13, 6CKINE/CCL21
3	**Attempt to restore homeostasis, neuroprotective phenotype**	**T cell recruitment to brain through blood brain barrier regulation & microglial chemokine production**
	Fractalkine/CX3CL1, IL-10, CRP, sVEGFR2, serum amyloid A	*Fractalkine/CXCL1, IL-10, CRP, sVEGFR2, MIP3b/CCL19, MIG/CXCL9, ITAC/CXCL11*
4	**Inducing neurogenesis through anti-inflammatory pathways to maintain neuronal function**	**Neuroprotection as a mechanism to minimize damage**
	IL-10, FGF-2, Fractalkine/CX3CL1, IL-6	*IL-10, FGF-2, Fractalkine/CXCL1, IL-17*
5	**Anti-inflammatory microglial activity**	**Metabolic dysfunction**
	Myeloperoxidase, MIP-1a/CCL3, IL-8	TRAIL/CD253, serum amyloid A, *CRP, IL-10*, Adiponectin
6	**Balance between pro- & anti-inflammatory states**	**Inflammation-induced inhibition of neurogenesis**
	IL-6, IL-10	*IL-6, serum amyloid A, MIP3b/CCL19, MIG/CXCL9, ITAC/CXCL11, FGF-2, Fractalkine/CX3CL1*
7	**Early Alzheimer's pathology**	**Oxidative stress**
	Fractalkine/CX3CL1, FGF-2, serum amyloid A, CRP	Myeloperoxidase, *IL-6, sVEGFR1, IL-17, IL-10*



Note. Markers in italics were inversely associated with the component otherwise the markers were positively associated with the component. W-matrix=how much each inflammatory marker contributes to the seven latent immune components. WM=working memory; *p<0.05; **p<0.01; ***p<0.001

408 LONGITUDINAL PHENOTYPING OF DECLARATIVE MEMORY AMONG WOMEN LIVING WITH HIV

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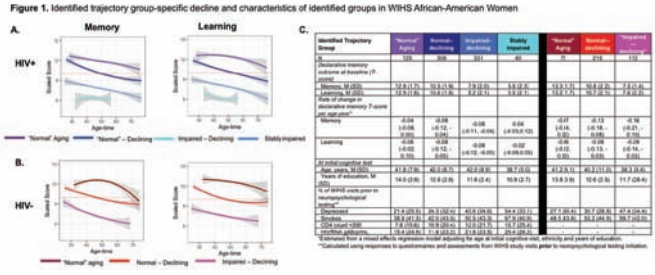
Background: There is considerable heterogeneity in patterns of cognitive decline in HIV-infected (HIV+) individuals. Age, sex, and race contribute to individual differences in patterns of cognitive decline, including in the domain of verbal memory. Advanced statistical models can be applied to parse out the heterogeneity in cognitive decline and to identify subgroups of individuals who might benefit from interventions tailored to their particular pattern of change and risk factors. Here, we applied a novel statistical method to identify clusters of individuals with distinct patterns of age-related change in declarative memory in HIV+ and HIV-uninfected (HIV-) women.

Methods: We included 1530 women from the Women's Interagency HIV Study who completed the Hopkins Verbal Learning Test at two or more visits. To derive subgroups with similar patterns of decline by HIV-serostatus, we applied a novel modeling strategy that simultaneously considers multiple longitudinal declarative memory outcomes. This model adopts a linear mixed-effects framework to model the trajectory of each cognitive outcome over time, while also jointly clustering individuals via a factor analysis model. We tested for differences in demographic and clinical characteristics between the clusters using a multivariable-adjusted multinomial model.

Results: Of the 1530 included participants, 1167 were HIV+ (69% African-American [AA]; 31% white/other [W/O]) and 586 were HIV- (68% AA; 32% W/O). Stratification by race was necessary to optimize clustering. In the HIV+ AA's, we identified four distinct subgroups with differential patterns of change in memory: a subgroup with minimal decline, two with accelerated decline, and a subgroup with stable impairment in learning and memory (**Fig 1A**). In the HIV- AA's, we identified three subgroups: one with lesser decline and two with accelerated decline (**Fig 1B**). In multivariable adjusted models, individuals with accelerated decline were more likely to be less educated (P<0.001) and have a history of depression (P<0.001) versus those in the minimal decline subgroups (**Fig 1C**). Similarly classified subgroups were identified in W/O HIV+ and W/O HIV- participants.

Conclusion: Our data-driven modeling approach successfully identified clinically meaningful subgroups of individuals with distinct phenotypes of declarative memory decline. Depression was a key, potentially modifiable determinant of membership in a subgroup characterized by more rapid decline.



409 CAPTURING DNA METHYLATION CHANGES IN MONOCYTES WHEN INITIATING ART IN ACUTE HIV

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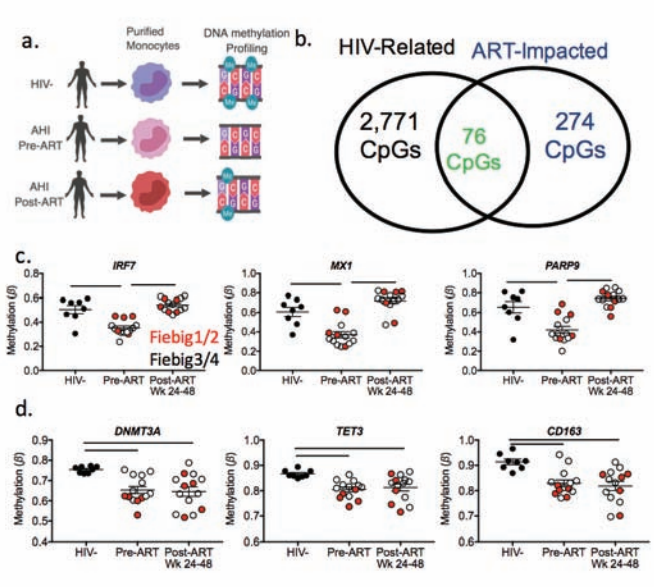
Background: Monocytes are involved in HIV pathogenesis, persistence, and are associated with adverse clinical outcomes. We previously revealed in monocytes the identification of an epigenetic footprint of HIV-related cognitive impairment in chronic infection (PMCID: PMC5024304). Yet, knowledge about epigenetic changes during acute HIV infection (AHI) in monocytes, the effects of early initiation of combination anti-retroviral therapy (cART), and the implications on CNS outcomes remains unknown.

Methods: We investigated early HIV-related DNA methylation changes in highly purified monocytes from AHI adults initiating early ART in a prospective study (RV254/ SEARCH010) and uninfected controls (RV304/ SEARCH013). DNA methylation was measured genome-wide using the Illumina HumanMethylationEPIC array. We also examined DNA methylation changes longitudinally during AHI at entry and post-cART.

Results: We examined 15 AHI adults (n=6 Fiebig stage (F) I/II and n=9 (FIII) with median days of infection of 17.5 days (baseline). Twelve adults were examined after initiating cART up to 48 weeks (post-cART). Matched HIV-uninfected adults (n=8) served as controls. In cell sorted purified monocytes obtained from peripheral blood, we observed 2,847 CpG sites showing absolute mean differences in methylation greater than 5% between during AHI and uninfected participants (Δβ-value > |0.05| and significant at FDR adjusted P < 0.05). The majority (94.55%) of sites were hypomethylated in AHI compared to uninfected and related to genes involved in the type I interferon signaling pathway and activating transcription factor binding pathway. We utilized a paired differential methylation analysis of donors at baseline and post-cART and observed 350 CpG sites showing absolute mean differences in methylation greater than 5% (Δβ-value > |0.05| and significant at FDR adjusted P < 0.05). We evaluated if the HIV-related DNA methylation changes in monocytes were impacted by immediate ART and observed that less than 3% (76 methylation sites) of the 2,847 HIV-related CpGs were overlapping with the 350 CpGs impacted by cART treatment.

Conclusion: HIV-related DNA methylation changes were identified as early as FI/II in AHI and early cART minimally restored these changes suggesting HIV embeds an indelible epigenetic memory. Further investigation is needed to determine whether HIV epigenetic changes relate to viral persistence, residual inflammation or CNS decline that are seen in chronic infection.



410 PLASMA (1→3)-B-D-GLUCAN LEVELS CORRELATE WITH NEUROCOGNITIVE PERFORMANCE IN HIV

Martin Hoenigl[1], Scott L. Letendre[1], Jennifer Iudicello[1], Donald Franklin[1], Magali Porrachia[2], Milenka Vargas[2], Ronald J. Ellis[1], Malcolm Finkelman[3], Sara Gianella[2]

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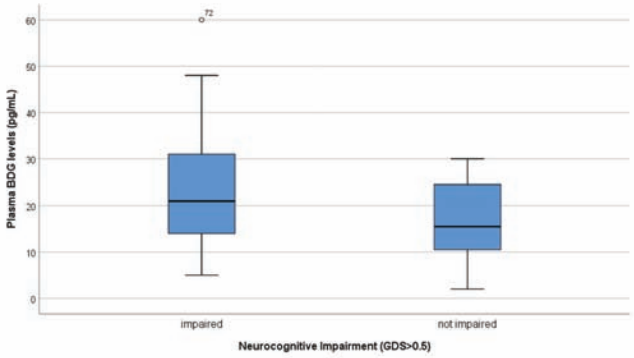
Background: Although antiretroviral therapy (ART) has improved survival and morbidity, people living with HIV (PLWH) have higher rates of non-AIDS disorders, such as neurocognitive (NC) impairment (NCI), than the general population. (1-3)-b-D-glucan (BDG) is a fungal cell wall component which – in the absence of fungal infections – serves as biomarker for gut barrier integrity failure and microbial translocation. The objective of this study was to determine whether higher plasma and cerebrospinal fluid (CSF) levels of BDG are associated with NCI in PLWH.

Methods: Paired blood and CSF samples were collected from 61 PLWH who underwent a NC assessment as part of the prospective CHARTER study between 2005- 2015. Raw NC test scores were converted to ddemographically-adjusted T-scores and used to derive a Global T-score (higher scores=better performance). Individual T-scores were also converted to deficit scores and averaged to derive a global deficit score (GDS) which was used to classify NCI (i.e., GDS≥0.5). Specimens were stored at -80°C within 90 minutes of collection. BDG was measured using the Fungitell assay (Associates of Cape Cod, Inc.) and soluble urokinase plasminogen activator receptor (suPAR; marker of monocyte activation and chronic inflammation) using the suPARnostic assay (ViroGates, Copenhagen, Denmark). Blood plasma samples were also tested for sCD14 (marker of monocyte activation), intestinal fatty acid binding protein (IFABP, marker of gut epithelial dysfunction), and blood CD4/CD8 ratio. Spearman's rho correlation analysis assessed associations between BDG, other biomarkers and NC performance variables.

Results: Overall, 58/61 participants had undetectable HIV RNA in blood plasma at the time of sampling. Median BDG level was 18 pg/mL in plasma (range: 2-60 pg/mL) and 20 pg/mL in CSF (range: 0-830 pg/mL). Higher levels of plasma BDG were associated with lower Global T Scores (Spearman rho=-0.32; p=0.013) and NCI (p=0.027, see Figure). A plasma BDG cut-off of >30pg/mL showed 30% sensitivity for NCI and 100% specificity. There was also a trend towards higher CSF BDG levels among those impaired versus unimpaired (p=0.083). No other significant associations were observed between the remaining biomarkers and the NC variables. Plasma levels of BDG correlated significantly with plasma suPAR levels (rho=0.31, p=0.016), but not with other biomarkers.

Conclusion: Elevated plasma levels of BDG may be a biomarker for detection of NCI in PLWH on suppressive ART.



411LB NEURON-DERIVED EXOSOMES IDENTIFY COGNITIVE IMPAIRMENT AND GENDER DIFFERENCES IN HIV

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Background: Cognitive impairment in chronic well-controlled HIV infection continues to affect up to 60% of individuals. Mechanisms are still unknown but probably associated with continued neuroinflammation. Plasma neuron-derived exosomes (NDE) are a peripheral biomarker for investigating the health

of neurons in real time. NDE carry proteins that can serve as new and more accurate biomarkers of cognitive impairment.
Methods: We obtained 80 plasma specimens from NIH-sponsored tissue banks, that included 8 groups of 10 persons with various neurocognitive diagnoses, HIV positive and negative, 51 women and 29 men, with 4 groups ≤ 45yo and 4 groups ≥50yo. All had extensive epidemiology, clinical and neurocognitive data. We isolated NDE from plasma using a 2-step procedure and L1CAM, a neuron specific antibody. We performed mass spectrometry (M/S) on 10 NDE samples. ELISA was used to quantify several proteins of interest. Proximity extension analysis (PEA) for 184 neural-associated proteins was performed on 48 samples.
Results: Neuronal enrichment of NDE was confirmed with elevated synaptophysin as well as over 100 neuronal proteins identified by M/S. HMGB1 and neurofilament light (NF-L) proteins were significantly increased in NDE from cognitively impaired men but not for women. NDE from HIV+ men had decreased p-T181-tau, a positive marker for Alzheimer's disease, compared to no difference in women. Using PEA, 25 proteins were significantly differentially expressed in HIV infection alone. Eleven proteins significantly identified cognitive impairment, both asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), in HIV+ women; 2 were also markers for MND in men. NDE from men and women had statistically significant divergent results with ezrin, an axonal protein and SCARA5, a scavenger protein in neurons. NDE from women had significantly increased cathepsin S, tau, neuronal cell adhesion molecule and granzyme A, in ANI.
Conclusion: These findings show that NDE are from a neuronal source and that HIV infection alone causes neuronal dysfunction. There are several significantly differentially expressed NDE proteins that can separate ANI from MND in women and some can identify cognitive impairment in men compared to women. These results may explain variability in previous findings for HIV cognitive impairment biomarkers when men and women are grouped together. The results suggest possible mechanistic gender differences to therapy associated with cognitive impairment.

412 REDUCED SCYLLO-INOSITOL CORRELATES WITH NEUROCOGNITIVE IMPAIRMENT IN HIV+ INDIVIDUALS

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Background: Biochemical mechanisms underlying HIV-associated neurocognitive disorder (HAND) and the depressive symptoms seen in many HIV+ individuals are unclear. In Alzheimer's disease, scyllo-inositol (sI) treatment has ameliorated cognitive deficits in transgenic mice and in clinical trials has decreased cerebrospinal fluid amyloid-β42 and increased brain sI. However, sI has been little studied in HIV. We examined sI and other metabolites as potential biomarkers of neuropsychiatric measures in an HIV+ population.
Methods: HIV+ individuals on stable antiretroviral therapy > 1 year and diagnosed with mild-to-moderate neuropsychological (NP) impairment at screening underwent cross-sectional magnetic resonance spectroscopy (MRS) and NP testing. The Beck Depression Inventory (BDI)-II was administered. We computed global and 8 domain-specific NP z-scores (working memory [NPZwm], language [NPZlang], motor [NPZmotor], etc.). Single-voxel 1H-MRS at 3T (PRESS sequence with TE/TR=35/2000 ms) quantified metabolites including sI (concentrations; ratios to total creatine [tCr]) using 'LCModel' analysis in left frontal white matter (FWM) and basal ganglia (BG). Multi-voxel magnetic resonance spectroscopic imaging yielded ratios of N-acetylaspartate (NAA) to choline (Cho) in bilateral regions. Pearson (R) or Spearman (ρ) correlation and bootstrapped 95% confidence intervals assessed metabolite relationships to NP and BDI-II scores.
Results: We evaluated 30 HIV patients [26 males; age 57± 7 years; 90% with plasma HIV RNA < 20 copies/mL; median current and nadir CD4 count 594 and 165 cells/μL]. Decreased FWM sI and sI/Cr related to NP deficits (Table); e.g., sI/Cr correlated with NPZlang (ρ=0.59, p=0.003). Total NAA (tNAA) in FWM and BG also showed significant positive associations with NP z-scores. Lower gamma-aminobutyric acid (GABA) in BG related to slower psychomotor speed (ρ=0.41, p=0.033). Frontal, temporal and BG tNAA/Cho correlated positively with NP performance. Reduced GABA and glycerophosphocholine (GPC) in BG were linked to higher BDI-II (ρ~ −0.4, p~0.03). Among NP z-scores, only NPZmotor related to BDI-II (ρ= −0.40, p=0.028). Nadir CD4 correlated with FWM sI (ρ=0.58, p=0.006) and sI/tCr (ρ=0.48, p=0.029) but not NP z-scores.
Conclusion: Scyllo-inositol in FWM of HIV+ individuals may provide a biomarker of NP functioning not mediated by mood. Reduced sI may reflect NP effects of past HIV disease. The role of sI in HAND warrants further study, as do GABA and GPC in relation to HIV-associated depression.

Table. Significant correlations (p<0.05) between NP z-scores and metabolite levels measured by single-voxel ^{1}H MRS in left frontal white matter of 30 HIV+ participants. Bootstrapped 95% confidence intervals (CI) are given. We required Cramér–Rao Lower Bounds (CRLB)<50 for scyllo-inositol (sI) concentrations and CRLB<20 for total N-acetyl compounds (tNAA), resulting in N=23 for sI and N=30 for tNAA correlations.

Metabolite	NP domain	Correlation[1]	P-value	95% CI
sI	Psychomotor	0.53	0.009	0.15, 0.78
sI	Language	0.49	0.017	0.05, 0.75
sI	Motor	0.42	0.047	0.03, 0.70
sI	Global[2]	0.43	0.039	0.05, 0.72
sI/tCr	Language	0.59	0.003	0.22, 0.80
sI/tCr	Psychomotor	0.43	0.040	0.06, 0.71
tNAA	Executive	0.45	0.013	0.14, 0.75
tNAA	Visuospatial	0.45	0.013	0.08, 0.64
tNAA	Language	0.43	0.018	0.08, 0.72
tNAA	Global[2]	0.43	0.018	0.08, 0.65

MRS=magnetic resonance spectroscopy; NP=neuropsychological; sI=scyllo-inositol; N-acetyl compounds (tNAA)=N-acetylaspartate (NAA) + N-acetylaspartylglutamate (NAAG); tCr=total creatine; CI=confidence interval.

[1] Bivariate correlation coefficients were computed by Spearman correlation for sI and by Pearson correlation for tNAA.
[2] Based on 20 tests.

413 LEGACY EFFECTS ON COGNITIVE FUNCTIONS AMONG HIV-INFECTED MEN

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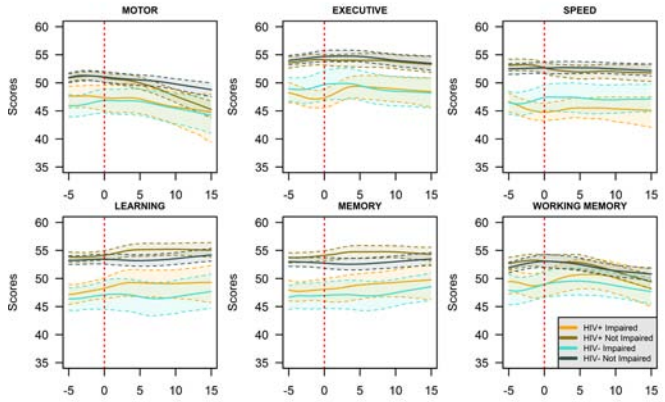
[1]University of Pittsburgh, Pittsburgh, PA, USA, [2]University of California Los Angeles, Los Angeles, CA, USA, [3]Rush University Medical Center, Chicago, IL, USA, [4]Johns Hopkins University, Baltimore, MD, USA, [5]Northwestern University, Chicago, IL, USA
Background: Prior to the use of combination antiretroviral therapy (cART), HIV-infected subjects were at high risk for developing significant neurological and neuropsychological dysfunction. However, such risk has declined after using cART, while the rate of milder forms of impairment has remained relatively unaffected. It is unclear from existing data how cognitive functions in HIV-infected subjects changed after beginning cART and the extent to which impairment prior to cART is associated with subsequent cognitive functions (i.e., legacy effect). This report aims to describe trajectories of cognitive functions in HIV-infected subjects over 15 years following the use of cART.
Methods: We matched HIV-infected subjects from the Multicenter AIDS Cohort Study who had used cART with uninfected men using propensity scores computed with demographics and baseline cognitive functions (measured in 1996). These matched pairs were aligned such that time T0 corresponded to the first cART use visit by the HIV-infected men. We applied the Multivariate Normative Comparison method to all six NP domain scores to detect any abnormality in cognitive functions. We coded subjects as having prior impairment if there were any cognitive abnormalities at any visit prior to T0. We plotted the LOWESS trajectories of cognitive functions from T-5 to T+15 separated as a function of HIV and cognitive status prior to cART.
Results: 537 matched pairs were utilized in the study. 121 of the infected men and 100 of the uninfected controls were found to have prior impairment. We did not observe significant differences between HIV-infected and uninfected men in trajectories of cognitive functions regarding executive processing, speed of information processing, learning and memory, working memory, and attention. However, faster decline in motor speed and coordination was observed among HIV-infected subjects without prior impairment approximately 10 years after the start of cART. Overall, subjects without prior impairment had higher scores in all six NP domains compared with subjects with prior impairments. Cognitive functions of HIV-infected men with prior impairment did not improve after beginning cART.
Conclusion: By matching HIV-infected subjects with uninfected controls we were able to evaluate the relative cognitive decline among the infected men after they began using cART. The trajectories suggest that cognitive functions remain largely stable and that any prior impairments in cognition have a lasting effect over follow-up.



414 CLUSTER ANALYSIS OF COGNITIVE FUNCTIONING IN HIV+ AND HIV- SUBJECTS

Lillian Ham[1], Joseph Snow[1], Brian K. Agan[2], Bryan Smith[1], Avindra Nath[1], Seung Hyun Won[3], Xiuping Chu[3], Elizabeth F. Horne[1], Gina Norato[1], Tracyann Mburu[1], for the Neuro-HIV Research Consortium

[1]NIH, Bethesda, MD, USA, [2]Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [3]Henry M Jackson Foundation, Bethesda, MD, USA

Background: Although several definitions have been proposed to define HIV-associated neurocognitive disorders, no universally accepted definition has emerged. Previous investigations have employed cluster analyses (CA) to identify neurocognitive performance subgroups among HIV patients. However, no previous studies have included both HIV+ and HIV- subjects in such CAs.

Methods: Baseline visits of 324 HIV+ and HIV- subjects (M_{age}=50.4; 245 males; 47.8% Black, 44.8% White, 23% Other) who underwent comprehensive neuropsychological assessment were included. HIV+ and HIV- subjects did not differ in age, gender, or race (ps>.13), but controls were more educated (p<.01). In the first of a two-stage CA, 15 measures of attention, executive functioning, information processing, verbal fluency, learning, psychomotor, and memory that are commonly used to assess HAND were entered into a hierarchical CA, in which two clusters were identified. Group membership was finalized through a k-means CA which produced two groups defined as low or high performing. Out of 96 controls, 40 (41.7%) were classified as low performing and 56 (58.3%) were high performing. Out of 228 HIV+ subjects, 120 (52.6%) were classified as low performing and 108 (47.4%) were high performing.

Results: The two clusters were compared to cognitive impairment (CI) based on Global Deficit Score (GDS; ≥0.5). In comparison to CI, the CA had high sensitivity (100%) but low specificity (62.1%). Chi-square analyses found that the low performers were characterized by lower employment (p<.01), more PTSD (p=.03), higher rate of current smokers (p<.01), and more individuals taking psychiatric medication (p<.01). Mann-Whitney tests also found that the low performers endorsed more symptoms of depression (Beck Depression Inventory; p<.01), lower premorbid IQ (Wechsler Test of Adult Reading; p<.01), and lower everyday functioning (Texas Functional Living Scale; p<.01). As expected, the low performers had significantly lower GDS (p<.01) and overall T-scores on cognitive measures (p<.01). Low and high performers did not differ in HIV status (p=.07), education (p=.38) or age (p=.64).

Conclusion: Using CA on neuropsychological performance of HIV+ and HIV- subjects, we identified low and high cognitive performers. We concluded that cognitive impairment is not HIV-status specific. Other psychiatric, health, and functional characteristics had stronger associations with cognitive performance than HIV status did.

Measure (T-scores)	Cognitive Domain	Rank (1-15)
Paced Auditory Serial Addition Test	Attention/Working Memory	8
Wechsler Adult Intelligence Scale-III: Letter Number Sequencing	Attention/Working Memory	11
Trail Making Test B	Executive Functioning	3
Wisconsin Card Sort: Perseverative Responses	Executive Functioning	13
Wisconsin Card Sort: Categories Completed*	Executive Functioning	10
TMT A	Information Processing	12
WAIS-III: Digit Symbol-Coding	Information Processing	6
WAIS-III: Symbol Search	Information Processing	1
Controlled Oral Word Association Test: F, A, S	Verbal Fluency	14
COWA Animals	Verbal Fluency	15
Hopkin's Verbal Learning Test-Revised: Total Recall	Learning	5
Brief Visuospatial Memory Test-Revised: Total Recall	Learning	2
Grooved Pegboard (most impaired hand)	Psychomotor	9
HVLT-R: Delayed Recall	Memory	7
BVMT-R: Delayed Recall	Memory	4

Note. *Raw score. Rank based on F-statistics of k-means cluster analysis ANOVA (Rank 1 indicates largest F-statistic and contributes to greatest separation between clusters).

415 ALZHEIMER'S DEMENTIA CEREBROSPINAL FLUID BIOMARKERS IN HIV-POSITIVE PATIENTS ON cART

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Background: Evidence regarding cerebrospinal fluid (CSF) Alzheimer's dementia (AD) biomarkers in HIV-positive patients is conflicting. The study aimed to describe total tau (tTau), phosphorylated tau (ptau) and β Amyloid 1-42 (βA42) CSF concentrations and clinical correlates among on cART HIV-positive patients

Methods: On cART HIV-positive adults undergoing lumbar puncture for clinical reasons were enrolled and divided into 4 groups by CSF age-adjusted tTau and βA42 cut-offs: A (both normal), B (normal tTau, low βA42), C (high tTau, normal βA42), D (both altered). CSF biomarkers were measured by immune-enzymatic (tTau, ptau, βA42), ELISA (neopterin) and immunoturbidimetric (CSF-serum albumin ratio [CSAR], CSF IgG synthesis) methods. Data were analysed through non-parametric tests

Results: 181 patients were included: 150 (82.9%), 15 (8.3%) and 15 (8.3%) resulted in group A (CSF tTau 116 [51-199], βA42 899 [788-1079] pg/mL), B (CSF tTau 37 [37-128], βA42 374 [302-443] pg/mL) and C (CSF tTau 544 [466-750], βA42 965 [754-1267] pg/mL). Only 1 patient was in group D (tTau 580 and βA42 404 pg/mL) and was diagnosed with AD. Demographic, clinical, viroimmunological and CSF variables are shown in the Table. CSF tTau positively correlated with CSF ptau (.68, p<.01), βA42 (.48, p<.01), neopterin (.43, p<.01), and PBMC HIV-DNA (.44, p.012). Higher CSF tTau levels were associated with worse score at verbal long and short-term memory tests (-.41 and -.42, p.027 and p.024). CSF βA42 positively correlated with CSF ptau (.62, p<.01) and working memory task (.78, p<.01). Compared to group A, group B presented higher CSF neopterin (p<.01), cells (p.<01), proteins (p.04), IgG synthesis (p.01) and Tourtelotte index (p<.01) and showed wider proportion of non-caucasian ethnicities and past iv drug use (p<.01 and .03) and higher risk of having altered brain MRI (OR 16.3, p.05) and executive functioning task (OR 45.0, p.02)

Conclusion: In HIV-positive patients on cART, CSF tTau and βA42 resulted to be informative of different stages of CNS involvement by HIV and were associated differently from what is observed in AD. While elevated CSF tTau related to recent infection, poor viral control and/or CNS opportunistic infections, low CSF βA42 levels featured a small subgroup of patients with ongoing intrathecal synthesis and CNS inflammation/immune activation despite effective and long-term peripheral viral suppression. Longitudinal studies assessing evolution or persistence of such CSF patterns are warranted.

Parameters	Group A (n=150)	Group B (n=15)	Group C (n=15)	P
Age, years	49 (42-56)	50 (40-58)	43 (39-49)	0.13
Male, n	111 (74%)	9 (60%)	9 (60%)	0.30
Ethnicity, n				
Caucasian	140 (93.3%)	11 (73.3%)	11 (73.3%)	**<0.01**
Others	10 (6.7%)	4 (26.7%)	4 (26.7%)	
Risk factor, n				
Homosexual	48 (32%)	3 (20%)	2 (13.3%)	0.22
Previous IDUs	27 (18%)	6 (40%)	6 (40%)	**0.03**
Others	75 (50%)	6 (40%)	7 (46.7%)	0.75
Clinical conditions, n				
Asymptomatic	37 (24.7%)	2 (13.3%)	1 (8.7%)	0.19
HIV-related syndromes	20 (13.3%)	3 (20%)	0	0.23
CNS OIs	9 (6%)	1 (6.7%)	8 (53.3%)	**<0.01**
Altered brain MRI only	13 (8.7%)	3 (20%)	1 (6.7%)	0.33
CNS infections	6 (4%)	2 (13.3%)	0	0.17
CVDs	9 (6%)	0	0	0.39
HAND only	38 (25.3%)	4 (26.7%)	2 (13.3%)	0.59
Others	18 (12%)	0	3 (20%)	0.24
CSF Ptau, pg/mL	35 (27-43)	19 (17-22)	57 (35-93)	**<0.01**
CSF Neopterin, ng/mL	0.86 (0.53-1.4)	0.67 (0.46-3.2)	6.0 (1.3-10.3)	**<0.01**
Tourtellotte index	2.2 (0.0-12.9)	8.7 (3.4-58.1)	12.1 (0.0-67.7)	**0.011**
CSAR	5.5 (3.9-7.3)	5.6 (4.4-7.8)	5.2 (4.4-8.5)	0.78
CSF IgG Synthesis, %	0 (0-27)	13 (0-55)	26 (0-48)	**0.034**
CSF cells, cells/mmc	0 (0-0)	0 (0-48)	0 (0-15)	**<0.01**
CSF proteins, mg/dL	44 (36-57)	58 (42-81)	53 (34-96)	0.058
Current CD4, cells/mmc	376 (170-647)	429 (326-648)	116 (51-524)	0.059
CD4 Nadir, cells/mmc	108 (31-227)	114 (25-214)	40 (18-167)	0.39
Pl HIV-RNA <50 cp/ml, n	117 (78%)	11 (73.3%)	8 (53.3%)	0.10
CSF HIV-RNA <50 cp/ml, n	105 (70%)	8 (53.3%)	6 (40%)	**0.047**
HIV infection, months	166 (45-229)	155 (111-278)	71 (3-202)	0.15
Time on cART, months	28 (9-87)	28 (10-94)	27 (8-82)	0.29
CPE score	7 (6-8)	6 (6-7)	7 (7-10)	0.10
HAART, n				
NNRTIs	25 (16.7%)	1 (6.7%)	1 (6.7%)	0.37
PIs	47 (31.3%)	5 (33.3%)	3 (20%)	0.64
INIs	22 (14.7%)	2 (13.3%)	5 (33.3%)	0.16
Others	56 (37.3%)	7 (46.7%)	6 (40%)	0.77

Legend: IDU, Intravenous Drug Users; CNS, Central Nervous System; OIs, Opportunistic infections; MRI, Magnetic Resonance Imaging; CVDs, Cerebrovascular Disorders; HAND, HIV-Associated Neurocognitive Disorders; CSAR, CSF-Serum Albumin ratio; CSF, Cerebrospinal fluid; Pl, Plasma; CPE, CNS Penetration-Effectiveness.

416 CSF HIV-SPECIFIC T CELLS PERSIST DURING ART AND ASSOCIATE WITH LOWER CNS INFLAMMATION

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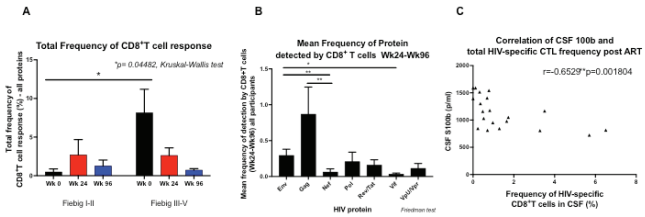
Background: During acute HIV infection (AHI), CD8 T cells compose the majority of cells infiltrating the cerebrospinal fluid (CSF). They are highly activated and contain HIV-specific cells. It is unknown whether these HIV-specific CD8 T cells persist in the CSF during antiretroviral therapy (ART) and how their presence associates with markers of HIV neuropathogenesis. Their presence could serve as a surrogate marker of HIV persistence in the CNS.

Methods: Twelve RV254 Thai participants treated in AHI underwent lumbar punctures and Magnetic Resonance Spectroscopy (MRS) scans at diagnosis and at 24 and 96 weeks post-ART. CD4 and CD8 T cells from the CSF samples were polyclonally expanded in vitro. CD8 T cells were cocultured with autologous B-EBV cells loaded with CRF01_AE HIV peptide pools and HIV-specific CD8 T cell responses were assessed by flow cytometry using intracellular staining for IFN-γ. HIV DNA was measure in CD4 T cells by ultrasensitive qPCR.

Results: In AHI, HIV-specific CD8 T cells were detected in the CSF at low frequencies in Fiebig I-II (0.5%, n=4), and at higher frequencies in Fiebig III-V (8%, n=8, Fig 1A). As previously shown, HIV-specific CD8 T cell frequency was positively associated with CSF viral load and inflammation in AHI. After 24 weeks of ART, plasma and CSF HIV RNA were undetectable. However, HIV DNA was detected in CSF CD4 T cells from 1 participant at week 24, and from 2 participants at week 96. HIV-specific CD8 T cells were still detected in 9 donors at week 24 and in 8 donors at week 96 (Fig 1A). They targeted all HIV proteins (Fig 1B). After ART, the frequency of CSF HIV-specific CD8 T cells negatively associated with CSF inflammatory markers sCD14, IL-6Rα, sgp130 and TNFR1 (all r<-0.50, and p<0.04) and with the CSF neuronal injury marker S100b (r=-0.65, p=0.001; Fig. 1C). It was also positively associated with MRS neuronal integrity marker, N-acetylaspartate, in basal ganglia (r=0.4, p=0.04) and frontal gray matter (r=0.5, p=0.01) and negatively associated with MRS inflammatory markers including choline (r=-0.63, p=0.02) and glutamate/glutamine (r=-0.49, p=0.02) in frontal white matter.

Conclusion: These data highlight the persistence of HIV-specific CD8 T cells over 2 years of suppressive ART started in AHI. The persistence of these cells after treatment suggests the presence of HIV antigen in the CNS during effective ART. Nonetheless, associations with CNS biomarkers indicate that they may play an effective role in resolving neuroinflammation after treatment.



417 CSF HIV-TAT AS A BIOMARKER OF NEUROCOGNITION AND AGING IN HIV-INFECTED PATIENTS

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Background: Virus-specific markers are limited when researching the neurologic complications of HIV infection, especially for participants on antiretroviral therapy. HIV-Tat protein can be released from infected cells despite antiviral therapy and experimental studies show that it can cause neuroglial dysfunction. Hence we investigated its presence in CSF, in an HIV-Tat/amyloid protein transgenic animal model and in vitro to determine interactions between Tat and amyloid beta (Aβ) peptide.

Methods: Tat was measured by ELISA in CSF of patients with HIV infection on antiretroviral therapy. Evaluations included neurocognitive tests, CSF cytokines, Aβ peptide, tau, and neurofilament-light chain by Quanterix SIMOA immunoassay. Tat levels were dichotomized: undetectable or detectable; or <1000 or ≥ 1000 pg/ml and associations with clinical outcomes (GDS, average T score), with neurocognitive impairment (NCI) defined by GDS ≥ 0.5. APP-PS1 transgenic mice were injected with Tat protein or crossed with Tat transgenic mice, and amyloid plaques were examined for Tat by immunohistochemistry. Aβ peptide-Tat complexes were studied by atomic force microscopy, circular dichroism and single fiber imaging by TIRF and molecular modeling.

Results: All patients (n=48; mean age 53.2 yrs; 62.5% AA; 64.6% men) had a plasma viral load <40 c/ml. CSF VL was >40 c/ml in 5 (10.4%). Tat was detectable in CSF in 21 (43.8%) and >1000 pg/ml in 12 (25%). Tat was detectable in 4 (80%) with CSF escape and 17 (39.5%) without escape (p=0.08). Tat levels >1000 pg/ml associated with higher likelihood of NCI (41.7% vs. 11.10%). Detectable CSF Tat was associated with lower Aβ40 (p=0.03), lower Aβ42 (though not significantly at p=0.08), and higher total tau/Aβ42 ratio (p=0.03). Tat localized to the amyloid plaques in the brains of both animal models and in vitro studies showed that in the presence of Tat, uniform amyloid fibrils become double twisted fibrils and formed populations of thick unstructured filaments and aggregates. Tat binding to the exterior surfaces of the Aβ fibrils increased β-sheet formation and lateral aggregation into multifibrillar structures, producing fibers with increased rigidity and mechanical resistance.

Conclusion: The presence of Tat in CSF is an indicator of restricted viral replication and may be associated with cognitive impairment. It also indicates the formation of Tat-amyloid complexes in the brain which may contribute to the pathophysiology of HAND.

418 NEUROCOGNITION, FRAILTY, AND MORTALITY AMONG PERSONS AGING WITH HIV AND SUBSTANCE USE

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Background: With effective antiretroviral therapy (ART), HIV-infected persons are living longer. Yet, survival disparities remain, particularly for persons with a history of injecting drugs (PWID). Such disparities have been attributed to

an increased burden of aging-related phenotypes including frailty, which we have shown to be heightened in HIV and predictive of mortality. Cognitive impairment is a key aging-related phenotype prevalent in HIV. However, limited data exist on the relationship of cognitive impairment to frailty and its impact on mortality in the ART era.

Methods: Standard neurocognitive assessments were performed cross-sectionally among HIV-infected and uninfected PWID in the ALIVE cohort from 2010 through 2012 in 5 domains: executive function, attention, learning/memory, information processing and motor processing. Global cognitive performance was determined as the average of z scores from each domain. Frailty was assessed based on the 5 physical frailty phenotype domains – weight loss, low physical activity, exhaustion, decreased grip strength, and slow gait speed. Mortality was ascertained through 2016 through linkage to the National Death Index. Cox proportional hazards models were used to estimate the risk (hazard ratios [HR] with 95% confidence intervals [CI]) for all-cause mortality.

Results: Among 519 ALIVE participants with a median age of 52 years, 41% were HIV positive. In multivariate analyses, older age and hazardous alcohol use were significantly associated with impairments in executive function, information processing, motor processing and global cognitive impairment. Being both frail and HIV-infected was associated with heightened information and motor processing impairments. Adjusting for sociodemographics, premorbid IQ, comorbidity, substance use and HIV disease stage, impaired information processing (aHR 1.41; 95% CI, 1.06, 1.88), motor processing (aHR 1.61; 95% CI, 1.30, 1.98) and global cognitive impairment (aHR 1.67; 95% CI, 1.10, 2.56) were significantly associated with increased mortality; global cognitive impairment and frailty (aHR 2.32; 95% CI, 1.03, 5.20) were independently associated with mortality.

Conclusion: Cognitive impairment is a significant predictor of death among persons with HIV, independent of HIV disease stage, chronic disease comorbidity, and frailty. Further elucidation of the epidemiologic and biological underpinnings of cognitive impairment in HIV and PWID could facilitate interventions to improve survival for these populations.

419 ASSOCIATIONS BETWEEN PLASMA NRTI CONCENTRATIONS AND COGNITIVE FUNCTION

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Background: Limited data exist on the effects, either beneficial or detrimental, of nucleoside-reverse transcriptase inhibitor (NRTI) exposure on cognitive function in people living with HIV (PLWH). We investigated the associations of plasma tenofovir (TDF), emtricitabine (FTC), lamivudine (3TC) and abacavir (ABC) pharmacokinetics (PK) with cognitive function among PLWH recruited in the POPPY study.

Methods: PK sampling and cognitive function (6 domains) were obtained from 638 PLWH on TDF, FTC, 3TC or ABC. For each drug, four different PK parameters were considered: area under the curve over 24 hours (AUC), maximum concentration (CMAX), trough concentration (CT) and clearance (CL/F). Cognitive scores were standardized into Z-scores (mean=0, sd=1) and averaged to obtain domain and global Z-scores. Associations between PK parameters and Z-scores were assessed using rank regression adjusting for age, gender, race, education, BMI, weight, recreational drug use, alcohol consumption, use of boosted protease inhibitors or efavirenz, as appropriate.

Results: The 638 PLWH were predominantly male (87%), with a median (IQR) age of 52 (47, 59) years and 93% had a HIV RNA <50 copies/mL. 520 were on TDF, 485 on FTC, 125 on 3TC and 93 on ABC. The median (IQR) global Z-score was 0.06 (-0.31, 0.40), 0.08 (-0.29, 0.40), 0.09 (-0.32, 0.32) and 0.11 (-0.36, 0.33) in recipients of TDF, FTC, 3TC and ABC, respectively. After adjusting for potential confounders, including efavirenz use, none of the four TDF and FTC PK parameters were associated with global cognitive scores, with only weak associations with 3TC PK parameters (Table). Higher ABC AUC and CT were associated with better cognitive scores (both p's=0.02), while increased CL/F was associated with poorer scores (p=0.04). In particular, ABC AUC [adjusted rho: 0.26 (0.05, 0.47), p=0.02] and CT [adjusted rho: 0.24 (0.03, 0.45), p=0.03] were associated with better visual attention, while associations with other domains were non-significant [adjusted rho's ranging from 0.12 and 0.08 (executive function) to 0.18 (psychomotor) for AUC and CT, respectively; all p's>0.05].

Conclusion: Whilst we found no evidence of detrimental effects of NRTI exposure on cognitive function, greater ABC (but not TDF, FTC and 3TC) plasma exposure was associated with better cognitive scores. Although confounding due to adherence and other unmeasured factors may exist, these results could have implications for the design of future research programmes for PLWH with cognitive disorders.

Table: Adjusted association (estimated using rank regression) of global Z-scores with TDF, FTC, 3TC and ABC PK parameters

PK parameter	TDF		FTC		3TC		ABC	
	regr. coef. (95% CI)	p	regr. coef. (95% CI)	p	regr. coef. (95% CI)	p	regr. coef. (95% CI)	p
AUC	-0.03 (-0.13, 0.06)	0.48	-0.05 (-0.15, 0.04)	0.25	0.16 (-0.02, 0.33)	0.08	0.23 (0.04, 0.41)	0.02
CMAX	-0.05 (-0.16, 0.07)	0.42	-0.06 (-0.15, 0.04)	0.23	-0.17 (-0.34, 0.01)	0.05	0.17 (-0.01, 0.36)	0.06
CT	-0.02 (-0.11, 0.07)	0.64	-0.05 (-0.14, 0.04)	0.27	0.15 (-0.03, 0.32)	0.09	0.22 (0.03, 0.40)	0.02
CL/F	0.08 (-0.02, 0.18)	0.12	0.05 (-0.04, 0.15)	0.26	-0.15 (-0.32, 0.02)	0.09	-0.19 (-0.38, -0.01)	0.04

Note: all associations are adjusted for age, gender, ethnicity, education, use of boosted protease inhibitors, use of efavirenz plus: BMI and recreational drug use (TDF PK parameters only), weight and recreational drug use (FTC PK parameters only)

420 VARIABILITY IN COGNITIVE IMPAIRMENT OVER TIME IN PEOPLE WITH HIV AND MATCHED CONTROLS

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Background: Although cognitive impairment (CI) is frequently reported in people with HIV (PWH), limited data exist on the dynamics of change in treated individuals meeting definitions of CI over time. A greater understanding of these dynamics would assist in targeting individuals at risk of cognitive decline.

Methods: Treated PWH with HIV RNA <50 copies/mL for ≥1 year and comparable controls underwent assessment of cognitive function (six domains) at baseline and after two years. Demographically-adjusted T-scores at baseline and follow-up were derived and the multivariate normative comparison (MNC) criterion was used to determine CI. Fisher's exact test was used to assess differences in the number of people moving over time from CI to no CI (and vice versa) between PWH and controls. Individuals showing a significant change over time in their cognitive function, whilst accounting for practice effect, were identified by applying the MNC criteria to the differences between follow-up T-scores and those expected given baseline T-scores, socio-demographics and time between testing.

Results: The 123 PWH and 77 controls were predominantly male (93% in both), with a median (IQR) age of 55 (50-61) and 56 (51-63) years, respectively. At baseline, the prevalence of CI was 20% in PWH and 4% in controls (p<0.001). Whilst none of the controls with CI at baseline improved to no CI at follow-up, 9/21 (43%) PWH moved from CI to no CI (p=0.50, Table). Moreover, 2% and 4% of PWH and controls without CI at baseline were classified as impaired at follow-up (p=0.70). Twelve (10%) PWH and 5 (6%) controls experienced a significant decline in cognitive function over two years (p=0.42): 6/12 (50%) PWH and 2/5 (40%) controls were classified with no CI at both baseline and follow-up; 1 (8%) PWH and 2 (40%) controls moved from not having CI to have CI.

Conclusion: We observed different dynamics of change in cognitive function within this cohort. A substantial proportion of PWH who were classified as having CI initially, did not meet criteria for CI after 2 years; only less than half of both PWH and controls who significantly declined, stably met the definition of CI. Linkage of these detailed cognitive phenotypes with biomarker and neuroimaging findings may assist in understanding the underlying pathogenic mechanisms and developing future targeted management approaches.

Table: Classification of CI at baseline and follow-up in HIV-negative controls (n=77), PWH (n=123) and in those who significantly declined over time (n=5 and n=12)

Group	Baseline	Follow-up	
		No CI	CI
HIV-negative (n=77)	No CI	72	3
	CI	0	2
PWH (n=123)	No CI	99	3
	CI	9	12
HIV-negative who significantly declined (n=5)	No CI	2	2
	CI	0	1
PWH who significantly declined (n=12)	No CI	6	1
	CI	0	5

421 ASSOCIATION BETWEEN NEUROFILAMENT LIGHT PROTEIN AND IMPAIRED COGNITION IN TREATED HIV

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Background: Neurofilament light protein (NFL) concentrations in CSF can be used as sensitive biomarkers to evaluate CNS injury and dysfunction. Elevated NFL has been associated with CNS dysfunction in untreated HIV infection. This study investigates NFL concentrations in virologically controlled HIV patients in correlation with clinical variables and neuropsychological testing in men and women compared to matched controls.

Methods: 67 patients with chronic HIV-infection on ART for >12months (HIV+) and 21 demographically matched control subjects (HIV-) were included in this study. All participants completed a research lumbar puncture for CSF and a standardized battery of neuropsychological tests. CSF was analyzed for HIV RNA and NFL was analyzed using the QuanterixTM SIMOA Digital Immunoassay. NFL levels were correlated with clinical outcomes including Global Deficit Score (GDS) and average T-scores. An abnormal GDS score (≥0.5) was classified as Neurocognitive Impairment (NCI).

Results: There were no significant differences in age, race, or sex between the HIV+ and HIV- groups. In the HIV+ group, plasma viral load was <40 c/mL in 67 (100%), CSF NFL was higher in those with NCI compared to those with a normal GDS (1086pg/mL, 731pg/mL respectively, p<0.01); in the HIV- control group, there were no differences in NFL by cognitive impairment (465pg/mL, 612pg/mL, p=0.22). Similarly, when looking at average demographically corrected T-scores across the battery of NP tests, higher NFL was associated with lower T-scores only in the HIV group (p=0.03), not in the control group (p=0.88). The Brief Visual Memory Test and Wisconsin Card Sort Test were significantly correlated with higher NFL in the HIV+ group (p<0.001, p<0.01, respectively). In the HIV+ group, this increase in NFL in those with NCI was significant for men only (n=44, p<0.01, Cohen's d=6.12 for men; n=23, p=0.97, Cohen's d=0.07 for women). There were no significant associations between NFL and HIV CSF escape (n=7) with CSF HIV > 40c/mL, nadir CD4 (median 206.3 c/mL), time since HIV diagnosis (mean 17.3 years) or time on ART (mean 8.5 years).

Conclusion: Even when HIV-infected individuals have been on ART for >12months, there is still a significant association between higher levels of NFL and NCI. This is particularly significant in men, but a larger sample of women is needed to establish a significant effect size to determine whether this association between elevated NFL and NCI can be applied to HIV+ women.

	HIV+		
	Normal Cognition (n=46)	Neurocognitive Impairment (n=21)	p-value
Gender n (%) female	17 (36.9)	6 (28.6)	0.51
Age (mean years)	53.1	53.5	0.81
Race n (%) African American)	22 (47.6)	9 (41.3)	0.63
NFL mean(pg/mL)	731.30	1086.10	<0.01

Summary of demographics and NFL for HIV+ individuals (n=67).

422 SCD14, SICAM-1, AND SVCAM-1 CORRELATE WITH NEUROCOGNITIVE FUNCTION IN YOUTH WITH HIV

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Background: HIV infection affects cognitive performance through immune activation and related mechanisms. We hypothesized that in youth with HIV (YWH), biomarkers of macrophage activation and vascular injury are associated with impairment in distinct neurocognitive domains.

Methods: YWH, ages 20 to 28, enrolled in ATN 071/101 were assessed for biomarkers of macrophage activation and vascular injury using ELISA/ multiplex assays. Participants completed standardized neurocognitive tests. Demographically corrected z-scores were combined to form indices of attention, motor functioning, executive functioning, and both verbal and nonverbal memory. We performed a cross sectional analysis of the relationship between blood levels of four key biomarkers (sCD163, sCD14, sICAM-1, and sVCAM-1) and performance in each of these neurocognitive domains. Linear regression models were fit for the log-transformed biomarker value for each combination of biomarker and cognitive domain score. These models were adjusted for demographics, socioeconomic status, substance use, and depression.

Results: Study included 128 YWH [mean age 23.8 (SD 1.7) years, 86% male, 68% African American]. We found moderate evidence for the following associations: sCD14 was negatively associated with executive function [adjusted estimate -0.69 (95% CI -1.43, 0.05)] and non-verbal memory [-0.99 (-1.89, -0.10)]. Soluble ICAM-1 was negatively associated with verbal memory [-0.31 (-0.64, 0.03)], while sVCAM-1 was positively associated with attention [0.32 (-0.04, 0.69)], executive function [0.68 (0.29, 1.08)], and non-verbal memory [0.56 (0.04, 1.07)]. Soluble CD163 was not significantly associated with any domain. None of the key biomarkers were significantly associated with the motor domain.

Conclusion: Biomarkers of macrophage activation and vascular injury were differentially associated with distinct cognitive domains, especially executive function and memory, among YWH. Intriguing positive associations of soluble VCAM-1 with executive function and nonverbal memory may indicate a link between vascular flow and cognitive performance among YWH who are at early stage of disease.

423 METABOLOMIC PROFILING OF HIV PATIENTS WITH AND WITHOUT HIV-ASSOCIATED DEMENTIA

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Background: HIV-associated dementia (HAD) is the most important clinical expression of HIV-mediated neurotoxicity, and even though cART has lowered its incidence, HIV-related neurocognitive disorders remain a major issue. The exact mechanism explaining the neurological decline observed in HIV-infected patients is still only partly understood. Thus, we have exploited metabolomics as a new approach to detect novel biomarkers of HAD among the small molecules of both cerebrospinal fluid (CSF) and plasma.

Methods: Metabolomics was performed in paired CSF and plasma samples of 20 untreated patients with HAD, 20 HIV-infected, neurologically asymptomatic patients (ASYM) and 20 HIV negative controls (NEG) by Metabolon (Durham, NC) using both liquid and gas chromatography/mass spectrometry. Molecules were identified by comparison to library entries or purified standards and analysed by Welch's two samples t-test. Differences with a p value <0.05 and a q value <0.1 were considered significant.

Results: HAD and ASYM had, respectively, a median CD4+ cell count of 22 (IQR, 3-148) and 151 (IQR, 91-261) cells/mm3, a median plasma HIV RNA of 202,000 (IQR, 53,000-679,500) and 22,424 (IQR, 711-70,550) cp/mL and a median CSF HIV

RNA of 106,250 (IQR, 13,570-218,250) and 2327 (IQR, 49-70,550) cp/mL. A total of 146 and 312 metabolites have been identified respectively in CSF and plasma, grouped in 19 and 23 different metabolic pathways. Significant differences were identified in molecules involved in glutamate, biliary acids and fatty acid metabolism. Table displays metabolic pathways found to have >1 molecule showing a fold change of HAD vs. ASYM >1.5 or < 0.5, either in CSF or plasma.
Conclusion: HAD untreated patients show a perturbation in glutamate, bile acids and fatty acids homeostasis, which may result from impaired cell metabolism induced by HIV both systemically and in the central nervous system. The increased production of compounds possibly exerting neurotoxic effects, such as glutamate, 5-oxoproline and primary bile acids, might contribute to the neuronal damage and foster neurological impairment in HAD. On the other hand, changes in lipid metabolism may reflect both an enhanced adipose reserves' breakdown and mitochondrial dysfunction with impairment in β-oxidation. These markers, tested in untreated patients, may have a potential for the identification and studying the pathogenesis of HIV-mediated neuronal damage also in cART treated patients.

Metabolic pathway	Compound	CSF				Plasma			
		HAD vs. ASYM		HAD vs. NEG		HAD vs. ASYM		HAD vs. NEG	
		Fold change	p value	Fold change	p value	Fold change	p value	Fold change	p value
Glutamate metabolism	Glutamate	43.13	0.0097*	76.9	< 0.001*	9.47	< 0.001*	17.85	< 0.001*
	Glutamine	0.71	0.0098*	0.76	0.0142*	0.57	< 0.001*	0.58	< 0.001*
	5-oxoproline	5.02	< 0.001*	5.71	< 0.001*	1.5	0.0469*	1.57	0.0227*
Bile acids metabolism	Glycocholate	5.39	0.027*	5.9	0.016*	2.49	0.6016	14.52	0.0194*
	Taurocholate	11.29	0.3302	16.9	0.182	3.95	0.446	55.49	0.0166*
Lipid metabolism	Glycerol 3-phosphate	nd	nd	nd	nd	5.28	0.0485*	5.15	0.0202*
	Acetylcarnitine	0.77	0.0141*	1	0.061	0.62	0.0075*	0.71	0.011*
Lipid metabolism (long chain fatty acids)	Palmitate	nd	nd	nd	nd	1.49	0.011*	1.59	0.002*
	Myristate	nd	nd	nd	nd	1.48	0.0128*	1.66	0.0011*
	10-heptadecenoate	nd	nd	nd	nd	1.59	0.0198*	2.11	< 0.001*
	Oleate	nd	nd	nd	nd	1.41	0.0198*	2.1	< 0.001*
	Mead acid	nd	nd	nd	nd	4.01	0.0014*	4.65	< 0.001*
	Arachidonate	nd	nd	nd	nd	2.68	0.0011*	2.66	< 0.001*
Lipid metabolism (dicarboxylated fatty acids)	Tetradecanedioate	nd	nd	nd	nd	2.52	0.0069*	2.11	0.0057*
	Hexadecanedioate	nd	nd	nd	nd	3.51	0.0156*	2.62	0.0174*
	Octadecanedioate	nd	nd	nd	nd	3.91	0.023*	3.29	0.0312*

* p value <0.05

424 IMPAIRED COGNITION PREDICTS FALLS AMONG HIV+ AND HIV- WOMEN

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Background: Emerging evidence suggests that objectively assessed neurocognitive (NC) function in the domains of psychomotor speed, attention, and executive function are strong predictors of falls in older adults. Domain-specific NC impairments may be stronger predictors of fall risk in HIV+ compared to HIV- women.
Methods: We analyzed data from 825 HIV+ and 392 HIV- women in the Women's Interagency HIV Study (WIHS) who underwent NC testing within two years prior to completing a self-reported falls survey. The primary exposure variables of interest were NC impairment (T score <40) on each of 7 domains: executive function, psychomotor speed, attention, learning, memory, fluency, and fine motor skills. For NC domains associated with falls in simple logistic regression (p<.05), hierarchical regression models evaluated associations between NC impairment and odds of any fall in the prior 6 months after adjusting for: (1) study site and HIV status (2) demographics, (3) comorbid conditions, (4) substance use/CNS active medications, and HIV-specific factors.
Results: Median age was higher in HIV+ than HIV- women (51yrs vs. 48yrs, p <0.0001); the 6-month prevalence of falls (18%) did not differ by HIV. In the overall sample, executive function (odds ratio, OR:1.82;95%CI:1.21-2.74;p= 0.004), psychomotor speed (OR:1.59;95%CI:1.05-2.42;p= 0.03), and motor skills (OR:1.70;95%CI:1.11-2.61;p=0.02) were associated with greater odds of falls in fully adjusted models. Among HIV+ women, associations of executive function, psychomotor speed, and motor skills were attenuated and no longer significant after adjustment for demographic and comorbid conditions (Table). Among HIV- women, impaired executive function and motor skills were associated in unadjusted models and the associations were strengthened in fully adjusted models.
Conclusion: NC impairment in executive function, psychomotor speed, and motor skills domains is associated with falls among women in the WIHS cohort. Among HIV+ women, associations between NC impairment and falls were no longer significant after adjustment for demographics and comorbid conditions, whereas in HIV- women, the associations were strengthened after adjustment, suggesting that these relationships may be modified by different factors. Additional studies are needed to understand mechanisms by which domain-specific NC impairment impacts fall risk, and whether cognitive interventions can reduce falls among aging women with or without HIV.

Table: Relationship between Cognitive Impairment and Odds of Any Fall in WIHS

	Executive Function				Psychomotor Speed				Motor Skills			
	HIV+ only		HIV- only		HIV+ only		HIV- only		HIV+ only		HIV- only	
	AOR (95%CI)	P value	AOR (95%CI)	P value	AOR (95% CI)	P value	AOR (95% CI)	P value	AOR (95% CI)	P value	AOR (95% CI)	P value
Model 1: Impaired Cognitive Domain	1.73 (1.11, 2.68)	.02	2.14 (1.08, 4.22)	.03	1.87 (1.21, 2.90)	.005	1.48 (0.72, 3.06)	.29	1.72 (1.09, 2.69)	.02	2.65 (1.24, 5.70)	.01
Model 2: Adjusted for Model 1 + Demographics	1.55 (0.98, 2.45)	.06	2.37 (1.16, 4.84)	.02	1.69 (1.07, 2.67)	.03	1.52 (0.72, 3.22)	.28	1.64 (1.03, 2.61)	.04	2.85 (1.27, 6.42)	.01
Model 3: Adjusted for Model 2 + Comorbidities	1.43 (0.89, 2.32)	.14	2.87 (1.37, 6.04)	.005	1.57 (0.96, 2.56)	.07	1.76 (0.81, 3.81)	.15	1.58 (0.97, 2.58)	.06	2.85 (1.22, 6.64)	.02
*Model 4: Adjusted for Model 3 + Substance use & CNS active agents	1.50 (0.91, 2.49)	.11	3.75 (1.70, 8.25)	.001	1.57 (0.93, 2.63)	.09	1.89 (0.84, 4.28)	.13	1.55 (0.92, 2.61)	.10	2.72 (1.10, 6.71)	.03

All models are adjusted for study site. Demographics include: age, race/ethnicity, income, and study enrollment year. Comorbidities include: neuropathy symptoms, obesity (body mass index ≥30 kg/m^2), depressive symptoms (Centers for Center for Epidemiologic Studies-Depression score ≥16), diabetes, hypertension, renal impairment, and hepatitis C virus infection. Substance use includes: (current, former, vs never) for smoking, cocaine or heroin, and marijuana, as well recent alcohol use. Central Nervous System (CNS) active agents include anticonvulsants, antidepressants, antipsychotics, sedatives (including benzodiazepines, barbiturates, and non benzodiazepine sleep aids) and the number of classes currently used are summed and categorized as (0,1,2,3+) in model 4.
* For HIV+ women only, Model 4 is additionally adjusted for prior AIDS

425 HIV-ASSOCIATED NEUROCOGNITIVE DISORDER LEADS TO DEATH

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Background: Neurocognitive impairment has been associated with increased mortality in both antiretroviral therapy (ART)-treated and ART-naïve populations. However, mortality risk associated with specific HAND stages (i.e. normal, asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND), and HIV-associated dementia (HAD)) has not been assessed. Moreover, there is current debate regarding the clinical significance of ANI.
Methods: 399 HIV+ ART-naïve participants in rural Rakai, Uganda were assessed with a neuromedical examination, neuropsychological test battery, depression screening, and functional status assessments, and a HAND stage was assigned based on Frascati criteria. All participants were immediately offered ART. After two years and again after 5 years, participants were traced with phone calls and, if unreachable, through a proxy phone contact and/or study personnel home visits to confirm vital status. Those unable to be traced were classified as lost to follow-up (LTFU). Logistic regression analyses were used to assess the relationship between baseline HAND stage and two-year and five-year all-cause mortality.
Results: At baseline, participants' mean age was 35 (SD 8) years, 53% were male, and mean years of education was 5 (SD 3). After two years, 337 participants (84%) were alive, 17 (4%) were confirmed dead, and 45 (11%) were LTFU. After five years, 157 participants (39%) were alive, 20 (5%) were dead, and 222 (56%) were LTFU. Omitting those LTFU, every one-stage increase in baseline HAND severity was associated with a 68% increased odds of death at two years and 96% increased odds of death at 5 years (Table). There was a trend for a dose-dependent increased odds of death for each HAND stage compared to participants with normal cognition at both two and five years. In multivariate analyses controlling for baseline CD4 count and demographic factors, each one-stage increase in HAND severity was associated with a 58% increased odds of death at two years, which was borderline significant [OR 1.58, 95%CI (0.97, 2.57), p=0.06], and 83% increased odds of death at 5 years [OR 1.83, 95%CI (1.13, 2.96), p=0.01] (Table).

Conclusion: We found a dose-dependent relationship between death during follow up and HAND at baseline. This is the first study of mortality and HAND in a resource-limited setting in the ART era. Our results suggest that early initiation of ART, prior to progression in HAND stage with advanced immunosuppression, may reduce mortality.

TWO-YEAR MORTALTIY				FIVE-YEAR MORTALITY			
	Odds Ratio	95% Confidence Interval	p		Odds Ratio	95% Confidence Interval	p
Odds of Death for Every One-Stage Increase in HAND Severity*				**Odds of Death for Every One-Stage Increase in HAND Severity***			
Every one-stage increase in HAND severity	1.68	(1.06, 2.67)	0.03	Every one-stage increase in HAND severity	1.96	(1.24, 3.08)	0.004
Odds of Death for Each HAND Stage Compared to Normal Cognition				**Odds of Death for Each HAND Stage Compared to Normal Cognition**			
ANI	2.38	(0.24, 24.0)	0.46	ANI	2.36	(0.22, 24.8)	0.47
MND	3.69	(0.98, 13.92)	0.054	MND	5.84	(1.55, 22.0)	0.009
HAD	4.54	(0.98, 21.1)	0.053	HAD	6.84	(1.50, 31.2)	0.01
Multivariate Analysis				**Multivariate Analysis**			
Age (years)	1	(0.94, 1.07)	0.97	Age (years)	1.01	(0.95, 1.07)	0.83
Female Sex	0.84	(0.30, 2.41)	0.75	Female Sex	0.88	(0.30, 2.54)	0.82
Education (years)	0.92	(0.79, 1.07)	0.28	Education (years)	0.82	(0.70, 0.96)	0.02
CD4 < 200 cells/µL	5.31	(1.43, 19.7)	0.01	CD4 < 200 cells/µL	6.33	(1.79, 22.4)	0.004
Every one-stage worsening in HAND classification	1.58	(0.97, 2.57)	0.06	Every one-stage worsening in HAND classification	1.83	(1.13, 2.96)	0.01

*HAND stages from mild to severe: normal, asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), HIV-associated dementia (HAD)

426 ANEMIA AND NEUROCOGNITIVE IMPAIRMENT: A LONGITUDINAL MULTICOHORT STUDY

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Background: Anemia in persons living with HIV (PLWH) may occur from multiple causes and has been identified as a predictor of morbidity and mortality. Prior studies identified associations between anemia and worse neurocognitive (NC) performance in PLWH, but most studies have been cross-sectional and were not limited to those taking antiretroviral therapy (ART). This study compared erythrocyte and anemia biomarkers to NC performance over time in a large cohort of PLWH taking ART.
Methods: We evaluated 1,338 participants from multiple neuroHIV cohorts in San Diego, all on ART and followed for a mean of 29.5 months. Demographic and medical characteristics, including hemoglobin and erythrocyte indices, were collected. Anemia was defined as hemoglobin concentration of <14.0 g/dl in men and <12.0 g/dl in women, macrocytosis as mean corpuscular volume> 99fL. NC performance was assessed using demographically adjusted domain and global T scores. Statistical methods included linear regression and mixed effects modeling.
Results: At baseline, participants were mostly middle aged (mean 43 years), men (77.8%), of European (54.9%), Hispanic (23.9%) or African (16.7%) ancestry. Most (69.8%) had undetectable viral load; the median nadir CD4+ cell count was 206 cells/µL; and 18.8% were currently on zidovudine. 297 (22.3%) were anemic. Anemia ($p<0.0001$) and macrocytosis ($p=0.07$) were associated with worse NC performance at baseline (model $p<0.0001$). Anemia remained significant ($p= 0.02$) on multivariate analysis. Anemia was specifically associated with worse NC performance in speed of information processing ($p<0.01$), recall ($p=0.04$), working memory ($p<0.01$) and motor speed ($p<0.01$) with trends in executive function ($p=0.06$) and learning ($p=0.08$). Over time, lower hemoglobin concentration ($p<0.0001$) was associated with worse global T scores (model $p <0.0001$). Adjusting models for covariates, including age, sex, CD4+ count and HIV RNA did not weaken this association.
Conclusion: Anemia and macrocytosis are associated with worse NC performance over time in PLWH on ART. Macrocytosis is an indicator of mitochondrial dysfunction which is implicated in pathogenesis of neurological decline. Diagnosis of anemia is relatively easy; prompt and adequate treatment may prevent or improve the severity of NC deficit.

427 SHIV GENE EXPRESSION IN CSF CD4 T CELLS DURING ACUTE INFECTION OF RHESUS MACAQUES

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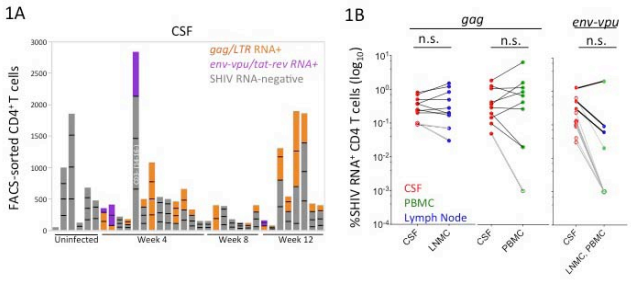
Background: The origin and extent of viral replication within the CNS during early HIV-1 infection remains unclear. We aimed to assess cerebral spinal fluid (CSF) for host cells actively transcribing virus in acutely SHIV infected macaques and compare infected cell frequency and cellular activation status to that observed in peripheral blood and lymph nodes.
Methods: Rhesus macaques (n=18) were infected intrarectally with a subtype C, HIV-1 env SHIV (1157ipd3N4). CSF, peripheral blood, and lymph node mononuclear cells (PBMC and LNMC) were analyzed at weeks 2-12 post-infection (PI). CD4 and CD8 T cells and macrophages were sorted, using flow cytometry, from each specimen directly ex vivo. SHIV RNA+ cells were identified by RT-qPCR assays specific for unspliced (gag) and spliced (env) viral RNA. Infected cell frequency was estimated by Poisson distribution statistics for PBMC and LNMC or assigning one infected cell to positive CSF replicates. Markers of cellular activation were measured by flow cytometry (surface staining) and gene expression (RT-qPCR).
Results: CSF specimens yielded an average 620 (120-2,840) CD4 T cells and 130 (2-400) macrophages after sorting. Infected, transcriptionally active (env+gag+) CD4 T cells were detected within the CSF in 25% of animals 4 weeks PI and 12% 12 weeks PI. In animals with SHIV RNA+ CSF CD4 T cells, infected (gag or env RNA+, respectively) CD4 T cell frequency was similar across CSF (0.05-2%, 0.3-1%), PBMC (0.02-7%, 0.02-2%), and LNMC (0.03-2%, 0.06-0.09%), indicating comparable T cell infection rates in these compartments in early infection (Figure 1). CSF blood contamination was minimal by ELISA and distinct cell composition. While macrophage infection was less frequently observed in CSF, the limited number of these cells constrained sampling depth. Surface expression of CD38 was elevated on CD4 and CD8 T cells in both PBMC and CSF during acute SHIV compared to uninfected controls ($p<0.05$). In contrast, the monocyte activation marker CD169, as well as CD38, was elevated on monocytes in PBMC ($p<0.05$) but not CSF, indicating T cell but not monocyte activation in CSF during acute infection. CSF CD4 T cells and macrophages both upregulated CXCL10 compared to uninfected controls and therefore might contribute to early CSF inflammation.
Conclusion: Our data supports a model of productive CD4 T cell infection within the CNS during acute HIV/SHIV infection, distinct from the role of macrophages in end-stage neuroencephalitis.



428 IN VIVO REPLICATION AND NEUROPATHOGENESIS OF T/F CLADE C SHIVs

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Background: Several substantial vaccine efforts against HIV-1 have so far failed primarily because to date we have failed to identify the correlates of protective immunity and the optimal vaccine formulation that can induce such protective immune responses in vivo. The knowledge that only select single or limited virus species are transmitted via the mucosal route has advanced the concept of transmitter/founder (T/F) viruses that are preferentially transmitted should be the target of HIV vaccine. Therefore, we developed T/F SHIVs using env of HIV molecular clones from Zambian transmission pairs.
Methods: Env gene of HIV3618MTF was cloned in to SHIVAD8-EO using In-Fusion cloning, named SHIV-4MTF.tS. To enhance macaque CD4 binding, we introduced N375 mutation. New SHIVs were transfected to 293T cells and supernatant was used to infect macaque PBMCs to generate virus stock. Viruses were inoculated via intra-vaginally (IVAG) route under the temporarily ablation of NK cells using JAK3 inhibitor. Sample collection was carried out (blood, CSF, RB, CVL, LN and feces) on various time points. Immune dynamics and degree of

pathogenesis was measured using multiparametric flowcytometry. Next some macaques were treated with ART starting from week 10 for 3 months to monitor post-treatment interruption and to evaluate viral variants. Tissues and organs including brain were evaluated using immunohistochemistry.
Results: The newly generated SHIVs are replication competent and shown to be tier 2 neutralization sensitive phenotype. Animals inoculated under the depletion of JAK3 inhibitor showed persistently high viral loads in both plasma and CSF for more than 6 months. After necropsy tissues were investigated for viral loads in different tissues and organs. Next CNS tissues showed mild pathology and very few virus positive cells suggesting that mild infection to CNS. The reisolated virus was again inoculated IVAG to non-JAK treated animals and showed peak viral loads (108) and persistent viral loads up to 6 months. Next, Animals with ART treated showed virus rebounded after post treatment interruption and currently monitoring for viral set points and measuring viral variants.
Conclusion: The newly generated SHIVs are replication competent in macaques, maintained viral set points for longer periods and neurotropic. These novel SHIVs will be useful tools for HIV cure studies as well as evaluating anti-HIV drugs, microbicides, and vaccine strategies.

429 EVOLVING SIV REGIONAL BRAIN INJURY AND RECOVERY ARE LINKED TO ANTIOXIDANT EXPRESSION

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Background: Brain dysfunction in HIV infection can evolve despite ART suppression. Brainstem regions, including those with dopaminergic functions, may be more vulnerable to injury, for unclear reasons. In the SIVmac251 model, we previously demonstrated regional brain differences in protective host anti-oxidant responses (heme oxygenase-1/HO-1) and we hypothesized that such differences would predict regional brain injury. To define evolving brain injury, we have now assessed neuronal markers of pre- and post-synaptic integrity and neurotransmitter phenotype in these animals, and correlated expression with oxidative response markers.
Methods: Eighteen rhesus macaques (2-3 yo) infected with SIVmac251 were sacrificed 5, 10, 13, 20, 41, and 90 days post infection (dpi). Nine brain regions (midbrain, parietal, basal ganglia, medulla, pons, frontal, pre-frontal, deep frontal, and cerebellum) were analyzed by western blot for neuronal markers PSD95, SYN1, synaptophysin, and tyrosine hydroxylase (TH), and the anti-oxidant response markers, HO-1, GPX1. Statistical analyses were by two-way ANOVA, post-hoc tukey's test, post-test for linear trend, and multivariate linear regression.
Results: Acute SIV infection (13-20dpi) correlated with neuronal injury markers (decreased PSD95, synaptophysin, $p<.01$) and neuronal functional responses (increased SYN1, $p<.05$) in most brain regions (brainstem and cortical), and specific dopaminergic neuronal responses (decreased TH, $p<.05$) in basal ganglia. Chronic infection (40-90dpi), showed sustained, but not progressive, neuronal injury from day 20 to day 90 (no significant changes in PSD95, synaptophysin), and no changes in dopaminergic responses (TH). However, cortical regions, but not brainstem regions, did show significant increases in PSD95 from day 13 to day 90pi, which suggests possible spontaneous regional brain recovery from acute injury. In acute and chronic phases antioxidant HO-1 expression correlated with PSD95 and synaptophysin ($p<.001$).
Conclusion: Neuronal injury in both brainstem and cortical regions occurs early in SIV infection and is sustained through chronic infection, with evidence for spontaneous recovery in cortical, but not brainstem regions. Because brainstem regions express lower antioxidant response enzymes (HO-1, GPX1) and because neuronal injury correlates negatively with HO-1 expression, our results support the hypotheses that lower brainstem antioxidant capacity accounts for brainstem vulnerability to, and less recovery from, SIV/HIV injury.

430 DOLUTEGRAVIR ACCUMULATES IN THE FETAL BRAIN FOLLOWING IN UTERO EXPOSURE

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Background: Dolutegravir (DTG)-based antiretroviral drug regimens will roll out worldwide with up to 15 million people receiving the drug within the next five years in resource-limited countries (RLCs), where most people infected with the human immunodeficiency virus (HIV) are women of child-bearing age. To this end, DTG has been shown to be highly effective due to its potent antiretroviral activities and high-barrier to viral resistance. Cautionary notes have surfaced, in recent months, regarding its safe use during pregnancy. Increased number of birth defects have emerged which warrants further investigation. Indeed, an observational study conducted in Botswana identified a potential risk of DTG in the development of neural tube defects. We recently reported that DTG crosses the blood brain barrier and can induce brain oxidative stress in adult mice. Herein, initial experiments were designed to determine whether administration of DTG to mothers could result in high levels of the drug in fetal brains.
Methods: DTG was administered intramuscularly to C57BL/6 female mice every 72 hours at 45 mg/kg dose. Treatment was initiated 3 days prior to mating and continued throughout pregnancy. Treatment was stopped at the day of birth of pups. Plasma was collected from dams for DTG quantification before and during pregnancy. At post-natal day 0.5, neonatal whole brains were processed to quantitate DTG following in utero exposure by UPLC-MS/MS.
Results: Plasma DTG concentrations were consistent among female mice with 13.5 µg/mL (Cmax) during pregnancy (Panel a). DTG concentrations in brains of all neonates from the same litter were similar (Panel b), averaging 114.2 ng/g.
Conclusion: We conclude that placental transfer of DTG during pregnancy can result in high drug levels in fetal developing brain. With previous data in hand, we posit that such an exposure could lead to oxidative stress subsequently affecting fetal brain development. Future experiments are designed to determine such linkages.

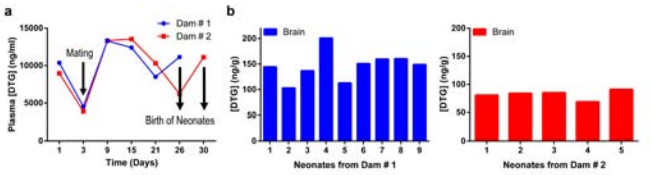

Figure. (a) Concentrations of DTG in plasma of two dams during pregnancy and **(b)** related DTG concentrations in the brains of post-natal day 0.5 old neonates following in utero exposure. Blue color represents Dam # 1 and its neonates and red color represents Dam # 2 and its neonates. Native DTG was administered intramuscular (IM) to each dam every 72 hours at 45 mg/kg dose, initiated 3 days prior to mating and continued throughout the pregnancy.

431 HIV BASAL-GANGLIA INJURY CORRELATES WITH ANTIOXIDANT & ENDOTHELIAL ADHESION MARKERS

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Background: Regional brain vulnerability to HIV is well-known but its determinants are not. Blood-brain barrier damage in the highly vulnerable basal ganglia correlates with cognitive impairment, suggesting vulnerability linked to endothelial dysfunction. We previously identified reduced pre-frontal cortex expression of the antioxidant heme oxygenase-1 (HO-1), as a risk for HIV encephalitis and cognitive dysfunction; in recent macaque studies we identified regional brain HO-1 variation that correlated with neuronal injury. We hypothesize that human brain HO-1 expression also varies regionally and correlates with endothelial cell adhesion molecule expression and neuronal injury in HIV.
Methods: Thirteen brain regions grouped as: i) cortical: frontal, temporal, occipital, anterior and posterior cingulate, motor, and sensory cortices; ii) basal ganglia: caudate, globus pallidus; and iii) others: frontal white matter; amygdala; cerebellum; pons) were dissected from 10 autopsies (7 HIV+, 3 HIV-) provided by the National NeuroAIDS Tissue Consortium. Endothelial cell adhesion molecules (ICAM-1, VCAM-1, PECAM-1), neuronal integrity (PSD95, synaptophysin), and HO-1 were quantified (Western blot, RT-qPCR). Expression was compared by one-way ANOVA/Sidak's correction, or two-way ANOVA/Tukey's correction, and Pearson's correlation.
Results: We found that brain HO-1 RNA, but not protein, varies regionally, and, in HIV+ subjects, it correlates with endothelial adhesion molecules (ICAM-1,

p<.05; VCAM, p<.01; PECAM, p<.001) and post-synaptic neuronal integrity (PSD95, p<.0001; synaptophysin, ns) in cortical regions, but not in basal ganglia. Additionally, within HIV+ subjects: i) HO-1 RNA is higher (p<.05), and PSD95 is lower (p<.0001) in basal ganglia vs. cortical regions, consistent with our recent macaque findings; ii) endothelial adhesion molecules are higher in basal ganglia vs. cortical regions (ICAM-1 p<.01, VCAM p<.01, PECAM, ns); and iii) PSD95 is lower in basal ganglia, but not cortical regions, in HIV+ vs HIV- subjects (p<.01).
Conclusion: We identified regional human brain variation in the anti-oxidant response (HO-1 RNA) that links it to post-synaptic neuronal injury and increased endothelial adhesion molecule expression. This suggests greater vulnerability of the basal ganglia (vs cortical regions) to HIV neuronal injury, possibly due to increased drive for transendothelial immune cell adhesion and migration. Such endothelial cell function may be regionally regulated by HO-1 expression.

432 PLATELET-ENDOTHELIAL INTERACTIONS MAY PROTECT AGAINST VIRAL ENTRY IN THE BRAIN

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Background: The brain is an important sanctuary site for HIV and these viral reservoirs are an important barrier to cure. In the SIV-infected macaque model, perivascular infiltrates of infected cells are characteristic of central nervous system (CNS) disease. Platelet decline occurs due to multiple mechanisms in SIV, and is associated with increased risk for the development of CNS disease. We sought to determine if activated platelet-endothelial interactions contribute to platelet decline and are associated with these infected perivascular infiltrates in the SIV-infected pigtailed macaque, and to define how these interactions affect the blood brain barrier.
Methods: Platelet activation was monitored throughout infection for SIV-infected macaques and uninfected controls. Brains were evaluated to determine CNS disease status and for immunohistochemistry for platelet-endoethelial binding and perivascular macrophage cuffs. Confluent monolayers of brain microvascular endothelial cells (BMECs) were exposed to washed platelets or media in transwells and permeability quantified.
Results: Platelets harvested from infected macaques that went on to develop CNS disease during terminal infection demonstrated less activation than macaques without CNS disease during acute (P = 0.04) and asymptomatic (P < 0.0001) infection. Brains from SIV-infected macaques were more likely than brains from uninfected controls to have platelets bound to vascular endothelium during acute (RR 4.0, P=0.03) and terminal (RR 3.6, P=0.04) infection. 6 of the 10 SIV+ macaques had CNS disease during terminal infection, and resident Mac387+ (RR 3.4, P=0.0001) or CD163+ macrophages (RR 1.44, P=0.0005) but not non-resident CD68+ macrophages (RR 1.2, P=0.2) were observed with increased likelihood around platelet-lined vessels in these animals. SIV-infected macrophages were similarly observed with increased likelihood around platelet-lined vessels (RR 1.5, P=0.007). Permeability of BMECs decreased two-fold following incubation with platelets from SIV infected macaques compared with uninfected macaques (P=0.01).
Conclusion: Activated platelet-endothelial interactions may represent a protective mechanism against development of infected macrophage infiltrates in CNS disease that is removed in the context of HIV-associated thrombocytopenia.

433 HIV-1 INDUCED NEUROPATHOLOGY OF A HUMANIZED MICROGLIAL MOUSE

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Background: Studies on HIV central nervous system infection and brain viral reservoirs have been hampered with the dearth of small animal models. Immune deficient mice reconstituted with human immune system are susceptible to HIV infection and have proven to be potent tools to study HIV pathogenesis, prevention and therapeutic development. However, any reflection of CNS has been hampered by a lack of human glial cells in any currently available rodent models. Human perivascular macrophages, microglia and astrocyte need be present to mimic brain viral reservoirs and virus-induced neuropathogenesis. To this end, we developed a new immunodeficient strain supplemented with human interleukin-34 (IL-34) transgene to support microglial development in humanized mice. These human microglial mice were used to study HIV-1 induced neuropathogenesis.
Methods: Human CD34+ hematopoietic stem cells transplanted NOD.Cg-Prkdcscidll2rgtm1SugTg(CMV-IL34)1/Jic (CD34-NOG-hIL-34)mice developed human "microglia like" in the presence of tissue specific ligand-IL-34. To identify relationships between HIV-1 infection of microglia and neuropathology, mice at 6 months of age were infected with HIV-1ADA and brain tissues were subjected for histopathologic (glial and neuronal) and transcriptomic (mouse and human) profiling by next generation sequencing.
Results: CD34-NOG-hIL-34 mice showed sustained plasma viremia with CD4+T cell loss and productive human microglial infection. Reductions in neuronal and synaptic architectures was observed in brain subregions by reduced expression of synaptophysin, MAP2 and neurofilament-H. Astrogliosis and microgliosis were evident. Molecular profiling of these infected brains revealed a significant increase in human genes such as IFIT1-5, ISG15, MX2, OAS1 pertaining to interferon signaling. The other pathways which were upregulated included toll-like receptor and pattern-recognition receptor indicating activation of innate immune response and increased inflammation. Whilst analysis of mouse genes indicated that ERK, integrin, MAPK, apoptosis signaling etc. were differentially regulated in association with neurodegeneration.
Conclusion: Human microglial mouse closely reflects the pathobiology of HIV-1 infection with astrogliosis, microgliosis, productive viral infection of microglia, synaptic alterations and inflammatory responses. This model will prove useful for studies of neural-glial cross talk and studies designed to locate and eliminate the viral reservoir.

434 MTDNA HAPLOGROUP B IS ASSOCIATED WITH EXECUTIVE FUNCTION AND RECALL IN HISPANIC PLWH

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Background: Neurocognitive impairment (NCI) is common among persons living with HIV (PLWH) and impacts quality of life and functional status. Mitochondrial DNA (mtDNA) haplogroups are associated with HIV-related outcomes. NCI appears to be more frequent in persons of Hispanic ethnicity with HIV. We previously observed less NCI in Hispanic-ancestry PLWH having mtDNA haplogroup B. The current analysis focused on domains of NC performance in this population.
Methods: CHARTER is a prospective observational study of neurologic outcomes of PLWH. Comprehensive neuromedical, neurocognitive (NC), and laboratory assessments were performed. Haplogroups were assigned using mtDNA sequence data. Outcomes were age-, sex-, and education-corrected domain deficit (DDS) and mean T scores (TS), and impairment status by clinical rating score for seven NC domains: motor, working memory, verbal, executive function, processing speed, learning and delayed recall. Race/ethnicity-stratified analyses of baseline domain scores/status included univariate Wilcoxon rank sum and Chi2 tests. Linear regression models adjusted for nadir CD4 cell count, neurocognitive comorbidity status, and current ART use.
Results: Major haplogroups and NC domain data were available in 1016 persons (median age 43 years, 23% female, 478 [47%] non-Hispanic black, 440 [43%] non-Hispanic white, and 98 [10%] Hispanic). Major haplogroups were not independently associated with NC domains among non-Hispanic black or white PLWH. Among 98 Hispanic PLWH, mean executive function, learning, and recall TS were higher and DDS lower (less impaired) among 17 with haplogroup B compared to other haplogroups (Wilcoxon p<0.05 for all comparisons). Three Hispanic PLWH (18%) with haplogroup B had impaired delayed recall vs. 34 (42%) with other haplogroups (Chi2 p=0.06). With adjustment for the covariates above, haplogroup B was no longer associated with learning DDS and TS (p=0.1 and 0.2) or recall DDS (p=0.08), but remained significantly associated with executive function DDS and TS (p≤0.05 for both), and recall TS (p=0.03). Other domains did not differ by haplogroup B status.
Conclusion: Previously identified NC differences in Hispanic CHARTER participants with mtDNA haplogroup B were greatest for the delayed recall and executive function domains. If validated in independent cohorts, this finding could inform neuroimaging and other assessments to define mechanisms by which mtDNA variation may influence NC performance in PLWH.

435 MECHANISMS OF WHITE-MATTER LOSS DUE TO HIV INFECTION AND ANTIRETROVIRAL THERAPY

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Background: White matter pathologies including corpus callosum thinning and disruption of white matter microstructures persist in HIV-positive patients on combination antiretroviral (ARV) therapy (cART). Thinning of the corpus callosum increases with time on cART. Thus, we hypothesized that HIV-infected macrophages and/or antiretroviral compounds alter oligodendrocyte differentiation, function, and/or survival and sought to identify the mechanism underlying this effect.

Methods: To model the effect of HIV infection in the CNS on oligodendrocytes, we stimulated primary rat oligodendrocyte precursor cells (OPCs) to differentiate into mature oligodendrocytes in vitro, with concomitant treatment with HIV-infected monocyte-derived macrophage supernatant (HIVMDMS) or ARV compounds from the integrase strand transfer inhibitor class, elvitegravir, raltegravir or cobicistat, the bioavailability boost. To examine the effect of ARV drugs on remyelination, we treated mice with cuprizone, a demyelinating compound, for five weeks and allowed them to recover for three weeks (a time frame that permits remyelination) or treated them with daily intrajugular injection of elvitegravir and cobicistat during the three-week recovery phase. Brains were harvested, and the corpus collosum was sectioned and stained for myelin by luxol fast blue, mature oligodendrocytes by ASPA and neuroinflammation by GFAP and Iba1.

Results: In our in vitro model, OPC differentiation was inhibited by HIVMDMS and elvitegravir, whereas raltegravir and cobicistat did not affect oligodendrocyte differentiation. The inhibition of OPC differentiation by HIVMDMs and elvitegravir was reversed by inhibiting the integrated stress response using the small molecule trans-ISRIB. Finally, administration of elvitegravir during the recovery phase following cuprizone-induced demyelination resulted in failure of remyelination, indicated by reduced ASPA and luxol fast blue staining. Persistent neuroinflammation was evident in the corpus callosum in elvitegravir-treated mice compared with the untreated controls.

Conclusion: These studies suggest that both HIV infection and elvitegravir inhibit OPC differentiation in vitro and in vivo. Further studies of the effects of HIV and/or first-line ARV compounds are warranted to provide insights into the observed persistent white matter changes seen in patients with HIV-associated neurocognitive disorders and their potential contribution to cognitive impairment.

436 SWITCHING TO FTC/TAF FROM ABC/3TC OR FTC/TDF DOES NOT AFFECT CNS HIV-1 INFECTION

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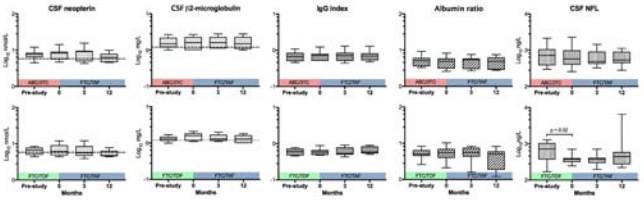
Background: Despite suppressive antiretroviral therapy (ART), many HIV-infected individuals have low-level persistent immune activation in the central nervous system (CNS). Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) and abacavir/lamivudine (ABC/3TC) have been the most widely used nucleoside analogues for several years. In 2015, when this study was initiated, a new prodrug for tenofovir, tenofovir alafenamide fumarate (TAF), was introduced. One potential concern regarding TAF and its effect in CNS is that TAF is a stronger substrate for P-glycoprotein (P-gp) than TDF, which could theoretically decrease its CNS exposure since substrates for P-gp are subject to active blood-brain barrier efflux. Our aim was to investigate if switching from FTC/TDF or ABC/3TC to FTC/TAF would lead to changes in residual intrathecal immune activation, viral load, or neurocognitive function.

Methods: In this prospective study, we included 20 HIV-infected neuroasymptomatic adults (11 on ABC/3TC and 9 on FTC/TDF) selected from the prospective Gothenburg HIV CSF study cohort who for backward comparison recently had undergone a previous research lumbar puncture when on treatment with the same regimen as on baseline. We performed lumbar punctures, veni punctures, and neurocognitive testing at baseline and after three and 12 months. At the baseline visit all participants changed their nucleoside analogues to FTC/TAF without any other changes to the ongoing ART regimen. We analysed CSF and plasma HIV RNA, CSF neopterin, CSF β2-microglobulin, IgG index, albumin ratio, and CSF NFL at the pre-study visit, baseline and follow-up. Cognitive function in five domains was assessed by CogState.

Results: After three and 12 months of follow-up, there were no significant changes in CSF and plasma HIV RNA, CSF neopterin, CSF β2-microglobulin, IgG index, albumin ratio, CSF NFL, or neurocognitive function in any of the groups (see figure, CSF and plasma HIV RNA and Cogstate results not shown).

Conclusion: Switching to FTC/TAF from ABC/3TC or FTC/TDF was neutral on HIV CNS infection and inflammation.



437 POLYPHARMACY IS ASSOCIATED WITH WORSE NEUROCOGNITIVE PERFORMANCE IN AGING ADULTS

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Background: Persons living with HIV (PLWH) have more aging-related diseases, use more prescribed drugs, and are more likely to have neurocognitive (NC) impairment than the general population. Medical and psychiatric comorbidities increase risk of NC impairment in PLWH but the neurotoxicity of drugs used to treat these diseases remains underinvestigated.

Methods: 956 PLWH taking antiretroviral therapy (ART) and enrolled in neuroHIV cohorts underwent NC assessment. Demographically-adjusted T-scores were computed for seven cognitive domains and global performance. The most common classes of concomitant drugs were antidepressants (31.1%), antimicrobials (26.2%), non-steroidal anti-inflammatory drugs (21.0%), opioids (16.0%), gastric acid drugs (15.8%), antipsychotics (12.6%), antihypertensives (11.2%), and anxiolytics (10.9%). Polypharmacy was defined as taking ≥5 concomitant drugs. Psychiatric and substance use diagnoses were available for 719 participants. Stepwise multivariable linear regressions using the Akaike Information Criterion modeled NC performance as a function of concomitant medications, adjusting for age, sex, and HIV disease and treatment characteristics.

Results: Participants were generally middle-aged (mean 44.1) white (53.1%) men (86.2%) who had AIDS (56%), viral suppression (71.7%), and immune recovery (median CD4+ count 488/μL). The mean number of concomitant drugs was 3.3 (range 0-24). Overall, PLWH who took more concomitant drugs had worse global performance ($r=0.15$, $p<0.001$), as did those who took ≥5 concomitant drugs ($d=0.28$, $p<0.001$). Worse global performance was associated with use of anxiolytics ($p<0.001$), protease inhibitors ($p=0.006$), opioids ($p=0.008$), antimicrobials ($p=0.009$), and antipsychotics ($p=0.03$) (Model $p<0.001$). Concomitant drug classes were most frequently associated with worse executive functioning and learning (see Figure). Accounting for psychiatric, medical, and substance use diagnoses and did not significantly weaken the associations between concomitant drugs and global performance.

Conclusion: Concomitant drug use is associated with worse NC performance. Distinguishing the effects of concomitant drugs from those of underlying diseases is complex but our analyses support that certain drug classes may cause reversible or irreversible neurotoxicity. Different drug classes were associated with different cognitive patterns, suggesting that they differently affect the neurobiological pathways underlying these abilities.

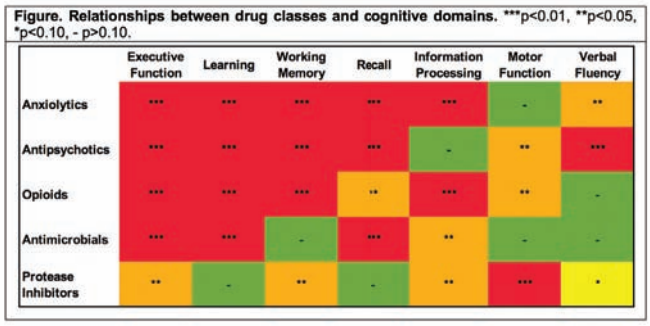

Figure. Relationships between drug classes and cognitive domains. ***p<0.01, **p<0.05, *p<0.10, - p>0.10.

438 CENTRAL NERVOUS SYSTEM SAFETY OF A KICK-AND-KILL STRATEGY WITH ROMIDEPSIN

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Background: Romidepsin (RMD) is a histone deacetylase inhibitor (HDACi) able to induce HIV transcription in vitro and in vivo. Its effects on the brain during cure strategies are unknown. We investigated cognitive, neuroimaging, and functional outcomes in the BCN02-Romi Study, a trial that assessed the effects of an HIVconsv vaccine in combination with RMD in early-treated HIV-infected persons (clinicaltrials.gov: NCT02616874).

Methods: The BCN02-Romi Study tested a kick&kill strategy that combined 2 administrations of an HIVconsv vaccine (pre and post RMD, weeks 0 and 9), with 3 weekly infusions of RMD (5mg/m2; weeks 3, 4, and 5), a monitored antiretroviral pause (MAP, starting at week 17), and a 24-week period after the reinitiation of cART. Inclusion in the BCN02-Neuro Substudy was offered to the 15 individuals recruited in the BCN02-Romi Study and 11 accepted to participate (Intervention Group, IG, n=11). Early-treated but not vaccinated individuals were recruited as controls (Control Group, CG, n=10). CNS assessments were performed before RMD administration (Pre), after final RMD administration (Post), and after MAP + 24-week cART reinitiation (Final). Study variables comprised cognitive functioning (NPZ6), 3T magnetic resonance imaging (voxel-wise whole-brain structural changes), and functional outcomes (daily functioning, adverse events, and emotional symptoms). Study endpoints were based on between-arm differences in change from Pre to Post and Final assessments.

Results: Global cognitive functioning was comparable between groups at the 3 study timepoints (mean NPZ6 [SD]): Pre: IG: 0.28 (0.64), CG: 0.28 (0.63), p=0.98; Post: IG: 0.42 (0.54), CG: 0.31 (0.61), p=0.66; Final: IG: 0.41 (0.59), CG: 0.55 (0.76), p=0.69. Analysis of change confirmed these results (mean NPZ6 change [SD]): Post: IG: 0.13 (0.31), CG: 0.03 (0.32), p=0.45; Final: IG: 0.15 (0.43), CG: 0.27 (0.35), p=0.56. Neuroimaging analyses did not find differences between groups at any timepoint (all p values >0.10). No differences were also observed in daily functioning outcomes, CNS adverse events, or emotional symptoms.

Conclusion: No detrimental effects of a kick&kill strategy with RMD were observed on cognitive functioning, neuroimaging, or functional outcomes in this small study. The HIV cure approach investigated, including the use of an HIVconsv vaccine, administration of RMD, and cART interruption with posterior 24-week therapy reinitiation, appears to be safe for the brain.

439 CENTRAL NERVOUS SYSTEM EFFECTS OF THERAPY INITIATION WITH INTEGRASE INHIBITORS

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Background: Data about the possible CNS toxicity of integrase strand transfer inhibitors (INSTI) in people living with HIV (PLWH) are growing. We investigated this in the ARBRE Study, an observational trial that assessed the impact of antiretroviral therapy with INSTI on brain outcomes according to the time of therapy initiation.

Methods: The ARBRE Study included 3 study arms: early-treated PLWH (G1: <3 months since estimated date of infection, n=12), chronically treated (G2: >6 months, n=15), and matched seronegative controls (G3, n=15). Both HIV+ groups were treated with an INSTI-containing regimen (dolutegravir, elvitegravir, raltegravir). Assessments were performed at baseline (prior to therapy initiation), week 4, and week 48, and evaluated cognitive functioning (6 domains, NPZ12), 3T magnetic resonance imaging (voxel-wise whole-brain structural changes), and functional outcomes (daily functioning, adverse events, and emotional symptoms). Study endpoints were based on difference in change at week 48 among arms.

Results: Baseline cognitive functioning and neuroimaging parameters were comparable among groups. Regarding functional outcomes, daily functioning and CNS adverse events were also comparable, although participants in G1 had more depressive symptoms (p=0.03), anxiety (p=0.04), and perceived stress (p=0.03) than the other groups. At week 4, no significant changes were observed in cognitive functioning or functional outcomes. Neuroimaging analyses detected a significantly more reduced gray matter volume in the medial orbitofrontal cortex in G2 (p=0.005). At week 48, cognitive performance did not significantly improve or differ between groups (p=0.14). The decreased medial orbitofrontal volume found in G2 persisted, although to a lesser extent (p=0.04). Emotional symptoms improved significantly in G1, reaching comparable levels among groups (p>0.10).

Conclusion: Cognitive outcomes were similar between PLWH initiating therapy with INSTI during early infection or later than 6 months after HIV transmission. However, participants who initiated therapy later had more reduced gray matter volume that persisted for 48 weeks, which is consistent with prior reported data showing cortical thickness abnormalities in virally suppressed HIV+ patients. An extended follow-up is required to ascertain the future progression of CNS outcomes in PLWH on therapy with INSTI.

440 NEUROPSYCHIATRIC OUTCOMES BEFORE AND AFTER SWITCHING TO DOLUTEGRAVIR-BASED THERAPY

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Background: Dolutegravir (DTG) is a 2nd generation HIV integrase inhibitor currently recommended as 1st-line antiretroviral therapy (ART). Neuropsychiatric (NP) adverse events have been reported with DTG but NP symptoms have not been systemically quantified using structured scales. This study examined mood and cognitive parameters before and after a planned transition from a non-DTG to a DTG-based regimen within a longitudinal study.

Methods: Participants on ≥ 24 weeks of ART started in acute HIV infection (AHI) underwent NP assessments before and after transition to DTG. They underwent: 1) Patient Health Questionnaire-9 (PHQ-9), a 9-item survey (score range 0-27) that evaluates both somatic and affective/cognitive symptoms of depression; 2) a 2-Questions screening that has been validated locally for major depression; 3) Distress Thermometer for anxiety/stress (scores 0-10); and 4) a 4-test battery that included Color Trails 1 and 2, Trails Making A and non-dominant hand grooved pegboard test. Outcomes before and after DTG were compared by McNemar and Wilcoxon signed-rank tests; multivariate linear regression examined factors that were correlated with the change of PHQ-9 scores.

Results: 256 individuals (95% male, median age 30 [IQR 25-36]) switched to DTG-based ART after a median 144 [IQR 24-192] weeks of ART (82% efavirenz-based) initiated in AHI. Serial assessments were done at median 19 [IQR 8-35]

weeks before and median 37 [IQR 24-48] weeks after the switch. PHQ-9 scores were higher in 48% of participants, lower in 31%, and unchanged in 21% after switching. The proportion of participants with at least moderate depression symptoms (PHQ-9≥10) rose from 9% to 16% (p=0.007), while the percentage of those with moderately severe symptoms (PHQ-9≥15) did not change (3% vs. 3%). The PHQ-9 sub-scores of somatic symptoms (sleep/appetite/energy level) had a more significant increase than that of cognitive/affective symptoms (p=0.005 vs. p=0.052). Multivariate analysis showed that viral suppression (Mean difference -2.9, 95%CI [-0.9 to -5.0], p=0.005) and higher PHQ-9 scores (Mean difference -2.7, 95%CI [-1.2 to -4.2], p<0.001) prior to DTG were linked to decrease in PHQ-9 score after DTG. NPZ-4, CD4+ T-cell counts and CD4/CD8 ratio improved after DTG (Table).

Conclusion: DTG-associated NP adverse effects in this cohort were primarily related to somatic symptoms including insomnia, whereas there was no change in the prevalence of severe depressive symptoms or major depression.

Table. Parameters Before and After Transition to Dolutegravir (N=256)

	Pre-switch**	Post-switch**	P value
CD4+ T-cells (cells/ul)	624 (513-782)	662 (530-829)	< 0.001
CD8+ T-cells (cells/ul)	578 (452-792)	618 (487-798)	0.205
CD4/CD8	1.09 (0.85-1.41)	1.11 (0.87-1.42)	0.024
NPZ-4	0.70 (0.31-1.10)	0.88 (0.58-1.19)	< 0.001
Color Trails 1 z-score	1.15 (0.59-1.56)	1.30 (0.65-1.74)	< 0.001
Color Trails 2 z-score	0.61 (0.14-1.11)	0.86 (0.39-1.23)	< 0.001
Grooved Pegboard Test z-score	0.54 (-0.18-1.05)	0.65 (-0.08-1.11)	0.126
Trail Making A z-score	0.75 (0.14-1.15)	0.80 (0.07-1.33)	0.026
PHQ-9 score	5 (1-7)	5 (2-8)	0.004
PHQ-9 ≥ 10, n(%)	24 (10)	40 (16)	0.006
PHQ-9 ≥ 15, n(%)	8 (3)	8 (3)	1.000
^ PHQ-9 Somatic Sub-score	2 (0-3)	2 (1-3)	0.005
# PHQ-9 Cognitive/Affective Sub-score	2 (0-4)	2 (0-5)	0.052
Major Depression by 2Q-Depression Screening, n(%)	2 (1)	3 (1)	1.000
Distress Thermometer Score	2 (1-5)	2 (1-4)	0.897
*Viral Suppression, n(%)	244 (95)	251 (98)	0.039

**Median (IQR) is presented unless specified; Wilcoxon and McNemar Test were used accordingly.
^ Questions 3, 4, 5; # Questions 1, 2, 6, 7, 8, 9.
* Defined as plasma HIV RNA < 50 copies/ml.
Abbreviations: NPZ-4 = Composite z-score of the 4 neuropsychiatric tests; PHQ-9 = Patient Health Questionnaire-9.

441 NEUROPSYCHOLOGICAL CHANGES IN EFAVIRENZ SWITCH REGIMENS IN MACS

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Background: Efavirenz (EFV) has been associated with side effects involving the central nervous system including depression, vivid dreams and sleep impairment. However, it remains largely unknown whether switching off EFV improves neuropsychological performance and depression.

Methods: We utilized data from the Multicenter AIDS Cohort Study (MACS). Participants were categorized by their use of EFV: never on EFV (No EFV), on EFV then switched off (Switch-OFF) and continuously on EFV (No Switch-OFF). Baseline time point was defined as visits when first neuropsychological data were available. In the first analysis, we compared neuropsychological and Center for Epidemiologic Studies Depression (CES-D) scores before and after EFV switch in Switch-OFF group, aligning participants at the time of switch. Linear mixed effects models were fitted to examine the change of each of scores before and after switching. In the second analysis, we compared the trajectory of neuropsychological/CES-D scores among the three groups.

Results: This analysis included 1,989 HIV-seropositive participants with neuropsychological data, with 1,675 participants in No EFV group, 270 in Switch-OFF group, and 44 in No Switch-OFF group. Participants at baseline had a median age of 37 years, median CD4 cell count 442 cells/μL, and 22.9% of viral suppression rate. Prevalence of HIV-associated dementia was 3.24%, 4.09% and 2.78% in No EFV, Switch-OFF, and No Switch-OFF groups (P=0.197). Baseline CES-D scores were 9, 9 and 6 in No EFV, Switch-OFF, and No Switch-OFF groups (P=0.16). In Analysis 1, viral suppression rate before switch was 62.8% and median CD4 cell count was 548 cells/μL in Switch-OFF group; neuropsychological T scores and CES-D scores did not show clinically significant changes over 1.5 years prior to and 1.5 years after switch for each of neuropsychological domains (Table). In a sensitivity analysis only including participants with viral suppression prior to switch, neuropsychological and CES-D scores did not change significantly after switching off EFV. In Analysis 2, trends in neuropsychological and CES-D scores in the three different groups did not show significantly differences during a median of 3.2 years of follow up.

Conclusion: Discontinuation of EFV is not associated with changes in neuropsychological performance or severity of depression in men. Furthermore, we did not observe differences among participants who were never on EFV, on EFV and then switched off and continuously on EFV.

Table. Neuropsychological and CES-D mean scores before and after EFV switch (with 95% confidence intervals).

	N	Mean before switch		Mean after switch		P Value
Neuropsychological scores						
Motor	200	44.54	(42.60,46.48)	43.79	(41.96,45.63)	0.39
Speed	201	48.33	(46.85,49.81)	48.22	(46.82,49.62)	0.87
Memory	201	49.34	(47.87,50.82)	48.05	(46.66,49.43)	0.06
Working memory	185	48.75	(47.13,50.38)	47.47	(45.91,49.02)	0.11
Executive functioning	201	48.67	(46.95,50.39)	47.59	(45.96,49.22)	0.16
Learning	201	49.00	(47.41,50.58)	48.69	(47.21,50.16)	0.70
CES-D	198	14.86	(12.86,16.87)	13.34	(11.45,15.22)	0.15

Each score was modelled separately. High neuropsychological T scores indicate good performance. Higher CES-D scores indicate worse depression.
EFV, efavirenz; CES-D, Center for Epidemiologic Studies Depression Scale.

442 MEMORY AND LEARNING DYSFUNCTION WITH INTEGRASE STRAND TRANSFER INHIBITORS USE

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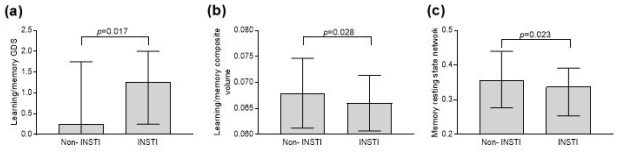
Background: Integrase strand transfer inhibitors (INSTIs) have been associated with neuropsychiatric symptoms in post marketing analysis. However, limited data exists on the effect of these drugs on neurocognitive function. We assessed neurocognitive function and neuroimaging in people living with HIV (PLWH) on INSTI-based regimens

Methods: We performed a cross-sectional analysis of PLWH on ART aged >18 years. PLWH with<="" div="">

Results: Of 202 PLWH, median (IQR) age 55 (48, 60) years, 152 (75%) male, 136 (67%) black, median recent CD4+ T cell count 576 (401, 818) cells/mm3, 96% HIV RNA <200 copies/ml, 99 (49%) were on INSTI-based ART (40.4% raltegravir, 29.3% elvitegravir, 30.3% dolutegravir), while 103 (51%) were on non-INSTI based ART. No between group difference was identified in age, sex, race, education, smoking status, depression scores, psychiatric medication use, HIV infection duration or nadir and recent CD4+ T cell count. On neuropsychological assessment, PLWH in the INSTI group had worse learning/memory domain scores compared with those on non-INSTI based ART (1.25 (0.25, 2) versus 0.25 (0, 1.8); p=0.02) (figure a). This remained significant when corrected for nadir CD4+ T cell count, current ART regimen duration, current NNRTI or PI use, current psychiatric medication use or having previously received another ART regimen (p=0.04). A composite volumetric measurement for learning/memory brain regions was significantly smaller in the INSTI group compared to non-INSTI group (figure b). Functional connectivity was reduced in the memory resting state network in the INSTI group compared to the non-INSTI group (figure c).

Conclusion: We demonstrated worse learning/memory neuropsychological performance; smaller volumetric measurement in regions associated with learning/memory and decreased functional connections in the resting state memory network in those on INSTI-based regimens. Our results suggest a dysfunction in the learning/memory network but prospective studies are required to explore this further.



443 CEREBRAL FUNCTION PARAMETERS IN PEOPLE LIVING WITH HIV SWITCHING INTEGRASE INHIBITOR

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Background: Different antiretroviral therapy (ART) agents and combinations may have differing effects on cerebral function. We assessed detailed changes in cerebral function parameters in people-living-with HIV (PLWH) on ART switching integrase inhibitor.

Methods: Neurologically asymptomatic PLWH on tenofovir-DF/emtricitabine plus raltegravir 400mg twice daily with plasma HIV RNA <20 copies/mL for at least 3 months were randomly allocated on a 1:2 basis to remain on raltegravir (Arm1) or to switch to dolutegravir 50 mg once daily (Arm2) for 120 days. Changes in several cerebral function parameters were assessed which included cognitive function (reported as a z-score composite of 7 domains), patient-reported outcome measures (PROMs; PHQ-9 and Beck's depression questionnaires), cerebrospinal fluid (CSF) parameters (CSF HIV RNA, tryptophan and phenylalanine metabolites, neopterin, ART exposure and an in-vitro CSF antiretroviral infectivity assay using astrocyte derived cell cultures) and cerebral magnetic resonance (MR) imaging (proton spectroscopy (H1-MRS) in three anatomical locations). CSF infectivity models are expressed as half-maximal inhibitory concentration scores (-log2IMIC50) and ART concentrations were measured by HPLC–tandem mass spectrometry with geometric means (GMs) and 95% CIs calculated.

Results: Of 20 subjects completing study procedures, 19 were male, 14 were of white ethnicity, median age (IQR) was 43 (11.5) years and mean (SD) baseline CD4+count was 717 (298) cells/μL. No treatment related adverse events were observed and plasma HIV RNA remained <20 copies/mL in all. Over 120 days, no statistically significant differences in changes in overall cognitive performance, PROMs, CSF tryptophan metabolite ratios, CSF antiretroviral activity scores or cerebral metabolite ratios were observed (table 1). A small difference was observed in CSF neopterin concentration between treatment arms (table 1). CSF HIV RNA was <5 copies/mL at day 120 in all subjects. GM CSF dolutegravir concentration assessed pre-dose was 7.6 ng/mL (95% CI: 5.2-11.1).

Conclusion: In this comprehensive assessment of cerebral function parameters in virologically suppressed PLWH switching integrase inhibitor, we observed no significant changes in clinical, CSF biomarker or cerebral imaging parameters.

Table 1. Cerebral function parameters over study period

Parameter		Overall result		Changes at 120 days		
		Baseline	Day 120	Arm1 (raltegravir)	Arm2 (dolutegravir)	Arm1 vs. Arm2
		n=21	n=20	n=8	n=12	*P-value*
Cognitive function	Global cognitive score; z-score, (SD)	-0.001 (0.66)	0.22 (0.69)	0.14 (0.37)	0.14 (0.40)	0.98
PROMs	PHQ-9 questionnaire (median/ range)	2 (0/9)	1.5 (0/5)	0 (-5/1)	-0.5 (-5/3)	0.57
	Beck's questionnaire (median/ range)	2 (0/20)	1.5 (0/15)	-1.5 (-10/2)	-1.0 (-15/9)	0.38
CSF bio-markers	antiretroviral scores; log_2IMIC_{50} (95%CI)	4.00 (0.69)	4.15 (0.87)	-0.17 (-0.58/0.24)	0.36 (-0.33/1.05)	0.28
	kinurenine/tryptophan; μmol/mmol, mean (SD)	40.6 (20.7)	38.2 (24.5)	-0.48 (10.8)	-5.27 (10.9)	0.51
	phenylalanine/tyrosine; μmol/mmol, mean (SD)	1.01 (0.14)	0.99 (0.18)	-0.04 (0.14)	0.00 (0.18)	0.57
	neopterin; nmol/L, mean (SD)	8.30 (5.99)	7.66 (4.84)	-1.93 (2.54)	0.23 (2.03)	0.05
Cerebral metabolite ratios (H^1-MRS)		n=21	n=19	n=7	n=12	
	FGM NAA/Cr, mean (SD)	1.01 (0.10)	1.04 (0.11)	-0.06 (0.16)	0.08 (0.14)	0.07
	FWM NAA/Cr, mean(SD)	1.21 (0.27)	1.19 (0.15)	-0.13 (0.34)	0.01 (0.13)	0.20
	RBG NAA/Cr, mean (SD)	0.93 (0.19)	0.90 (0.20)	-0.13 (0.24)	.0066 (0.33)	0.35

Table 1 legend:
PROM= Patient reported outcome measures; SD= standard deviation; CI=Confidence interval; $IMIC_{50}$= infectivity model half-maximal inhibitory concentration H^1-MRS= proton magnetic resonance spectroscopy; FGM= Frontal Grey Matter; FWM= Frontal White Matter; RBG= Right Basal Ganglia NAA= N-acetyl aspartate; Cr= creatinine

444 EARLY ART IN ACUTE HIV LIMITS DETRIMENTAL CX3CR1 MONOCYTES LINKED TO CNS DYSFUNCTION

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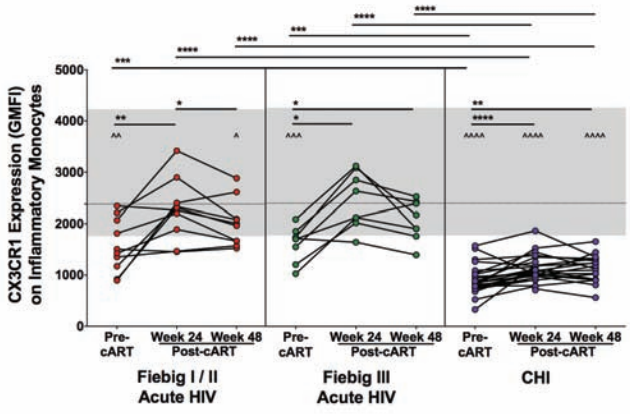
Background: CX3CR1 on immune cells drives tissue homing. In chronic HIV (CHI), inflammatory and patrolling monocytes express reduced CX3CR1 density compared to uninfected (HIV-) controls. In addition, CX3CR1 on microglia has been reported to have neuromodulatory effects in the brain. We investigated the dynamics of CX3CR1 density on monocyte subpopulations in individuals who initiate combination antiretroviral therapy (cART) during acute HIV infection (AHI) and assessed the relationship with central nervous system (CNS) outcomes.

Methods: We examined 18 AHI adults (n=10 Fiebig stage (F)I/II and n=8 FIII) who initiated cART. As controls CHI adults (n=27 pre-cART; n=30 and n=19 at 24 and 48 weeks post-cART, respectively) and demographically matched HIV- adults (n=13) were included. CX3CR1 density (geometric mean fluorescence intensity [GMFI]) was measured on monocytes (classical and CD16+ inflammatory and patrolling subsets) from peripheral blood mononuclear cells by multiparametric flow cytometry using a protocol capturing maximal chemokine receptor recycling and expression. Neuropsychological (NP) tests performed included Trail Making A, Color Trails 1 and 2, and Grooved Pegboard to compute a summary NPZ-4. Nonparametric statistics were used.

Results: The median age was 30, 33, and 31 years for AHI, CHI and HIV-, respectively. 61% of HIV+ and 67% of HIV- were male. In CHI at baseline, CX3CR1 density on inflammatory monocytes was lower compared to HIV- and AHI (p's<0.001). Despite up to 48 weeks of cART, CX3CR1 density did not normalize to HIV- levels (p's<0.0001) and residual CX3CR1 monocyte density correlated with worse NP testing scores (global NPZ; rho=-0.308, p=0.038 and rho=-0.486, p=0.035 for 24 and 48 weeks post-cART, respectively). At baseline, CX3CR1 density on inflammatory monocytes in AHI was lower than in HIV- (p's<0.01). However post-cART, CX3CR1 levels normalized and unlike in CHI, were not associated with NP test scores. While differential CX3CR1 densities on classical and patrolling monocytes were noted between AHI, CHI and HIV- at baseline and post-cART, these subsets were not associated with either global or subdomain NP test scores.

Conclusion: Unlike in treated CHI, early cART instituted in AHI restores perturbed CX3CR1 density on inflammatory monocytes. This may halt a detrimental cascade initiated by monocyte trafficking to the CNS that is linked to cognitive decline. These data reveal the benefits of initiation of cART early during infection.



445 ART IN EARLY INFECTION IMPROVES NEUROCOGNITION REGARDLESS OF INFECTION DURATION

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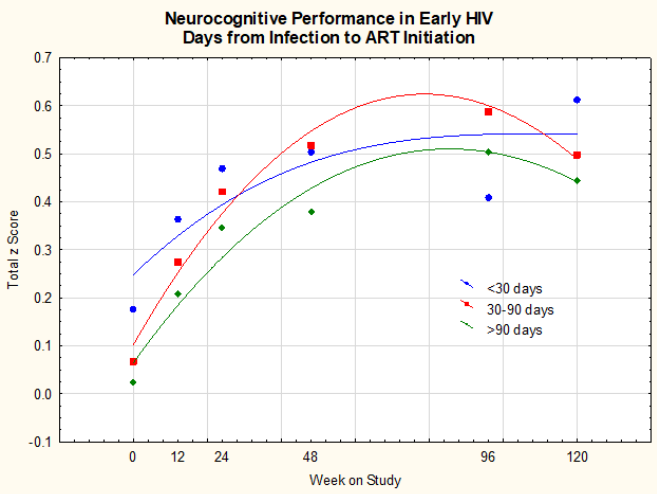
Background: The CNS is a sanctuary and reservoir for HIV, which is known to enter the CNS within days of primary infection. We sought to assess whether early ART would improve neurocognitive performance (NP) in the Sabes study, a cohort of men who have sex with men (MSM) and transgender women (TW) in Lima, Peru randomized to start ART at diagnosis (within 30-90 days of estimated date of detectable infection (EDDI)) vs. after a short delay. We hypothesized that, by limiting CNS infection, ART initiation within 30 days of HIV acquisition would improve NP compared to ART initiation later in early infection.

Methods: A subset of Sabes participants had neurocognitive assessments and blood collection, and in some cases, lumbar puncture. NP was measured with a 15-test battery covering Gross motor, Attention, Executive, Learning, Memory, Speed of Processing, and Fine Motor domains at weeks 12, 24, 48, 72, 96 and 120 after randomization. Estimated date of infection (EDDI) was derived from an algorithm compiling test parameters of last negative and first positive HIV tests.

Results: The 112 participants were all hispanic MSM or TW, had a mean age of 26.4 years (SD=7.4), mean education grade level of 12.5 (SD=2.3) and mean baseline CD4+ cell count of 443.4 (SD=210.4). Seventy-seven observations came from participants with an EDDI to ART initiation interval of <30 days, 190 from participants who started ART after 31-90 days, and 262 from those who started ART 91 to 249 days after EDDI (>90 days). NP did not differ significantly between the EDDI to ART categories over time (mean total z for <30 = .42, 31-90= .39, >90=.32; p=ns). However, NP significantly improved with ART out to 120 weeks of follow up (F=(5, 394)=35.9, p<.0001), across categories (mean total z score at week 0=0.09, week 12=0.28, week 24=0.41, week 48=0.47, week 72 = 0.50, week 96=0.52). As a check for practice effects, gait (resistant to practice) was significantly improved over time (F(5.391)=2.94, p<.05), indicating that ART had a substantial impact on NP.

Conclusion: In this unique early infection cohort, time between primary infection and ART initiation was not associated with neurocognition. Initiation of ART improved neurocognitive functioning regardless of treatment category: this cohort of persons who started ART during or just following acute infection had improved cognitive performance as time on ART increased. These findings underscore the importance of initiating ART early to protect the CNS.



446 NEUROSYMPTOMATIC HIV CSF ESCAPE CAN BE PRODUCED BY REPLICATION IN T CELLS IN THE CNS

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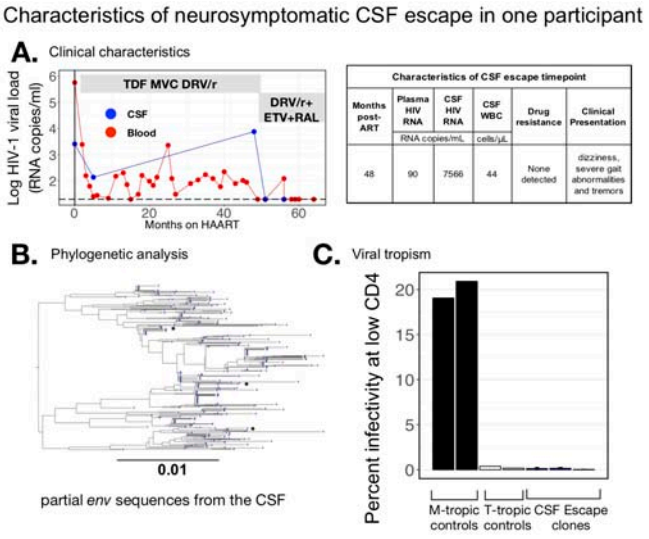
Background: Some HIV-infected individuals presenting with neurologic symptoms have increased levels of cerebrospinal fluid (CSF) HIV-1 RNA despite being on antiretroviral therapy (ART) and having undetectable, or low, plasma viral load (VL)-i.e. neurosymptomatic (NS) CSF escape. Genetic diversity and phenotypic characteristics of NS CSF escape viruses have not been previously examined, and the cells producing these populations are unknown.

Methods: We examined archived blood plasma and CSF samples from 11 individuals with NS CSF escape. All individuals were ART-treated and had a CSF VL >40 copies/ml and greater than the VL in plasma. Single genome amplification (SGA) and/or Illumina MiSeq deep sequencing with Primer ID were used to assess diversity in env and drug resistance in pro-pol. Full-length env genes were cloned from the CSF of three individuals and assessed for macrophage tropism based on their ability to efficiently enter cells with a low density of CD4 on their surface.

Results: For these 11 participants, median values were: CSF VL = 1,493 copies/ml, plasma VL = 163 copies/ml, blood CD4 count = 552 cells/µl and CSF WBC = 44 cells/ µl. 73% (8/11) of participants had a genetically diverse CSF escape HIV-1 population. 67% of individuals examined for drug resistance (4/6) had mutations in their CSF virus conferring at least partial resistance to their current ART regimen. 5 of 6 participants experienced an improvement in neurologic symptoms upon ART optimization. Four individuals were examined longitudinally and three had persistent CSF escape. The three participants examined for viral tropism had CSF HIV-1 variants that were adapted to entering CD4+ T cells rather than macrophages (i.e. R5 T cell-tropic).

Conclusion: Most individuals with symptomatic CSF escape have characteristics that are consistent with ongoing viral replication such as genetically diverse CSF viral populations, CSF drug resistance and resolution of neurologic symptoms after ART optimization. The results here suggest that NS CSF escape virus can be adapted to entering T cells and is likely produced by CD4+ T cells in the CNS (Example shown in Fig. 1). It remains unknown whether these infected cells represent long-lived viral reservoirs in the CNS or transient populations producing virus during treatment failure due to drug resistance or nonadherence.



447 RELAPSE OF SYMPTOMATIC CSF HIV ESCAPE UPON PREVIOUSLY OPTIMIZED cART REGIMEN CHANGES

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Background: Neuro-symptomatic cerebrospinal fluid (CSF) viral escape is a condition of persons receiving combination antiretroviral treatment (cART), who show a discordant HIV replication between CSF and plasma, associated with

neurological symptoms and magnetic resonance imaging (MRI) white matter changes, and it is usually reverted upon cART optimization. Our aim was to identify and characterize possible cases of relapse in the long-term follow-up.
Methods: A cohort of 21 cases of symptomatic CSF escape was followed between 2003 and 2017. Cases were defined as onset of new neurological symptoms and/or signs in cART-treated patients with HIV-RNA detectable in CSF, but not in plasma, or CSF HIV-RNA higher than plasma level. Relapse was defined as the re-occurrence of symptomatic CSF escape following clinical and, when follow-up CSF sample of first episode was available, virological regression of first episode.
Results: In the 21 CSF escape cases, median CSF HIV-RNA was 1056 c/mL (IQR 63-75,000); plasma HIV-RNA was detectable in 10 of 21 patients, median 1055 c/mL (IQR 92-8194); cognitive impairment was observed in 12 patients and cerebellar symptoms in 11. MRI demonstrated diffuse bilateral white matter hyperintensities on T2-weighted sequences in 15 of 20 patients. During a median follow-up of 66 months (range 12-121) after cART optimization, CSF escape relapsed in 5 of 21 cases (24%) as a consequence of cART simplification, which included zidovudine (AZT) withdrawal, in 3, or poor adherence in 2 (Table). CSF resistance mutations were identified in 2 cases. There were no significant differences between first escape and relapse as for current CD4+ cells (median 300 vs. 722/µL), CSF HIV-RNA (median 1000 vs. 853 c/mL), HIV-RNA detectability in plasma (40% vs. 60%), clinical and MRI findings. cART re-optimization according to resistance profile and/or predicted neuropenetration, including AZT in 3 patients, lead to clinical resolution in all patients and HIV-RNA clearance in all of the tested cases. At last follow-up, 3 patients had underwent cART simplification, either maintaining AZT (n=1), or switching to a new dolutegravir-containing regimen without AZT (n=2), with no new escape episodes.
Conclusion: CSF escape may relapse months to years after recovery, if cART efficacy in the CNS is weakened by simplification or loss of adherence. These observations also support, at least in some patients, the presence of a viral reservoir within the CNS.

	CSF escape, 1st episode			CSF escape, 1st episode, follow-up				CSF escape relapse				CSF escape relapse, follow-up				Last follow-up [a]	
Patient ID	Ongoing ART (duration, months)	Plasma VL (c/mL)	CSF VL (c/mL)	Optimized ART (duration, weeks)	Plasma VL (c/mL)	CSF VL (c/mL)	Clinical outcome	Optimized ART (duration, months)	New ongoing ART (duration, months)	Plasma VL (c/mL)	CSF VL (c/mL)	Re-optimized ART (duration, weeks)	Plasma VL (c/mL)	CSF VL (c/mL)	Clinical outcome	Follow-up from relapse (months)	Current ART (duration, months)
2588	ABV, 3TC FPVr (42)	<40	53	AZT, ABV, 3TC, FPVr (12)	<1	n.a.	Recovery	11	ABV, 3TC FPVr (6)	<40	576	AZT, ABV, 3TC, FPVr (20)	<1	<1	Recovery	76	FTC, TDF, DTG (7)
8289	TDF, FTC, ATV (7)	98	5200	AZT, 3TC, DRVr bid (6)	<1	<1	Recovery	41	ABV, 3TC DRVr OD (3)	<40	1596	AZT, 3TC, DRVr bid, RAL (12)	<40	n.a.	Recovery	47	AZT, 3TC, DRVr bid (39)
4017	TDF, FTC FPVr (28)	4067	75000	ABC, 3TC, LPVr (12)	<1	n.a.	Recovery	43	TDF, FTC, NVP (20)	205	3439 [b]	AZT, 3TC, DRVr bid (12)	<1	n.a.	Recovery	46	3TC, ABV, DTG (2)
9544	TDF, FTC, DRVr OD (143)	43	837 [b]	AZT, 3TC, DRVr bid, MVC (10)	<1	<1	Recovery	22 (MVC changed to RAL after 8 weeks)	ABV, 3TC, DRVr bid (2)	86	853 [b]	AZT, 3TC, DRVr bid (8)	<1	191	Improved	43	Unchanged (41)
												AZT, 3TC, DRVr bid (21), plus DTG (2)	<40	<1	Recovery		
1318	TDF, FTC, DRVr bid (9)	<40	1000	AZT, 3TC, TDF, DRVr bid, RAL (12)	<1	n.a.	Recovery	38	AZT, 3TC, TDF, DRVr bid, RAL (unchange d)	<40	83	AZT, 3TC, DRVr bid, MVC, DTG (14)	<1	<1	Recovery	46	Unchanged (40)

Notes
VL, Viral Load; ABV: abacavir, 3TC: lamivudine, FTC, tenofovir, ATV: atazanavir, FPV: fosamprenavir, r: ritonavir, DRV: darunavir, LPV: lopinavir, MVC: maraviroc, RAL: raltegravir, DTG: dolutegravir; bid, bis in die; OD, once daily.
a. Last follow-up: August, 30, 2018
b. Patient 4017, CSF resistance mutations at CSF escape relapse: M184I; NNRTI: V106A/V, E138A, G190A (nucleoside reverse transcriptase inhibitors, NRTIs); patient 9544, CSF resistance mutations at 1st CSF escape: M41L, D67N, M184I, L210W, T215Y, K219E (NRTIs). Y181C (non nucleoside RTIs, NNRTIs); patient 9544, CSF resistance mutations at relapse: M41L, D67N, K70R, M184V, L210W, T215Y, K219E (NRTIs); L100I,I, Y181C (NNRTIs); PI: M46I, L76V (protease inhibitors).

448 CNS ESCAPE OF DRUG-RESISTANT HIV IN PML-IRIS AND CONSEQUENT PERIPHERAL DISSEMINATION

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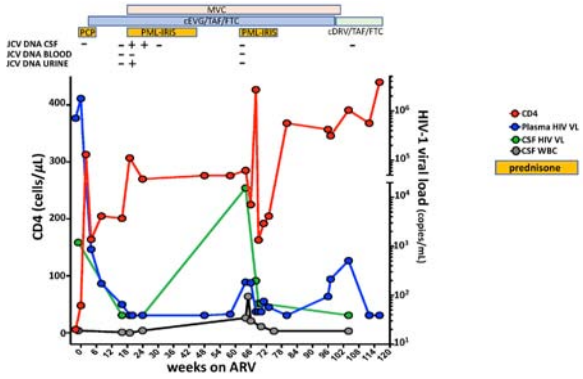
Background: Inflammation and tissue influx of activated T cells affects the compartmentalization and dynamics of HIV viral replication, but the role of compartmentalized virus populations in the emergence of drug resistant mutations (DRMs) and virological failure is uncertain. Herein, we describe viral escape with high viral RNA levels and DRMs in CSF during an episode of unmasking PML-IRIS
Methods: PBMCs and CSF mononuclear cells were used for immunophenotyping along with a flow cytometric T cells responses assay to JC virus (JCV), BKV and CMV. Plasma and CSF ARV concentrations were measured by tandem mass spectrometry. Phylogenetic analysis of CSF, plasma, rectal mucosa and cervical lymph node HIV variants was performed
Results: A man with HIV/AIDS [CD4: 6 cells/µL, HIV plasma viral load (VL): 716531 c/mL, CSF VL: 1200 c/mL, no DRMs] presenting with PCP, achieved prompt clinical improvement after TMP-SMX, Prednisone and cEVG/TAF/FTC initiation. 12 weeks after starting ARV, with suppressed HIV VL <40c/mL (bLOD) in plasma and CSF, he developed new ataxia and dysmetria with multiple parenchymal enhancing lesions on MRI. JCV DNA was detectable in CSF, HIV VL remained bLOD and unmasking PML-IRIS was diagnosed, which resolved with addition of Prednisone, Maraviroc and Mirtazapine. After Prednisone was tapered, PML-IRIS flared with new hand tremor: CSF analysis revealed pleocytosis with CSF HIV VL of 15441 c/mL and plasma VL to 185 c/mL. HIV genotype in CSF revealed a new E92Q DRM in Integrase (INT) and M184V/I in RT. Prednisone was restarted with clinical improvement and suppression of both plasma and CSF HIV VL bLOD. Follow-up monitoring of plasma VL showed a progressive increase up to 509 c/mL with the new appearance of E92Q INT and M184I/V RT in plasma. Retrospective drug level analysis documented subtherapeutic EVG concentration in CSF (5.5 ng/ml), which was >300 fold lower than concurrent plasma EVG (1730 ng/mL). Robust specific CD4 T cells responses to JCV, but not to BKV or CMV were documented in CNS and peripheral blood at the time of PML-IRIS flare
Conclusion: Rebound viremia with DRMs emerged in the setting of CNS immune activation from PML-IRIS and suboptimal CSF EVG levels. HIV-1 RNA was >100 fold higher in CSF than plasma, suggesting selection of resistant variants in CNS and consequent dissemination to peripheral blood and lymphnode. The case highlights the role of localized inflammatory processes and trafficking of immune cells in shaping HIV populations in CNS, plasma and lymphoid tissue



449 DEEP SEQUENCING REVEALS EXTENSIVE CSF COMPARTMENTALIZATION IN HIV+ PEOPLE IN UGANDA

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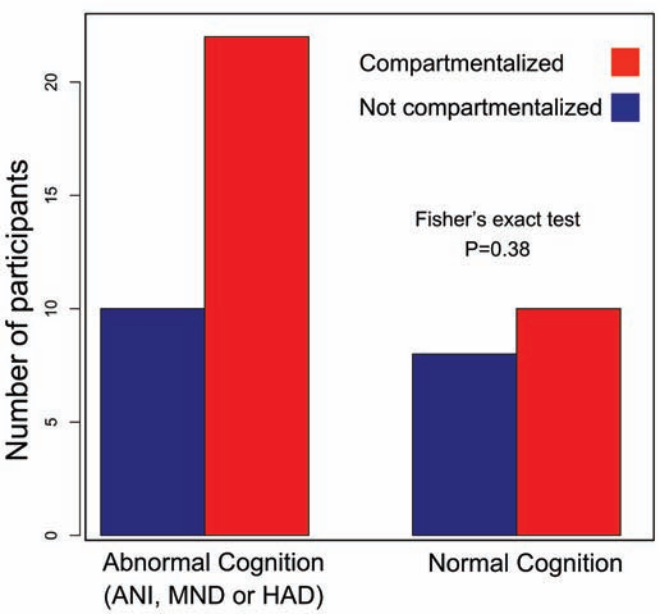
Background: Sustained viral replication and evolution in a tissue can produce compartmentalized viral lineages that are genetically distinct from populations in the blood. Compartmentalized viral populations have previously been observed in the cerebrospinal fluid (CSF) of individuals infected with subtype B HIV-1, particularly those with HIV-associated dementia (HAD). Less is known about rates of CSF compartmentalization in individuals infected with other viral subtypes and/or lacking severe neurocognitive disorders. HIV-1 replication in the CNS is thought to contribute to neurocognitive impairment in HIV-infected people, but this hypothesis has not been previously examined.
Methods: 50 antiretroviral-naïve HIV+ individuals were enrolled in Rakai, Uganda and assessed with a neuromedical examination, neuropsychological test battery, and functional status assessments to define HAND staging based on Frascati criteria. Viral RNA was isolated from plasma and CSF samples, and Illumina MiSeq deep sequencing with Primer ID was used to sequence env V1-V3. A neighbor joining phylogenetic tree was constructed for each person to compare HIV-1 populations in the CSF and blood. Phylogenetic trees were visually examined and CSF compartmentalization identified when approximately half or more of the CSF sequences formed lineages that were genetically distinct from blood sequences.

Results: Individuals in this cohort had moderate CD4+ T cell counts (median=356 cells/µl) and CSF viral loads (median=38,905 RNA cp/ml). HIV-1 subtype frequency was A (33%), D (19%), A-D recombinants (33%), A-C recombinants (5%), and other recombinants (10%). HAND stage frequency was: 36% normal cognition, 8% with asymptomatic neuropsychological impairment, 34% with mild neurocognitive disorder, and 22% with HAD. 64% of individuals had CSF compartmentalization. There was a trend for compartmentalization to be associated with impaired cognition (p=0.37, figure 1) and compartmentalization was a significant predictor of impaired verbal fluency (p=0.006).
Conclusion: A cohort of HIV+ individuals with subtypes A, D, and recombinants was observed to have a very high rate of CSF compartmentalization. This rate exceeds our previous estimate for a similar cohort of individuals infected with subtype B HIV-1, suggesting that subtypes A and/or D may colonize and establish replicating populations in the CNS more readily than subtype B variants. High rates of compartmentalization may impact long-term neurocognitive performance in this cohort.



450 MINIMAL INCIDENCE OF CSF ESCAPE AFTER INITIATION OF ART IN ACUTE HIV INFECTION

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Background: Despite suppression of HIV viral replication in the periphery by antiretroviral therapy (ART), up to 10% of treated individuals have quantifiable HIV in the CSF, termed CSF escape. CSF escape may be asymptomatic but has also been linked to progressive neurological disease. CSF escape has not yet been assessed after initiation of ART during acute HIV infection (AHI).
Methods: Thai AHI participants underwent blood sampling and optional cerebrospinal fluid (CSF) sampling at baseline followed by immediate ART, and then longitudinally at weeks 24 and 96. HIV RNA was quantified using Roche Amplicor and COBAS TaqMan assays with a lower limit of quantitation of 20-50 copies/mL in plasma and 80 copies/mL in CSF. Participants with quantifiable CSF HIV RNA and plasma HIV RNA less than 50 copies/mL or CSF HIV RNA greater than 1-log higher than plasma HIV RNA during ART were identified as cases of CSF escape.
Results: 187 participants had paired blood and CSF sampling in at least one visit at baseline, week 24, or week 96. The participants were 97% male (182/187) with median age 26 years and baseline Fiebig stage 3 (83/186, 45%), CD4 count 388 cells/mm3, and plasma HIV RNA 5.84 log10 copies/mL. ART was started at a median of 19 days post estimated infection. At baseline, 126/149 participants (85%) had quantifiable CSF HIV RNA (median 3.15 log10 copies/mL). At week 24 (n=89), four participants (4%) had quantifiable CSF HIV RNA, with one case of CSF escape identified with plasma HIV RNA < 50 copies/ml and CSF HIV RNA 2.50 log10 copies/mL. At week 96 (n=46), one participant (2%) had quantifiable CSF HIV RNA, which did not meet criteria for CSF escape. All other cases of quantifiable CSF HIV RNA were due to ART failure. The participant with CSF escape was treated with efavirenz/tenofovir/lamivudine and had a CD4 count of 840 cells/mm3 and CSF WBC and CSF protein of 4 cells/mm3 and 30 mg/dL. His MRI at week 24 showed a small nonspecific T2/FLAIR hyperintense focus in the right high frontal white matter. He did not have a lumbar puncture performed at baseline nor at subsequent visits.
Conclusion: While levels of CSF HIV RNA in untreated AHI are high, initiating treatment during AHI results in a very low rate of CSF escape in the first two years of ART. The low rate of CSF escape may also be impacted by high levels of adherence to ART in this cohort or the short duration of ART. Longitudinal monitoring will be required to verify if CSF escape remains rare under long-term ART in early treated individuals.

	All participants (n=187)	Baseline (n=149)	Week 24 (n=89)	Week 96 (n=46)
Age at enrollment (range)	26 (18-60)	27 (18-60)	27 (18-60)	28 (18-48)
Male, n (%)	182 (97)	144 (97)	85 (96)	44 (96)
Fiebig I&II at enrollment, n (%)	75 (40)	60 (40)	32 (36)	17 (37)
CD4+ T-cells, cells/mm3 (range)	388 (91-1302)	389 (101-1302)	611 (291-1464)	642 (378-1357)
CD8+ T-cells, cells/mm3 (range)	515 (81-4556)	515 (102-4556)	561 (178-1352)	597 (260-1575)
Plasma HIV RNA, log10 copies/mL, (range)	5.84 (2.43-7.75)	5.81 (2.43-7.75)	<1.30 (<1.30-5.44)	<1.30 (<1.30-4.42)
Undetectable blood HIV RNA, n (%)	0 (0)	0 (0)	85 (96)	44 (96)
CSF HIV RNA, log10 copies/mL, (range)	-	3.15 (<1.90-6.61)	<1.90 (<1.90-3.84)	<1.90 (<1.90-3.14)
Undetectable CSF HIV RNA (%)	-	23 (15)	85 (96)	45 (98)
CSF viral escape, n (%)	-	-	1 (1)	0 (0)

451 TREATMENT REGIMENS FOR MANAGING SYMPTOMATIC CSF HIV ESCAPE IN PUNE, INDIA

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Background: Symptomatic CSF HIV escape(sCVE) in limited resource countries(LRCs) has been reported in patients on 2nd line protease inhibitor(PI) based ART. Management includes performing CSF and plasma genotypic resistance testing(GRT) and changing ART accordingly; however GRT is not routinely available in LRCs. Hence ART optimization is done by including drugs with excellent CNS penetration like Zidovudine(AZT intensification) or shifting to a new PI and Integrase inhibitor(PI/INSTI intensification).
Methods: In this retrospective cohort study conducted between 1st March 2009 and 1st March 2018, we included patients developing sCVE on 2nd line PI-based ART. sCVE was defined as either a)detectable CSF viral load(VL >20 copies/ml) with undetectable plasma VL or b)CSF VL ≥0.5 log10 higher than plasma VL. Individuals in whom GRT could not be performed or drug resistance mutations(DRM) could not be identified were prescribed AZT intensification to current ART(Group 1).Those patients demonstrating DRM on GRT or already taking AZT as part of PI based ART or having history of AZT toxicity were shifted to a new PI,INSTI +/- Maraviroc(Group 2). Plasma and CSF VL was repeated after 6 months of ART modification.
Results: 41 patients with sCVE were identified: 20 in Group 1 and 21 in Group 2. Baseline characteristics in both groups are shown in Table 1. After AZT intensification there was complete resolution of symptoms in 17(85%) patients.

Follow up plasma and CSF VL were available for 18 patients: 16(88.9%) had undetectable plasma VL. Of these,13(81.2%) had undetectable CSF VL while 3 had CSF VL between 20-100 copies/ml. In 2 subjects,AZT intensification failed with non-suppression of both plasma and CSF VL and triple class DRM were observed in CSF. After PI/INSTI intensification,complete resolution of symptoms occurred in 18(85.7%) patients. Follow up plasma and CSF VL were available for 20 patients: all had undetectable plasma VL. 16 patients(80%) had undetectable CSF VL while 4 had CSF VL between 20-100 copies/ml. PI/INSTI intensification successfully suppressed plasma and CSF VL in all subjects.

Conclusion: Despite potential selection bias(lack of GRT in Group 1) this is a unique cohort of patients with sCVE with homogeneous treatment interventions. AZT intensification was effective in improving symptoms and reducing plasma and CSF VL in majority of subjects. Additional studies including GRT,pharmacokinetics and adherence measurements are needed to select the most appropriate treatment for sCVE in LRCs.

Table 1: Pretreatment characteristics of patients with sCVE

Characteristics	Group 1 (n=20)	Group 2 (n=21)	p value
Age(yrs), Median, IQR	42 (40 - 47.25)	38 (34 - 44)	0.0232
Nadir CD4(cells/mm3), Median, IQR	61 (38 - 99)	78 (28.0 - 113)	0.326
Duration of ART(months), Median, IQR	82 (68 -99)	104 (72 - 120)	0.359
Most common ART regimen at sCVE	TDF/3TC/ATV/r (n=18) TDF/3TC/LPV/r (n=2)	TDF/3TC/ATV/r (n=10) AZT/3TC/TDF/ATV/r (n=3) LPV/r/raltegravir (n=3)	NA
Plasma VL(copies/ml), Median, IQR	305 (77 - 598)	240 (47 - 500)	0.464
CSF VL(copies/ml), Median, IQR	3500 (1850 - 17750)	4600 (3100 -13000)	0.462
CSF GRT done	0/20	13/21	NA
Triple class resistance	0/20	9/13	NA
CD4 at event(cells/mm3), Median, IQR	315 (202 - 423)	396 (313 - 465)	0.227

ART= antiretroviral therapy; TDF=Tenofovir Disoproxil Fumarate; AZT=Zidovudine; 3TC=Lamivudine; ATV/r=Ritonavir boosted Atazanavir; LPV/r=Ritonavir boosted Lopinavir; CSF=cerebrospinal fluid; VL=viral load; GRT=genotypic resistance testing.

452 PRESENCE OF INTACT HIV DNA VARIANTS IN THE BRAIN AND LYMPHOID TISSUES DURING ART

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Background: Although antiretroviral therapy (ART) reduces HIV RNA below the detection limit in blood plasma, HIV reservoirs persist in cellular compartments. Here, we characterize the size and composition of the HIV DNA reservoirs in brain and lymphoid tissues.

Methods: We evaluated post-mortem brain and peripheral lymphoid tissues from 12 persons living with HIV (PLWH) obtained from the National NeuroAIDS Tissue Consortium. All donors died between 2001-2014, with virologic suppression on ART (<50 or 400 copies/ml, assay-dependent), and without evidence of central nervous system opportunistic disease. Presence of ART in post-mortem brain was confirmed by mass spectrometry. Total DNA was extracted from each tissue sample and levels of HIV DNA (gag) were quantified by droplet-digital PCR. The genotypic composition of the HIV DNA populations was evaluated by high-throughput single genome amplification using the PacBio platform to sequence Full-length HIV envelope (FL HIV-env).

Results: We evaluated post-mortem tissues from 9 men and 3 women with a median age of 52 years (range: 40-66). Donors were on ART at the last visit, which occurred a median of 3 months prior to death (range: 1-4). Presence of Tenofovir or Lamivudine was confirmed in 6 out of 8 donors' brain tissues by mass spectrometry. All donors had detectable HIV DNA in brain (frontal [FC] or occipital [OCC] cortex) and lymphoid tissues (lymph node [LN] or spleen [SP]). A total of 180 individual FL HIV-env sequences were obtained across donors (FC, n= 7 donors; OCC, n=3; LN, n=3; SP, n=8). For 10 donors, FL HIV-env sequences were obtained from paired brain and lymphoid tissues. Maximum likelihood phylogeny (figure) suggests that HIV compartmentalization patterns differ between donors, with four donors showing evidence of HIV DNA compartmentalization ($p<0.05$). Overall, 143 FL HIV-env sequences were genetically intact, while 37 sequences were non-functional, with major deletions, frameshift and stop codon mutations (figure). For one donor, we found 23 clonal sequences with a frameshift mutation that was present in both brain and spleen, suggesting migration of cells with clonal provirus between tissue compartments.

Conclusion: HIV DNA was detected in brain and lymphoid tissues despite long-term ART. Most HIV DNA populations in brain and lymphoid tissues appeared to have intact env genes and were often compartmentalized. Characterizing the composition of the HIV reservoirs in anatomic compartments is crucial for future HIV cure strategies.

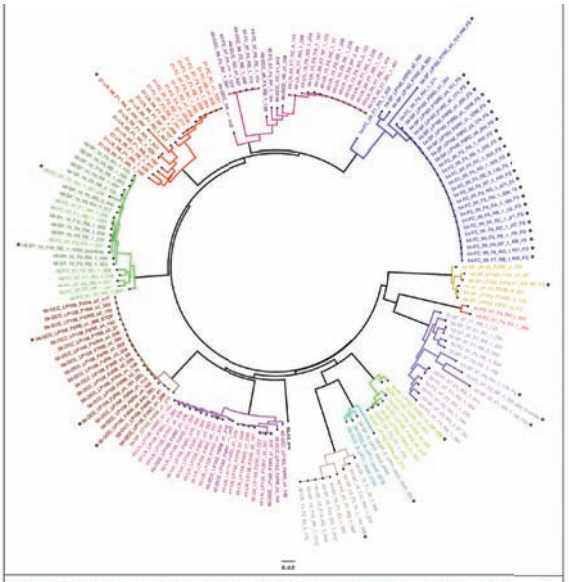

Figure: Maximum likelihood phylogeny tree showing FL HIV-*env* sequences obtained from post-mortem brain and lymphoid tissues from 12 PLWH donors. Colors represent different participants and shades of colors represent different body tissues. Asterisks indicate non-intact *env* sequences containing major deletions (del), hyper-mutation (HM), stop-codon mutations (stop) and frameshift (FS) mutations.

453 ASSOCIATION OF CEREBRAL SMALL VESSEL DISEASE WITH THE BRAIN IN HIV INDIVIDUALS

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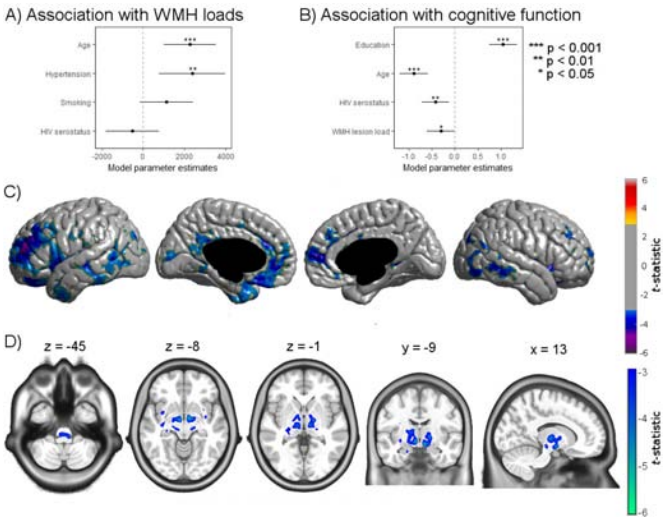
Background: Emerging evidence has suggested that people living with HIV (PLWH) have increased risk of developing cerebral small vessel disease (CSVD). This may account for some of the cognitive impairment that continues to be common even in those with good viral suppression. In this study, we investigated whether PLWH had worse CSVD compared to demographically similar controls (CTL), and provide evidence of the impact CSVD has on brain volumetrics and cognition.

Methods: Virologically suppressed PLWH on combination antiretroviral therapy (cART) and CTL participants underwent MRI and comprehensive neuropsychological testing. The total volume of white matter hyperintensities (WMH) on MRI was used as a surrogate marker for CSVD severity. Tensor-based morphometry and cortical modeling estimated regional brain volumes and cortical thickness, respectively. Rasch measurement theory was applied to the cognitive test scores, yielding an estimate of overall cognitive ability. Linear models were used to compare the WMH load, brain volumes and cognition between the two groups. These models controlled for age and sex. In addition, separate linear models assessed the association of brain volumes, cognition and factors commonly linked with vascular disease, including hypertension (defined as systolic blood pressure ≥140mmHg or diastolic ≥90mmHg), smoking, body mass index and waist circumference, with the WMH load. These models included all participants and controlled for HIV serostatus, age and sex.

Results: 119 PLWH and 55 CTL were included in the study (PLWH age [mean±SD]:56±8; education:13±3; sex:81% male; CTL age:56±12; education:14±2; sex:51% male). PLWH had smaller brain volumes and poorer cognitive performance compared to the CTL group. Total WMH load and factors commonly linked with vascular disease were similar between the two groups. Older age and hypertension were significantly associated with greater WMH loads for all participants (Fig. 1A). Higher WMH load was significantly associated with reduced brain volumes and cortical thickness and worse cognitive function in all participants, independent of HIV status (Fig. 1B-D).
Conclusion: We observed that the PLWH in this study did not have greater WMH load. However, WMH load was associated with reduced brain volumes and poorer cognition in the entire sample. These findings suggest that CSVD could explain some of the brain atrophy and cognitive impairment found in people living with HIV.



454 1H MRS IDENTIFIES SUBCLINICAL NEURONAL INJURY DESPITE CHRONIC VIRAL SUPPRESSION

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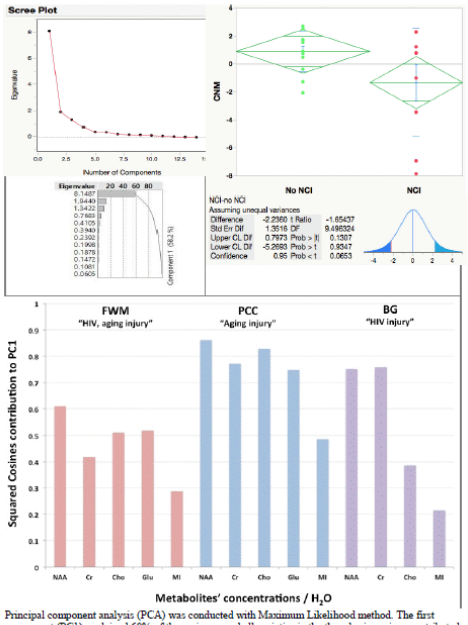
Background: The significance of proton Magnetic Resonance Spectroscopy (1H MRS) abnormalities in chronic suppressed HIV infection is unclear. Previous studies have included unsuppressed patients and did not relate findings to markers of current neuronal injury such as neurofilament light-chain (NFL), nor to non-AIDS comorbidities. We hypothesized that 1H MRS would identify active brain injury.
Methods: 22 HIV+ men (aged 48.7±12.3) with plasma and CSF viral suppression (<20cp/mL) underwent 1H MRS scanning to assess in vivo brain injury in the frontal white matter (FWM), posterior cingulate cortex (PCC), and basal ganglia (BG). Brain metabolite concentrations for N-Acetyl-Aspartate (NAA), Choline (Cho), Creatine (Cr), Glutamate (Glu) and myo-Inositol (MI) were quantified in jMRUI and referenced to H2O. As MRS data are amenable to data reduction techniques to yield a single robust component, we extracted a composite neurochemical in vivo marker – "CNM" (more negative values indicate greater brain injury; Fig. 1). Participants also completed neuropsychological testing and lumbar puncture to assess CNM's potential as a marker of active brain injury. Besides NFL, CSF biomarkers included neopterin, CCL2, and CSF tat. Neurocognitive impairment (NCI) was classified using standard criteria (37.5%, none demented). Univariate correlations with CNM were tested for CSF biomarkers, HIV disease markers, demographics, neurocognition, psychiatric and alcohol/drug use comorbidities, current psychological distress, and non-AIDS comorbidities (cardiovascular/kidney diseases, sleep disorders, malignancies, neuropathy/pain, and loss of consciousness>30min from non-traumatic causes). Predictors at p<0.10 were retained in a logistic regression model (stepwise forward selection, best model fit by Akaike information criterion (AIC)).
Results: CSF NFL (r=-.53, p<.02), non-AIDS comorbidities (r=.48, p<.03), nadir CD4 (r=.41, p=.05), age (r=-.42, p<.05), and NCI (r=-.39, p=.07) were associated with greater brain injury (lower CNM). Non-AIDS comorbidities remained a significant predictor (p<.03) yielding the best model fit (AIC=111.17).
Conclusion: Composite 1H MRS signal identifies currently active brain injury, well below the threshold for NCI, in regions known to be associated with HIV-related brain injury and pathological aging. This injury is dominantly driven by non-AIDS co-morbidities and expressed through an HIV-related pathway, implying that HIV is the driver of the co-morbidities.

Figure 1: The *in vivo* composite neurochemical marker – "CNM" extraction and validation



Principal component analysis (PCA) was conducted with Maximum Likelihood method. The first component (PC1) explained 60% of the variance, and all moieties in the three brain regions contributed significantly to PC1.

455 INFLAMMATORY PLASMA BIOMARKERS CORRELATE WITH DIFFUSION TENSOR IMAGING IN CHRONIC HIV

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Background: Despite adherence to combination antiretroviral therapy (cART) and suppression of plasma viral RNA, a large proportion of people living with HIV experience cognitive symptoms. This study investigated correlations between plasma inflammatory biomarkers and diffusion tensor imaging (DTI) measures of brain white matter injury.
Methods: Participants underwent neuropsychological testing, blood draw, and DTI scans on one of two separate 3 Tesla MRI scanners. Plasma biomarkers, sCD163, sCD14, neopterin, IP-10, and MCP-1, were quantified by Luminex/ELISA. DTI metrics fractional anisotropy (FA) and mean diffusivity (MD) were averaged across a priori defined regions known to be affected by HIV – the corpus callosum (CC), corona radiata (CR), and superior longitudinal fasciculus (SLF). These were regressed against biomarker levels and the results of global, executive domain, and attention domain neuropsychological testing, reported as z-scores relative to standard norms (NPZ), controlling for age, duration of infection, and scanner model. Voxelwise analysis by Tract-Based Spatial Statistics (TBSS) compared FA and MD to biomarker levels, controlling for age and duration of infection.
Results: 43 HIV+ participants (median age 64 [IQR 62-66] years, 91% male) enrolled, all of whom were on cART with suppressed plasma HIV RNA and self-reported cognitive symptoms. 38 met criteria for HIV-associated neurocognitive

disorder (37 with Mild Neurocognitive Disorder, 1 with dementia), and 5 were considered cognitively normal. ROI analysis revealed positive correlations between MCP-1 and MD in the CC, bilateral anterior and superior CR, and left SLF, and between neopterin and MD in the genu of CC ($p<0.05$). Negative correlations existed between MCP-1 and FA in the CC, and between sCD14 and FA in the bilateral superior CR ($p<0.05$). Voxelwise analysis detected areas of direct correlation between MCP-1 and MD ($p<0.05$). Lower FA in parts of the CC, CR, and SLF directly correlated with worse neuropsychological performance globally and in the executive domain, and increased MD in the CC and left superior CR directly correlated with lower global neuropsychological scores ($p<0.05$).
Conclusion: In virally suppressed HIV+ elders, inflammatory markers correlate with worse metrics of brain white matter injury. These metrics predict poorer cognitive performance, supporting the hypothesis that inflammation persisting despite viral suppression impacts brain integrity and may contribute to cognitive impairment in the cART era.

456 WHITE MATTER HYPERINTENSITIES INCREASE AS A FUNCTION OF CVD RISK AND HIV DISEASE

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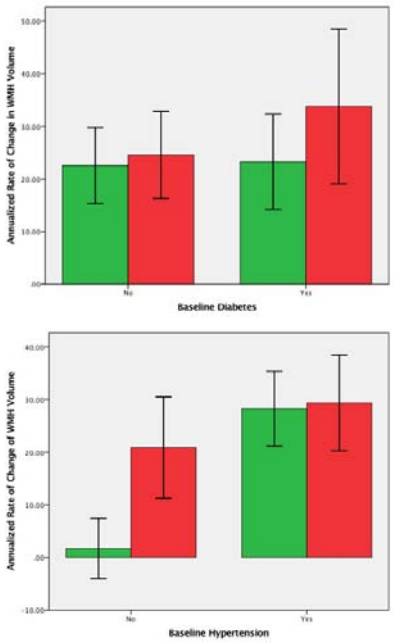
Background: White Matter Hyperintensities (WMH) are a marker of cerebral small vessel disease. We have previously shown that HIV infection and diabetes mellitus interact to increase the volume of WMHs. The purpose of the present study was to evaluate the rate of change of WMH volume over a four year follow-up.
Methods: 119 men from the MACS MRI subsidy contributed data: 43 uninfected and 76 with HIV Disease. There were no differences between the infected and uninfected men in the rates of diabetes, hypertension, Caucasian race, or syndrome depression. A greater proportion of the infected men were enrolled after 2000. 16% of the infected men had had an AIDS-defining illness. Cerebral WM and cerebellum WM masks were created using both T1w MPRAGE and T2w FLAIR images using unified multispectral segmentation/normalization procedure in SPM12. Given the observation that there were very few lesions in the cerebellum in our patients, the mean and standard deviation of the cerebellar WM was used to Z-transform the T2w FLAIR image (Z-T2w FLAIR). On the Z-T2w FLAIR images, voxels greater or equal than 2 and within the cerebral WM mask were identified white matter lesions in the brain. WMH volume was expressed as the ratio between WMH and total WM. The dependent variable was the rate of change ((T2-T1)/T1)/year
Results: First, we replicated and extended our cross-sectional data (Wu, et al., 2018) by finding that the annualized rate of change in WMH volume was elevated only among the HIV-infected men with diabetes (See Figure). The rate of change was virtually identical among the uninfected men and those with HIV Disease but not diabetes. Second, although we did not find a relationship between hypertension and WMHs in the cross-sectional analysis, this was not true as we tracked change over time. The normotensive, uninfected men had no change in their WMH volume over time. By contrast, the men with hypertension had a nearly 30% annual increase in WMH volume. The normotensive, infected men had a rate of change that was almost as high (20%) as that of the hypertensive men, and greater than that of the normotensive, uninfected me.
Conclusion: These data emphasize the importance of cerebrovascular risk in the brain health of men with HIV Disease. The presence of infection acts to increase the rate of change of WMH as a function of hypertension and diabetes - even though these conditions were treated. Abnormal levels of WMHs reduce brain reserve capacity and increase risk of expressing cognitive impairment.



Annualized rate of change of WMH volume as a function of serostatus, diabetes (top figure), and hypertension (bottom figure) at baseline visit. HIV-infected men are in red, seronegative in green.

457 RESTING-STATE CONNECTIVITY ASSOCIATES WITH DEPRESSION SYMPTOMS IN ACUTE HIV

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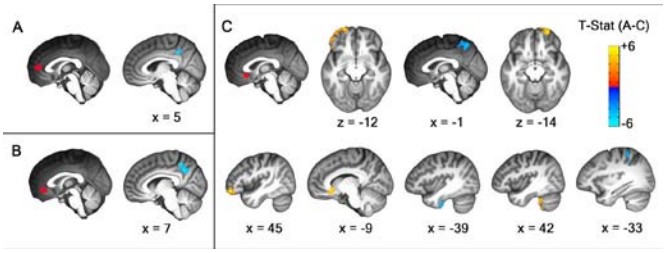
Background: The prevalence of depression symptoms in HIV can be relatively high and has been associated with increased morbidity and mortality. Previous research has revealed that HIV-related biological factors (e.g., CD4 count) are related to depressive symptoms in acute HIV (AHI). However, it is unclear whether neurobiological measures are also correlated with depression symptoms in AHI. The purpose of this study was to determine whether resting-state functional connectivity (rsFC, i.e., correlations in spontaneous low frequency fluctuations in brain activity) of anterior cingulate cortex (ACC) regions implicated in depression was associated with depression symptoms or anxiety and distress in AHI.
Methods: Thai participants with AHI (n=74) and uninfected controls (C0; n=30) underwent resting-state functional magnetic resonance imaging. Seed-based voxelwise rsFC was computed for 3 ACC seed regions of interest (ROIs) implicated in depression. T-tests were performed to compare rsFC of ACC seed ROIs for AHI versus C0 groups. Within the AHI group, we conducted voxelwise regression analyses to examine the relationship between depression symptoms, anxiety, and distress and rsFC for the ACC seed ROIs. All significant rsFC findings were family-wise error (FWE) corrected at the whole brain level, $pFWE<0.017$.
Results: The AHI group had a mean (SD) CD4 count of 395 (±209) cells/uL, 6.03 (±1.1) log10 copies HIV RNA and estimated duration of infection of 19.0 (±6.6) days. There were no differences in rsFC of ACC for AHI versus C0 groups. Within the AHI group, greater depression symptoms were associated with increased rsFC of ACC seeds with lateral and medial prefrontal regions as well as cerebellum ($pFWE<0.017$; Fig. 1). Greater depression symptoms were also related to decreased rsFC of ACC regions with precuneus/posterior cingulate cortex, ventral temporal and lateral parietal regions ($pFWE<0.017$; Fig. 1). Anxiety symptoms and distress were unrelated to rsFC of ACC. Only HIV RNA was

negatively correlated with rsFC between posterior subgenual ACC and left uncus ($p<0.05$).

Conclusion: We found that depression symptoms were associated with altered rsFC of ACC regions in AHI, consistent with previous neuroimaging literature in depression. Longitudinal research in this cohort will be necessary to determine whether these early alterations in rsFC of ACC are associated with long-term depression symptoms and HIV-related biological factors after antiretroviral therapy.



458 LOWER FRONTAL GREY-MATTER BRAIN VOLUMES AND BASAL-GANGLIA ENLARGMENT IN PERINATAL HIV

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Background: Brain volume loss has been observed in HIV patients despite initiation on combined antiretroviral treatment (cART), but studies on perinatally HIV-infected patients (PHIV) are scarce. We aim to evaluate the neurologic state and neuroimaging phenotype of stable PHIV youths.

Methods: Cross sectional study. 30 PHIV patients and 33 HIV negative peers (HIV-) matched by age, sex and socioeconomic status (SES) participated. Magnetic Resonance Imaging (MRI) and neuropsychological (NP) testing was conducted. The Computational Anatomy Toolbox (CAT12) standard processing pipeline was used for quantification of the MRI T1-W images. Native segmented images were parceled in regions of interest (ROI) and tissue volumes (mm3) were estimated for each ROI and normalized by total intracranial volume for each subject. These normalized data were used to explore differences between groups (ANCOVA tests). NP assessment tested fluid intelligence and Processing Speed (PS) by 7 NP tests (PSZ7). Psychopathological symptoms were also obtained. Differences between groups and effects of HIV-related variables on brain volumes were studied using appropriate statistical tests.

Results: 63 participants were included (58.7% females, median age 20 years [IQR 19-23], 65.1% caucasians). No differences regarding level of education, fluid intelligence, PSZ7 or psychopathological symptoms were found between groups. Regarding PHIV: 40% AIDS (13% encephalopathy), median CD4% nadir 11(IQR 5-17). At assessment, 80% had viral load <50 cp/ml (uVL) , median CD4 706 cel/mm3 (IQR 488-916), median time on cART 16.6 years (IQR 13.3-18.5) and median time with uVL 9.8 years (IQR 6.4-12.4). No differences were observed between groups for total grey matter (GM), total white matter, total intracranial volume or cerebrospinal fluid. In relation to GM regional volumes, a decrease was observed in PHIV in left(l) Inferior Frontal Gyrus, right(r) Inferior Frontal Orbital Gyrus, and Median Precentral Gyrus(r) when compared with HIV- ($p=0.019$, $p=0.029$, $p=0.031$). Regarding basal ganglia (BG), larger volumes in caudate(r/l) were associated with lower CD4 nadir (%) ($p=0.049$, $p=0.049$) and AIDS ($p=0.034$, $p=0.014$). AIDS also showed a negative relation with pallidum(r/l) ($p=0.001$, $p=0.009$).

Conclusion: Despite good control of HIV infection and no differences in PSZ7 values, PHIV show lower volumes in frontal areas. Moreover, a negative correlation between BG volumes and CD4 Nadir and AIDS suggests that HIV may cause structural compromise to these regions.

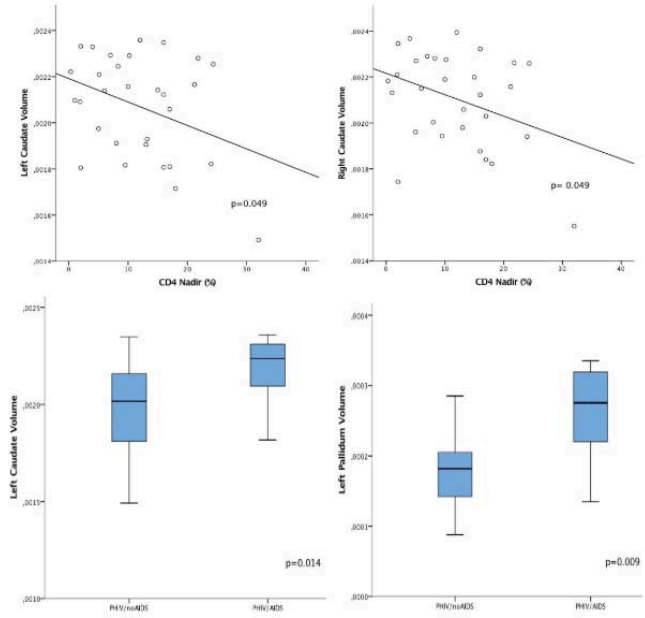

Figure. Basal ganglia volumes are correlated with HIV- related variables.

459 BENEFICIAL EFFECTS OF CANNABIS ON BLOOD-BRAIN BARRIER AND INFLAMMATION IN HIV

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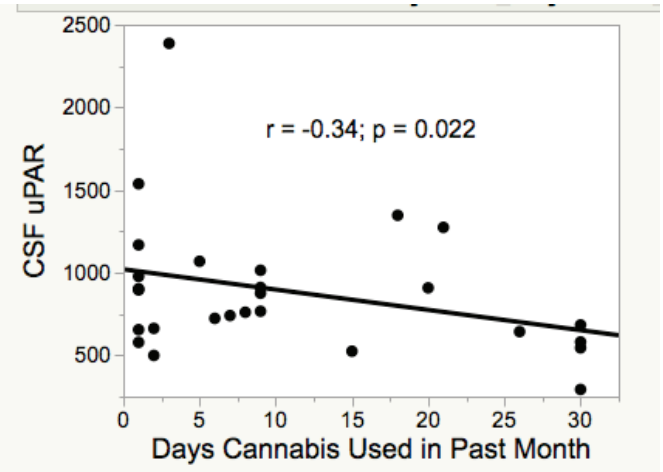
Background: HIV infection is associated with increased permeability of the blood-brain barrier (BBB), which may permit increased entry of toxins with consequent CNS injury. Cannabis, which is commonly used among people living with HIV (PLWH); has anti-inflammatory effects; and stabilizes the BBB in animal models. One potential mechanism of increased BBB permeability is upregulation of the urokinase plasminogen activator (uPA), a matrix-degrading proteolytic enzyme, and its receptor, uPAR, disrupting the basal lamina around cerebral capillaries. This study sought to determine the effects of recent cannabis use on cerebrospinal fluid (CSF) concentrations of uPAR, CSF-to-serum albumin ratio (CSAR, an indicator of BBB permeability), and neuroinflammation among PLWH.

Methods: Participants were 45 recent (i.e., within the past month) cannabis users with (HIV+) or without HIV (HIV-) who were comparable in age (mean age=39.3) and sex (93.3% male). CSF levels of soluble uPAR, soluble CD14 (sCD14) and CXCL-10 were measured by immunoassay. Albumin was measured in CSF by nephelometry and in serum by a clinical assay. Data were analyzed using standard statistical methods, including regression and t-tests.

Results: A statistically significant interaction ($p=0.025$) was present between HIV and cannabis use frequency (total days over the past month): more frequent use of cannabis was associated with lower concentrations of uPAR in CSF in the HIV+ group ($p=0.043$) but not in the HIV- group. The CSAR showed similar but non-statistically significant effects. Within the HIV+ group, higher CSF uPAR levels correlated with higher CSAR values ($rho=0.47$; $p<0.001$), and more inflammation [higher concentrations of CXCL-10 ($p=0.003$) and sCD14 ($p<0.0001$)].

Conclusion: These preliminary findings suggest that cannabis may have a beneficial impact on HIV-associated BBB injury and neuroinflammation. Given the role of the BBB in HIV-associated CNS injury, these results support the potential therapeutic role of cannabis among PLWH, and may have important treatment implications for antiretroviral therapy effectiveness and toxicity.



460 PBR-PET IMAGING OF NEUROINFLAMMATION NOT ELEVATED IN HIV+ PARTICIPANTS

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Background: Despite combined antiretroviral therapy (cART), HIV associated neurocognitive disorder (HAND) still develops in people living with HIV (PLWH). Persistent neuroinflammation caused by viral reservoirs in the brain is a potential contributor. This study used the positron emission tomography (PET) tracer [11C]-PBR28 (PBR28) to evaluate neuroinflammation in virologically suppressed (<200 copies/mL) PLWH.
Methods: 13 HIV- controls and 24 PLWH underwent neuroimaging (magnetic resonance imaging (MRI) and PET) and cognitive testing. Standard uptake value ratios (SUVRs) were calculated for 20 predefined regions of interest (ROIs) affected by HIV. The whole cerebellum was used as a pseudo-reference region. SUVRs were compared between the two groups using a Wilcoxon Rank-Sum test after correcting for genotype which can affect the tracer's affinity for TSPO. Within PLWH, additional analyses compared SUVR with clinical markers (current CD4 cell count, nadir CD4, and duration of infection) and cognition (global deficit score (GDS)).
Results: SUVRs in the 20 ROIs were not significantly different ($p > 0.05$) between PLWH and HIV- controls (Table 1). Within PLWH, GDS correlated with SUVR in the superior parietal and supramarginal white matter ($p \leq 0.05$); duration of infection correlated with SUVR in the lateral occipital cortex ($p \leq 0.05$). After correcting for multiple comparisons, these three correlations were not significant. No association was seen between other clinical measures (current and nadir CD4 cell count) and SUVR for the 20 ROIs.
Conclusion: This study reveals no significant increase of neuroinflammation as measured by PBR28 in PLWH compared to HIV- controls. Within PLWH, neither cognitive status nor clinical disease markers correlated with SUVR. Limitations exist for PBR28 and additional studies using magnetic resonance imaging (diffusion basis spectral imaging) and cerebrospinal fluid markers of neuroinflammation need to be performed in virologically suppressed PLWH.

Table 1: ROI *p*-values from comparison of control and HIV+ SUVRs adjusted for genotype

REGIONS OF INTEREST	*P*-VALUE
AMYGDALA	0.404
CAUDATE	0.913
CAUDAL ANTERIOR CINGULATE CORTEX	0.189
CAUDAL ANTERIOR CINGULATE WM	0.762
HIPPOCAMPUS	0.911
INSULA CORTEX	0.224
INSULA WM	0.169
LATERAL OCCIPITAL CORTEX	0.089
LATERAL OCCIPITAL WM	0.975
PALLIDUM	0.863
PUTAMEN	0.212
SUPERIOR FRONTAL CORTEX	0.404
SUPERIOR FRONTAL WM	0.962
SUPERIOR PARIETAL CORTEX	0.814
SUPERIOR PARIETAL WM	0.849
SUPERIOR TEMPORAL CORTEX	0.089
SUPERIOR TEMPORAL WM	0.445
SUPRAMARGINAL CORTEX	0.589
SUPRAMARGINAL WM	0.838
THALAMUS	0.148

WM: white matter

461 PI DRUG-LEVEL TESTING AS A SCREENING TOOL FOR DRUG RESISTANCE IN 2ND-LINE ART FAILURE

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Background: An increasing number of patients are on 2nd line PI-based ART in low- and middle-income countries (LMIC). In event of virological failure a switch to individualized 3rd line ART is recommended if PI resistance is present. We hypothesize that qualitative PI drug level testing could identify patients most at risk for harboring PI resistance.
Methods: We performed a single-centre pilot study followed by a large regional feasibility study in patients with virological failure of LPV/r-based 2nd line ART. In the pilot, LPV level testing on dried blood spots (DBS) was performed by liquid chromatography mass spectrometry (LCMS). In the feasibility study LCMS was performed as a reference and compared to a low-cost qualitative immunoassay (IA; ARK diagn). LPV levels were defined positive or negative based on prespecified limits of detection (LCMS-DBS: 0.25, LCMS-plasma: 0.01, IA-plasma: 0.04 mg/L). Population sequencing of pol was performed. PI-resistance was defined as presence of at least one major IAS-USA listed PI mutation.
Results: 548 patients with confirmed LPV/r based ART failure were included (50 pilot, 498 feasibility). Overall, median age was 41.1 years [IQR: 33.5–48.6], 58.8% was female. Median HIV-RNA was 4.9 [4.3–5.4] c/ml. PI-resistance was detected in 12% of patients in the pilot and 27.2% in the feasibility study. Most common mutation profiles were M46I+I54V+L76V+V82A (26.1%) and M46I+I54V+V82A (25.4%). In the pilot, only 40% of patients had a positive LPV level. Sensitivity and negative predictive value (NPV) of a positive LPV level for presence of PI-resistance was 100%, with a specificity of 68%. In the feasibility study, 52.9% of patients had positive LCMS-LPV level and 54.4% had a positive IA-LPV level. Positive LCMS-LPV level had a sensitivity of 89% [95%CI: 83–94], NPV of 94% [90–97], and specificity of 61% [55–66] for PI-resistance. A positive IA-LPV level had a sensitivity of 89% [95%CI: 82–93], NPV of 93% [89–96], and specificity of 58% [53–63] for presence of PI-resistance.
Conclusion: In this largest-to-date analysis of PI-based 2nd line failure, non-adherence was objectively demonstrated in half of cases. PI resistance was infrequent, but extensive when present. Negative LPV levels established either

by LCMS or a low-cost qualitative assay excluded the presence of PI mutations in pol with a high degree of certainty. Drug level testing at PI failure is a highly accurate screening strategy to identify patients who would benefit from costly drug resistance testing.

462 PLASMA EFV AND TFV VS DRIED BLOOD SPOT TFV-DP TO PREDICT VIRAL SUPPRESSION IN WOMEN

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Background: Tenofovir-diphosphate (TFV-DP) in dried blood spots (DBS) strongly predicts viral suppression (VS) in people on antiretroviral (ARV) treatment but the assay is expensive and time-consuming. There are no data on the relative performance of DBS TFV-DP and plasma ARV concentrations to predict VS.
Methods: A cross-sectional analysis was done among HIV-positive, non-pregnant, black South African women who started tenofovir disoproxil fumarate, emtricitabine, and efavirenz (EFV) in a prior pregnancy and had not switched regimens. Blood was drawn to analyse EFV and tenofovir (TFV) concentrations in plasma and TFV-DP in DBS. A three-item scale measured 30-day self-reported adherence. Logistic regression (reported as adjusted odds ratios [aOR] with 95% confidence intervals [CI]) and area under the curve (AUC) from receiver operating characteristic (ROC) analyses were used to estimate the relationship between ARV concentration and VS (<50 copies/mL).
Results: We enrolled 137 women (mean 33 years old; median 4 years on ART). The proportions of plasma EFV, TFV and DBS TFV-DP concentration below the limit of quantification differed by VS (p<0.001): 76%, 78% and 74% in 49 unsuppressed women, versus 2%, 11% and 2% in 88 suppressed women. In women with VS, median plasma EFV, TFV and DBS TFV-DP concentrations were 1.9µg/mL (IQR 1.4-2.7), 44.3ng/mL (IQR 26.6-61.5) and 961.5 fmol/punch (IQR 695.5-1364.5), respectively. All ARVs were predictive of VS in ROC analyses: DBS TFV-DP (0.926 [0.876-0.976]) had a higher AUC than plasma TFV (0.864 [0.797-0.932]; p=0.006) while plasma EFV (0.903 [0.839-0.967]) was not significantly different from DBS TFV-DP (p=0.138) or plasma TFV (p=0.140). All ARV assays performed better than self-report (Figure). Using existing thresholds for TFV-DP in DBS from healthy volunteers, the association with VS strengthened with increasing concentration (reference <350 fmol/punch: 350-699 fmol/punch aOR 37 [8-178]; 700-1249 fmol/punch aOR 47 [13-175]; ≥1250 fmol/punch aOR 175 [20-1539]); this dose-response relationship was not evident for plasma EFV or TFV. "White coat adherence" (defined as DBS TFV-DP <350 fmol/punch with any detectable plasma TFV) was only detected in 4 women.
Conclusion: Plasma EFV, TFV and DBS TFV-DP were all strong predictors of VS in this cohort. While TFV-DP concentrations provide additional insight into adherence behaviour, plasma EFV and TFV concentrations performed almost as well and may warrant consideration as adherence tests in low-resource settings.

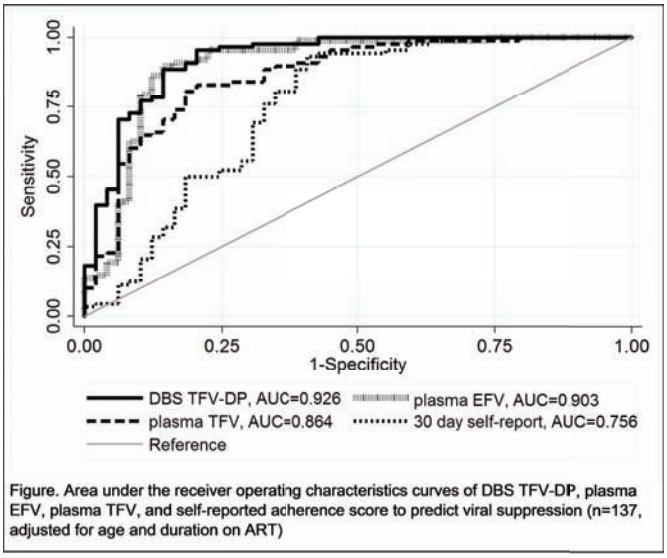

Figure. Area under the receiver operating characteristics curves of DBS TFV-DP, plasma EFV, plasma TFV, and self-reported acherence score to predict viral suppression (n=137, adjusted for age and duration on ART)

463 TENOFOVIR DIPHOSPHATE IN DRIED BLOOD SPOTS FOLLOWING ESCALATING TAF/FTC DOSING

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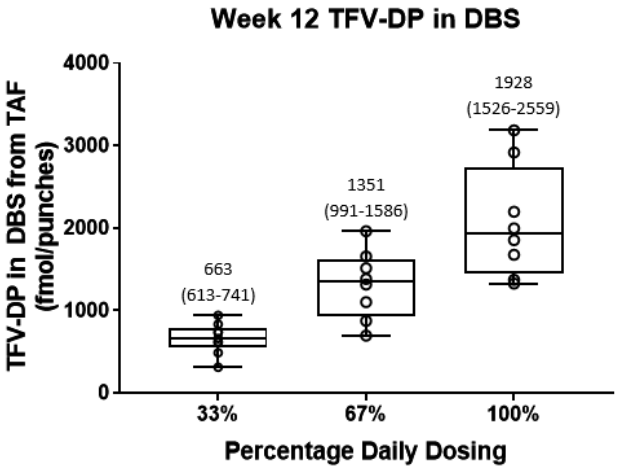
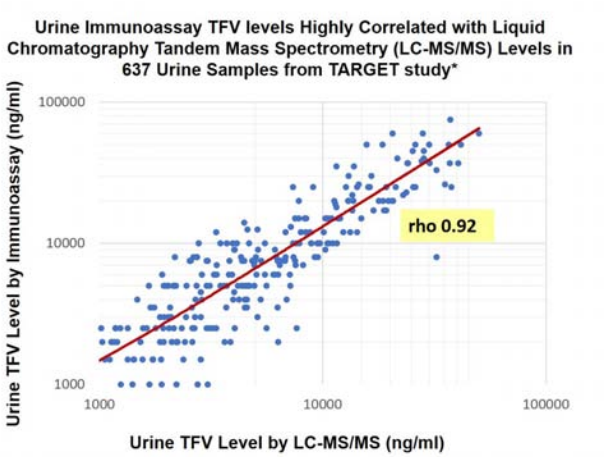
Background: The DISCOVER study will compare daily tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) versus tenofovir alafenamide (TAF)/FTC (25mg/200mg) as HIV pre-exposure prophylaxis (PrEP). DISCOVER uses tenofovir-diphosphate (TFV-DP) in red blood cells measured with dried blood spots (DBS) as an objective adherence measure as it exhibits a 17 day half-life and has a large dynamic range of accumulation that is proportional to adherence. Adherence benchmarks were previously established following TDF/FTC dosing, but not TAF/FTC dosing. This independent study assessed expected benchmarks for TFV-DP in DBS with TAF/FTC dosing.
Methods: HIV-uninfected adults at low risk for HIV infection were randomized to one of 6 sequences consisting of two directly observed TAF/FTC dosing regimens (33%, 67% or 100% of daily dosing). Each regimen was given for 12 weeks, separated by a 12-week washout. Doses were observed in person or by video streaming. Blood was collected pre-dose and 4 hours post-dose on day 1, then weekly throughout the study including washout. DBS (5x25 µL) were collected on protein saver cards. TFV-DP was quantified from various punch sizes to target adherence benchmarks close to those previously observed for TDF/FTC dosing. Available samples from weeks 10, 11, & 12 (first TAF/FTC regimen) were analyzed.
Results: Twenty-six participants began study treatment; one was excluded from the analysis for protocol violations. Nine of 25 were randomized to receive 33% of daily dosing, 8 to 67%, and 8 to 100%. Eleven of 25 were male, 16 white, 5 African-American, and 4 Hispanic. Mean (SD) BMI was 25.4 (5.1) kg/m2. TFV-DP values varied by < 10% across weeks 10-12, suggesting steady-state by week 10. When using a 3mm punch, TFV-DP was ~1/8th the median values previously established for TDF/FTC (based on a 3mm punch). These previously established medians were 518, 946, and 1542 fmol/punch for 33%, 67%, and 100% of daily TDF/FTC dosing; coefficients of variation (CVs) were 25-30%. Using 2x7mm punches resulted in TFV-DP median (IQR) values at week 12 of 663 (613-741), 1351 (991-1586), and 1928 (1526-2559) fmol/punches for 33%, 67%, and 100% daily dosing (Figure). Week 12 CVs ranged from 28-33%.
Conclusion: Following TAF/FTC dosing, two 7mm punches resulted in TFV-DP benchmarks and CVs comparable to those previously established for TDF/FTC. TFV-DP concentrations appeared to increase in direct proportion to dose, supporting the use of TFV-DP in DBS as an objective adherence measure for TAF/FTC regimens.





*Cressey TR et al. A randomized clinical pharmacokinetic trial of tenofovir in blood, plasma and urine in adults with perfect, moderate and low PrEP adherence: the TARGET study. *BMC Infect Dis.* 2017

464 VALIDATION OF A URINE TFV IMMUNOASSAY FOR REAL-TIME PrEP AND ART ADHERENCE TESTING

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Background: Pharmacologic measures are widely used to assess adherence to tenofovir (TFV) disoproxil fumarate (TDF)/emtricitabine (FTC)-based PrEP and ART. Currently-available measures in plasma, dried blood spots, hair and urine involve liquid chromatography/tandem mass spectrometry (LC-MS/MS), which is expensive and labor intensive. Only a point-of-care (POC) test can monitor and support adherence in real-time and TFV-specific antibody-based assays allow for POC adherence monitoring. We developed an immunoassay to quantify TFV in urine and validated it against the gold standard of LC-MS/MS in a large directly-observed therapy (DOT) pharmacokinetics study.

Methods: The randomized TARGET study administered TDF 300mg/FTC 200mg directly-observed 7 (high adherence), 4 (moderate adherence) and 2 doses per week (low adherence) to 30 volunteers (10 per group) in Thailand, collecting urine samples over 6 weeks of administration and during wash-out. In total, 637 urine samples were collected (average 21 samples per participant). We measured urine TFV levels by the immunoassay using ELISA (lower limit of quantification LLOQ <1000 ng/ml) and by a validated LC-MS/MS-based method (LLOQ 500 ng/ml) and calculated the sensitivity and specificity of the novel assay compared to the gold standard. We calculated Spearman's correlation between TFV levels via both assays.

Results: Among all participants, median TFV urine levels were 12,000 ng/mL (IQR 7500-25,000) by the immunoassay 1 day after dosing; 5000 ng/mL (IQR 2500-8000) 2 days after dosing; 1500 ng/mL (IQR 500-2750) 3 days after dosing and below the immunoassay's LLOQ thereafter (≥4 days). The specificity and sensitivity of the TFV immunoassay compared to the gold-standard of LC-MS/MS were 98.8% and 87.3% respectively. The correlation between TFV levels measured by the immunoassay and LC-MS/MS in all 637 urine samples from TARGET was 0.92 ($p<0.00001$) (Figure).

Conclusion: We have developed a novel TFV immunoassay that is highly specific (99%) and sensitive (87%), and correlates strongly with urine TFV concentrations measured by the gold standard of LC-MS/MS (rho=0.92) across a wide range of typical concentrations. TFV concentration cutoffs in urine for different degrees of adherence from this DOT study can now guide the development of an immunoassay into a POC rapid strip test. Real-time monitoring of TFV adherence using an easy-to-perform low-cost assay should allow for immediate intervention and optimization of outcomes for both HIV treatment and prevention.

465 URINE FTC AND TFV CONCENTRATIONS AS POTENTIAL BIOMARKERS FOR ARV ADHERENCE

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Background: Antiretroviral drug (ARV) efficacy in both treatment of chronic HIV infection and prevention of HIV infection in pre-exposure prophylaxis (PrEP) regimens is contingent on high levels of adherence to daily dosing regimens. Urine provides a potential noninvasive specimen that could be amenable to the development of rapid point of care (POC) tests to detect ARV adherence to track and improve individual adherence. This study sought to determine if urine could provide an accurate biomarker of plasma drug exposure for currently approved PrEP and HIV treatment regimens.

Methods: Urine and peripheral blood were collected from 34 HIV-negative men who have sex with men aged 18-49 years enrolled in a clinical trial comparing pharmacokinetics of 2 ARV regimens. Specimens were collected 4 and 24 hours after a single oral dose of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) (n=10) or tenofovir alafenamide (TAF)/FTC/cobicistat (COBI)/elvitegravir (EVG) (n=9), or after 4 and 10 days of daily oral TDF/FTC (n=8) or TAF/FTC/COBI/EVG (n=7). Tenofovir (TFV), FTC, and EVG were measured by high performance liquid chromatography-mass spectrometry with a lower limit of quantification of 10 ng/mL and specific gravity was evaluated by urine dipstick analysis.

Results: Median urine FTC concentrations at 4 and 24 hours were similar between men receiving TDF/FTC (4 hours 147 µg/mL; 24 hours 10 µg/mL) and men receiving TAF/FTC/COBI/EVG (4 hours 333 µg/mL, $p=0.173$; 24 hours 13 µg/mL, $p=0.681$). However, median urine TFV concentrations were significantly reduced among men receiving TAF/FTC/COBI/EVG (4 hours 1.2 µg/mL; 24 hours 0.8 µg/mL) compared to men receiving TDF/FTC (4 hours 17 µg/mL, $p<0.001$; 24 hours 7 µg/mL, $p=0.001$). Urine FTC, but not TFV or EVG, concentrations suggested recent dosing among all men receiving daily dosing as values were greater than minimum concentrations observed 24 hours following a single dose. Urine FTC concentrations, but not TFV or EVG, were correlated with plasma concentrations for all study participants at all visits ($r=0.766$, $p<0.001$). Urine FTC ($p=0.022$) and TFV ($p=0.039$) concentrations were associated with specific gravity measures.

Conclusion: Urine FTC levels, but not TFV or EVG, may provide a good surrogate for plasma FTC concentrations and could be useful in developing POC tests to assess adherence. These results suggest urine may provide an appropriate noninvasive specimen type for measuring adherence to FTC-containing regimens used in HIV treatment and prevention.

466 POLYPHARMACY, INAPPROPRIATE DRUGS, AND DRUG-DRUG INTERACTIONS IN HIV-INFECTED ELDERLY

Perrine Courlet[1], Catia Marzolini[2], Matthias Cavassini[1], Manuel Battegay[2], Susana Alves Saldanha[1], Deolinda Alves[1], Vreneli Waelti Da Costa[1], Chantal Csajka[1], Laurent A. Decosterd[1]
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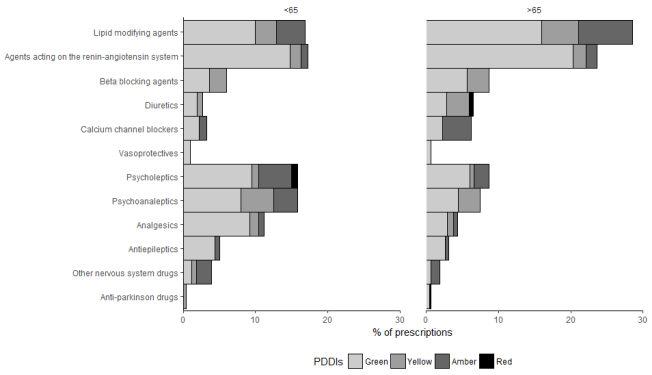
Background: Antiretroviral therapy has transformed HIV infection from a deadly disease into a chronic condition. HIV-infected individuals live longer, experience age-related physiological changes and comorbidities and are thus predisposed to the risk of polypharmacy, drug-drug interactions (DDIs) and inappropriate medication use which may harm this vulnerable population. This study compared the prevalence of these issues in young and elderly person living with HIV (PLWH).

Methods: Individuals enrolled in 2 centres from the Swiss HIV Cohort Study were contacted before their bi-annual follow-up visit to fill in a form with all their current medications. Drugs were grouped according to the ATC classification. The medications use, polypharmacy (defined as being on > 5 non-HIV drugs) and potential DDIs (PDDIs) were compared in patients < 65 and ≥ 65 years old (elderly). Inappropriate medications included anticholinergic drugs (anticholinergic risk scale > 3) and benzodiazepines, as these drugs have been associated to an increased risk of falls, impaired cognition, loss of independence and hospitalization in the elderly. PDDIs for the most prescribed therapeutic classes (i.e. cardiovascular and central nervous system (CNS) drugs) were screened using the Liverpool drug interaction database.

Results: A total of 906 PLWH were included: 794 were < 65 (median 49, IQR 40-55) and 112 ≥ 65 (71, 67-73) years old. 47% of PLWH received an integrase inhibitor based regimen and this proportion did not differ between the 2 groups. Elderly had a higher number of comedications (median 4, IQR 2–6) than younger PLWH (1, 0–3). Polypharmacy was more frequent in elderly compared to the younger group: 44% vs 12%. Type of medications and PDDIs differed according to the age group: cardiovascular drugs use and PDDIs (amber, red) with this drug class were more common in elderly (21% of overall prescribed drugs; 14% of cardiovascular drugs involved in PDDIs) whilst CNS drugs were more prescribed and mainly involved in PDDIs in younger PLWH (12%; 12%) (figure 1). Inappropriate medications were found in 13% of elderly, mostly benzodiazepines.

Conclusion: PDDIs remain common in the era of integrase inhibitors and inappropriate prescribing practices constitute an additional burden in elderly. Research efforts must be pursued to improve the care of PLWH, particularly elderly. Clinicians should maintain a proactive approach for the recognition and management of DDIs or prescribing issues traditionally encountered in geriatric medicine.



467 DRUG INTERACTION MAGNITUDES IN YOUNG VS ELDERLY: EXAMPLE OF RIVAROXABAN–DARUNAVIR/R

Felix Stader[1], Marco Siccardi[2], Hannah Kinvig[2], Manuel Battegay[1], Melissa A. Penny[3], Catia Marzolini[1]
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Background: Aging of the HIV population complicates patient care due to a higher prevalence of comorbidities and related use of comedications leading to an elevated risk for drug-drug interactions (DDIs). However, our understanding how age impacts the magnitude and subsequently the management of DDIs in elderly is limited. This study aimed to simulate the DDI magnitude between boosted darunavir (DRV/r) and rivaroxaban in young and elderly subjects using a physiologically based pharmacokinetic (PBPK) model. Rivaroxaban is a narrow therapeutic index drug characterized by a complex metabolism; thus, its DDI with boosted HIV regimens has not yet been fully elucidated.

Methods: A whole-body PBPK model was built in Matlab® including age-dependent physiological changes for the simulation of elderly subjects. The DRV/r drug model was successfully verified against observed clinical data in young volunteers. The predictive performance of our rivaroxaban model was checked against observed clinical data in a) young, b) elderly and c) young individuals treated with ritonavir (600 mg BID at steady state) and rivaroxaban. The verified drug models were used to assess the effect of age on the DDI magnitude between DRV/r (800/100 mg QD at steady state) and rivaroxaban (10 mg single dose) in 100 virtual subjects considering 5 age groups: a) 20-49, b) 50-64, c) 65-74, d) 75-84 and e) 85-94 years.

Results: The developed PBPK model predicted the pharmacokinetics of rivaroxaban in young and elderly correctly. Predicted versus observed mean rivaroxaban AUC were 1148 and 1000 ng*h/mL for young and 1491 and 1839 ng*h/mL for elderly volunteers. The simulated versus observed rivaroxaban AUC in the presence of ritonavir was 2655 ng*h/mL and 2529 ng*h/mL with a resulting AUC ratio (rivaroxaban with / without ritonavir) of 2.31 and 2.53, respectively. Age did not impact the DDI magnitude between rivaroxaban and DRV/r (Tab. 1), because all drugs are similarly affected by age-dependent physiological changes. Of interest, virtual individuals aged 50-64 years commonly defined as "elderly" in HIV medicine, showed only a 12% increase in the AUC compared to younger subjects suggesting that this age cut-off is too low for pharmacological studies.

Conclusion: PBPK modelling is a useful tool to overcome limited clinical data. Our predictions showed an age-dependent increase in the AUC of rivaroxaban in the absence and presence of DRV/r, but no changes in the DDI magnitude with age suggesting a similar management of this DDI in the elderly.

Tab. 1: Predictions of DDI magnitudes between DRV/r and rivaroxaban. a = age group and r = reference group (20-50 years).

Age [years]	AUC [ng*h/mL] (Rivaroxaban alone)		AUC [ng*h/mL] (Rivaroxaban + DRV/r)		AUC ratio	
	geomean	ratio a/r	geomean	ratio a/r	geomean	ratio a/r
20 – 49	1055	1.0	2341	1.0	2.22	1.0
50 – 64	1180	1.12	2611	1.12	2.21	1.0
65 – 74	1332	1.26	2817	1.20	2.12	0.95
75 – 84	1405	1.33	3044	1.30	2.17	0.98
85 – 94	1481	1.40	3176	1.36	2.14	0.97

468 THE ROLE OF OATP1B1 IN GRAZOPREVIR DRUG-DRUG INTERACTIONS AND THE ELDERLY

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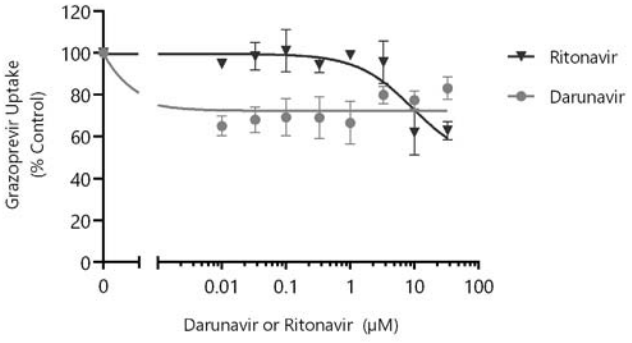
Background: Grazoprevir (GZR) is a hepatitis C (HCV) NS3/4A protease inhibitor which can be combined with antiretroviral drugs to treat HIV/HCV co-infected patients. Coadministration with boosted darunavir (DRV/RTV) is contraindicated as it increases GZR AUC and Cmax 7.5-fold and 5.3-fold. Although assumed to be caused by OATP1B1 and CYP3A4 inhibition, the mechanism of this drug-drug interaction (DDI) has not been fully elucidated. GZR also exhibits a 20% increase in AUC in elderly patients and the role of OATP1B1 remains unclear. The current study quantified OATP1B1-mediated transport of GZR in the presence of DRV and RTV *in vitro* and evaluated the expression of OATP1B1 in primary hepatocytes from both young and elderly donors.

Methods: Pooled human cryopreserved hepatocytes were suspended in Krebs-Henseleit buffer in 24-well cell culture plates and incubated with GZR (0.1μM) and either DRV or RTV (0.01-33μM) for 2 minutes at 37°C. Transporter uptake was terminated using ice cold phosphate buffered saline (PBS) followed

by immediate centrifugation, washing with ice cold PBS and freeze thaw for cell lysis. GZR concentrations were quantified using LC-MS/MS and IC_{50} were calculated. The abundance of OATP1B1 in pooled human cryopreserved hepatocytes aged 18-60 years old and three individual elderly donors aged 74-80 years old were quantified using a sandwich ELISA. Statistical significance was assessed using an unpaired t-test.

Results: DRV reduced OATP1B1-mediated uptake of GZR by 35% (maximal inhibition at 0.01µM; IC_{50} of 4.4×10^{-8}µM) whilst RTV decreased uptake by 40% (maximal inhibition at 10µM; IC_{50} of 9.4µM) (see figure). When compared to pooled hepatocytes from donors aged 18-60 years old, abundance of OATP1B1 in three individual elderly donors aged 74-80 years old were between 35% and 56% lower with P values between 0.005 and 0.032.

Conclusion: The *in vitro* model identified that RTV does not inhibit OATP1B1-mediated transport in the range of physiologically relevant concentrations, unlike DRV which produced a moderate inhibition of OATP1B1. Our experimental approach represents an effective strategy to characterize the role of transporters in DDIs and may be useful to identify clinically relevant DDIs. Furthermore, the lower expression of OATP1B1 in hepatocytes from elderly donors provides a plausible mechanistic basis for the increased GZR AUC reported in this sub-population and justifies further investigation.



469 INTRACELLULAR SOFOSBUVIR (SOF) CONCENTRATIONS IN PERSONS WITH HCV AND COCAINE USE

Kristina M. Brooks[1], Jose R. Castillo-Mancilla[1], Mary Morrow[2], Samantha MaWhinney[2], Ryan T. Huntley[1], Joshua Blum[3], David L. Wyles[3], Lane R. Bushman[1], Peter L. Anderson[1], Jennifer J. Kiser[1]

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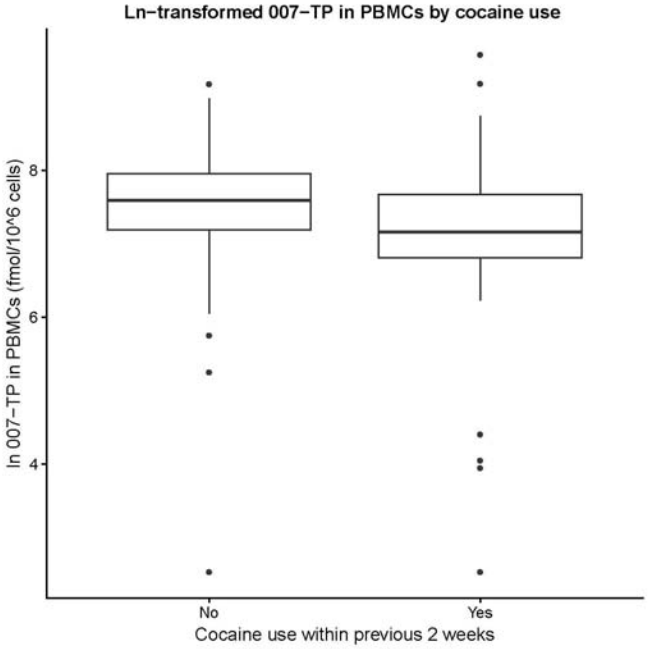
Background: There are limited data on the effects of drug use on direct acting antiviral (DAA) pharmacokinetics (PK). Certain drugs, such as cocaine, may affect DAA PK through enzyme or transporter modulation or immune activation. We examined the influence of cocaine on GS-331007 triphosphate (007-TP; also known as GS-461203) concentrations, the active anabolite of SOF, in PBMCs and dried blood spots (DBS) in persons who use drugs receiving ledipasvir (LDV)/SOF for HCV treatment.

Methods: Persons with HIV/HCV or HCV mono-infection and self-reported drug use within 30 days of screening were eligible for the study. Adherence to LDV/SOF was monitored through directly (video-based) or wirelessly (Wisepill®) observed therapy. A self-reported (SR) drug use questionnaire documenting yes/no use of cocaine, a urine toxicology screen (UTox), and convenience PK samples were collected bi-weekly over 12 weeks of LDV/SOF. 007-TP concentrations in PBMCs and DBS were quantified using LC/MS-MS. A mixed-effects model was used to analyze the influence of average adherence over the previous 2 weeks (adh2wk) and cocaine use (yes/no) on log-transformed 007-TP in PBMCs and DBS. Cocaine use was examined by SR, UTox, and both combined.

Results: Samples and questionnaires were available from 46 participants (43 HIV/HCV, 3 HCV only; 235 person-visits). Fifteen participants (33%) used cocaine by SR or UTox at 39 person-visits. Median (IQR) adh2wk in cocaine users was 86% (64%, 100%) vs. 100% (91%, 100%) in non-users. Adh2wk was a significant predictor of 007-TP concentrations in PBMCs and DBS ($p<0.0001$ for both). After controlling for adherence, overall cocaine use was associated with 43% lower 007-TP concentrations in PBMCs ([95% CI -60%, -19%]; $p=0.0017$). SR showed a trend towards 25% lower 007-TP in PBMCs ([95% CI -47%, 7%]; $p=0.11$) and UTox-positive revealed 46% lower 007-TP PBMC concentrations ([95% CI -63%, -23%]; $p=0.0009$). 007-TP in DBS did not significantly differ by cocaine use ($p>0.3$).

Conclusion: Intracellular 007-TP concentrations in PBMCs, but not DBS, were lower in cocaine users. This difference was stronger by UTox, suggesting a temporal or frequency effect of cocaine use on 007-TP in PBMCs. Differences in findings between cell types may be due to differences in cell-specific expression of DAA-converting enzymes or transporters, or immune activation of PBMCs by cocaine. Further research is needed to elucidate a possible mechanism consistent with this interaction and whether these differences impact SVR.



470 PREDICTION OF RENAL OAT1 AND OAT3 INHIBITION BY CABOTEGRAVIR USING PBPK MODELLING

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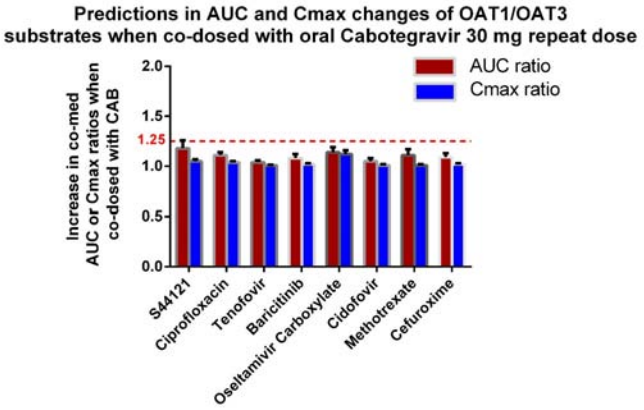
Background: Cabotegravir (CAB) is an integrase strand transfer inhibitor being investigated for the treatment and prevention of HIV-infection. It is being developed as a long acting (LA) intra-muscular injection to facilitate every 1 or 2-month dosing. It is necessary to evaluate the impact of CAB on the exposure and clearance of co-medications. In vitro studies indicated that CAB inhibits renal transporters OAT1 and OAT3 with half maximal inhibitory concentrations of 0.81 and 0.41 µM, respectively. The objective of the present analysis was to build a physiologically based pharmacokinetic (PBPK) model of CAB to predict the clinical implications of renal OAT1/OAT3 inhibition on co-medications.

Methods: A mechanistic PBPK model of CAB in the adult population was built using the Simcyp® v17.1 simulator by incorporating physico-chemical properties, in vitro clearance mechanisms, and in vivo data and validated as per regulatory specifications. The CAB PBPK model was validated through comparison with available clinical PK data following oral CAB 30mg administration in healthy volunteers. The simulator was qualified for predicting observed OAT1 and/or OAT3 inhibition based DDIs. DDI simulations were performed to evaluate the effect of CAB oral doses on the exposure of OAT1/OAT3 substrates (methotrexate, tenofovir, ciprofloxacin, cidofovir, cefuroxime, oseltamivir carboxylate, baricitinib, and S44121).

Results: Simulated DDIs for above mentioned OAT1/OAT3 substrates and inhibitors (probenecid, diclofenac) were within two-fold of the observed clinical DDIs. This qualified the Simcyp® v17.1 simulator and related files as appropriately sensitive for predicting OAT1/OAT3 inhibition-mediated clinical

DDIs. CAB PBPK model accurately predicted CAB PK parameters (all within acceptable bioequivalence criteria (0.80-1.25) for single as well as repeat dose studies). DDI simulations predicted a mean change in systemic exposure for tested OAT1/OAT3 substrates of <25% after co-administration with CAB at steady state.

Conclusion: A PBPK model of CAB was developed and validated that accurately predicted human pharmacokinetics observed in healthy volunteers. OAT1/OAT3 substrate drugs such as tenofovir, cidofovir, methotrexate were predicted to have a minimal risk of DDIs when administered with CAB. Similar CAB concentrations following oral and LA administration suggest that these results would apply to CAB LA. The predicted lack of interactions supports co-administration with OAT1/OAT3 substrates without dose adjustments.



471 INFLUENCE OF UGT1A1*28 ON RALTEGRAVIR PK/PD IN THE NEAT001/ANRS143 STUDY

Rohan M. Gurjar[1], Laura Dickinson[1], Daniel F. Carr[1], Wolfgang Stohr[2], Stefano Bonora[3], Andrew Owen[1], Antonio D'Avolio[3], Adam Cursley[2], Jean-Michel Molina[4], Gerd Fätkenheuer[5], Giovanni Di Perri[3], Anton Pozniak[6], Laura Richert[7], François Raffi[8], Marta Boffito[9]

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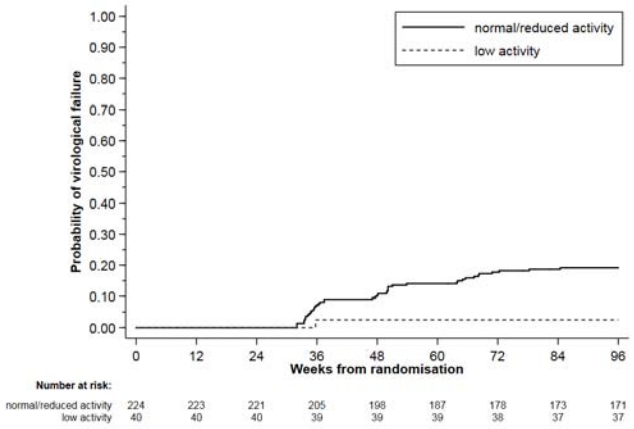
Background: Raltegravir (RAL) is metabolised by UGT1A1 and polymorphisms in the *UGT1A1* gene have been associated with plasma concentrations in some but not all previous studies. This analysis represents the largest study to date for the effect of *UGT1A1* polymorphisms on RAL PK/PD.

Methods: NEAT001/ANRS143, a randomised study (n=805 participants), demonstrated non-inferiority of first-line darunavir/ritonavir (DRV/r; 800/100 mg o.d) plus RAL (400 mg b.d) compared with DRV/r plus tenofovir/emtricitabine (245/200 mg o.d). Random, single samples were collected at weeks 4 and 24 post-therapy initiation for drug measurement. DNA was extracted and *UGT1A1* polymorphisms genotyped using the Sequenom MassARRAY iPLEX. Nonlinear mixed effects modelling (NONMEM v. 7.3) was used to estimate PK parameters. Weight, age, sex, ethnicity and genotypes were investigated in the model for association with RAL apparent oral clearance (CL/F). Kaplan-Meier estimates and Cox regression were used to assess the relationship between virological failure by week 96 and *UGT1A1* genotypes.

Results: A total of 602 samples (n=313 week 4, n=289 week 24) from 349 patients were used in the model (n=264 with genotypes). UGT1A1 activity was defined as normal (*1/*1, *1/*36), reduced (*1/*6, *1/*28, *1/*37, *28/*36, *36/*37) or low (*28/*28, *28/*37, *37/*37). Although none of the covariates were statistically significant, RAL CL/F was reduced by 21% in patients with *28/*28 *UGT1A1*. A post-hoc analysis assessed the impact of *UGT1A1**28 on predicted RAL AUC_{0-12} and C_{12} [low activity (n=40) vs normal/reduced activity (n=224)]. Geometric mean ratios (95% CI) were 1.35 (0.99-1.84; p=0.062) and 1.32 (0.99-1.77; p=0.062), respectively, suggesting minimal impact of *UGT1A1**28 on RAL PK. By week 96, virological failure was seen in 16%, 22% and 2.5% of patients with normal, reduced and low *UGT1A1* activity, respectively. Failure rates were lower in patients with low activity *UGT1A1* (p=0.012; Figure). The relationship remained significant when adjusted for baseline CD4 count (p=0.048) but not when adjusted for baseline VL (p=0.082) or both CD4 and VL [HR (95% CI): 0.18 (0.02-1.30); p=0.08].

Conclusion: The NEAT001/ANRS143 study analysed *UGT1A1* genotypes with the largest sample size to date and suggested little impact on RAL PK. However, *UGT1A1* genotype may be a better correlate of RAL pharmacodynamics because of the high intra-subject variability in RAL PK.



472 PHARMACOGENETICS OF WEIGHT GAIN AFTER SWITCH FROM EFAVIRENZ TO INTEGRASE INHIBITORS

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Background: Weight gain has been reported in virologically suppressed HIV-positive patients who switch to integrase inhibitor (INI)-based antiretroviral therapy (ART). We studied pharmacogenetics of weight gain following switch from efavirenz (EFV)- to INI-based ART.

Methods: Patients at an HIV clinic in the southeastern USA were on EFV-based ART for at least 2 years and with no viral load >1000 copies/mL within 6 months prior to switch. Weight gain from date of switch to weeks 24 and/or 48 (± 4 weeks) was assessed. We genotyped *CYP2B6* and *UGT1A1* polymorphisms that predict increased plasma EFV and INI exposure, respectively. Associations were tested with linear regression models.

Results: The 101 evaluable participants (n=83 for week 24, n=66 for week 48) included 65 (64%) white, 27 (27%) black, 84 (83%) male, and 17 (17%) female participants. INIs were 58 (57%) dolutegravir, 34 (34%) elvitegravir, and 9 (9%) raltegravir. Median baseline weight was 81.7 kg (interquartile range: 69.7, 94.7). There were 30 (30%), 54 (55%), and 15 (15%) *CYP2B6* normal, intermediate, and slow metabolizers, respectively, and 38 (40%), 41 (43%), and 16 (17%) *UGT1A1* normal, intermediate, and slow metabolizers, respectively. *CYP2B6* slow metabolizer genotype was associated with weight gain at week 48 (β= 7.2, p=0.009). In *CYP2B6* normal, intermediate, and slow metabolizers, at week 48, average weight gain was 0.2 kg, 2.8 kg and 2.0 kg, respectively. After controlling for sex, age, and weight at switch, associations persisted at week 48 (β=6.97, p=0.012). *CYP2B6* genotype was associated with weight gain in whites at week 48 (β=11.25, p=0.003), but not in blacks (β= -0.58, p=0.090) (Figure). The above significant associations also tended to be present at week 24 (p=0.05 to p=0.09). *UGT1A1* genotype was not associated with weight change at week 24 (β= -0.33, p=0.83) or week 48 (β=0.70, p=0.77).

Conclusion: Among virologically suppressed patients who switch from EFV-based ART to INI-based ART, *CYP2B6* genotype that is known to predict higher EFV plasma exposure pre-switch may be associated with greater weight gain after switch. These findings warrant replication in other cohorts. We hypothesize that patients with greater plasma EFV concentrations before switch

may have sub-clinical intolerance. These patients may therefore gain more weight after switch from EFV-based ART to INI-based ART.

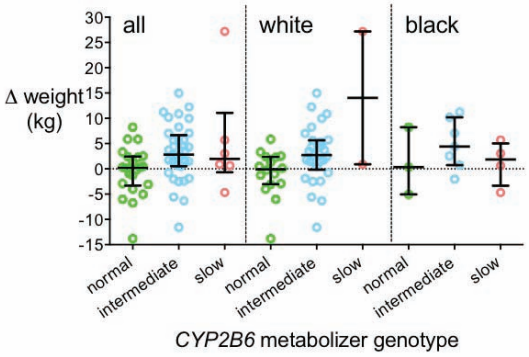

Figure: *CYP2B6* genotype and weight change from date of switch from EFV-based ART to week 48 on INI-based ART. Error bars represent median and IQR.

473 HORMONAL CONTRACEPTIVES DO NOT ALTER CABOTEGRAVIR PK IN HIV-UNINFECTED WOMEN HPTN 077

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Background: Long-acting Injectable Cabotegravir (CAB LA) is a novel strand-transfer integrase inhibitor, currently in development for HIV prevention and treatment. Unexpected drug-drug interactions (DDI) between ARVs and hormones for contraception or cross-sex therapy have been noted for other ARVs, ranging from 13% to 38% reduction in tenofovir exposure (AUC) in the setting of estrogen with or without anti-androgen use. Understanding such DDIs is critical to acceptability and scale up of novel treatment and prevention paradigms.

Methods: We performed a secondary analysis of cisgender women who were enrolled in HPTN 077, a Phase 2a multicenter study that enrolled HIV-uninfected, low risk individuals in Malawi, Brazil, South Africa, and the US. Participants received a 4 week oral CAB lead-in, followed by CAB LA 800mg Q12w IM (Cohort 1) or 600mg q8w IM (after a 4 week initial interval between injections, Cohort 2) over 41 weeks. Participants were followed 52-76 weeks subsequent to their final injection. Linear regression was used to evaluate differences in pharmacokinetic (PK) parameters (peak concentration [Cmax], trough [Cτ], exposure after the last injection [AUC0-τ], and apparent terminal half-life after the last injection [T1/2app]) between hormonal contraception (use vs not) and contraception type (oral, injectable, vaginal ring, implants, other) controlling for body mass index (BMI) and CAB dose cohort.

Results: 85 cisgender females enrolled in HPTN 077 and received at least 1 dose of active CAB LA. In this study population, BMI associated with 1% reduction (per unit increase in BMI) in Cmax, Cτ, and AUC0-τ and 2% increase in T1/2app. Median BMI was 27.2 in Cohort 1 and 25.7 in Cohort 2. Use of any type of hormonal contraceptive, individually or in aggregate, did not result in statistically significant changes in Cmax, Cτ, AUC0-τ, or T1/2app (Table, all $p > 0.05$, Cmax, AUC0-τ not shown). No pregnancies occurred among those receiving active CAB LA during the study period. We did not assess the impact of CAB on estrogen concentrations.

Conclusion: Among HIV-uninfected females in HPTN 077, use of hormonal contraception did not alter the CAB concentration profile during injections or during the pharmacokinetic tail. While there is no anticipation of an effect of CAB on estrogen concentration, the effects of CAB LA on hormonal treatment for both contraception and gender-affirming treatment warrant evaluation.

Variable	PK Parameter	Estimate	SE	p value
Contraceptive use (yes [n=79] vs no)	log C_τ	0.02	0.08	0.80
	log $T_{1/2}$app	-0.32	0.28	0.54
Oral Contraceptive (yes [n=18] vs no)	log C_τ	0.01	0.04	0.81
	log $T_{1/2}$app	0.05	0.16	0.75
Injectable Contraceptive (yes [n=26] vs no)	log C_τ	0.01	0.04	0.89
	log $T_{1/2}$app	-0.12	0.15	0.44
Vaginal Ring Contraceptive (yes [n=2] vs no)	log C_τ	-0.19	0.13	0.15
	log $T_{1/2}$app	0.24	0.44	0.59
Implantable Contraceptive (yes [n=11] vs no)	log C_τ	0.05	0.06	0.35
	log $T_{1/2}$app	-0.21	0.22	0.34
Other Contraceptive (yes [n= 8] vs no)	log C_τ	0.04	0.06	0.45
	log $T_{1/2}$app	-0.03	0.21	0.87

474 BICTEGRAVIR CONCENTRATIONS AND VIRAL SUPPRESSION IN CSF HIV–INFECTED PATIENTS

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Background: Bictegravir (BIC) is a novel, potent, once-daily, unboosted inhibitor of HIV-1 integrase specifically targets IN strand transfer activity. BIC differs from previously known structures in that it contains a unique bridged bicyclic ring and a distinct benzyl tail consisting of a tri substituted 2,4,6-trifluorobenzyl moiety. These changes resulted in increased plasma protein binding to improve its solubility. These two physicochemical characteristics are crucial determinants of drug penetration. The aim of our study was to determine BIC levels in cerebrospinal fluid (CSF) as well as HIV viral load in this compartment.

Methods: This is a single-arm, open-label, single-center study. After an initial assessment, 15 participants switched from stable ART to FTC/TAF/BIC (Biktarvy®). At week 4, plasma and CSF concentrations of BIC were measured 24 hs post-dose, using a validated LC-MS methodology (assay calibration range is 10-10,000 ng/ml for plasma and 1-100 ng/ml for CSF). HIV RNA was measured in plasma and CSF by RT-PCR (LLQ 40 copies/mL).

Results: A total of 15 plasma an 15 CSF samples were collected. At baseline, median CD4 count was 776 cells/uL (613 – 905). Most patients switched from Genvoya® and Triumeq® (57,2%). One patient presented with unexpected low BIC concentrations in plasma and CSF while concomitantly taking self-prescribed magnesium supplements*.

Conclusion: Although the target concentrations are unknown, total trough BIC concentrations in CSF were near or just above the in vitro 50% inhibitory concentration for wild-type HIV (IC50: 3.54 ng/mL), suggesting that BIC given in combination with FTC/TAF may contribute to inhibit viral replication in this compartment.

ID	HIV RNA CSF copies/ml	HIV RNA Plasma copies/ml	Bictegravir plasma ng/ml	Bictegravir CSF ng/ml	BIC ratio CSF/plasma
*1	<40	<40	97.99	<LLQ	n/a
2	<40	<40	1297.36	4.76	0.003
3	<40	<40	2702.29	12.86	0.004
4	<40	<40	2925.05	12.91	0.004
5	<40	<40	1199.95	6.58	0.005
6	<40	<40	4082.08	10.33	0.002
7	<40	<40	1932.53	7.34	0.003
8	<40	<40	1512.40	5.59	0.003
9	<40	<40	1003.97	4.56	0.004
10	<40	<40	1254.78	5.08	0.004
11	<40	<40	2586.70	7.21	0.002
12	<40	<40	2030.67	8.77	0.004
13	<40	<40	2488.22	16.30	0.006
14	<40	<40	1741.80	4.88	0.002
15	<40	<40	1237.26	4.74	0.0038
Median (range)			1837.17 (1250.4 – 2615.6)	6.9 (4.86 – 10.97)	0.003 (0.003 – 0.004)

475 WHICH PRECLINICAL SPECIES MIMICS TISSUE PENETRATION OF ARV DRUGS IN HUMANS?

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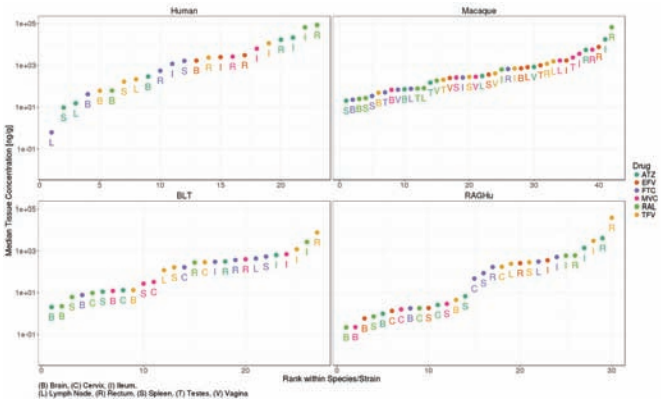
Background: For HIV cure strategies like "kick and kill" to succeed, antiretroviral (ARV) drugs must reach protective concentrations in putative viral reservoirs, including lymphoid tissue and sequestered sites like the brain and genital tract. Extrapolating outcomes of animal studies to humans requires understanding the specifics of ARV tissue distribution. Here, we characterize penetration of 6 ARVs in 2 humanized mouse models, nonhuman primates (NHPs), and HIV+ humans.

Methods: ARVs/doses were selected based on published strategies for animals and humans (Thompson, AIDS, 2017). 12 BLT humanized mice and 36 RAG-hu mice (female) were used. 17 macaques (5 female, 12 male) and 19 human subjects (3 women/16 men) were used. Animals were dosed for 10 days before necropsy. Human samples were obtained from the National NeuroAIDS Tissue Consortium harvested 8-47h post dose. These drugs were investigated: tenofovir (TFV), emtricitabine (FTC), raltegravir (RAL), maraviroc (MVC), efavirenz (EFV) and atazanavir (ATZ). 8 tissue types were snap frozen and stored at -80°C. ARV concentrations were assayed by LC-MS/MS (LLOQ: 0.002-0.01 ng/mL). A Bayesian measurement-error model was used to characterize plasma and tissue concentration relationships.

Results: Across species, variability in ARV concentrations was similar among plasma (CV 0.4-3.2) and tissues (CV 0.3 - 3.3). For a given plasma concentration, tissue concentrations were most similar among NHPs and humans. With few exceptions, tissue exposure from highest to lowest were: human > NHP > BLT > RAG-hu (Figure). For RAL and FTC, under most conditions, the relationship between plasma and tissue concentration was flat (95% highest density interval (HDI) includes 0). Across all tissues/species, only EFV and TFV concentrations were proportional to plasma. Largest slopes (log-log scale) were seen for EFV and TFV in NHP spleen with median values and lower and upper bounds of the 95% HDI of 0.95 (0.71,1.17) and 0.78 (0.50, 1.06) respectively.

Conclusion: NHP dosing strategies result in similar tissue concentrations to humans. For RAL and FTC, it is unlikely that increasing doses will increase tissue penetration substantially. For TFV and EFV, it may be possible to increase tissue penetration by adjusting doses. Changing tissue concentrations for other ARVs is dependent on drug/tissue type. These results add to current data on tissue penetration of ARVs and have implications on interpreting HIV treatment, prevention, or cure interventions between models.



476 ANTIRETROVIRALS CONCENTRATIONS IN THE OLFACTORY MUCOSA OF HIV-POSITIVE PATIENTS

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Background: Antiretrovirals (ARVs) long-term efficacy and HIV-functional cure require the abolition of viral replication in every body compartment as well as the effect of the immune system. The olfactory mucosa (OM) is a unique tissue at the intersection of the central nervous (CNS) and lymphatic system; preliminary data suggest that HIV may persist in the OM despite antiretroviral treatment.

Methods: Patients with neurocognitive disorders were included in a diagnostic study and OM samples were obtained through nasal brushing. The analysis of ARVs concentrations in swabs was performed as follows on frozen swabs. They were weighted upon extraction and then inserted in PTFE tubes along with 40µl of internal standard (marked with stable isotopes) working solution plus 500 µl of water:methanol solution (30:70 v:v). These tubes were then vortex-mixed 10 sec and sonicated for 10 minutes at 40°C. The dry extracts were dissolved in 110 µL of water:acetonitrile:acetic acid (94.9:5:0.1 v:v:v) solution and 10 µl of acid phosphatase (0.5 X) and incubated for 1 hour at 37°C, in order to convert phosphate metabolites of NRTIs to the free form. The resulting extracts were analyzed by using HPLC/MS-MS, obtaining absolute amounts (ng): these results were then normalized for the estimated weight of the extracted material (the difference between the initial weight and after the extraction process). The lower limit of quantification was 0.3 ng per sample, corresponding to a mean concentration of 3 pg/mg of OM swab.

Results: 31 patients were included. They were mostly male (80.6%) and of European ancestry (96.8%); median age and BMI were 51 years (46-58) and 23.5 Kg/m2 (19.7-27.7). Median current and nadir CD4+ T-cells were 649/uL (360-965) and 185/uL (88-278); after a median o 33 months (8-123) months of virological suppression plasma, CSF and OM HIV RNA were below 20 copies/mL in 27 (87.1%), 22 (71%) and 29 (93.5%) participants. OM concentrations as well as OM to plasma and OM to CSF ratios are shown in Table 1: a marginal correlation between OM and plasma (rho=0.30, p=0.007) and CSF concentrations (rho=-0.22, p=0.072) was observed.

Conclusion: We developed a novel method for quantifying ARVs in mucosal tissues obtained through brushing swabs. In this small pilot study antiretroviral concentrations in the OM were highly variable with protease inhibitors showing the highest exposure. Further studies are needed to compare ARVs' penetration and residual viral replication.

	Samples	OM concentrations (pg/mg)	OM to plasma ratio	OM to CSF ratio
Lamivudine	7	15 (10-38)	9.6 (7-51)	175 (62-550)
Emtricitabine	14	4 (1-12)	10.4 (0-20)	42 (0-54)
Abacavir	6	1 (0-9.7)	0 (0-72)	0 (0-14)
Tenofovir	12	0 (10/12 not detectable)	0	0
Nevirapine	2	10-12.5	2.3-2.6	5.7-33.2
Rilpivirine	4	5.5 (1.7-15.2)	76 (25-76)	6*
Etravirine	3	9 (5-9)	33.8 (6-34)	1000 (136-1000)
Atazanavir	1	160	356	26666
Darunavir	11	106 (22-286)	58 (17-83)	11047 (2650-16426)
Ritonavir	4	133 (45-360)	1190 (458-1190)	0*
Cobicistat	11	288 (119-662)	1052 (731-7721)	0*
Raltegravir	6	12 (4.5-45.7)	18 (6-93)	70 (38-220)
Elvitegravir	3	3 (0-3)	4.4*	0*
Dolutegravir	9	8 (4.5-16)	7 (2-20)	1636 (775-2602)
Maraviroc	4	57 (34-73)	193 (47-193)	5333*

*Only one available concentration

477 INFLUENCE OF TENOFOVIR-MONOESTER AND TENOFOVIR ON INTRACELLULAR TENOFOVIR-DIPHOSPHATE

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Background: Tenofovir (TFV)-monoester (TFV-mE) is the intermediate moiety formed during the hydrolysis of TFV disoproxil fumarate (TDF) to TFV. TFV-mE is more lipophilic than TFV, and thus may influence intracellular TFV-diphosphate

(TFV-DP) concentrations in vivo. Here, we examined the influence of TFV-mE and TFV on intracellular TFV-DP concentrations in peripheral blood mononuclear cells (PBMC) and dried blood spots (DBS) in HIV-uninfected adults.
Methods: Samples were obtained from a randomized, crossover bioequivalence study of single-dose TDF/emtricitabine unencapsulated or co-encapsulated with the Proteus® Ingestible Sensor. Visits were separated by a 14-day washout. Blood for PK assessments were collected serially through 72 hours post-dose, and PBMC and DBS were isolated at 24 hours post-dose at both visits. TFV-mE and TFV were quantified via LC/MS-MS. Area under the concentration-time curve extrapolated to infinity (AUC) of plasma TFV-mE and TFV were calculated via noncompartmental methods (Phoenix WinNonlin v8.0). A mixed-effects model was used to examine TFV-mE AUC, TFV AUC, visit, randomization sequence, formulation, sex, BMI, and eGFR as fixed effects and subjects as random effects, with TFV-DP in DBS or PBMC as primary outcomes (SAS Enterprise v9.4).
Results: Samples were available from 24 participants (48 observations). Geometric mean (%CV) for TFV-mE and TFV AUC were 93.9 (46.8%) and 1986.0 (26.9%) h*ng/mL. Visit 1 TFV-DP was 45.3 (48.2%) fmol/punch in DBS and 10.8 (42.4%) fmol/10^6 cells in PBMCs. Visit was a significant predictor of TFV-DP in DBS, but not PBMC, with 95.1% higher concentrations at visit 2 ([95% CI 59.2%, 139.0%]; p<0.0001) (Table), consistent with the ~17-day half-life for TFV-DP in DBS. TFV-mE AUC was a significant predictor of TFV-DP in both PBMC and DBS. For every 10 h*ng/mL increase in TFV-mE AUC, TFV-DP concentrations increased by 3.8% ([95% CI 0.8%,6.8%]; p=0.015) in PBMCs and 4.3% ([95% CI 1.5%,7.2%]; p=0.005) in DBS, the latter of which was controlled for study visit. Conversely, TFV AUC was not significantly associated with TFV-DP concentrations in PBMCs (p=0.11) or DBS (p>0.99). Randomization sequence, formulation, and other clinical variables did not significantly influence TFV-DP in either cell type.
Conclusion: Plasma TFV-mE AUC was a significant predictor of intracellular TFV-DP concentrations in PBMC and DBS, whereas plasma TFV AUC was not. TFV-mE contributes to cell loading in vivo, influencing TFV-DP concentrations in PBMC and DBS.

Variable	TFV-DP in PBMCs			TFV-DP in DBS[a]		
	% change in TFV-DP	[95% CI]	P-value	% change in TFV-DP	[95% CI]	P-value
Visit (2 vs. 1)	-5.0%	[-24.7%, 20.0%]	0.66	95.1%	[59.2%, 139.0%]	<0.0001
Randomization sequence (encaps vs. unencaps)	5.1%	[-23.8%, 44.9%]	0.75	25.0%	[-11.0%, 75.6%]	0.19
Formulation (encaps vs. unencaps)	-10.0%	[-28.5%, 13.1%]	0.35	-4.8%	[-22.7%, 17.2%]	0.63
Sex (female vs. male)	-9.3%	[-34.1%, 24.9%]	0.53	-5.9%	[-33.9%, 33.9%]	0.73
BMI (kg/m^2)	-2.2%	[-6.0%, 1.7%]	0.25	-1.0%	[-5.3%, 3.5%]	0.63
eGFR (mL/min/1.73 m^2)	0.1%	[-0.6%, 0.8%]	0.84	-0.0%	[-0.8%, 0.7%]	0.97
Tenofovir-monoester $AUC_{0-\infty}$ (per 10 ng*h/mL)[b]	3.8%	[0.8%, 6.8%]	0.015	4.3%	[1.5%, 7.2%]	0.005
Tenofovir $AUC_{0-\infty}$ (per 10 ng*h/mL)[b]	0.2%	[-0.1%, 0.5%]	0.11	0.0%	[-0.3%, 0.3%]	>0.99

Key: $AUC_{0-\infty}$ = area under the concentration vs. time curve from time 0 extrapolated to infinity (∞); CI = confidence interval, DBS = dried blood spots, PBMCs = peripheral blood mononuclear cells, TFV-DP = tenofovir-diphosphate
[a] Reported point estimates for TFV-DP in DBS were controlled for study visit
[b] Percent changes reported per 10 ng*h/mL increase in tenofovir-monoester or tenofovir

478 DEPO-MEDROXYPROGESTERONE EFFECTS ON TENOFOVIR-DP AND LAMIVUDINE-TP IN CERVICAL TISSUE

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Background: Effective concentrations of antiretrovirals in the female genital tract (FGT) are critical for suppression of viral shedding, or, in the case of pre-exposure prophylaxis, HIV prevention. The disposition of tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) in the FGT have been previously described. However, despite widespread lamivudine use, lamivudine triphosphate (3TC-TP) exposure in FGT is unknown. Furthermore, to facilitate development of multipurpose prevention for contraception and HIV, a better understanding of exogenous hormone effect on FGT antiretroviral exposure is needed.
Methods: HIV-positive, virologically suppressed, non-pregnant women, receiving combination TDF/3TC as part of antiretroviral therapy, were recruited in Kampala, Uganda. Women receiving depot-medroxyprogesterone (DMPA group) or using non-hormonal contraception (non-HC group) participated in a single visit study . Cervical biopsies were obtained for quantification of TFV-DP, 3TC-TP, and endogenous dATP and dCTP using liquid chromatography with tandem mass spectrometry. Blood plasma was collected to assess medication adherence. Differences between groups were tested using multiple linear regression on log-transformed data and adjusted for age, weight, and plasma drug concentrations (for tissue) or time since last dose (for plasma).
Results: Fifty women aged 21-34 years were enrolled between Nov 2017 and March 2018. One subject in the DMPA group and two in the non-HC group were excluded from antiretroviral quantification as plasma concentrations were indicative of non-adherence. One additional biopsy in DMPA group was excluded due to sample processing error. Unadjusted medians (25th, 75th percentile) are reported in attached table. Concentrations of 3TC-TP were significantly higher than TFV-DP in cervical tissues with a geometric mean ratio of 17.3. Cervical TFV-DP was 64% higher in DMPA users compared to non-HC users (p=0.02). No differences were found between groups for TFV or 3TC in plasma, or in 3TC-TP, dATP, dCTP in cervical tissues.
Conclusion: These data provide the first information on drug exposure of 3TC-TP in the FGT following oral dosing. Similar to reports of FTC-TP, 3TC-TP was significantly higher than TFV-DP in cervical tissue, suggesting it may be an option for prophylaxis. TFV-DP was significantly higher in DMPA users compared to women using non-hormonal contraception, suggesting prevention efficacy is unlikely to be compromised by injectable progestin contraceptive use.

Drug and endogenous metabolite concentrations in non-hormonal contraceptive users and DMPA users.
Median (25th, 75th) percentile of analytes measured in cervical tissue and plasma

	Non-HC	DMPA	Adjusted* p-value
TFV-DP fmol/g cervix	10,520 (6269-17,471) n=23	18,477 (10,836-27,851) n=23	p=0.02
3TC-TP fmol/g cervix	242,415 (140,800-467,329) n=23	253,469 (133,613-358,607) n=23	p=0.46
dATP fmol/g cervix	87,088 (58,695-120,890) n=25	91,025 (58,242-114,262) n=24	p=0.84
dCTP fmol/g cervix	39,930 (28,393-69,822) n=25	47,167 (31,169-67,672) n=24	p=0.94
TFV ng/mL plasma	74.1 (58-84) n=23	63.5 (44-87) n=24	p=0.82
3TC ng/mL plasma	195.0 (117-268) n=23	186.5 (99-267) n=23	p=0.62

*Tissue models were adjusted for age, weight, and plasma drug concentrations; Plasma models were adjusted for age, weight, and time since last dose; Endogenous nucleotide models were adjusted for age.

479 A QUANTITATIVE APPROACH TO EVALUATE ARV PROXIMITY TO VIRUS AND CELLS IN LYMPH NODES

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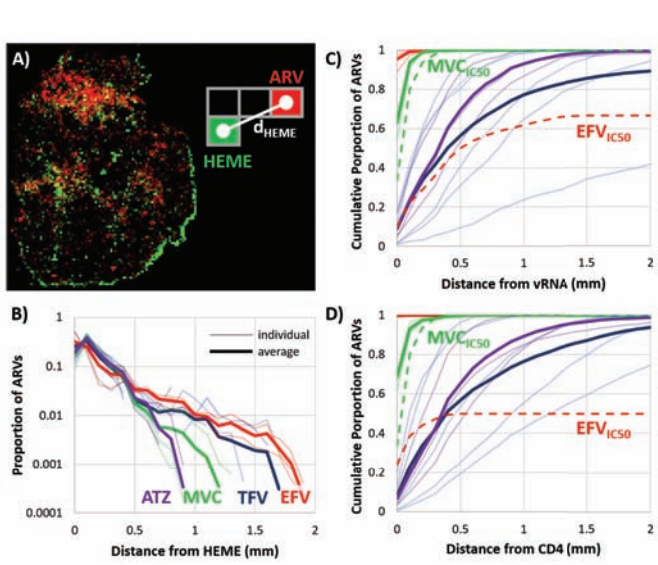
Background: We have previously shown that ARV distribution within lymphoid tissue can be highly heterogeneous. Understanding potential consequences of diverse ARV accumulation requires quantitative methods to characterize ARV proximity to virus and target cells. Here, we developed a novel analytical approach based on a combination of mass spectrometry imaging (MSI), in situ hybridization (ISH) and immunohistochemistry (IHC) to understand the consequences of ARV distribution in lymph nodes (LN).
Methods: Axillary LN were collected and snap frozen at necropsy from RT-SHIV infected rhesus macaques dosed 10 days with emtricitabine (FTC) + tenofovir (TFV) (N=6) in combination with either efavirenz (EFV) + raltegravir (RAL) (N=3), cohort FTER, or maraviroc (MVC) + atazanavir (ATZ) (N=3), cohort FTMA. Tissue accumulation of ARVs and metabolites was measured by infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) MSI from 10 mm thick cryosections at 0.1 mm spatial resolution. Serial sections of tissue were analyzed for viral RNA (vRNA) by RNAscope ISH and for CD4+ cells by IHC. Spatial relationships were evaluated by nearest neighbor search (NNS) on co-registered images using MATLAB (Fig A).
Results: MSI simultaneously measured all detectable ARVs (FTC, RAL < limits of detection: 0.05-0.37 ng/mg tissue) and the blood biomarker, HEME. Based on NNS analysis between ARVs and HEME (reflecting ARV in the vasculature), 57% of all ARVs in LN were ≤0.1 mm from HEME. The greatest tissue penetration was

found for TFV and EFV (up to 1.7 mm from HEME). The degree of colocalization between ARVs and vRNA varied (Fig B. TFV: 1-9%; ATZ: 4-16%; MVC: 54-68%; EFV: 89-99%). Yet NNS analysis indicated that >95% of all vRNA was ≤0.1 mm of a detectable ARV response in each cohort (Fig C). However, proximity of vRNA to ARV concentrations >in vitro IC50 values was farther (vRNA≤0.3 mm: FTER=0-60%; FTMA=88-97%). Similar results were observed for NNS analysis of CD4+ T cells (Fig D. CD4≤0.3 mm: FTER=0-94%; FTMA=96-99%).

Conclusion: A quantitative approach has been developed for analysis of spatial relationships between drug and targets such as blood, virus, and T cells. ARV coverage extends to >73% of the LN, better for CD4 (>64%) than vRNA (>58%), but may not be adequate everywhere relative to known inhibitory concentrations. The flexibility of this framework allows ARVs to be evaluated individually or in aggregate, and offers a tool help optimize pharmacokinetics and pharmacodynamics to ARV treatment.



480 GS-6207, A POTENT AND SELECTIVE FIRST-IN-CLASS LONG-ACTING HIV-1 CAPSID INHIBITOR

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Background: We describe the in vitro pharmacological profile of GS-6207, a first-in-class HIV capsid (CA) inhibitor optimized for long-acting antiretroviral (ARV) treatment administered monthly or less frequently.

Methods: GS-6207 binding to HIV-1 CA hexamer was evaluated by surface plasmon resonance and x-ray crystallography. Antiviral potency and cytotoxicity were assessed in human T-cell lines and primary cells. HIV-1 and -2 laboratory strains and clinical isolates as well as HIV-1 recombinant mutants resistant to other ARV drug classes were used for antiviral profiling. Effect of the multiplicity of infection (MOI) on antiviral potency was tested using a reporter HIV-1. Cytotoxicity was profiled in 4 non-target human cell lines and primary hepatocytes. GS-6207 activity was evaluated in combination with marketed classes of ARVs.

Results: GS-6207 binds with high affinity to CA hexamers (K_D = 0.2 nM) at the interface between two adjacent CA monomers. GS-6207 displays potent and selective antiviral activity in MT-4 cells (EC_{50} = 0.1 nM, CC_{50} = 27 μM) and exhibits a mean EC_{50} of 0.05 nM (0.02 - 0.16 nM) in human PBMCs against 23 HIV-1 clinical isolates spanning all major subtypes. The human serum protein-adjusted EC_{95} for GS-6207 (4 nM) is >10-fold lower than that of efavirenz (EFV), rilpivirine, dolutegravir (DTG) and atazanavir (ATV). In primary human CD4+ T-cells and macrophages, GS-6207 is >10-fold more potent and >22-fold more selective than EFV, DTG and ATV. GS-6207 also suppresses HIV-2 replication. As with other ARVs, GS-6207 antiviral activity decreases with increasing MOI but remains 5- to >100-fold more potent than 4 commonly used ARVs. GS-6207 exhibits low cytotoxicity in 4 human cell lines and primary hepatocytes (CC_{50} > 44 μM) and shows synergistic antiviral activity when combined pairwise with agents from each of 4 marketed ARV classes. Finally, GS-6207 retains full potency against a broad range of HIV-1 mutants resistant to other ARV classes, including those with naturally occurring Gag polymorphisms conferring resistance to maturation inhibitors.

Conclusion: GS-6207 is a novel HIV capsid inhibitor with picomolar potency and a unique resistance and pharmacokinetic (PK) profile that make it a suitable candidate for a low-dose long-acting subcutaneous administration to treat HIV-1 infection, including variants resistant to current ARV therapies. The safety and PK of GS-6207 is now being evaluated in healthy human subjects.

481 MK-8591 POTENCY AND PK PROVIDE HIGH INHIBITORY QUOTIENTS AT LOW DOSES QD AND QW

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Background: MK-8591, a nucleoside reverse transcriptase translocation inhibitor (NRTTI), has demonstrated HIV-1 suppression for ≥ 7 days with single doses as low as 0.5 mg. It is currently in a Phase 2 clinical trial (NCT03272347) for the treatment of HIV-1 infection with once daily (qd) administration of 0.25 mg, 0.75 mg, or 2.25 mg in combination with doravirine. Inhibitory quotients (IQ) for nucleoside inhibitors, based on the ratio of intracellular phosphorylated drug concentrations at trough ($C_{trough,IC}$) and the intracellular concentrations required for efficacy ($IC_{50,IC}$), predict virologic response. We evaluated the IQ of MK-8591-triphosphate (MK-8591-TP) in relation to other NRTIs for WT and NRTI-resistant HIV-1 to assess the likelihood of virologic response and barrier to resistance at clinically relevant doses.

Methods: MK-8591-TP, TFV-DP, 3TC-TP, and FTC-TP $IC_{50,IC}$ levels were determined in activated, uninfected human peripheral blood mononuclear cells (hPBMCs) after 24 hr incubation with varying concentrations of MK-8591, TDF, 3TC, or FTC followed by lysis and analysis by LC-MS/MS. MK-8591 IQs for wild-type (wt) HIV-1 were calculated as the ratio of steady state $C_{trough,IC}$, as observed with qd or weekly (qw) dosing in Phase 1 clinical studies,to the $IC_{50,IC}$ in hPBMCs. TDF, TAF, 3TC, and FTC IQs were calculating using their corresponding $C_{trough,IC}$s, as determined after dosing in humans at clinical dose levels, and hPBMC $IC_{50,IC}$s . IQs for NRTI-resistant HIV-1 were calculated using fold-shifts for NRTI-resistant clinical isolates.

Results: The MK-8591-TP $IC_{50,IC}$ for wt HIV-1 is >4-fold lower than any marketed NRTI. MK-8591 IQs at steady state with 0.25 mg qd and 10 mg qw dosing are 85.3 and 101, respectively, and proportionately greater for higher dose levels. Common NRTI mutations, including M184I/V, thymidine analog mutations, K65R, and K70E, confer low fold-shifts in antiviral potency, and MK-8591 retains greater IQs against these NRTI-resistant viruses than those of TDF, TAF and 3TC with wt virus.

Conclusion: The IQs of MK-8591 for both wt and NRTI-resistant HIV-1 at low qd and qw doses are substantially higher than those of any NRTIs approved for HIV treatment. Coupled with the long intracellular half-life of the MK-8591-TP, these IQs suggest the opportunity for multiple low dosing options with the potential for a high barrier to the development of resistance.

Drug	*Dose Levels*	*Active Form*	*IC_{50} (fmol/10^6 hPBMCs) Mean±SD*	*Steady State Ctrough (fmol/10^6 hPBMCs) Mean (CV%)*	*N*	*IQ (90% CI)*
MK8591	0.25 mg QD	MK8591-TP	9.74±4.06[3]	831 (28.5)	9	85.3 (44.8-126)
	10 mg QW			983 (26)	6	101 (53.1-149)
3TC	150 mg BID/300 mg QD	3TC-TP	635±331[2]	2620 (112)[4,5,6]	68	4.13 (1.47-6.79)
FTC	200 mg QD	FTC-TP	113[1]	4160 (63.7)[7,8,9]	64	36.9 (32.1-41.7)
TAF	25 mg QD	TFV-DP	41.5±19.7[2]	311 (19.8)[11,12]	160	7.48 (3.37 – 11.6)
TDF	300 mg QD	TFV-DP	41.5±19.7[2]	95.0 (59.7)[7,8,10]	63	2.29 (1.00-3.58)

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482 FAVOURABLE OUTCOME OF IN VITRO SELECTIONS WITH NOVEL NRTI PRODRUG GS-9131

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Background: GS-9131 is an NRTI candidate for treatment of patients with resistance to other NRTIs. HIV reverse transcription is inhibited by GS-9131 by chain termination. In this study, we employed cell culture models to shed light on the ability of escape mutants to emerge under increasing drug pressure.

Methods: Cord blood mononuclear cells (CBMC) and MT-2 cells were infected with clinical isolates and passaged in increasing concentrations of GS-9131 and tenofovir (TFV). Virus growth was monitored by weekly determinations of reverse transcriptase (RT) activity. For MT-2 cells, supernatants were collected at the peak of infection by cytopathic effect scoring. In order to identify alterations in the RT region, viral RNA was extracted from tissue culture supernatants and sequenced.

Results: After 40 weeks of sustained drug treatment, none of the CBMC viral cultures tested yielded major resistance mutations. Despite the lack of changes in the RT region, most of the isolates were able to endure moderate to very high concentrations of the drugs, 500-20,000 -fold increase for GS-9131 and 100-20,000 -fold for TDF. Using 3TC as a control, the M184I or V mutations rapidly arose in most viruses. Previous studies with GS-9148, for which GS-9131 is a pro-drug, were done in MT-2 cells, and some resistance patterns were identified. In our experiment using MT-2 cells, no major resistance pathways emerged. One isolate did select for the L187M mutation, which was also identified in the previous study.

Conclusion: Two methods were employed in order to obtain a better picture of the ability of GS-9131, a drug in development, to put pressure on viruses to escape. The lack of emergent variants indicates that GS-9131 is a promising antiretroviral for HIV treatment, which has also been shown to be suitable for individuals harbouring NRTI mutations. Its versatility for use in combination with other drugs may provide more precise and potent options to patients with limitations due to NRTI resistance.

483 LONG-TERM SAFETY & EFFICACY OF FOSTEMSAVIR IN TREATMENT-EXPERIENCED HIV PARTICIPANTS

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Background: Fostemsavir (FTR) is an investigational first-in-class attachment inhibitor prodrug of temsavir (TMR). TMR binds to HIV-1, locking gp120 in a conformational state that prevents initial attachment to and infection of host immune cells. Study 205889 (AI438011, NCT01384734) is a recently completed Phase 2b dose-ranging trial in treatment-experienced (TE) HIV-1-infected participants. Herein, we present efficacy results through Week 192 (latest visit achievable by all participants prior to study conclusion) and cumulative safety data.

Methods: TE adults (≥1-week of prior ART and naïve to integrase inhibitors) were randomized to 1 of 4 FTR arms (400 or 800mg BID; 600 or 1200mg QD) or reference (REF; atazanavir/ritonavir [ATV/r] 300/100mg QD), each with raltegravir (RAL, 400mg BID) and tenofovir (TDF, 300mg QD). After the Week 48 interim analysis, those randomized to FTR switched to open-label FTR at 1200mg QD with RAL+TDF. REF participants remained on ATV/r+RAL+TDF.

Results: 251 adults were treated: 200 FTR, 51 REF. Median time on FTR was 4.5 years (max 5.6); 2.9 years for REF. Rates of virologic suppression (HIV-1 RNA <50 c/mL, Table 1) and mean improvement in baseline CD4 count (+279.9 and +263.7 cells/µl) were comparable between FTR and REF through Week 192. Most adverse events (AEs) were low-grade (Grade 1-2) in intensity. A greater percentage of REF than FTR participants experienced Grade 2-4 AEs related to study drug or Grade 3-4 AEs (39% vs. 12%; 33% vs. 18% respectively). Fewer participants in the FTR arm had an AE leading to discontinuation (4% vs. 12% for REF). No participant discontinued due to a FTR-related AE. There were 3 drug-related SAEs (overdose in FTR arm, and overdose and influenza on REF). The most common drug-related AEs for FTR were headache (6%) and nausea (5%), and for REF were nausea, dizziness (8% each), and AEs related to bilirubin elevation (e.g., jaundice, scleral icterus; 8-18%).

Conclusion: Among HIV-1-infected TE participants, FTR with RAL+TDF demonstrated favorable safety compared to ATV/r with RAL+TDF with lower cumulative rates of Grade 2-4 related AEs, Grade 3 4 AEs, and AEs leading to discontinuation despite longer median exposure (4.5 vs. 2.9 years). FTR had comparable rates of virologic suppression to ATV/r throughout 192 weeks.These results support the ongoing Phase 3 evaluation of FTR in heavily TE adults with limited therapeutic options (≤2 classes of ARVs remaining) due to resistance, tolerability issues or contraindications (NCT02362503).

Table 1 Summary of Proportion of Participants with HIV-1 RNA[a] <50 copies/mL by Visit: Snapshot Analysis and Observed Analysis

Analysis	Timepoint	FTR 600mg QD n=51	FTR 400mg BID n=50	FTR 1200mg QD n=50	FTR 800mg BID n=49	FTR 1200 mg QD Pooled n=200	REF n=51
Snapshot Analysis % (n)	Week 24	76% (39)	80% (40)	72% (38)	69% (34)	--	75% (38)
	Week 48	69% (35)	82% (41)	68% (34)	61% (30)	--	71% (36)
	Week 96[b]	63% (32)	78% (39)	58% (29)	49% (24)	--	57% (29)
	Week 144[b]	--	--	--	--	58% (116)	45% (23)
	Week 192[b]	--	--	--	--	53% (105)	43% (22)
Observed Analysis % (n/N)	Week 24	78% (38/49)	87% (40/46)	79% (34/43)	81% (34/42)	--	83% (35/42)
	Week 48	69% (31/45)	91% (39/43)	79% (33/42)	71% (27/38)	--	85% (35/41)
	Week 96[b]	86% (31/36)	88% (38/43)	97% (29/30)	86% (24/28)	--	90% (28/31)
	Week 144[b]	--	--	--	--	90% (111/123)	92% (23/25)
	Week 192[b]	--	--	--	--	90% (103/115)	96% (22/23)

a. Mean baseline HIV-1 RNA (log10 copies/mL) for the arms was as follows: 4.946 (600mg QD), 4.756 (400mg BID), 4.654 (1200mg QD), 4.848 (800mg BID) and 4.688 (REF)
b. After the Week 48 interim analysis, those randomized to FTR switched to open-label FTR at 1200mg QD with RAL and TDF. The switch to the FTR 1200 mg QD continuation dose took place on a rolling basis.

484 ACTIVITY OF ECD4-IG AGAINST CCR5 ANTAGONIST-RESISTANT HIV-1

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Background: The anti-HIV molecule eCD4-Ig targets CD4 and chemokine coreceptor binding sites of HIV-1 gp120. eCD4-Ig neutralizes a broad range of HIV-1 isolates from various clades, and protects humanized mice and macaques from infection with HIV and SHIV, respectively. To investigate whether eCD4-Ig can neutralize HIV-1 isolates resistant to the CCR5 antagonists maraviroc (MVC) and vicriviroc (VCV) we determined the eCD4-Ig susceptibility of infectious HIV-1 recombinants expressing env from MCV-susceptible and -resistant viruses.

Methods: HIV-1 resistant to VCV and MVC was identified from 3 participants in ACTG protocol A5211, a phase 2 trial of VCV. Infectious recombinant viruses carrying env genes of the paired baseline and MVC-resistant viruses cloned from plasma HIV-1 RNA were generated by transfection into 293T cells together with the recombination vector pNL4-3ΔEnv. Susceptibility to eCD4-Ig, MVC and the CXCR4 antagonist AMD3100 was determined by a standardized drug susceptibility assay on TZM-bl cells. HIV-1 recombinants expressing env from HIV-1 Bal, Hxb2 and 89.6, respectively, served as controls. Susceptibility was expressed as the 50% inhibitory concentrations (IC50) or percent maximum inhibition (PMI).

Results: As reported, VCV and MVC resistance emerged after 24, 103 and 138 weeks of VCV treatment (sub07, sub57 and sub85, respectively). At baseline, the IC50s for MVC ranged from 0.2 to 5.2 nM and IC50s to eCD4-Ig ranged from .07 to 4.3 µg/mL. The PMI for MVC of the paired resistant viruses ranged from 0% to approximately 45% (IC50s could not be calculated). By contrast, susceptibility to eCD4-Ig showed three distinct patterns: unchanged (sub57); increased susceptibility (0.4-fold change in IC50; sub85); and decreased (14.8-fold change in IC50; sub07). By comparison, recombinant viruses expressing env from Bal, Hxb2 or 89.6 ranged from 2-13 ng/mL.

Conclusion: Recombinant HIV-1 resistant to MVC showed disparate patterns of susceptibility to eCD4-Ig, suggesting that mutations conferring resistance to small-molecule CCR5 antagonists affect interactions with the CCR5mim1 sulfonated peptide moiety of eCD4-Ig in different ways. Analysis of additional

HIV-1 isolates with varying susceptibility to CCR5 antagonists and eCD4-Ig may help refine our understanding of the interaction between this promising novel HIV-1 entry inhibitor and the CCR5mim1 binding domain on gp120.

485 IBALIZUMAB: 96-WEEK DATA AND EFFICACY IN PATIENTS RESISTANT TO COMMON ANTIRETROVIRALS

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Background: Ibalizumab (IBA) is a CD4-directed post-attachment HIV-1 inhibitor that binds to the CD4 domain 2 and blocks viral entry into host cells without immunosuppression. Here, we report the efficacy outcomes of IBA with OBR in patients resistant and susceptible to two widely used antiretrovirals (ARV), dolutegravir (DTG) and darunavir (DRV) as well as the the long-term safety and efficacy through 96 weeks of treatment.
Methods: In TMB-301, heavily treatment-experienced patients with MDR HIV-1 received an intravenous loading dose of 2000 mg followed by 800 mg doses every 2 weeks up to Week 25. An OBR with at least 1 additional sensitive agent was added 7 days after the loading dose. Following completion of the TMB-301 study, eligible patients continued to receive IBA at 800 mg every 2 weeks under TMB-311 for up to 96 weeks.
Results: Among the 40 enrolled patients in TMB-301, 18 (45%) had DTG resistance, of which 11 had major DTG resistance mutations (Q148 plus additional mutations). Of 18 DTG resistant patients, 10 received DTG in their OBR while 16 of 22 DTG susceptible patients received DTG as OBR. Twenty-seven patients (68%) had DRV resistance. DRV was included as OBR in 26 patients: 18 with DRV resistant HIV and 8 with DRV susceptible HIV. Long-term results were obtained for 27 patients who continued to receive treatment in study TMB-311, of which 22 (82%) completed treatment up to 96 weeks. The reasons for 5 discontinuations were death (2 patients) consent withdrawal (2 patients) and physician decision – all 5 were non IBA-related. IBA plus OBR was well tolerated with no new safety concerns emerging between Week 25 and 96. For these 27 patients, median viral load (VL) reduction from Baseline (of TMB-301) was 2.5 log10 at Week 25 and 2.8 log10 at Week 96 in the Intent-to-Treat-Missing-Equals-Failure analysis. Of 16 patients with HIV RNA <50 copies/mL at Week 25, 14 maintained viral suppression through Week 96, with one additional patient achieving viral suppression by Week 96. Median CD4+ T cell increase was 42 cells/µl from Baseline to Week 25 (n=27), and 45 cells/µl at Week 96 among those who remained on study (n=22).
Conclusion: Safety and efficacy of IBA observed at Week 25 in the Phase 3 trial were maintained through 96 weeks for patients continuing on treatment. IBA is an effective, safe and durable treatment for MDR HIV-1 infected patients.

	DTG Resistant	DTG Susceptible	DRV Resistant	DRV Susceptible
Overall Susceptibility Score	1.1	2.1	1.2	2.5
>0.5$\log_{10}$ VL reduction - Day 14	78% (14/18)	86% (19/22)	81% (22/27)	85% (11/13)
>0.5$\log_{10}$ VL reduction - Week 25	44% (8/18)	82% (18/22)	67% (18/27)	62% (8/13)
Median VL reduction - Day 14	1.0 $\log_{10}$	1.1 $\log_{10}$	1.2 $\log_{10}$	1.0 $\log_{10}$
Median VL reduction - Week 25	0.2 $\log_{10}$	2.7 $\log_{10}$	1.8 $\log_{10}$	1.7 $\log_{10}$
<50 copies/mL - Week 25	22% (4/18)	59% (13/22)	44% (12/27)	39% (5/13)
<200 copies/mL - Week 25	28% (5/18)	68% (15/22)	52% (14/27)	46% (6/13)

486 PRO 140 SC: LONG-ACTING, SINGLE-AGENT MAINTENANCE THERAPY FOR HIV-1 INFECTION

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Background: The development of a monoclonal antibody (mAb) as a long-acting, single-agent maintenance therapy (SAMT) represents a major milestone in the treatment of HIV-1 infection. PRO 140 (humanized CCR5 mAb) demonstrates potent antiviral activity as a SAMT for >4 years as a weekly subcutaneous injection (SC) in patients infected exclusively with CCR5-tropic HIV-1 (Dhody, K. et al. (2018). HIV Clin Trials 19(3):85-93). In addition, PRO 140 presents a high genetic barrier to block HIV-1 entry, favorable tolerability, and limited drug-drug or -food interactions.
Methods: PRO 140_CD03 (N=350) is a three part, phase 2 study enrolling virally suppressed HIV-1 patients with CCR5-tropic HIV-1 receiving combination antiretroviral (cART) therapy. Patients received weekly doses of PRO 140 on SAMT following one week of overlap of the existing cART regimen that is then discontinued. In part 1, 156 participants received 350 mg PRO 140 SC in a single-arm design. In part 2, 147 participants received 350 or 525 mg PRO 140 SC in a 1:1 ratio as randomized controlled, two-arm study. In an ongoing part 3, 47 participants are to be randomized to receive 525 or 700 mg PRO 140 SC in a 1:1 ratio.
Results: Of the 327 patients enrolled, median age was 51 yrs (21-77) with the majority reported as male (79%) and 37% were non-white. On average, participants were diagnosed with HIV-1 infection for 16.8 yrs and were on cART regimen for 14.8 yrs. This abstract focuses on preliminary results from patients randomized 1:1 to 350 mg (N=73) or 525 mg (N=74) PRO 140 SC on SAMT. While the study is ongoing, a key interim finding from 147 patients (4-48 weeks on SAMT) indicate that an odds ratio of 4.43 for the virologic response rates with 525 mg compared with 350 mg PRO 140 SC. Virologic failure is defined as two consecutive plasma HIV-1 RNA levels of ≥200 c/mL. The frequency and severity of injection site reactions were comparable between the three dose groups and the incidence or severity of injection site reactions was not increased in patients receiving higher doses. Overall, PRO 140 SC was generally well tolerated at all dose levels in this study.
Conclusion: Higher doses of PRO 140 SC are required to maintain virologic suppression on SAMT in the majority of patients infected exclusively with CCR5-tropic HIV-1. After testing both 350 mg and 525 mg, 700 mg of weekly PRO 140 SC is currently underway and will be presented. PRO 140 SC has the potential as a SAMT for long-term suppression of HIV-1 replication.

487 IN SILICO SIMULATION OF LONG-ACTING TENOFOVIR ALAFENAMIDE SUBCUTANEOUS IMPLANT

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Background: Subcutaneous implants support the long-acting delivery of drugs, circumventing non-adherence issues with daily oral regimens. The aim of this study was to simulate pharmacokinetic (PK) profiles of tenofovir alafenamide (TAF) subcutaneous implants for HIV pre-exposure prophylaxis using physiologically-based pharmacokinetic (PBPK) modelling.
Methods: A subcutaneous mechanistic modelling approach was integrated into a previously published whole-body PBPK model using Simbiology 2018a. The model was qualified against available PK data of oral TAF at steady state (GS-US-320-1382). The PBPK model was assumed to be qualified if the mean simulated values were within ± 50% from the mean observed values as per convention. TAF subcutaneous implants were simulated in five hundred virtual healthy women (average BMI – 29.2 kg/m^2) for 28 consecutive days and the area under the plasma concentration curve (AUC) and average plasma concentration (C_{avg}) were described. PK of plasma TAF and tenofovir, tenofovir diphosphate (TFV-DP) in peripheral blood mononuclear cells (PBMCs), and TFV-DP in cervical and rectal tissues were simulated considering data from clinical studies. TAF PK from the subcutaneous implant was simulated with zero-order release rates between 0.5-0.8 mg/day. TFV-DP concentrations of 48 fmol/10^6 PBMCs was considered as the target trough concentration.
Results: AUC and C_{avg} of plasma TAF/TFV and PBMC TFV-DP concentrations resulting from administration through subcutaneous implants at different zero-order release rates are shown in the table. Our simulations indicate that TAF subcutaneous implant with a minimum release of 0.6 mg/day will support sustained TFV-DP concentrations well above the target concentration of 48 fmol/10^6 cells. The TFV-DP cervical and rectal concentrations ranged between 1.47 – 2.44 fmol/10^6 cells and 0.95 – 1.57 fmol/10^6 cells, respectively between the release rates of 0.5 – 0.8 mg/day.
Conclusion: These data inform the possible dosing and release rate needed for TAF such that the simulated PBMC TFV-DP concentrations remained over the target concentrations. A 2.5mm x 40mm implant rod, like that of contraceptive implants, containing 120 mg of TAF and delivering at 0.6 mg/day could provide protective levels for over 6-months. TAF subcutaneous implants may represent a valuable strategy to address issues arising from sub-optimal adherence to oral regimens, and may find application in HIV prevention.

Release rate	Compound	Simulated AUC (ng.h/ml)	Simulated C_{avg} (ng/ml)
0.8 mg/day	TAF, plasma	430 ± 41.9	0.641 ± 0.062
	TFV, plasma	598 ± 58.2	0.892 ± 0.087
	TFV-DP, PBMCs‡	-	79.7 ± 46.1
0.7 mg/day	TAF, plasma	374 ± 37.5	0.557 ± 0.056
	TFV, plasma	520 ± 52.1	0.775 ± 0.078
	TFV-DP, PBMCs‡	-	70.5 ± 41.1
0.6 mg/day	TAF, plasma	321 ± 32.1	0.479 ± 0.048
	TFV, plasma	446 ± 44.6	0.666 ± 0.067
	TFV-DP, PBMCs‡	-	58.3 ± 32.6
0.5 mg/day	TAF, plasma	269 ± 27.2	0.401 ± 0.040
	TFV, plasma	374 ± 37.8	0.558 ± 0.057
	TFV-DP, PBMCs‡	-	47.6 ± 27.2

Values are represented as mean ± standard deviation. AUC is measured for 28 days (672 hours) subsequent to implant administration. ‡ Intracellular concentrations representec in fmol/10^6 cells. TAF – tenofovir alafenamide, TFV – tenofovir, TFV-DP – tenofovir diphosphate, PBMCs – peripheral blood mononuclear cells

488 LONG-ACTING EMTRICITABINE PRODRUGS PROVIDE PROTECTION FROM HIV INFECTION IN VIVO

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Background: Antiretroviral drugs are predominantly administered orally for both therapy and pre-exposure prophylaxis (PrEP). Despite ease of administration, oral delivery is prone to patient non-adherence exacerbated for some drugs by pill fatigue and gastrointestinal intolerance. By decreasing frequency of administration, long-acting injectable (LAI) medications are effective strategies to circumvent these issues. We report here a preclinical assessment of LAI semi-solid prodrug nanoparticle (SSPN) formulations of novel emtricitabine (FTC) prodrugs to prevent HIV infection.
Methods: SSPNs of FTC carbamate/carbonate prodrugs were generated using a proprietary emulsion-templated freeze-drying technology. 2 lead formulations were tested for their ability to prevent HIV infection in NSG-cmah$^{-/-}$ mice humanised by CD34+ cell transplantation. Animals received 140 mg/kg FTC equivalent (SSPN 9 or 10) via 2 intramuscular injections vs an untreated control (n= 7-6 per group). At days 7 and 14 mice were challenged intraperitoneally with a 103 TCID50 dose of HIVADA. Animals were sacrificed at 28 days post infection. Plasma samples were taken for determination of viral load (VL). Tissue samples were collected for viral RNA and proteins detection via RT-PCR and immunohistology.
Results: Mice treated with SSPN 9 and 10 demonstrated undetectable VL (700 copies/mL detection limit), and HIV RNA remained undetectable 28 days post infection in plasma, spleen, lung and liver in all animals for the 7 challenge. Following 14-day challenge, mice treated with SSPN 9 demonstrated undetectable HIV in plasma and all tissues. Mice treated with SSPN 10 demonstrated 2 mice had detectable plasma VL (4.77 x 10^3 copies/mL) and 3 mice showed presence of HIV RNA in plasma and proteins in spleen, lung and liver in day 28. HIV was detectable in all untreated animals.
Conclusion: The data presented here demonstrate both formulations were 100% effective at preventing HIV infection 7 days post LAI administration. Following 14 days SSPN9 prevented HIV infection in 100% of mice while SSPN 10 prevented infection in 50% of mice. These data indicate great potential for delivering FTC via LAI and the approach may support LAI development for PrEP. Further studies will aim to optimise formulations to produce exposure beyond 14 days and to assess applications in therapy as part of a combination.

489 PRODRUGS EXTEND THE HALF LIFE AND POTENCY OF CABOTEGRAVIR

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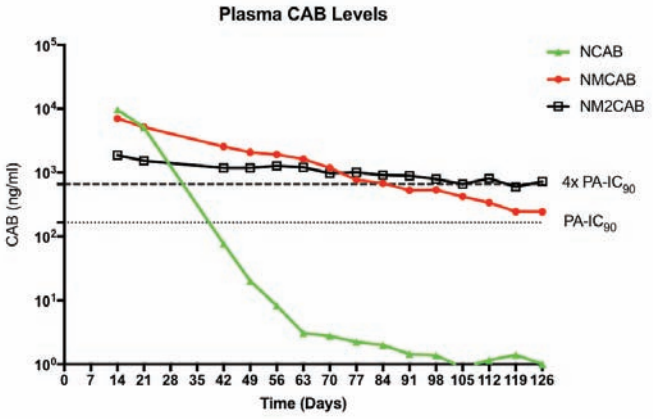
Background: Prevention of new infections, reduction in transmission rates and management of chronic infection characterize once a month dosing of the current long acting cabotegravir (CAB). Previously we demonstrated that potency, bioavailability and tissue distribution of CAB can be improved up to 3-fold by myristoylation, increasing drug lipophilicity. This extended PA-IC_{90} up to 3 months in Rhesus macaques after a single 45 mg/kg CAB equivalent intramuscular (IM) injection. We now report stearoylation of CAB (termed M2CAB) designed to reduce dosing frequency while improving viral reservoir targeting and drug activity.
Methods: We reacted CAB with stearoyl chloride in anhydrous dimethylformamide using N,N-diisopropylethylamine base under argon. The created M2CAB ester was purified by silica column chromatography and characterized by ^{1}H-NMR and FTIR spectroscopy. Nanoparticles were produced by high pressure homogenization (NM2CAB). Human monocyte derived macrophages (MDM) were used as a biological platform to measure drug uptake and retention. Drug levels were quantitated in cell lysates by UPLC-TUV. After MDM treatment with 100 µM NM2CAB cells were challenged with HIV-1_{ADA} at a MOI of 0.1 at five day intervals for one month. Culture fluids were assayed for reverse transcriptase activity and cell-based HIV-1p24 antigens recorded by immunohistochemistry. Female NSG mice were injected with 45 mg/kg CAB equivalents of NCAB, NMCAB and NM2CAB (unmodified CAB, first and second generation prodrug nanoformulatios). Plasma was collected weekly after injection and CAB and prodrug levels were analyzed.
Results: NM2CAB, NMCAB and CAB LAP (referred to as NCAB) uptake in MDM was 57, 44 and 2 nmol/10^6 cells over 24 hours. Only NM2CAB was retained in MDM (levels of 8 nmol/10^6 cells) at the end of one month. NM2CAB antiretroviral activity in MDM was observed over 30 days compared to 15 and 1 day for NMCAB and NCAB respectively. After a single 45 mg/kg CAB equivalent IM injection of NM2CAB in mice, plasma CAB levels were consistently 4 times PA-IC_{90} for 4 months compared to 2.5 and 1 month for NMCAB and NCAB.
Conclusion: The hydrophobicity and sustained slow hydrolysis of prodrug M2CAB facilitate NM2CAB to harness the injection site as a primary drug depot as well as macrophages and other tissues as secondary drug depots for months. This can potentially reduce frequent dosing and injection volume improving patient adherence to antiretroviral therapy.



490 HIV REPLICATION AT <40C/ML FOR DTG+3TC VS DTG+TDF/FTC IN THE GEMINI 1 & 2 STUDIES

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Background: The GEMINI-1&2 studies in treatment-naïve adults with screening HIV-1 RNA ≤500,000c/mL showed dolutegravir+lamivudine (DTG+3TC, 2DR) was non-inferior to dolutegravir+tenofovir disoproxil/emtricitabine (DTG+TDF/FTC, 3DR) at Week 48 by FDA snapshot algorithm; 91% (655/716) in the 2DR group versus 93% (669/717) in the 3DR group achieved HIV-1 RNA <50c/mL. Abbott RealTime HIV-1 assay used in the studies measures viral load (VL) from 40c/mL to 10,000,000c/mL, and provides qualitative target detected (TD) or target not detected (TND) for VL<40c/mL. Clinical and subject management implications of more stringent low level VL data needs clarification. We assessed the proportion of participants with TND over time and by baseline (BL) VL for 2DR versus 3DR.
Methods: Subjects were randomised 1:1 to treatment with 2DR or 3DR. The proportion of subjects with HIV-1 RNA <40 c/mL and TND status at Week 48 was analysed using a Cochran-Mantel-Haenszel test stratified by plasma HIV-1 RNA (≤100,000 vs >100,000 copies/mL) and CD4+ cell count (≤200 vs >200 cells/mm3) at BL. Proportion of subjects with TND Status were summarised by Visit and at Week 48 by BL HIV-1 RNA Subgroup. Time to Plasma HIV-1 RNA <40 c/

mL and TND Status Overall and by BL HIV-1 RNA Subgroup were estimated using non-parametric Kaplan-Meier method.

Results: At Week 48 similar proportion of subjects had snapshot TND in the 2DR and 3DR arms (77% [553/716] vs 73% [525/717], adjusted difference 3.8%, 95% CI -0.6%, 8.2%) and proportions were also similar at earlier visits: Weeks 4 (34% vs 32%), 8 (52% vs 49%), 12 (60% vs 57%), 16 (59% vs 56%), 24 (65% vs 63%), and 36 (65% vs 68%). While similar response rates were seen in subjects with BL VL ≤100,000c/mL, response rates were higher in 2DR vs 3DR subjects with BL VL >100,000 c/mL. (Table). Median time for 2DR vs 3DR to TND was 57 days for both overall, 57 days for both in ≤100,000c/mL at BL strata, and 113 days vs 169 days for BL >100,000c/mL subgroup.

Conclusion: DTG/3TC and DTG+TDF/FTC had similar proportions of TND by snapshot at all Weeks. Snapshot response rates based on TND status at Week 48 were similar between arms at ≤100,000c/mL BL subgroup and higher for DTG/3TC in >100,000c/mL BL category. Median time to TND was similar overall and in BL VL≤100,000c/mL subgroup, and less for DTG/3TC vs DTG+TDF/FTC if >100,000c/mL at BL. These data, utilizing a more stringent snapshot criteria, continue to demonstrate the effectiveness and potency of DTG+3TC in treatment-naïve subjects.

Table. Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL and TND at Week 48 (Snapshot Analysis) by Baseline Plasma HIV-1 RNA Levels

Baseline VL strata (c/mL)	DTG + 3TC n/N(%)[a]	DTG + TDF/FTC n/N(%)[a]	Treatment difference[b]
≤100,000	463/576 (80)	446/564 (79)	1.3 (–3.4 to 6.0)
>100,000	90/140 (64)	79/153 (52)	12.7 (1.4 to 23.9)
>250,000	25/51 (49)	20/46 (43)	5.5 (–14.3 to 25.4)
>400,000	5/18 (28)	6/24 (25)	2.8 (–24.2 to 29.8)

[a] - Number Responded/Number Assessed (%); [b] - Unadjusted proportion of DTG+3TC - proportion of DTG+TDF/FTC (95% CI). >250,000c/mL and >400,000c/mL are subgroups of >100,000c/mL.

491 RESIDUAL HIV-1 RNA, HIV-1 DNA, AND DRUG PLASMA CMIN IN DUAL DTG+3TC, ANRS 167 LAMIDOL

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Background: The aim of this study was to assess HIV cellular reservoir size, plasma residual viremia and drug plasma concentrations in virologically-suppressed patients receiving a dual-class therapy: DTG+3TC.

Methods: Patients were those included in the ANRS 167 LAMIDOL, a non comparative open-label, single arm, multicenter trial. HIV total DNA was measured at D0 and W48 of DTG+3TC using real-time PCR (Biocentric®; limit of quantification [LOQ]=10 c/PCR). Ultra-sensitive plasma viral load (USpVL) was measured to assess plasma residual viremia at D0, W24 and W48. The maximum volume of available plasma was centrifuged, the pellet was resuspended, and USpVL was determined using COBAS® HIV-1, v2.0. The LOQ depended on the available volume of plasma (3 c/mL in 90% of cases). USpVL was considered to be below the limit of detection (LOD) when no PCR signal was detected. The evolution of the USpVL over time was analyzed using a linear mixed effects model. The relationship between HIV DNA and USpVL was studied using linear regression. Total and unbound plasma DTG concentrations (Cmin) were measured using UPLC-MS/MS.

Results: Paired D0 and W48 HIV total DNA results were obtained in 100 patients. Two and four patients showed HIV DNA below the LOQ at D0 and W48, respectively. Median (IQR) HIV DNA was 2.49 log10 c/106 PBMC (2.17-2.95) at D0 and 2.52 (2.09-2.89) at W48 (p=0.28). Plasma residual viremia was measured in 101, 101 and 99 patients at D0, W24 and W48 of DTG+3TC, respectively. The proportion of patients with USpVL

Conclusion: No change was observed, during the first year of DTG+3TC maintenance dual therapy, in plasma residual viremia level or in HIV cellular reservoir size with stable plasma DTG Cmin. As described under triple-class therapy, we observed a positive relationship between plasma residual viremia and HIV cellular reservoir size under the maintenance DTG+3TC dual therapy.

Virology	D0 (n=101)	W24 (n=101)	W48 (n=99)
USpVL < LOD	38%	41%	49%
LOD < USpVL < LOQ	30%	30%	21%
USpVL > LOQ	32%	29%	30%
Pharmacology Median (IQR25-75%)			
Total DTG Cmin (ng/mL)	1677 (1301-2224 ; n=87)	1815 (1322-2227 ; n=93)	1710 (1237-2216 ; n=88)
Unbound DTG Cmin (ng/mL)	3.6 (2.7-5.1 ; n=85)	3.6 (2.6-5.2 ; n=92)	3.4 (2.3-5.0 ; n=88)

Table 1: Description of the ultra-sensitive plasma viral load and DTG plasma Cmin during the ANRS167 LAMIDOL trial

492 IMPACT OF DUAL THERAPY ON THE CD4/CD8 RATIO IS SIMILAR TO TRIPLE THERAPY AT 48 WEEKS

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Background: The requirement for lifelong ART for HIV infection has highlighted interest in dual therapy (DT) to minimize cumulative drug exposure. One of the enduring concerns regarding DT is its impact on markers of immune dysfunction and its potential clinical implications. A recent retrospective study suggests that when compared with triple therapy (TT), DT regimens might decrease the CD4/CD8 ratio. A low CD4/CD8 ratio has been associated to an increase in non-AIDS associated events, and thus warrants further investigation in patients treated with DT

Methods: Sub-analysis of the GARDEL and ANDES randomized controlled trials, both based on ritonavir-boosted protease inhibitors (bPI) plus 3TC. Patients' CD4/CD8 ratios were compared between DT and TT arms at baseline and at 12, 24, 36 and 48 weeks. Follow-up was censored at any of the following: virological failure, opportunistic infection, severe disease (defined as requiring hospitalization) or pregnancy. Main outcomes were median CD4/CD8 ratio and proportion of patients achieving a CD4/CD8 ratio >1, both measured at 48 weeks of follow-up. Subgroup analysis of patients >50 years of age, baseline CD4 count <200 cells/ml, HIV viral load >100,000 copies/ml and bPI treatment were performed. Comparisons were made utilizing regression to the median and multilevel models. Analyses were performed with STATA v12.0.

Results: All 571 patients from both studies were included (292 with DT and 279 with TT). 268 with DT and 243 with TT completed 48 weeks of follow-up. DT had no statistically significant difference when compared to TT on the median CD4/CD8 ratio at 48 weeks of follow-up (0.632 vs 0.617, p=0.729) or on the proportion of patients that achieved a CD4/CD8 ratio >1 (17.9% vs 19.3%, p=0.678). Median increase in CD4/CD8 ratio from baseline to week 48 was similar between both groups (0.273 vs 0.261, p=0.125). The rest of the subgroup analysis showed no further differences

Conclusion: With the recently reported virologic success of DT regimens, addressing its long-term impact on immune markers remains an important subject. These results show that the impact of DT regimens on the CD4/CD8 ratio is similar to that of TT during the first year of treatment. Longer follow-up of larger populations of patients on DT should address the rates of non-AIDS associated events related to these regimens. Also, these results should be confirmed in InSTI-based DT

Table 1. CD4/CD8 ratios after dual or triple ART						
Weeks	Median CD4/CD8			Proportion with CD4/CD8 ratio >1		
	Dual therapy	Triple therapy	P value	Dual therapy	Triple therapy	P value
0	0.337 (0.202-0.479)	0.333 (0.240-0.500)	0.690	12 (4.12)	10 (3.62)	0.758
12	0.462 (0.313-0.702)	0.463 (0.328-0.694)	0.960	28 (10.07)	24 (9.16)	0.720
24	0.545 (0.367-0.784)	0.523 (0.365-0.750)	0.656	32 (11.72)	37 (14.34)	0.370
36	0.592 (0.408-0.846)	0.600 (0.398-0.898)	0.882	38 (14.07)	49 (20.08)	0.070
48	0.632 (0.425-0.879)	0.617 (0.415-0.905)	0.937	48 (17.91)	47 (19.34)	0.678

493 FACTORS ASSOCIATED WITH THERAPEUTIC FAILURE OF 2-DRUG REGIMENS, DAT'AIDS COHORT

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Background: 2 Drug Regimens (2DRs) are becoming a key strategy in maintenance therapy to spare antiretroviral (ARV) classes, decrease toxicities and minimize drug-drug interactions. Data in real life setting are scarce and most often limited to small sample size and short time follow-up. We investigated factors associated with therapeutic failure on the most frequently prescribed 2DRs in the large French National Dat'AIDS cohort (NCT02898987).

Methods: HIV1-infected adult patients starting a 2DR as a switch strategy (plasma HIV RNA (pVL) <50c/ml) between 2010 and 2017 were included in a retrospective analysis. Most frequent 2DRs were selected: dolutegravir/rilpivirine (DTG/RPV), raltegravir/etravirine (RAL/ETR), DTG/xTC, darunavir/ritonavir/RAL (DRV/RAL) and DRV/xTC. Primary objective was to investigate the associated factors with virologic failure (VF) defined as 2 consecutive pVL>50c/ml and occurrence of adverse events (AE). A Cox proportional hazards model adjusted on socio-demographic, immuno-virologic and ARV history-related variables was used for analyses.

Results: Overall, 3484 patients receiving 2DR were included: DTG/RPV (n=974, 28%), RAL/ETR (n=869, 25%), DTG/xTC (n=677, 19%), DRV/RAL (n=604, 18%) and DRV/xTC (n=360, 10%). Characteristics of patients on 2DR are presented in the table. Treatment interruptions occurred in 1178 cases due to AE (n=417, 12%), simplification (n=245, 7%), VF (n=122, 3.5%) and miscellaneous reasons (n=394, 11.3%). Treatment interruptions for AE and VF occurred in 12% and 2% of cases in the DTG/RPV group, 10% and 12% in RAL/ETR, 9% and 6% in DTG/xTC, 17% and 6% and in DRV/r/RAL and 14% and 3% in DRV/r/xTC, respectively. In multivariate analysis, factors associated with VF were zenith pVL> 5 log10 c/mL (HR 1.85 [CI95 1.27-2.74], duration of undetectable pVL < 12 months (HR 2.29 [1.45-3.63]), history of VF (HR 1.63 [1.09-2.46]), and treatment with RAL/ETR (HR 1.85 [1.05-3.27]).

Conclusion: In this large cohort, 2DRs were prescribed mostly to an aging and highly experienced population and show a high efficacy as a switch strategy with a low rate of virologic failure. These results confort the place of 2DRs in maintenance strategies.

Table: Characteristics of patients receiving a 2DR

	DTG/RPV	RAL/ETR	DTG/xTC	DRV/RAL	DRV/∩TC
N	974	869	677	604	360
Age, years (yrs.), med. (IQR)	54 (44,62)	54 (49,61)	53 (45,61)	52 (46,59)	49 (42,59)
Male, %	68.2	71.0	69.4	68.4	59.7
HBV/HCV co-infection, %	19.5	19.6	17.4	23.0	23.6
CDC Stage C, %	71.7	67.7	81.1	60.4	72.8
Nadir CD4 <200/mm3, %	51.1	55.9	32.6	63.8	45.8
Zenith pVL >5 log10 c/mL, %	55.1	53.4	57.5	48.8	58
Time of HIV infection, yrs., med. (IQR)	20 (12,26)	21 (15,25)	15 (7,23)	19 (14,24)	14 (7,21)
History of VF, %	40	48	20	51	36
Undetectable pVL < 12 months, %	6.6	6.7	6.6	18	16.7
Duration of 2DRs, months, med. (IQR)	13 (5,24)	23 (10,37)	11 (4,23)	24 (10,48)	13 (4,30)

494 EFFECTS OF ART SIMPLIFICATION IN THE SPANISH AIDS RESEARCH NETWORK, CORIS

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Background: The number of drugs needed to maintain lifelong HIV RNA suppression is currently debated. We aimed to compare the effects of ART simplification strategies on the risk of virological failure in CoRIS.

Methods: We selected ART-naive patients initiating triple ART from 2004 to 2017 in CoRIS who achieved undetectable viral load in the first 48 weeks of ART and either remained in triple therapy during their entire follow-up or were subsequently simplified to dual or monotherapy. The outcome was virological failure, defined as at least two consecutive viral loads >50 copies/ml. The type of regimen (triple, dual or mono) and time on regimen were analyzed as time-varying covariates. We calculated cause-specific cumulative incidence curves and used multivariate Cox proportional hazards models adjusted for potential confounders to estimate hazard ratios (HR). The proportional hazards assumption was checked graphically and by tests based on Schoenfeld residuals. HR were calculated for <24 and ≥24 months of ART to meet the proportional hazards assumptions.

Results: From 14458 patients, 8416 met the inclusion criteria; 7665 remained in triple therapy, 424 switched to dual therapy and 327 to monotherapy. At baseline, subjects who remained in triple therapy were more likely to be men, younger, HCV negative, HBs antigen positive, showed higher pre-ART CD4 counts and initiated ART more recently than those who switched to dual or monotherapy (all P<0.05). The median time from enrolment to censoring date was 4.9, 6.9 and 8.4 years in the triple, dual and monotherapy groups, respectively (P<0.001). In the dual and monotherapy groups, the median time of regimen maintenance was 1 and 1.3 years, and 15% and 34% switched to triple therapy during follow-up, respectively. After adjustment for potential confounders, ART simplification was associated with greater risk of virological failure after 24 months from simplification (P=0.003), which was driven by higher risk in the monotherapy group.

Conclusion: Conclusions: In this large cohort representative of a real-life setting, we found that the durability of the simplified ART regimens was limited and, compared to triple therapy, monotherapy was associated with greater risk of virological failure in the monotherapy group, with no significant differences between dual and triple therapy. While additional information on long-term outcomes is needed, our results are consistent with the data reported in clinical trials.

Outcome	Group	No. Events/persons-year	Adjusted HR (95% CI)	p-value
Virological failure First 24 month of ART	Triple	532/13623	Ref.	0.73
	Dual	7/409	0.91 (0.30-2.78)	
	Mono	36/421	1.26 (0.50-3.19)	
Virological failure After 24 months of ART	Triple	300/17446	Ref.	0.003
	Dual	2/127	1.55 (0.37-6.40)	
	Mono	13/315	2.92 (1.56-5.43)	

Cox proportional hazards models adjusted for *sex, age, transmission group, educational level, country of origin, CD4+ cell count, CD4/CD8 ratio, HIV-1 viral load, AIDS, HCV serostatus, HBsAg positivity, and year of ART initiation.*

ART regimens
Triple therapy: 2NRTI+1PI; 2NRTI+INSTI; 2NRTI+NNRTI
Dual therapy: DTG+RPV (143), 3TC+bDRV (104), 3TC+bATV (75), 3TC+DTG (56), CAB+RPV (25, excluded in sensitivity analysis without changes in the adjusted HR and P values), 3TC+bLPV (21)
Monotherapy: bDRV (241), bLPV (86)

495 DISCONTINUATIONS & VIROLOGIC RESPONSE IN LATE PRESENTERS WITH InSTI- OR PI-BASED ART

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Background: Active opportunistic infections and/or low CD4+T-cell (CD4+) counts are exclusion criteria in most clinical trials. Late presenters (LP) are therefore inadequately represented in studies comparing efficacy of antiretroviral regimens, leading to a lack of data on optimal treatment options. Our study aimed to investigate the efficacy and safety of first line ART with integrase-inhibitor (INSTI) or protease-inhibitor (PI) based regimens in patients with low CD4+ counts and/or an AIDS-defining disease.

Methods: We conducted a retrospective, multicenter analysis to investigate discontinuation rates and clinical outcome in patients with a CD4 cell count <200/µL and/or an AIDS defining disease after starting first line ART. Data were collected in three European HIV clinics: Universityhospital Frankfurt, Kings College London and Hospital Fundación Jiménez Díaz Madrid. All patients with CD4<200/µL and/or an AIDS defining disease who started INSTI or PI-based first line ART between January 2014 and December 2016 were included in this study. Proportions of those discontinuing ART and with adverse events were compared using univariate analysis. Virologic response was analyzed by using FDA snapshot analysis (HIV-1 RNA <50 copies/mL at week 48).

Results: A total of 218 LP were included in the study, 13.8% women, 23.8% non-European ethnicity with a mean (SD) baseline CD4 91/µL (112) and CD4/CD8 ratio of 0.11 (0.19). 131 LP were started on INSTI-based regimen and 87 on PI`s. Between-group differences are presented in table 1. Those commenced on PI were more likely to be older; 91.8% of the INSTI and 92.4% of PI treated patients had a viral load <50 copies/mL at week 48, discontinuation rates due to adverse events were 3.4% in the INSTI and 8.1% in the PI group respectively. No significant differences in discontinuation rates were observed at week 12 or 48 between INSTI and PI-based regimens (p=0.78 and 0.47 respectively). Virologic response was equally good in those receiving integrase or protease inhibitors (91.8% vs. 92.4%; p = 0.88; odds ratio (95% CI) 1.05 (0.38– 2.82).

Conclusion: In a European cohort of LP starting first line INSTI or PI based ART regimens, there were no significant differences in discontinuation rates or virologic response at week 48. Our results indicate that the choice between INSTI and PI can be made on an individual basis of the patient presenting late for first line ART. Future research will focus on the identifying factors associated with regimen selection in this cohort.

Variable	Integrase Inhibitors (n = 131)	Protease Inhibitors (n = 87)	P
Age (years; mean ± SD)	43 ± 15.5	53 ± 16.7	**0.016**
Sex (% male/female)	84.7 / 15.3	88.5 / 11.5	0.429
n / % of non-European origin	26 / 19.8	26 / 29.9	0.192
Baseline CD4 /µL (mean ± SD)	103 ± 137	90 ± 109	0.144
Baseline CD4 / CD8 ratio (mean ± SD)	0.12 ± 0.16	0.10 ± 0.18	0.309
Week 48 CD4 /µL (mean ± SD)	360 ± 205	315 ± 216	0.412
Week 48 CD4 / CD8 Ratio (mean ± SD)	0.33 ± 0.17	0.31 ± 0.20	0.679
Baseline Viral load (mean copies/mL ± SD)	329200 / 10910	115700 / 33980	0.665
Week 48 Viral load < 50 copies n / %	113 / 86.2	71 / 81.3	0.444
Mortality (n / %; week 12)	1 / 0.8	2 / 2.3	0.341
Mortality (n / %; week 48)	3 / 2.29	3 / 3.44	0.679
Discontinuation at week 12 (n / %)	23 / 17.6	14 / 16.1	0.778
AE's* at week 12 (n / %)	28 / 21.3	21 / 24.1	0.593
Discontinuation due to AE at week 12 (n / %)	8 / 6.2	6 / 7.1	0.816
Discontinuation at week 48 (n / %)	41 / 32.0	32 / 36.8	0.471
Virologic failure at week 48 (n / %)*	11 / 8.2	6 / 7.6	0.883
AE's* at week 48 (n / %)	11 / 8.3	13 / 14.6	0.205
Discontinuation due to AE at week 48 (n / %)	4 / 3.4	7 / 8.1	0.097

496 QUALITY OF LIFE AND ADHERENCE AS PREDICTORS OF SECOND-LINE ART VIROLOGICAL FAILURE

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Background: Poor adherence to antiretroviral therapy (ART) predicts virologic failure (VF). Self-reported adherence and health-related quality of life (QoL) have been associated with 1st-line ART failure in resource-limited settings (RLS). Our objective was to assess whether QoL metrics add to self-reported adherence data at 4 weeks after starting 2nd-line ART in predicting early VF.

Methods: ACTG A5273 was a randomized clinical trial conducted between 2012 and 2014, which showed non inferior virologic efficacy of lopinavir/ritonavir (LPV/r) + raltegravir compared to LPV/r + nucleos(t)ide reverse transcriptase inhibitors as 2nd-line ART in participants failing non-nucleoside reverse transcriptase inhibitor ART at 15 sites in 9 RLS. Early 2nd-line VF was defined as HIV-1 RNA >400 c/mL at week 24 with subsequent confirmation. At baseline and week 4, participants completed the ACTG SF-21, which has 8 QoL domains each scored between 0 (worst) and 100 (best). Adherence was dichotomized as incomplete (self-report of any dose missed in the first 4 weeks of 2nd-line ART) and complete (no missed dose). Logistic regression was used to assess whether QoL at week 4, categorized in each domain as high (score 100), medium (75-<100) and low (<75), enhanced prediction of early 2nd-line VF in addition to adherence.

Results: 512 eligible adults (49% male, median age 39 years) were included including 500 with assessments for QoL and adherence at week 4 and for early VF; 7.4% (n=37/500) had early VF and 20.6% (103/500) reported incomplete adherence at week 4. Mean QoL improved (p<0.04) from baseline to week 4 in all domains: from 67 to 72 (general health perceptions), 91 to 93 (physical functioning), 80 to 83 (role functioning), 91 to 93 (social functioning), 91 to 94 (cognitive functioning, CF), 83 to 84 (pain, 85 to 89 (mental health), and 80 to 83 (energy/fatigue, E/F). Early VF was more common among participants who self-reported incomplete (14/103, 13.6%) versus complete adherence (23/397, 5.8%) at week 4 (OR: 2.56; 95%CI: 1.27-5.17; p=0.009). In analyses (both unadjusted and adjusted for adherence), lower QoL in CF and E/F categories at week 4 were associated with significantly higher odds of early 2nd-line VF (overall p<0.04) (Table).

Conclusion: Poorer QoL, particularly CF and E/F, adds to self-reported incomplete adherence after 4 weeks of 2nd-line ART in predicting VF at week 24. Evaluation is needed to assess whether patients with poorer QoL might be targeted for greater support to reduce risk of VF.

Table. Associations of QoL domains at week 4 with early 2nd-line VF (unadjusted and adjusted for adherence)

QoL Domain	QoL Score Category	N at week 4	Early 2nd-line VF N (%)	OR (95%CI)	p-value	OR adjusted for adherence	p-value
Cognitive Functioning (CF)	High	332	19 (5.7)	Ref.		Ref.	
	Medium	137	12 (8.8)	1.58 (0.75-3.35)	0.23	1.38 (0.64-2.97)	0.41
	Low	31	6 (19.3)	**3.95 (1.45-10.8)**	**0.007**	**3.80 (1.37-10.49)**	**0.010**
Energy/Fatigue (E/F)	High	161	6 (3.7)	Ref.		Ref.	
	Medium	232	17 (7.3)	2.04 (0.79-5.30)	0.14	1.80 (0.69-4.72)	0.23
	Low	107	14 (13.1)	**3.89 (1.44-10.5)**	**0.007**	**3.52 (1.29-9.55)**	**0.014**

497 LOW LEVEL VIREMIA AND VIROLOGIC FAILURE IN PERSONS WITH HIV TREATED WITH ART

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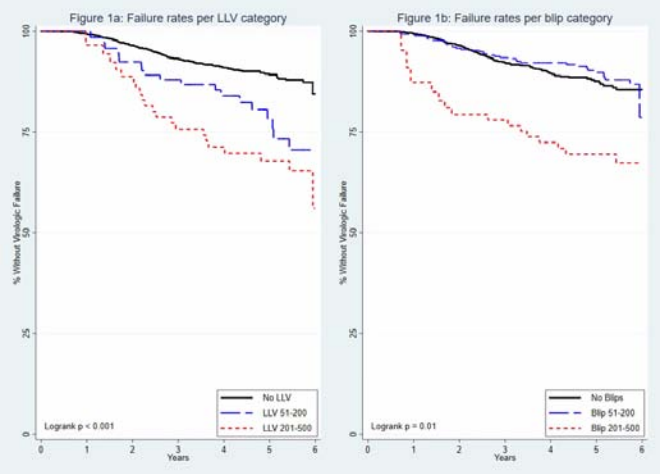
Background: The clinical management of low level viremia remains unclear. The objective of this study was to investigate the association of blips and low level viremia with virologic failure.

Methods: We included patients who enrolled into the HIV Research Network between 2005-2015 at one of 17 geographically diverse sites. Patients were included who achieved virologic suppression (HIV-1 RNA ≤ 50 c/ml on two consecutive viral loads) and had 2 viral loads following suppression. Blips and low level viremia (≥ 2 consecutive viral loads) were categorized separately: no blips/LLV, 51-200, 201-500 copies/mL. Cox proportional hazards regression was used to assess association between rates of blips/low level viremia and virologic failure (two consecutive viral loads > 500 c/ml).

Results: The 2625 patients were mostly male (75.4%), black (49.9%), and MSM (53.3%). Median age was 39 years old (IQR 29-48). Most patients (89.1%) were ART naïve at study entry. The principal anchor drugs at virologic suppression were NNRTI (48.9%), PI (36.5%) and INSTI (17.4%). Overall, 208 (7.9%) patients experienced virologic failure. A total of 155 (5.9%) patients experienced LLV to 51-200 copies/mL and 117 (4.5%) patients experienced LLV to 201-500 copies/mL. There was a higher risk of virologic failure for successively higher LLV categories (Figure 1a), while only the blip 200-500 category was associated with a higher failure rate (Figure 1b). Both LLV 51-200 (Adjusted Hazard Ratio (aHR) 2.06 [1.26,3.37]) and LLV 201-500 (aHR 4.05 [2.49,6.58]) were associated with virologic failure (VF) in univariate and multivariate analysis. In sensitivity analysis excluding ART experienced patients, the association between LLV51-200 and VF was no longer statistically significant. Blip 201-500 was directly associated with VF (aHR 2.25 [1.29,3.93]). Compared with NNRTIs, PIs were directly associated with VF. Black race (compared to white race: aHR 1.78 [1.20,2.64]) and PWID (compared to MSM: aHR 2.63 [1.50,4.61]) were associated with an increased risk of VF.

Conclusion: Low level viremia between 201-500 copies/mL was associated with virologic failure. LLV between 51-200 copies/mL was also associated with virologic failure, particularly among ART experienced patients. Our findings suggest that patients with LLV below the current DHHS threshold for virologic failure (persistent viremia ≥ 200 copies/mL) may also be at increased risk for failure.



498 SECOND-LINE ANTIRETROVIRAL THERAPY (ART) AFTER FIRST VIRAL FAILURE ON ART, 2008-2016

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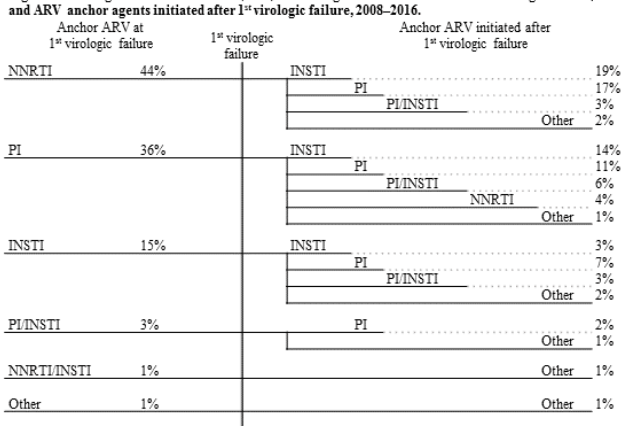
Background: Antiretroviral therapy (ART) regimens currently recommended for initial HIV treatment are efficacious and tolerable, with a high likelihood of achieving and maintaining virologic suppression. However, managing patients with virologic failure can be challenging, and data on second-line ART following first virologic failure with current regimens is very limited.

Methods: We included UNC CFAR HIV Clinical Cohort patients in care 2008–2016, who were receiving ART with no prior evidence of virologic failure. Our outcome was defined as an ART change (including at least a change in anchor agent within 6 months) following first virologic failure (FVF) on ART, defined as the first detectable viral load (>1000 copies/ml) >24 weeks after ART initiation. Alternate definitions of FVF were considered in sensitivity analyses. We characterized the ART history of these patients and estimated incidence rates (new cases of second-line ART after FVF, divided by number of person-years without the outcome), overall and by calendar year, using Poisson regression. We examined genotype tests performed at FVF and defined resistance by class as ≥1 major IAS-USA mutation.

Results: Between 2008 and 2016, among 2671 patients who contributed 13 814 person-years, 100 changed ART after FVF. Of these 100 patients, 44% were currently on an NNRTI anchor agent at FVF, 36% on a PI, 15% on an INSTI, and 3% on PI/INSTI (Fig.). The median year of ART initiation was 2008 (IQR 2004–2010). The overall incidence rate of FVF with ART change was 7.2 per 1000 person-years (95% CI 6.0, 8.8), and stable across calendar years, for example 5.0 (95% CI 2.0, 12.5) in 2008 and 8.2 (95% CI 4.8, 14.2) in 2016 (P for trend = 0.13). A genotypic resistance test was obtained for 61 patients at FVF: 18 of 28 (64%) patients on an NNRTI had NNRTI resistance, 1/19 (5%) on a PI had PI resistance, and 0/13 (0%) on an INSTI had INSTI resistance. After FVF, second-line ART regimens most commonly contained a PI (38%), INSTI (37%), PI/INSTI (12%), or NNRTI (4%). Of 19 patients on an INSTI at FVF, 9 initiated second-line ART with a PI, 3 with an INSTI, 3 with PI/INSTI, 2 with PI/NNRTI/INSTI.

Conclusion: In 2008–2016 in this cohort, one-fifth of patients who had FVF and subsequently changed ART were on an INSTI at the time of FVF and one-half on an NNRTI, and many had NNRTI resistance at switch. Over half of second-line ART regimens after FVF contained an INSTI. Assessing clinical outcomes on second-line ART is important for managing first virologic failure.

Figure. Flow diagram of antiretroviral (ARV) anchor agents used at the time of 1st virologic failure, and ARV anchor agents initiated after 1st virologic failure, 2008–2016.



499 PREDICTORS OF VIROLOGIC OUTCOME WHILE CONTINUING A PI-BASED ART REGIMEN IN ACTG A5288

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Background: Antiretroviral (ARV) choices are challenging in resource-limited settings (RLS) after failure of 2nd-line therapy because of accumulated resistance. Many failing 2nd-line therapy without resistance remain on their 2nd-line therapy. Our objective was to evaluate demographic and predictors of successful virologic suppression in this prospective study.

Methods: A5288 was an open-label strategy study in RLS in HIV-1 infected persons with confirmed plasma HIV RNA (VL) ≥ 1000 c/mL after 24 weeks of PI-based 2nd-line ART. The study sought to use newer ARVs (darunavir/r, etravirine and raltegravir) along with genotyping (GT), a cellphone adherence intervention (CPI) or standard of care (SOC), and real-time HIV VL monitoring to achieve VL suppression at week 48. Participants were assigned to 1 of 4 cohorts based on GT at time of study entry, previous ART history and any other GT available. This analysis focuses on the 287 (53%) enrolled in Cohort A (no lopinavir resistance) from Feb-2013 to Dec-2015. These 287 participants remained on 2nd-line PI-based ART regimen, with flexibility to change their NRTIs. Logistic regression was used to evaluate sex, age, baseline HIV-1 RNA, CD4 count, presence of resistance to at least one NRTI, and adherence support (CPI+SOC vs SOC) as predictors of the study's primary endpoint: suppression of HIV-1 RNA ≤200 c/mL at week 48 (ITT).

Results: 56% of Cohort A participants were female, median age was 40. Median HIV-1 RNA was 4.3 log10 c/mL and CD4 count was 171 cells/mm3; 113 (39%) had

resistance to at least 1 NRTI and 26 (9%) had minor resistance to at least one PI. 44% of participants achieved VL suppression at week 48. In both unadjusted and adjusted analysis (table), older age, lower baseline HIV-1 RNA, higher CD4 count, and lack of resistance to any NRTI (multivariable only) were significantly associated with higher virologic suppression rate at week 48. Associations with sex and with CPI+SOC were not statistically significant. 145 (51%) experienced confirmed virologic failure ≥ 1000 c/mL and 141 had GT available at failure; 48 (34%) had development of new resistance mutations, predominantly NRTI-related.

Conclusion: In this 3rd-line ART trial in RLS, fewer than 50% of participants with no lopinavir resistance at entry who continued their 2nd-line ART had VL suppression at 48 weeks. Participants with more advanced disease or any resistance mutations had worse rates of suppression. This group likely represents individuals with continued poor ARV adheren

Variable	Categories	N	N (%) with HIV-1 RNA ≤200 c/mL at week 48	Odds ratio (95% CI)	Odds ratio, adjusted for other variables shown (95% CI)
Sex	Male	127	62 (49%)	1.47 (0.92, 2.35)	1.12 (0.66, 1.89)
	Female	160	63 (39%)	Reference	
Age (years)	≥40	162	84 (52%)	2.21 (1.36, 3.58)	**2.10 (1.23, 3.59)**
	<40	125	41 (33%)	Reference	
HIV-1 RNA (c/mL)	<10,000	113	66 (58%)	2.74 (1.68, 4.46)	**2.04 (1.18, 3.53)**
	≥10,000	174	59 (34%)	Reference	
CD4 count (cells/mm³)	≥200	129	78 (60%)	3.61 (2.21, 5.90)	**3.11, (1.81, 5.34)**
	<200	158	47 (30%)	Reference	
Resistance to any NRTI	No	174	82 (47%)	1.45 (0.90, 2.35)	**1.81 (1.05, 3.11)**
	Yes	113	43 (38%)	Reference	
Adherence support intervention	CPI+SOC	133	60 (45%)	1.21 (0.75, 1.96)	1.31 (0.77, 2.25)
	SOC	136	55 (40%)	Reference	
	Site opted out	18	10 (56%)	1.84 (0.68, 4.96)	2.45 (0.85, 7.06)

500 WEEK 96 SUBGROUP ANALYSES OF D/C/F/TAF IN HIV-1 TREATMENT-NAIVE & SUPPRESSED ADULTS

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Background: Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10mg, currently approved in the EU, US and other countries, is being investigated in two Phase 3 randomized non-inferiority trials, EMERALD (virologically suppressed adults; NCT02269917) and AMBER (ART-naïve adults; NCT02431247). We present a wk 96 preplanned subgroup analysis of the D/C/F/TAF arms by baseline viral load (VL) and CD4+ count (screening stratification factors), WHO clinical stage in AMBER, and prior virologic failure (VF), ART experience, screening bPI (stratification factor) and boosting agent in EMERALD.

Methods: Patients in the D/C/F/TAF and control arms of both trials (study designs described previously) continued on or switched to D/C/F/TAF in a single-arm, open-label extension phase until wk 96 provided they consented and continued to derive benefit. Wk 96 efficacy endpoints were % patients with cumulative confirmed VL≥50c/mL (virologic rebound) (EMERALD) and VL<50 c/mL (virologic response) and VL≥50c/mL (VF) (FDA snapshot) (both trials). No wk 96 comparisons were made between arms during the open-label phase. This analysis focuses on long-term efficacy and safety of D/C/F/TAF over 96 wks in the D/C/F/TAF arms.

Results: In AMBER, high response and low VF rates were seen at wk 96 across the baseline VL, CD4+ count and WHO clinical stage subgroups (Table). In EMERALD, 58% had received ≥5 ARVs (including screening ARVs and boosters) and 15% had prior non-DRV VF. High response rates, low VF and low virologic rebound rates were maintained through wk 96 across ART experience and prior VF, and screening bPI and boosting agent subgroups (Table). In both trials, low denominators in some subgroups resulted in wider 95% CIs and data should be interpreted with caution. No DRV, primary PI or TFV RAMs were seen through wk 96. Grade 3-4 and serious AEs were similar across subgroups, with a low percentage of AEs leading to D/C (Table). eGFR improved or was stable in the D/C/F/TAF arms across subgroups (Table). Wk 96 results for the late switch arm were consistent with wk 48 results for D/C/F/TAF (data not shown).

Conclusion: Through 96 wks, D/C/F/TAF had a high genetic barrier to resistance and maintained high response rates, with few discontinuations due to AEs and favorable renal outcomes across patient subgroups in ART-naïve and experienced virologically suppressed adults.

Table. Preplanned Subgroup Analyses of Efficacy and Safety in the D/C/F/TAF arms of AMBER and EMERALD through 96 weeks (Intention-to-Treat)

AMBER	Overall population	Baseline VL		CD4+ cell count		WHO clinical stage[a]	
		≤100,000 c/mL	>100,000 c/mL	<200 cells/µL	≥200 cells/µL	Stage 1	Stage 2
N (%)	362	303 (84)	59 (16)	22 (6)	340 (94)	314 (87)	42 (12)
Efficacy endpoints, % (95% CI)[b]							
Response (FDA snapshot <50c/mL)	85 (81 ; 89)	86 (81 ; 90)	81 (69 ; 90)	73 (50 ; 89)	86 (82 ; 89)	85 (81 ; 89)	88 (74 ; 96)
VF (FDA snapshot ≥50c/mL)	6 (3 ; 8)	4 (2 ; 7)	12 (5 ; 23)	18 (5 ; 40)	5 (3 ; 8)	6 (3 ; 9)	2 (<1 ; 13)
Safety							
Drug-related Grade 3-4 AEs, %	3	3	5	5	3	2	7
Serious AEs, %	11	12	5	9	11	10	14
D/C due to AE, %	3	3	0	9	3	3	5
Δ eGFR$_{epi}$, mL/min/1.73m²	+4	+3	+12	-4	+6	+4	+3

EMERALD	Overall population	Number of ARVs previously used[c]				Prior VF		Screening bPI[d]		Screening boosting agent	
		5	6	7	>7	0	≥1	DRV	ATV or LPV	rtv	COBI
N (%)	763	98 (13)	69 (9)	69 (9)	211 (28)	647 (85)	116 (15)	537 (70)	226 (30)	659 (86)	104 (14)
Efficacy endpoints, % (95% CI)[b]											
Cumulative confirmed rebound[e]	3 (2 ; 5)	4 (1 ; 10)	7 (2 ; 16)	0	3 (1 ; 6)	3 (2 ; 5)	4 (1 ; 10)	3 (2 ; 5)	4 (2 ; 7)	3 (2 ; 5)	2 (<1 ; 7)
Response (FDA snapshot <50c/mL)	91 (88 ; 93)	90 (82 ; 95)	93 (84 ; 98)	88 (78 ; 95)	87 (81 ; 91)	91 (89 ; 93)	87 (80 ; 93)	93 (90 ; 95)	86 (81 ; 90)	90 (88 ; 92)	94 (88 ; 98)
VF (FDA snapshot ≥50c/mL)	1 (1 ; 2)	1 (0 ; 6)	0 (0 ; 8)	0	2 (1 ; 5)	1 (<1 ; 2)	3 (1 ; 9)	1 (1 ; 3)	1 (<1 ; 3)	1 (1 ; 3)	0
Safety											
Drug-related Grade 3-4 AEs, %	2	ND	ND	ND	ND	ND	ND	2	1	2	0
Serious AEs[f], %	9	ND	ND	ND	ND	ND	ND	8	11	9	8
D/C due to AE, %	2	ND	ND	ND	ND	ND	ND	1	5	2	2
Δ eGFR$_{epi}$, mL/min/1.73m²	-1	ND	ND	ND	ND	ND	ND	-1	-1	-1	+2

VL, viral load; CI, confidence interval; VF, virologic failure; AE, adverse event; D/C, discontinuation; eGFR$_{epi}$, eGFR based on serum cystatin C (CKD-EPI formula); ARV, antiretroviral; bPI, boosted protease inhibitor; DRV, darunavir; ATV, atazanavir; LPV, lopinavir; rtv, ritonavir; COBI, cobicistat; ND, not determined
[a]Data not reported for WHO clinical stage 3 and 4 subgroups due to small sample sizes; [b]Two-sided Exact Clopper-Pearson 95% CI; [c]Includes ARVs and booster used at screening. Data not reported for patients who had previously used 3 or 4 ARVs prior to baseline; [d]DRV with rtv or COBI, ATV with rtv or COBI, and LPV with rtv; [e]Confirmed VL ≥50 c/mL or premature discontinuation with last VL ≥50 c/mL (cumulative through wk 96); [f]Three deaths occurred after wk 48 due to metastatic pancreatic carcinoma and two cases of myocardial infarction, one of which was in a patient who was a smoker, with an ongoing medical history of hyperlipidemia and hypertension and one was in a patient with an ongoing medical history of obesity and hypertension

501 INTEGRATED EFFICACY ANALYSIS OF DORAVIRINE IN HIV-1-INFECTED TREATMENT-NAIVE ADULTS

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Background: DOR is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with once-daily dosing and potent in vitro activity against wild-type virus and the most common NNRTI-resistant variants (K103N, Y181C, G190A). DOR has demonstrated non-inferior efficacy to darunavir plus ritonavir (DRV+r) and efavirenz (EFV) in two ongoing, double-blinded, phase 3 trials: DRIVE-FORWARD (NCT02275780) and DRIVE-AHEAD (NCT02403674).

Methods: This prespecified analysis pooled Week 48 data from DRIVE-FORWARD and DRIVE-AHEAD. Data from the DOR groups were pooled, in which 747 participants received DOR/3TC/TDF or DOR (100 mg QD) with FTC/TDF or ABC/3TC. The control groups were analyzed separately, in which 383 received DRV+r (800/100 mg QD) with FTC/TDF or ABC/3TC, and 364 received EFV/FTC/TDF (600/200/300 mg QD). Efficacy was assessed by proportion of participants with HIV-1 RNA <50 copies/mL (primary) and change in CD4+ T-cells (secondary) after 48 weeks of treatment.

Results: At Week 48, HIV-1 RNA <50 copies/mL was achieved by 84.1% of DOR-treated participants versus 79.9% of the DRV+r, and 80.8% of the EFV/FTC/TDF groups (Table). No clinically meaningful differences in proportions of patients with HIV-1 RNA <50 copies/mL was seen across demographic/prognostic subpopulations, including baseline plasma HIV-1 RNA (≤ vs >100,000 copies/mL), gender (male/female), race (white vs black/African American), ethnicity (yes vs no Hispanic/Latino), and subtype (B vs non-B). Mean increases from baseline in CD4+ T-cell count at week 48 were 195.5 cells/mm³ for DOR, 185.6 cells/mm³ for DRV+r, and 188.4 cells/mm³ for EFV/FTC/TDF.

Conclusion: DOR, as a single entity (administered in combination therapy with other antiretroviral agents) and as a fixed-dose combination consisting of DOR/3TC/TDF, was efficacious compared with DRV+r and EFV as assessed by the proportion of HIV-1-infected, treatment-naïve adults with HIV-1 RNA <50 copies/mL. Consistent efficacy was seen regardless of demographic/prognostic baseline characteristics.

	DOR (DRIVE-FORWARD, DRIVE-AHEAD)		DRV/r+/ (DRIVE-FORWARD)		EFV/FTC/TDF+/ (DRIVE-AHEAD)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Total	628/747	84.1 (81.2, 86.6)	306/383	79.9 (75.5, 83.8)	294/364	80.8 (76.3, 84.7)
Baseline plasma HIV-1 RNA (copies/mL)						
≤100,000 copies/mL	508/591	86.0 (82.9, 88.7)	250/308	81.2 (76.3, 85.4)	235/282	83.3 (78.5, 87.5)
>100,000 copies/mL	120/156	76.9 (69.5, 83.3)	55/74	74.3 (62.8, 83.8)	59/82	72.0 (60.9, 81.3)
Baseline CD4 cell counts (cell/mm³)						
≤200 cells/mm³	63/86	73.3 (62.6, 82.2)	44/67	65.7 (53.1, 76.8)	36/46	78.3 (63.6, 89.1)
>200 cells/mm³	565/661	85.5 (82.6, 88.1)	262/316	82.9 (78.3, 86.9)	258/318	81.1 (76.4, 85.3)
Gender						
Male	526/624	84.3 (81.2, 87.1)	268/326	82.2 (77.6, 86.2)	250/311	80.4 (75.5, 84.7)
Female	102/123	82.9 (75.1, 89.1)	38/57	66.7 (52.9, 78.6)	44/53	83.0 (70.2, 91.9)
Race						
White	393/457	86.0 (82.5, 89.0)	232/280	82.9 (77.9, 87.1)	138/170	81.2 (74.5, 86.8)
Black/African American	115/153	75.2 (67.5, 81.8)	63/88	71.6 (61.0, 80.7)	51/68	75.0 (63.0, 84.7)
Ethnicity						
Hispanic/Latino	187/219	85.4 (80.0, 89.8)	70/86	81.4 (71.6, 89.0)	101/120	84.2 (76.4, 90.2)
Not Hispanic/Latino	433/520	83.3 (79.8, 86.4)	230/290	79.3 (74.2, 83.8)	189/238	79.4 (73.7, 84.4)
Subtype						
B	419/498	84.1 (80.6, 87.2)	222/272	81.6 (76.5, 86.0)	202/253	79.8 (74.4, 84.6)
Non-B	207/247	83.8 (78.6, 88.2)	84/111	75.7 (66.6, 83.3)	92/111	82.9 (74.6, 89.4)

502 96 WEEK EFFICACY AND SAFETY OF B/F/TAF IN TREATMENT-NAÏVE ADULTS AND ADULTS ≥50 YRS

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Background: As the population living with HIV ages, identifying effective and safe regimens for older patients is of heightened importance. The single-tablet bictegravir, emtricitabine, tenofovir alafenamide (B/F/TAF) is a guidelines-recommended regimen that may benefit older patients due to its favorable adverse event (AE) profile and few drug interactions.

Methods: We conducted two randomized, double blind, phase 3 studies of B/F/TAF in treatment-naïve adults, Study 1489: B/F/TAF vs dolutegravir, abacavir, and lamivudine (DTG/ABC/3TC) and Study 1490: B/F/TAF vs DTG + F/TAF. A pre-specified pooled analysis assessed efficacy as the proportion with HIV-1 RNA <50 c/mL (FDA Snapshot) and safety at Week (W) 96. Proteinuria and bone mineral density (BMD) were measured in Study 1489 only. We performed a post-hoc analysis in adults ≥50 yrs.

Results: 1274 were randomized and treated (634 B/F/TAF, 315 DTG/ABC/3TC, 325 DTG + F/TAF); 196 were age ≥50 yrs (96 B/F/TAF, 41 DTG/ABC/3TC, 59 DTG + F/TAF). Efficacy was high for all treatments and for age ≥50 subgroup (Table). Overall, the most common AEs were nausea (10% B/F/TAF, 24% DTG/ABC/3TC , 11% DTG + F/TAF [p<0.001 B/F/TAF vs DTG/ABC/3TC]), diarrhea (17% B/F/TAF, 16% DTG/ABC/3TC, 16% DTG + F/TAF), and headache (15% B/F/TAF, 16% DTG/ABC/3TC, 15% DTG + F/TAF). Treatment-related AEs occurred in 24% B/F/TAF, 40% DTG/ABC/3TC (p<0.001 B/F/TAF vs DTG/ABC/3TC), and 28% DTG + F/TAF. The most common treatment-related AE was nausea: 4% B/F/TAF, 17% DTG/ABC/3TC (p<0.001 B/F/TAF vs DTG/ABC/3TC), and 5% DTG + F/TAF. Treatment related AEs in those age ≥50 yrs were similar to the full population: 23% B/F/TAF, 37% DTG/ABC/3TC, 29% DTG + F/TAF. Overall, AEs leading to study drug discontinuation were reported for 1% on B/F/TAF, 2% on DTG/ABC/3TC and 2% on DTG + F/TAF, and in age ≥50 yrs: 2% B/F/TAF, 5% DTG/ABC/3TC and 7% DTG + F/TAF. In Study 1489 mean % changes in hip and spine BMD, proteinuria, and renal biomarkers were similar. There were small changes from baseline in fasting lipids at W96 overall and no significant differences between treatments in participants ≥50 yrs.

Conclusion: Through two years of treatment B/F/TAF resulted in high rates of virologic suppression, was safe and well tolerated with fewer treatment-related AEs compared to other guidelines-recommended regimens; similar results were found in adults ≥50 yrs. There were no clinically significant impacts on bone and renal safety or on fasting lipids.

Table. Efficacy and safety for all adults and adults ≥ 50 yrs in Studies 1489 and 1490 at Week 96

	Overall			Age ≥ 50 yrs		
	B/F/TAF (n=634)	DTG/ABC/3TC (n=315)	DTG + F/TAF (n=325)	B/F/TAF (n=96)	DTG/ABC/3TC (n=41)	DTG + F/TAF (n=59)
HIV-1 RNA <50 c/mL, %	86	90	86	88	85	86
difference in % (95% CI) B/F/TAF vs comparator		-3.8 (-8 to 1)	-0.4 (-5 to 4)	--	1.4 (-13 to 16)	1.3 (-11 to 13)
Renal and bone safety						
eGFR, median change, mL/min (Q1, Q3)	-8 (-17, 3)	-10 (-20, 0)	-9 (-19, 2)	-8 (-16, 3)	-10 (-20, 2)	-10 (-19, -3)
p-value, B/F/TAF vs comparator		0.002	0.076	--	0.47	0.27
Proteinuria, median % change (Q1, Q3)[a,b,*]						
UACR	0 (-34, 60)	+5 (-26, 57)		-15 (-41, 71)	+8 (-25, 88)	
RBPCR	+21 (-12, 67)	+22 (-13, 79)		+11 (-27, 49)	+14 (-34, 37)	
β2MCR	-31 (-58, 21)	-29 (-58, 12)		-44 (-69, 10)	-43 (-80, 3)	
BMD, mean, % change from baseline (SD)[a]						
Hip[c]	-1.1 (2.8)	-1.3 (2.9)		-0.4 (2.2)	-1.3 (2.2)	
Spine[d]	-0.7 (3.9)	-0.2 (3.5)		+0.6 (3.4)	-0.5 (2.7)	

[a] Renal biomarkers and BMD measured for Study 1489 only
[b] Overall n= 272 (B/F/TAF), n=284 (ABC/DTG/3TC); Age ≥ 50yrs n=40 (B/F/TAF), n=36 (ABC/DTG/3TC)
[c] Overall n= 250 (B/F/TAF), n=257 (ABC/DTG/3TC); Age ≥ 50yrs n=35 (B/F/TAF), n=29 (ABC/DTG/3TC)
[d] Overall n= 256 (B/F/TAF), n=258 (ABC/DTG/3TC); Age ≥ 50yrs n=35 (B/F/TAF), n=31 (ABC/DTG/3TC)
2-sided Wilcoxon rank sum test used to compare B/F/TAF to DTG/ABC/3TC and B/F/TAF to DTG + F/TAF for eGFR, proteinuria
ANOVA model including treatment as a fixed effect used for BMD comparison of B/F/TAF and DTG/ABC/3TC
*p-values for were non-significant for the difference in changes in proteinuria and BMD
UACR, urine albumin to creatinine ratio, RBPCR, retinol binding protein to creatinine ratio, β2MCR, β2-microglobulin to creatinine ratio

503 CD4+ RECOVERY AFTER ART INITIATION: A COMPARISON BETWEEN DOLUTEGRAVIR AND EFAVIRENZ

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Background: CD4 cell count recovery is an important predictor of AIDS-related morbidity and mortality, especially among those who start antiretroviral therapy (ART) with lower counts. In this study, we aimed to compare CD4 count recovery in patients starting ART in Brazil with TLE (tenofovir+lamivudine+efavirenz) vs TLD (tenofovir-lamivudine-dolutegravir). These were the regimens recommended as preferred 1st-line in the most recent treatment guidelines in the country, released in Dec 2013 (TLE) and in Jan 2017 (TLD).

Methods: Data was extracted from two information systems from the Brazilian Ministry of Health, which record every viral load (VL) and CD4 counts performed within the country's public health system, and every ART prescription. We included patients aged 15 and over, starting ART from Jan 2014 to Jul 2017 on either TLE or TLD and who had a CD4 count at baseline (-180 to 30 days) and after a year (365±90 days) from treatment initiation. CD4 count recovery was calculated as the difference between these values, adjusted by the time interval between ART initiation and the follow up measurement to report a standardized 365-day change. We present median absolute yearly CD4 changes and proportions which achieved 50, 100 and 200-cell/mm^3 increases, with respective p-values for the Mann-Whitney U and χ2-tests. We also performed a logistic regression model adjusting for sex, age, baseline VL and presence of viral suppression (at 365±90 days), with a 200-cell increase as the outcome, and report the aOR and 95%CI. All analyses are stratified by baseline CD4 count.

Results: 61,297 individuals were included in the analysis, of whom 7,509 (12.3%) were on TLD. Median age was 34yo, median baseline CD4 was 351 cells/mm^3, and 71.2% were male. Median increase in CD4 count was higher with TLD than with TLE in all baseline CD4 strata (all p-values <0.001). A higher absolute difference was observed in the 350+ cells/mm^3 group (36 cells/mm^3) and a lower in the 100-199 cells/mm^3 group (24 cells/mm^3). In the multivariable analysis patients on TLD remained significantly more likely to present a 200-cell/mm^3 increase than those on TLE in all strata.

Conclusion: In this study, dolutegravir led to a higher CD4 cell recovery after the 1st year of ART than did efavirenz, in all strata of CD4 analyzed, both in the unadjusted analyses and after controlling for other factors. These findings should be taken into account when choosing initial ART, especially in patients for whom immunologic recovery is a priority.

Baseline CD4 strata	ART regimen	n	Yearly increase (cells/mm3)			% with increases of at least (cells/mm3)								Multivariable model (200-cell increase)	
			Median	IQR	p-value[2]	50	p-value[2]	100	p-value[2]	200	p-value[2]	aOR	95%CI
<100	TLE	8476	187	(106-283)		87.0		76.5		46.1		1.35	(1.20-1.52)
	TLD	1424	215	(135-310)		93.9		84.4		55.5			
100-199	TLE	6826	166	(82-274)		83.4		69.9		41.1		1.25	(1.09-1.43)
	TLD	1071	190	(105-298)	all <0.001	88.2	all <0.001	76.2	all <0.001	46.9	all <0.001		
200-349	TLE	11133	192	(93-313)		83.4		73.2		48.2		1.31	(1.17-1.46)
	TLD	1613	219	(121-344)		87.6		79.2		56.0			
350+	TLE	27353	187	(49-347)		74.9		66.6		47.7		1.25	(1.16-1.35)
	TLD	3401	223	(72-391)		77.9		70.4		53.8			

[1] Mann-Whitney U test, [2] Chi-Square test

504 VIROLOGIC AND IMMUNOLOGIC OUTCOMES OF INTEGRASE INHIBITORS (InSTIs) IN RESPOND

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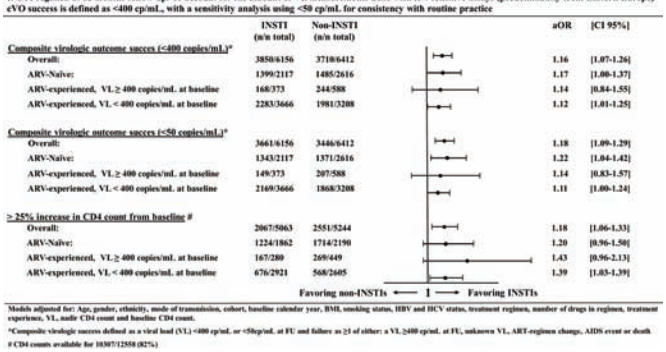
Background: Although outcomes of INSTI use have been evaluated in several randomized controlled trials, experiences from large, demographically heterogeneous real-life settings are limited.
Methods: Logistic regression was used to analyse virologic and immunologic outcomes from 1/1/12 to 1/10/17 among participants in the RESPOND cohort collaboration, starting an INSTI- compared to other contemporary non-INSTI containing regimens (efavirenz, rilpivirine, boosted darunavir- or atazanavir) with 12 months follow-up (FU) ± 3 months. Virologic outcomes were assessed by a composite endpoint (cVO) with success defined as viral load (VL) <400 cp/mL at FU and failure as ≥1 of either: VL ≥400 cp/mL, unknown VL, any antiretroviral treatment (ART)-regimen change, AIDS event or death. Immunologic success was defined as a 25% increase in CD4 count from baseline at 12 ± 3 months. Analyses were repeated at 6 ± 3 months. Sensitivity analyses using VL< 50 cp/mL for cVO success, excluding those with unknown VL or any ART change were also performed.
Results: Of the 12568 persons included, 6156 were on an INSTI (2117 (34%) ART-naïve) and 6412 on non-INSTI regime (2616 (41%) ART-naïve). In an on-treatment analysis, 4982/5106 (98%) on INSTIs and 4979/5211 (96%) on non-INSTIs had a VL<400 cp/mL at 12 months (p<0.0001). A total of 7560 (60%) experienced cVO success (3850 (63%) on INSTIs and 3710 (58%) on non-INSTIs, P<0.0001). The most common reasons for cVO failure were any regimen change (1375 (22%) vs 1618 (25%), p<0.0001) and unknown VL (1050 (17%) vs 1201 (19%), p<0.0001). There were few viral failures (124 (2%) vs 232 (4%), p<0.0001), AIDS events (79 (1%) vs 122 (2%), p=0.008) or deaths (62 (1%) vs 44 (1%), p=0.6). After adjustment, the odds of cVO success at 12 months was significantly higher for persons on INSTIs compared to non-INSTIs (adjusted odds ratio 1.16 [95% CI, 1.07-1.26]), consistent for ART-naïve and ART-experienced with or without viral suppression at baseline (figure, p=0.4, interaction test). The odds of immunologic success at 12 months were also higher on INSTIs than non-INSTIs (1.18 [1.06-1.33]), consistent according to ART and VL status at baseline (figure, p=0.1, interaction test). Similar results were seen at 6±3 months and across all sensitivity analyses.
Conclusion: In this large cohort collaboration, persons on INSTIs were more likely to achieve cVO success and immunologic success at 12 months, compared to non-INSTIs, although confounding by indication cannot be excluded.

Figure: Forrest plot of adjusted odds ratio (aOR) of composite virologic success (cVO) and immunologic success for persons on a INSTI compared to non-INSTI regimen at 12 months follow-up. To account for the amount of VL measurements done with low sensitive assays (predominantly from Eastern Europe) cVO success is defined as <400 cp/mL, with a sensitivity analysis using <50 cp/mL for consistency with routine practice



Models adjusted for: Age, gender, ethnicity, mode of transmission, cohort, baseline calendar year, BMI, smoking status, HBV and HCV status, treatment regimen, number of drugs in regimen, treatment experience, VL, nadir CD4 count and baseline CD4 count.
*Composite virologic success defined as a viral load (VL) <400 cp/mL or <50cp/mL at FU and failure as ≥1 of either: a VL ≥400 cp/mL at FU, unknown VL, ART-regimen change, AIDS event or death
CD4 counts available for 10307/12558 (82%)

505LB 12 MONTH OUTCOMES ON DOLUTEGRAVIR-BASED REGIMENS IN BOTSWANA: THE BEAT COHORT STUDY

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Background: Botswana became the first country in Africa to implement a "Treat All" strategy using Dolutegravir based regimens (DBR) in June 2016. The Botswana Epidemiological ART Treatment Cohort Study (The BEAT), is an observational research cohort tracking virologic and clinical outcomes of people living with HIV (PLHIV) starting DBR. We present 12-month outcomes for treatment naïve, switched and highly treatment experienced patients (HTE) on DBR in routine care settings.
Methods: Data were extracted from the Botswana Ministry of Health and Wellness electronic records and National HIV and laboratory databases from 11 urban and semi-rural facilities. Additional Information was extracted from clinic registers and patient files. Rates of adverse events (AEs) using toxicity grading scale of the Division of AIDS (DAIDS) 2017 v.2.1, Lost to follow-up (LTFU), death and viral load (VL) suppression (HIV RNA load <400 copies/mL) were assessed by site and treatment category.
Results: A total of 2,257 PLHIV were included in this analysis: 1523 previously treatment naïve, 638 treatment switches and 140 HTEs. Median age was 39 years (range 32-48), 63% were women. Overall VL suppression was high among individuals initiating DBR within the past year (Table 1). AEs requiring intervention and treatment switch from DBR occurred in <0.1% (n=2) of treatment naive patients (severe itching and rash that resolved upon discontinuation of DBR) and 1 HTE patient (subsequently not considered related to DBR). All patients had advanced AIDS - cryptococcal meningitis, cervical cancer, and pulmonary TB with anemia of unknown origin. Deaths occurred in 1.3% (n=30) of patients. Men comprised 67% of all deaths. Average time to death was 43.7 days. No neural tube defects were recorded in 77 deliveries (11 receiving DTG before conception).
Conclusion: The introduction of DBR in Botswana is associated with favorable clinical outcomes with high rates of viral load suppression at 12 months and few toxicities or evidence of treatment failure. These findings are reassuring and suggest that the decision to implement "Treat All" and introduce DBRs was an important step to controlling the HIV epidemic in Botswana. Efforts to maintain high retention in care and identify and treat pre-existing opportunistic infections prior to DBR initiation are critical, particularly with the introduction of same day initiations as part of the Treat All Strategy. Additional resources are also required to improve electronic VL laboratory results.

Table 1: Virologic & Clinical Outcomes at 12 Months Across 4 Districts and Treatment Cohort.

District (n=)	% with 12-Month Electronic Viral Load Measurements	% VL Suppression <400 copies/mL with (95% CI) Overall and by Gender.	Adverse Events % (#) (DAIDS – Grade 3)	LTFU % (#)	Deaths % (#)
Gaborone-Urban (n= 1,373)	42% (n=578)	Overall: 95.5% *(93.5-96.9)* Female: 95.2% Male: 96.1%	<1% (n=3)	1.0 % (n=14)	<1.4% (19)
Molepolole-Semi-Rural (n=375)	69% (n=259)	Overall: 99.2% *(96.9, 99.8)* Female: 99.4% Male: 98.8%	0	2.6 % (n=10)	<1.0% (4)
Mahalaype Semi-Rural (n=260)	69% (n=178)	Overall: 99.4% *(96.1,99.9)* Female: 100% Male: 98.6%	0	2.3% (n=6)	1.1% (3)
Francistown-Urban (n=248)	49% (n=122)	Overall: 100%	0	1.2% (n=3)	1.6% (4)
Naive (n= 1523)	41% (n=632)	Overall: 98.6% *(97.3, 99.3)* Female: 98.8% Male: 98.2%	<1% (n=1)	6.3% (n=33)	1.9% (n=30)
Switched (n=638)	70% (n=449)	Overall: 96.9% *(94.8, 98.1)* Female: 96.3% Male: 98.3%	0	0	0
Highly Treatment Experienced (n=95)	79% (n=71)	Overall: 89.1% *(77.3, 95.1)* Female: 90.1% Male: 86.4%	1% (n=1)	0	0
Total *(n=2,257)*		**97.4%** *(96.4, 98.2)*	**<1% (n=3)** Women: 66.6%	**1.4% (n=33)** Women: 51.6%	**1.3% (n=30)** Women: 33%

506 PREDICTORS OF SWITCHING FROM TDF TO TAF: REAL-WORLD DATA FROM A NATIONWIDE STUDY

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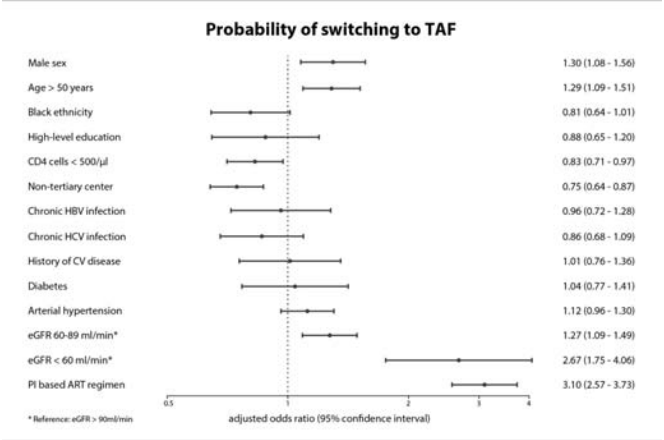
Background: Since its availability in October 2016, tenofovir alafenamide (TAF) has replaced tenofovir disoproxil fumarate (TDF) in the antiretroviral therapy (ART) regimen of many HIV-infected persons. We used data of the Swiss HIV Cohort Study (SHCS) to explore individual predictors for being switched to TAF.

Methods: We included all HIV-infected adults on TDF-containing ART in January 2016 with clinical follow-up thereafter. We determined the proportion of patients who switched to TAF and used multivariable logistic regression to explore related predictors. We repeated the analyses in patients with risk factors for TDF-related toxicity, namely osteoporosis or impaired renal function (estimated glomerular filtration rate [eGFR] <60ml/min and/or proteinuria ≥50mg/mmol).

Results: Of 5'012 patients included, 3'645 (72.7%) were male, 789 (15.8%) were of black ethnicity and median age was 49 years (interquartile range [IQR] 41-56). The eGFR was <60 ml/min in 213 patients (4.2%), 407 patients (8.1%) had proteinuria, and osteoporosis was diagnosed in 261 patients (5.2%). Protease inhibitors (PI) were part of the ART regimen in 1'178 individuals (23.5%). As of 1st July 2018, 2'732 (54.5%) had TDF replaced by TAF. Men (adjusted odds ratio [aOR] 1.30, 95% confidence interval [CI] 1.08-1.56), patients >50 years (aOR 1.29, CI 1.09-1.51), and those with an eGFR <60ml/min (aOR 2.67, CI 1.75–4.06) or PI-based ART (aOR 3.10, CI 2.57-3.74) were most likely to switch. Individuals with a CD4 cell count <500/µl (aOR 0.83, CI 0.71-0.97) and those followed in non-tertiary centers (aOR 0.75, CI 0.64-0.87) were less likely to receive TAF (Figure). We observed large differences in switching rates across centers, ranging from 32.6% to 65.3% (p<0.001). Of 795 patients with at least one risk factor for TDF-toxicity, 533 (67.1%) switched to TAF, with an increased probability in those with an eGFR <60 ml/min (aOR 2.17, CI 1.24-3.78) or a PI-based regimen (2.83, CI 1.66-4.81). Of patients remaining on TDF despite the presence of risk factors, the most common regimens were fixed-dose combinations including rilpivirine (35.9%) or efavirenz (29.2%).

Conclusion: Two years after its introduction in Switzerland, more than 50% of patients within the SHCS were switched to TAF, with the highest proportions among men, patients >50 years, as well as in those with renal impairment or on PI-based ART. However, we noted large differences in switching rates across centers, potentially driven by clinical and programmatic factors.



507 SEVEN-YEAR TREATMENT RESPONSES IN SUBTYPE A1 VS D HIV-1 INFECTIONS IN MBARARA, UGANDA

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Background: Subtype D HIV-1 has been associated with more rapid progression to AIDS in untreated infections. In a previous study, we found that subtype A1 and D infections did not differ in initial response to short term therapy: 86% of individuals achieved undetectable viremia within 6 months. Here, we compared long-term treatment responses and odds of detecting drug resistance between subtype A1 versus D HIV-1 infections.

Methods: 500 chronically-infected individuals enrolled just prior to initiation of NNRTI based therapy between 2005-2010 were followed >7 years in the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort. Pre-therapy plasma HIV-1 genotype was obtained by Sanger sequencing of HIV-1 *pol* and subtyped by RIP 3.0. Piecewise linear mixed-effects models were used for trajectory analyses. Definitions used were: viral load blips (>=1000 copies/mL), virologic suppression (<=400 copies/mL to accommodate older detection limits), adherence (Medication Event Monitoring System), loss to follow-up (lack of viral load measurements within 180 days before study cutoff on Jan-1-2013), post-therapy stool microbial community compositions (V3-V4 16S rRNA sequences processed with QIIME, R, and Phyloseq).

Results: A total of n=198 subtype A1 and n=156 subtype D infections were detected. Pre-treatment, subtype D was associated with a marginally lower pre-therapy CD4 count (A1 versus D: median 141 vs 123, Mann-Whitney p=0.06) but baseline viral load did not differ (median 5.1 vs 5.1, Mann-Whitney p=0.8). Upon therapy initiation, 84% A1 and 88% D individuals achieved virologic suppression within 6 months. Over the >7 years follow up, neither viral load, CD4 trajectories nor adherence differed (piecewise linear mixed-effects models p=1.0 and p=0.6 Table1; mean adherence 91% vs 89%, unpaired t-test p=0.2). Infections by the two subtypes also did not differ in (i) percentage of individuals experiencing blips (10% vs 7%, Fisher's 2-tailed p=0.4), (ii) odds of developing drug resistance over the span of 7 years (all Fisher's 2-tailed p>0.4; 10% vs 9% of participants had drug resistance by year 5), (iii) loss to follow-up by year-7 (30% vs 32%, Fisher's 2-tailed p=0.8), and (iv) stool microbial community compositions at year-7 (p=0.8, n=45 A1 and n=19 D, PERMANOVA of inter-community Jensen-Shannon Distance).

Conclusion: We found no difference in treatment outcomes between people in Uganda infected with subtype A1 or D HIV-1 and initiated on NNRTI -based therapy over 7-years of observation.

Table 1. Median of median CD4 counts/uL per participant by year. Trajectories between subtype A1 and D infections were similar and gradually increased over the span of 7-year follow-up (all Mann-Whitney p>0.3).

Year Post-Therapy	A1 median (IQR)	D median (IQR)	Mann-Whitney p-value
1st	224 (159-290) n=194	216 (148-304) n=153	0.7
2nd	275 (213-370) n=184	266 (204-393) n=143	1
3rd	337 (236-418) n=171	329 (227-431) n=137	0.9
4th	345 (263-443) n=148	384 (257-482) n=121	0.3
5th	374 (276-479) n=119	387 (295-514) n=93	0.4
6th	412 (303-586) n=49	446 (367-531) n=46	0.3
7th	535 (359-587) n=12	509 (340-679) n=12	0.7

508 HIV CONTROLLERS MAINTAIN VIRAL SUPPRESSION DESPITE WANING T-CELL RESPONSES ON ART

Nikolaus Jilg[1], Pilar Garcia-Broncano[2], Michael Peluso[3], Florencia Pereyra[4], Ronald Bosch[5], Carla Roberts-Toler[5], Cornelius N. Van Dam[6], Michael Keefer[7], Daniel R. Kuritzkes[4], Alan Landay[8], Steven G. Deeks[3], Xu G. Yu[2], Paul E. Sax[4], Jonathan Z. Li[4]

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Background: Robust HIV-specific T cell responses are a hallmark of HIV controllers (HCs). We assessed the impact of antiretroviral therapy (ART) on HIV-specific T cell responses and the ability of HCs to maintain HIV suppression after discontinuation of ART.

Methods: A5308 is a prospective, open-label study of rilpivirine, emtricitabine and tenofovir disoproxil fumarate (RPV/FTC/TDF) in ART-naive HCs with viral loads (VLs) <500 cp/mL for ≥12 months. HIV-specific T cell responses were measured by intracellular cytokine staining assays in response to HIV gag pool stimulation. Outcomes were evaluated by repeated measures GEE models. In addition, viral load outcomes from HCs in the UCSF SCOPE cohort were included if they had been treated with ART with subsequent VL measurements after ART discontinuation.

Results: Thirty-five HCs completed ≥24 weeks of ART in A5308 and were analyzed. Before ART, higher levels of HIV-specific CD4+ and CD8+ T cell responses were associated with undetectable viremia either by the integrase-single copy assay or the Abbott viral load assay. After 24-48 weeks of ART, significant decreases were observed in a broad range of HIV-specific CD4+ and CD8+ T cell responses. These included CD4+ T cells expressing IFN-γ (-0.32 percentage points (%) [95% confidence interval -0.50%, -0.14%], p<0.001), IL2 (-0.19% [-0.37%, -0.02%], p=0.03), TNFα (-0.53% [-1.1%, 0.02%], p=0.06), and CD8+ cells expressing IFN-γ (-0.23% [-0.47%, 0%], p=0.05), TNFα (-0.32% [-0.58%, -0.07%], p=0.01), and CD107 (-0.38% [-0.82%, 0.06%], p=0.09). Furthermore, significant reductions were found in the percentages of polyfunctional HIV-specific CD4+ and CD8+ cells expressing multiple cytokines (CD4+ IFN-γ+ TNFα+ CD107+: -0.08%, p=0.004; CD8+ IFN-γ+ TNFα+ CD107+: -0.13%, p=0.001). Four HCs from A5308 and 6 HCs from the UCSF SCOPE study discontinued ART after a median [Q1, Q3] of 33 [25, 65] weeks of treatment. Two of the HCs had detectable VLs immediately preceding ART initiation. In the first 24 weeks after ART discontinuation, only 1 of the 10 HCs had a detectable VL (107 HIV-1 RNA copies/mL). This participant also had the highest pre-ART VL (53 HIV-1 RNA copies/mL).

Conclusion: ART significantly reduces both HIV-specific CD4+ and CD8+ T cell responses in HIV controllers. ART did not adversely affect controller status as HIV controllers maintained a low viral load after ART discontinuation.

509 RESTRICTED MEAN SURVIVAL TIME AS A TREATMENT MEASURE IN HIV/AIDS CLINICAL TRIALS

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Background: Under- or over-estimation of the hypothesized failure rates in the definition of non-inferiority bounds for a hazard ratio (HR) estimand can significantly impact on the probability of a trial demonstrating non-inferiority for a hazard ratio and complicate the interpretation of the study findings. The restricted mean survival time (RMST) measure have not been used as primary measure of efficacy in HIV/AIDS clinical trials and may offer a powerful alternative to the hazard ratio. We compared analysis based on the difference in RMST (Δ-RMST) measure with 2 treatment-effect measures in a recent HIV equivalence trial, and investigated the performance and characteristics of Δ-RMST-based analysis.

Methods: Primary and secondary virologic failure (VF) outcome measures from ACTG A5257 were reanalyzed using hazard ratio (HR) and Δ-RMST estimands and compared the to the original study results based on risk difference estimated by Kaplan-Meier (RDKM). A5257 equivalence bounds were transformed for each estimand assuming exponential VF distributions and A5257 design characteristics. The performance and operating characteristics of Δ-RMST-based analysis in the setting of non-proportional hazards ratio were investigated in a simulation study.

Results: Table summarizes results of the analyses in the ACTG 5257 study and alternative analyses. Analyses based on Δ-RMST globally led to similar conclusions as the published finding based on RDKM. In contrast, analyses based on HR provided some discordant equivalence conclusions compared both with the initial analyses based on RDKM and the Δ-RMST despite that appeared driven by very low failure rates in one group. Results of our simulation study indicated that the violation of the proportional hazards assumption may negatively an impact the probability of declaring equivalence for a Δ-RMST based analysis.

Conclusion: The RMST based analysis could be a promising alternative measure of efficacy in HIV/AIDS clinical trials although further discussion to define non-inferiority bounds is needed.

		Comparison					
		ATV/r vs RAL		DRV/r vs RAL		ATV/r vs DRV/r	
Method	Equivalence bounds*	Point estimate	97.5% CI	Point estimate	97.5% CI	Point estimate	97.5% CI
Virologic failure							
RD_{KM}	+/-10%	3.4%	[-0.6 to 7.4]**	5.6%	[1.4 to 9.8]**	-2.2%	[-6.7 to 2.2]**
HR	0.56 , 1.50	1.14	[0.82 to 1.58]	1.40	[1.0 to 1.93]	0.81	[0.6 to 1.10]**
Δ-RMST	- 5.47, +5.18	-2.32 wk	[-4.7 to 0.08]**	-3.67	[-6.2 to -1.1]	1.35	[-1.4 to 4.1]**
Virologic or Tolerability failure							
RD_{KM}	+/-10%	14.9%	[10.2 to 19.6]	7.5%	[3.2 to 11.8]	7.5%	[2.3 to 12.7]
HR	0.63 , 1.43	2.4	[1.7 to 3.0]	1.55	[1.1 to 2.1]	1.46	[1.1 to 1.9]
Δ-RMST	- 5.50, +5.30	-9.5 wk	[-12.6 to -6.3]	-4.06	[-6.8 to -1.4]	-5.4	[-8.8 to -1.9]

*** Equivalence shown.*

510 HOME VS SELF-INITIATED ART REFILL: CLINICAL, IMMUNOLOGICAL, AND VIROLOGIC OUTCOMES

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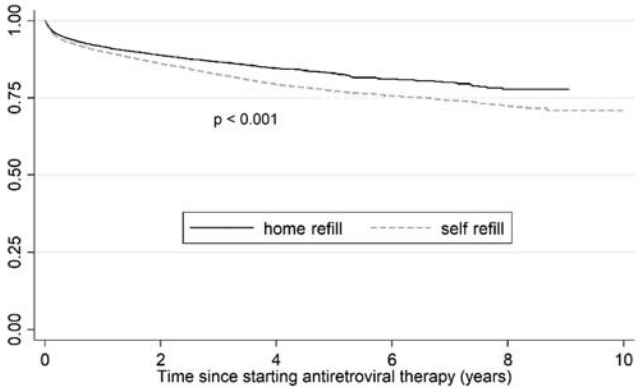
Background: Antiretroviral therapy (ART) delivery by courier to the patient's home (home refill) is a novel intervention that may improve clinical outcomes and reduce indirect costs for individuals in low- and middle-income countries (LMICs). We aimed to compare clinical and virologic outcomes for patients obtaining medication refills at their local pharmacy (self refill) vs. home refill in Aid for AIDS (AFA), a large South African private sector HIV/AIDS programme.

Methods: Retrospective cohort analysis of ART naïve HIV-infected adults in AFA who initiated first line NNRTI based ART regimen between January 2002 and July 2010 was performed. Patients were selected to switch to home refill based on the discretion of AFA. Primary endpoint was all-cause mortality; secondary endpoints were viral suppression (VL< 400 copies/mL) and median CD4+ T-cell response (cells/μl) (from baseline) at 6-month intervals. We compared the crude survival between self-refill and home refill using Kaplan–Meier plots and a log-rank test. We performed Cox regressions to model the individual and simultaneous effects of baseline variables and mode of ART delivery on all-cause mortality, adjusting for propensity score.

Results: 40,939 patients, contributing 66,204 years of follow-up were recorded. The most common first line regimen was efavirenz + lamuvidine + zidovudine, followed by efavirenz + emtricitabine + tenofovir in later years. Emerging at 24 months, the home refill group had improved median CD4+ T-cell count response (451 vs. 387, respectively, p < 0.01), and the likelihood of

virologic suppression (81% versus 71%, respectively, p-value <0.001), compared to the self-refill group. Home refill (vs. self-refill) was associated with better survival (adjusted hazard ratio = 0.90 [95% CI: 0.84-0.96], p-value for log-rank test < 0.001) (Figure 1).

Conclusion: Home refill is associated with improved clinical, immunological, and virologic outcomes compared to self-refill for HIV-infected adults in this private AIDS programme in South Africa. Home refill offers a promising additional option to the growing ART service delivery models and should facilitate the UNAIDS 90-90-90 targets in LMICs.



511 EFFECTIVENESS OF SINGLE- VS MULTIPLE-TABLET REGIMENS AS 1ST-LINE ART IN ICONA COHORT

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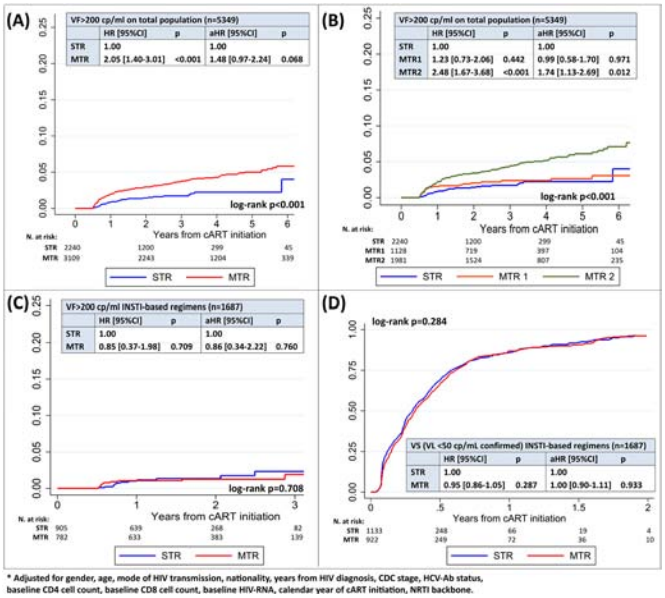
Background: Complexity of antiretroviral therapy (ART) has been associated with adherence and virological control. Single-tablet regimens (STRs) are currently recommended for ART initiation. However, the availability of both new and generic treatment options prompts the need of an updated comparison of STRs vs multiple tablet regimens (MTRs)' effectiveness as first-line therapy.

Methods: All naïve patients (pts), enrolled in Icona cohort, starting ART from 2011 to 2017 with currently recommended STRs or MTRs, were included. MTRs were divided in: MTR1 (2 pills QD) and MTR2 (3 pills QD or BID). Probability of virological failure (VF) [confirmed viral load (VL)>200 cp/mL after 6 months of ART] was estimated by Kaplan-Meier curves according to treatment group. The risk of VF in STRs vs MTRs group was compared by Cox regression analysis. In the subset of patients starting an integrase-inhibitors (INSTI)-based regimen a sensitivity analysis on the main end point of risk of VF and a separate analysis on the chance of achieving virological suppression (VS) [confirmed VL<50cp/mL] were performed. An ITT approach, ignoring treatment changes, was applied.

Results: 5,349 pts were included. STRs were started in 2,240 pts and MTRs in 3,109 pts (1,128 pts MTR1; 1,981 pts MTR2). ART was started in: 2011-2013 in 2,098 pts, 2014-2015 in 1,904 pts, 2016-2017 in 1,347 pts (STRs were 22%, 52% and 59% of the regimens, respectively). Regimens were based on: INSTI in 31%, PI/b in 33% and NNRTI in 36% pts, respectively. The 2-year probability of VF was higher in MTR versus STR group (2.9% vs 1.4%, p<0.001). However, after stratifying MTR group by number of pills/administrations, the risk of VF was higher in MTR2 vs STR group (p<0.001), but comparable between MTR1 and STR groups (p=0.442). By multivariable analysis, after controlling for main confounders, MTR2 group was associated to a higher risk of VF compared to STR (aHR=2.69, p=0.012), whereas no differences were observed between MTR1 and STR groups [Fig 1a, 1b]. In pts starting an INSTI-based regimen, the 2-year probability of VF (1.35% in STRs vs 1.27% in MTRs, p=0.708) and of VS (93.3% in STRs vs 93.9% in MTRs, p=0.284) did not significantly differ between the treatment groups [Fig 1c, 1d].

Conclusion: Among currently recommended ART regimens, STRs and 2-pills QD MTRs showed a similar impact on virological control, a proxy of patient's adherence. Among INSTI-based regimens, the number of pills/ daily administrations does not seem to influence virological outcome.



512 BETTER VIROLOGICAL OUTCOMES WHEN INITIATING EARLY ART IN THE HPTN 071 (POPART) TRIAL

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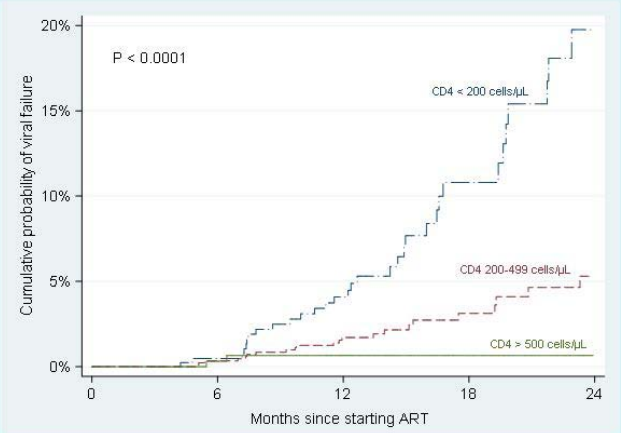
Background: There have been concerns about reduced adherence and HIV viral suppression (VS) amongst clinically well HIV-positive people initiating antiretroviral treatment (ART) with high pre-ART CD4 counts. We compared virological outcomes in individuals initiating ART irrespective of CD4 count in the HPTN 071 (PopART) trial in South Africa, in which ART initiation irrespective of CD4 count was offered prior to routine implementation.

Methods: This cohort study included adults initiating ART between Jan. 2014–Nov. 2015 at three facilities providing ART irrespective of CD4 count. VS (viral load <400 copies/ml), time to first virological failure (VF) (>1000 copies/ml) and viral rebound (>400 copies/ml) amongst those achieving VS were compared between individuals in three strata of baseline CD4 count up to 30 months after starting ART, using routine facility data.

Results: 1901 participants were included, of whom 477 (25.1%), 1024 (53.9%) and 400 (21.0%) had baseline CD4 counts <200, 200–499 and ≥500 cells/µL, respectively. Amongst those with baseline CD4 count ≥500 cells/µL, VS was ≥94% at all six-monthly intervals to 30 months. Between months 18–30, the risk of an elevated viral load (>400 copies/ml) was 70% lower amongst those with baseline CD4 count ≥500 cells/µL (3.3%) compared to those with baseline CD4 count 200-499 cell/µL (9.2%), adjusted relative risk (aRR)=0.30 (95% CI: 0.12–0.74, P=0.010); while those with baseline CD4 count <200 cells/µL had an increased risk (23.4%), aRR=2.40 (95% CI: 1.52–3.79; P<0.0001). The incidence of VF was inversely related to baseline CD4 count, declining from 7.0 per 100 person-years for those with baseline CD4 count <200 cells/µL, to 2.0 for those with CD4 count 200–499 cells/µL to 0.5 for those with CD4 count ≥500 cells/µL (P<0.0001); and after 24 months the cumulative probability of VF was 19.8%, 5.3%, and 0.7% in those same groups, respectively (Figure 1). In multivariable analyses, participants with baseline CD4 count ≥500 cells/µL had

an independently reduced risk of VF, adjusted hazard ratio (aHR)=0.23 (95% CI: 0.05–0.97; P=0.045), while those with CD4 <200 cells/μL had a three-fold raised risk, aHR=3.49 (95% CI: 2.00-6.14; P<0.0001).
Conclusion: Despite initial concerns of reduced ART adherence amongst clinically well HIV-positive people initiating ART with high CD4 counts, participants in this study initiating ART with CD4 count ≥500 cells/μL had much better virological outcomes than those with baseline CD4 count <500 cells/μL.

Figure 1: Kaplan-Meier failure estimates of confirmed virological failure (two consecutive viral loads >1000 copies/ml) according to baseline CD4 count strata after starting antiretroviral treatment.



513 RCT OF INDIVIDUALIZED COMMUNICATION STRATEGY AMONG HIV-INFECTED PERSONS STARTING ART

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Background: Several strategies have been designed to improve retention in care and viral suppression (VS) in patients starting antiretroviral therapy (ART). In Latin America few strategies have been locally tested in a randomized way and evidence-based decisions are scarce.
Methods: We conducted a multicentric RCT including naïve patients prescribed ART. The main goal was to compare retention in care and VS between arms. Subjects starting ART were randomly assigned to standard of care follow-up (SOC) or SOC plus an individualized communication strategy (ICS). At weeks 2,4 and every 4 weeks up to 1 year, trained personnel contacted patients using patient-selected communication method to screen for retention and adherence problems with a semi-structured interview. The primary outcome was successful linkage, defined as ambulatory care in the last 6 months with no ART interruption; secondary outcomes were VS defined as HIV-RNA <200 cps in the last measurement and successful treatment defined as the presence of successful linkage and/or VS. Descriptive statistics were used for baseline characteristics. Risk differences (RD) and 95% confidence intervals (CI) were estimated using linear regression for primary and secondary outcomes obtaining crude and adjusted estimates.
Results: A total of 207 participants were randomized (107 to SOC, 100 to ICS). Median age was 31 yrs (IQR 26,40), 80.2% were male, 59% were MSM, 26.4% were immigrants. Median baseline HIV-RNA log was 4.43 (IQR 3.73,5.05) and CD4 count/mm3 was 398 (IQR 220,576). There was not significant RD in treatment success across arms in the crude (SOC=0.62, ICS=0.68, RD=0.06, 95%CI: -0.07,0.19) and adjusted by sex, age, transmission category, immigration status and baseline CD4 (SOC=0.29, ICS=0.38, RD=0.09, 95%CI: -0.04,0.22) estimates. VS was higher in the SOC arm, but not statistically significant (SOC=0.55, ICS=0.49, RD=-0.06, 95%CI: -0.15, 0.12). Successful treatment was lower among SOC (0.66) than among ICS (0.72) but not statistically significant (RD=0.06, 95%CI: -0.07, 0.18).
Conclusion: In a mostly male MSM cohort in Argentina, linkage was successful one year after ART initiation in approximately two thirds of the population. However, over one quarter was not linked to care at one year. The strategy showed increased linkage and treatment success but lower VS. None of these findings was statistically significant. New strategies need to be developed to engage hard-to-retain patients, and to increase VS among those retained under care.

Table: Summary table of baseline characteristics and RCT outcomes with Risk Differences and 95% Confidence Intervals

	Total (n:207)	ARM A (n:107)	ARM B (n:100)	Crude RD (95%CI)	Adjusted RD (95%CI)
Demographic Characteristics					
Age (median, IQR)	31 (26,40)	31 (26,40)	31 (26,40)	---	---
Male at Birth	0.8	0.79	0.814	---	---
MSM	0.59	0.59	0.59	---	---
Education Years (median, IQR)	12 (10,13)	12 (10,14)	12 (9,13)	---	---
Non-Immigrant	0.73	0.76	0.71	---	---
Commorbidities					
Recreational Drug User	0.25	0.238	0.26	---	---
Alcohol User	0.51	0.49	0.53	---	---
History of Psichiatric Treatment	0.03	0.05	0.01	---	---
Clinical and laboratory data					
Baseline Events	0.03	0.038	0.021	---	---
Baseline Viral Load (log) (median, IQR)	4.43(3.73,5.05)	4.60(3.90,5.15)	4.32(3.60,5.02)	---	---
Baseline CD4 Count (median, IQR)	398 (220,576)	389 (197, 559)	398 (266,587)	---	---
Outcomes					
Successful Linkage	0.647	0.617	0.68	0.063 (-0.067,0.193)	0.090 (-0.042,0.222)
Viral Suppression	0.57	0.551	0.49	-0.061 (-0.197,0.075)	-0.016 (-0.156,0.125)
Successful Treatment	0.691	0.664	0.72	0.056 (-0.069,0.182)	0.100 (-0.024,0.225)

RD: Risk difference, CI: Confidence Intervals, MSM: men who have sex with men. Adjusted models considered age, sex, transmission category, immigration status and baseline CD4.

514 PROJECT RHAE: A PILOT STUDY OF RAPID ART START AND RESTART IN BALTIMORE CITY

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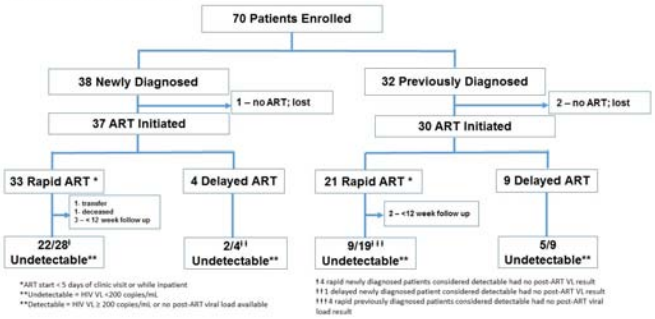
Background: Rapid HIV Treatment Initiation (RHTI) has shown good clinical outcomes in a variety of settings. Data are limited on the feasibility of RHTI in areas predominately affecting African Americans with high rates of poverty and in previously diagnosed patients. We conducted a pilot study of RHTI and treatment reinitiation (RHTRI) in an academic medical center and public health STD clinic in Baltimore.
Methods: We recruited patients newly diagnosed (ND) or previously diagnosed (PD) with HIV not on ART from the Johns Hopkins (JH) John G. Bartlett Specialty Practice, the JH inpatient HIV service, the JH Emergency Department and the Baltimore City Health Department STD clinics. A baseline and 4 week survey of demographics; mental health and substance use; barriers and facilitators to care; and acceptability of RHTI/RHTRI was performed. A survey-only phase began 2/13/17 and 8/30/17 a RHTI and RHTRI phase was added in which clinic and inpatient providers prescribed ART at first clinic visit or during hospitalization. We evaluated survey, ART initiation (rapid vs. delayed) and VL data for patients recruited through 9/1/18 with >12 week follow up. VL ≥ 200 copies/mL or no post-ART VL was considered detectable.
Results: From 2/13/17 to 9/1/18, 70 patients enrolled (38 ND, 32 PD). Most were African American (84%), male (70%) with HIV risk factor MSM (34%) or heterosexual sex (30%). Mean age was 35±12 years and 41% had an annual household income of <$5,000/yr. 25% reported recent panic symptoms (PHQ-A), 22% major or severe depressive symptoms (PHQ-8) and 41% at-risk alcohol use (AUDIT-C). 99% reported they would start same-day ART if available. 87% of ND and 66% of PD patients received rapid ART (Figure 1). 22/28 (79%) rapid ND patients achieved an undetectable VL (UDVL) vs. 2/4 (50%) delayed. 9/19 (47%) rapid PD patients had UDVL vs. 5/9 (56%) delayed. Median time to UDVL was 50 days for ND (50 days rapid vs. 42 days delayed) and 56 days for PD (31 days rapid vs. 83 days delayed).
Conclusion: RHTI and RHTRI were highly acceptable and demonstrated promising rates of UDVL in this predominately African American population with high rates of poverty, mental health issues and hazardous alcohol use. Rapid PD patients had lower rates of UDVL than delayed PD but median time to UDVL was faster in the rapid group and sample size is small. Ongoing recruitment and follow up will help characterize the effectiveness of RHTI/RHTRI in achieving and maintaining durable VL suppression in these key patient groups.

Figure 1: ART and VL outcomes of patients recruited as of 9/1/18



515 HIGH RATES OF VIROLOGIC SUPPRESSION AFTER RAPID ART START IN A SAFETY-NET CLINIC

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Background: Little is known about long-term viral suppression outcomes for patients initiating antiretroviral therapy (ART) the same day as or shortly after HIV diagnosis (RAPID ART).

Methods: The Ward 86 HIV Clinic in San Francisco is a public health funded clinic that adopted immediate ART for persons newly diagnosed with HIV in 2013. Patients were referred from San Francisco testing sites or the hospital to Ward 86, offered same or next-day intake appointments, and received multidisciplinary evaluation, with education, support, and insurance enrollment/optimization. Patients were offered same-day ART and provided 3-5-day starter packs and prescriptions of ART, check-in calls, and follow-up appointments within 1-2 weeks. Demographic characteristics, baseline CD4 counts, and viral loads (VL) were extracted from the medical record. Subsequent VLs were obtained from public health surveillance data, regardless of testing site. Kaplan-Meier curves summarized distribution of times to 1st virologic suppression and suppression at the last VL measurement.

Results: Of 225 patients referred to the Ward 86 RAPID ART program from 2013-17, 4 declined ART, 3 were not offered ART and 2 were lost to follow-up before the RAPID visit. Of the 216 patients (96%) started on immediate ART, median age was 31 years; 7.9% women; 11.6% African American, 26.9% Hispanic, 36.6% white; 51.4% with substance use disorder; 48.1% with major mental health diagnosis; 30.6% unstably housed; median baseline CD4 441; median VL 37,011 copies/mL. Median time from HIV diagnosis to ART start: 7 days; from RAPID intake to ART start: 0 days; from HIV diagnosis to VL <200: 60 days. The median follow-up time for the sample was 1.09 years (0-3.92). By 1 year after follow-up, 95.8% had achieved VL suppression to <200 at least once. Among patients who initially suppressed, 15% experienced one or more episodes of viral rebound, but most (75%) resuppressed to <200 copies/mL. The median number of VL measures for the cohort over the period of follow-up was 4 (1-22). At the last recorded VL result, 92.1% of all patients were suppressed.

Conclusion: In an urban HIV clinic with high rates of mental illness, substance use and housing instability, immediate ART initiation after HIV diagnosis resulted in virologic suppression in >90% at last VL measurement at a median of 1.09 years after ART start. Rapid ART implementation within safety-net populations is acceptable, feasible, and successful with a multidisciplinary care team and municipal support.

516 DEPRESSION IS A STRONGER PREDICTOR OF EXECUTIVE DYSFUNCTION IN HIV+ WOMEN THAN MEN

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Background: HIV-infected (HIV+) women appear more vulnerable to neurocognitive impairment (NCI) than HIV+ men, perhaps due to mental health factors. We assessed the combined effects of depression, HIV-serostatus, and biological sex on NCI.

Methods: 858 HIV+ (429 women; 429 men) and 562 HIV- (281 women; 281 men) from the Women's Interagency HIV Study (WIHS) and Multicenter AIDS Cohort Study (MACS) completed the Center for Epidemiologic Studies Depression (CES-D; 16 cutoff) scale and measures of psychomotor speed/attention (Trail Making Test [TMT] Part A, Stroop word reading and color naming trials, Symbol Digit Modalities Test [SDMT]), executive (TMT Part B, Stroop color-word [interference] trial), and motor function (Grooved Pegboard) over multiple visits. WIHS and MACS participants were matched according to HIV-serostatus, age, race, and education. Generalized linear mixed models were used to examine the combined and separate associations of depression (time-varying), sex, and HIV-serostatus on NCI (T-scores<40) after covariate adjustment. Covariates included education, age, income, alcohol, recreational, and cigarette use, and prior test exposure. In HIV+ analyses, we also controlled for antiretroviral use, CD4 count (current and nadir), viral load, and prior AIDS diagnosis.

Results: The association between depression and Stroop interference trial performance differed by HIV-serostatus and sex. HIV+ depressed women had a greater odds of impairment versus HIV+ depressed men (OR=3.29, 95%CI 1.25-8.69, P=0.02) whereas HIV- depressed women and men showed a similar probability of impairment. Not only did depression exacerbate the interactive association between HIV and sex, but it also exacerbated the HIV+ female vulnerability as HIV+ depressed women also had a greater odds of impairment versus HIV- depressed women (OR=5.03, 95% CI 1.36-18.61, P=0.01) and HIV-depressed men (OR=3.14, 95%NCI 1.09-9.06, P=0.03). Among HIV+ depressed individuals, women remained at a higher odds of impairment after accounting for HIV-related factors (OR=3.93, 95%CI 1.24-12.46, P=0.02). Regardless of HIV-serostatus and sex, depression was associated with greater impairment on SDMT, Stroop word reading, TMT Part B, and GP non-dominant hand (P's<0.05).

Conclusion: Depression contributes to NCI across a broad range of cognitive domains in HIV+ and HIV- individuals, but HIV+ depressed women show greater vulnerabilities in executive function. Treating depression may help to improve cognition in patients with HIV infection.

517 GENDER AND COINFECTIONS CONTRIBUTE TO IMMUNE ACTIVATION IN TREATED HIV INFECTION

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Background: Immune activation, a central component of HIV pathogenesis, has been associated with morbidity and mortality even in successfully ART-treated individuals. However, the underlying mechanism of persistent immune activation is not well understood. Here we analyze how gender and co-infections such as hepatitis B (HBV), hepatitis C (HCV) or tuberculosis contribute to persistent, low-level immune activation.

Methods: From the observational African Cohort Study (AFRICOS), 2745 specimens were collected from January 2013 to December 2016 along with medical history, sociodemographic, non-infectious comorbidities and co-infection (tuberculosis, hepatitis B/C, syphilis) data at 11 HIV clinical care and treatment sites across 5 programs in the 4 countries (Nigeria, Uganda, Tanzania, and Kenya). In total, 13 soluble immune parameters were measured by Luminex and ELISA and the data were evaluated using univariate and multivariate methods such as random forest, principal component analyses (PCA) and Bayesian multilevel logistic regression models. *P- : Probability of negative effect from Bayesian multilevel logistic regression model

Results: 2745 specimens from 2268 HIV-positive and 477 HIV-negative individuals were included in this analysis. Within the 1147 cART treated and virologically suppressed HIV-positive individuals (<50 copies/ml), our study revealed significant gender specific immune activation expression patterns not present in HIV-negative individuals. Levels (pg/mL) of IP-10 (Male= 58.19, Female= 70.45, p <0.0001), sCD163 (M= 232233, F= 252025, p= 0.0001), and sCD25 (M= 337.9, F= 383.3, p= 0.0012) were significantly higher in females compared to males. We next applied Bayesian multilevel logistic regression models to find associations between immune parameters and the presence of co-infections. We observed that the parameters IL-6, IP-10, and CXCL9 were significantly upregulated in patients with tuberculosis (Probability of no association p< 0.01). HCV Bayesian logistic regression model analyses revealed that patients with high levels of IFN-alpha are less frequently infected with HCV (P- = 0.008).
Conclusion: Taken all together, we demonstrate the contribution of gender to immune activation in virologically suppressed individuals infected with HIV on cART (<50 copies/ml). Furthermore, elevated immune activation markers in co-infected individuals reveal that co-infections contribute to immune activation.

Median Values of Cytokines (pg/mL)

	Male	Female	p-value
TNF-alpha	1.948	1.989	0.6527
IL-6	0.7493	1.04	0.1404
CXCL10/IP-10	58.19	70.45	<0.0001
IL-10	0.36	0.36	0.318
CCL2/ MCP-1	86.38	90.1	0.2474
IL-1beta	1.75	1.75	0.6515
IFN-gamma	5.13	5.13	0.0711
MIP-1beta	147.9	145.8	0.5361
CD163	232233	252025	0.0001
CD25/ IL-2Ra	337.9	383.3	0.0012
CXCL9	49.98	49.98	0.5982
TNF RII	2174	2315	0.1669
IFN-alpha	0	0	0.5603

518 IMPORTANT SEX DIFFERENCES IN OUTCOMES FOR INDIVIDUALS PRESENTING FOR THIRD-LINE ART

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Background: Sex differences in antiretroviral therapy (ART) outcomes and in drug exposure have been reported supporting the conclusion that some ART combinations may not be as well tolerated in women compared to men. We evaluated disparities in outcomes between men and women participating in ACTG A5288, an interventional strategy trial for individuals failing 2nd-line ART in low and middle-income countries (LMIC).
Methods: Participants were assigned to cohorts based on resistance profiles and ART history: Cohort A had no LPV/r resistance, susceptibility to at least one NRTI, and stayed on their LPV/r- or ATV/r-based 2nd-line regimen; others with increasing resistance were assigned to Cohorts B, C or D and changed to a regimen that generally included DRV/r, RAL with ETR or best available NRTIs (except for those with DRV/r resistance or prior RAL exposure). The primary endpoint was virologic suppression at week 48 (VL ≤200 c/ml). In this secondary analysis, we evaluated sex differences in the primary endpoint; in confirmed virologic failure (VF: VL ≥1000 c/mL); clinical outcomes and adverse events (intent-to-treat).
Results: Women comprised 258/545 (47%) of the study population. More women than men were assigned to Cohort A. Median follow-up was 72 weeks. Fewer women than men had virologic suppression at week 48 (table). This trend occurred in all cohorts, including in Cohort A whose participants stayed on their 2nd-line regimen (39% vs 49%) and in Cohorts B, C and D who received novel regimens (83% versus 89%). Significantly more women experienced VF, Grade 3 signs and symptoms, serious adverse events and hospitalizations, but not more frequent Grade 3+ diagnoses or laboratory abnormalities.
Conclusion: More women than men entered the study in cohort A, with a resistance profile suggesting they could be suppressed on their current regimen and therefore stayed on that regimen in the study. Regimens including LPV/r or ATV/r frequently failed. The more frequent occurrence of Grade 3 signs and symptoms in women suggests that tolerability issues were under recognized in women on 2nd-line therapy with demonstrated clinical consequences. More work is needed to identify determinants of drug exposure and tolerability in women in LMIC.

	All Cohorts (n=545)		Cohort A (n=287)		Cohorts B, C and D (n=258)		Difference between M and F*
	M (n=287)	F (n=258)	M (n=127)	F (n=160)	M (n=160)	F (n=98)	
HIV-1 RNA ≤200 c/mL at week 48	205 (71%)	144 (56%)	62 (49%)	63 (39%)	143 (89%)	81 (83%)	P=0.029
Confirmed VF (≥1000 c/mL)	66 (23%)	100 (39%)	54 (43%)	91 (57%)	12 (8%)	9 (9%)	P=0.018
Grade 3+ signs and symptoms	27 (9%)	52 (20%)	18 (14%)	37 (23%)	9 (6%)	15 (15%)	P=0.002
Grade 3+ laboratory abnormalities	90 (31%)	73 (28%)	50 (39%)	52 (33%)	40 (25%)	21 (21%)	P=0.18
Grade 3+ diagnoses	48 (17%)	58 (22%)	26 (20%)	42 (26%)	22 (14%)	16 (16%)	P=0.21
SAEs	40 (14%)	58 (22%)	20 (16%)	41 (26%)	20 (13%)	17 (17%)	P=0.024
AIDS-defining events	12 (4%)	19 (7%)	7 (6%)	14 (9%)	5 (3%)	5 (5%)	P=0.19
Targeted non-AIDS-defining events	19 (7%)	15 (6%)	5 (4%)	6 (4%)	14 (9%)	9 (9%)	P=0.96
Hospitalizations	29 (10%)	47 (18%)	16 (13%)	32 (20%)	13 (8%)	15 (15%)	P=0.016
Deaths	11 (4%)	12 (5%)	8 (6%)	10 (6%)	3 (2%)	2 (2%)	P=0.98

* Cochran-Mantel-Haenszel Test stratified by cohort group (A vs. B/C/D)

519 TENOFOVIR ALAFENAMIDE VS TENOFOVIR DF IN WOMEN: POOLED ANALYSIS OF 7 CLINICAL TRIALS

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Background: Globally, the majority of people living with HIV are cis-women, who are underrepresented in clinical trials. Tenofovir alafenamide (TAF) has demonstrated an improved renal and bone safety profile relative to tenofovir disoproxil fumarate (TDF) in multiple randomized trials with similar efficacy. We pooled 7 studies to evaluate the efficacy and safety of TAF vs. TDF for ART initiation or switch in women.
Methods: Data from 779 cis-women in 7 randomized, double-blind clinical trials (2 in treatment-naïve adults, 5 in virologically suppressed adults) through W96 were analyzed. All participants who initiated or switched to TAF-based regimens (elvitegravir/cobicistat/emtricitabine [FTC]/TAF, rilpivirine/FTC/TAF, FTC/TAF, or bictegravir/FTC/TAF) were compared with those who initiated or continued TDF-based regimens. Virologic suppression (VS; HIV-1 RNA <50 c/mL) rates at W96 were determined by FDA snapshot analysis. Bone mineral density (BMD) and the renal tubular biomarkers urine beta-2-microglobulin (B2m):creatinine (Cr) ratio and retinol binding protein (RBP):Cr ratio are reported at W96. Differences were compared using Wilcoxon rank sum test.
Results: A total of 779 cis-women were enrolled (n=429 TAF, n=350 TDF). Treatment-naïve women (WTN) had a median age of 37, 35.4% were black, 26% were Hispanic/Latina, with median HIV-RNA 4.47 log10 c/mL and CD4 365 cells/mm3. Women with VS (WVS) had a median age 47 years, 50% were black, 25% were Hispanic/Latina, with median CD4 711 cells/mm3. Of WTN, 86% (TAF) and 85% (TDF) achieved VS (p=0.71) at W96. VS was maintained in

86% of WVS switching to TAF and 85% continuing TDF (p=0.99). Overall TAF and TDF were well-tolerated. Discontinuation due to adverse event/death was 0% (TAF) vs. 1.6% (TDF) in WTN and 1.3% (TAF) vs. 2.2% (TDF) in WVS. At W96 there was less impact on renal biomarkers in WTN initiating TAF- vs TDF-based regimens (p<0.001; Table), and decreases in BMD were smaller (p<0.001; Table). Women switching from TDF to TAF experienced decreases in tubular proteinuria (p<0.001; Table) and increases in BMD (p<0.001; Table) at W96.

Conclusion: Similar to the overall results in pivotal naïve and switch trials of FTC/TAF-based regimens, cis-women who initiated or switched to TAF had significantly improved bone and renal safety parameters compared to TDF, with similar rates of virologic suppression through W96. These pooled data from 7 studies demonstrate a safety advantage for initiating therapy with or switching to TAF compared to TDF in women.

Table: Renal Urine Biomarkers and Bone Mineral Density at Week 96: Female Participants

Treatment-Naïve Participants				
		TAF-Based (n=133)	TDF-Based (n=127)	p-value
RBP: Cr	% Change at W96	12.1 (-34.3, 68.3)	67.5 (-6.6, 209.9)	<0.001
B2M: Cr	% Change at W96	-37.4 (-64.8, -3.4)	13.1 (-33.9, 125.5)	<0.001
Spine BMD	% Change at W96	-0.292 (-2.500, 2.136)	-2.606 (-5.719, -0.999)	<0.001
Hip BMD	% Change at W96	-1.296 (-3.032, 0.469)	-3.938 (-5.922, -1.827)	<0.001
Virologically Suppressed Participants who Switched from TDF- to TAF-Based Regimens				
		Switched to TAF (n=296)	Continued TDF (n=223)	p-value
RBP: Cr	% Change at W96	8.0 (-33.6, 68.5)	50.8 (2.2, 142.5)	<0.001
B2M: Cr	% Change at W96	-9.5 (-48.6, 38.8)	29.2 (-15.0, 129.5)	<0.001
Spine BMD	% Change at W96	1.703 (-0.834, 4.435)	-1.055 (-3.252, 1.787)	<0.001
Hip BMD	% Change at W96	1.699 (-0.181, 3.386)	-0.831 (-3.167, 1.435)	<0.001

Data are presented as median (Q1, Q3); p-values were from Wilcoxon rank sum test.

520 EFFECT OF ANTIRETROVIRAL THERAPY AND IMMUNE RECONSTITUTION ON VAGINAL MICROBIOME

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Background: Host factors, including menarche, menstruation, and pregnancy are known to impact vaginal microbiome composition. Both HIV infection and the immune reconstitution associated with antiretroviral therapy (ART) can cause broad immunological changes in the vaginal microbiome. We assessed vaginal microbiome after starting ART and its association with immune reconstitution (>50 increase of CD4+ T-cells post ART initiation).

Methods: We characterized the vaginal microbiota of HIV-1 and HSV-2 coinfected women (n=94) who initiated ART in a trial of HSV-2 suppression with acyclovir in Rakai, Uganda. Vaginal swabs were collected 1-month pre-ART and at 4- and 6-months after ART initiation. Proportional and absolute abundance of vaginal bacteria was estimated by sequencing of the 16S rRNA V3V6 region. Vaginal community state types (CSTs) were identified using proportional abundance data with Bray-Curtis distance and hierarchal clustering by Ward's method. Microbiome composition was compared using permutational MANOVA. Changes in absolute and proportional abundance of indicator bacteria were assessed using Wilcoxon signed-rank test. Characterizing anaerobes selected by indicator analysis.

Results: We identified five vaginal CSTs among HIV+ women prior to ART initiation: one characterized by Gram-positive anaerobes (CST1), one characterized by Gram-negative anaerobes (CST2), one characterized by Gardnerella (CST3), and one characterized by Lactobacillus iners (CST4). Prior to ART, the likelihood of having a particular vaginal CST did not vary by HIV viral load or CD4+ T-cell count. ART did not have a significant impact on overall vaginal microbiome composition (p=0.74). However, among two CSTs-CST1 and CST3-abundance of Gram-positive (Anaerococcus, Finegoldia) and Gram-variable (Gardnerella) indicator bacteria decreased significantly six-months post-ART (Table 1). In contrast, indicator bacteria abundance did not change significantly for women with CST2 and CST4 post-ART. Immune reconstitution was not associated with significant vaginal microbiome changes and pre-ART vaginal CST was not associated with immune reconstitution.

Conclusion: ART initiation was associated with decreases in abundance in indicator bacteria from two vaginal CSTs, which are associated with bacterial vaginosis; however, other CSTs, including one characterized by Prevotella and one characterized by Lactobacillus iners remained stable. Overall, vaginal microbiome did not change significantly with immune reconstitution.

Table 1. Absolute abundance of vaginal microbiome indicator taxa pre- and post-ART initiation, within baseline CSTs.

Indicator taxa	Pre-ART within CST Median absolute abundance[1] (IQR)	4-month post-ART within CST Median absolute abundance[1] (IQR)	p-value	6-month post-ART within CST Median absolute abundance[1] (IQR)	p-value
CST1 (n=14)					
Anaerococcus	2.42 (1.60-2.96)	**0.84 (0.00-2.14)**	**<0.01**	**0.03 (0.00-0.99)**	**0.01**
Finegoldia	1.60 (0.00-2.04)	**0.024 (0.00-1.30)**	**<0.01**	**0.00 (0.00-0.51)**	**0.03**
CST2 (n=20)					
Prevotella	2.49 (1.79-4.02)	2.65 (0.00-4.20)	0.21	3.73 (1.36-5.06)	0.37
Sneathia	0.00 (0.00-3.23)	0.00 (0.00-2.89)	0.46	0.84 (0.00-3.23)	0.57
Bacteroidia<0.97	0.00 (0.00-2.61)	0.00 (0.00-0.86)	0.46	0.75 (0.00-2.77)	0.48
Atopobium	0.00 (0.00-3.28)	0.00 (0.00-4.21)	0.19	0.47 (1.47- 3.94)	0.21
Parvimonas	0.00 (0.00-3.59)	0.00 (0.00-2.51)	0.28	0.00 (0.00-2.96)	0.44
CST3 (n=21)					
Gardnerella	4.66 (3.43-5.06)	**2.71 (0.97-4.46)**	**<0.01**	**3.87 (2.16-4.33)**	**0.02**
CST4 (n=22)					
Lactobacillus iners	3.75 (1.83-4.76)	2.57 (0.78-4.20)	0.08	3.71 (0.89-4.02)	0.08

Pre-ART measurements taken 1 to 0 months before ART initiation. Post-ART measurements taken 5-6 months post-ART initiation (median=6 months). Wilcoxon signed rank test was used to compare vaginal microbiota pre- and post-ART and generate p-values.

1 Absolute abundances of vaginal microbiota are log-10 transformed.
Results in bold have p-value <0.05.

521 IMMEDIATE ART INITIATION IN ACUTE INFECTION IMPROVES CLINICAL OUTCOMES, SABES STUDY

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Background: Current standard of care recommends immediate ART initiation after HIV diagnosis, but recommendations are grounded in data on established infections. Aside from the high public health benefit of reduced transmission, individual benefits of starting ART in early (acute and recent) HIV infection have not been well characterized.

Methods: Two-hundred sixteen participants diagnosed with early HIV infection via monthly screening in the Sabes study (a treatment-as-prevention intervention among MSM and transwomen in Lima, Peru) were randomized to start ART immediately or after a short delay, and were categorized as having started ART within 30, 90, or >90 days after estimated date of detectible HIV infection (EDDI). Survival analyses with log-rank tests evaluated rates of virologic suppression and adverse events in the first year after HIV diagnosis. We tested differences in CD4+ counts with Kruskal-Wallis tests. Analyses were adjusted when appropriate, for time under observation or time on ART.

Results: All 105 participants who were offered same day ART started ART; five of 111 offered delayed ART did not start during the study period (p=0.03). Total adverse events and non-ART-related adverse events were less frequent in persons starting ART within 30 days of EDDI, with a trend toward fewer ART-related events than in those who started ART after 30 or 90 days (Table). While a higher proportion of the >90-day group reached virologic suppression by 24 weeks on ART, enrollment HIV viral load was highest in the <30-day group. CD4+ counts and CD4+/CD8+ ratio increased in all groups but normalized more completely in the <30-day group; adjusted for time on ART, median CD4+ at 48 weeks remained significantly higher than in those who started ART after 30 days (p=0.009). Increase in CD4+ on study was not different when adjusted by time on ART, but the greatest improvements in CD4+/CD8+ ratio were in the 31-90 day group, which began with the lowest ratios (+0.55, p=0.005).

Conclusion: In early HIV infection, those who began ART within 30 days of estimated date of HIV infection had better clinical outcomes, including fewer adverse events during the first year. While several observational studies have suggested similar findings, the Sabes study is likely the only demonstration of this effect in a randomized study, where risk of confounding is minimized.

Long-term follow-up of this cohort is ongoing to understand whether benefits of starting ART during acute infection are maintained over years.

Clinical outcomes at one year in persons starting on ART within 30, 90, or >90 days since estimated date of detectable HIV infection

	Time from estimated date of detectable infection to ART initiation			
	≤30 Days (N=38)	31-90 Days (N=76)	>90 Days (N=97)	P value
Any Adverse Event, incidence per person-year[a]	0.9	1.6	1.3	0.03
Non-ART related events	0.5	1.3	1.1	0.008
ART-related events	0.4	0.3	0.4	0.07
Viral Load @ Diagnosis (log_{10} copies) Median (IQR)	6.63 (6.11-7.15)	5.42 (4.72, 6.18)	5.79 (5.09, 6.58)	0.0001
VL suppression by 24 weeks of ART, N (%)	24 (63.2)	47 (61.8)	68 (70.1)	0.08
CD4 @ diagnosis, median (IQR)	505 (285, 572)	427 (237, 578)	412 (299, 567)	0.50
CD4 @ Week 24, median (IQR)	643 (499, 829)	536 (396, 708)	415 (321, 560)	<0.001
CD4 @ Week 48, median (IQR)	670 (509, 819)	590 (4452, 732)	543 (448, 743)	0.05[b]
CD4/CD8 ratio @ diagnosis, median (IQR)	0.77 (0.51, 0.98)	0.35 (0.18, 0.61)	0.49 (0.26, 0.75)	<0.001
CD4/CD8 ratio @ week 24, median (IQR)	1.03 (0.84, 1.38)	0.92 (0.66, 1.35)	0.54 (0.34, 0.71)	<0.001
CD4/CD8 ratio @ week 48, median (IQR)	1.16 (0.96, 1.36)	0.96 (0.61, 1.38)	0.90 (0.62, 1.16)	0.01[b]

[a] Adverse events include all reported events excepting incident bacterial sexually transmitted infections (syphilis, gonorrhea, chlamydia). [b]Additional CD4 analysis adjusted for time on ART (given differential start weeks) still resulted in significant between-group differences by week 48 (p<0.009), but non-significant difference in CD4 ratio (p=0.12)

522 VIRAL BLIPS AFTER TREATMENT INITIATION DURING ACUTE HIV INFECTION

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Background: Transient episodes of low-level HIV viremia, or blips, are observed in up to 50% of individuals on suppressive antiretroviral therapy (ART) initiated during chronic HIV infection and may be associated with clinical failure, viral evolution, and blunted reservoir decay. We described the incidence and predictors of blips after ART initiation during acute HIV infection (AHI).

Methods: Participants were offered ART during AHI from May 2009 to August 2018 in Bangkok, Thailand. Those who continued ART for ≥1 year after viral suppression (confirmed HIV RNA <50 copies/mL) were included in these analyses. A blip was defined as any HIV RNA 50-999 copies/mL immediately preceded and followed by HIV RNA <50 copies/mL without a change in ART. Negative binomial regression was used to calculate rate ratios (RRs) and 95% confidence intervals (CIs) for associations of participant characteristics at ART initiation with blips. Fiebig stage and factors that were significant (p<0.05) in unadjusted models were included in the final multivariable model.

Results: Of 299,004 samples screened, 564 participants were enrolled during AHI and 416 satisfying inclusion criteria were monitored for blips for a median of 2.7 (interquartile range [IQR] 1.9-3.9) years after achieving viral suppression. Participants had median age 26 (IQR 23-31) and were predominantly men who have sex with men (92.6%) with HIV subtype CRF01_AE (77.2%). Thirty (7.2%) participants demonstrated blips with incidence 2.7 (95% CI 1.8-3.7) per 100 person-years. Among 35 blips observed, 18 (51.4%) were 50-75 copies/mL, 14 (40.0%) were 76-199 copies/mL, and 3 (8.6%) were 200-999 copies/mL. Characteristics at ART initiation that were independently associated with blips included HIV RNA >6 log10copies/mL (RR 2.51 [95% CI 1.04-6.04], compared to ≤6 log10copies/mL) and CD4 ≤350 cells/mm3 (RR 2.46 [95% CI 1.00-6.03], compared to >350 cells/mm3). There was a non-significant trend towards increased blips after ART initiation in later Fiebig stages (Fiebig III/IV RR 1.45 [95% CI 0.63-3.31], Fiebig V [RR 2.74 [95% CI 0.73-10.35], compared to Fiebig I/II), controlling for HIV RNA and CD4.

Conclusion: Viral blips were uncommon and of generally low magnitude after ART initiation during AHI, suggesting a potential benefit of early ART initiation. As with ART initiation during chronic infection, higher HIV RNA and lower CD4 were predictive of blips. Further follow-up is needed to evaluate associations with viral reservoirs and clinical outcomes.

523 BENEFITS OF InSTI-BASED REGIMEN AT THE TIME OF PRIMARY HIV INFECTION

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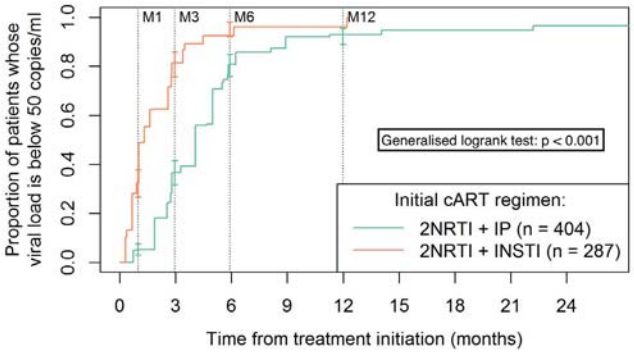
Background: Combined antiretroviral therapy (cART) containing integrase strand transfer inhibitor (INSTI) has been shown to be superior to boosted protease inhibitor (PI) in chronic HIV-infected patients. We thus compared, on a large dataset of 712 patients, the efficacy of INSTI versus PI-containing cART initiated at the time of primary HIV infection (PHI), a key period in the HIV natural history.

Methods: This multicentre observational cohort study was conducted among patients initiating cART between 2013 and 2017. Data were pulled from 2 sources: the ongoing ANRS PRIMO cohort which enrolls patients during PHI, and Dataids', a French hospital database which uses computerised medical record collected during clinical visits. The primary outcome was the time from cART initiation to reach plasma HIV-1 RNA below 50 copies/ml. Turnbull interval-censored estimator was used to draw cumulative-event curves, and groups were compared with a generalized logrank test. The CD4 T cells restoration was estimated with a segmented mixed linear model. Results were adjusted for the data source.

Results: 712 patients initiating cART during PHI were included in the study, 299 initiating with an INSTI and 413 with a PI. Patients characteristics (age, sex, sub-Saharan origin, transmission group, and baseline HIV-1 RNA, CD4 count and CD4/CD8 ratio) were similar in the two groups, except for the year of treatment initiation: the proportion of patients initiating an INSTI-based regimen increased in more recent years. Time to virological response was faster for INSTI-treated patients vs PI-treated ones (logrank test: p<0.001). Proportions of patients showing a virological response was 37% vs 6% at 1 month (±7 days) of treatment, 77% vs 38% at 3 months (±15 days), 92% vs 79% at 6 months (±30 days) and 93% in both groups at 12 months (±60 days). During the first month, INSTI-treated patients gained on average 41 more CD4 cells/µl (p = 0.046) than PI-treated ones; mean CD4 counts were similar in the 2 groups at 1 year. CD4/CD8 ratio followed the same pattern. Results were similar on a per-protocol analysis, or when comparing only Dolutegravir vs Darunavir-containing cART.

Conclusion: We show here, using 'real-life' data, both an earlier virological response and a faster immune restoration in PHI patients treated with an INSTI-based regimen.

Cumulative event curves of viral suppression



524 RECTAL AND SEMINAL HIV-1 RNA DECAY IN INFECTED MSM INITIATING WITH DTG/ABC/3TC

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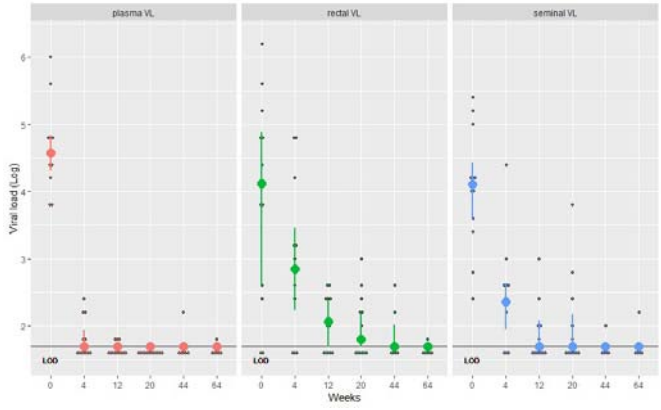
Background: Antiretroviral therapy (ART) reduces significantly the risk of HIV-1 transmission. However, after starting ART, it is not clearly established at what time the protective effect of ART is achieved in reservoirs, e.g. the rectum or semen, which is particularly important in men who have sex with men (MSM). We carried out this study to quantify HIV-1 RNA decay in rectal mucosa and semen over 64 weeks (64w) in ART-naïve HIV-infected MSM starting dolutegravir+abacavir+lamivudine (DTG/ABC/3TC).
Methods: Longitudinal cohort study of ART-naïve HIV-infected MSM. Rectal mucosal sampling was performed by high-resolution anoscopy (HRA) when possible, or by insertion of swab directly into rectum. Seminal plasma was obtained by centrifugation of semen collected at home within 2 hours before. HIV-1 RNA quantification (COBAS® Ampliprep/Taqman) of rectal mucosa and seminal plasma samples was performed at day 1 of initiating-ART (baseline) and every 4 weeks until w20 (all) and w64 (6 of 12).
Results: 118 plasma, 117 rectal (86-HRA and 31-direct) and 89 seminal samples from 12 MSM, with median (IQR) age 36 (32-42) years and median baseline-CD4+ 465 (411-520) cell/µL, were included. At baseline, HIV-1 RNA was detectable in all plasma, seminal and 10 of 12 rectal samples with median viral load (VL) of 4.58 (4.32-4.84) $\log_{10}$ copies/mL, 4.10 (3.59-4.44) $\log_{10}$ cp/mL and 4.54 (3.82-5.11) $\log_{10}$ cp/swab, respectively. All participants achieved plasma virologic suppression by w20 (7 of them by w4) (Figure). At w20, HIV-1 RNA was detectable in 5 of 12 seminal and 6 of 12 rectal samples with median VL of 2.50 (2.08-2.73) $\log_{10}$ cp/mL and 2.24 (2.14-2.46) $\log_{10}$ cp/swab, respectively. Of them, 3 seminal and 3 rectal samples were from aviremic individuals at w4. Median w20-CD4+ was 678 (532-797) cell/µL. At w64, HIV-1 RNA was only detectable in 1 of 6 seminal (VL=2,26 $\log_{10}$ cp/mL) and 1 of 6 rectal (VL=1,81 $\log_{10}$ cp/swab) samples.
Conclusion: Viral decay after initiating DTG/ABC/3TC is slower in rectal mucosa and semen than in plasma. Half of the patients achieve undetectable HIV-1 RNA level in secretions at six months, although in some patients viral shedding persists up to one year.



525 MODELING ANTIRETROVIRAL DRUG RESISTANCE IN SOUTH AFRICA, THE MARISA PROJECT

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Background: The scale-up of antiretroviral therapy (ART) from 2004 in South Africa substantially reduced AIDS-related deaths and new HIV infections. However, its success is threatened by the emergence of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI). In this context, the MARISA project (Modelling Antiretroviral drug Resistance In South Africa) aims at investigating the time trends and driving factors of NNRTI resistance by integrating local specificities of HIV epidemiology and the evolution of drug resistance.
Methods: MARISA is a compartmental model built to capture the emergence and spread of NNRTI resistance in South Africa in 2005-2016. A first dimension accounts for the continuum of care: infection, diagnosis, first-line treatment with suppression or failure, and second-line treatment. Other dimensions include: disease progression (CD4 counts), NNRTI resistance, and gender. Model parameters are informed using data from the IeDEA-SA cohorts and literature estimates, or fitted using outputs from the Thembisa/UNAIDS models. Counterfactual scenarios are examined to assess the impact of increased treatment rates, earlier implementation of the treat-all policy, early switch to second-line treatment in case of failure, and drug-resistance testing of ART initiators.
Results: MARISA can reproduce the time trends of HIV in South Africa in 2005-2016, with a decrease of new infections, undiagnosed individuals, and AIDS-related deaths (Fig 1). It also captures the dynamics of NNRTI resistance spread: a steady increase of acquired drug resistance (ADR, affecting 83% of individuals failing first-line treatment in 2016), and of transmitted drug resistance (TDR, reaching 7% of ART initiators in 2016). During that period, increasing treatment coverage would have resulted in fewer new infections and deaths, at the cost of higher TDR (+34% in 2016 for doubling the treatment rate). Earlier implementation of the treat-all policy by 5 years would have had a similar effect. Conversely, improving switching to second-line treatment would have led to lower TDR (-18% in 2016 for doubling the switching rate) and fewer new infections and deaths. Implementing baseline drug resistance testing would have had little impact.
Conclusion: A rapid ART scale-up and delayed switching to second-line treatment were the key drivers of the observed spread of NNRTI-resistance in South Africa. Timely switch to second-line ART would have reduced but not prevented the spread of NNRTI resistance.

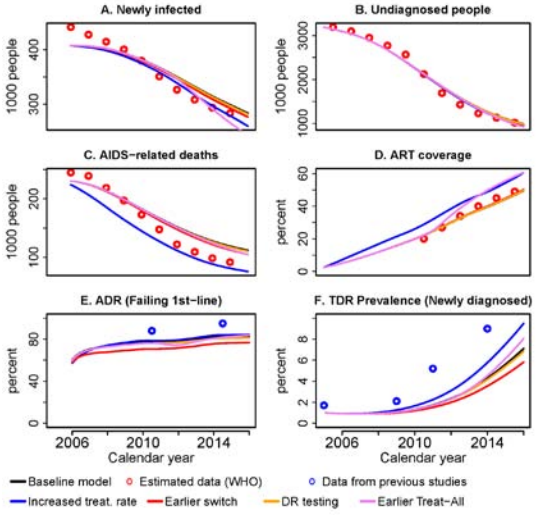

Figure 1: The MARISA model was fitted to Thembisa/UNAIDS estimates: (A) annual number of new infections; (B) number of undiagnosed infected individuals; (C) annual number of AIDS−related deaths; and (D) ART coverage. Outputs from the MARISA model included (E) the prevalence of acquired drug resistance among individuals with first−line treatment failure and (F) the prevalence of transmitted drug resistance among newly diagnosed people, which are compared to results from cross−sectional surveys (blue points). The colored lines represent the following scenarios: doubled treatment initiation rate (blue), doubled switching rate from first− to second−line treatment (red), implementation of baseline drug resistance testing (yellow) and 5−year earlier implementation of the Treat−All policy (violet).

526 INTEGRASE AND OTHER TRANSMITTED HIV DRUG RESISTANCE: 23 US JURISDICTIONS, 2013-2016

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Background: Drug resistance testing based on protease (PR) and reverse transcriptase (RT) gene mutations is recommended for all patients at entry to HIV care and should include testing for integrase (IN) mutations when transmitted resistance to integrase strand transfer inhibitors (INSTIs) is a concern. HIV sequence data from drug resistance tests are reported to the U.S. National HIV Surveillance System (NHSS) as a part of routine surveillance activities. We analyzed data from 2013—2016 to understand trends in HIV

sequence reporting and the prevalence of transmitted drug resistance-associated mutations (TDRMs).
Methods: For persons with HIV infection diagnosed during 2013–2016 and no evidence of prior antiretroviral therapy use, we analyzed sequences collected within 3 months of diagnosis and reported to NHSS by 12/2017. We included states in which ≥20% of HIV diagnoses during the 4-year period had an analyzable sequence and defined TDRMs using the CDC HIV-1 surveillance mutation list. We examined reporting by sequence type, prevalence of TDRMs and temporal trends for sequence types reported and TDRMs detected from 2013–2016.
Results: The 23 states reported sequences for 36,288 (32%) of 113,121 HIV diagnoses from 2013–2016. Among persons with eligible sequences, prevalence of IN sequences obtained increased from 3.7% in 2013 to 23.0% in 2016 while prevalence of PR/RT sequences decreased from 99.2% to 93.0%. TDRMs were detected for 6,880 (19.0%) sequences, including TDRMs to non-nucleoside reverse transcriptase inhibitors (NNRTIs) (11.9%), nucleoside reverse transcriptase inhibitors (nRTIs) (6.8%), protease inhibitors (PIs) (4.3%), and INSTIs (0.8%). INSTI TDRM prevalence did not differ by sex, age group, or race/ethnicity. Prevalence was low for TDRMs to 2 drug classes (2.4%) or ≥3 drug classes (0.3%). TDRM prevalence increased from 2013 to 2016 for NNRTIs (11.3% to 12.4%, p=0.012) and INSTIs (0.8% to 1.1%, p=0.041) but not for other drug classes.
Conclusion: NNRTI TDRM prevalence continues to increase, outpacing all other HIV drug classes. During this period of increasing INSTI use (and IN sequence reporting) INSTI TDRM prevalence also increased. Though drug resistance testing based on PR/RT gene sequencing is recommended for all new HIV diagnoses, an increasing proportion have only an IN sequence reported, precluding detection of TDRMs for nRTIs, which remain a critical backbone of multidrug therapy.

527 IMPACT OF PRETREATMENT DRUG RESISTANCE ON TREATMENT OUTCOME IN THE ITREMA TRIAL

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Background: Prevalence of pre-treatment drug resistance (PDR) in sub-Saharan Africa has risen during scale-up of antiretroviral treatment (ART) and may result from either exposure to previous ART or infection with resistant viral strains. We assess prevalence of PDR and its impact on treatment outcomes in the first year of ART.
Methods: The ITREMA open-label randomized clinical trial (ClinicalTrials registration NCT03357588) compares treatment monitoring approaches in response to viral rebound in rural South Africa. Of 501 participants, 294 were on stable first-line ART, and 207 initiated first-line ART. For these 207, plasma collected prior to initiation was analysed batchwise. Population-based RT sequencing was performed. PDR was defined as detection of at least one 2017 IAS-USA listed major mutation. Viral load testing was performed at week 24 and week 48 of ART, and annually thereafter. Logistic regression adjusted for gender, age and baseline CD4-count was used to estimate adjusted odds ratios (aOR) for viral rebound (viral load ≥1000 copies/mL) within the first year of ART.
Results: All 207 newly initiated patients received efavirenz-based ART. 60.4% (125/207) were female. Median age was 38.8 years (IQR: 31.4–46.7). Median CD4-count at ART initiation was 191 cells/mm3 (IQR: 70–355). 194 patients had a baseline sample with viral load >250 copies/mL available for sequencing. PDR was detected in 12.9% (25/194). 20.6% of patients (34/165) with available follow-up had viral rebound during the first year of ART. Patients with PDR more frequently experienced rebound (53.3% versus 17.4%, p=0.003). 13 patients reported prior use of ART, which was associated with PDR (aOR 1.37 [95%CI: 1.13–1.67], p=0.0017). When correcting for sex, age, baseline CD4 and disclosed previous ART exposure, PDR remained associated with viral rebound (aOR 1.42 [1.22–1.64], p<0.0001). Upon differentiation between NNRTI-PDR and dual-class PDR, dual-class PDR was strongly associated with viral rebound (aOR 2.56 [2.00–3.27], p<0.0001), but NNRTI-PDR was not (aOR 1.12 [0.96–1.31], p=0.16).
Conclusion: PDR was detected in 13% of patients initiating first-line ART in this study. Dual-class PDR increased the risk of viral rebound, but solitary NNRTI-PDR did not. Reported prior ART use increased the risk of PDR. Efforts to uncover previous ART use should be made before initiating first-line treatment.

528 INTEGRASE GENOTYPIC TESTING AND DRUG RESISTANCE AMONG NEW HIV DIAGNOSES IN NEW YORK

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Background: HIV treatment guidelines state that genotypic resistance testing should be obtained at diagnosis. Integrase strand transfer inhibitors (INSTIs) have emerged as initial regimens for persons newly diagnosed with HIV because of their clinical effectiveness and tolerability. However, with widespread use of INSTIs, the concerns of transmitted integrase (IN) drug resistance and risk of virologic failure are rising among clinicians. The aims of this analysis were to explore 1) the frequency of IN testing and risk factors associated with IN testing, 2) the rate of transmitted IN drug resistance, and 3) common clinically significant INSTI-resistance mutations among persons with newly diagnosed HIV in New York State (NYS).
Methods: Persons age 13 and older diagnosed between 2013-2017 and reported to the NYS HIV registry were included in the study. The first IN nucleotide sequence for an individual was identified and flagged as an "initial" test if ordered within 3 months of the HIV diagnosis date. Persons with 1) incomplete diagnosis or test dates or 2) invalid sequences were excluded. Multivariable analysis was used to test the association between IN initial testing and sociodemographic factors. Sequences were analyzed using the NYS in-house Resistance Analysis System and compared with major INSTI resistance mutations published on Stanford HIVdb Program website.
Results: Overall, 15,345 persons were included; 59.2% had any resistance testing within 3 months of diagnosis. 20.9% (3,209) had initial IN testing; 2.5% had only IN testing. Initial IN testing increased significantly from 5.6% in 2013 to 32.4% in 2017. The likelihood of having initial IN test was lower in minorities than whites (RR:0.87, 95%CI:0.79-0.96), and higher among males with a history of male-to-male sexual contact than heterosexuals (RR:1.31, 95%CI:1.09-1.58). Resistance to ≥1 IN drug was seen in 0.7% (24) of 3,209 persons with initial tests. The most common clinically significant INST-resistance mutations were: E138A/K, N155H/S, Q148H/K/R, E92G/Q, T66A/I, G140C/S, Y143C/R.
Conclusion: Clinician ordering of initial resistance testing lags current guidelines. These data indicate that initial IN testing has increased among persons newly diagnosed with HIV. While IN drug resistance remains low, clinically significant major mutations observed suggests that transmitted IN resistance is emerging; it is importance for clinicians to order IN test at time of HIV diagnosis for treatment decision.

529 HIV-TRANSMITTED DRUG RESISTANCE IN CISGENDER MSM AND TRANSGENDER WOMEN IN LIMA, PERU

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Background: Transmitted drug resistance (TDR) mutations threaten the efficacy of first-line antiretroviral therapy (ART) in individuals initiating treatment. In Peru, genotypic resistance profiling is not routinely performed at ART initiation, and administration of a partially effective regimen can select for further resistance and lead to virologic failure. In Peru, previously reported TDR prevalence ranged from 1.0 – 4.7% as last reported before 2012.
Methods: We obtained HIV sequence data from 3 parent studies conducted in 2013 – 2017 of ART naïve cisgender men who have sex with men (cis-MSM; n=332) and transgender women (TW; n=144) in Lima, Peru. Consensus gene sequences of the 2,510 – 3,209 region of HIV pol (not codifying the entire protease and integrase genes) were interrogated for TDR using the Stanford HIVdb interpretation algorithm and scored for resistance to common nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). We calculated binomial proportions with a 95% confidence interval. χ^2 and Fisher's exact tests or generalized linear models were used to examine possible predictors of TDR.
Results: Eighty (16.8%) of 476 individuals had TDR (95% CI: 13.6, 20.5). Twenty-two unique base changes totaling 94 TDR mutations were present. Mutations conferring resistance to NNRTIs represented 88% of total TDR, and prevalence of a singular mutation (15.1%) was more common than 2 (1.3%), or 3+ (0.4%)

mutations. TDR conferring high-level resistance to any ART was found in 44 (9.2%) individuals (95% CI: 6.8, 12.2). Cis-MSM were not more likely than TW to have acquired TDR (16.9% vs 16.7%, p=1.00). Year of diagnosis, age, diagnosis as incident or prevalent infection, or residence district were likewise not associated with risk of TDR.

Conclusion: TDR prevalence within these cohorts was nearly 4-fold higher than the highest previously reported prevalence in any population in Peru. Over half of observed TDR conferred high level resistance to drugs used in first-line ART, and resistance was largely to NNRTIs. Our findings support the WHO recommendation to consider integrase strand transfer inhibitors in first-line regimens, since empiric use of NNRTIs may often fail in this population. Our study also represents the first differentiated evaluation of TDR in cis-MSM vs TW in Peru and demonstrates that although TW are at higher risk of HIV acquisition than cis-MSM, they are at similar risk of acquiring virus with TDR.

Prevalence of Transmitted Drug Resistance and Mutations Conferring High-Level Resistance Among a Population of Cisgender MSM and Transgender Women in Lima, Peru (n=476)

Type	# Mutations	Prevalence (95% CI)
Total TDR	80	16.8% (13.6-20.5)
1 Mutation	72	15.1% (12.0-18.7)
2+ Mutations	8	1.7% (0.7-3.3)
High-Level NNRTI Resistance		
K103N/S	35	7.4% (5.2-10.1)
G190A/E	5	1.1% (0.3-2.4)
Y181C	1	0.2% (0.0-1.2)
Y188C	1	0.2% (0.0-1.2)
High-Level NRTI Resistance		
M184V	4	0.8% (0.2-2.1)
L74I	1	0.2% (0.0-1.2)
TAMs*	5	1.1% (0.3-2.4)

*Thymidine Analog Mutations (TAMs), including both Type I and Type II.

530 PRE-TREATMENT HIV DRUG RESISTANCE IN BOTSWANA

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Background: Population-level monitoring of pre-treatment drug resistance (PDR) to nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and integrase strand transfer inhibitors (InSTI) in the era of antiretroviral therapy (ART) scale-up and the treat-all strategy, can inform public health strategies and interventions.

Methods: We investigated the rate of PDR in a large community cluster-randomized study termed Botswana Combination Prevention Project (BCPP) conducted across 30 Botswana communities in 2013-2018. BCPP enrolled all consenting adult citizen residents age 16-64 who lived in a random sample of approximately 20% of households. Blood specimens from HIV-positive ART-naïve participants including seroconverters were collected from 2013 to 2018. HIV sequences were obtained by long-range HIV genotyping. PDR was identified by the presence of surveillance drug resistance mutations (SDRM) associated with NRTI, NNRTI and major InSTI according to the Stanford HIV DRM database. Viral sequences were screened for G-to-A hypermutations (HM).

Results: Among 4473 participants with available viral sequences, 807 (18%) were ART-naïve at the time of sampling. Prevalence of pre-treatment SDRM associated with NRTI-, NNRTI- and InSTI among ART-naïve participants was 1.6%, 4.9% and 1.5%, respectively. The proportion of communities with pre-treatment SDRM and ranges of SDRM across communities are shown in Table 1. Overall, prevalence of SDRMs was low across participating communities. Among NRTI SDRM, M184V was the most common and was identified in 20% of the communities. NNRTI SDRM were detected in all the communities, with the most common K103N found in 30% of communities. The most common InSTI SDRM was R263K which was identified in 17% of communities. In a subset of 83 ART-naïve seroconverters, the prevalence of TDR mutations associated with NRTI-, NNRTI- and InSTI-resistance was 1.2%, 3.6% and 5.2%, respectively. The most common TDR mutations were: NRTI (K219E/S, 1.2%), NNRTI (A98G, 1.2%; K103N/S, 1.2%; V106M, 1.2%) and InSTI (E92Q, 1.2%; Q95K 1.2%; G163K/R, 1.2%, R263K, 1.2%).

Conclusion: We found a low prevalence of pre-treatment NRTI-, NNRTI- and InSTI-associated SDRM and TDR among ART-naïve persons in this large population-based sample of HIV-positive adults from across Botswana. Seroconverters identified in large cohorts and trials provide valuable assessment of TDR mutations on a population level.

Table 1. Distribution of pre-treatment drug-resistant mutations among ART-naïve Ya Tsie participants across Botswana communities (NRTI SDRM, NNRTI SDRM and major InSTI DRM)

NRTI			NNRTI			InSTI		
SDRM	Proportion of communities§	SDRM prevalence range #	SDRM	Proportion of communities§	SDRM prevalence range #	Major DRM	Proportion of communities§	DRM prevalence range #
M41	3.3%	0 - 3.8%	L100	3.3%	0 - 11.1%	T66	0	0 - 0
K65	0	0 - 0	K101	13.3%	0 - 3.8%	E92	10%	0 - 3.7%
D67	0	0 - 0	K103	30%	0 - 11.1%	E138	10%	0 - 3.8%
T69	0	0 - 0	V106	10%	0 - 2.9%	G140	3.3%	0 - 3.8%
K70	10%	0 - 2.9%	V179	13.3%	0 - 5%	Y143	0	0 - 0
L74	0	0 - 0	Y181	6.7%	0 - 3.7%	S147	0	0 - 0
V75	0	0 - 0	Y188	3.3%	0 - 2.8%	Q148	0	0 - 0
F77	0	0 - 0	G190	10%	0 - 3.7%	N155	0	0 - 0
Y115	0	0 - 0	P225	3.3%	0 - 2.5%	R263	16.7%	0 - 11.1%
F116	0	0 - 0	M230	20%	0 - 10%			
Q151	0	0 - 0						
M184	20%	0 - 3.8%						
L210	0	0 - 0						
T215	6.7%	0 - 3.7%						
K219	3.3%	0 - 11.1%						

§: Proportion of BCPP communities with specified identified DRM (total n=30 communities)
#: Prevalence range of specified SDRM across Ya Tsie communities (per community)
SDRM: Surveillance drug-resistant mutations

531 HIV DRUG RESISTANCE IN ADOLESCENTS AND ADULTS ON SECOND-LINE ART IN KWAZULU-NATAL

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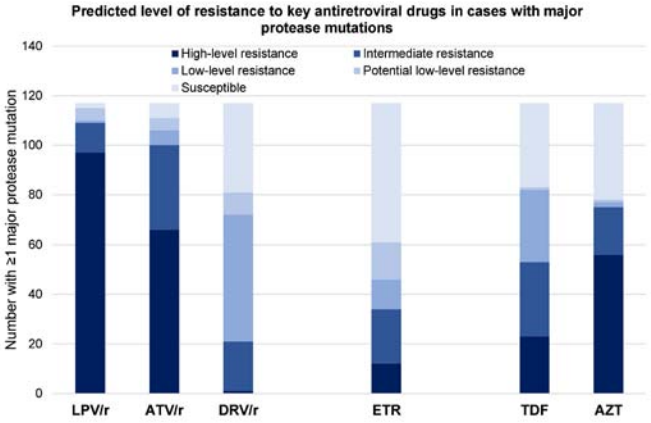
Background: Increasing numbers of HIV-positive adolescents and adults in South Africa are developing virological failure on second-line, protease inhibitor-based antiretroviral therapy (ART) regimens. HIV drug resistance testing is performed routinely in the public sector to determine the need for third-line ART and to inform regimen selection. We conducted an analysis of the routine data to assess the frequency and patterns of HIV drug resistance and to estimate the predicted need for third-line ART.

Methods: Cross-sectional analysis of all HIV genotypic resistance tests conducted by the National Health Laboratory Service in KwaZulu-Natal, South Africa (Jan 2015 – Dec 2016), for adults and adolescents (age ≥10 years) on second-line, protease inhibitor-based ART, with two consecutive viral loads ≥1000 copies/mL. We genotyped HIV-1 reverse transcriptase (RT) and protease (PR) genes by Sanger sequencing, and assessed drug resistance using the Stanford HIVdb algorithm. PR mutations were defined as major, accessory, or other according to the HIVdb algorithm.

Results: Three hundred and fifty-two people were included (59% female, median age 34 years). The median duration of second-line ART was 30 months (IQR 18-48), and 93% were on a lopinavir/ritonavir-based regimen. Median viral load at time of genotyping was 4.98 log10 copies/mL. Overall, 284/352 (81%) had at least one RT mutation and 117 (33%) had at least one major PR mutation. Among those with major PR mutations, the median number of major PR mutations was 3 (IQR 3-4) and the median number of total PR mutations was 5 (IQR 4-6). Presence of at least one major PR mutation was associated with longer duration on second-line ART (>24 months vs. ≤24 months, aOR 2.28, 95% CI 1.39-3.73) and older age (for each additional year, aOR 1.03, 95% CI 1.01-1.05). Of those requiring third-line ART, 21 (18%) had intermediate or high-level resistance to darunavir/ritonavir, 34 (29%) had intermediate or high-level resistance to etravirine, and 44 (38%) had intermediate or high-level resistance to both tenofovir and zidovudine (Figure).

Conclusion: Most people did not have major PR mutations and thus would not need third-line ART. Of those requiring third-line ART, most would need an integrase inhibitor ± etravirine in addition to DRV/r and recycled nucleoside reverse transcriptase inhibitors to form a suitable third-line regimen.



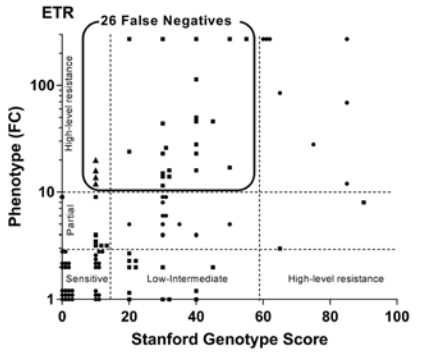


Figure: ETR Phenotype (Fold-Change in IC50) does not strongly correlate with genotypic score (r=0.47) for HIV Subtype C isolates. 52% of genotype scores were concordant (●), 44% partially discordant (■) and 4% completely discordant (▲) relative to the phenotype clinical cut-offs. 26 of 100 isolates with ETR FC >10 were misclassified as having low or intermediate resistance.

532 FREQUENT DISCORDANCE BETWEEN ETRAVIRINE PHENOTYPE & GENOTYPE IN SUBTYPE cART FAILURE

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Background: Etravirine (ETR) is a second-generation NNRTI that is used as a component of combination ART for treatment-experienced persons. The extent of cross-resistance between nevirapine (NVP) and efavirenz (EFV) and ETR is not well defined especially in low and middle-income countries (LMIC) where switches from first-line ART may be delayed. To address this gap, we investigated the susceptibility to ETR of subtype C HIV-1 among individuals on failing first-line NNRTI-containing regimens in South Africa (SA) and compared ETR phenotype to genotype.

Methods: Recombinant HIV-1_{LAI} containing bulk-cloned full-length RT amplified from plasma of 100 HIV-1 subtype C-infected individuals failing first-line ART (>10000 cp/ml and >1 NNRTI RAM) were phenotyped for ETR susceptibility in TZM-bl cells. Fold-change was calculated using a composite IC_{50} of 12 treatment-naïve individuals from SA. Genotypic scores (Stanford HIVdb v8.4) were categorized as partial or complete discordance if deviated from phenotype clinical cut-offs (DUET trials) by one or two tiers respectively. Correlations were determined using Pearson›s coefficient (r). WT reversions of K65 were made in clonally isolated plasmids with the QuikChange II Site-Directed Mutagenesis Kit.

Results: Of 100 first-line ART failures, 54 had reduced ETR susceptibility above the clinical cut-off of 2.9-fold higher than the control IC_{50}. The fold-change (FC) did not strongly correlate with genotypic score (r=0.47) with 44% of samples partially and 4% completely discordant. Of the 33 samples with FC>10, 26 samples were categorized as 'low' or 'intermediate' resistant by the HIVdb (Figure). The ETR-associated mutations L100I, Y181C and/or M230L were present in 79% (26/33) of samples with FC>10 but only in 4% (2/46) of samples with a FC<2.9. By contrast, the HIVdb NNRTI mutations A98G, K101H, E138A/K, V179D, Y188L, G190A, H221Y and P225H did not correlate with ETR resistance. The NRTI mutation 65R was associated with ETR resistance but reversion to 65K had no effect on ETR susceptibility. Rather, 65R was a marker of more prolonged ART failure and the accumulation of NNRTI mutations that conferred ETR resistance.

Conclusion: Phenotypic cross-resistance to ETR is common after first-line NNRTI-containing ART failure in SA. Genotype-based algorithms differentially classify ETR susceptibility in Subtype C. More appropriate weighting of combinations of ETR associated mutations are needed to improve genotype predictions of ETR phenotype.

533 IN-DEPTH CHARACTERIZATION OF HIV RESISTANCE TO INTEGRASE INHIBITORS IN BRAZIL

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Background: Due to increasing HIV drug resistance, Brazil was one of the first countries to adopt Dolutegravir (DTG) in first-line antiretroviral therapy (ART). The Ministry of Health of Brazil offers genotyping tests to all individuals under an integrase inhibitor (INI) based regimen experiencing virological failure. Using real life data, we aimed to characterize HIV genotypic resistance to Raltegravir (RAL) and DTG in Brazil in order to better understand factors related to the development of INI resistance-associated mutations (RAM), and to depict INI RAM transmission chains.

Methods: HIV integrase sequences from 2012-2018 were selected from the National System for Genotyping Control. The presence of INI RAM (Stanford HIVdb Program) and HIV subtype (Rega HIV Subtyping tool) were characterized. Socio-demographic, clinical (CD4 count and viral load/VL), and ART history data were assessed. A Pearson Chi-square test was carried out. INI RAM transmission clades were characterized by Bayesian phylogenetics.

Results: We analyzed 1,467 HIV integrase sequences from RAL- and/or DTG-experienced individuals. HIV resistant strains were identified in 21.7% for RAL and 0.7% for DTG. In 2017, following the use of DTG in first-line ART, individuals on RAL-based regimen switched to DTG. As a reflection of DTG's higher genetic barrier, resistance to INI has have been slightly decreasing to 13.7% and 0.3% in 2018 for RAL and DTG, respectively. Indeed, we did not identify any DTG resistant lineages in samples from individuals under DTG first-line ART. The prevalence of RAL and DTG resistant strains was similar, regardless of demographic and clinical data, including regional sustained VL levels. INI RAMs at positions G140 (7.0%) and E138 (1.0%) were most prevalent. Overall, subtype B (69.9%) was the most prevalent, followed by C (13.7%), F (8.9%) and recombinant forms (6.7%). Sequences presenting INI RAM were dispersed in phylogenetic trees for subtypes B and C, showing no specific INI RAM transmission clade, considering both the national level and the five Brazilian geographic regions, separately.

Conclusion: INI RAM monitoring revealed a short-term decrease in resistance to INI, even after DTG large-scale use. In addition, phylogenetics revealed that INI RAM does not occur in a particular population group or geographic region. Hence, the successful pioneering implementation of DTG goes beyond costs savings but healthcare efficacy, corroborating to sustaintability of DTG as first-line ART in a public health program.

534 HIV DRUG RESISTANCE AMONG PWID IN EASTERN EUROPE AND ASIA, HPTN 074

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Background: People who inject drugs (PWID) have high HIV incidence and prevalence, and may have limited access to antiretroviral therapy (ART) in some settings. We analyzed baseline HIV drug resistance and antiretroviral (ARV) drug use among PWID enrolled in a clinical study conducted in Indonesia, Vietnam, and Ukraine: HIV Prevention Trials Network (HPTN) 074.

Methods: HPTN 074 enrolled 502 HIV-infected index participants who had a viral load ≥1,000 copies/mL; 54 (11%) reported that they were on ART at enrollment. HIV genotyping was performed using the ViroSeq HIV-1 Genotyping System for index participants who had HIV viral loads >400 copies/mL at enrollment. ARV drug testing was performed using a qualitative assay that detects 20 ARV drugs in five drug classes.

Results: HIV drug resistance was detected in HIV from 54 (12.0%) of 449 participants; 29 (53.7%) of the 54 participants had multiclass resistance (non-nucleoside reverse transcriptase inhibitor [NNRTI] + nucleoside/nucleotide reverse transcriptase inhibitor [NRTI] resistance). The most common resistance mutations detected were K103N and M184V. ARV drugs were detected in samples from 51 (11.4%) of the 449 participants: 37 (72.5%) had an NNRTI with one or two NRTIs, 10 (19.6%) had an NNRTI only, and two (3.9%) had a boosted protease inhibitor with one or two NRTIs; two participants had an unusual combination of ARV drugs detected (two NNRTIs and one NRTI). Almost half of the participants who had ARV drugs detected (23/51=45.1%) did not have resistance to at least one of the ARV drugs detected, indicating that they were at risk of acquiring additional resistance mutations. The prevalence of drug resistance was significantly higher among those with ARV drugs detected than in those with no ARV drugs detected (30/51=58.8% vs. 24/398=6.0%, p<0.001). Drug resistance was also detected more frequently among participants in Indonesia (27/112=24.1%) compared to Ukraine (4/165=2.4%; p=0.001) or Vietnam (23/172=13.4%; p=0.014), and among participants who reported a history of incarceration compared to those who did not (6/14=42.9% vs. 48/435=11.0%; p=0.012).

Conclusion: This study revealed a high prevalence of HIV drug resistance and multiclass drug resistance in a cohort of PWID from Eastern Europe and Asia. This is likely to impact use of ARV drugs for HIV treatment and prevention, and highlights the need for improved HIV care in this high-risk population.

535 INI-RESISTANCE DYNAMICS FROM 2007 TO 2017 IN ITALIAN CLINICAL ISOLATES

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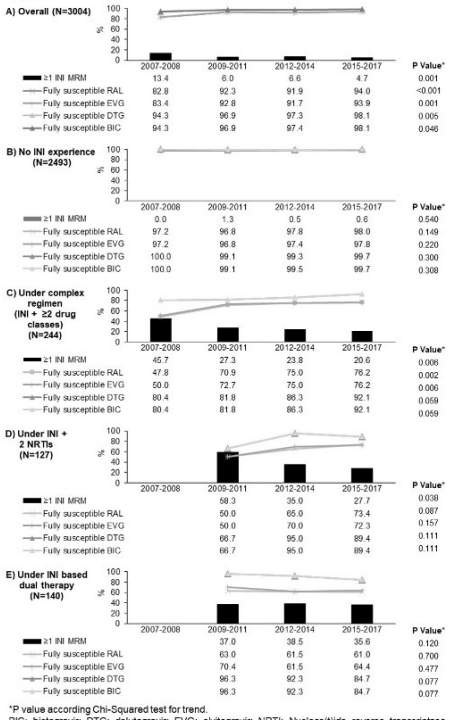
Background: We evaluated the prevalence of resistance to integrase inhibitors (INIs) over-time in clinical isolates from HIV-1 infected patients (pts) according to the type of treatment received.

Methods: We included 3004 integrase plasma genotypic resistance tests (GRTs) from 2598 HIV-1 infected pts (INI-naïve [drug-naïve and -experienced] and INI-treated). INI-resistance (INI-R) prevalence and genotypic susceptibility (GS) were evaluated from 2007 to 2017. To estimate the extent of pts with limited drug-options, cumulative class resistance (≥1 major resistance mutation [MRM] to PI, NRTI, NNRTI and/or INI among all GRTs available) was evaluated.

Results: Overall, INI-R decreased from 13.7% in 2007 to 4.7% in 2017 (p=0.001), in conjunction with an increased full GS to all INIs (p<0.05; Figure 1A). Among 2493 isolates from INI-naïve pts (N=2224), INI-R was stably low over time (≤1.3%) in association with a high GS to all INIs (≥96.8%; Figure 1B). INI MRMs were found in 10 drug-naïve pts: T66I (N=1); E138K (N=1); Y143C/H/R (N=1); Q148H+G140S (N=1); N155H (N=1); R263K (N=5). Among 511 isolates from 374 INI-treated pts, INI-R decreased from 42.9% in 2007 to 27.8% in 2017 (p=0.039). Concerning the type of treatment, in isolates under INI+≥2 drug classes INI-R decreased from 45.7% to 20.6% (p=0.006), in conjunction with an increased full GS to INIs (Figure 1C). Similar trends were found in isolates under INI+2NRTIs (Figure 1D). In isolates under INI-based dual therapy, INI-R remained stable from 2009 to 2017 (~36%) in conjunction with a stable proportion of isolates with full GS to RAL and EVG (Figure 1E). Whereas, under INI-based dual therapy, full GS to DTG or BIC slightly decreased from 96.3% to 84.7% (p=0.077; Figure 1E). In the 374 INI-treated pts the cumulative prevalence of INI-R was 33.4%. Pts who experienced only DTG showed lower cumulative INI-R compared to those who experienced only RAL or EVG or more than one INI (DTG: 7.7%; RAL: 32.1%; EVG: 45.2%; >1 INI: 41.9%, p=0.060). 46 (12.3%) pts showed cumulative four-drug class resistance. Of them, only 21 (45.7%) showed full GS to DTG or BIC.

Conclusion: INI-R is decreasing in Italy, confirming a good clinical practice. However, the first cases of transmitted INI-R, the stable INI-R prevalence under dual regimens and the consistent proportion of INI-exposed pts showing exhausted treatment options remain important concerns. These findings confirm that INI-R monitoring remains crucial for all categories of pts to avoid loss of treatment options.

Figure 1. Prevalence of resistance to integrase inhibitors (INIs) and proportion of isolates with full genotypic susceptibility to INIs from 2007 to 2017 in Italy according to treatment types.



*P value according Chi-Squared test for trend.
BIC: bictegravir; DTG: dolutegravir; EVG: elvitegravir; NRTI: Nucleos(t)ide reverse transcriptase inhibitor; MRM: major resistance mutation; RAL: raltegravir.

536 ANTIRETROVIRAL DRUG RESISTANCE IN PATIENTS RECEIVING CARE AT ETHIOPIAN HEALTH CENTERS

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Background: We have previously reported high rates of virological suppression in patients starting antiretroviral treatment (ART) at Ethiopian health centers, with no impact related to concomitant tuberculosis (TB) therapy. We further investigated patterns of antiretroviral drug resistance during ART among these persons, with particular regard to the effect of TB on selection of drug resistance.

Methods: Participants were identified from a cohort of 812 ART-naive adults at Ethiopian health centers (recruited 2011-2013). At inclusion into the cohort, all subjects were investigated for active TB. Sequencing was performed on plasma samples from subjects with viral load (VL) ≥500 copies/ml (cpm) at 6 and/or 12 months after ART initiation. Antiretroviral drug resistance (DRM) was defined as Stanford score ≥60 for NRTI and/or NNRTI. If DRM was detected, sequencing was also performed on samples obtained before ART initiation (pre-ART) to determine if DRM was acquired during ART. Logistic regression was used to investigate the association between concomitant TB and risk of acquiring DRM,

adjusting for age, gender, VL, CD4 count, and mid-upper arm circumference (MUAC). Subjects with VL ≥500 cpm without DRM and those with DRM pre-ART were excluded from this analysis.

Results: Among 621 individuals with VL data at 6 and/or 12 months after starting ART (17.7% with TB), 101 had VL ≥500 cpm (16.3%); DRM was detected in 64/98 (65.3%; sequencing failure in 3 subjects). All 64 had NNRTI resistance and 35 (54.7%) had both NRTI and NNRTI resistance. Pre-ART resistance (according to WHO SDRM 2009) was detected in 7/56 (12.5%; pre-ART samples missing from 8 subjects). Acquisition of DRM was associated with pre-ART VL, CD4 count, and MUAC in univariate analysis (Table 1). In multivariate analysis, VL and MUAC remained significantly associated with acquired DRM. TB was not associated with acquisition of DRM; 12/64 (18.8%) patients with DRM had TB.

Conclusion: DRM was detected in a majority of patients with VL ≥500 cpm during ART at Ethiopian health centers, and was mostly due to acquired drug resistance. The risk of DRM acquisition was associated with high pre-ART VL and low MUAC, but was not associated with concomitant TB.

Table 1. Factors associated with acquiring antiretroviral drug resistance in patients receiving ART at Ethiopian health centers.

Factor	N	Value*	OR (95% CI)	P	aOR (95% CI)	P
Age (years)	577	32 (28-40)	1.0 (1.0-1.0)	0.20	1.0 (1.0-1.0)	0.93
Male gender	577	214 (37.1%)	1.7 (1.0-3.0)	0.05	1.5 (0.8-2.9)	0.18
CD4 count (cells/mm^3)	576	195 (121-274)	1.0 (1.0-1.0)	<0.01	1.0 (1.0-1.0)	0.07
Viral load (log)	552	5.11 (4.49-5.54)	2.6 (1.7-4.1)	<0.01	2.0 (1.2-3.3)	0.01
Tuberculosis	577	95 (16.5%)	1.1 (0.5-2.2)	0.82	0.8 (0.3-1.7)	0.52
MUAC (cm)	577	23 (21-25)	0.9 (0.8-0.9)	<0.01	0.9 (0.8-1.0)	0.03

*Values as median (interquartile range) or n (%) for all subjects included in this analysis.
Abbreviations: OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; MUAC, mid-upperarm circumference.

537 BASELINE HIV DRUG RESISTANCE AMONG TREATMENT-NAIVE PATIENTS IN ESWATINI, MAXART TRIAL

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Background: The Kingdom of Eswatini (formerly known as Swaziland) has the highest global adult prevalence of HIV at 27.2%. The country has expanded access to HIV testing services and increased antiretroviral treatment (ART) coverage in recent years from 49% (2013) to 85% (2017). The MaxART Early Access to ART for All Implementation Trial launched in 2014 to assess the scalability and clinical outcomes of offering ART to all people living with HIV (PLHIV) in Eswatini, regardless of CD4 cell count and WHO clinical stage. As a secondary endpoint, we sought to determine the extent of HIV drug resistance (HIVDR) in all treatment-naïve individuals initiating ART in the Hhohho region of Eswatini.

Methods: The trial was a 3-year randomized stepped-wedge design open to enrolment for PLHIV attending 14 rural health facilities in the Hhohho region. Exclusion criteria included age (<18yo), pregnancy, breastfeeding, and previous antiretroviral (ARV) drug exposure except for prevention-of-mother-to-child-transmission interventions. Pre-ART plasma samples were genotyped at the BC Centre for Excellence in HIV/AIDS, Canada. Sanger sequences were generated targeting the protease and reverse transcriptase genes. HIVDR was predicted using the Stanford HIVdb algorithm (v.8.6.1).

Results: 3485 PLHIV were enrolled, with pre-ART samples and HIV sequences available for 2626 (75.4%) and 2585 (74.2%) participants, respectively. HIVDR was detected in 658 (25.5%) sequences, with 289 sequences (11.2%) containing mutations conferring HIVDR to first-line drugs efavirenz/nevirapine (EFV/NVP; Table 1). E138A alone was detected in over 13% of sequences, accounting for over half of the inferred HIVDR to non-nucleoside reverse transcriptase inhibitors (NNRTI). HIVDR to EFV/NVP was associated with being female, younger age, and CD4 cell count ≥ 200 cells/mm3 ($p<0.05$). Female sex was also associated with longer time from diagnosis to ART initiation, and less advanced clinical status at enrolment ($p<0.05$). Dual-class HIVDR to nucleoside reverse transcriptase inhibitor and NNRTI drugs was rare (n=15/2585).

Conclusion: Moderate levels of HIVDR to EFV and NVP warrant re-assessment of first-line ARV regimens in Eswatini. These findings are critical to evaluate the national progress towards 90-90-90 targets and assess the long-term sustainability of a national ART programme. Nationally representative HIVDR surveys should be routinely implemented to assess predicted efficacy of current and possible future ARV regimens as the programme expands.

Table 1: Prevalence of HIV drug resistance among treatment-naïve people living with HIV in Eswatini initiating ART. A total of 2585 HIV sequences were available for analysis. Resistance interpretations were performed using the Stanford HIVdb algorithm (v.8.6.1). Confidence intervals adjusted by one-stage cluster analysis.

	Sequences with HIVDR (n, %, (95% CI))			
Resistance Level	PI Class	NRTI Class	NNRTI Class	NNRTIs: NVP or EFV
Low-level	39, 1.5% (1.2-1.8%)	8, 0.3% (0.2-0.5%)	321, 12.4% (11.4-13.5%)	7, 0.3% (0.1-0.4%)
Intermediate level	8, 0.3% (0.2-0.5%)	4, 0.2% (0-0.3%)	51, 2% (1.3-2.6%)	59, 2.3% (1.6-3%)
High-level	9, 0.3% (0.2-0.5%)	12, 0.5% (0.3-0.6%)	237, 9.2% (7.8-10.6%)	223, 8.6% (7.3-10%)
Total	56, 2.2% (1.8-2.5%)	24, 0.9% (0.7-1.1%)	609, 23.6% (21.8-25.3%)	289, 11.2% (9.6-12.8%

HIVDR = HIV drug resistance; PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; EFV = efavirenz

538 MODELING THE IMPACT OF DOLUTEGRAVIR INTRODUCTION ON NNRTI RESISTANCE IN SOUTH AFRICA

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Background: The success of the global scale-up of antiretroviral therapy (ART) is threatened by rising HIV resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI). First-line regimens including dolutegravir (DTG) could help mitigate this problem due to its higher genetic barrier to resistance. We extended the previously-developed MARISA model to simulate the impact of DTG introduction on NNRTI pre-treatment drug resistance (PDR) in South Africa in 2018-2038.

Methods: MARISA (Modelling Antiretroviral drug Resistance In South Africa) is an epidemiological model describing the emergence and transmission of NNRTI resistance from 2005. It is parameterized with data from IeDEA Southern African cohorts, and with Thembisa/UNAIDS and literature estimates. We extended MARISA to account for the introduction of DTG in 2018 under two scenarios: DTG as first-line regimen for ART-initiators, or DTG for all patients. Considering potential safety issues of DTG during pregnancy, we assessed the impact of prescribing DTG to a) all eligible men, b) all men and all women out of reproductive age (older than 49, that is 17.5% of adult women on ART in 12 IeDEA South African cohorts), c) all men and all women out of reproductive age or using modern contraception methods (62% of adult women according to World Bank data), and d) all men and all women. For DTG, we assumed a similar efficacy compared to NNRTI but no resistance.

Results: The model projections show that introducing DTG would lead to a noticeable reduction of NNRTI PDR in all scenarios compared to the continuation of the current situation (Fig 1). DTG could lead to the virtual disappearance of NNRTI PDR (1% by 2038) if given to all adult patients regardless of treatment status and gender. Limiting DTG to ART-initiators would allow for the stabilization then decrease of NNRTI PDR to 13% by 2038. In both scenarios, NNRTI PDR would continue to rise if DTG is restricted to men, but may be reduced to 12% by 2038 if also provided to women aged >49, or even to 1% if also provided to women using contraception.

Conclusion: Our model shows the potential benefit of the introduction of DTG for attenuating the rise of NNRTI PDR. As safety issues related to neural tube defects in newborns may limit the use of DTG in women with child-bearing potential, the model shows that the effect of introducing DTG would be largely reduced if its use is limited to men only. However, this can be almost completely overcome if DTG is used in women with low risk of pregnancy.

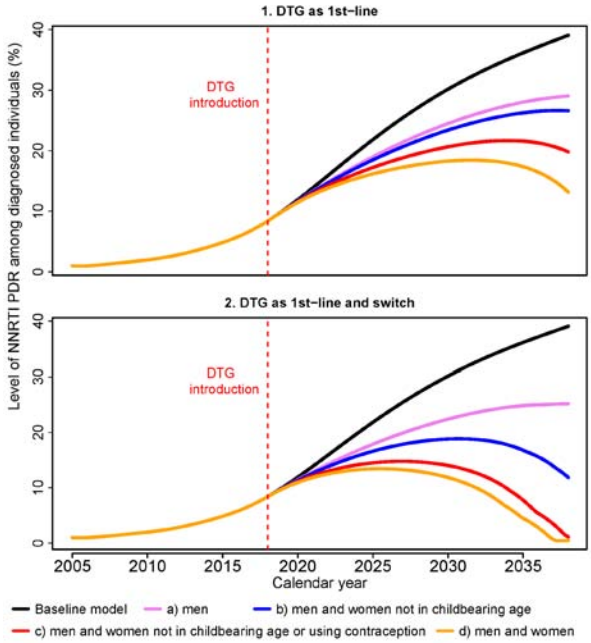

Figure 1: Simulated levels of NNRTI pre−treatment drug resistance in South Africa during 2005−2038 as dolutegravir is introduced in 2018 under two scenarios: DTG as first−line regimen for ART−initiators (panel 1) or DTG for all patients (panel 2), and with different restrictions of prescription based on gender. Baseline model shows the situation without the introduction of dolutegravir.

539 A COMPARATIVE EVALUATION OF HIV-1 CAPSID INHIBITOR SUSCEPTIBILITY

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Background: Inhibitors that target HIV capsid assembly and virion maturation represent a promising new class of antiretroviral compounds. In this study, we used an enhanced cell-based infectivity assay, based on the assembly of resistance test vectors (RTV), to evaluate the susceptibility of patient isolates and gag gene site-directed mutants to several maturation and assembly inhibitors.

Methods: Gag-protease coding regions from 111 HIV patient isolates, previously submitted for routine drug resistance testing, were amplified from plasma specimens and used to generate gag-pro RTVs that express firefly luciferase. In addition, gag-pro substitutions associated with reduced susceptibility to assembly or maturation inhibitors were introduced into an RTV containing a "wild-type" gag-pro sequence; site-directed mutants (SDM). Susceptibility to two maturation (CA-SP1 cleavage site) inhibitors and one capsid assembly/disassembly inhibitor (CAI) were determined.

Results: Susceptibility to both CA-SP1 cleavage site inhibitors varied more than 100-fold across the 111 patient isolates, while susceptibility to the CAI varied less than 4-fold. Consistent with previous studies, viruses containing naturally occurring polymorphisms (68/111, 61%), or site directed mutations, within the "QVT" motif (aa positions 369-371) exhibited large reductions in CA-SP1 cleavage site inhibitor. In addition, six of 43 isolates lacking QVT polymorphisms also exhibited notable reductions in CA-SP1 inhibitor susceptibility. In contrast, only one patient isolate contained a polymorphism (N74D) that has been associated with reduced susceptibility to CAI (L56I, M66I, Q67H, N74D, A105E). SDMs containing single L56I, M66I and A105E substitutions exhibited large reductions in CAI susceptibility (FC>200), whereas the impact of Q67H and N74D was small (FC=1.8 and 2.6, respectively). Notably, L56I, M66I and Q67H substitutions also conferred modest cross-resistance (3 to 10-fold) to the CA-SP1 cleavage site inhibitors.

Conclusion: Susceptibility to HIV-1 capsid inhibitors that vary in their mechanism of action were assessed using a cell-based pseudovirus reporter assay. Variation in susceptibility across more than 100 patient isolates was much more pronounced for CA-SP1 cleavage site inhibitors compared to a CAI. A small number of mutations conferred large reductions in CAI susceptibility and cross resistance to CA-SP1 cleavage site inhibitors.

540 IDENTIFICATION OF ARV-RESISTANCE MUTATIONS OUTSIDE OF THE DRUG-TARGET GENE

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Background: Resistance to antiretrovirals (ARVs) continues to impair the overall quality of life for some HIV-infected individuals, despite the effectiveness of combination antiretroviral therapy (cART). The goal of this study was to explore the ability of HIV-1 to escape inhibition by ARVs in vitro by acquiring resistance mutations outside of the drug-target gene.

Methods: We propagated HIV-1 in T-cell lines and measured virus replication kinetics in the presence or absence of low (sub-IC50) concentrations of ARVs, testing at least one representative of each class of inhibitor. We selected for viral escape mutants exhibiting at least partial resistance to ARVs as indicated by efficient replication in the presence of the inhibitors. A number of analyses were then performed to validate the ability of the selected mutations to confer ARV resistance.

Results: Long-term passage of wild-type (WT) virus in the presence of ARVs led to the selection of ARV-escape mutants lacking changes in the target gene, but instead containing substitutions in the envelope (Env) glycoprotein and occasionally in Vpu. We have now identified a panel of partially ARV-resistant NL4-3 Env mutants that arose in the presence of protease, reverse transcriptase (RT), and integrase inhibitors. Mutations were selected in the context of two different T-cell lines, Jurkat and CEM12D7, that favor cell-cell and cell-free transmission, respectively. Remarkably, the same ARV-resistant Env mutant was selected in both cell lines. We extended our analyses to a transmitted-founder, subtype C virus, CH185_TF, which acquired a mutation in Env when propagated in the presence of Dolutegravir (DTG). These data demonstrate that ARV-resistant Env mutants arise in the context of three different T-cell lines and two viral subtypes with different coreceptor tropism. Finally, we found that several of the Env mutation positions are highly conserved within and across HIV-1 clades but that these mutations do appear in patient isolates.

Conclusion: These results demonstrate that mutations in Env can contribute to HIV drug resistance in vitro. A combination of in vitro selections and in vivo analyses is ongoing and may establish a role for Env mutations in ARV resistance in patients and help guide the development of more effective therapies.

541 EMERGENCE OF GAG MUTATION, A364V, IDENTIFIED AS THE KEY IN VITRO RESISTANCE MUTATION

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Background: The in vitro virology profile has been previously presented (Jeffrey et al, CROI 2015). These data demonstrated that GSK2838232, a second-generation HIV maturation inhibitor, has a broad spectrum antiviral profile against viruses from various clades and viruses resistant to marketed antiretrovirals. The current study was aimed to identify drug resistance mutations via in vitro resistance passage.

Methods: Recombinant viruses containing the gag/protease fragments of two representative protease-treated HIV-infected individuals susceptible to GSK2838232 (R6877: IC50 1.8nM and R7104: 0.9nM) and laboratory strain NL4-3 (IC50 1.5nM) were serially passaged in SupT1 cells. Experiments were started with drug concentrations around the IC50 value and gradually increased in each passage (all experiments were done in 5-fold increments).

Results: After 5 passages, at GSK2838232 concentrations 10-20 fold over the initial IC50 (~24nM) for inhibiting the parent virus, gag and protease was fully sequenced. Remarkably, in all experiments the gag A364V amino acid change at the p1' site in the CA/P2 cleavage site was observed. A site-direct mutant containing the A364V was generated in the NL4-3 parental virus and demonstrated a high level of resistance to GSK2838232 (>400nM). Lastly, the frequency of A364V among HIV gag sequences in the Los Alamos National Labs HIV database was investigated and found to be less than 0.1% of these sequences.

Conclusion: The resistance profile of GSK2838232 is consistent with previous maturation inhibitors. Based on the infrequent presence of the A364V mutation, pre-existing resistance in an HIV-positive human patient population is expected to be low. As GSK2838232 progresses through clinical development, these in vitro resistance data will help decipher the genotypic and phenotypic observations from those clinical studies.

542 COMPARISON OF NEXT-GENERATION SEQUENCING ANALYSIS PIPELINES FOR HIV-1 DRUG RESISTANCE

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Background: NGS is a potentially useful tool for HIV-1 drug resistance (HIVDR) testing because of its sensitivity for detecting low abundance drug resistant variants. Many NGS HIVDR data analysis pipelines have been independently developed, with variable outputs and potential discrepancies. Standardization of analytic methods and comparison of pipelines are lacking, yet may impact interpretation and be significant in downstream applications.

Methods: We compared the performance of five NGS pipelines using samples from the Sanger-based genotyping proficiency testing administered by the NIAID Virology Quality Assurance (VQA) program. Ten VQA panel specimens were genotyped (protease and reverse transcriptase) by each of six laboratories using their in-house NGS assays. Raw NGS data were processed in each laboratory using one of five different pipelines: HyDRA, MiCall, PASeq, Hivmmer and DEEPGEN (Table 1). All laboratories uploaded their raw NGS and analytic comparisons were performed centrally, including: linear range for AAV frequency (linear regression analysis), analytical sensitivity and specificity, and variation of detected AAV frequencies. Amino acid variants (AAV) detected by at least four of the five pipelines at median frequency ≥1% were considered for subsequent performance assessment.

Results: A total of 657 AAVs were detected; median 67 per sample. All pipelines demonstrated good linearity in AAV frequency measurements between 1% and 100%. The pipelines showed an average sensitivity of 99.3% (range: 98.8-99.8%) and specificity of 94.1% (85.7-99.7%). The majority (473 of 657, 72%) of AAVs were present at frequencies ≥20% and these frequency measurements contained fewer discrepancies as compared to AAVs with median frequencies ≤ 20% (Table 1).

Conclusion: Comparison of five different NGS-based HIVDR genotyping analysis pipelines in detection of AAVs present at frequencies ≥20% using VQA panel specimens demonstrated good correlation across pipelines. Specificity was decreased at AAV frequencies ≤20% and more outliers were observed, which may be due to differences in quality control criteria among the pipelines. Findings from this study highlight the need for well-defined quality assurance strategies for NGS HIVDR data processing, especially for low abundance variant reporting.

Table1. Comparison of Pipelines for automated NGS-based HIVDR data analysis

	MiCall	HyDRA	PASeq.org	Hivmmer	DEEPGEN
URL	https://github.com/cfe-lab/MiCall	https://hydra.canada.ca	https://www.paseq.org	https://github.com/kantorlab/hivmmer	N/A
Bioinformatic IT needs	No	No	No	Yes	N/A
Compatible NGS Platform	Illumina	Illumina, Ion Torrent	Illumina	Illumina	Illumina, Ion Torrent
Cloud Based	Yes	No	Yes	No	No
Web Interface	Yes	Yes	Yes	No	No
Designed for HIVDR	Yes	Yes	Yes	Yes	Yes
Ref Database	HIVdb	HIVdb	HIVdb	HIVdb	HIVdb
Output (aa)	csv	aavf	csv	csv	csv
N outliers ≥ 20%*	2	6	12	3	10
N outliers < 20%	10	9	15	19	9

*Outliers were determined using a %CV ≤1%, 5%, 10% and 20 % for variant frequencies at >90%, 70-90%, <70 - >10%, and <10% respectively.

543 HIV RESISTANCE–ASSOCIATED MUTATIONS OBSERVED IN CELL-ASSOCIATED DNA SEQUENCING ASSAY

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Background: HIV DNA sequencing was developed to provide HIV antiretroviral resistance information when viral loads are insufficient to permit standard RNA-based sequencing assays, especially when historical resistance tests are unavailable or incomplete. Here we evaluated the results from a large set of specimens submitted for routine HIV DNA resistance testing.

Methods: HIV DNA sequencing was performed using an assay that evaluates all of protease and integrase and amino acids 1 – 400 of reverse transcriptase from HIV-1 DNA extracted from whole blood. Briefly, target sequences are amplified from genomic DNA using triplicate nested PCR followed by sequencing on the Illumina MiSeq platform. A Bayesian model is applied to assign a probability that individual reads have been modified by APOBEC-induced hypermutation and flagged for removal from the analysis. Variants are reported at a sensitivity level that is equivalent to Sanger sequencing. The list of resistance associated mutations (RAMs) was derived from multiple sources, avoiding polymorphic positions and low-impact or secondary RAMs. HIV DNA sequence results from >64,000 patient samples submitted for routine testing in the US were included in the analysis. The data were evaluated to assess frequency of RAMS, temporal trends from 2015 to 2018 and associations with gender, age and geography.

Results: At least one RAM was identified in 58.6% of specimens with 1, 2, 3 and 4-class RAMs observed in 28.2%, 19.1%, 10.2% and 1.1%, respectively. The most frequent RAMs observed in each class were PI: L90M (7.5%), NRTI: M184V (27.2%), NNRTI: K103N (19.8%), and INI: N155H (1.5%). Common TAMs (M41L, D67N, K70R, T215F/Y) were present in 9 – 13% of specimens. Overall, the prevalence of individual RAMs, as well as samples with any RAMs, was observed to decrease between 2015 and 2018. The prevalence of RAMs was higher in patients under 20 and over 50. Differences across gender and geographic regions were subtle but statistically significant.

Conclusion: Analysis of a large set of HIV DNA sequencing test results submitted for routine testing demonstrated that RAMs are commonly identified. Minor differences in the prevalence of RAMs were associated with gender and geographic location. More striking changes were associated with age. Increased prevalence of RAMs was observed in patients over 50 and may reflect increased rates of exposure to multiple regimens. We also noted an increased prevalence of RAMs in patients under 20 that warrants further study.

544 DETECTION OF ARCHIVED MUTATIONS IN PATIENTS INFECTED WITH MULTICLASS RESISTANT HIV-1

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Background: Deep sequencing (DS) assays may represent a reproducible approach to analyse HIV-1 mutation patterns in proviral DNA, even at frequencies well below those routinely detectable by population sequencing. DS data on pts with multiple drug resistance-associated mutations (DRMs) and with VS (less than 50 HIV RNA copies) is scarce.

Methods: LOWER is a nation-wide study of 243 pts with presence of major DRMs (defined according to Stanford HIVdb v8.6.1) in at least three classes of NRTIs, NNRTIs, PIs or INSTIs. In pts with VS, mutational patterns in proviral DNA (using different cut-offs of 15% and 2% after APOBEC filtering) were compared with cumulative DRMs available from all historical resistance reports.

Results: In 195/243 pts who had achieved VS for a median of 8.5 years (range, 0-18.6), a mean of 11.1 DRMs (range, 3-28) were identified. Re-detection rate was highest for NRTI DRMs and lowest for INSTI DRMs. Almost 10% of all DRMs were newly detected with DS, and a lower cut-off of 2% yielded a total of 14.9% additional DRMs (Table 1). However, re-detection rates showed a high inter-class variability even in highly prevalent DRMs (= total prevalence > 10%). Among NRTI DRMs, re-detection rates were highest for T69D/N (77.1%) and M41L (75.4%) and lowest for K65R/E/N (21.1%) and L74V (26.2%). For NNRTIs

and PIs, the rates were highest for Y188C/H/L (63.6%) and L90M (65.9%) and lowest for V108I (33.3%) and I54L/M (29.0%). Re-detection rates showed no association with length of ART or of VS, current antiretroviral regimens or other factors such as current or nadir CD4 cells.

Conclusion: In this large cohort study of pts with multidrug resistant HIV infection, DS of proviral DNA regained more than half of the DRMs that had emerged during previous virologic failures. Almost 10% were newly detected and a lower cut-off of 2% yielded almost 15% additional DRMs. However, detection consistency between DS and historical testings was low for specific mutations. Re-detection rates were not associated with any factor analysed, including length of viral suppression or current ART regimen.

	Total	NRTI	NNRTI	PIs	INSTIs
Total DRMs (historical and newly detected), n	2,157	1,059	435	618	45
% historical DRMs re-detected, cut-off 15 %	45.9	55.5	37.6	35.5	23.3
% historical DRMs re-detected, cut-off 2 %	57.2	65.0	48.0	50.3	40.0
% newly detected DRMs, cut-off 2 %	9.2	5.5	15.6	9.2	33.3
% of all DRMs (new and historical) detected, 2-15 %	14.6	11.7	17.5	16.7	24.4

545LB LTR TRANSLOCATION MUTATIONS UNDER HIGH-LEVEL CABOTEGRAVIR MAINTAIN HIV REPLICATION

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Background: Recent reports have described HIV replication under high levels of the integrase (IN) inhibitor, dolutegravir (DTG), was associated with mutations in the 3'PPT with no resistance mutations observed in the integrase gene (int). Cabotegravir (CAB), a longer-acting analogue of DTG, has a high genetic barrier to resistance emergence. We examined for int drug resistance mutations in vitro both with increasing concentrations of CAB and under continuous high concentration. We also looked for changes in IN-binding regions in the long terminal repeats (LTR).

Methods: For dose escalation, CEMx174 cells were infected with wild-type HIV-1IIIB (5.0X10^8 cp/1M cells) beginning with 0.1nM CAB. After visualization of cytopathology (CPE), CAB concentration was doubled for 12 culture passages up to 205nM. In a second experiment, 300nM CAB (~350-times EC90) was added to cultures 24h after infection with wild-type HIV-1IIIB. Int sequences in viral RNA (vRNA) and DNA were analyzed weekly by both Sanger and deep sequencing. vRNA LTR 5'R-U5 and 3'U3-R, proviral U3-U5 LTR and 2-LTR DNA junction regions were also sequenced.

Results: Increasing CAB concentrations over a year generated no int mutations despite continued, albeit prolonged, appearance of CPE. Initiating cultures with 300nM CAB quickly yielded vRNA LTR mutations by day 7 at a 1% frequency (f) (VL=3x10^7cp/ml) and 48% at day 105 (VL=3x10^9). Proviral LTR mutations were first detected (f =14%) at day 14, with 98% of amplified proviral LTRs mutated at day 105. These mutations were in the LTR U3 and are similar to previously described DTG-associated 3'PPT mutations. We have identified the mutations as translocated copies of the LTR U5 IN cleavage site, which introduced adjacent to the U3 cut site another IN binding/cleavage site but in complementary orientation. Deletions in U3 were also observed. 2-LTR circles accumulated rapidly and had majority wild-type junction sequences; also present were circles with tandem repeats in U3 3'-flanking the junction.

Conclusion: We propose that replacing sequences adjacent to the U3 IN cleavage site with a U5 cleavage motif is a functional mutation that permits HIV integration in the presence of high-level IN inhibitor, possibly by an altered IN complex conformation. These variant proviruses may form by erroneous IN processing of preintegration LTRs. The nearly ubiquitous presence of the U5 site in U3 proviral LTRs after 100 days in culture supports this as a mechanism for HIV persistence in vitro under CAB.

546 ANTIVIRAL ACTIVITY OF TENOFOVIR ALAFENAMIDE AGAINST HIV-1 HARBORING K65R

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Background: Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) and are prodrugs of the HIV-1 nucleotide reverse transcriptase (RT) inhibitor tenofovir (TFV). In vivo, TAF achieves ~4-fold higher intracellular levels of TFV diphosphate (TFV-DP) in PBMCs, compared to TDF. Although rare, K65R is a resistance associated mutation (RAM) for several NRTIs, including TAF and TDF, and is the main RAM to emerge during in vitro selection studies with tenofovir. Here, we evaluated the in vitro activity of TAF at physiological concentration in a large set of K65R-containing HIV-1, with or without M184V/I.

Methods: HIV primary isolates (n=42) with K65R ± M184V/I spanning 5 different subtypes were selected. Samples with mutation mixtures at RT residues K65 and/or M184 were not included. The PR-RT region was amplified and cloned into the pXXLAI proviral DNA vector and transfected into virus producing cell lines; viral isolates were harvested after 48 h. Antiviral drug susceptibilities (EC50 fold change [FC] relative to wild-type) were determined in MT-2 cells using a 5-day Multi-Cycle HIV assay. Comparison of TAF and TDF resistance barriers were further assessed in viral breakthrough assay performed at clinically relevant drug concentrations.

Results: TAF mean FC for all tested viruses was 4.0 (n=42; range: 1.0-27.4). The TAF FC of the viruses harboring K65R with M184V/I (average FC of 3.3; n = 28) was numerically lower than the TAF FC of the viruses without M184V (average FC of 5.4; n = 14). All 42 mutant isolates were subsequently assayed at TAF or TDF physiological concentration in viral breakthrough assay (28 days), resulting in 4/42 mutants breaking through under TAF treatment (average FC of 12.2 for viruses breaking through; range 6.1-27.4), and 18/42 mutants breaking through under TDF treatment (average FC of 6.1 for viruses breaking through; range 3.2-27.4).

Conclusion: In a viral breakthrough assay mimicking the 4-fold higher intracellular levels of TFV-DP delivered by TAF compared to TDF in vivo, TAF inhibited breakthrough of the majority of K65R-containing HIV-1 evaluated compared to TDF, emphasizing the higher resistance barrier provided by TAF vs TDF. These differences were observed for HIV isolates regardless of their subtypes or genetic diversity around the K65 position.

547 GSS OF NRTI-BACKBONE PREDICTS TIME TO VIROLOGICAL FAILURE OF INI-BASED REGIMENS

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Background: INI-based regimens are the mainstay of antiretroviral therapy (ART). We evaluated the impact of NRTIs backbone-associated drug resistance mutations (DRM) at the start of a INI-based regimen on the onset of virological failure (VF).

Methods: The sum of genotypic susceptibility scores (GSS) obtained by Stanford HIVdb algorithm version 8.6.1 (classified as: 0 for high-level resistance, 0.5 for low or intermediate-level resistance, 1 for potential low-level resistance or susceptible) for each NRTI was calculated for patients starting 2 NRTIs (3TC/FTC, ABC or TDF/TAF) plus RAL, EVG/c or DTG or 1 NRTI plus DTG in the INTEGRATE - EuResist cohort. Probability of VF (defined as the criterion for regimen discontinuation) after 1 year was estimated for each regimen, and the association of GSS with VF was evaluated by Cox regression.

Results: From 1998 to 2017, 7,972 pts were eligible for the study (44% men, 47 yrs median age): 26.9% of them started 2NRTIs+RAL, 10.5% 2NRTIs+EVG, 56.3% 2NRTIs+DTG, 6.3% 1NRTI+DTG. Median time since HIV diagnosis and ART initiation were 8 and 5 yrs, respectively; zenith HIV-RNA was >100k cp/mL in 51.4% of pts and nadir CD4 count was <200 cells/μL in 47.1%; at baseline (BL) HIV-RNA was <50 cp/mL in 62.9% of pts and CD4 count was >500 cells/μL in 49.0%. Pts mainly switched from a 3-drug regimen (60.7%), mostly for simplification (28.2%) and toxicity (6.8%); 1,420 (17.8%) pts were naive to ART. Historical genotype was available for 4,265 pts: 105 (2.5%) had DRM for at least 1 NRTI included in the backbone. Over 10,485.5 pt-yrs of follow-up (1 yr median follow-up time) 108 VF were detected (1.03 per 100 pt-yrs). Probability of VF after 1 yr was 2.1% (95% CI 1.3-2.9) with 2NRTIs+RAL, 1.2% (95% CI 0.2-2.2) with NRTIs+EVG/c, 0.2% (95% CI 0.0-0.4) with 2NRTIs+DTG, 2.1% (95% CI 0.5-3.7) with 1NRTI+DTG (p<0.001). Higher GSS (per 1 unit increase, aHR 0.12, p<0.001) and the use of 2NRTIs+DTG (vs 2NRTI+RAL, aHR 0.11, p=0.002) were associated with reduced risk of VF. Viral subtype G (vs B, aHR 8.51, p=0.016), zenith HIV-RNA>500k cp/mL (vs <100k cp/mL, aHR 6.36, p=0.005), and continent of infection (Africa vs Europe, aHR 107.82, p<0.001) predicted VF independently from HIV risk factor and gender, BL HIV-RNA, previous VF with

a INI-based regimen, cumulative ART exposure, previous ART and reasons for switching, being naïve.

Conclusion: Despite the low incidence of VF with INI-based regimen, DRMs, HIV subtype and zenith HIV-RNA still suggest caution in prescribing INI-based regimens.

548 GENOTYPIC AND PHENOTYPIC SUSCEPTIBILITY TO FOSTEMSAVIR IN MULTIDRUG-RESISTANT HIV-1

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Background: Fostemsavir (FTR) is a prodrug of the investigational HIV-1 attachment inhibitor temsavir (TMR) currently under evaluation for the treatment of highly experienced patients with limited treatment options. This study aims to characterize the genotypic profile and the phenotypic susceptibility to TMR in a panel of samples collected from patients harboring multi resistant HIV-1 enrolled in the Italian PRESTIGIO cohort and potentially candidate for FTR treatment.

Methods: Plasma samples from 24 patients included in the PRESTIGIO cohort were used for the sequencing of gp120 region, while viral tropism and susceptibility to TMR were assessed through a home-made phenotypic assay involving pseudotyped viruses expressing patient derived Env protein. Patient demographics and laboratory data are described as median (Q1-Q3), mean (±SD) or frequency (%).

Results: Among 24 patients, 18 (75%) were male, median age 54 years (52-59), time since HIV-1 diagnosis 26 years (24-29), time on ART 25 years (22-26), 11 (46%) with a previous AIDS diagnosis, a median viral load at first sample collection of 3.87 log10 copies/mL (3.1-5.0) and a median CD4+ cell count of 242 cells/µl (137-387). At the time of sample collection, 12 (50%) were receiving entry inhibitors (MVC and/or T-20). Among 21/24 (88%) gp120 sequences obtained, all belonged to subtype B and TMR RAMs (L116P, A204D, S375M/H/N, M426L, M434I, M475I) were detected in only 3 cases (13%), two 426L and one 375N. Viral tropism was X4, R5, and dual-mixed (DM) in 8, 9 and 7 out of 24 cases, respectively. Pseudotyped viruses were obtained from 23/24 samples and median IC50 to TMR was 0.5 nM (0.3-1.2). The reference wild-type viruses NL4-3 (X4), AD8 (R5) had mean IC50 of 1.1±0.6 nM and 1.3±0.7 nM, respectively, while the two samples harboring RAM 426L (both X4-tropic) had mean IC50 of 6.9±2.9 nM and 1110.6±798.2 nM, resulting in FC values of 6.2 and 1009, respectively. According to viral tropism, median IC50 values were 1.2 nM (0.4-4.2), 0.4 nM (0.3-1.2) and 0.6 nM (0.3-0.8) for X4, R5 and DM viruses, respectively. Concomitant use of MVC or T-20 also did not impact TMR IC50 values.

Conclusion: In this study, TMR RAMs were detected in 3/21 samples and the polymorphic RAM M426L was associated with variable reduction of TMR susceptibility. Except for viruses harboring M426L, the susceptibility to TMR was comparable to wild-type strains in all the samples, irrespective of coreceptor usage or exposure to other entry inhibitors.

549 IN VITRO ACTIVITY OF DTG/BIC/E/CAB ON FIRST-GENERATION InSTI-RESISTANT HIV-1

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Background: Exposure to INSTIs raltegravir (RAL) or elvitegravir (EVG) is frequently associated with the selection of RAMs at virological failure. This study aimed to assess cross-resistance to dolutegravir (DTG), bictegravir (BIC) and the investigational INSTI cabotegravir (CAB).

Methods: Plasma samples from 19 patients harbouring major INSTI mutations (T66A/I/K, E92Q, G118R, E138A/K/T, G140A/C7S, Y143C/H/R, S147G, Q148H/K/R, N155H, R263K) were used for the generation of recombinant viruses containing the patient derived integrase coding region. In vitro susceptibility to DTG, BIC and CAB was determined in a phenotypic assay as fold change (FC) with respect to the reference isolate. Laboratory data are described as median (IQR1-IQR3).

Results: Samples were collected from patients exposed to RAL only, EVG only, RAL and EVG, and RAL and DTG in 9, 4, 1 and 5 cases, respectively. Globally, median FC for DTG, BIC and CAB were 3.5 (1.2-7.3), 2.4 (1.4-5.4) and 2.3 (1.3-21.7), respectively. Median DTG, BIC and CAB FC values from patients not exposed to DTG were 2.9 (1.0-4.4), 2.1 (1.3-3.3) and 2.3 (1.2-4.7), respectively, while exposure to RAL and then DTG resulted in FC >100 in three cases (Q148+2 INSTIs RAMs) and FC <3.5 in two cases (samples with E92Q and with R263K) for all drugs. Median DTG, BIC and CAB FC values were higher following exposure to RAL only vs. EVG only (3.5 [1.6-5.9], 2.4 [1.6-3.9], 2.3 [1.4-12.3] vs. 1.1 [0.8-3.6], 1.8 [0.3-3.3], 1.6 [0.8-8.0], respectively). According to the three major INSTI resistance pathways, median DTG, BIC and CAB FC values were 2.3 (1.0-3.5), 2.5 (2.4-2.5), 1.7 (1.2-2.2), respectively, with Y143R/C alone (n=2); 3.6 (2.6-4.4), 1.8 (1.7-2.7) and 2.3 (1.5-2.6) with N155H alone (n=6); 0.5, 0.8, and 1.2 with Q148R alone (n=1); 7.3 (1.0-8.0), 5.4 (3.2-8.0), 21.7 (9.9-66.3) with Q148R+1 additional INSTI RAM (n=3); and >100 for all the drugs with Q148H+2 additional INSTI RAMs (n=3). Among samples with other INSTIs RAMs (2 with E92Q, 1 with R263K and 1 with T66A+S147S/G), FC ≤3.5 were measured with all drugs. In particular, one sample from a failing DTG based regimen harboring 263K had DTG and CAB FC of 3.5, while BIC FC was 1.1.

Conclusion: DTG, BIC and CAB retain comparable activity against major INSTIs RAMs, with the 148+1 or 2 additional INSTI RAMs resulting in substantially decreased susceptibility for all drugs. Consequent to selection of the 148 pathway, failing RAL appeared to compromise second generation INSTIs more than failing EVG in this dataset.

550 SUSCEPTIBILITY TO BICTEGRAVIR IN HIGHLY ARV-EXPERIENCED PATIENTS AFTER InSTI FAILURE

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Background: Integrase strand transfer inhibitors (INSTIs) are a potent drug class. Bictegravir (BIC) has a favorable in vitro resistance profile with improved activity compared to all other INSTIs. Non-inferior efficacy with no resistance development was shown for BIC/emtricitabine/tenofovir alafenamide (B/F/TAF) in two studies in treatment naïve patients through Week 96 and in two switch studies in virologically suppressed patients through Week 48. The goal of this study was to characterize the genotypic and phenotypic resistance profile to BIC and other INSTIs in patients who have failed twice daily raltegravir (RAL)- or DTG-based regimens.

Methods: This analysis used samples collected after failure on an INSTI-based regimen in highly treatment-experienced HIV-1 infected patients with multi-drug resistant virus and recorded in the Italian PRESTIGIO registry. Genotypic resistance mutations and phenotypic susceptibility to INSTIs were detected by GeneSeqIN and PhenoSenseIN assays with individual INSTI resistance cutoffs defined separately by the assay. Patients' demographics are described as median (Q1,Q3) or frequency (%).

Results: Twenty-two samples from 17 patients were evaluated: 12 (71%) were male, median age 49 years (45, 53), time since HIV-1 diagnosis 20 years (Q1,Q3; 16, 25), time on ART 20 years (Q1,Q3; 16, 18), 10 (59%) with a previous AIDS diagnosis, median viral load at first sample collection of 4.5 log10 copies/mL (4.1, 5.3) and median CD4+ cell count of 168 cells/µl (68, 439). The primary INSTI-resistance substitutions E138A/K, Y143C/H/R, Q148H, and N155H were found in 14/22 samples and were associated with resistance to one or more INSTIs, with G140S+Q148H present in 11/22 samples. Of these 14 samples, all showed resistance to EVG and RAL and two were resistant to BIC and DTG. The two isolates with resistance to BIC and DTG contained L74M, E138K, G140S, and Q148H or L74M, T97A, S119T, E138K, G140S, Y143R and Q148H. Intermediate resistance was reported for 8/14 isolates for BIC and 9/14 isolates for DTG. Overall, for the 14 INSTI-resistant isolates, the median fold-change (range) values were: BIC 3.1 (0.6, 66), DTG 6.1 (0.8, >186), EVG >164 (2.6, >164), and RAL >188 (2.7, >197).

Conclusion: In vitro, BIC retained activity against most isolates derived from patients failing INSTI regimens. These data support the study of BIC once-daily in patients with INSTI-resistance.

551 HIGH LEVEL OF PREEXISTING NRTI RESISTANCE PRIOR TO SWITCHING TO B/F/TAF: STUDY 4030

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Background: Bictegravir (B) is coformulated with the nucleoside/tide reverse transcriptase inhibitors (NRTIs) emtricitabine (F) and tenofovir alafenamide fumarate (TAF) (B/F/TAF). Study 4030 is an ongoing, fully enrolled, phase 3, randomized, double-blinded study (n=565) of HIV-1 RNA suppressed participants on QD dolutegravir (DTG) + F/TAF or F/tenofovir disoproxil fumarate (TDF) switching 1:1 to DTG + F/TAF or B/F/TAF for 48 weeks. Documented INSTI resistance was not enrolled if known at randomization, but all NRTI, NNRTI, and PI resistance was allowed.

Methods: Proviral DNA genotypes (GenoSure Archive) from baseline samples and historical plasma HIV-1 RNA genotypes were analyzed. Documented or suspected NRTI resistance was assigned to group 1) K65R/E/N or ≥3 TAMs containing M41L or L210W (TAMs: D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), group 2) M184I/V, any other set of TAMs, K70E/G/M/Q/S/T, L74I/V, V75A/S/M/T, Y115F, T69D, or Q151M, or group 3) no major NRTI resistance. Virologic outcomes used last available on-treatment HIV-1 RNA with the blinded Week 12 IDMC data cut.

Results: Historical genotypes were available from 285/565 participants (50%). Retrospective analysis of archived mutations by HIV DNA genotype were determined for 377/565 participants; 200 also had historical genotypes. In total, 82% (462/565) of participants had pre-switch genotypic data available resulting in 24% with major NRTI resistance: 5% (29/565) in group 1 (K65R or ≥3TAMs) and 18% (104/565) in group 2 (other NRTI mutations). M184V/I was present in 17% (77/462) of participants with data. HIV DNA genotyping identified previously unknown major NRTI resistance in 15% of participants (58/377). Pre-existing INSTI mutations were found in 5% of participants (19/399): T97A (n=12), N155S (N=1), Y143H (n=2), R263K (n=2), Q148H+G140S (n=1), and S147G (n=1). Primary non-nucleoside RT inhibitor and protease inhibitor resistance mutations were present in 24% (113/462) and 8% (36/462) of participants. At this interim analysis, HIV-1 RNA <50 copies/mL was maintained in 99% of participants, 97% (28/29) in group 1, 99% (103/104) in group 2, 97% (75/77) with M184V/I, and 100% (19/19) with INSTI-R.

Conclusion: This study found frequent NRTI resistance in suppressed participants switching from a DTG + F/TDF or F/TAF regimen, much of which was previously undocumented. Early data show high suppression using potent triple therapy of B/F/TAF or DTG + F/TAF.

552 LONG-TERM B/F/TAF SWITCH EFFICACY IN PATIENTS WITH ARCHIVED PREEXISTING RESISTANCE

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Background: Studies 1844 and 1878 demonstrated non-inferior efficacy of switching suppressed HIV-1-infected adults to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) versus continuing dolutegravir- (DTG) or boosted protease inhibitor (PI)-based regimens. At week 48, 93% in the B/F/TAF groups versus 95% in the DTG group and 89% in the PI group had HIV-1 RNA <50 copies/mL by snapshot algorithm, after which B/F/TAF treatment continued open-label. Here, we present resistance analyses and virologic outcomes after 2 years of B/F/TAF treatment.

Methods: Archived preexisting HIV-1 drug resistance was assessed by historical genotypes (documented resistance to study drugs was exclusionary) and retrospective baseline proviral DNA genotyping (Archive assay, Monogram Biosciences). Participants with resistance to study drugs detected post-randomization were allowed to continue on study. Virologic outcomes were based on last available on-treatment HIV-1 RNA.

Results: Altogether, 572 participants switched to B/F/TAF and were treated for a median of 108 weeks (IQR 106-118 weeks). Pre-switch reverse transcriptase (RT) genotypic data were available for 78% (447/572) of B/F/TAF-treated participants; integrase data were available for 55% (314/572). Preexisting primary NRTI resistance (-R), NNRTI-R, and INSTI-R substitutions were observed in 16% (71/447), 21% (93/447), and 1.9% (6/314), respectively. High frequencies of NRTI-R substitutions M184V or M184I (9.8%, 44/447) and thymidine analog mutations (TAMs; 8.5%, 38/447) were detected by DNA genotyping. Substitutions associated with resistance to the NNRTI rilpivirine (RPV) were observed in 9.6% (43/447). At the time of analysis, 99% (564/572) of B/F/TAF-treated participants were suppressed (HIV-1 RNA <50 copies/mL), including 95% (42/44) with archived M184V/I, 95% (36/38) with TAMs, 98% (42/43) with RPV-R, and 100% (6/6) with INSTI-R. There was no resistance development in B/F/TAF-treated participants through week 48, and no participants met criteria for resistance testing after week 48.

Conclusion: Preexisting RT resistance was common among suppressed participants switching to B/F/TAF, notably RPV-R and previously unidentified M184V/I and TAMs. High rates of virologic suppression were observed in the overall and drug resistant populations through 108 weeks of B/F/TAF treatment with no resistance development, indicating that B/F/TAF is a durable switch option for suppressed patients, including those with evidence of this archived NNRTI and NRTI resistance.

553 ACTIVITY OF BICTEGRAVIR AGAINST HIV-2 ISOLATES AND INI-RESISTANT HIV-2 MUTANTS

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Background: Bictegravir (GS-9883; Gilead Sciences, Inc.) is the most recent second-generation integrase inhibitor (INI) to be approved by the FDA for use in HIV-1–infected patients. For HIV-2, published data regarding the activity of bictegravir are limited to in vitro testing of single group B isolate (Tsai et. al., Antimicrob. Agents Chemother. 60:7086). To evaluate the potential suitability of bictegravir for HIV-2 treatment, we tested the activity of the drug against a panel of group A and group B HIV-2 isolates that were originally obtained from antiretroviral-naïve individuals. HIV-1 isolates representing group M subtypes A, B, C, and D, and group O, were included for comparison. We also determined the antiviral activity of bictegravir against raltegravir-resistant mutants of HIV-2.

Methods: Antiviral activity was measured in single-cycle assays using the MAGIC-5A indicator cell line (HeLa-CD4-LTR-βgal cells). Site-directed mutants of HIV-2 integrase were constructed in the pROD9 HIV-2 molecular clone using QuikChange II XL reagents and procedures (Agilent Technologies). The cytotoxicity of bictegravir was assessed via the CellTiter-Glo® assay (Promega)

Results: 50% effective concentrations (EC_{50} values) for bictegravir ranged from 1.2–2.4 nM for HIV-1 (n = 6 isolates), and 1.4–5.5 nM for HIV-2 (n = 15 isolates). Average EC_{50}s (± SD) for HIV-1 and HIV-2 were 1.6 ± 0.4 nM and 2.4 ± 1.1 nM, respectively. HIV-2_{ROD9} variants Q91R+T97A+Y143C and Q91R+T97A+Y143C+A153S were fully susceptible to bictegravir (EC_{50} = 1.2 nM and 1.6 nM, respectively, versus 2.1 nM for virus from the parental pROD9 clone). Mutations G140A+Q148R, E92Q+T97A+N155H, and I84V+E92Q+T97A+A153S+N155H conferred low-level (4–5-fold) resistance to bictegravir, whereas G140S+Q148R conferred 34-fold resistance to the drug. The 50% cytotoxic concentration (CC_{50}) for bictegravir in MAGIC-5A cells was >10 μM.

Conclusion: Bictegravir is highly active against HIV-2 in culture, with EC_{50} values comparable to those seen for HIV-1. The available data suggest that, for HIV-2, the resistance profile for bictegravir is similar to the profiles observed for dolutegravir and cabotegravir. These findings suggest that bictegravir could be useful for HIV-2 ART and should be further assessed in clinical trials.

554 SPECIFICITY OF 4 POINT-OF-CARE RAPID HIV TESTS IN A SETTING WITH HIGH PrEP USE

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Background: In the United States, performance evaluations of recently FDA-approved rapid HIV tests have been conducted in laboratory settings using plasma and simulated whole blood. Previously published specificity estimates for newer rapid HIV tests when used in point-of-care (POC) settings have not included estimates for persons on Pre-Exposure Prophylaxis (PrEP).

Methods: During September 2015 – August 2018, persons at risk for HIV and seeking HIV testing at a public health clinic in Seattle, WA were invited to participate in the study. Consenting participants completed a behavioral questionnaire that assessed history of PrEP use and were tested with four POC tests using whole blood (see table).Additional blood specimens were collected for laboratory processing and testing. Specimens with a non-reactive

antigen/antibody (Ag/Ab) test result were tested with a nucleic acid test (NAT) in 10-member pools. Specimens with reactive Ag/Ab results and negative or indeterminate supplemental antibody test results, were tested individually using a NAT. For both situations, specimens with a negative NAT result were classified as HIV-uninfected. Specificity of the POC tests with exact 95% confidence intervals (CI) were calculated based on the HIV-uninfected status of the specimen stratified by participant's report of current PrEP use.

Results: Among 1,434 HIV-uninfected specimens, 16.7% were from persons on PrEP at the time of the clinic visit, 80% from persons not currently on PrEP, and 3.5% missing data on PrEP status. There were 8 specimens with false-positive results, 2 from persons on PrEP. No specimen tested false positive on more than one test. False-positivity rates were 0.4% for Determine and 0.1% for INSTI. DPP and OraQuick performed on whole blood produced no false-positive test results. Specificity was high and comparable for all tests and was not affected by PrEP use.

Conclusion: Point estimates for specificity are higher than what we have previously published. The high specificity of these HIV POC tests, including when used with participants taking PrEP, should reassure organizations implementing rapid HIV testing using whole blood specimens. However, the possibility of false-positive results should still prompt organizations to establish mechanisms for either additional HIV testing onsite (using a different rapid HIV test) or follow-up laboratory testing to confirm any positive result.

Table. Specificity of point-of-care (POC) screening tests, by participant-reported PrEP use at time of study visit (n = 1434)

Rapid HIV Test	Not on PrEP (n=1143)	Currently on PrEP (n=240)	HIV-uninfected specimens [a] (n=1434)
DPP	100 (99.68-100.00)	100 (98.47-100.00)	100 (99.74-100.00)
OraQuick	100 (99.68-100.00)	100 (98.47-100.00)	100 (99.74-100.00)
INSTI	99.83 (99.37-99.98)	100 (98.47-100.00)	99.86 (99.50-99.98)
Determine	99.74 (99.23-99.95)	99.17 (97.02-99.90)	99.58 (99.09-99.85)

Abbreviations: POC, point of care; PrEP, pre-exposure prophylaxis; DPP, DPP HIV1/2 Assay (Chembio Diagnostics System, Inc.); OraQuick, OraQuick Advance HIV-1/2 (Orasure Technologies); INSTI, INSTI HIV-1/HIV-2 Rapid Antibody Test (bioLytical Laboratories Inc.); Determine, Determine HIV-1/2 Ag/Ab Combo (Abbott Laboratories).
Footnotes:
[a] Includes 51 specimens that were missing data about PrEP

555 PERFORMANCE OF HIV DIAGNOSTIC ALGORITHMS IN THE PRESENCE OF VACCINE-INDUCED IMMUNITY

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Background: Participants in HIV vaccine trials are at risk of being misclassified as HIV-infected since routine tests may fail to distinguish vaccine induced antibodies from those elicited by infection. We assessed the performance of HIV testing algorithms to distinguish vaccine-induced seroreactivity (VISR) from true infection.

Methods: Stored serum/plasma samples from healthy Swedish and Tanzanian volunteers who participated in any of three previously conducted phase I/II vaccine trials evaluating an HIV-DNA prime HIV-modified vaccinia virus Ankara (MVA) boost strategy were analyzed. HIV infection in participants was ruled out by HIV RNA PCR. Samples were tested for VISR using the HIV testing algorithms of Tanzania and Mozambique, which use two sequential rapid diagnostic tests. SD Bioline HIV1/2 (Standard Diagnostic Inc, Republic of Korea) for screening and Uni-Gold HIV-1/2 (Trinity Biotech, Ireland) for confirmation of HIV infection in Tanzania. Determine HIV-1/2 (Alere Medical Co. Ltd, Japan) for screening and Uni-Gold HIV-1/2 for confirmation of HIV infection in Mozambique. In both countries, patients are considered HIV-infected if both assays are reactive, and discrepant results are resolved by repeated testing. The vaccinees' samples were also tested for VISR using Enzygnost HIV Integral 4 ELISA (Siemens, Germany). Antibodies to subtype C gp140 were determined using an in-house ELISA.

Results: VISR as determined by the Enzygnost HIV Integral ELISA was 92% (61/66). The proportion of vaccine recipients that would have been falsely labeled as HIV positive by the HIV diagnostic algorithm used in Mozambique was half of that by the Tanzanian algorithm, 10/66 (15%) and 21/66 (32%), respectively, p= 0.039. The median anti-Env titer was 3200 (IQR; 3200-12800) in vaccinees with VISR according to the Mozambican algorithm compared to median 800 (IQR; 400-1600) in participants without VISR, p<0.0001. Similarly, the median anti-Env titer was 3200 (IQR; 2400-6400) in participants with VISR according to the Tanzanian algorithm and 800 (IQR; 400-1600) in those without VISR, p<0.0001.

Conclusion: HIV diagnostic algorithms currently used in sub-Saharan Africa will misclassify a proportion of HIV vaccine recipients, but fewer than the Enzygnost Integral ELISA. The Mozambican HIV rapid test algorithm was significantly more accurate than the Tanzanian algorithm. Development of HIV rapid assays that can adequately differentiate VISR from true HIV infection should be prioritized.

556 DIFFERENTIATION CAPABILITY OF THE GEENIUS ASSAY FOR HIV-2 AND HIV-1/2 DUAL INFECTIONS

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Background: Detection and discrimination of HIV-1 and HIV-2 antibodies is a key component of the US CDC HIV diagnosis algorithm. However, differentiation between HIV-2 single- and HIV-1/HIV-2 dual infection by serology alone is challenging. The Bio-Rad Geenius HIV 1/2 supplemental assay (Geenius) is a commonly used, US FDA-approved, assay for HIV-1 and HIV-2 immuno-differentiation. In this study, we evaluated the Geenius assay's output characteristics in the United States (US) HIV positive patient plasma samples that had a clinical diagnosis of HIV-2.

Methods: HIV-2 patients' plasma samples, originating from US clinics and laboratories that were referred for HIV-2 quantitative RNA viral load testing to the University of Washington Retrovirology Laboratory between 2011 to 2018, were retrospectively tested by the Geenius assay. Results were read and interpreted by the Geenius Reader with the proprietary US software (Bio-Rad).

Results: Senegalese plasma samples from known HIV-2-infected (n=20) and HIV-1/HIV-2 dually-infected (n= 8) subjects were used to verify the Geenius assay (Table 1). The Geenius assay algorithm output from 65 US patients' plasma samples with clinically diagnosed HIV-2 was as follows: 27 (41.5%) were HIV-2 positive; 31 (48%) were HIV-2 positive with HIV-1 cross-reactivity; 6 (9%) were HIV positive-untypable; and 1 (1.5%) was HIV-2 indeterminate (Table 1). Notably, 7 samples designated by Geenius as HIV-2 positive with HIV-1 cross-reactivity were reactive to all HIV-2 gp36, gp140 and HIV-1 p31, gp160, p24 and gp41 antigen (Ag) bands. The Geenius interpretation for 4 HIV positive-untypable and one HIV-2 Indeterminate samples were confirmed by additional plasma samples from subsequent dates.

Conclusion: Although the Geenius assay confirmed 20 HIV-2 single- and 8 HIV-1/-2 dual- infection diagnosed from Senegalese plasma samples; nearly half of HIV-2 single-infection plasma samples were also reactive to HIV-1 Ag bands. Variable results were also obtained by Geenius for HIV-2 samples collected from the US, with 7/65 (10.8%; 95% CI 4.4-20.9%) giving untypable or indeterminate results and nearly half showing some cross-reactivity to HIV-1. Additional tests are needed for confirming HIV-2 single infection and differentiating HIV-1/HIV-2 dual infections. Validated nucleic acid amplification testing for HIV-2 and HIV-1/HIV-2 dual infection may improve the CDC algorithm in this patient population.

Table 1. Selections of HIV seropositive samples from Senegal and US tested by the Geenius assay.

Source	HIV sero-status	# of infected patients	Interpretation by the Geenius assay			
			HIV-2 positive	HIV-2 positive with HIV-1 cross reactivity	HIV positive-untypable	HIV-2 in-determinate
Senegal	HIV-1/-2 dual-infection	8	0	0	8	0
	HIV-2 mono-infection	20	11	9	0	0
US	HIV sero-positive* (referred for HIV-2 RNA testing)	65^	27	31	6	1°

*HIV reactivity confirmed by the GS HIV-1/HIV-2 PLUS O EIA assay.
^A subset of HIV seropositive patients.
°Reactive to HIV-2 gp36 only.

557 HIV-1 RNA DETECTION BY ABBOTT M2000 CORRELATES WITH INTEGRASE SINGLE-COPY ASSAY

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Background: The correlation between single copy plasma HIV-1 RNA assays (research tests) and less sensitive but automated, FDA-cleared plasma HIV-1 RNA assays is not well-defined. We examined this association by testing plasma with both a single copy qRT-PCR assay and the Abbott M2000 automated, commercial platform.

Methods: The single copy qRT-PCR assay targeting integrase (iSCA) was performed as published (Cillo, J Clin Micro 2016) with a limit of detection (LoD) 0.4 cp/mL for a 5 mL sample tested. iSCA results were classified as HIV-1 RNA "detected" or "not detected". The FDA-cleared Abbott M2000 RealTime HIV-1 Viral Load assay has a LoD of 40 cp/mL for a 1.0 mL sample. Results below 40 cp/mL were reported as either <40 cp/mL detected but not quantifiable (<40 target detected) or target not detected (TND). Plasma samples obtained at entry into the ACTG A5321 cohort study were tested with both assays. Participants were on suppressive ART with HIV RNA <40 cp/mL by the Abbott assay.

Results: Participants are mostly men (82%), median age of 49, and median of 7 years on ART. Paired samples from 309 participants were tested with both assays. 52% of iSCA results had undetectable HIV-1 RNA; the undetectable iSCA results were primarily (94%) <0.4 cp/mL; nine were <0.5 to <1.1 cp/mL because of lower sample volume. By Abbott M2000, 17% of samples were <40 target detected and 83% were TND. Of the samples TND by Abbott, 43% had HIV-1 RNA detected by iSCA. Of the samples <40 target detected by Abbott, 73% had detectable HIV-1 RNA by iSCA (Figure; p<0.001). Results were similar excluding nine with lower iSCA plasma volume, categorizing iSCA as <0.4 vs. ≥0.4 cp/mL: 44% ≥0.4 cp/mL if TND by Abbott and 73% ≥0.4 cp/mL if target detected (p<0.001).

Conclusion: 73% of plasma samples with an Abbott HIV-1 RNA result of <40 cp/mL target detected also had HIV-1 RNA detected by iSCA, whereas 43% of samples that were TND by Abbott had HIV-1 RNA detected by iSCA. The difference between <40 cp/mL target detected and TND by Abbott has meaningful information, and can be used to estimate the likelihood of HIV-1 RNA detectability by iSCA. The strong association between the results of both assays indicates that a high-throughput automated assay such as Abbott M2000 could be used in epidemiologic investigations of low-level viremia and to screen for changes in low-level viremia following therapeutic interventions, thereby reducing the need for more labor-intensive research single copy assays.

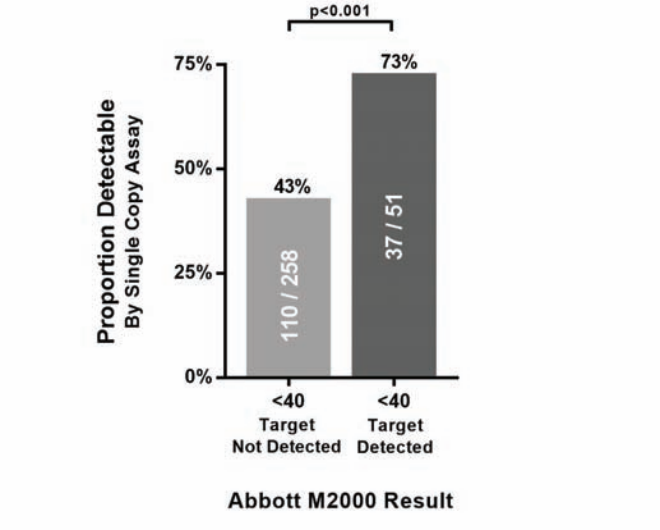

Figure 1 - Proportion SCA Detectable by M2000 Readout

558 REPLICATE APTIMA ASSAY FOR QUANTIFYING RESIDUAL PLASMA VIREMIA IN INDIVIDUALS ON ART

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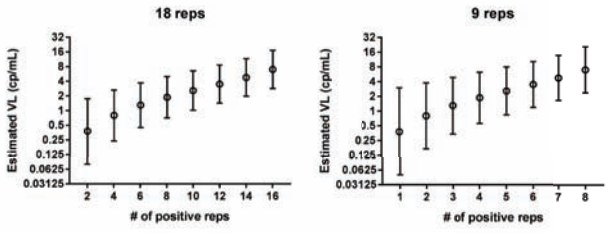
Background: Quantification of residual low-level viremia in research participants on anti-retroviral therapy (ART) and during curative interventions requires ultrasensitive plasma HIV RNA assays. Current single copy assays based on ultracentrifugation are limited in throughput.

Methods: The Aptima HIV-1 Quant Assay is performed on a fully automated platform using 0.5 ml sample with limits of detection (LOD) of 12 cp/ml and quantitation (LOQ) of 30 cp/ml. To detect lower-level viremia, the instrument can generate 9 replicates (reps) per 5 ml plasma input, with the option of loading multiple 5 ml aliquots to further enhance sensitivity. To validate this approach, samples [4 plasma samples from blood donors with acute infection (2 each subtype B and C) as well as the WHO 3rd international standard] with quantified working stock low viral loads (VL), ranging from 16 to 291 cp/ml, were serially diluted in defibrinated plasma to ~0.2 cp/ml, and tested in 38-90 reps per dilution. A Poisson model-based hybrid algorithm was developed to estimate the viral RNA copy number. The replicate testing strategy (45 reps) was then applied to 102 apheresis-derived plasma samples from 50 well-suppressed RAVEN study participants on ART.

Results: For each of the 5 serially diluted samples, estimated concentrations were calculated using standard limiting dilution analysis (LDA) software and they ranged from no underestimation to underestimation of the expected VL by up to 2-fold, reflecting imperfect sensitivity for detection of a single copy. The ratio between expected and estimated VLs was 1.6 with 95% CI 1.04-2.45. Using the replicate testing approach with 45 reps, requiring 25 ml plasma, the median VL in the well-suppressed RAVEN cohort (N=50 participants) was 0.54 cp/ml (range 0.07-13 cp/ml). All 50 participants had detectable low-level viremia in at least one longitudinal visit (range 1-6 visits spanning up to 18 months). At 0.54 cp/ml, the false negative rate was estimated to be 21.7% and 4.7% with 9 and 18 reps, respectively. The figure shows the impact of rep number on precision of low VL estimates, with higher confidence interval widths at 9 relative to 18 reps.

Conclusion: Quantification of low-level viremia can be achieved based on reactive/non-reactive digital readouts on multiple replicates of the Aptima assay via Poisson analysis, with a correction factor that accounts for imperfect sensitivity. Viremia can be detected in all or most individuals on long-term ART, although most have VL <1 cp/ml.



559 THE USE OF EXTERNAL QUALITY-ASSURANCE DATA TO COMPARE HIV-1 RNA ASSAY PERFORMANCE

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Background: The NIAID Virology Quality Assurance (VQA) program provides well-characterized quality control materials (QCMs) for HIV-1 RNA proficiency testing and assay validations to participating labs as part of an external quality assurance (EQA) program. Seventy-eight labs from 22 countries currently participate in this program using a variety of assays. Data generated for purposes of proficiency or assay validation were used to evaluate HIV-1 RNA cross-platform performance.

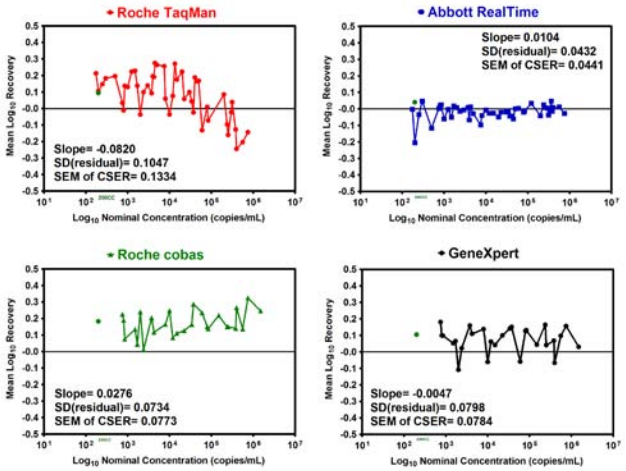
Methods: Data generated on Roche TaqMan (RT), Abbott RealTime (AR), Roche cobas (RC), and Cepheid GeneXpert (GX) HIV-1 RNA assays were included in this

analysis. Controls with a nominal value of 50cp/mL and 0cp/mL were used to evaluate sensitivity and specificity, respectively. Controls with nominal values ≥100 cp/mL (175-1,500,000cp/mL) were used to evaluate precision, accuracy, and linearity (not all concentrations were included in each data set). Variance components models of log10 recovery (with effects for laboratory and assay run) were used to obtain concentration-specific estimates of log10 recovery (CSER). CSER values were related to log10 nominal concentration in a regression model to estimate the slope and residual SD, which were used to evaluate linearity. Targets for linearity were established using historical VQA data.

Results: Even though detection limits varied across the assays, sensitivity for RT, AR, RC, and GX was similar based on a 50cp/mL control (false negative rates: 0.15%, 0.36%, 0.17%, 0.00%). Specificity was also similar (false positive rates: 0.02%, 0.02%, 0.00% and 0.00%). The residual SD of log10 recovery across all control samples was 0.14, 0.13, 0.11, and 0.08 (target of <0.15) and the CSER (min, max) for the combined data set was 0.053 (-0.244, 0.275), -0.020 (-0.205, 0.047), 0.130 (0.009, 0.337), and 0.083 (-0.109, 0.181) for RT, AR, RC, and GX, respectively. Linearity targets were exceeded in the RT assay indicating that log10 recovery varied with concentration (targets for linearity: slope=0.56, SD(resid)=0.96, SEM=0.91); no problems with linearity were noted in the other assays (Figure 1).

Conclusion: EQA data provide a valuable resource for comparing HIV-1 RNA assay performance. Sensitivity, specificity, and precision were comparable across the four assays. However, systematic differences in log10 CSER were noted, with RC demonstrating the highest average log10 recovery and RT demonstrating a lack of linearity primarily due to lower CSER in samples with higher nominal values.

Figure 1. Comparison of mean log10 recovery across assays



560 A REAL-WORLD STUDY OF EFFICACY AND SAFETY OF GLECAPREVIR/PIBRENTASVIR IN HCV PATIENTS

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Background: Data on the effectiveness and safety of Glecaprevir/Pibrentasvir for the treatment of HCV infection in a 'field-practice' scenario are still scant. This study (MISTRAL: MavIret SouTh italy ReAl Life), currently ongoing, evaluates this therapy in a large cohort of HCV-infected patients from Southern Italy.

Methods: All HCV-infected patients, consecutively treated with Glecaprevir/Pibrentasvir at 22 Centers all over Southern Italy were considered. Fibrosis was determined histologically or non-invasively, through liver stiffness measurement. We report here baseline characteristics of patients and available data on end of treatment (EOT). Efficacy of treatment was defined as undetectable HCV-RNA in patients' blood sample obtained twelve weeks after the end of therapy (sustained virological response).

Results: In total, 1178 patients were enrolled (mean age, 60±15 years; 581 males, 49.4%). Most common etiologies were HCV 1b (n=432; 36.8%) and HCV 2 (n=405; 34.5%). One hundred and twenty-three patients (10.5%) were infected from genotype-3 HCV. METAVIR score was F0 in 269 patients (22.9%), F1 in 477 (40.6%), F2 in 209 (17.8%), F3 in 92 (7.8%) and F4 in 103 (8.8%). The wide majority of patients showed normal (CKD1; n=572, 48.7%) or mildly impaired (CKD2; n=472, 40.2%) renal function; 28 subjects had kidney failure (CKD5; 2.4%). Ninety patients (7.7%) were diabetics. Laboratory parameters were as follows: creatinine, 1.02±1.17 mg/dl; bilirubin, 0.76±0.44 mg/dl; hemoglobin, 14.2±1.6 g/dl; platelets, 206874±64111/µl; ALT 45±38 U/L and AST 55±56 U/L. Most patients (n=918; 78.1%) were treatment-naïve. Planned duration of Glecaprevir/Pibrentasvir treatment was 8 weeks for 1067 patients (90.8%), 12 weeks for 102 (8.7%) and 16 weeks for 5 (0.4%). At the time of analysis, data concerning EOT were available for 1178 patients 100% of the total). Almost all of them reached EOT (99.5%). Data on sustained virological response at 12 weeks after EOT are not complete at the time of the present analysis we then here reported data on 885 patients showing a prevalence of 99.3% of SVR. SAE, not related to the drug, were documented in 1% of patients and 8.5% of AE (mostly pruritus).

Conclusion: The large MISTRAL study, conducted in a field-practice scenario, provides a still better prevalence, compared to registration trial, of SVR confirming the extraordinary efficacy and safety of Glecaprevir/Pibrentasvir association also for only 8 weeks treatment. Complete final results will be presented at the CROI meeting.

561 GRAZOPREVIR/ELBASVIR FOR HCV-INFECTED PWID IN REAL-WORLD SETTINGS: THE ZEPALIVE STUDY

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Background: Grazoprevir/elbasvir (GZR/EBR) has demonstrated high efficacy and tolerability in a wide range of settings. In the setting of drug use, GZR/EBR is supported by a specific clinical trial dedicated to drug users on opiate agonist therapy (OAT). In that trial, the rates of SVR were within those found in the rest of the GZR/EBR development. In real life conditions of use, there is a potential for a lower efficacy, particularly of a greater rate of reinfections, and more frequent drop-outs. Thus, we aimed at evaluating the SVR rates of GZR/EBR among PWID with and without OAT in real world conditions of use.

Methods: The HEPAVIR-DAA 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 treatment against HCV infection in clinical practice. Patients starting GZR/EBR included in the HEPAVIR-DAA or the GEHEP-MONO cohorts were analyzed. Overall SVR12 (ITT), discontinuations due to adverse effects and drop-outs were evaluated. The same analysis was carried out for PWID with and without OAT.

Results: 272 patients have started GZR/EBR in the cohorts, and 171 have reached the SVR12 date of evaluation. 84 (49%) were PWID and 32/84 (38%) were on OAT. 49 (29%) individuals were coinfected by HIV. 112 (66%) were men and median (Q1-Q3) age was 48 (37-55) years. HCV genotype distribution was: 1a, 21%; 1b, 46%; 1 other subtype 5%; 4, 28%. 30 (18%) patients presented cirrhosis. All treatments were scheduled for 12 weeks without ribavirin (RBV), but for 5 patients (2.9%) (4 cirrhosis, 1 dialysis) planned for 16 weeks with RBV. One (0.6%) non-PWID dropped-out. Overall, 163/171 (95%) patients have reached SVR12. SVR12 by groups were: non-PWID, 95%; PWID not on OAT, 94%;

PWID on OAT, 97%. There were three relapses, two among PWID not on OAT and one in PWID on OAT. There were three breakthroughs in two non-PWID and one in PWID not on OAT. The SVR12 rates by genotype were: 1a, 92%; 1b, 96; 4, 96%.
Conclusion: SVR rates achieved with GZR/EBR were high in real-world conditions of use. This drug combination is a safe and effective option for PWID with and without OAT managed outside the clinical trial setting.

562 REAL-WORLD DATA ON ELBASVIR/GRAZOPREVIR FOR HCV INFECTION IN HIV/NON-HIV PATIENTS

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Background: There are few real-world data on the effectiveness of elbasvir/grazoprevir (EBV/GZR) for treatment (Rx) of chronic hepatitis C (CHC). We assessed the effectiveness and safety of EBV/GZR in a large prospective registry of individuals receiving DAAs for HCV.
Methods: RUA-VHC (Madrid Registry of Use of DAA for HCV) is a prospective registry of HCV-monoinfected (MoP) and HIV/HCV-coinfected (CoP) individuals receiving all-oral direct-acting antivirals (DAAs) in hospitals of the Madrid Regional Health Service. RUA-VHC was created in November 2014 (Hepatology 2017; 66:344). We selected patients with CHC who had received EBV/GZR and were scheduled to finish Rx on or before 01/03/2018. Retreatment after all-oral DAA was excluded. We assessed sustained virologic response (SVR) at 12 wk by intention-to-treat (ITT) and by a modified intention-to-treat approach (m-ITT), in which non-virological failures for reasons other than discontinuation of Rx after adverse events or death were not analyzed.
Results: A total of 1620 patients (1486 MoP/134 CoP) met the inclusion criteria. Duration of Rx was 12 wk in 1459 patients (1351 MoP/108 CoP), 16 wk in 159 patients (133 MoP/26 CoP), and 8 wk in 2 MoP. Ribavirin (RBV) was used in 8.1% of patients. Median age was 58 y. Men accounted for 52.5% of patients, 23.5% were previously treated, and 15.2% had cirrhosis. Genotype distribution was as follows: G1b, 69.9%; G1a, 16.9%; G4, 12.2%; G1 not subtyped, 1.0%. HCV-RNA was ≥800K IU/mL in 66.5%. Statistically significant differences between MoP and CoP were observed for age, gender, genotype distribution, Rx duration, and use of RBV. Rx outcomes by duration and patient group are shown in the table. SVR rates were 93.8% (95% CI, 92.5%-94.9%) by ITT and 96.9% (95% CI, 96.0%-97.7%) by m-ITT analysis. HIV infection was not associated with Rx failure in the adjusted multivariable analysis including age, sex, liver stiffness, HCV genotype, HCV RNA, HIV, Rx duration, and RBV use (ITT and m-ITT). Factors independently associated with Rx failure by m-ITT included HCV G1a or G4, taking G1b as a reference (aOR 2.59 [95%CI, 1.32-5.08] and 2.96 [95%CI, 1.38-6.37], P=.003) and HCV RNA ≥800K IU/mL taking <800K IU/mL as a reference (aOR 2.16 [95%CI 1.06-4.42], P=.035).
Conclusion: In this large prospective cohort, Rx outcomes for EBV/GZR against HCV were similar to those found in pivotal clinical trials. Factors associated with Rx included infection by HCV G1a or G4 and HCV RNA ≥800K IU/mL.

Table. Outcomes of EBV/GZR for HCV categorized by RX duration and HIV infection

	12 wk N=1459	16 wk N=159	MoP N=1486	CoP N=134	Total N=1620
Ribavirin – n (%)	6 (0.4)	125 (78.6)	111 (7.5)	20 (14.9)	131 (8.1)
Cirrhosis – n (%)	211 (14.5)	35 (22.0)	226 (15.2)	20 (14.9)	246 (15.2)
SVR ITT	1374 (94.2)	143 (89.9)	1399 (94.1)	120 (89.6)	1519 (93.8)
SVR ITT (95% CI)	92.8-95.3	84.2-94.1	92.8-95.3	83.1-94.2	92.5-94.9
Relapse	27 (1.8)	8 (5.0)	29 (1.9)	6 (4.5)	35 (2.2)
Breakthrough	4 (0.3)	0	3 (0.2)	1 (0.7)	4 (0.2)
DC due to AE	5 (0.3)	1 (0.6)	5 (0.3)	1 (0.7)	6 (0.4)
DC other reasons	47 (3.2)	6 (3.8)	47 (3.2)	6 (4.5)	53 (3.3)
Death	2 (0.1)	1 (0.6)	3 (0.2)	0	3 (0.2)
SVR m-ITT	1374 (97.3)	143 (93.5)	1399 (97.2)	120 (93.7)	1519 (96.9)
SVR m-ITT (95% CI)	96.3-98.1	88.3-96.8	96.2-98.0	88.1-97.3	96.0-97.7

563 EFFECTIVENESS OF HEPATITIS C TREATMENT IN HIV/HCV COINFECTED PATIENTS IN MYANMAR

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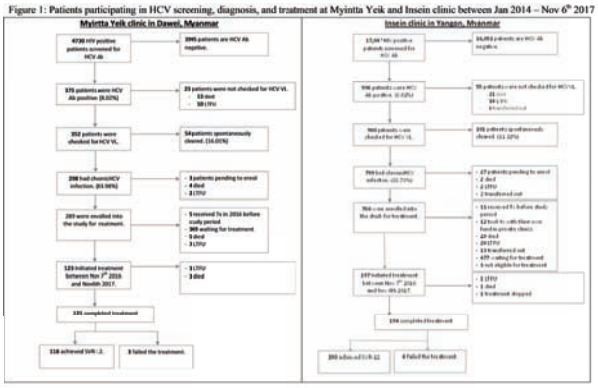
Background: Approximately 5 million people are estimated to be co-infected with HIV and HCV, the majority of which live in low and middle income countries. The safety and success of new direct-acting antiviral (DAA) therapy based regimens has considerably improved. However, there is little data on the effectiveness of HCV treatment in populations of people living with HIV. The purpose of this study was to assess the effectiveness and feasibility of DAA treatment of HCV in HIV co-infected patients in a low resource setting.
Methods: This study used a prospective longitudinal design. Liver fibrosis stage was evaluated by transient elastography using FibroScan. HCV viral load was determined using GeneXpert. Dried blood samples were genotyped at Geneva University Hospital. HCV treatment included sofosbuvir + daclatasvir, with or without ribavirin depending on genotype and cirrhotic stage. Individuals were eligible for treatment if they met the following criteria: 1) were 18 years old or older, 2) On ART and HIV viral load undetectable or asymptomatic with CD4 >500 µL, 3) confirmed chronic HCV infection 4) Liver fibrosis ≥F3 or ≥F2 if treatment is available. The primary endpoint was sustained virologic response (SVR) at the end of 12 weeks of treatment, defined as HCV-RNA response either undetectable or below a concentration of 12UI/mL.
Results: Of the 320 individuals treated, 307 (95.9%) achieved SVR while 7 individuals failed treatment (2.1%) and 6 either died or were lost to follow-up (1.8%) (Figure 1). Between January 2014 and November 6th 2017 4,730 HIV positive individuals attending Myintta Yeik clinic in Dawei, Myanmar and 17,047 HIV positive individuals attending either Thaketa or Insein clinic in Yangon, Myanmar were screened for HCV antibodies. Of the 21,777 individuals screened, 1,371 (6.3%) tested positive. 320 individuals initiated treatment between November 7th, 2016 and November 6th, 2017, the time from which the Myanmar Ministry of Health and Sports gave permission to initiate HCV treatment for this study. The average age of the combined cohorts was 44.7 (SD 6.3).The majority were male (78.2%). More than half (53.3%) of participants reported previous substance abuse. Previous time in prison was reported by 29.2% of participants.
Conclusion: Our study demonstrates that treatment for HIV/HCV co-infected patients is feasible and highly successful in a resource limited setting. Our study suggest that clinicians can be trained to integrate treatment of hepatitis C into existing HIV services.

Figure 1: Patients participating in HCV screening, diagnosis, and treatment at Myintta Yeik and Insein clinic between Jan 2014 – Nov 6th 2017



564 HCV LATE RELAPSE IN PATIENTS WITH DIRECTLY ACTING ANTIVIRAL–RELATED SVR 12

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Background: The IFN-free regimens yield a sustained virological response rate at week 12 (SVR12) of approximately 95%, even in patients with cirrhosis. However, an important unresolved question is how long follow-up should last after stopping treatment and when effectively a patient is considered free of HCV infection. Aim: The aim of the present study was to identify, among the patients with failure to DAA regimen, those with a late relapse (after the achievement of a sustained virological response at week 12) and to characterize the clinical, epidemiological and virological features of these patients.

Methods: 129 HCV patients with non-response to an IFN-free regimen were enrolled. Sanger sequencing of NS3, NS5A and NS5B was performed at failure by home-made protocols

Results: Of the 129 patients enrolled, 8 (6.2%) experienced a breakthrough, 15 (11.7%) non-response, 99 (76.7%) a relapse by week 12 after the end of DAA therapy, and 7 (5.4%) a late relapse (after week 12; median 24 weeks, range 24-72). Table 1 shows the clinical and virological data of the 7 patients with a late relapse. For 2 of the 7 patients with a late relapse a serum sample collected before the start of the DAA regimen was available; phylogenetic analysis showed no change in sequences of NS3, NS5A and NS5B regions, suggesting a reactivation of the initial HCV strain. The prevalence of patients with RASs was higher in the 7 with a late relapse than in the 99 with a relapse by week 12. In fact, at least one RAS or RASs in all 3 regions of HCV was more frequently identified in the first group (100% vs. 66.7%, p=0.09; and 28.6% vs. 5%, p=0.06, respective); however, because of the low number of patients with a late relapse, these differences were not significant to the statistical analysis. Moreover, a RAS in the NS5A region was observed in all patients with a late relapse and in 53 (53.5%, p=0.018) in those with a relapse by week 12.

Conclusion: In conclusion, our real-life study demonstrates that a late relapse may occur in patients who had obtained an SVR12 with a DAA treatment. This is in good agreement with the data recently published by Sarazzin and coworkers (Sarrazin C. et al. Clin Infect Dis. 2017, PMID: 27737953) but partially disagrees with the indication of the international guidelines suggesting a post-treatment follow-up of 12 weeks. Thus, further studies on a larger patient population are needed to clarify this topic.

Table 1: Clinical and virological data of the 7 patients with a late relapse

Pt n°	HCV genotype before DAA	HCV Therapy	Duration of HCV therapy	Risk factors* for reinfection	Time of relapse	HCV genotype at DAA failure	RASs at DAA failure		
							in NS3	in NS5A	in NS5B
1	1a	Sof+Riba	12	no	72	1a	/	M28T, Q30H	/
2	1b	Sim+Sof	12	no	72	1b	/	P58S	C316N
3	4	Sof+Ldv+Riba	12	no	24	4	/	L28M, Y93H	/
4	1b	Sof+Ldv+Riba	12	no	24	1b	V170A	L28M, Y93H	/
5	1b	Sof+Riba	12	no	24	1b	V107T, S122N	L28M, Y93[C,S]	S556G
6	1b	3D	12	no	24	1a	Y56H, D168V	Y93H	L159F, C316N, S556G
7	1b	Sof+Ldv	12	surgery	48	1b	/	L31M	/

Notes: Sof: sofosbuvir; Riba: ribavirin; Sim: simeprevir; Ldv: ledipasvir; 3D: ombitasvir, dasabuvir, paritaprevir+ritonavir
*: HIV infection; Intravenous drug use; men who have sex with men; prisoners; recent history of surgery

565 CLINICAL OUTCOMES IN PERSONS COINFECTED WITH HIV AND HCV: IMPACT OF HCV TREATMENT

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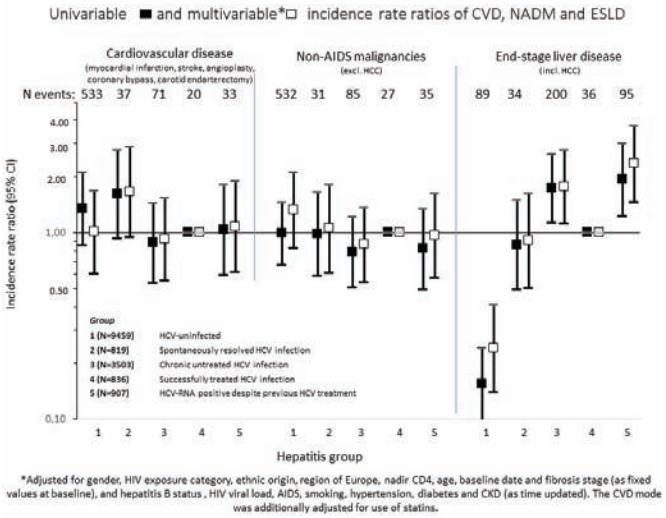
Background: Previous studies have found changes in lipids and inflammatory biomarkers after HCV cure, but there is little data on clinical endpoints in HIV/HCV coinfected persons. We investigated the impact of HCV coinfection status and clearance of HCV-RNA following treatment on the risk of non-AIDS malignancies (NADM), cardiovascular disease (CVD) and end-stage liver disease (ESLD) in HIV/HCV infected persons in the EuroSIDA study.

Methods: All HIV positive persons with known HCV status after January 2001 were included and stratified into five groups based on time-updated HCV-RNA and use of HCV treatment: 1) HCV-uninfected, 2) spontaneously resolved HCV infection, 3) Chronic untreated HCV infection, 4) Successfully treated HCV infection, 5) HCV-RNA positive despite previous HCV treatment. Separate analyses were performed with each clinical event (fatal and non-fatal) ESLD (including hepatocellular carcinoma, HCC), NADM (excluding HCC) and CVD (myocardial infarction, stroke, angioplasty, coronary bypass, carotid endarterectomy). Poisson regression was used to compare incidence rates between HCV groups.

Results: A total of 15,524 HIV positive persons were included. The majority were male (74%), White (87%), on cART (85%) and current smokers (55%) with a median (IQR) age of 41 (35-49) years and CD4 cell count of 446 (290-641) cells/µl. During a median of 6.6 (IQR 2.3–12.6) person years of follow up (PYFU), a total of 694 CVD, 710 NADM and 375 ESLD events occurred; crude incidence rates/1000 PYFU (95% CI) were 6.1 (5.7–6.6) for CVD, 6.2 (5.8–6.7) for NADM and 3.2 (2.9–3.6) for ESLD. In univariable and multivariable analysis, there were no differences in incidence of both NADM and CVD between those who were untreated, had cleared HCV-RNA after HCV treatment and those with chronic infection (figure). In contrast, the incidence of ESLD was significantly lower among persons who had cleared HCV-RNA after treatment compared to those with chronic infection, and similar to those with spontaneous HCV-RNA clearance.

Conclusion: Although HCV cure has been shown to perturb levels of lipid and inflammatory biomarkers, studies of HIV/HCV coinfected persons have lacked power to focus on clinical events. We found no evidence of any impact of HCV infection status or HCV treatment on incidence of both NADM and CVD in coinfected persons while successful HCV treatment significantly lowered the incidence of ESLD to what was observed for those with spontaneous HCV-RNA clearance.



*Adjusted for gender, HIV exposure category, ethnic origin, region of Europe, nadir CD4, age, baseline date and fibrosis stage (as fixed values at baseline), and hepatitis B status , HIV viral load, AIDS, smoking, hypertension, diabetes and CKD (as time updated). The CVD mode was additionally adjusted for use of statins.

566 INTERFERON-FREE REGIMENS IMPROVE RENAL FUNCTION IN PATIENTS WITH CHRONIC HEPATITIS C

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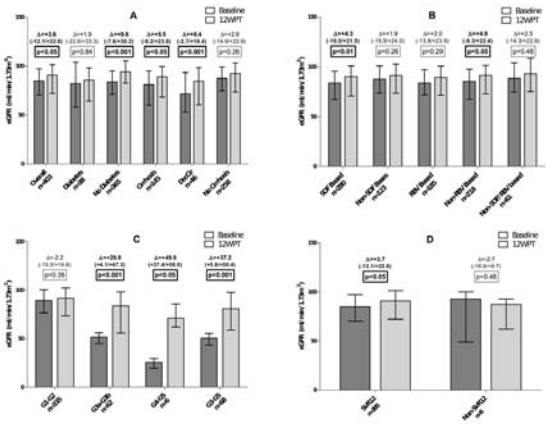
Background: In literature there are few data on the impact of direct-acting antivirals regimens (DAAs) on renal function. We examined estimated glomerular filtration rate (eGFR) trend during and post treatment with DAAs.
Methods: A retrospective analysis of a multicentre Italian cohort enrolling 403 patients with chronic HCV infection treated with DAAs between March 2015 and December 2017 for up to 12 weeks post treatment (12WPT) was performed. Patients with HIV, Child C cirrhosis, hepatocellular carcinoma or that refused consent were excluded. Impaired renal function (IRF) was defined as a CKD (chronic kidney disease) stage G3-G5 according to the KDIGO (Kidney Disease Improving Global Outcomes) stage. The reduction in CKD of at least 1 KDIGO stage was defined as an improvement.
Results: Of the 403 patients, 40% had a KDIGO stage of G1, 43% were stage G2, 15% were G3 and 1.4% were G4-5. Sofosbuvir(SOF) plus Ledipasvir(LDV)±Ribavirin(RBV) and Ombitasvir(OMB), Paritaprevir(PAR), Dasabuvir(DAS)+Ritonavir(r)±RBV were the most used regimens [34% and 30%, respectively] with an overall SVR12 rate of 98%. The median eGFR increased from 12WPT and baseline of +3.6 (IQR: -12.1/+22.6). The rate of patients with a CKD stage of G3-G5 significantly decreased from 16.9% to 12.2% at 12WPT ($p<0.05$). Figure1 shows the change in eGFR between baseline and 12WPT according to different comorbidities(1A) DAAs(1B), CKD stage(1C) and presence of SVR(1D). Patients without diabetes showed an improvement in eGFR from 84.05 ml/min/1.73m2 at baseline to 95.01 ml/min/1.73m2 at 12WPT ($p<0.001$), as well as patients with cirrhosis (from 79.06 to 84.61 ml/min/1.73m2 $p<0.05$), and patients with decompensated cirrhosis (from 71.07 to 79.46 ml/min/1.73m2 $p<0.001$). SOF-based regimens (from 88.49 to 91.44 ml/min/1.73m2 $p<0.01$) and patients not receiving RBV (from 84.46 to 89.37 ml/min/1.73m2 $p<0.05$) improved too. Finally, the 395 patients who achieved SVR12 showed an increased in eGFR (from 84.60 to 88.30 ml/min/1.73m2 $p<0.05$). At multivariate analysis, independent factors associated with renal improvement were decompensated cirrhosis at baseline [aHR 3.43 (95IC 1.44-8.18) $p<0.05$] and the achievement of SVR12 [aHR 12.20 (95CI 1.26-118.11) $p<0.05$].
Conclusion: Conclusions: Our findings suggest that DAAs correlates with an improvement in renal function, especially if SVR12 is achieved and in patients with baseline IRF or cirrhosis. However, further studies are needed to confirm these data.

Figure 1. eGFR difference between baseline and 12WPT according to comorbidities (A) treatment received (B) KDIGO stage at baseline (C) and SVR12 (D)



eGFR: estimated glomerular filtration rate. 12WPT: twelve weeks post-treatment. KDIGO: kidney disease improving global outcomes. SVR12: sustained virologic response at twelve weeks post treatment. DecCir: decompensated cirrhosis. SOF: sofosbuvir. RBV: ribavirin. G1-G5: stages of chronic kidney disease according to KDIGO.
Δrefers to the difference of eGFR between 12WPT and baseline. Data are presented as median and interquartile range

567 PCSK9 LEVELS DECLINE WITH HCV DIRECT-ACTING ANTIVIRAL THERAPY IN HIV/HCV COINFECTION

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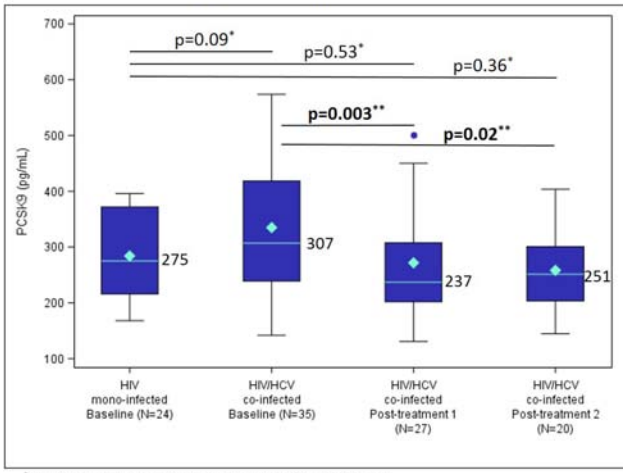
Background: Proprotein convertase subtisilin/kexin 9 (PCSK9) regulates levels of low-density lipoprotein (LDL) cholesterol, which are altered in hepatitis C virus (HCV) infection. PCSK9 levels may also be associated with inflammation and immune activation. We hypothesized that PCSK9 levels would be higher in HIV/HCV co-infected compared to HIV mono-infected individuals, and decline to levels in mono-infected persons with HCV clearance with direct-acting antivirals (DAAs).
Methods: HIV-infected adults on antiretroviral therapy with HIV RNA<50 copies/mL, HCV RNA>10,000 IU/mL or HCV antibody negative and without cardiovascular disease (CVD) were enrolled. Circulating PCSK9 and CVD/inflammatory biomarkers (sCD14, sCD163, sE-selectin, Lp-PLA2, IL-6, sTWEAK and standard lipid panel), and HOMA-IR were measured at entry and post-treatment. Baseline characteristics and biomarker levels were compared by chi-square, Fisher's exact, or Wilcoxon rank sum tests. Within-person changes (absolute and %) in PCSK9 level with HCV therapy were examined by Wilcoxon signed-rank test, and correlations between changes in PCSK9 and changes in biomarkers by Spearman rank correlations.
Results: Twenty-four HIV and 35 HIV/HCV-infected persons were included (85% male, 85% non-white or Hispanic). Median age was 52 years and CD4 count 622 cells/mm^3. Co-infected persons had higher ALT, FIB-4 scores, and HOMA-IR, and lower LDL-C and CD4 counts. Twenty-nine completed DAA therapy, all of whom achieved sustained virologic response. The Figure summarizes comparisons of PCSK9 levels at baseline, post-treatment 1 (median 7.3 weeks after end of treatment (EOT)), and post-treatment 2 (median 43.5 weeks after EOT). PCSK9 dropped significantly from baseline to post-treatment 1 and post-treatment 2: median within-person change was -20.8% ($p=0.006$) and -18.2% ($p=0.033$), respectively. Change in PCSK9 correlated with change in sE-selectin and sCD163 from baseline to post-treatment 1 ($r=0.46$, $p=0.016$ and $r=0.39$, $p=0.047$, respectively) and to post-treatment 2 ($r=0.64$, $p=0.002$ and $r=0.58$, $p=0.008$, respectively), but not with change in LDL or other biomarkers.
Conclusion: Prior to HCV treatment, PCSK9 levels trended towards being higher in HIV/HCV co-infected persons compared to HIV mono-infected persons. PCSK9 levels declined significantly with HCV treatment, to levels similar to or below those in HIV mono-infection. Elevated PCSK9 levels in the setting of HCV infection may reflect HCV-associated inflammation rather than cholesterol homeostasis.

Figure. PCSK9 levels in HIV mono-infected persons and HIV/HCV co-infected persons before and following HCV direct-acting antiviral therapy.



*Wilcoxon rank sum test for comparison of median PCSK9 level
**Wilcoxon signed rank test for absolute within-person change in PCSK9 levels (N=27 participants with paired baseline and post-treatment 1 PCSK9 and N=20 participants with paired baseline and post-treatment 2 PCSK9)

568 LIVER STIFFNESS AT SVR PREDICTS HEPATIC COMPLICATIONS IN HCV-INFECTED PATIENTS

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Background: A minority of HCV-infected patients with sustained virological response (SVR) subsequently develops hepatic complications. Determining the factors that may identify patients with SVR at risk of poor clinical outcome are of the maximum interest. The objective of the study was to analyze the predictive ability of liver stiffness (LS) at the time of SVR for the emergence of liver complications in patients with advanced liver fibrosis treated with direct anting antiviral (DAA)-based therapy.

Methods: Multicentric prospective cohort study. HCV-infected patients who met the following criteria were selected: 1) Achieved SVR with DAA-including regimens; 2) LS ≥9.5 kPa before starting therapy and; 3) LS measurement available at SVR. The primary end-point was the occurrence of a liver complication -hepatic decompensation or hepatocellular carcinoma (HCC)- or requiring liver transplant after SVR. The relationship between the time to the end-point and potential predictors of liver complications was assessed in a multivariate regression model for competitive risks.

Results: 843 patients were included, 573 (68%) coinfected with HIV. 463 (55%) showed previous compensated cirrhosis. 50 (6%) had developed a liver decompensation prior to treatment and 787 (93%) had been treated with an interferon-free regimen. During a median (Q1-Q3) follow-up of 25.2 (15.8-30.6) months, 27 (3.2%) patients reached the primary end-point and 23 (2.7%) patients died. In the multivariate analysis, variables (subhazard ratio [SHR] [95% CI]) associated with developing a hepatic complication or requiring transplant were: pretreatment LS (1.03 [1.01-1.08] for 1 kPa increase), HCV genotype 3 (5.77 [2.33-14.33]), having achieved SVR with Peg-IFN-based therapy (3.70 [1.16-12.50]), prior hepatic decompensations (5.58 [1.95-15.99], CPT class B at SVR time (6.60 [2.02-21.50] and LS at the time of SVR (1.03 [1.01-1.01] for 1 kPa increase). Notably, none out of 482 patients with LS <14kPa at SVR time-point developed a liver complication or required hepatic transplant. 175 (34%) of the patients with LS>14 kPa prior to treatment had a value below this level at SVR-time point.

Conclusion: LS at the time of SVR after DAA therapy predicts the clinical outcome of HCV-infected patients with advanced fibrosis, thus identifying candidates to be withdrawn from surveillance programs. Discontinuing HCC screening programs in patients with LS <14kPa at SVR may spare surveillance in over 30% of the patients currently undergoing it.

569 INFLAMMATION, ARTERIAL STIFFNESS, AND DIRECTLY ACTING ANTIVIRALS IN HCV AND HIV/HCV

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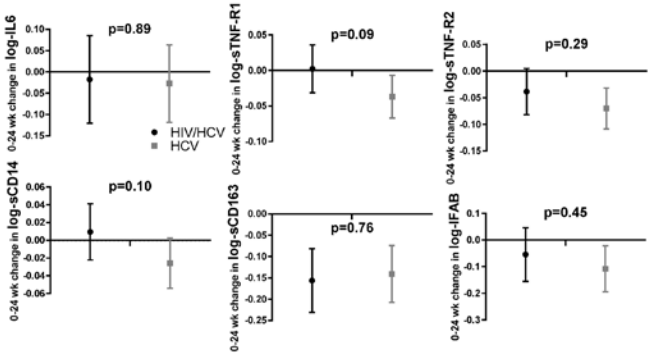
Background: Coinfection with HCV increases cardiovascular disease (CVD) risk in HIV. Insulin resistance and heightened inflammation may contribute. While directly-acting antivirals (DAAs) improve glucose homeostasis and CVD risk in HCV-infected persons, the effect in HIV/HCV coinfection is less clear.

Methods: This is a 24-week prospective, cohort study to compare baseline and changes in aortic pulse wave velocity (PWV), glucose homeostasis (HOMA-IR), systemic inflammation [interleukin-6 (IL6), soluble tumor necrosis factor α receptors 1 and 2 (sTNF-R1 and -R2)], monocyte activation (soluble CD14 and CD163), and gut integrity [intestinal fatty acid binding protein (IFAB)] among adults with HIV, HCV, HIV/HCV or neither infection (controls) and after HCV treatment in HCV and HIV/HCV. Adults without CVD or diabetes and on stable antiretroviral therapy (HIV and HIV/HCV) were included. Pairwise comparisons of log-transformed outcome variables were made at baseline and absolute changes over 24 weeks were compared within and between groups that underwent HCV treatment. Analysis of covariance (ANCOVA) was used for adjustment.

Results: 126 subjects (25 HIV, 35 HCV, 39 HIV/HCV, 27 controls) were included. 54 (30 HCV, 24 HIV/HCV) received DAAs and attained sustained virologic response (SVR). Groups were similar except HCV subjects were older (56 vs 51 years) and more likely to have HTN (51 vs 23%); controls were more likely Caucasian (85 vs 48%) and non-smokers (81 vs 38%). Of those who underwent HCV treatment, 77% initiated ledipasvir/sofosbuvir. Baseline PWV was not different among groups and 0-24 week changes were not significant within or between groups treated for HCV (p=0.46 for between group test). Baseline HOMA-IR was higher in HIV/HCV than HIV and HCV trended to be higher than controls, but did not change after DAAs (p=0.89 for between group test). Baseline IFAB and sCD163 were greater in HIV/HCV than HCV and HIV, respectively. Most inflammatory markers were higher in HCV and HIV than controls. The figure shows 0-24 week changes in the markers tested. Most markers improved in HCV, while they did not change in HIV/HCV. Changes in sTNF-R1 and sCD14 tended to be different between groups with improvements in HCV group only.

Conclusion: After DAA treatment, immune activation and gut markers improved in the HCV group; no change was observed in the HIV/HCV group. Further, PWV did not improve in either group. Cardiac risk may remain elevated in HIV/HCV despite SVR with DAAs.



Symbols represent mean changes over 24 weeks in each marker adjusted for baseline value. Error bars show 95% confidence intervals. P-values shown are for between-group tests. Adjustment for age, sex, race, smoking status, presence of hypertension, BMI and HOMA-IR did not change the results qualitatively.

570 EFFECT OF LIVER FIBROSIS STAGE AND DAA TREATMENT ON RISK OF CVD EVENTS IN ERCHIVES

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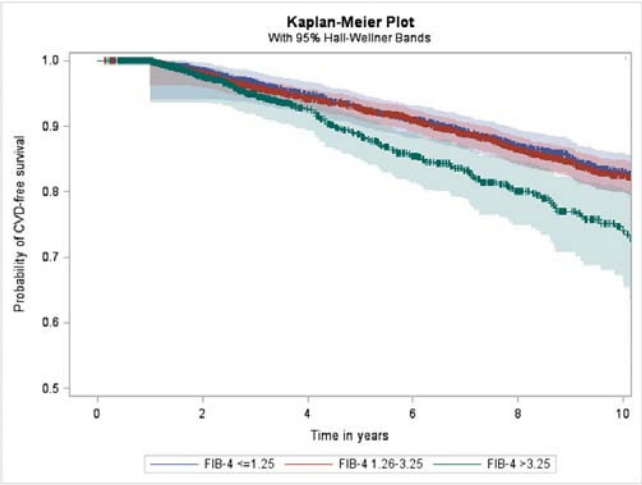
Background: Hepatitis C virus (HCV) infection is associated with a higher risk of cardiovascular disease (CVD) events. Treatment with directly acting antiviral (DAA) regimens has been shown to reduce this risk in most, but not all studies. How liver fibrosis stage affects risk of incidence CVD events after treatment with DAA regimens is unknown. We undertook this study to determine the effect of baseline liver fibrosis stage upon the risk of incident CVD events in DAA-treated HCV infected persons, and compare it with untreated and those treated with older pegylated interferon-based (PEG) regimens.

Methods: Within ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans), we identified all persons treated for HCV for >=7 weeks and propensity-score matched group who never received HCV treatment. We excluded those with HIV, HBV and previously diagnosed CVD. Incidence rate (per 1,000 person-years) and risk factors for CVD events (Cox proportional hazards analysis) were stratified by liver fibrosis stage. Liver fibrosis stage was determined by FIB-4 score. CVD events were identified using ICD-9CM/ICD-10 codes. Kaplan-Meier plots were generated to show and compare CVD-free survival by fibrosis stage and treatment regimen.

Results: Among 32,575 treated and same number of propensity-score matched untreated persons in the final dataset, median age was 58 years, 27% were Black race and 96% were male. The incidence rate for CVD events/1,000 person-years (95% CI) among the treated was as follows: FIB-4<1.25: 19.3 (17.2,21.4); FIB-4 1.26-3.25: 19.9 (18.4,21.5); FIB-4>3.25: 24.5 (21.5,27.6). Rates among

untreated were as follows: FIB-4<1.25: 25.6 (23.8,27.5); FIB-4 1.26-3.25: 33.2 (31.2,35.1); FIB-4>3.25: 44 (39.6,48.3). The absolute difference in rate was 6.3 for FIB-4<1.25, 13.3 for FIB-4 1.26-3.25 and 19.5 for FIB-4>3.25.
Conclusion: Risk of CVD among HCV infected persons is higher with increasing liver fibrosis stage. Treatment reduces the risk of incident events at all fibrosis stages, but the benefit is highest for those with most advanced fibrosis. HCV infected persons with more advanced liver fibrosis should be targeted for treatment to reduce future risk of CVD events.



571 LIVER FIBROSIS HINDERS T-CELL HOMEOSTASIS RESTORATION AFTER HCV ERADICATION WITH DAAs

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Background: A significant impact of HCV coinfection on several immune parameters of HIV pathogenesis has been recently shown. However, to what extent these alterations are diminished or even abolished after HCV eradication with direct acting antivirals (DAAs) treatment has not been clarified to date. Herein we have analyzed the effect of HCV on several immune parameters of HIV pathogenesis and its evolution after HCV eradication in HIV patients coinfected with HCV
Methods: Twenty-five HIV-monoinfected (HIV group), 25 HIV/HCV coinfected (HIV/HCV group) and 20 healthy controls (HC group) were included. All patients were on antiretroviral therapy and undetectable HIV viremia. Maturation, activation, apoptosis, senescence and exhaustion of CD4 and CD8 T cells were assessed by polychromatic flow cytometry. Cross-sectional and longitudinal (comparing baseline and post-HCV treatment data in HIV/HCV patients) analyses were performed. Non-parametric tests were used to establish inter and intra-group differences
Results: Compared to HC group, HIV patients showed increased exhaustion and senescence of CD4 and CD8 cells, and increased activation of CD8 cells ($p<0.0001$ for all comparisons). Compared to HIV group, HIV/HCV patients presented higher exhaustion of effector CD4 ($p=0.001$) and CD8 ($p=0.006$) cells; and higher activation of total ($p=0.026$) effector memory ($p=0.006$) and effector ($p<0.0001$) CD8 cells. HIV/HCV patients with liver fibrosis (stage ≥F2), showed increased senescence and activation in several subsets of CD8 cells ($p<0.05$ for all comparisons) compared to patients without liver fibrosis (stage F0/F1). After HCV eradication with DAAs, differences between HIV/HCV and HIV groups diminished, except activation ($p=0.002$) and exhaustion ($p=0.053$) of effector CD8 cells that remained increased in HIV/HCV group. Interestingly, the effect of HCV eradication on immune parameters restoration (measured as the ratio of post-treatment vs. baseline values) was less pronounced in HIV/HCV patients with liver fibrosis compare to those without liver fibrosis, especially for senescence of CD8 cells ($p=0.003$)
Conclusion: Both the presence of HCV coinfection and liver fibrosis significantly impact on several immune markers of HIV pathogenesis. Eradication of HCV with DAAs ameliorates but does not normalize these alterations, what is hindered by the presence of liver fibrosis. These data prompts HCV treatment in HIV/HCV coinfected patients at the earliest stages of liver damage to enhance restoration of T cell homeostasis

572 IMPACT OF DIRECT-ACTING ANTIVIRALS ON RATES OF HCC IN HCV- AND HIV-INFECTED PATIENTS

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Background: HCV and HIV co-infection is known to be associated with increased risk of HCC. While we have data showing a significant decline in the rate of HCC in HCV patients undergoing treatment with DAA, the rate of HCC in HCV-HIV co-infected patients treated with DAA is not known. The aim of our study was to evaluate the impact of DAA therapy on the incidence of HCC in HCV-HIV co-infected patients.
Methods: This retrospective analysis included all patients co-infected with both HCV and HIV, followed at Grady Memorial Hospital between January 2012 and December 2017. Patients were divided into two groups based on whether they received or did not receive DAA therapy and followed for development of HCC. Data included age, sex, race, HCV genotype, type of DAA regimen and SVR (in the treated group), cirrhosis, hepatitis B status, HIV control, CD4 trend and rates of HCC in both groups. Chi-square and Hazard ratio were used to calculate levels of statistical significance.
Results: 819 patients co-infected with HIV and HCV were included in the analysis. 387 were treated with DAA while 432 were not. Median age in the treated group was 57 years with 79% males and 86% African americans while in the untreated group the corresponding numbers were 56 years, 78% males and 92% African americans. Median follow up was 42 months. There were 37 cirrhotics in the treated and 42 in the untreated group ($p=0.93$). 20 patients were HbsAg positive in the treated group and 11 in the untreated group ($p<0.05$). HIV was detectable in 14 patients in the treated and 147 in the untreated group ($p<0.00001$). 1 patient developed HCC in the treated group compared to 10 in the untreated group ($p<0.01$). Patients who developed HCC had poor HIV control (in 8 out of 11) and had a low CD4 count (median 119 cells/µl). HbsAg was positive in 3 patients with HCC, all in the untreated group. 8 of the 11 patients with HCC had cirrhosis. In the untreated group cirrhosis ($p<0.00001$) and HbsAg positivity ($p<0.00001$) was significantly associated with the development of HCC. Relative risk of HCC in the HCV HIV co-infected cohort treated with DAA compared with untreated cohort was 0.11 (95% CI 0.014 to 0.868) ($p=0.03$).
Conclusion: DAA therapy significantly reduced rates of HCC in HCV-HIV co-infected patients. Eradicating HCV appears to overcome the significant role of HBV and cirrhosis in the development of HCC in these patients. Poor HIV control appears to be a big reason for withholding DAA therapy in these patients.

573 BARRIERS TO INITIATING DAA THERAPY IN HCV/HIV COINFECTED PATIENTS

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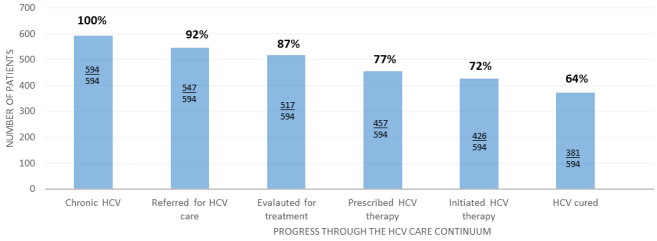
Background: HCV continues to be a leading cause of liver disease and hepatocellular carcinoma (HCC), both of which are accelerated in HCV- HIV co-infected patients. The advent of DAA has significantly reduced the rate of HCC, but a large proportion of patients continue to be deprived of this beneficial therapy. Our aim was to determine the barriers to initiation of DAA in co-infected patients.
Methods: This retrospective analysis included all patients co-infected with both HCV and HIV, followed at Grady Memorial Hospital between January 2012 and December 2017 but did not receive DAA therapy. We evaluated reasons for not initiating DAA in these patients and looked at patient characteristics including age, sex, race, HCV genotype, cirrhosis, hepatitis B status, HIV control, the presence of other cancers, and social issues including drug abuse and health insurance.
Results: Out of 819 patients co-infected with HIV and HCV, 387(47%) received and 432 (53%) did not receive any DAA therapy. The median age in the untreated group was 56 years, 78% of patients were males and 92% African Americans. HIV was detectable in 3.7% patients in the treated and 34% in the untreated

group (p<0. 00001). As compared to the treated group, the untreated group had 11. 5% patients with active cancer, for which they were receiving therapy (p=. 024), 78% patients with alcohol and/or drug abuse issues (p<0. 00001) and 5% patients with end-stage renal disease (ESRD), on hemodialysis (p=0. 000018). 46% of patients had Medicaid while 23% had no health care coverage. About 40 patients were lost to follow up. Poor HIV control with active drug abuse was the most common reason for withholding DAA therapy accounting for up to 60 % of untreated patients. Active cancer requiring therapy (10%), loss to follow up (10%) and ESRD (5%) were the other major reasons for not receiving therapy. Other reasons included patient non-compliance (3%), intolerable side effects (2%), patient refusal (2%) (Figure 1). In the rest, the reason for non-therapy could not be ascertained. At our center, all patients, irrespective of insurance status received DAA.

Conclusion: 53% patients did not receive DAA though health insurance is not a barrier at our center. Poor HIV control and active drug use remain the predominant reasons for not receiving DAA therapy in HCV-HIV co-infected patients. Active cancer and loss of follow up were other major barriers. Thus, control of HIV and its consequent sequelae like cancers and nephropathy remains the biggest challenge in

Figure 1: HCV care continuum among 594 HIV/HCV infected patients in an urban HIV clinic



574 PROGRESS TOWARDS HCV MICRO-ELIMINATION IN AN URBAN HIV-INFECTED COHORT

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Background: Direct-acting antivirals (DAA) lead to high rates of Hepatitis C (HCV) cure. Bolstered by the results of DAA treatment, the World health Organization has called for HCV elimination by 2030. Given this task, HCV mirco-elimination has gained burgeoning support, and people with HIV have been identified as a population in which micro-elimination may be feasible. Here, we describe the HCV care continuum and progress towards HCV elimination in an urban HIV clinic population.

Methods: We examined progress through the HCV care continuum among patients infected with HIV/HCV receiving HIV care in an HIV clinic at Johns Hopkins Hospital in Baltimore, MD. Individuals were eligible for inclusion in the study if they had HIV visits in at least 2 consecutive years between January 1, 2013 and December 31, 2016 and had a detectable HCV RNA. Patients were followed through March 31, 2018 for referral to HCV care, HCV treatment initiation and cure (undetectable HCV RNA 12 weeks post-treatment). Multivariable logistic regression was used to identify demographic and clinical characteristics associated with HCV treatment initiation.

Results: Among 594 HIV/HCV coinfected individuals, the median age was 57 years (interquartile range (IQR) 52-61), 89% were black, 67% male, 51% had a psychiatric history, 73% had a history of injection drug use and 34% reported heroin and/or cocaine use in the preceding 3 months. The median CD4 count was 462 (IQR 295-673) cells/mm3; most (79%) were on antiretroviral therapy (ART), had HIV RNA <400 copies/ml (75%) and were infected with HCV genotype 1 (96%). The majority were insured by Medicaid (51%). Assessing the HCV care continuum in these 594 coinfected patients, 547 (92%) were referred for care, 517 (87%) were evaluated for treatment, 457 (77%) were prescribed treatment, 426 (72%) initiated treatment, and 381 (64%) had achieved HCV cure as of March 31, 2018. In multivariable analyses, >F2 liver fibrosis (odds ratio [OR], 3.12, 95% confidence interval [CI], 1.40-6.96) was positively associated with HCV treatment initiation. Conversely, being on ART with an HIV RNA >400 (OR, 0.22 (95% CI 0.13-0.35) and ≥50% missed HIV care visits (OR, 0.33; 95% CI, 0.17-0.62 compared to no missed visits) were independently negatively associated with HCV treatment initiation. Recent illicit drug use was not associated with treatment initiation.

Conclusion: Oral DAAs alone are not sufficient to achieve HCV micro-elimination. Improved engagement in HIV care is critical to this goal.

575 NETWORK-BASED RECRUITMENT FOR HEPATITIS C THERAPY AMONG PEOPLE WHO INJECT DRUGS

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Background: HCV treatment models based on an individual's drug use network have the potential to accelerate HCV elimination through increased rates of treatment uptake and reduced rates of reinfection among injection partners. Data to support the feasibility of this approach is limited.

Methods: Persons who reported recent (within < 1 year of enrollment) injection drug use were iteratively recruited from an urban infectious diseases clinic. We conducted detailed egocentric network inventories in which participants enumerated all network members including injection partners. These Egos (initial person recruited) received a brief intervention which included provision of information about HCV and its treatment and were instructed to recruit members of their injection network for HCV/HIV testing and, if positive, linkage to care. Egos received $10 for each listed member who presented for evaluation. Multivariable logistic regression analysis was conducted using generalized estimating equations (GEE) to assess for factors associated with the successful recruitment of ≥ one drug using network member.

Results: Between January and August 2018, 67 PWID with active injection drug use and HCV (with or without prior treatment) completed egocentric network surveys with the following characteristics: Median age, 54 years (interquartile range (IQR) 45-58); male, 72%; Black, 81%; homeless, 50%; unemployed, 87%; mean income, $735/month; prior incarceration (median time incarcerated, 4 years), 97%. In this group 26 (38%) had been previously HCV treated of which 12(18%) reported previous HCV cure. Egos reported injecting heroin (40%) and cocaine + heroin (37%), and 42% ≥ daily injection in the last 30 days. PWID reported a median of 7 (IQR 5-10) network members of which a median of 3 (IQR 1-5) were injection partners. Mean network density (proportion of ego's network members that are connected controlling for network size) was 0.6. Of the 67 Egos, 27 recruited ≥ 1 drug using network member (range 1-5). In multivariate analysis, Egos were more likely to successfully recruit if they had been treated for HCV (Odds ratio (OR) 4.1, 95% Confidence Interval (CI) 1.1-16.1), were injecting at least daily (OR 3.4, 95% CI 0.9-11.7) and reported a dense network (OR 9.0, 95% CI 1.0-74.2).

Conclusion: HCV treated PWID may be particularly effective at recruiting their drug using network members for HCV testing and linkage to care. Further work is needed to systematically assess network recruitment methods for HCV treatment

576 CAN'T BUY ME LOVE? OBSTACLES TO MICRO-ELIMINATION OF ACUTE HCV COINFECTION IN EUROPE

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Background: Several trials have shown high sustained viral response (SVR) rates with shortened direct acting antivirals (DAA) containing therapy in acute hepatitis C (AHC) coinfection. In addition, data from modelling and real life cohorts have shown a reduced AHC incidence with early DAA therapy. However, with no DAA currently being licensed for the treatment of AHC and with the high drug prices low DAA treatment uptake poses the biggest obstacle to HCV micro-elimination in a high-risk population. Here we evaluate rates of DAA treatment initiation of AHC coinfection in a large European cohort.

Methods: The PROBE-C study is an observational cohort on AHC in HIV coinfection. Between 2007 and 2017 465 AHC episodes were documented in HIV-infected patients with at least 12 months of follow-up from Austria, Denmark, France, Germany, Great Britain and Spain. Fisher's exact, chi-square and Mann-Whitney U test were used for statistical analysis.

Results: 457/465 (98%) patients were male, median age was 41 years (IQR 38-46). Main risk groups for HCV transmission were MSM (98.9%) and injecting drug use (IDU) (1.1%). 78.3% of patients were infected with HCV genotype (GT) 1, 2.6% with GT3 and 18.6% with GT4. Median baseline HCV-RNA was 230,000 IU/mL (135,000-474,432), median CD4+ T cell count 574 cells/µL (547-604). 92% of all patients received cART, 91% had baseline suppressed HIV-RNA (<200 copies/mL). Median maximum ALT was 445 U/l (402-522). In 324/465 (70%) HCV treatment was initiated. In 277/324 (85%) treatment was interferon (IFN)-containing, in 47/324 (15%) DAA-based. Median time from AHC diagnosis to treatment initiation was 11 weeks (10-13). 241 of 277 (87%) AHC patients receiving INF were treated within 24 weeks of AHC diagnosis, only 8 of 47 (17%) AHC patients receiving DAA were treated within 24 weeks of AHC diagnosis. Overall rates of treatment uptake within 24 weeks of diagnosis dropped from 75% in 2007 to 14% in 2017 (table 1).

Conclusion: IFN-containing therapy was no longer used for treatment of AHC coinfection in our pan-European cohort after 2015. Although available and recommended by guidelines during the acute phase, DAA-based therapy was mostly deferred to the early chronic phase of HCV infection. With more patients being viremic now than in the interferon-era drug labels need to be urgently amended to allow usage of DAA during the acute phase to limit HCV transmission in high-risk populations.

Table 1. Annual rates of treatment initiation within 6 months for new AHC diagnoses from 2007 to 2017

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Number of treatment initiations within 6 mths/total number of treatment initiations (%)	6/8 (75)	16/17 (94)	27/30 (90)	38/40 (95)	44/47 (94)	50/54 (93)	42/47 (89)	16*/ 23 (70)	4*/ 14 (29)	3**/ 22 (14)	3**/ 22 (14)

*Including 1 DAA-based treatment
**DAA-based treatments only

577 HCV REINFECTION RISK FOLLOWING DAA THERAPY IN PEOPLE LIVING WITH HIV IN AUSTRALIA

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Background: Given unrestricted access to direct-acting antiviral (DAA) therapies from March 2016 in Australia, HCV elimination should be achievable among people living with HIV (PLWH). Increasing HCV risk behavior and HCV reinfection, however, have the potential to compromise HCV elimination.

Methods: The Control and Elimination of HCV from HIV-infected individuals within Australia (CEASE-D) is an ongoing observational cohort study. HIV/HCV (antibody positive) co-infected individuals (≥18 years) were enrolled from 14 primary and tertiary clinics in Australia. Participants completed a questionnaire at enrolment (July 2014-March 2017) and first follow-up visit (June 2017-May 2018). We compared participants' clinical and behavioural features at enrolment and follow-up. Reinfection incidence was calculated with follow-up censored May 2018.

Results: Of 402 HIV/HCV antibody-positive participants (mean age 49 years, gay and bisexual male (GBM) 80%, cirrhosis 13%), 288 (72%) had detectable HCV RNA at enrolment. Injecting drug use (IDU) ever was reported by 79%. Current IDU (within six months) was reported by 36% at enrolment and 35% at follow up, predominantly amphetamines (30% for both). Among people reporting more recent IDU (within one month), 33% reported ≥weekly injecting and 11% reported needle/syringe sharing at enrolment, compared with 33% ≥weekly injecting and 13% needle/syringe sharing at follow up. Among GBM, 53% reported condom-less anal intercourse (CLAI) with one or more casual male partners (CMP) and 34% reported group sex at enrolment, compared to 40% CLAI with CMP and 25% group sex at follow-up (p=0.002 and p=0.020 respectively). HCV treatment uptake among those with detectable HCV RNA was 7% in 2014, 10% in 2015, 80% in 2016, and 35% in 2017, and was accompanied by a substantial decline in the proportion with detectable HCV RNA, from 79% in 2014 to 8% in 2018. Reinfection was reported in five participants through follow-up (incidence 0.81 per 100 person years, 95% CI 0.34-1.94), all of whom identified as GBM.

Conclusion: A substantial reduction in HCV viraemic prevalence was observed among PLWH in Australia following unrestricted DAA access. There was no evidence of increasing HCV risk behavior with injecting risk remaining stable and some reduction in sexual risk behaviour. HCV elimination should be achievable among PLWH in the near future.

578 CARE FACILITATION FOR HIV/HCV COINFECTED INCREASES MOVEMENT ON THE HCV CARE CASCADE

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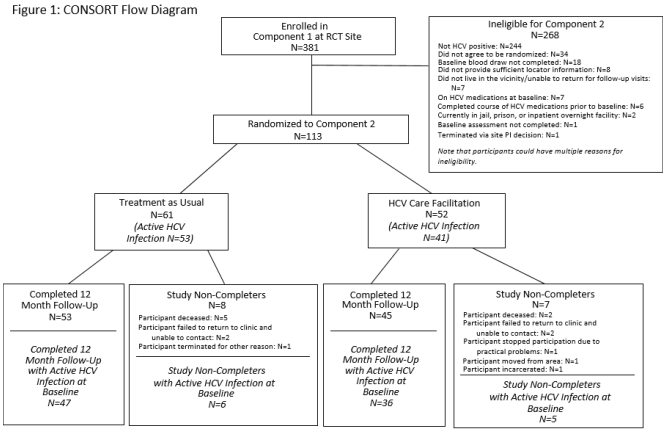
Background: HIV-HCV co-infection increases morbidity and mortality more than infection with either virus alone. CTN-0064 examined the efficacy of an HCV care-facilitation (CF) intervention on progression along the HCV care cascade.

Methods: HIV-infected substance-using participants previously enrolled in CTN-0049 from 8 sites (Miami, FL, New York, NY, Atlanta, GA, Baltimore, MD, Boston, MA, Philadelphia, PA, Chicago, IL, and Dallas, TX) were enrolled from Feb 2016 to Jan 2017. After informed consent, participants were HCV tested and, if positive, were randomized to either treatment as usual (TAU) or CF. Individuals randomized to CF received up to 12 in-person 30-minute sessions. CF included motivational encouragement to receive HCV viral load results and engage in ongoing HCV care and strengths-based case-management to provide support in HIV/HCV care engagement and adherence. The outcome was number of steps achieved along 8 steps of the HIV/HCV care cascade over 12 months: receiving HCV viral load results, HIV primary care engagement, initiating ART, having an

HCV (liver) evaluation, receiving an offer of HCV medications, initiating HCV medications, completing HCV treatment, and achieving sustained viral response at 12 weeks (SVR12). Power analyses called for a sample of 100-125 to have adequate power. The outcome was assessed using a Poisson regression.
Results: Of the 517 CTN-0049 participants alive as of Feb 2016, 485 (94%) were contacted and 381 (79%) enrolled for HCV testing. Of those enrolled, 268 were ineligible, with 244 HCV negative. There were 113 participants randomized (61 to TAU, 52 to CF). Participants were mostly male (58%), mean age 50 (SD=8), 14% Hispanic, 71% Black, 20% White, and 76% had insurance. CF participants achieved, on average, 2.8 steps along the HCV care cascade while TAU participants achieved approximately 2 steps (p=.018). Participants in CF had higher rates of receiving HCV viral load (94% vs 54%), liver evaluation (42% vs 28%), an HCV treatment offer (21% vs 11%) and SVR12 (12% vs 8%). Men had a larger response to the CF intervention (CF=3.3 steps, TAU=1.9) than women (CF=2.1, TAU=2.3; p=.015). Women in TAU received HCV viral load results significantly more than did men in TAU (74% vs 42%, p=.016).
Conclusion: A strengths-based care facilitation intervention significantly increased progress along the HCV care cascade, with a greater effect on men than women. Rates of sustained viral response were low within the 12 months of follow-up. ClinicalTrials.gov # NCT02641158

Figure 1: CONSORT Flow Diagram



579 HEPATITIS C TESTING OF TRAUMA SURGERY PATIENTS: INCIDENCE, PREVALENCE, & CARE CASCADE

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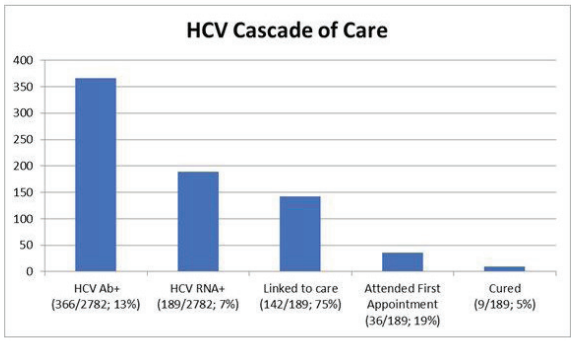
Background: Trauma surgery patients often miss opportunities to engage in routine healthcare, including Hepatitis C (HCV) screening. We developed a HCV screening and linkage program to assess the incidence, prevalence, linkage to care rates, and HCV cure rates among this vulnerable population.
Methods: From August 2016 to March 2018, HCV screening was performed on patients evaluated at an urban Level I trauma center. Data were collected including HCV antibody status, HCV RNA status, sex, race, age, year of birth, and history of intravenous drug use (IVDU). Midway through the study (May 2017), a reflex HCV screening test was introduced, in which a HCV antibody positive sample would automatically undergo the HCV RNA test without an additional blood draw and/or return visit. Patients with a positive test result were linked to care or re-engaged in care by the navigator. Follow-up was performed to assess the cascade of care among patients who tested HCV RNA positive.
Results: There were 2,953 patients eligible for HCV screening and 2,782 were screened (94.2%). There were 366 patients with HCV antibodies (13.2%) and 189 (6.8%) with detectable HCV RNA and 36 (1.3%) patients were newly diagnosed. Of the patients with a positive HCV antibody, 292 (79.8%) underwent a confirmatory HCV RNA test. Before the reflex test, there were 0.21 positive HCV RNA tests per day compared to 0.41 positive HCV RNA tests per day after the reflex test was introduced. Men comprised 148 (78.3%) of the chronic HCV patients. The average age was 47 (22-87). There were 70 (37%) Black, 65 (34.3%) White, and 42 (22.2%) Hispanic patients. There were 85 (44.9%) patients born between 1945-1965 and117 (61.9%) patients with a history of IVDU, but 28 (14.8%) were neither a baby boomer nor a person who injected drugs. Of the 189 patients with detectable viral loads, 142 (75.1%) were linked to care either by education or attending their first HCV medical appointment. Of these patients, 9 (4.8%) were cured of HCV.
Conclusion: The high rate of patients with chronic HCV (6.8%) in the trauma surgery service suggests that trauma surgery patients are at risk for HCV and should be routinely screened. Reflex HCV antibody to RNA testing increased the identification of patients living with chronic HCV. This program linked 75% of patients and cured 5% of HCV. The trauma surgery setting has significant potential to screen, diagnose, link to care and cure a vulnerable population that may not engage in routine medical care.



580 A RANDOMIZED TRIAL OF HIV/HCV NURSE CASE MANAGEMENT FOR LINKAGE TO HCV CARE

Laura Starbird[1], Hae-Ra Han[1], Mark Sulkowski[2], Chakra Budhathoki[1], Nancy Reynolds[1], Jason Farley[1]
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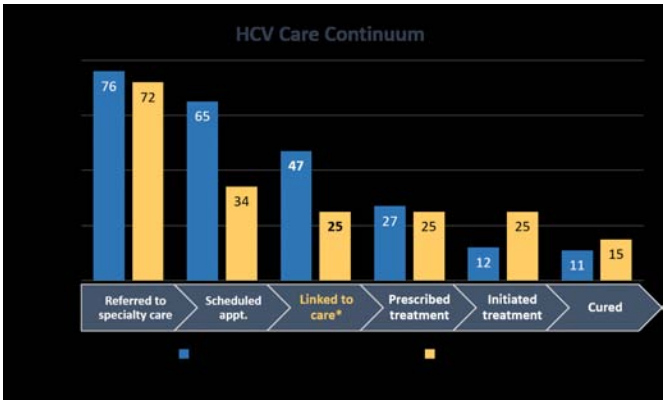
Background: The opportunity to eliminate hepatitis C virus (HCV) is at hand, but challenges across the care continuum persist. These challenges are particularly poignant for persons co-infected with HIV, who are a high-priority to cure but historically not well engaged in HCV care. Case management interventions have shown success in linking patients to HIV care. We hypothesized that a strengths-based nurse case management intervention (Care2Cure) adapted from evidence-based HIV studies could improve HCV care continuum outcomes for persons with HIV/HCV co-infection.
Methods: We conducted a prospective, single-blinded, randomized controlled trial to test the effect of Care2Cure in 68 adults (intervention n=35 and control n=33) with HIV/HCV co-infection. The Care2Cure intervention consisted of nurse-initiated referral to HCV care, scheduling assistance in the HCV practice, and HCV education. The comparison group (usual care) received an HCV fact sheet only. Primary outcomes included 1) linkage to HCV care (i.e., attendance at an HCV clinic appointment within 60 days of enrollment) and 2) time to DAA initiation (number of days from enrollment to first dose of DAAs). Study participants were followed for 6 months.
Results: Our sample was predominantly Black/African American (81%) and low income (85% Medicaid). Nearly half (46%) reported illicit drug use and 43% had an undetectable HIV viral load. There were no demographic differences between groups at baseline. At day 60, a greater proportion of participants in the Care2Cure arm linked to HCV care (47%) compared to the comparison arm (25%) (p=0.036 by z test for difference in proportions; 95% confidence bound=3.2-40.9%). Among participants who initiated HCV treatment (n=12), the median time to DAA initiation was 100 days (interquartile range 69.5-118.5 days), with a median of 72 days for participants in the Care2Cure arm and 98 days for those in the comparison arm. This did not result in a significant difference in time to treatment initiation between the two arms at 6 months by logrank test (p=0.192).
Conclusion: Our results support provision of nurse case management as a successful strategy to link persons co-infected with HIV to HCV care. Nonetheless, linking to care alone is not sufficient to cure HCV in those who remain untreated. Interventions that address the intersection of HCV and HIV that continue from linking to care through treatment initiation and cure are needed to achieve HCV elimination in this high-priority population.



581 DEMOGRAPHIC TRENDS IN HCV DIAGNOSIS AND LINKAGE TO HCV CARE AMONG JAIL DETAINEES

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Background: The changing epidemiology of hepatitis C infection (HCV) has important implications for screening and prevention. However, HCV surveillance is limited as chronic hepatitis C is not a reportable illness and acute hepatitis C is under-reported to public health departments. The criminal justice system, which houses a large number of individuals at risk for HCV, is a key venue to identify hepatitis C infection, evaluate HCV epidemiology and initiate linkage to HCV treatment.
Methods: Opt-out HCV antibody (Ab) testing was offered at the time of routine blood draw for individuals incarcerated at the Dallas County Jail beginning in June 2015 and occurring in three separate testing cycles. HCV RNA testing was added in 2017. Demographics and testing results were extracted from electronic medical records; HCV risk factor and health insurance status were self-reported. Patients with a positive HCV RNA were initiated in a linkage-to-care protocol beginning in 2017 including disease education, prevention counseling, and information about linkage to HCV care including a hotline number routed to a navigation specialist. Post-release, the navigation specialist followed up by phone to facilitate linkage to community HCV care. Data analyses were completed using SAS v. 9.4.
Results: The prevalence of HCV Ab positivity remained stable over the three testing cycles 16.4% (500/3042), 16.5% (708/4260) and 15.9% (421/2635). The number of younger individuals (born after 1965) with HCV Ab + increased over time, from 48% to 57% to 63%, as did the proportion of women with HCV Ab+, from 20% to 24% to 25%. Injection drug use was more commonly cited as a risk factor from year 2 to 3 (39% to 56%). Education was provided to 85% of individuals with HCV RNA+ in both years 2 and 3. In years 2/3, 198 HCV RNA+ individuals were released to the community, 149 were called at least once after release, 21 called the hotline after release and 17/21 had scheduled or pending appointments in liver clinic.
Conclusion: A larger proportion of women, younger individuals and injection drug users tested positive for HCV infection over consecutive years of an opt-out HCV testing program at the Dallas County Jail. Rates of HCV education were high during incarceration. Successful linkage to community HCV care was characterized by a combination of: (a) nurse navigator initiatives of education and outreach both during and after incarceration and (b) patient activation through post-release, patient-initiated engagement with healthcare.

582 HEPATITIS C CASCADE OF CARE AMONG PEOPLE WHO INJECT DRUGS IN BRITISH COLUMBIA IN 2017

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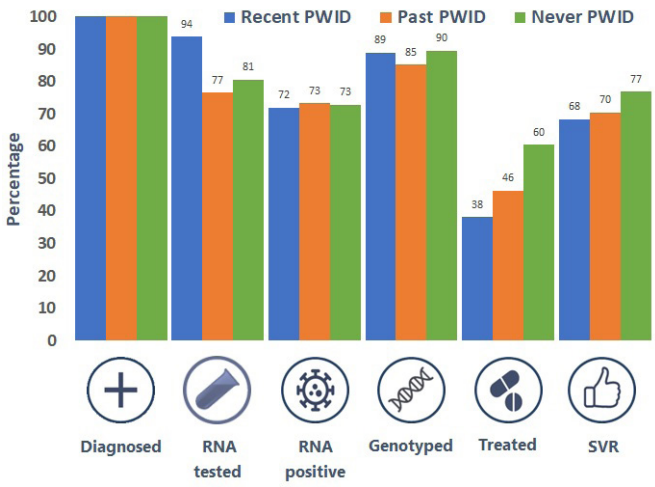
Background: New short course well-tolerated direct acting antivirals (DAAs) are expected to increase treatment rates among people living with hepatitis C virus (HCV), particularly among People Who Inject Drugs (PWID). We constructed the HCV cascade of care among people diagnosed with hepatitis C virus infection living in British Columbia (BC), Canada in 2017, stratified by history of injecting drug use to compare progress in care and treatment.
Methods: The BC Testers Cohort (BC-HTC) was used for this analysis. BC-HTC includes all individuals tested for HCV in BC since 1990, linked to date on all prescription drugs, medical visits, hospitalizations and mortality data. We defined six cascade of care stages: 1) anti-HCV positive (diagnosed); 2) RNA tested; 3) RNA positive; 4) genotyped; 5) initiated treatment; and 6) achieved post-treatment sustained virologic response (SVR). People diagnosed with HCV infection were stratified by history of injecting drug use (recent PWID, people who injected drugs <3 years; past PWID, >3 years ago; or never PWID) and progression through care cascades compared among these groups.
Results: In 2017, there were 52,987 individuals diagnosed with HCV infection (anti-HCV positive) in BC. Among those diagnosed, 22% (11806/52987) were recent PWID, 17% (9118/52987) past PWID and 61% (32063/52987) never PWID. Confirmation of infection by RNA or genotype testing was highest among recent PWID, and lowest among never PWID (Figure 1). Of people with genotype testing, HCV treatment initiation was lowest among recent PWID, with 38.1% (2698/7081), compared to 46.3% (2016/4350) among past PWID, and 60.4% (10162/16812) among never PWID. Among both past and never PWID, a higher proportion of individuals were born before 1965, whereas among recent PWID a higher proportion of individuals were born after 1965.
Conclusion: Through integration of provincial testing, treatment, mortality, medical visits and hospitalization datasets, it is possible to assess population-level HCV prevention and care cascades among PWID, which is essential to monitoring progress towards HCV elimination goals. Overall, progression through the HCV cascade of care in BC has improved since DAAs were available, but it remains lower among recent PWID. Treatment uptake may improve with the recent removal of fibrosis restrictions on treatment eligibility; however, factors associated with treatment uptake among PWID should be further investigated to help identify strategies to enhance HCV treatment uptake among this group.



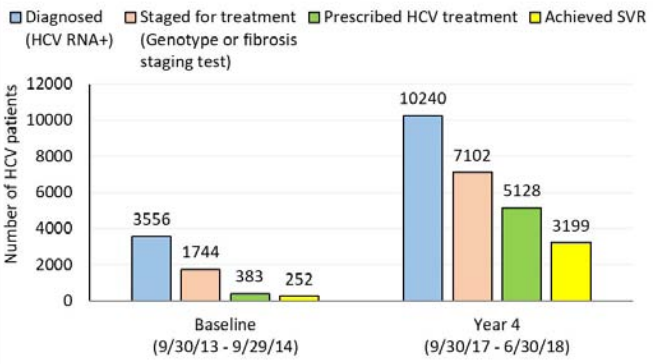
583 A COMMUNITY INTERVENTION INCREASED HCV SCREENING AND TREATMENT IN KING COUNTY, WA

John D. Scott[1], Meaghan Munn[2], Atar Baer[2], Sara N. Glick[1], Elizabeth Barash[2], Hilary Armstrong[2], Kris Kowdley[3], Matthew Messerschmidt[4], Pallavi Patel[5], Michael Ninburg[6], Matthew R. Golden[1], Jeff Duchin[2]
[1]University of Washington, Seattle, WA, USA, [2]Public Health—Seattle & King County, Seattle, WA, USA, [3]Swedish Medical Center, Seattle, WA, USA, [4]HealthPoint, Auburn, WA, USA, [5]Kaiser Permanente Washington, Seattle, WA, USA, [6]Hepatitis Education Project, Seattle, WA, USA

Background: Hepatitis C virus (HCV) infection is common in HIV+ patients and in the general US population, leading to significant morbidity and mortality, and the incidence of HCV-related chronic liver disease and cancer continues to increase. However, simplified screening recommendations and highly effective direct acting antivirals for HCV present an opportunity to reverse this trend. We report the results of a community-based program to increase the testing, linkage to care, treatment and cure of persons with HCV infection.

Methods: Public Health - Seattle & King County collaborated with three community health centers, three large multi-clinic health care systems (private, public and capitated), and a HCV patient education and advocacy group. Patients seen at least once in the last year at a partner clinical site were included. In order to increase screening of patients born between 1945-65, electronic medical record prompts and reports were created, as well as lower cost interventions such as birthday card reminders and posters. Case management linked patients to care. Primary care providers received education and training through class-room didactics, an online customized curriculum, specialty clinic shadowing and through a telemedicine program, Project ECHO.
Results: At baseline, 18% of all birth cohort patients in partner primary care clinics had documentation of HCV testing; this proportion increased to 54% by 2018. Of the 75479 patients screened at 87 clinics, 2147 (3%) were newly HCV antibody positive. Among 10240 patients previously or prospectively screened and with active HCV infection (RNA+), the majority were male (65%) and white (71%); 602 (6%) were HIV infected. The number of patients staged for liver disease (either by genotype or a fibrosis test) increased by 307% and those treated increased by 1239% (Fig 1). Of those treated, 6% were still undergoing treatment, 62% achieved a sustained viral response, 4% did not and 28% had not returned for 12 week lab testing.
Conclusion: Using a combination of EMR-based healthcare system interventions, active linkage-to-care, and educational and training strategies, we were able to markedly improve HCV screening and treatment, resulting in a tripling in the number of patients screened and >tenfold increase of those treated. Treatment failure was rare, although a significant proportion of patients did not receive definitive testing for cure. The interventions are sustainable, scalable and foundational to the broader goal of HCV elimination.

Figure 1. Comparison of HCV Continuum of Care at Baseline and Year 4
Data for Year 4 shows the cumulative outcomes since beginning of baseline



584 LOW PERFORMANCE OF THE ORAQUICK HCV RAPID ANTIBODY TEST IN HIV/HCV-INFECTED PEOPLE

Serena Vita, Irene Pozzetto, **Raffaella Marocco**, Ilenia Mastrini, Laura Fondaco, Blerta Kertusha, Valdo Rossi, Pasquale Dolce, Tiziana Tieghi, Claudio M. Mastroianni, Miriam Lichtner
Sapienza University of Rome, Rome, Italy

Background: There is a global need to expand hepatitis C virus (HCV) diagnostic testing and saliva sampling may provide an easier access to HCV screening test. An estimated 2.3 million people living with HIV are coinfected with HCV globally. Despite this high numbers, the performance of HCV rapid test has not been extensively studied in HIV population.
Methods: We enrolled consecutive patients (pts) attending the Outpatient Infectious Disease Clinic of S. M. Goretti in Latina from Oct 2017 to Jan 2018 and 30 healthy donors (HD) with a known plasma test for HCV and HIV. We performed the OraQuick HCV Rapid Antibody Test (OraSure Techn, Inc.). We collected anagraphical, clinical and laboratory data. The OraQuick HCV Rapid Antibody Test was used according to kit instruction. Statistical analysis was performed using Kruskall-Wallis, Mann-Whitney and 2 test. The 95% confidence interval (CI) was estimated for sensitivity, specificity, and positive and negative predictive values.
Results: A total of 227 persons were recruited into the study: 83 pts with known HCV infection (30F, 43M); 84 with known HIV/HCV coinfection (16F, 68M); 30 HD (12F, 18M); 30 HIV positive subjects known HCV uninfected (18F, 12M) pts. In the group of HIV-/HCV+ and HIV+/HCV+ no statistically significant differences in HCV-RNA level, fibrosis and year living with HCV were observed. The results of OraQuick in the 4 groups are showed in table 1. In all the study population a sensivity of 53% (95% CI, 45%–60%) and specificity of 100% was found. The positive predictive value (PPV) was 1 (95% CI 0.96-1), while the negative predictive value (NPV) was 0.43 (95% CI 0.35-0.52). Analyzing the 4 subgroups of pts interestingly in the HCV+/HIV+ group the OraQuick test showed a sensitivity of 6% (95% CI, 2%–13%) and specificity of 100%. In HIV+/HCV+ pts the PPV was 1 (95% CI, 0.48-1), while the NPV was 0.28 (95% CI 0.19-0.37). Conversely in the HCV+ group, the OraQuick test showed a sensitivity and specificity of 100%. The PPV was 1 (95% CI 0.96-1) and NPV was 1 (95% CI 0.88-1). No associations were found between false positive results and CD4 count, HCV-RNA, liver fibrosis, DAA use, sex.
Conclusion: In the context of HCV eradication goal the development of easy and quick tests may offer relevant opportunities to facilitate HCV screening. However, in our study the OralQuick test performance is strongly impaired in the HIV-infected people showing a very low sensitivity thus it should be discouraged in known HIV pts where serology can not be replaced.

	Known HCV+/HIV- (n=83)	Known HCV+/HIV+ (n=84)	Known HCV-/HIV- (n=30)	Known HCV-/HIV+ (n=30)
OraQuick POS	83	5	0	0
OraQuick NEG	0	79	30	30

Table 1. Results of the OraQuick test in the 4 subgroup.

585 UTILITY OF HCV CORE ANTIGEN FOR THE DIAGNOSIS OF ACUTE HCV IN HIGH-RISK INDIVIDUALS

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[1]Mortimer Market Centre, London, UK, [2]University College London, London, UK, [3]University College London Hospitals NHS Trust, London, UK, [4]Royal Free Hospital, London, UK

Background: To achieve micro-elimination of HCV in high-risk groups, early detection of acute HCV is important in order to link individuals into care/ treatment and harm-reduction programmes. Current guidelines suggest regular anti-HCV screening with additional HCV-RNA for high-risk individuals with unexplained elevated serum aminotransferases. HCV core antigen (HCV-cAg) offers an alternative to HCV-RNA testing to confirm HCV viraemia. We describe the use of HCV-cAg testing for early diagnosis of acute HCV in high-risk individuals attending for sexual health screening (SHS) at a large central London Sexual Health/HIV clinic.
Methods: Architect HCV-cAg testing (Abbott Diagnostics) was introduced in 5/2015 replacing anti-HCV to screen all high-risk patients attending for a SHS. High-risk HIV+ patients were offered 3-6 monthly screening in addition to routine 6-monthly HIV-monitoring blood tests (inclusive of liver function tests). All HCV-cAg positive samples were tested for HCV-RNA. We reviewed all acute HCV diagnoses screened with HCV-cAg from 5/2015–5/2018. Data were collected on patient demographics, HIV status, HCV reinfection, HCV genotype, anti-HCV and seroconversion, transmission risk factors and serum ALT.
Results: 76 acute HCV infections were diagnosed; all men, 98.7% MSM, 80% Caucasian, median age 44.5 years, majority (64/76, 84%) HIV co-infected. 9 (12%) were HCV re-infections; 8/9 HIV co-infected. 73/76 (96%) were diagnosed with a positive HCV-cAg test; 3/76 (4%) had negative HCV-cAg but were HCV RNA+ (all 3 had raised ALT >300 at diagnosis). Median ALT at HCV diagnosis was 138 IU/l (IQR 67-360). 11 (15%) had ALT <50 IU/l at time of first HCV-cAg+. All were HCV RNA+. Median time to peak ALT was 36 days (IQR 6.5-66.5) from first HCV-cAg+. 41/67 (61%) had anti-HCV testing at HCV diagnosis; 18 (44%) were anti-HCV+; 15/23 seroconverted a median 37 days (IQR 21-64) later. Table 1 summarises risk-factors and HCV characteristics. If acute HCV diagnosis was dependent on anti-HCV seroconversion and HCV-RNA testing with raised ALT, 34 (45%) patients may have been missed at the visit diagnosis was made.

Conclusion: Screening for acute HCV infection with HCV-cAg test provides an effective tool for early detection of HCV in high-risk populations. HCV-cAg tests are cheaper with a quicker turnaround time than HCV-RNA tests. The addition of ALT testing to a screening strategy based on HCV-cAg maybe a cost-effective method to reliably detect acute HCV cases.

Table 1. Acute HCV infection diagnoses from May 2015 – May 2018.

	May 2015 – April 2016 (%)	May 2016 – April 2017 (%)	May 2017 – May 2018 (%)	Total (%)
Total	**28**	**30**	**18**	**76**
Route of transmission				
MSM	9 (32)	19 (63)	10 (56)	38 (50)
MSM + Chems	15 (54)	7 (23)	0	22 (29)
MSM + Chems + IDU	4 (14)	4 (13)	7 (39)	15 (19)
Heterosexual + IDU	0	0	1 (6)	1 (1)
Alcohol excess	4 (15)	4 (14)	1 (6)	9 (13)
HCV reinfection	2 (7)	2 (7)	5 (28)	9 (12)
HCV genotype				
1a	22 (78.6)	23 (76.7)	15 (83.3)	60 (79)
1b	1 (3.6)	1 (3.3)	2 (11.1)	4 (5)
3	2 (7.1)	4 (13.3)	0	6 (8)
4	3 (10.7)	2 (6.7)	1 (5.6)	6 (8)
Median ALT IU/l at HCV diagnosis (IQR)	159.5 (67-370)	170 (78-285)	82.5 (58-230)	138 (67-360)
ALT<50 IU/l at HCV diagnosis	6 (21.4)	2 (6.7)	3 (16.7)	11 (15)
Median peak ALT IU/l (IQR)	498 (263-836)	549 (377-900)	393 (118-914)	495 (252-889)
Median time from HCV diagnosis to ALT peak, days(IQR)	29 (3.5-74.5)	41 (6-109)	36 (17-54)	36 (6.5-66.5)

MSM=Men who have sex with men, IDU=intravenous drug use

586 DIVERSE OBSTETRICIAN HCV-SCREENING PRACTICES IN A LARGE REGIONAL HEALTH CARE SYSTEM

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Background: Given the onslaught of the opioid epidemic, the incidence of HIV and Hepatitis C (HCV) infection is increasing in reproductive age women. Unlike recommendations for universal HIV screening, HCV testing in pregnancy has been risk-based. Recent AASLD/IDSA guidelines recommend universal HCV screening. We hypothesized that prior to revised screening recommendations there was diversity in HCV testing practices amongst obstetrical practices.

Methods: We extracted HCV testing (HCV antibody/RNA) and reactivity data from the EHR for the first outpatient prenatal visits at MedStar Health, a large regional healthcare system, from January 2017 through April 2018. We used Chi-square, Fisher's Exact and Student's t-tests, as appropriate for the bivariate analyses, and multivariate logistic regression to determine predictors of HCV screening and antibody positivity. Variables included age, race, ethnicity, HIV screening and infected, HBV infected, insurance, birth outcome, delivery method, and location. SAS statistical software was used for the analyses.

Results: There were 10,415 women who met study eligibility; 3,081 (29.6%) were HCV tested, and 44 (1.4%) were HCV antibody positive. Pregnant women were more likely to be screened for HCV if they were older (ORadj 1.02, CI95 [1.01-1.02]), African American or other race as compared to Caucasian (2.24 [2.02-2.49]; 1.74 [1.53-1.98]), HIV tested (4.25 [3.65-4.94]), HIV infected (8.37 [4.77-14.70]), and had private insurance (1.51 [1.37-1.66]). Pregnant women were more likely to be HCV antibody positive if they were Caucasian as compared to African American (ORadj 11.44 [CI95 3.99-32.82]), HBV infected (15.27 [2.32-100.46]) and living in Maryland vs. DC (2.93 [1.17-7.32]). There was no difference in the latter analysis for age, ethnicity, HIV status, birth outcome or insurance.

Conclusion: Universal HCV testing has not yet been fully deployed in pregnant women at this large healthcare system, which includes urban, suburban and rural practices. However, the 30% screening rate is higher than other published reports. There appears to be racial discordance in screening practices, with more African Americans tested; however, more Caucasians were HCV antibody positive. This could be due to prior universal testing adoption in the urban vs. the suburban/rural environment and requires further exploration. Providers and practices will need to adapt to changing universal screening guidelines, especially given the demographics and burgeoning of the opioid epidemic.

587 TRANSFORMING PRIMARY CARE PRACTICES FOR HEPATITIS C TREATMENT CENTERS

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Background: It is estimated that 80,000 persons in Maryland are chronically infected with hepatitis C virus (HCV). The clinical infrastructure and specialist workforce are insufficient to provide HCV treatment access to all HCV infected persons. In 2014, we developed Sharing the Cure, a provider training program and practice transformation model, with support from the CDC-funded Maryland Department of Health's Community-based Programs to Test and Cure Hepatitis C to improve treatment access.

Methods: Sharing the Cure is composed of a one-day workshop, mini-preceptorship, and teleconference for primary care clinicians. The program runs from January-September each year. A 20 question HCV knowledge exam developed by a faculty educator and reviewed by a cohort of national faculty experts is administered at the end of each training period to certify the clinicians as HCV providers. Partner site medical staff are trained in HCV education and treatment monitoring through a lunch lecture series. Treatment outcomes have been described through July 2018.

Results: Thirty-five primary care clinicians from eight partner sites completed the program in cohorts 1-3. Nineteen clinicians (cohort 4) are currently completing training. Thirty-two clinicians (91%) passed the exam (score ≥ 70%). Of the 3 clinicians that did not achieve a passing score, 2 passed on second attempt which included a different subset of 20 questions and 1 clinician did not pass the second exam and was denied certification. The providers have started HCV treatment in 702 individuals with treatment ongoing in 71 patients (10%), complete in 598 (85%) patients, and discontinued in 33 (5%) patients. Notably, 592 patients are currently at least 12 weeks post treatment. Of the 462 patients with virologic data reported, 449 (97%) have documented sustained virologic response/cure. Despite providers evaluating an additional 665 patients with chronic HCV infection, treatment was not started. Barriers to treatment initiation in primary care were failure to meet prior authorization criteria in 370 (56%) patients (criteria for Maryland Medicaid includes liver fibrosis of ≥ F2), lack of patient follow-up in 81 (12%) patients, and specialist referral in 73 (11%) patients.

Conclusion: Primary care practices can effectively be transformed into HCV treatment centers to expand HCV treatment access. However, prior authorization criteria by insurance providers remains a major barrier to HCV treatment access.

588 DECENTRALIZATION AND TASK-SHIFTING FOR HEPATITIS C: SYSTEMATIC REVIEW & META-ANALYSIS

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Background: Worldwide, 71 million persons are HCV infected but only a small proportion have been diagnosed and treated. Increasing access to care in low and middle income countries (LMICs) will require adoption of simplified service delivery models such as decentralization and task shifting to non-specialists. The evidence base for their effectiveness in HCV care remains limited. We conducted a systematic review and meta-analysis to establish the effectiveness of decentralization and task-shifting on outcomes across the continuum of HCV care in different populations.

Methods: Bibliographic databases and conference abstracts were searched for English language clinical trials or observational studies published between 01/2008 to 02/2018 that evaluated these interventions. Outcomes were testing and HCV viral load uptake, linkage to care, treatment uptake, and cure (SVR12)) in PWID, prisoners, PLHIV, and general population. Decentralisation was defined as either full (FD) (testing and treatment at same primary care or harm reduction site), or partial (PD) (testing at decentralized site and referral for treatment) and task-shifting as HCV treatment by non-specialists (primary care

physicians or nurses). Data were pooled using random effects meta-analysis and meta-regression was used to explore heterogeneity.

Results: 97 studies from 18 countries (11 were LMIC) were included. 82 were single arm studies and 15 had a comparator arm (RCTs, non-RCT or cohort studies). 40 (41.2%) were in PWID, 13 (13.4%) in prisoners, 42 (43.3%) in general population, and 2 in PLHIV. 34 and 35 studies respectively used DAA and IFN based regimens. Among PWID, FD (n=29) compared to PD (n=11) had higher testing uptake 88% (95%CI 78-98) vs. 47% (95%CI 4-99), and linkage to care 80% (95%CI 62-98) vs. 53% (95%CI 30-77), but similar SVR rates: FD 93% (95%CI 89-97) vs PD 88% (95% CI 84–93). Results were similar for FD (n=19) and PD (n=23) in general population studies. Task-shifting to non-specialists achieved similar SVR12 to specialist care for both PWID 92% (95%CI 88-97) vs. 92% (95%CI 85-99) and in general population 92% (95%CI 87–96) vs. 91% (95%CI 87–95).

Conclusion: Both decentralization and task-shifting to non-specialists achieved high levels of HCV cure across a range of populations and settings. These findings support adoption of these service delivery models to promote testing and treatment scale-up in national programmes.

589 THE COST-EFFECTIVENESS OF HCV SCREENING OF PREGNANT WOMEN IN THE UNITED STATES

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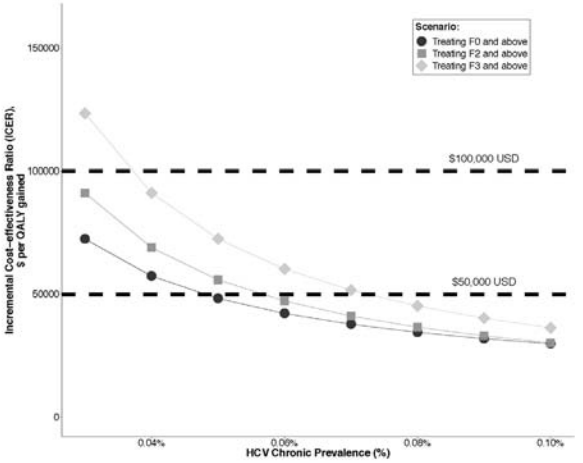
Background: Hepatitis C Virus (HCV) chronic prevalence among pregnant women in the United States (U.S.) is estimated at 0.7%, but can reach 8% in rural Tennessee, and doubled nationally from 2009-2014. Yet, screening for pregnant women is not currently recommended by the U.S. Centers for Disease Control, and many pregnant women remain undiagnosed. Recent AASLD/IDSA guidelines and the state of Kentucky recommend screening pregnant women but note low quality and strength of evidence supporting this recommendation. We assess the cost-effectiveness of HCV screening for pregnant women in the U.S.

Methods: A deterministic HCV natural history Markov model among pregnant women was used to evaluate the cost-effectiveness of HCV screening of pregnant women compared to no screening from a health care payer perspective. We assumed 0.73% (95%CI 0.71-0.75) HCV chronic prevalence among pregnant women based on national data. Given differing state-based Medicaid reimbursement policies, we explored the cost-effectiveness of antenatal screening in settings with differing treatment eligibility: METAVIR stage F3 or beyond (F3+), F2 or beyond (F2+), or F0 and beyond (F0+). We assessed cost (in US $) and health outcomes (in quality-adjusted life years, QALYs) over a lifetime horizon. We sampled 1000 parameter sets and calculated mean incremental cost-effectiveness ratios (ICERs), assessing cost-effectiveness under a willingness to pay threshold of $50,000/QALY gained. Using state-specific pregnancy rates and fibrosis restrictions, we estimate the impact of screening.

Results: The mean ICERs for antenatal screening were $6303, $8594 and $13677 per QALY gained in the F3+, F2+, and F0+, treatment eligibility scenarios, respectively compared to no screening. Screening was cost-effective under a $50,000 willingness-to-pay threshold in all simulations. Screening remained cost-effective for prevalences at or above 0.05-0.08% depending on treatment eligibility (Fig. 1). In a state with 8% prevalence and F2+ restrictions like Tennessee, the ICER was $5,288. Screening the estimated 5.04 million pregnant women in 2018 could result in detection and treatment of 33,000 women in the United States based on current fibrosis restrictions.

Conclusion: Screening pregnant women for HCV in the U.S. is likely cost effective assuming a national prevalence of 0.7%, and should be recommended. In geographical areas with higher prevalence, such as Appalachia, cost-effectiveness is even greater.

Figure 1: Impact of HCV chronic prevalence among pregnant women (x axis) on the incremental cost-effectiveness ratio (ICER, y axis) of screening pregnant woman compared to no screening. Results shown for the scenarios examining settings with treatment for F0 and above (black circles and line), F2 and above (dark gray squares and line), and F3 and above (light gray diamonds and line).



590 COST-EFFECTIVENESS OF HCV TREATMENT AMONG HIV-POSITIVE INDIVIDUALS IN MYANMAR

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Background: Over half of those co-infected with hepatitis C virus (HCV) and HIV live in low- and middle-income countries, and new HCV direct-acting antiviral therapies (DAAs) cure >90% of individuals. However, the cost-effectiveness of DAAs among HIV/HCV coinfected individuals in low-income settings is unclear. In 2016, Médecins sans Frontières (MSF) began HCV treatment within a HIV cohort in Myanmar. We evaluated the cost-effectiveness of the HCV treatment program among HIV/HCV coinfected patients in Myanmar.

Methods: We assessed the real-world cost and cost-effectiveness of HCV DAA treatment among HIV-positive individuals compared to no treatment from a program provider's perspective. Patient characteristics, costs and treatment outcomes were collected from an ongoing, prospective cohort study in Dawei, Myanmar. We performed a patient-level micro-costing analysis of DAA treatment delivery. A Markov model of HCV disease progression among HIV-infected individuals was developed and used to estimate lifetime costs (in 2017 $USD) and health outcomes (in disability-adjusted life-years (DALYs)), discounted at 3% per year. Disease state transitions and disability weights were informed from published literature. We calculate the incremental cost-effectiveness ratio (ICER, difference in costs divided by difference in DALYs), compared to a willingness to pay threshold of the per capita GDP in Myanmar ($1275). We additionally evaluate the potential cost-effectiveness utilizing a simplified treatment protocol with about 25% fewer visits and task-shifting from doctors to nurses.

Results: From November 2016 to October 2017, 122 patients initiated treatment (66 METAVIR stage F0-F3, 56 cirrhosis or later), 96% (n=117) achieved SVR. Under the current treatment protocol, the average cost of treatment per patient was $677 and $1302 for patients in F0-F3 and cirrhosis or later, respectively, mainly due to drug costs ($493 and $939 for 12 and 24 weeks, respectively for sofosbuvir/daclatasavir). The current treatment protocol costs an incremental $938.79 per patient treated, resulting in 1.33 DALYs averted per patient, resulting in an ICER of $707/DALY averted compared to no treatment. A simplified treatment protocol could result in an ICER of $424/DALY averted compared to no treatment.

Conclusion: HCV DAA treatment for HIV/HCV coinfected individuals is likely cost-effective in Myanmar. A simplified treatment protocol and/or lower drug costs could enhance cost-effectiveness.

591 TEMPORAL PATTERNS IN HCV PHYLOGENETIC CLUSTERING AMONG PWID IN BALTIMORE, MD

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Background: HCV infection occurs in 30-90% of people who inject drugs (PWID). Phylogenetic analysis can be used to inform strategies to interdict transmission. This study examines patterns in HCV phylogenetic clustering overtime among PWID in Baltimore city.
Methods: Community-based PWID were prospectively recruited for The AIDS Linked to the IntraVenous Experience (ALIVE) cohort in Baltimore, MD. Viral RNA underwent Polymerase Chain Reaction with primers targeting the 5′ end of the envelope-1 region and sequenced using Sanger Sequencing methods. There were 820 HCV RNA+ participants from 1988-1989 and an additional 512 unique HCV RNA+ participants from 2005-2016. Networks were rendered at a 4% genetic distance threshold using HIV-TRACE and participants were geographically mapped using Microreact. Prevalence ratios (PR) and 95% CIs of being in a cluster (≥2 participants) were calculated using Poisson regression with robust variance.
Results: There were 15 clusters found among the participants in 1988-89 and 22 clusters identified in 2005-16. In both time periods, two large genotype 1a clusters were observed with 586/716 (82%) in 1988-89 and 113/302 (37%) in 2005-2016. When combining data from 1988-89 with 2005-16, the two large genotype 1a clusters were maintained (Figure). Participants from 2005-16 (59% [303/512]) were less likely to be in a cluster compared to the participants from 1988-89 (87% [716/820]) independent of HIV status, age, sex, race, zip code (adjusted PR, 0.71 [95% CI, 0.64-0.79]). The percentage of individuals in a cluster was consistently lower across all two-year intervals in the 2005-16 period in comparison to the 1988-89 two-year interval. Similar findings were observed when stratifying the analysis by genotype 1a and 1b. Among the clusters, there was a greater number of linkages among the 1988-89 individuals (median, 28 [IQR, 9-78]) compared to 2005-16 individuals (median, 5 [IQR, 1-16.5]; (p<0.001)).
Conclusion: We observed greater cluster diversity in the participants recruited in 2005-16 indicative of a less connected network of individuals sharing transmission risk, though major viral strains did persist over time in this cohort.

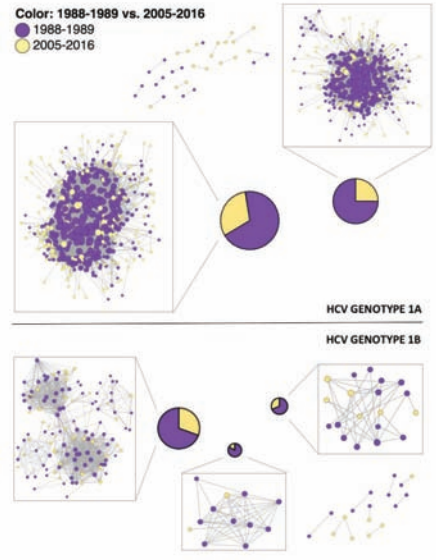

Figure. Cluster Network of participants from 1988-89, denoted by purple nodes, and 2005-16, denoted by yellow nodes. Clustering was defined as ≥ 2 participants that were genetically linked, denoted by gray edges, at a 4% genetic distance threshold.

592 COMPLEX PHYLODYNAMICS OF HCV AMONG PWID IMPACT INFERENCE OF TRANSMISSION NETWORKS

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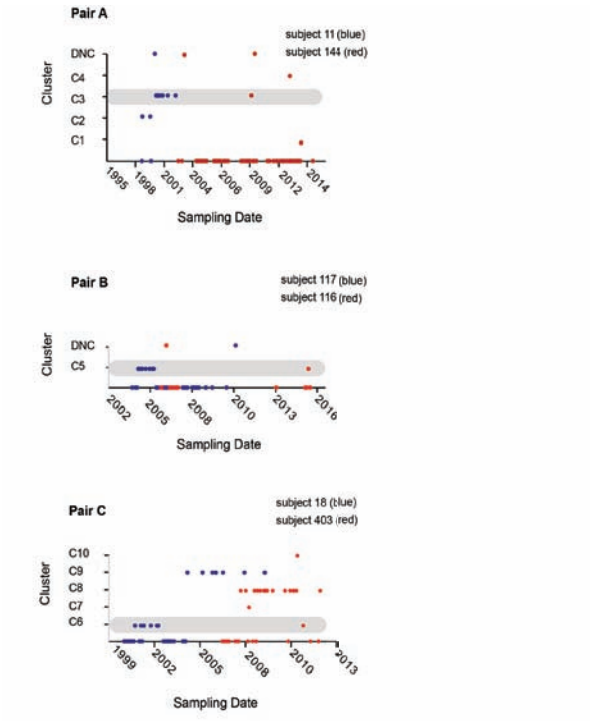
Background: The vast majority (up to 80%) of new HCV infections in high-resource countries are among people who inject drugs (PWID). Uncovering the common sources of infection and transmission networks is critical for effective intervention. Here, we study transmission dynamics in a highly-networked Baltimore cohort of PWID using longitudinally-sample HCV sequences.
Methods: Subjects were enrolled in the "Baltimore Before and After Acute Study of Hepatitis" (BBAASH) cohort, composed of PWID followed prospectively from 1996-2016. All subjects were seronegative at enrollment. We used a subset of 89 subjects who acquired HCV during the study with sequences from >1 visit over 1-14 years. Viremia status (RNA+/-) was available for an average of 14 visits per individual. Bulk HCV sequences from the E1 region (H77 nt 943-1288) were studied, with a final alignment comprising 743 sequences. We used HIV-TRACE to assign clusters. Maximum likelihood (ML) trees for each cluster were inferred using RaxML.
Results: Thirty clusters contained >1 subject whose sequences had <3% genetic distance. Trees showed that three clusters each contained a pair of subjects (A-C) who shared identical sequences, although detected 7-10 years apart. A longitudinal plot of viremia and cluster assignments (i.e. "variants") showed that in all three pairs, the subject with later detection of the shared variant previously had an RNA- visit and/or detection of a different viral variant, while in two pairs, the subject with earlier detection of the shared variant subsequently had both an RNA- visit and detection of a different viral variant (Figure).
Conclusion: HCV infection among PWID is dynamic and the resulting viral sequences reveal complex patterns of shared infection and superinfection from multiple sources. These data suggest that HCV transmission events are likely underestimated in most phylodynamic models.



Longitudinal visit outcomes for three pairs (A-C). Points represent the visit outcome (RNA+/-) and cluster assignment (y-axis) for each visit date (x-axis) and are colored by subject according to the legends. Cluster numbers are categorical. Points at y=0 indicate RNA- visit. Sequences that were not assigned to a cluster were plotted at "DNC" (Do Not Cluster). Grey bar highlights the shared cluster.

593 PHYLOGENETIC EVIDENCE FOR INTERCITY HCV CLUSTERS OF PEOPLE WHO INJECT DRUGS IN INDIA

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Background: Little data exist on HCV phylodynamics and transmission networks among people who inject drugs (PWID), especially from low- and middle-income countries (LMICs). HCV epidemics in a city can be considered a series of sub-epidemics caused by phylogenetically distinct viral lineages. Mapping these lineages to generate transmission clusters and overlaying epidemiologic data can be used to identify factors associated with clustering.
Methods: PWID were recruited via respondent driven sampling in 2016-17. Participants completed a survey and blood draw. HCV 5'UTR-core sequencing was performed on 486 HCV RNA positive samples from 4 cities (Amritsar [n=126], Delhi [n=128], Kanpur [n=138], Imphal [n=94]). Sequences were aligned using Multiple Sequence Comparison by Log-Expectation. The most appropriate nucleotide substitution model was determined using jModelTest and phylogenetic inference was carried out using Maximum Likelihood methods in RaXML with 500 bootstrap replications. Clusters were identified using ClusterPicker with posterior support and genetic distance thresholds of 70% and 4.5%, respectively. Given the large number of covariates of interest, a machine learning model utilizing the Boruta wrapper of the random forest algorithm was constructed to identify features predictive of clustering, as well as differences between clusters.
Results: Median age was 33 years, 99% were male and HIV prevalence was 75%. Mean p-distance for all sequences was 0.075. A total of 251 sequences fell into 19 transmission clusters (Fig). Mean cluster size was 7.4 (range: 2-49); 8 clusters were dyads. There were 6 large clusters comprised of >10 samples. 7 of the 19 clusters contained samples from multiple cities. Machine learning based analysis revealed that no history of HIV testing and living with friends were predictive of clustering (both $p<0.05$), and that state, residential zip code, injection zip code, time spent away from home, and buprenorphine injection could be predictive of membership in a given cluster (all $p<0.05$). Age, gender, and HIV status did not predict clustering.
Conclusion: These are among the first data from a LMIC setting to demonstrate clustering across multiple cities. The median size of the clusters identified were also larger than self-reported injection networks in India. Treatment as prevention efforts for HCV have emphasized network-based approaches for PWID, and these data suggest that networks may need to be defined by space (zip code) as opposed to egocentric injection networks.

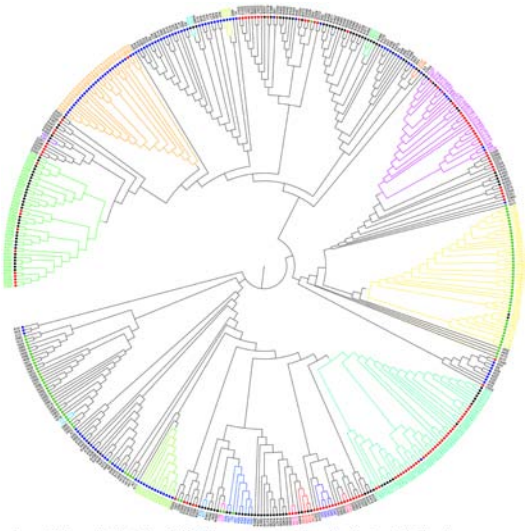

Figure. Phylogenetic clustering of 486 HCV core sequences inferred by Maximum Likelihood. Evolutionary history was inferred in RaXML using 506 positions in the HCV core region under a GTR+G+I model and 500 bootstrap replications. The tree with the highest log likelihood (-14029.39) is shown. A discrete Gamma distribution was used to model evolutionary rate differences among sites with 5 categories (= 0.4442) and 12.85% invariant sites. Transmission clusters are denoted by branch and tip label color and were identified using ClusterPicker v1.3 with a posterior support threshold of 70% and a 4.5% genetic distance threshold. Colored tip points denote city; Amritsar = blue, Delhi = red, Kanpur = black, Imphal = green.

594 PHYLODYNAMICS OF ACUTE HCV INFECTION IN MEN HAVING SEX WITH MEN

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Background: Opioid substitution and syringes exchange programs have drastically reduced HCV spread in France, while HCV sexual transmission in men who have sex with men (MSM) has recently arose as a significant phenomenon. Epidemiological data such as prevalence and incidence rates can quantify an epidemic at its chronic stage but are less meaningful at its early stages or if the transmission of the pathogen only occurs in a subgroup of individuals. Phylodynamic inferences use both pathogen phylogenies based on genetic sequences and epidemiological data to describe infectious diseases transmission dynamic. We used a phylodynamic approach to estimate key epidemiological parameters such as the reproduction number (R0) and the infectious period duration of acute HCV infection (AHI) in French MSM.
Methods: A birth-death epidemiological model with 2 host types corresponding to respectively the "classic" HCV epidemic (mostly IVDU-blood product recipients) and the "new" epidemic in MSM was implemented. Two periods (< and >1997) were considered for the classic epidemic. 30,000 simulated phylogenies were first generated under a variety of parameter set. These simulations were then used to "feed" a regression model and to infer epidemiological parameters using an approximate Bayesian computation approach. The model was then run on the true HCV phylogeny from AHI and chronic HCV infections, to infer R0, infectious period and assortativity estimates (the extent to which virus transmission is random or occurs mostly within groups) for both epidemics. The validity of the results was estimated using a parametric bootstrap approach.
Results: 213 NS5B sequences from HCV genotype 1a infections were analyzed (68 from AHI in MSM, 145 from chronic infections in non-MSM patients). Estimates of the beginning dates for the classic and the new epidemics were 1983 (95%CI 1981-1983) and 2000 (95%CI 1999-2002) respectively. Estimates of R0 for the classic epidemic >1997 and for the new epidemic were 1.5 (IQR 1.3-1.7) and 1.7 (IQR 1.4-2.1) respectively. Estimates for the infectious period duration for the classic and the new epidemics were 2.3 years (IQR 1.6-3.1 years) and 0.4 years (0.4-0.5 years) respectively.
Conclusion: AHI epidemic in French MSM was characterized by a similar R0, but a much shorter infectious period and a greater transmission rate per unit of time than the classic epidemic. These result shows how phylodynamic can help to understand the transmission dynamics of an epidemic spreading in different populations.

595 VALIDATION OF A GENOTYPE-INDEPENDENT HEPATITIS C WHOLE-GENOME SEQUENCING ASSAY

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Background: Recent development of direct-acting antiviral agents (DAA) has dramatically improved the effectiveness and tolerability of treatments for hepatitis C virus (HCV), resulting in >95% sustained virologic response (SVR) rates. However, cases of treatment failure have been associated with the emergence of resistance-associated substitutions (RAS). To better guide clinical decision-making, we developed and validated a near-whole-genome, HCV genotype (GT)-independent sequencing strategy on the Illumina MiSeq next-generation sequencing (NGS) platform.
Methods: HCV GT1-6 samples from treatment-naïve HCV-infected individuals as well as DAA-treated persons who did not achieve SVR were included. Viral RNA was extracted on a Biomerieux easyMag and underwent nested reverse-transcription-PCR. Libraries prepared by Nextera XT were sequenced on the MiSeq. NGS data were processed by an in-house pipeline that incorporates HCV reference sequence selection and an iterative mapping process for paired-end reads. Nucleotide consensus sequences were aligned to appropriate FDA reference strain sequences for downstream identification of RAS. Sequences were compared to data obtained from a previously validated in-house assay optimized for HCV GT1. A minimal threshold for minority species detection was estimated from the coefficient of variation of minor species quantification.

Results: Roughly 90% sequencing success rates, defined as achieving >100-fold NGS read coverage across NS3, NS5a and NS5b, was observed for most genotypes in samples with HCV RNA >5 log10 IU/mL (Table 1). The genotype-independent HCV method showed >99.8% nucleotide concordance with the GT1-optimized method in NS3, NS5a, and NS5b using a 20% mixture-calling threshold. The assay demonstrated near-perfect precision and reproducibility at detecting variants above 2% prevalence and showed no systematic bias in amplifying specific RAS. An absolute lower limit of 0.2% for reproducible minor species detection was estimated but warrants a more conservative threshold given MiSeq error rates (0.5%) and limitations of PCR.
Conclusion: This study highlights the performance of a freely available, near whole-genome NGS assay and bioinformatic pipeline for genotype-independent HCV genotyping and RAS detection. The method demonstrated similar performance to a validated GT1 assay and can now be extended to other HCV genotypes. This method has been implemented clinically and has been used to deliver ~3000 resistance test reports to physicians across Canada.

Table 1: Sequencing success rates NS3, NS5a and NS5b genes using a pan-HCV assay for genotypes 1-6. Genotypes were assigned based on data provided from external laboratories or were inferred through sequence analysis. HCV subtype information was obtained using phylogenetic analyses based on MiSeq data.

Genotype	Genotype Subtypes	Samples Attempted	Samples Sequenced (%)		
			NS3	NS5a	NS5b
1	1a	78	72 (92%)	72 (92%)	72 (92%)
	1b	11	11 (100%)	11 (100%)	11 (100%)
	1e	3	2 (67%)	2 (67%)	2 (67%)
2	2b	2	2 (100%)	2 (100%)	2 (100%)
3	3a	20	17 (100%)	17 (100%)	17 (100%)
4	4a, 4n	7	5 (71%)	5 (71%)	2 (29%)
5	5a	4	3 (75%)	3 (75%)	3 (75%)
6	6a, 6e, 6h, 6k, 6t	21	20 (95%)	20 (95%)	17 (85%)

596 HPTN 078: HIGH PREVALENCE OF HCV ANTIBODIES AMONG MEN WHO HAVE SEX WITH MEN

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Background: Sexual transmission of hepatitis C virus (HCV) is uncommon, yet has been documented among MSM, primarily among those who are HIV-infected. Recent phylogenetic analyses reveal that some HIV-uninfected MSM are infected with HCV strains circulating in HIV-infected MSM transmission networks. Data on the prevalence of HCV infection in HIV-uninfected MSM are limited.
Methods: In HPTN 078, which assessed the efficacy of an integrated strategy to achieve HIV viral suppression, 1305 MSM were screened using respondent driven sampling or direct recruitment across four geographically diverse US cities. HIV-infected MSM with viral loads >1,000 copies/mL were eligible for enrollment. At screening, demographic, behavioral, and psychosocial questionnaires were completed, along with HIV and HCV antibody testing. Multivariable logistic regression was used to evaluate associations with HCV antibody positivity.
Results: Of the 1305 men screened, median age was 41, 69% were Black, 85% had a high school diploma or more, 84% had either public or private insurance, 35% were employed, 69% were HIV-infected, and 20% had undergone substance use counseling/treatment. The median lifetime number of male sexual partners was 17 (IQR: 6, 50) and female partners was 5 (2, 13). HCV antibody test results were available for 1287 (99%) of the men of whom 246 (19%) were positive. HCV antibody positivity was high in both HIV-infected (20%) and HIV-uninfected (16%) MSM (P=0.12) and was higher in those receiving substance use counseling/treatment (36%) than those that had not (15%)(P=<0.01). After adjusting for other factors, older age [odds ratio (OR) 1.06 per year, 95% CI 1.05-1.08], less than a high school degree [OR 1.71, 95% CI 1.15-2.55], drug/alcohol counseling or treatment [OR 2.57, 95% CI 1.83-3.61] and unstable housing [OR 2.16, 95% CI 1.29-3.61] were associated with increased risk for HCV antibody positivity.
Conclusion: Nearly 1 in 5 MSM screened for HPTN 078 have been infected with HCV in a high HIV burden sample. The prevalence is high regardless of HIV infection status and is high even in those who did not undergo substance use counseling. These data raise concern that in HIV burden networks high HCV infection prevalence may occur in HIV-uninfected MSM. HCV transmission risk could increase as PREP implementation expands and condom use declines among HCV positive MSM. Further work is needed to understand the high HCV antibody prevalence in this cohort.

597 EPIDEMIC HISTORY OF HEPATITIS C VIRUS AMONG MSM IN AMSTERDAM, THE NETHERLANDS

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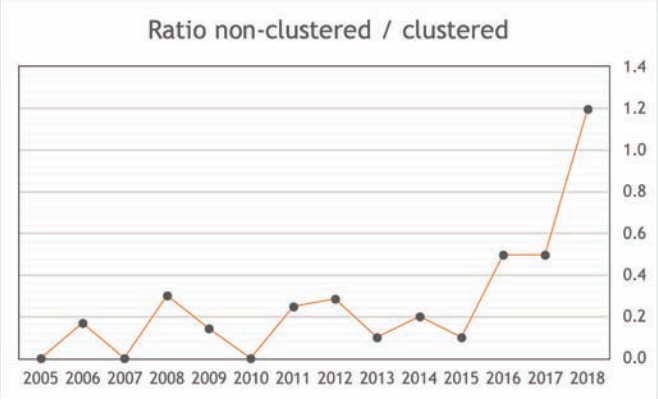
Background: To strengthen HCV micro-elimination efforts in the MSM community, a better understanding of transmission networks is vital. Insight in the proportion of new HCV infections that results from ongoing transmission of local variants versus new infections via external introductions may further guide specific local elimination efforts. We describe the epidemic history of HCV infections among MSM in Amsterdam from 1994 to 2018.
Methods: Sanger sequencing of part of the E1E2 genomic region (525 base pairs) was applied to 147 samples positive for HCV gt1a – the most prevalent genotype in Amsterdam (62%) – from MSM diagnosed between 1994 and 2018. The majority of MSM was HIV positive (87%) and diagnosed during the acute phase of the infection (91%). Time-resolved phylogenetic analyses were performed using BEAST software to estimate the temporal origin and progression of the HCV epidemic in Amsterdam. PhyCLIP software was used for statistically supported cluster designation.
Results: 114 sequences (78%) grouped into seven clusters with introduction dates ranging from 1996 to 2004. Cluster sizes ranged from three to thirty-seven sequences. A modest decrease in proportion of clustered sequences over time was observed: 80% (36/45) of samples from 2008-2013 and 70% (40/57) of samples from 2013-2018 were part of a cluster. We observed that the ratio non-clustered to clustered sequences remained fairly stable until 2015 (mean ratio 0.14, SD = 0.10), after which the ratio increased to 1.2 in 2018 (n=11) in favor of the non-clustered sequences.
Conclusion: The identification of both non-clustered and clustered infections, in particular in the past five years, indicates that both external introductions and ongoing transmission within existing clusters fuel the HCV epidemic among MSM in Amsterdam. The seeming increase in external introductions when compared to local transmission coincides with the beginning of the DAA era in the Netherlands. Prospective, phylogenetic analysis of recent HCV infections combined with data collection on network characteristics of the individuals infected with HCV (e.g. meeting location of sex partners) has the potential to guide targeted prevention measures and stresses the need for real-time HCV sequence monitoring in the Netherlands.



598 RISK FACTORS AND PATTERNS OF HCV TRANSMISSION IN MEN WHO HAVE SEX WITH MEN IN ENGLAND

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Background: We sought to characterise risk factors and patterns of HCV transmission in a cohort of men who have sex with men (MSM) in England.
Methods: MSM with recently-acquired HCV (AHCV) (n=40) were prospectively recruited from 01/2017-08/2017 ('clinic cohort'). Clinical data and risk behaviours were identified by notes review and questionnaires. Blood was obtained for HCV whole genome sequencing. Phylogenetic analyses for genotype (GT) 1a were performed, including MSM from the clinic cohort (n=18) and 2 other AHCV cohorts, TARGET3D (n=24) and CHAT (n=10), to identify transmission clusters.
Results: Sixteen (40.0%) men were HIV-. (See Table.) HIV- vs HIV+ men were significantly (sig.) younger (34, IQR 29-43 vs 44, 36-50 years, respectively). Most HCV infections were GT1a (13, 81.3% HIV- vs 14, 58.3% HIV+ men); GT4 was sig. less frequent in HIV- (n=1, 6.3%) vs HIV+ men (n=9, 37.5%). Most (22, 91.7%) HIV+MSM were aviraemic on antiretrovirals; most (13, 81.3%) HIV-MSM had taken HIV PrEP in the last year. Seven HIV-(43.8%) vs 11 HIV+(45.8%) men had a history of injection drug use (IDU), methamphetamine being used most often (11/18, 61.1%); 15(93.8%) HIV- vs 19(79.2%) HIV+ men reported non-injected drug use in the last year. HIV- men had sig. more partners (36, IQR 16-50 vs 16, 4-16); reporting of group sex (14, 87.5% vs 17, 70.8%), condomless anal sex (16, 100.0% vs 21, 87.5%) and fisting (12, 75.0% vs 13, 54.2%) in the last year was not sig. different for HIV- vs HIV+ men, respectively. The preferred way of meeting partners was via phone apps (13, 81.3% HIV- vs 21, 87.5% HIV+ men), with one app used by 26/29 (89.7%) respondees. For the question, 'how many partners in the past 12 months did you think had HIV?', a majority thought 'some', 'most' or 'all' partners had HIV (13, 81.3% HIV- vs 20, 83.3% HIV+ recruits); few men thought 'some', 'most' or 'all' partners had HCV (4, 25.0% HIV- vs 3, 12.5% HIV+ recruits). For 52 GT1a sequences, 47(90.4%) clustered with ≥1 other sequence. There were 7 clusters of 2-27 men; 6 clusters contained HIV- and HIV+MSM and 1 cluster only HIV+MSM. One mixed HIV-/HIV+ cluster was likely part of a larger cluster first described for HIV+ MSM in 2007.
Conclusion: PrEP-using MSM are at risk of HCV, with similar behaviours to HIV+MSM. Younger age and greater partner number for HIV-MSM raise the possibility of a rapid HCV epidemic, with transmissions likely bridging from HIV+ populations. Few men demonstrated HCV awareness and risk reduction strategies should be expanded.

Table. Characteristics of HIV-uninfected and HIV-infected men with recently-acquired HCV

	HIV- n=16	HIV+ n=24	All n=40	P value
Median age, years	34 (29-43)	44 (36-50)	39 (33-49)	0.021*
UK-born	9 (56.3)	18 (75.0)	27 (67.5)	0.215
Jaundice	2 (12.5)	2 (8.3)	4 (10.0)	>0.999
Median HCV RNA, log IU/mL	3.7 (3.2-5.7)	5.1 (4.3-6.3)	4.8 (3.4-6.2)	0.279
Genotype 1a[1]	13 (81.3)	14 (58.3)	27 (67.5)	0.177
Genotype 4	1 (6.3)	9 (37.5)	10 (25.0)	0.032*
Median duration HCV infection, months	4.1 (3.3-8.3)	4.9 (2.3-8.0)	4.8 (2.7-8.2)	0.687
Spontaneous HCV clearance	2 (12.5)	3 (12.5)	5 (12.5)	>0.999
Prior HCV episode(s)	4 (25.0)	5 (20.8)	9 (22.5)	>0.999
STI at HCV diagnosis	5 (31.3)	7 (29.2)	12 (30.0)	0.888
History of IDU	7 (43.8)	11 (45.8)	18 (45.0)	0.897
History of non-IDU in past year	15 (93.8)	19 (79.2)	34 (85.0)	0.373
Median no. of sex partners in past year	36 (16-50)	16 (4-16)	16 (8-39)	0.025*

1. Genotype distribution: 1a (n=27), 3a (n=3), 4d (n=9), 4 no subtype (n=1)
*<0.05 by chi-squared, Fishers exact or Mann Whitney U test Brackets denote % or IQR

599 SURGE IN HEPATITIS C INCIDENCE ASSOCIATED WITH SYPHILIS INFECTION AMONG THAI MSM

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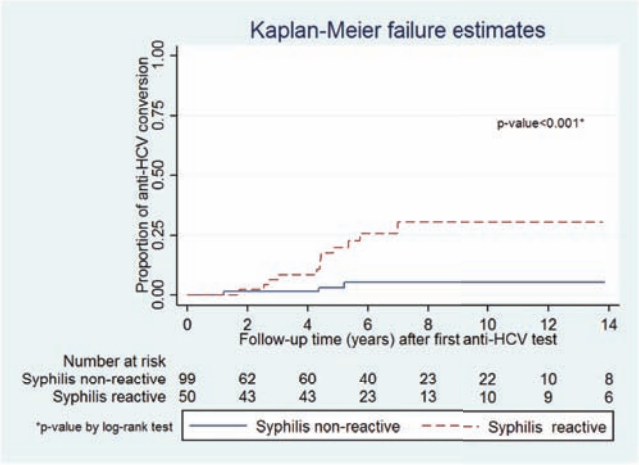
Background: Sexual transmission of hepatitis C viral infections (HCV) has been reported among men who have sex with men (MSM) living with HIV from major cities of the world, although less frequently from the Asia-Pacific region. We investigated the incidence of HCV among HIV-positive MSM taking antiretroviral therapy (ART) in a long-term clinical cohort in Bangkok, Thailand.
Methods: MSM with negative baseline anti-HCV antibody tests were identified in the Thai HIV-NAT 006 cohort from October 1996 to July 2018. HCV incidence among MSM was defined by two positive anti-HCV antibody tests and confirmed by detectable HCV RNA level. HCV genotyping was done using the Linear Array Hepatitis C Virus Genotyping Test. Recent syphilis infection was defined as a reactive RPR within 6 months of HCV seroconversion.
Results: A total of 464 MSM with median (IQR) baseline age of 38 (32-46) years and baseline median CD4 count of 303 (180-466) cells/mm^3 were included in the study. Participants had been treated with ART for a median of 7.5 (5.7-12.5) years. Of 464 MSM, 29 incident cases were identified during 2885 person-years (PYS) of follow-up. The crude incidence rate of HCV surged from 0.37 per 100 person-years of follow-up (PYS) before 2014 to 2.21 per 100 PYFU in 2014-2018. At the time of HCV seroconversion, most participants (82%) had suppressed HIV viremia and the median CD4 count was 581 (479-792) cells/mm^3. Of the HCV incident cases, (81%, N=13/16) had genotype 1a and 27.6% had hepatitis B co-infection (HBsAg positive). In multivariate analysis, age < 35 years (HR, 3.31, 95% CI, 1.42-7.71, p=0.005) and recent syphilis infection (HR, 3.84, 95% CI, 1.78-8.26, p=0.001) were strongly associated with incident HCV among Thai MSM living with HIV. Among 29 incident cases, three participants reported injecting methamphetamines use from collected behavioral risk assessment questionnaire. Spontaneous clearance was observed in 1 case. 4 participants (14%) were treated for HCV and all achieved SVR at week 12.
Conclusion: A recent surge in HCV incidence is noted among MSM receiving chronic HIV care in Bangkok, Thailand. In the era of effective direct acting agents (DAAs) and "Undetectable=Untransmissible", sexually transmitted infections, including hepatitis C and syphilis, need to be routinely screened and treated in HIV+ MSM to prevent further transmission to both HIV-positive-and HIV-negative partners, particularly among resource-limited settings where the access to DAAs are still low.

Figure: Kaplan-Meier curves showing the proportion of anti-HCV ab seroconversion among HIV-positive MSM with or without recent syphilis infection (+/- 6 months of HCV seroconversion)



600 HCV-GT1A SPATIOTEMPORAL DISTRIBUTION, EPIDEMIC HISTORY, AND NS5A RESISTANCE IN SPAIN

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Background: Any successful strategy to prevent and control HCV infection requires an understanding of the epidemic behaviour of the virus. HCV genotype (GT) 1 is the most prevalent worldwide and GT1a represents almost 40% of the GT1 infections in Spain. We aimed to characterize the origin, epidemic history, transmission dynamics and diversity of HCV-GT1a in Spain.
Methods: This study describes a nationwide multicenter (80 Spanish hospitals) cross-sectional study of 588 DAA-treatment naïve patients harboring HCV-GT1a. HCV population sequencing was used to identify relevant resistance-associated substitutions (RASs) to NS5A inhibitors. Phylogenetic analysis was used for subtyping and transmission cluster identification. HCV-GT1a lineages (clade I and clade II) were confirmed by geno2pheno[HCV]. Bayesian methods were used to reconstruct the epidemic history of HCV-GT1a.
Results: 51.0% (n=300) were HCV+ and 49.0% (n=288) were HIV+/HCV+ subjects. HCV-GT1a clade II was more prevalent than clade I (82.3%, n=484, vs. 17.7%, n=104; P<0.001). Viruses bearing RASs to NS5A inhibitors were present in 50 samples (8.5%), seven of those having viruses with double RASs. Higher prevalence of RAS was found in clade II (80%).The most common RASs were M28A/T/V (44.0%; n=22/50), Y93C/F/H/N (28.0%; n=14/50) and Q30E/H/R (24.0%; n=12/50). The double mutations 30H+93H, 28V+30R and 30R+93H were also observed. A prevalence of RASs of <10% was observed in eleven regions while a prevalence >10% was observed in five, highlighting Cantabria (15.9%; n=7/44) and Murcia (12.5%; n=1/8). Among patients harboring RASs, those that harbored mutations which confers high resistance were: 38.0% (n=19/50) to daclatasvir, 34.0% (n=17/50) to ledipasvir, 36.0% (n=18/50) to ombitasvir, 6.0% (n=3/50) to elbasvir, 8.0% (n=4/50) to velpatasvir, 4.0% (n=2/50) to pibrentasvir. GT1a clade II epidemic preceded clade I by 45 years [time to the most recent common ancestor (TMRCA), 95% highest posterior density (95%HPD): 1907, 1879–1932 vs 1952, 1939–1965] (Fig1 A-B-C). GT1a clade II epidemic started in Basque Country, was dispersed throughout the entire country and is now declining. The current GT1a clade I epidemic is still mostly concentrated in the North of Spain and Canary Islands (Fig1 D-E).
Conclusion: Current HCV GT1a epidemic in Spain is mainly driven by clade I viruses which seem to have different dispersion routes relative to clade II viruses. Close surveillance of patients with NS5A RAS will be important to prevent further therapeutic failures.

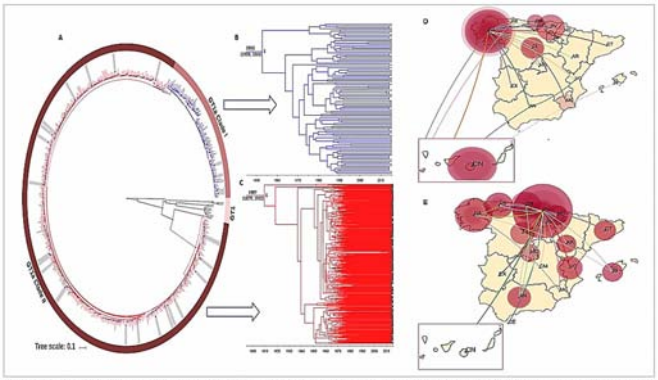

Figure 1: (A.) A maximum likelihood tree (ML) produced under the GTR+1 with 1000 bootstrap replicates segregates the GT1a into two clades, clade I (blue) and clade II (red). Bootstrap supports ≥ 70% are depicted as purple filled circles at the nodes and transmission clusters (TC ≥ 2) are highlighted in grey color. (B.) and (C.) Maximum clade credibility trees for each of the clades, clade I (blue) and clade II (red) are presented with the mean tMRCA (95% HPD interval) estimates in calendar years annotated at the root nodes for each of the GT1a clades. The geographic migrations of GT1a strains for clade I (D.) and clade II (E.) amongst the different autonomous regions of Spain (AN - Andalucía; AR – Aragón; AS – Asturias; CB – Cantabria; CE – Ceuta; CL - Castilla y León; CM - Castilla-La Mancha; CN – Canarias; CT – Cataluña; EX – Extremadura; GA – Galicia; IB - Islas Baleares; MC – Murcia; MD – Madrid; NC – Navarra, PV - País Vasco; RI – La Rioja; VC - Valencia). Inward migration lines are colored differently and increment in migration counts are colored in red circles with proportional magnitude of color intensity and circumference.

601 HCV ANTIBODY AVIDITY–BASED METHOD TO ESTIMATE POPULATION-LEVEL INCIDENCE

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Background: Accurate hepatitis C virus (HCV) incidence estimates are critical for monitoring progress towards hepatitis C elimination goals which include a reduction in HCV incidence of 80% by 2030. Moreover, incidence estimates can help guide local prevention and treatment programming, particularly in the context of the US opioid epidemic.
Methods: An inexpensive ($4/sample), Genedia-based HCV IgG antibody avidity assay was evaluated as a platform to estimate cross-sectional, population-level HCV incidence using 1840 anti-HCV+ and RNA+ samples from 875 individuals enrolled in 5 cohort studies in the US and India of whom 220 were HIV+. Using samples collected <2 years following HCV seroconversion, the mean duration of recent infection (MDRI) was calculated by fitting a binomial regression to the probability of appearing recent using a maximum likelihood approach. Among samples collected ≥2 years following HCV seroconversion, a subject-level false recent rate (FRR) was calculated by estimating the probability of appearing recent using an exact binomial test. Factors associated with falsely appearing recent using an avidity index (AI) cutoff <40% among samples collected ≥2 years post seroconversion were determined by Poisson regression with generalized estimating equations and robust variance estimators. We simulated populations reflecting low, moderate, and high burden HCV and HIV epidemics and assessed the approach's precision to estimate incidence, with a relative standard error (RSE) of 30%.
Results: Using an AI cutoff of <40% this approach had an MDRI of 113 days (95%CI:84-146), and FRR of 0.4% (95%CI:0.0-1.2) and 4.6% (95%CI:2.2-8.3) among HIV- and HIV+ individuals, respectively, and did not differ between HCV genotypes 1 and 3. In multivariable analysis, among samples collected from individuals infected for >2 years, an AI<40% was more likely to be observed in HIV+ individuals who had a CD4+ T-cell count <200 cells/μL, adjPRR = 22.0 (95% CI: 6.28, 77.01; p<0.001) compared to HIV- individuals. In hypothetical scenarios of high-risk settings, a sample size of <1000 individuals was needed to accurately estimate HCV incidence (Figure 1).
Conclusion: This cross-sectional approach can estimate HCV incidence for the most common genotypes, particularly in populations with low HIV prevalence. This tool can serve as a valuable resource for program and policy planners seeking to monitor and reduce the global burden of HCV.

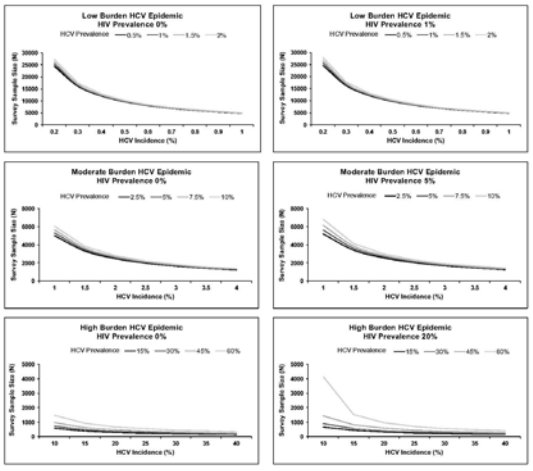

Figure 1. Precision of Genedia-Avidity Approach to estimate HCV incidence in various populations. The sample sizes represent the total number of HCV seropositive and seronegative individuals required in a single cross-sectional survey to achieve an incidence estimate with a relative standard error (RSE) of 30%. HCV and HIV seroprevalence was varied to represent different epidemic states. The RSE for the mean duration of recent infection and false recent rate was 14%, and 33%, respectively.

602 HIGH KYNURENINE:TRYPTOPHAN RATIO IS ASSOCIATED WITH LIVER FIBROSIS IN HIV INFECTION

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Background: The kynurenine:tryptophan ratio (KTR), a marker of tryptophan catabolism, is associated with impaired T-cell function. Higher KTR has been associated with increased mortality, cardiovascular disease, and neurologic conditions in HIV+ persons. Its role in liver fibrosis is unknown. We examined the association of KTR with liver fibrosis in women with and without HIV infection.
Methods: Serum KTR was measured in 58 HIV-monoinfected, 42 HIV/HCV-coinfected, and 37 uninfected women from the WIHS. Fibrosis was estimated in all 137 women using FIB-4. We used multivariable linear regression to evaluate the associations of HIV monoinfection, HIV/HCV coinfection, KTR, and FIB-4 adjusting for demographic, lifestyle, metabolic, and HIV-related factors. We performed a subgroup analysis using liver stiffness measurements (LSM) to assess fibrosis among a subgroup of 83 women who had undergone LSM.
Results: Median KTR[IQR] was 3.8[3.2-4.5] in HIV-monoinfected, 5.5[4.4-6.5] in coinfected, and 3.1[2.5-3.4] in uninfected groups ($p<0.001$ across groups). Women with HIV/HCV and HIV monoinfection had higher FIB-4 than uninfected women (2.17[1.24-3.38] and 0.98[0.79-1.53] respectively vs. 0.63[0.57-0.92];$p<0.001$). FIB-4 increased as KTR increased in HIV+ women (Spearman's rho=0.54;$p<0.001$) but not HIV- women (rho=-0.13,$p=0.44$). In the total cohort, factors associated with higher FIB-4 were older age (30% per 10 years;95%CI:16%-45%), HIV monoinfection (37%;95%CI:9%-73%), and HIV/HCV coinfection (164%;95%CI:100%-250%)(Table1a). When further adjusting for KTR, higher KTR was associated with higher FIB-4 (27% per doubling,95%CI:5%-53%), and the associations of HIV monoinfection (29%;95%CI:2%-63%) and HIV/HCV coinfection (123%;95%CI:63%-203%) were slightly attenuated. In the HIV+ group, higher CD4 count was associated with lower FIB-4 (-5.6%;95%CI:-9.8%,-1.1%), but the effect was attenuated after adjusting for KTR. In the 83 women with LSM, higher KTR was associated with higher LSM (43% per doubling,95%CI:15%-79%)(Table1b). HIV/HCV coinfection was associated with higher LSM after adjusting for KTR (47%;95%CI:3%-110%), while HIV monoinfection was not (-0.9%;95%CI:-23%-27%).
Conclusion: KTR is elevated in the setting of HIV infection and is associated with higher liver fibrosis. The associations of HIV monoinfection and HIV/HCV coinfection with elevated fibrosis were attenuated after adjusting for KTR, suggesting that the relationship between HIV and liver fibrosis may be mediated in part by the tryptophan pathway.

Table 1a. Factors associated with FIB-4 in the total cohort, with and without adjustment for KTR

	Entire Cohort (N=137)				HIV+ Cohort (N=100)			
	Adjusted model*		Adjusted model with KT ratio*		Adjusted model*		Adjusted model with KT ratio*	
Variable	% effect (95% CI)	p value	% effect (95% CI)	p value	% effect (95% CI)	p value	% effect (95% CI)	p value
KT ratio	N/A	N/A	26.7% (5%, 52.8%)	0.013	n/a	n/a	28.5%(4%, 58.9%)	0.02
HIV monoinfection	37% (8.6%, 72.9%)	0.008	28.6% (1.8%, 62.5%)	0.035	n/a	n/a	n/a	n/a
HIV/HCV coinfection	164.2% (99.5%, 249.9%)	<0.001	122.5% (63.2%, 203.3%)	<0.001	67.7% (25.8%, 123.7%)	<0.001	52.1% (13.5%, 103.7%)	0.005
CD4 count (per 100 cells/μL)	N/A	N/A	N/A	N/A	-5.6 (-9.8%, -1.1%)	0.016	-4.5% (-8.8%, 0%)	0.05

Table 1b. Factors associated with liver stiffness measurement by Fibroscan in the total cohort, with and without adjustment for KTR

	Entire Cohort (N=83)				HIV+ Cohort (N=59)			
	Adjusted model*		Adjusted model with KT ratio*		Adjusted model*		Adjusted model with KT ratio*	
Variable	% effect (95% CI)	p value	% effect (95% CI)	p value	% effect (95% CI)	p value	% effect (95% CI)	p value
KT ratio	N/A	N/A	43.3% (14.7%, 79.1%)	0.002	N/A	N/A	51.6% (17.8%, 95.2%)	0.001
HIV monoinfection	5.1% (-19.2%, 36.7%)	0.711	-0.9% (-22.9%, 27.3%)	0.941	N/A	N/A	N/A	N/A
HIV/HCV coinfection	94.2% (39.5%, 170.2%)	<0.001	46.9% (3%, 109.6%)	0.034	87.2 (33.2%, 163.1%)	<0.001	50.6% (7.6%, 110.7%)	0.017
CD4 count (per 100 cells/μL)	N/A	N/A	N/A	N/A	-4.3 (-9.2%, 1%)	0.108	-4 (-8.5%, 0.7%)	0.094

*Also adjusted for age, race, visceral adipose tissue, MRS-measured hepatic steatosis, alcohol use, current smoking, current marijuana, and ever injection drug use

603 MORTALITY AFTER DIALYSIS INITIATION AMONG PATIENTS WITH CHRONIC HEPATITIS C INFECTION

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Background: End-stage renal disease (ESRD) is an important extrahepatic manifestation among chronic hepatitis C virus (HCV)-infected individuals. However, there is little information on survival in these patients after initiating dialysis. Our objective was to investigate all-cause mortality among HCV-infected dialysis patients and whether survival differs with HIV and/or hepatitis B virus (HBV) coinfection or HCV treatment.
Methods: We included HCV-infected adults who initiated dialysis in the administrative-linked population-based British Columbia Hepatitis Testers Cohort between 1 Jan 1990 and 31 Mar 2015. Participants were followed from dialysis initiation until death, kidney transplant, or administratively censored on 31 Mar 2016. Coinfection with HBV or HIV (identified through public health reporting linkages and/or serologic testing), demographic characteristics, alcohol and injection drug use, comorbidities (diabetes, hypertension, cirrhosis, ischemic heart disease, mental health, chronic obstructive pulmonary disease), HCV treatment, social and material deprivation indices, all assessed prior to dialysis, and calendar time were included in multivariable Cox models to estimate adjusted hazard ratios (aHR) for death.
Results: A total of 2,801 individuals who initiated dialysis contributed 12,250 person-years and 1,617 deaths. The median time to death was 32 months (IQR 5, 115). Overall 69% were infected with HCV only, 9% had HBV coinfection, 15% had HIV coinfection and 7% were triply infected. Additional patient characteristics are shown in the Table. Compared with HCV monoinfection, coinfection with HIV (aHR 1.66, 95% CI: 1.42, 1.94) and triple infection (aHR 1.95, 95% CI: 1.60, 2.38) were associated with higher all-cause mortality. Existing liver disease (aHR 2.12, 95% CI: 1.88, 2.39) and diabetes (aHR 1.16, 95% CI: 1.02, 1.33) were also independently associated with mortality. After restriction to HCV treated patients, achieving sustained virologic response (SVR) prior to dialysis was associated with reduced mortality (HR 0.43, 95% CI: 0.26, 0.71) and attenuation of observed coinfection associations with mortality (HIV coinfection aHR 0.99, 95% CI: 0.42, 2.44; triple infection aHR 1.18, 95% CI: 0.40, 3.49).
Conclusion: HIV coinfection was associated with elevated mortality among HCV-infected dialysis patients, however, successful HCV treatment mitigated the excess mortality. Scaling up treatment with direct-acting antiviral therapy may improve clinical outcomes in this population.

Table. Baseline study characteristics (n=2,801)

	N(%) or Median (IQR)
Age at dialysis initiation, years	50 (41, 59)
Female sex	1,005 (36%)
Ethnicity (Caucasian vs. non-Caucasian)	2,605 (93%)
Birth Cohort	1920-1944: 414 (15%) 1945-1964: 1,700 (61%) 1965-2000: 687 (24%)
Year of dialysis initiation	2007 (2002, 2011)
Material deprivation quintiles	1 (most privileged): 378 (15%) 2: 393 (15%) 3: 341 (13%) 4: 541 (21%) 5: 929 (36%) Unknown: 219
Social deprivation quintiles	1 (most privileged): 219 (8%) 2: 253 (10%) 3: 381 (15%) 4: 600 (23%) 5: 1,129 (44%) Unknown: 219
Recent problematic alcohol use (last 3 years since dialysis)	651 (23%)
Recent injection drug use (last 3 years since dialysis)	756 (27%)
Chronic obstructive pulmonary disease	332 (12%)
Cirrhosis (with or without decompensation)	652 (23%)
Diabetes	584 (21%)
Hypertension	966 (34%)
Ischemic Heart Disease	478 (17%)
Mental health diagnoses	830 (30%)
Chronic viral coinfections	HCV Monoinfection: 1,929 (69%) HCV/HBV: 242 (9%) HCV/HIV: 433 (15%) Triple: 197 (7%)
Achieved sustained virologic response	Yes: 78/264 (30%) No: 186/264 (70%)

604 SYNDEMIC HIV AND HEPATITIS VIRAL COINFECTIONS AND INCIDENT END-STAGE RENAL DISEASE

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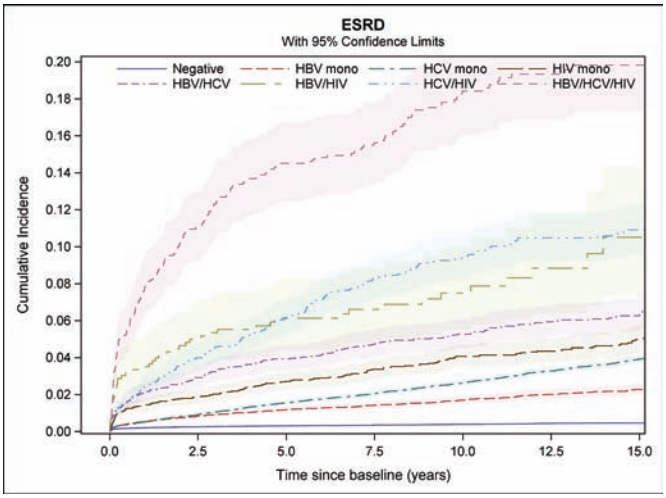
Background: Syndemic viral coinfections, including hepatitis B virus (HBV), hepatitis C virus (HCV) and/or HIV have been associated with premature mortality, however there is little data on their impact on chronic comorbidities,

including end-stage renal disease (ESRD). We evaluated the association between coinfections and incident ESRD, independent of traditional risk factors.
Methods: The British Columbia Hepatitis Testers Cohort includes ~1.7 million individuals tested for HBV, HCV or HIV, linked with laboratory and health-care administrative data. We defined ESRD through administrative codes for dialysis or kidney transplant. Individuals tested for all three infections, since 1990, were followed from the date of their last test (i.e baseline) until the earliest of i) incident ESRD, ii) death or iii) 12/31/2015. Fine and Gray models with adjustment for age, sex, ethnicity, alcohol and injection drug use (IDU), social/material deprivation, and history of diabetes and hypertension, were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of coinfections for ESRD, with death as a competing risk.
Results: Of 524,186 individuals tested for all infections, we observed 3,762 incident ESRD events (1%) and 22,741 deaths (4%) during a median follow-up of 4 years (interquartile range [IQR]: 2, 9). The cohort was mostly female (54%), Caucasian (88%), and had a median age of 37 years (IQR: 29, 47). Additional comorbidities of hypertension (12%), alcohol or IDU (6%) and diabetes (3%) were uncommon. At least one chronic viral infection was found in 11%. The highest ESRD incidence rate (per 1,000 person-years) was in individuals with triple infection (27), followed by HCV/HIV (10), HBV/HIV (10), and HBV/HCV coinfection (6). Cumulative incidence curves are shown in the Figure. In multivariate analysis, relative to those with no chronic infections, those with triple infection had the highest relative hazard for ESRD (HR 33, 95% CI: 28, 40), followed by coinfections: HCV/HIV (HR 18, 95% CI: 15, 21), HBV/HIV (HR 16, 95% CI: 12, 22), HIV monoinfection (HR 9.0, 95% CI: 7.6, 11), HBV/HCV coinfection (HR 8.0, 95% CI: 6.8, 9.5), and monoinfections: HCV (HR 6.0, 95% CI: 5.5, 6.7) and HBV (HR 4.5, 95% CI: 3.9, 5.2)
Conclusion: HIV-infected individuals with chronic HBV and/or HCV coinfection were at highest risk of ESRD progression. Management of these syndemic conditions, particularly through prevention of HBV or HCV infection could reduce the risk of ESRD among HIV-infected individuals in clinical care.



605 PREVALENCE OF HIV AND PATTERNS OF ART USE AMONG US LIVER-TRANSPLANT CANDIDATES

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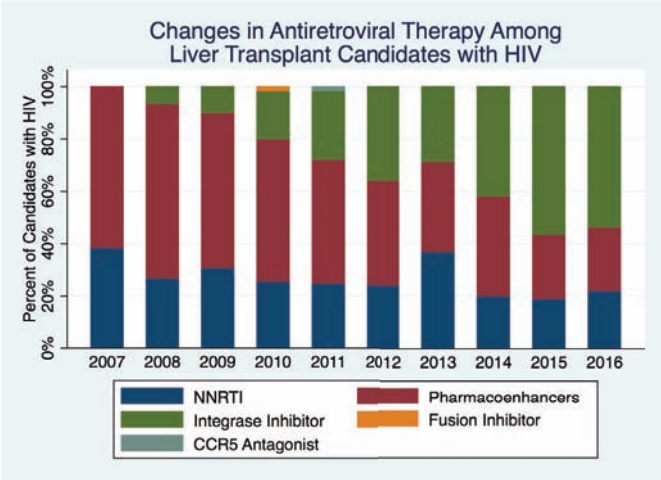
Background: Despite the high burden of liver disease among HIV-infected (HIV+) individuals, the prevalence of HIV among candidates on the US liver transplant waitlist is unknown. Additionally, since the class of antiretroviral therapy (ART), particularly the use of pharmacoenhancers (protease inhibitors, cobicistat) may complicate post-transplant immunosuppression management, it is critical to understand which regimens are commonly used in this population.Therefore, we sought to estimate the prevalence of HIV and to describe patterns in ART use among US liver transplant candidates.
Methods: We designed a retrospective cohort study (2007-2016) using pharmacy claims data (Symphony Health Solutions) linked to the national transplant registry (Scientific Registry of Transplant Recipients) using social security number with encrypted identifiers. We identified HIV+ candidates by fills of prescription medications exclusive to HIV treatment. After exploring potential mechanism(s) of missingness, we estimated HIV prevalence using multiple imputation by chained equations (MICE). We explored factors associated with ART regimens using logistic regression.
Results: The pharmacy data linkage contained 91.0% (n=99,376) of all candidates in the national transplant registry in the study period. We identified 857 HIV+ candidates with an overall estimated prevalence of 0.95% (95% Confidence Interval: 0.89%-1.02%). HIV+ candidates were more often young (median [IQR]: 53 [48-59] vs. 56 [50-62]), African American (21.4 vs. 9.0%), and male (80.6 vs. 64.4%), with liver disease due to hepatitis C virus (33.5 vs. 26.1%) than HIV- candidates ($p<0.001$ for all). The use of pharmacoenhancers (PI/PEs) decreased over time (48.4% in 2007 to 20.0% in 2016) and were more likely to be used by African American candidates (aOR: 1.80, 95%CI: 1.18-2.74, $p<0.01$), adjusting for age, year, and sex. Conversely, integrase inhibitor (INSTIs) use increased over time (7.8% in 2008 to 52.3% in 2016) and were not associated with race (aOR: 1.02, 95% CI:0.62-1.64, $p=.95$) adjusting for age, year, and sex.
Conclusion: We used a novel data linkage to identify a unique and previously unstudied population of HIV+ liver transplant candidates on the US waitlist. We found that the burden of HIV on the liver transplant waitlist was nearly 1%, ART use has shifted over time, and African Americans were almost twice as likely to be prescribed ART regimens containing pharmacoenhancers, which can interact with post-transplant immunosuppression.



606 CHANGES IN LIVER STIFFNESS MEASUREMENT IN HIV AND HIV/HBV COINFECTED NIGERIANS

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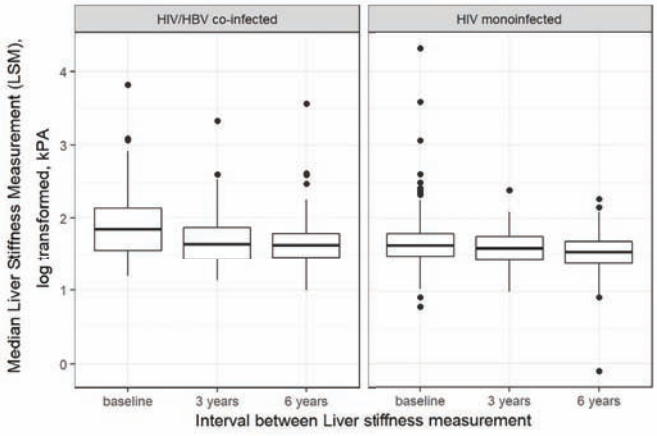
Background: There are limited data from sub-Saharan Africa on long-term liver fibrosis changes in HIV and HIV/HBV co-infected individuals. We assessed the effects of antiretroviral therapy (ART) on liver stiffness measurement (LSM) using transient elastography (TE) in HIV and HIV/HBV co-infected Nigerians and examined factors associated with liver fibrosis regression.
Methods: ART-naïve HIV and HIV/HBV co-infected adults (>18 years) were enrolled into a longitudinal study of liver disease between 7/2011 – 2/2015 and followed annually for 6 years at Jos University Teaching Hospital, Jos, Nigeria. Changes in LSM over time were examined in a subset of subjects with ≥1 follow-up TE at Y3 and Y6. Predictors of a >30% decrease in LSM score during follow-up were assessed using Cox Proportional-Hazards models (CPH).
Results: 232 HIV and 98 HIV/HBV co-infected subjects [71.2% female, median age 33.5 (IQR 12) yrs] were enrolled into the cohort. Among HIV/HBV co-infected subjects, median baseline HBV DNA was 1.67 [IQR 5.52] log10IU/mL and 6% were HBeAg seropositive. 79.4% initiated ART containing at least one HBV-active agent at enrollment and 100% were on ART at their last visit. Median duration of follow-up was 6.6 (4.1) yrs [HIV/HBV 6.4 (3.7), HIV 6.7 (4.8)]. 177/330 (54%) [45.7% HIV and 72.4% HIV/HBV co-infected] had a follow-up TE at Y3 and

148/330 (45%) [44.0% HIV and 46.9% HIV/HBV co-infected] at Y6. At baseline, LSM scores were significantly higher in HIV/HBV vs. HIV-infected subjects [6.4 (4.2) kPa vs. 5.1 (1.58) kPa; p<0.01]. LSM declined significantly from baseline to Y3 and Y6 in both groups (p <0.01) {Fig 1.}, with a trend towards larger declines observed in HIV/HBV co-infected vs. HIV-infected subjects (-1.35 [3.53] kPa vs. -0.45 [2.28] kPa; p=0.17). In multivariate analyses, HIV/HBV co-infection [HR 2.0 (95%CI 1.20, 3.33); p=0.01] and higher LSM scores at baseline [HR 2.84 (1.14, 7.08); p=0.03] were significantly associated with >30% LSM decrease. There was no independent association between >30% LSM decrease and duration of ART or HIV immunologic and virologic status at baseline.

Conclusion: Significant declines in LSM were observed in HIV/HBV co-infected and HIV-infected subjects in response to ART, highlighting the importance of early treatment initiation in both populations. LSM scores were low in HIV/HBV co-infected subjects, likely due to the relative inactive state of HBV infection (low baseline HBV DNA levels and low rates of HBeAg seropositivity) in this region.



607 IMPACT OF HBCAB+ ON ADVANCED LIVER FIBROSIS DEVELOPMENT IN HIV-HBV INFECTED PATIENTS

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Background: Coinfection with hepatitis B virus (HBV) and HIV is common, however there are few data on the influence of resolved HBV infection (i.e. HBcAb+/HBsAg- serology) on clinical progression of infection during antiretroviral therapy (ART).

Methods: HIV+ patients (pts) enrolled from the ICONA Foundation Study Cohort were prospectively evaluated to investigate the influence of resolved HBV infection (HBcAb+) on the risk of occurrence of advanced liver fibrosis (defined as Fibrosis-4 score[FIB-4]>3.25). We included pts free from liver fibrosis (FIB-4 <3.25) at the date of their first available serology test (baseline). We distinguished 3 subgroups according to HBV serology at baseline: HBsAg+, HBsAg-/HBcAb+ (HBcAb+) and HBsAg-/HBcAb- (HBV-) pts. Standard survival analysis by means of Kaplan-Meier curves and Cox regression models with time-fixed covariates measured at baseline was performed. A Poisson regression was also performed to evaluate the same associations after stratifying for ART regimen currently used (grouped as XTC/TDF-based vs. not).

Results: 2,528/8,880 pts (29%) HBcAb+ were identified: mainly males (75%) the majority having acquired HIV through sexual contacts (78%). With respect to HBV-, a significant higher proportion of HBcAb+ and HBsAg+ (12% and 14% vs. 9%, p<.001) pts had an AIDS event at baseline and a significant lower median number of CD4 cell nadir (315 and 330 vs 365, p<.001). Overall, 199 pts experienced a FIB-4 progression >3.25, among them 107/2528 HBcAb+ pts (4%), compared to 71/5907 HBV- (1%) and 21/445 HBsAg+ pts (5%). The estimated 10-year risk of death was 4.2 (95% CI:3.4-5.1) months in HBV- pts, 7.6 (5.9-9.2) in HBcAb+ and 14.1 (8.1-20.0) in HBsAg+ pts (log-rank p-value <0.0001). Compared to HBV- subjects, an increased risk of develop a FIB-4 >3,25 was shown in HBcAb+ (1.49,95%CI 1.03-2.15, p=0.035) and HBsAg+ subjects (2.62,95%CI 1.51-4,55, p<.001, Table). There was evidence that the difference in risk between HBcAb+ and HBV- was a lot larger in people currently not receiving a XTC/TDF-based ART (adjusted RR: 20.8 (95%: 2.94;147), interaction p-value =0.04).

Conclusion: HBcAb+(HBsAg-)/HIV+ pts showed a significantly higher risk of progression to liver fibrosis compared to HBV- pts, especially in those not receiving anti-HBV drugs. These findings suggest that HBV resolved infection should be monitored as it is an indicator of faster hepatic disease evolution in HBV/HIV coinfected pts.

TABLE: Unadjusted and adjusted relative hazards of Fib4>3.25 according to different HBV serologies.

	Unadjusted RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
HBV group				
HBcAb-	1.00		1.00	
HBcAb+	3.22 (2.39, 4.35)	<.001	1.49 (1.03, 2.15)	0.035
HBsAg+	3.97 (2.44, 6.46)	<.001	2.62 (1.51, 4.55)	<.001

*adjusted for age, gender, nation of birth, mode of HIV transmission, HCV co-infection status, AIDS, baseline and nadir CD4 count, viral load,CD8 count, prior exposure to ART, blood pressure or lipid lowering drugs, diabetes, cardiovascular disease, non-AIDS cancer, ESRD, smoking, alcohol consumption and calendar year of HBV serology tests

608 IMPACT OF HIV ON THE SURVIVAL OF HEPATOCELLULAR CARCINOMA IN HCV-INFECTED PATIENTS

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Background: Previous studies have suggested that hepatocellular carcinoma (HCC) has a more aggressive presentation and a lower survival in HIV-infected patients. However, the differences in survival found in older studies may be due to a later diagnosis or to lower rates of treatment against HCC, and not to a specific negative impact of HIV infection. Objective: To assess the impact of HIV infection on the survival of HCC in HCV-infected patients.

Methods: Multicenter cohort study (1999-2017). The GEHEP-002 cohort recruits all the HCC cases diagnosed in HIV-infected patients from 32 centers in Spain. For this study, 339 cases diagnosed in HIV/HCV-infected patients were selected. A control population of 118 HCC cases diagnosed in HCV-monoinfected patients during the study period at the Liver Unit from the Hospital de Valme was used. The survival after HCC diagnosis and its predictors, including HIV infection, were assessed.

Results: HCC was diagnosed by surveillance, considered when all scheduled ultrasound had been performed at least within 1 year prior to HCC diagnosis, in 192 (57%) and 73 (62%) HIV+ and HIV- patients, respectively (p=0.3). In spite of similar rates of HCC diagnosis by screening, cases diagnosed in HIV/HCV-coinfected patients were diagnosed at advanced stages. Barcelona-Clinic Liver-Cancer (BCLC) stage at diagnosis was: 0-A 133 (39.6%), B 28 (8.3%), C 118 (35.1%) and D 57 (17%) in HIV+ and 0-A 63 (53.4%), B 21 (17.8%), C 27 (22.9%) and D 7 (5.9%) in HIV- patients (p<0.001). 103 (77%) HIV/HCV-coinfected patients and 4 (70%) HCV-monoinfected patients diagnosed at BCLC stage 0-A underwent curative therapies (p=0.09). 334 (73.1%) patients died, 303 (91%) of them due to HCC. The probability of death at 1-year and 2-year was 53% and 65% in HIV+ and 35% and 57% in HIV- patients (p=0.13). In a Cox model adjusted by age, sex, alcohol consumption, HIV infection and previous SVR,

the independent predictors of mortality were BCLC stage at presentation, alfa-fetoprotein levels and lack of previous ultrasound surveillance. HIV infection did not show any trend for an independent association (HR 1.07; 95% CI: 0.74-1.54; p=0.7).

Conclusion: HIV coinfection has no impact on the survival after the diagnosis of HCC in HCV-infected patients. Although the mortality of HCC is somewhat higher in HIV/HCV-coinfected patients, these differences seem to be related with a later diagnosis of HCC in HIV-infected patients and not with HIV infection itself or a lower access to HCC therapy.

609 LOW PERFORMANCE OF ULTRASOUND SURVEILLANCE FOR THE DIAGNOSIS OF LIVER CANCER IN HIV

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Background: Surveillance of hepatocellular carcinoma (HCC) by hepatic ultrasound (US) every 6 months is recommended in HIV-infected patients with cirrhosis. However, there are no specific studies addressing the performance of such strategy in this population. As it has been reported that HCC could have a more aggressive course in the HIV-infected patient, the effectiveness of this surveillance policy needs to be specifically evaluated in the scenario of HIV infection. Objective: To assess the performance of US surveillance for the diagnosis of HCC in HIV-infected patients.

Methods: The GEHEP-002 cohort recruits HCC cases diagnosed in HIV-infected patients from 32 centers across Spain. The proportion of 'US lack of detection', defined as HCC diagnosed within the first 3 months after a normal surveillance US, and the proportion of 'surveillance failure', defined as cases in which surveillance failed to detect HCC at early stage (BCLC stage 0-A), were assessed. To assess the impact of HIV, a control population of 104 HCC cases diagnosed in HCV-monoinfected patients during the study period was used.

Results: 186 (54%) out of 346 HCC cases in HIV+ patients and 62 (60%) out of 104 cases from the control group were diagnosed within a US surveillance program. US lack of detection occurred in 16 (8.6%) of 186 HIV+ patients diagnosed by surveillance whereas this occurred in 5 (8.6%) in the control group (p=1.0). HCC cases after US lack of detection in HIV+ patients were more frequently at Child-Pugh stage C and had an advanced stage at diagnosis. The performance of US surveillance to achieve an early diagnosis of HCC was significantly lower for HIV+ patients. Thus, US surveillance failure occurred in 107 (57%) out of 186 cases diagnosed by screening in HIV+ patients whereas this occurred in 18 (29%) in the control group (p<0.0001). Similarly, US surveillance failed to detect HCC within Milan criteria in 104 (56%) out of 186 cases diagnosed by screening in HIV+ patients whereas this occurred in 18 (29%) in the control group (p< 0.0001). The probability of 1-year and 2-year survival after HCC diagnosis among those diagnosed by screening was 56% and 45% in HIV+ patients whereas it was 79% and 64% in HIV-negative patients (p=0.038).

Conclusion: The performance of US surveillance of HCC in HIV-infected patients is very poor and worse than that shown outside HIV infection. A HCC surveillance policy based on US examinations every 6 months might be insufficient in HIV-infected patients with cirrhosis.

610 INTRAHEPATIC HIV IS ASSOCIATED WITH ADVERSE LIVER OUTCOMES IN HIV-HBV COINFECTION

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Background: Individuals who are coinfected with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) have a 17 times increased risk of liver-related mortality than HBV mono-infected individuals. Given HIV can infect multiple cells in the liver including hepatocytes, Kupffer cells, stellate cells and intrahepatic T-cells, we hypothesized that the frequency of HIV-infected cells in the liver would be associated with HBV disease or liver-related clinical outcomes in a cohort of HIV-HBV coinfected individuals in Bangkok, Thailand.

Methods: Peripheral blood and matched liver biopsies were collected from 39 HIV and HBV coinfected participants prior to initiating antiretroviral therapy (ART). We measured cell-associated unspliced (US) HIV RNA and HIV DNA in CD4+ T-cells from blood and total liver biopsies and HBV covalently closed circular DNA (cccDNA) in liver biopsies by qPCR. Liver inflammation/damage was measured by transient elastography (TE). Lipopolysaccharide (LPS), CXCL10, and soluble CD14 (sCD14) were measured in plasma by ELISA and mRNA for CXCL10 and CXCR3 measured in liver biopsies by RT-qPCR.

Results: Participants were 90% male with a median age of 31.9 years and a median CD4 nadir of 320 (range 20-1197). All individuals were HBsAg+ and 64% were HBeAg+. HIV DNA and RNA were detected in liver biopsies in 63.2% and 44.7% of participants, respectively. There was a significant association between HIV DNA and RNA in liver (p<0.0001) and between liver and plasma HIV RNA (p=0.0320). There was no relationship between intrahepatic HIV and CD4 count. Intrahepatic HIV DNA was significantly associated with markers of liver disease, including AST (p=0.0250) and TE (p=0.0164), intrahepatic T-cell inflammatory markers CXCL10 (p=0.0165) and CXCR3 (p=0.0025), as well as sCD14 in plasma (p=0.0051). Intrahepatic HIV RNA was also significantly associated with CXCL10 (p=0.0061). There was a trend towards higher levels of cccDNA in individuals who had detectable intrahepatic HIV DNA. HIV DNA and RNA in circulating CD4+ T-cells were not associated with any liver or HBV related outcomes.

Conclusion: Prior to ART, HIV DNA and RNA are frequently detected in the liver and are associated with multiple clinical markers of liver disease in HIV-HBV coinfection. The cellular localisation of HIV DNA and RNA in the liver requires further investigation but we propose that this is not explained by trafficking T-cells given the absence of any associations between liver disease and HIV DNA and RNA in blood.

611 COMPARTMENTALIZATION OF NS3 AND NS5A RASS IN HIV/HCV GT 1A OR 4D INFECTED PATIENTS

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Background: Naturally occurring resistance-associated substitutions (RASs) in the NS3 and NS5a DAAs target regions are poorly investigated in the liver, the major site of HCV replication. We evaluated the RAS profile of NS3 and NS5a in liver and plasma of HIV/HCV coinfected patients (pts).

Methods: Twenty-one HIV/HCV coinfected pts naïve to anti-HCV treatment who performed liver biopsy for diagnostic purposes were included in the study. Fourteen pts harbored HCV genotype (GT)1a and 7 pts harbored GT4d. Median age was 41 years (inter quartile-range, IQR 38-43); 14 were males and 7 females; median alanine amino transferase (ALT) and aspartate amino transferase (AST) values were 66 IU/L (IQR 41-200, normal values < 59 IU/L), 65 IU/L, (IQR 49-137, normal values < 35 IU/L), respectively. CD4 cells count was 486 (IQR 443-614) HCV-RNA load was 5.6 Log IU/mL (IQR 5.5-6). The study was conducted in accordance with ethical principles stated in the Declaration of Helsinki and the patients gave written informed consent. NS3 and NS5a RASs profile was investigated by viral population sequencing in liver tissues and plasma, according to Lontok, 2015, Sarrazin, 2016 and Carrasco, 2018.

Results: RASs in the NS3 were detected in 9/21 (43%) coupled liver tissues and plasma samples. NS3 mutated strains in GT1a exhibited Q80K in plasma and liver. In GT4d infected pts, NS3 protease region resulted conserved in plasma and liver. The analysis of the NS5a domain showed RASs in 10/21 (47.6%) liver tissues and 6/21 (28.5%) corresponding plasma samples; in GT1a, 3/14 sequences from liver had RASs [M28R/Q30P/L31R in 1 pt, Q30R/L31R in one other pt, H58E in the remaining pt] while RASs were not revealed in the corresponding plasma. Interestingly, in GT4d 7/7 (100%) liver tissues and 6/7 plasma samples (85.7%) showed the amino acid substitution T58P at site of resistance.

Conclusion: We detected a different profile of RASs in the compartment explored concerning the NS3 and NS5a target region. So, in particular for GT1a the liver compartment could be responsible for the emergence of resistant variant not detected in the corresponding plasma sample by viral population analysis. This finding may have implication especially for GT1a patients with virological failure and absence of RASs in plasma sample at re-treatment.

612 SECOND HITS PROMOTE HEPATOCYTE DEATH AND LIVER INJURY IN HIV INFECTION

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Background: Liver disease became second cause of non-AIDS-related death in HIV-infected patients. Although immune and central nervous systems are well-characterized targets of HIV-infection, hepatocytes (Hep) were never considered as permissive cells for HIV. We hypothesize that "second hits" as HCV-co-infection or alcohol exposure make Hep HIV-permissive, facilitate apoptotic Hep death and promote liver inflammation and fibrosis development by activating non-parenchymal liver cells by apoptotic Hep engulfment.
Methods: Primary human hepatocytes or their experimental prototype, Huh7.5-CYP (RLW) cells were infected with HIV-1 ADA and then either exposed to HCV (co-infection model) or to ethanol (HIV+ ethanol model). HIVgag RNA was measured in these cells by RT-PCR and reverse transcriptase (RT) activity as evidence of HIV replication was determined in cell supernatants. As apoptotic cell death indication, we used cleaved caspase 3 (Western Blot) and M30 (ELISA). After engulfment of hepatic apoptotic bodies (AB) by monocyte-derived macrophages (MDM) and hepatic stellate cells (HSC, LX2 cell line) inflammasome activation and pro-fibrotic markers were quantified by RT-PCR.
Results: We observed that both HCV co-infection and co-treatment with ethanol substantially increased HIV gag RNA in hepatocytes and RT in cell supernatants. This increase was associated with enhanced HIV replication inside of cells since the removal of surface structures by low acid wash did not decrease HIV RNA levels triggered by HCV or ethanol exposure. Both insults push HIV-infected Hep to apoptosis prevented by co-treatment with pan-caspase inhibitor. Furthermore, apoptosis was attenuated by AZT, suggesting that it is initiated by HIV replication. AB generated from HIV-infected Hep spread the virus to intact MDM. Engulfment of HIV+ AB Hep activated inflammasome (based on NLRP3, caspase 1, IL-1 β and IL-18 expression) in MDM and pro-fibrotic markers (Col1A1, TGFβ and prostaglandin D receptor 2) in HSC. Activation of fibrotic changes in HSC was AB Hep -specific since engulfment of AB from HIV+ lymphocytes induced pro-inflammatory, but not pro-fibrotic events
Conclusion: We conclude that second hits, like co-infection with HCV and co-treatment with ethanol increase permissiveness of hepatocytes to HIV-infection and trigger their apoptosis, thereby initiating the cross-talk between hepatocytes, macrophages and stellate cells to promote liver inflammation and fibrosis progression.

613 INFLAMMATORY CHEMOKINES LINKED TO HIV GENETIC DIVERSITY DURING HIV/HBV COINFECTION

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Background: HIV-hepatitis B virus (HBV) co-infected individuals experience higher rates of liver disease than mono-infected individuals. Previous studies have found that HIV co-infection can impact the natural course of HBV infection, but the reverse has not been confirmed. We aimed to determine the frequency of intact provirus in HIV-HBV co-infected individuals prior to ART initiation and whether this frequency was associated with any clinical parameters.
Methods: HIV-HBV co-infected individuals and HIV mono-infected individuals naïve to ART were recruited in Bangkok Thailand as part of a prospective observational cohort study. HIV proviruses were sequenced from peripheral blood CD4+ T-cells using full-length individual proviral sequencing (FLIPS). Primers were adapted for specificity to HIV subtype AE and single near full-length HIV proviruses (92% of the genome) were sequenced using Next Generation Sequencing. Genetically intact HIV proviruses were identified as those lacking inversions, stop codons/hypermutation, insertions, deletions or frameshifts.
Results: A total of 522 HIV proviruses were sequenced and analysed from 17 HIV-HBV co-infected individuals, and 165 proviruses from 4 HIV mono-infected individuals; both cohorts being naïve to ART. Both the co-infected and mono-infected individuals had a similar and high proportion of genetically intact provirus (range = 7-66% and 23-59% respectively). Intact sequences from these cohorts had genetic diversity ranging 0.2-2% and 0.3-1.6% for the co-infected and mono-infected cohorts respectively. The mean diversity of genetically-intact provirus was lower in the mono-infected (0.7%) than the co-infected cohort (1.0%), but this did not reach significance (p=0.28). No correlation was found between HBV infection parameters (HBV DNA, HBsAg, and ALT levels, HBeAg status) and the proportion of genetically intact HIV proviruses or their genetic diversity in the co-infected individuals. However, higher levels of the inflammatory chemokines CCL2 in the blood and CXCL10 in the liver were associated with increases in overall genetic diversity of HIV (p=0.028 and p=0.0016).
Conclusion: Genetically unique and intact HIV proviral sequences were commonly identified in untreated HIV-HBV co-infected and HIV mono-infected participants. The frequency of intact virus was far higher than previous studies of individuals on suppressive ART. Inflammatory chemokines were associated with the genetic diversity of HIV proviruses in HIV-HBV co-infected participants.

614 INFLUENCE OF HCV INFECTION ON HIV-1 SPLICING IN CHRONICALLY COINFECTED PATIENTS

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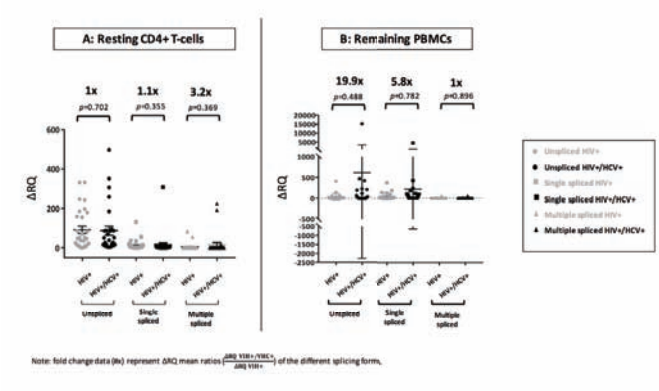
Background: HIV/HCV coinfection influences HIV-1 reservoir size. We previously observed a higher quantity of HIV-1 proviral DNA in coinfected patients regarding to HIV-monoinfected individuals. However, it is unknown whether this coinfection may also induce a higher proviral transcription, thereby increasing the viral load and influencing in the reservoir size. We assess if HCV coinfection influences HIV-1 proviral transcription and splicing forms in isolated, resting CD4+ (rCD4) T cells and the remaining non-resting PBMCs.
Methods: Cross-sectional study: 29 (49.1%) HIV-1/HCV coinfected subjects and 28 (50.9%) HIV-1 patients. PBMCs were obtained from 50 ml of peripheral blood and rCD4 T-cells were isolated (CD4+CD25-HLADR-CD69-). Total RNA was extracted from rCD4+ cells and the remaining non-resting PBMCs, and then analyzed by qPCR to measure the unspliced (~9kb), single spliced (~4kb) and multiple spliced (~2kb) transcripts. Linear correlations between viral reservoir size and viral splicing were also determined.
Results: An increase in HIV-1 reservoir size was observed in HIV+/HCV+ patients regarding to the HIV+ group [84.9 (48.3-154.2) vs. 28.5 (8.5-97.7) proviral DNA copies/10^6 rCD4 cells, respectively (p=0,003)]. Analysis of HIV-1 alternative slicing showed 3.2-fold increase of multiple spliced transcripts in HIV/HCV patients (ΔRQ=13.6 vs 4.3; p>0.05). Not significant increase in unspliced and single spliced forms (19.9- and 5.8-fold, respectively) was also observed in the remaining non-resting from HIV+/HCV+ subjects (Fig1). A significant positive correlation in HIV+/HCV+ individuals was identified between HIV reservoir size and some viral spliced forms.
Conclusion: Splicing of HIV transcripts is necessary for viral transcription. We previously observed that coinfection of HCV and HIV influences HIV reservoir size. Now we found that rCD4 cells isolated from HIV/HCV patients showed an increase of multiple spliced transcripts, suggesting that HIV-1 regulator Tat could be more active in these cells, yielding a higher number of viral particles and increasing the reservoir size. Moreover, coinfection with HCV could enhance HIV proviral transcription and splicing due to an interaction between HCV proteins and the cellular splicing machinery. The positive correlation between reservoir size and some viral splicing forms may support this hypothesis. This

may indicate that the elimination of HIV-1 reservoir in HIV+/HCV+ subjects might be even harder than in HIV+ patients.



615 PREVALENCE OF FATTY LIVER DISEASE IN INDIVIDUALS WITH AND WITHOUT HIV INFECTION

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Background: Fatty liver disease (FLD) is a growing cause of chronic liver disease. People living with HIV (PLWH) may be at a higher risk of FLD due to life style and antiretroviral medication. Here we assessed the prevalence of FLD in PLWH and matched HIV uninfected controls by unenhanced CT liver scan. Further, factors associated with hepatic steatosis were assessed and the effect of HIV per se evaluated.

Methods: PLWH (n=765) aged 40 years and above were recruited from the Copenhagen Co-morbidity (COCOMO) in HIV Infection study. Uninfected controls (n=1192), matched on gender and 5-years age strata, were recruited from the Copenhagen General Population Study (CGPS). Unenhanced CT liver scan was performed on all participants and liver attenuation measured. We defined FLD as a liver attenuation ≤ 48 Hounsfield Units (HU) equivalent with moderate to severe steatosis. Unadjusted and adjusted logistic regression analyses were performed. Sensitivity analyses were performed with exclusion of individuals with excessive alcohol intake (def.: 20 g/wk for females and 30 g/wk for males) and significant liver fibrosis (def.: Fibroscan ≥ 12kPa).

Results: Of PLWH, FLD was detected in 8.5 % compared to 17.4% of uninfected controls. After adjustment, 1 unit increase in BMI or waist circumference was associated with FLD in PLWH (OR (95% CI): 1.22 (1.03;1.45)) and 1.08 (1.01;1.14)) and (OR (95% CI): 1.12 (1.01;1.24) and 1.12 (1.08;1.17)) in uninfected controls. In PLWH, male sex was associated with FLD (OR (95% CI): 7.93 (1.01;61.97). A 1 unit increase in triglycerides was associated with FLD in uninfected controls (OR (95% CI):1.44 (1.24;1.69)), while there was no association for PLWH. HIV was significantly associated with lower odds of FLD (OR (95% CI): 0.30 (0.19;0.49)) and the association persisted after further adjustments for e.g. current antiretroviral treatment, lipids, use of statin, injection drug use and ethnicity. Sensitivity analyses did not change these results.

Conclusion: The prevalence of FLD was lower in well-treated PLWH compared to age and sex matched HIV uninfected controls. HIV per se was associated with lower odds of FLD. Higher BMI and waist circumference were associated with higher odds of FLD in both cohorts. These results may be explained by a more healthy lifestyle in PLWH or unmeasured residual confounding.

Table 1. Liver steatosis in PLWH and uninfected controls

	COCOMO (n=765)	CGPS (n=1192)	Total (n=1957)	p-value
No-mild steatosis, n (%)	700 (91.5)	985 (82.6)	1685 (86.1)	<0.001
Moderate-severe steatosis, n (%)	65 (8.5)	207 (17.4)	272 (13.9)	
Liver attenuation (HU), median [iqr]	61.1 [56.4, 65.6]	60.3 [51.8, 65.3]	60.6 [53.9, 65.5]	<0.001
Liver attenuation quartiles (HU), n (%)				<0.001
Q1 (0.90 – 53.90)	139 (18.2)	356 (29.9)	495 (25.3)	
Q2 (53.91 – 60.60)	225 (29.4)	267 (22.4)	492 (25.1)	
Q3 (60.61 – 65.50)	205 (26.8)	282 (23.7)	487 (24.9)	
Q4 (65.50 – 91.10)	196 (25.6)	287 (24.1)	483 (24.7)	

616 LIVER INFLAMMATION IS COMMON AND LINKED TO METABOLIC DERANGEMENTS IN TREATED HIV

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Background: Abnormal serum liver enzymes in people with HIV (PWH) are common and often unexplained. We sought to identify the prevalence of and underlying reasons for aspartate and alanine aminotransferase (AST and ALT) elevation in a well-characterized cohort of adults with treated HIV without hepatitis C or B virus (HCV or HBV) infection or heavy alcohol use.

Methods: Participants from the longitudinal observational AIDS Clinical Trials Group HAILO cohort who did not report heavy alcohol use, were negative for anti-HCV and hepatitis B surface antigen, and with at least 2 AST and ALT measures between 11/2013–2/2018 were included. Clinical and demographic characteristics, including the Hepatic Steatosis Index (HSI = 8x(ALT/AST)+BMI (+2 female, +2 diabetes)), FIB-4 score and metabolic syndrome (MetS) were compared between persons with and without ≥1 elevated AST or ALT (defined as AST >36 and ALT >30 U/L for men and AST >30 and ALT >19 U/L for women), using chi-square and Wilcoxon tests and multiple logistic regression models. Covariates with p<0.10 in univariate analysis were included in the multivariable models.

Results: Of 1035 participants, 662 met criteria for inclusion; 456 (69%) had ≥ 1 and 236 (36%) ≥ 2 elevated AST/ALT during a median of 4.0 years of follow-up. Median age at entry was 51 years; 138 (21%) female; 184 (28%) black and 122 (18%) Hispanic; median entry and nadir CD4 cell counts/mm^3 (CD4) 621 and 195, respectively; and 627 (95%) had plasma HIV RNA <200 copies/mL at entry. In univariate analysis, the elevated liver enzyme group was younger, had a higher proportion of Hispanic and female participants, higher entry CD4 without differences in nadir CD4, higher HSI score, and a higher proportion with MetS and HSI ≥ 36 (p<0.05 for all). There were no differences in the proportions with HIV RNA suppression or antiretroviral use (current or previous); FIB-4 score was similar in each group. The Table summarizes the results from multiple logistic regression models.

Conclusion: After exclusion of HCV, HBV and alcohol, liver enzyme elevation was remarkably common in this cohort and independently associated with metabolic disease, presence of hepatic steatosis by HSI, Hispanic ethnicity, and lower CD4 at entry. These findings suggest that NAFLD may be a common cause of liver inflammation in PWH receiving suppressive antiretroviral therapy (ART). Further research is needed to understand the contribution of NAFLD and other mechanisms of liver injury in PWH on suppressive ART.

Table: Unadjusted and adjusted odds ratios and 95 percent confidence intervals for the association between demographic and clinical characteristics and elevated ALT/AST

Variables		Univariate Odds Ratio (95% CI)	P-value	Model 1* Odds Ratio (95% CI)	P-value	Model 2* Odds Ratio (95% CI)	P-value
Sex	F vs M	1.57 (1.02,2.41)	0.04	1.3 (0.81,2.08)	0.27	1.53 (0.97,2.41)	0.07
Race/Ethnicity	Hispanic+Other vs Black	1.83 (1.1,3.04)	0.02	1.95 (1.15,3.31)	0.01	1.97 (1.17,3.33)	0.01
	White vs Black	1.01 (0.69,1.47)	>0.90	1.17 (0.77,1.76)	0.46	1.08 (0.72,1.62)	0.71
Age at study entry	Every 10 years older	0.81 (0.65,1)	0.05	0.89 (0.71,1.12)	0.33	0.82 (0.65,1.02)	0.07
CD4 cells/mm^3 nadir	<200 vs ≥200	0.95 (0.68,1.32)	0.75				
CD4 cells/mm^3 at entry	<500 vs ≥500	0.66 (0.47,0.94)	0.02	0.67 (0.46,0.97)	0.03	0.66 (0.46,0.94)	0.02
CD4 cells/mm^3 at entry	Every 50 cells increase	1.03 (1,1.06)	0.02				
Plasma HIV RNA copies at entry	≥200 vs <200	1.14 (0.54,2.41)	0.74				
Current use of PI at entry	Yes vs No	1.21 (0.86,1.71)	0.28				
Current use of INSTI at entry	Yes vs No	0.83 (0.56,1.24)	0.36				
Ever use of PI on or before entry	Yes vs No	1.36 (0.97,1.92)	0.08	1.35 (0.94,1.92)	0.1	1.4 (0.99,1.98)	0.06
Current use of any lipid lowering therapy at entry	Yes vs No	1.56 (1.07,2.27)	0.02				
Metabolic Syndrome at entry	Yes vs No	1.54 (1.07,2.21)	0.02			1.47 (1.01,2.13)	0.04
Hepatic Steatosis Index	Every 1 index score increase	1.08 (1.05,1.11)	<0.001	1.07 (1.04,1.1)	<0.001		
Hepatic Steatosis Index	≥30 vs <30	2.9 (1.8,4.67)	<0.001				
Hepatic Steatosis Index	≥36 vs <36	2.91 (2.07,4.08)	<0.001				
FIB-4	Every 1 score increase	0.96 (0.77,1.21)	0.74				
FIB-4	≥1.45 vs <1.45	0.92 (0.63,1.36)	0.69				
FIB-4	>3.25 vs ≤3.25	3.2 (0.39,26.13)	0.28				

*Model 1 is a multivariable model that includes Hepatic Steatosis Index, while Model 2 is a multivariable model that instead includes metabolic syndrome.

617 FENTANYL USE AND LIVER DISEASE IN THE MIAMI ADULT STUDIES ON HIV (MASH) COHORT

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Background: Human immunodeficiency virus (HIV) infection continues to be associated with liver disease, one of the major causes of morbidity and mortality in these patients. Substance abuse decreases adherence to antiretroviral therapy and increases risk for liver injury. Fentanyl is a synthetic opioid clinically used in anesthesia and management of chronic pain, recently mixed with heroin and cocaine, and ingested unintentionally. Fentanyl overdose leads to respiratory depression, brain damage and death; its effect on liver is not known.
Methods: Participants from the Miami Adult Studies on HIV (MASH) cohort were tested for fentanyl using BNTX Rapid Response TM fentanyl urine strip tests at a detection level of 40 ng/ml norfentanyl. Cocaine and heroin use were determined with questionnaires and confirmed with urine toxicology. Alcohol consumption was determined with Alcohol Use Disorders Identification Test (AUDIT). HIV infection, lack of hepatitis B and C coinfections, CD4 count and HIV viral load were documented from medical charts. FIB-4, a non-invasive measure of liver fibrosis, was calculated, and FIB-4 value of >1.45 was used as the cutoff to determine presence or absence of meaningful (moderate-severe) hepatic fibrosis. Statistical analyses included descriptive statistics and logistic regression performed with SAS 9.4. Models were adjusted for age, gender, BMI, AUDIT score>8, and HIV infection.
Results: Data were analyzed on a subsample of MASH cohort participants who were HIV infected (N=305, CD4 count mean 610.21cells/μL±362.06 SD, mean HIV viral load =2.58 $\log_{10}$±1.24 SD) or HIV uninfected (N=267). Mean age was 54.05years±8.28 SD; 60.03% were males, 62.16% Black and 22.93% Hispanic. Logistic regression indicated a significant association between the use of fentanyl and liver fibrosis (FIB-4>1.45), adjusted OR= 5.195 (95% CI 2.051,13.159, p=0.0005). When participants who were frequent users of cocaine and heroin were removed from the analyses, fentanyl continued to be associated with liver fibrosis (FIB-4>1.45), adjusted OR=4.76 (95% CI 1.67-13.56, P=0.0035). In addition, HIV infection status was significantly associated with FIB-4>1.45, adjusted OR=2.25 (95% CI 1.27-3.98, P=0.0056).
Conclusion: These data indicate that misuse of fentanyl among substance users in the MASH cohort may be associated with development of hepatic fibrosis. Strategies to identify risk and understanding of aberrant drug-related behaviors and treatments are needed.

618 THE SYNTHETIC OPIOID FENTANYL ENHANCES VIRAL REPLICATION IN VITRO

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Background: The US is in the midst of a major drug epidemic fueled in large part by the widespread recreational use of synthetic opioids such as fentanyl. Unfortunately, medications approved for the treatment of opioid use disorders (OUD) are underutilized and/or not offered in many settings. Thus, persons with OUD are at significant risk for transmission of the human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Moreover, commonly abused substances can antagonize immune responses and promote viral replication. However, the impact of synthetic opioids on virus replication has never been explored.
Methods: We evaluated the impact of fentanyl using in vitro systems that replicate infectious viruses. Fentanyl was available as a highly purified analytical reference standard and used at concentrations of 1 ng, 100 ng, and 10 ug. Viral protein synthesis was quantified by ELISA, while apoptosis and cell death were measured by M30 or MTT assays, respectively. HCV replicative fitness was evaluated in a luciferase-based system. RNAseq was conducted to evaluate cellular gene regulation in the presence of fentanyl.
Results: Low dose fentanyl had no impact on HCV replication in Huh7.5 JFH1 hepatocytes; however, higher doses significantly enhanced HCV replication. In the HepG2.2.15 hepatocyte cell line, fentanyl caused a dose-dependent increase in HBV replication, although the same low dose that caused increased HCV replication had a minimal effect on HBV. A dose-dependent increase in HCV replicative fitness was observed in the presence of fentanyl. Similarly, fentanyl increased HIV replication in two lymphocyte cell lines. Addition of fentanyl resulted in significant accumulation of soluble caspase-cleaved keratin 18 – a product of apoptosis – in two hepatocyte cell lines. Cell death was minimal at low drug concentrations. RNAseq identified a number of hepatocyte genes that were up or down regulated after fentanyl exposure including those related to apoptosis, viral gene expression, hepatocarcinogenesis, and NFKB.
Conclusion: Collectively, these preliminary data suggest that synthetic opioids promote viral replication but may have distinct effects depending on the drug dose and the viral target. As higher viral loads are associated with pathogenesis and virus transmission, additional research is essential to an enhanced understanding of opioid-virus pathogenesis and for the development of new and optimized treatment strategies.

619 A DECISION-TREE ANALYSIS FOR HEPATITIS A IMMUNITY AMONG HIV-INFECTED MSM IN TOKYO

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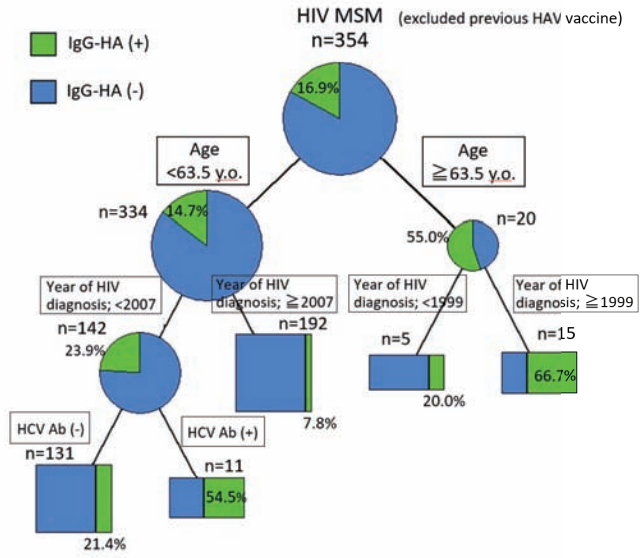
Background: Japan has very low endemicity for hepatitis A virus (HAV), and the prevalence of anti-HAV among general population aged < 50 years is < 5 %. However, the level of HAV immunity among HIV-infected patients in Japan is unknown. The epidemiology of HAV infection among HIV-infected men who have sex with men (MSM) is essential for an HAV vaccination program.
Methods: We examined the presence of IgG-HA antibody among HIV-infected patients from January 2017 to December 2017 in IMSUT Hospital, the University of Tokyo. Epidemiological data, including age, sex, mode of HIV transmission, year of HIV diagnosis, HAV vaccine status, previous HAV infection and other infectious disease status (hepatitis B, hepatis C and syphilis), were recorded. A decision tree algorithm (data-mining technique) was used to reveal factors and profiles most relevant to the prevalence of anti-HAV for further investigation.
Results: In total 468 HIV-infected patients were examined for the presence of IgG-HA antibody. Of these, 459 patients (male, 438; female; 21) had both HAV vaccine status and previous HAV infection. The mode of HIV transmission among male patients were as follows: MSM, 378; heterosexual, 47; contaminated blood (hemophilia), 4; unknown, 9. After excluding 24 MSM patients who were receiving HAV vaccine, data from 354 MSM patients were used for analysis (median age, 45 years. IQR, 39-51). Of 354 MSM patients, 60 (16.9 %) were IgG-HA antibody positive. Median age was significantly higher in the HA positive group than in the negative group (50 vs. 44 years; P< 0.001). The prevalences of hepatitis B core antibody and treponemal antibody were significantly higher in the HA positive group than in the negative group (71.7% vs. 57.1%; P=0.037 and 75.0% vs. 57.8%; P=0.013, respectively). Patient age > 63.5 years was the first variable in the initial classification of the decision-tree algorithm, and year of HIV diagnosis was the second-division variable for HAV immunity (Figure).

Conclusion: Our study, conducted just before HAV outbreak among MSM in Tokyo, showed that age and year of HIV diagnosis were the most relevant factors in the prevalence of anti-HAV. It is partly because there have hardly been HAV outbreak among younger people in Japan. IgG-HA antibody was present in 16.9% of the study population, which is far below the 60-70% immunity threshold necessary to prevent sustained transmission, suggesting that an extensive HAV vaccination program particularly for younger people is urgently needed.

Figure. Decision-tree algorithm for HAV immunity



620 LOW IMMUNE RESPONSE RATE OF HIV-POSITIVE PATIENTS TO SINGLE INJECTION OF HAV VACCINE

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Background: During the year 2017, a hepatitis A (HAV) outbreak occurred among men having sex with men (MSM) in France. Concomitantly, a shortage of HAV vaccines has led to the national recommendations of a single injection of HAV vaccine. Nevertheless, HIV-positive patients' vaccine response can be inferior to general population. This study aimed to evaluate the immune response of HIV-1 positive MSM patients to a single injection of HAV vaccine in this context.
Methods: We enrolled in this observational single center study all HIV-1 positive patients who had been vaccinated by a single injection of HAV vaccine in 2017. HAV serology was performed on a serum sample before and >30 days after the vaccine injection, using the routine system Architect® (Abbott) by chemiluminescent microparticulate immunoassays. Response to vaccine was defined by a ratio (signal of the sample/signal of the threshold value) ≥2. To compare responders and non-responders' characteristics, Student (continuous variables) or Chi 2 (categories) tests for univariate and logistic regression for multivariate statistical analyses were performed.
Results: In 2017, 73 patients mainly MSM (93.2%) with a median age of 49.4 years (IQR 36.0-57.1) received a single injection of HAV vaccine. HIV-1 viral load was ≤20 copies/mL in 83,6 % of the cases (93,2% ≤50 copies/mL). Patients were diagnosed for HIV since 14.9 years in median (IQR 7.4-27.6) and 16,4% of them were classified in the CDC stage C. Median CD4 and nadir CD4 cell counts were 658 (IQR 465-838) and 270/mm3 (IQR 93-381), respectively. Median ratio of T CD4/CD8 cells was 0,9 (IQR 0,56-1,21). One patient had already a positive HAV serology before the vaccine injection. The rate of immune response was 59.7% (n=43/72) after a median time of 106 days (IQR 68-171) between the vaccine injection and the collection of sample. The median response ratio was 7.97 (IQR 3.47-9.56). Non responders had significantly a lower T CD4/CD8 cells ratio than responders in univariate and multivariate analyses ($p<0.05$).
Conclusion: A low immune response rate was observed after a single injection of HAV vaccine among HIV-positive patients. A Low T CD4/CD8 cells ratio was a risk factor of non response. In a context of vaccine shortage, a serologic control of response to HAV vaccination should be recommended in this population to ensure their protection.

621 LOSS OF HEPATITIS A VIRUS SEROPROTECTION IN PERSONS LIVING WITH HIV

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Background: The Michigan hepatitis A virus (HAV) outbreak, which began in August 2016, persists today with 895 cases. A possible emerging issue has been identified during an ongoing outbreak of HAV in Michigan: loss of HAV seroprotection among patients co-infected with HIV. Immune responses to most vaccines are known to be impaired in HIV patients. Retrospective analyses of HIV infected patients who received HAV vaccination has shown that 90% of HIV patients remained seropositive at 3 years and 85% 6–10 years. No data exist on whether this decay is clinically meaningful. During the Michigan Hepatitis A outbreak, 26 outbreak cases were co-infected with HIV and HAV. 4 patients had received pre-exposure HepA vaccination, and 2 cases had positive HAV antibody test results upon entry into care for HIV without history of vaccination. These early findings are concerning for loss of seroprotection in persons living with HIV who may be susceptible and at risk of acquiring HAV infection. Here we describe a cohort of patients who have lost seroprotection against HAV at the University of Michigan HIV clinic.
Methods: The HIV Clinic at the University of Michigan began repeating HAV Ab screening for those patients who have not not been performed during the previous 5 years. We collected baseline demographics for those patients who seroreverted from a positive to negative HAV total Antibody.
Results: The Mean age at Time of Vaccination for seroreverters was 40 ± 5 years old. The proportion of patients with an undetectable viral load at the time of initial vaccination was 0.50. The mean viral load at the time of vaccination was $27{,}500 \pm 7{,}382$. All seroreverters had an undetectable viral load at the time of serorevertion. The Proportion of Seroreverters with history of AIDS defining Illness was 0.5. The mean time to repeat Serology was 11.37 ± 2.28 yrs.
Conclusion: Patients living with HIV previously vaccinated against HAV may be susceptible and at risk of acquiring HAV infection. Repeat screening HAV total Antibody can indentify those patients susceptible to HAV infection who would benefit from repeat vaccination.

622 HBV REVACCINATION AMONG HIV-POSITIVE MSM RECEIVING HAART: A RANDOMIZED CLINICAL TRIAL

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Background: The universal neonatal vaccination program against hepatitis B virus (HBV) in Taiwan has significantly reduced the HBV seroprevalence in general population and HIV-positive individuals. Optimal strategy of revaccination remains unknown among HIV-positive men who have sex with men (MSM) whose immunity against HBV have waned after neonatal vaccination. In this randomized controlled trial, we aimed to investigate the efficacy of HBV revaccination with standard- (20-µg) or double-dose (40-µg) of HBV vaccine among HIV-positive MSM.
Methods: HIV-positive MSM who were born after 1 July, 1986, have been receiving antiretroviral therapy, and tested negative for HBsAg and anti-HBc with anti-HBs titer <10 mIU/ml were eligible for revaccination. Subjects who were aged <20 years, allergic to the vaccine (Engerix-B®), and receiving chemotherapy, steroids, and immunosuppressants within 30 days prior to screening were excluded. Participants were randomized to receive standard- or double-dose HBV vaccine (1:1 ratio with the block size of 4 after stratification by CD4 count). HBV vaccine was administered at weeks 0, 4, and 24. Adverse events were recorded for 7 days after each injection and serological responses were assessed at weeks 4, 24, and 28.
Results: From September 2017 to August 2018, 67 HIV-positive MSM were enrolled with 35 in standard-dose arm and 32 in double-dose arm (Table). The serological response after revaccination was 93.3% for the standard-dose group

and 94.1% the double-dose group (p>0.999). The proportions of serological response (anti-HBs ≥10 mIU/ml) and high-titer responses (anti-HBs >100 mIU/ml) at weeks 4, 24, and 28 were not statistically significant between the two arms. All participants with baseline anti-HBs titer higher ≥1 mIU/ml achieved high-titer response after revaccination, regardless of the assigned regimen. In multivariate analysis, double-dose revaccination (adjusted odds ratio [aOR], 6.2; 95% CI, 1.6-24.8) and baseline anti-HBs titer ≥ 1mIU/ml (aOR, 12.5; 95% CI, 3.1-49.7) were associated with high-titer responses after the first dose of revaccination.

Conclusion: Revaccination with standard- or double-dose HBV vaccine results in similarly high serological response rates among HIV-positive patients receiving HAART. Patients with baseline anti-HBs titer ≥1 mIU/ml and undergoing double-dose vaccination achieved high-titer responses after after the first dose of HBV revaccination.

		Standard dose (n=35)	Double dose (n=32)	p-value
Baseline characteristics (at screening)				
Age, mean (SD), y		27.5 (2.4)	27.7 (2.5)	0.777
CD4 count, median (IQR), cells/mm^3		639 (537-743)	635 (580-819)	0.671
PVL <20 copies/µl, n (%)		31 (88.6)	27 (84.4)	0.727
Anti-HBs titer at baseline, ≥1.0 mIU/ml, n (%)		18 (51.4)	15 (46.9)	0.808
Syphilis, n (%)		12 (34.3)	13 (40.6)	0.622
Anti-HCV-positive, n (%)		1 (2.9)	2 (6.3)	0.603
Serological response after each dose				
Week 4	GMT (mIU/ml)	21.3	76.8	0.056
	Responder, n (%)	24 (68.6)	23 (71.9)	0.796
	High-titer responder	14 (40.0)	21 (65.6)	0.051
Week 24	GMT (mIU/ml)	33.7	178.5	0.003
	Responder, n (%)	15 (71.4)	17 (85.0)	0.454
	High-titer responder	8 (38.1)	13 (65.0)	0.121
Week 28	GMT (mIU/ml)	191.1	451.6	0.058
	Responder, n (%)	14 (93.3)	16 (94.1)	>0.999
	High-titer responder	11 (73.3)	13 (76.5)	>0.999

623 THE GLOBAL DISTRIBUTION OF HEPATITIS B VIRUS VACCINE ESCAPE MUTATIONS

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Background: Hepatitis B virus (HBV) infects over 250 million people and is the leading cause of hepatitis and hepatocellular carcinoma worldwide. Vaccination is effective at preventing infection, although vaccination rates are not optimal, and mutations within the 'a' determinant region of the HBV surface antigen (HBsAg) are associated with vaccine escape. The emergence of escape mutants raises concern of HBV infection in previously vaccinated individuals, particularly in the developing world where such mutations may be relatively common.

Methods: We evaluated the frequency, genotype, and global distribution of known escape mutations in 4,244 unique full-length HBV genomes from genotypes A to I. The 'a' determinant of the Surface gene (amino acids 124 to 147) was extracted using AliView and inspected for polymorphisms at previously identified vaccine escape mutations including T116, P120, T126, Q129, M133, P134, K141, P142, D144, or G145. Sequences were also evaluated in Geno2Pheno to confirm the genotype and the presence of polymorphisms.

Results: 268 (6.3%) sequences from 36 countries contained a polymorphism at a vaccine escape site. In genotype A, the most common mutation occurred at M133. In genotype B, Q129 and M133 occurred 45 and 51 times, respectively, accounting for 94% of mutations. Mutations at G145 were most frequent in genotype C, while P120 was most common in genotype D. Amongst all genotypes, mutations at M133 were the most common and accounted for 29.5% of escape mutations. Mutations at T116, P120, F134, K141, and P142 occurred across geographically diverse locations, whereas mutations at Q129, M133, D144, and G145 were concentrated in East Asia. The most prevalent mutation in the Middle East and North Africa was at position P120, whereas M133 was most prevalent in North America and Europe. Q129 accounted for 3 of 7 mutations in India, D144 for 4 of 18 mutations in Africa, and M133 for 4 of 15 mutations in South and Central America.

Conclusion: While the sample size is large, our approach relied on sequences that were previously uploaded to GenBank. Non-random, convenience sampling was often conducted, and many countries have no data available, thus highlighting the need for systematic and unbiased surveillance of vaccine escape mutations in more countries. Nonetheless, the prevalence of polymorphisms at sites associated with vaccine escape is high and may compromise efforts to control HBV infection.

624 HEPATITIS B CURE IN HIV PATIENTS IS MORE LIKELY IN HISPANICS AND THOSE WITH AIDS

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Background: Nucleoside analogues are thought to resolve chronic hepatitis B virus (HBV) very infrequently in most settings, especially in HIV. We examined a longitudinal cohort of HIV/HBV on combined ART (cART) to determine clinical predictors of HBV cure.

Methods: We retrospectively abstracted data of HIV and HBsAg+ patients obtaining care from 2005 -2018. Those without chronic HBV were excluded. Baseline characteristics obtained included demographics, insurance, HIV risk factors, CD4 cell count, HBV DNA, HIV RNA, Hepatitis B eAg, and liver function tests (LFT). Those who achieved HBsAg loss during follow-up were compared to those who did not. Predictors of HBsAg loss were examined using logistic regression analysis.

Results: Among 365 with HIV and HBsAg+ co-infection, 303 had sufficient data to classify as chronic HBV (87% were male, 58% Black, 24% White, and 14% Hispanic, 59% were HBeAg+). At baseline, median CD4 was 234 cells/mL, 45% had AIDS, and median log HIV RNA among those non-suppressed (ns) was 4.88 copies/mL, 22% had suppressed HIV RNA. First measured HBV DNA was suppressed in 28%, median log HBV DNA was 6.98 copies/mL among ns patients. Among those who suppressed HBV DNA, median time to suppression was 8.87 months. Among the 38 (12.54%) with HBsAg loss, differences were seen by race, baseline CD4 count, proportion with AIDS, HBeAg+, and time to HBV DNA suppression (see Table 1). Compared to Whites, Hispanics were more likely to have HBsAg loss (AOR 4.27, 95% CI 1.20, 15.18, p=0.03) and those with AIDS (AOR 3.57, 95% CI 1.50, 8.54, p=0.004). Every month without HBV DNA suppression decreased likelihood of HBsAg loss (AOR 0.97, 95% CI: 0.95, 0.99, p=0.03). Median change in CD4 count [cells/mL (IQR)] was higher in those HBsAg loss vs. not [204(98, 436) vs. 106 (-12, 265), p=0.004]. No differences were seen with regard to LFTs, gender, insurance, HIV risk factor, age, or HIV RNA.

Conclusion: HBsAg loss occurred in a surprisingly high percentage (12.54%) of HIV+ patients, more frequently in Hispanics and in those with AIDS. Longer time to HBV DNA suppression was associated with decreased likelihood to HBsAg loss. We hypothesize that HBV immune restoration is associated with HBsAg loss as a higher change in CD4 count occurred in those with HBsAg loss. Chronic hepatitis B can resolve in those with HIV, especially among those with AIDS, if effective HBV active cART is initiated leading to increase in CD4 and effective HBV viral suppression.

Table 1	HBSAg persistence	HBSAg Loss	P value	OR (95% CI), p value	AOR (95% CI), p value
Race					
White	67 (25)	5 (13)		Reference	Reference
Black	156 (59)	20 (51)		1.72 (0.62, 4.77), 0.3	1.35 (0.44, 4.20), 0.6
Hispanic	29 (11)	12 (31)		5.54 (1.79, 17.17), 0.003	4.27 (1.20, 15.18), 0.03
Other	12 (5)	2 (5)	0.006	2.23 (0.38, 12.86), 0.37	1.4 (0.21, 9.39),0.73
Median baseline CD4 c/mL (IQR)	248 (68- 450)	119 (24- 320)	0.047	0.99 (0.99, 1.00), 0.13	
AIDS	113 (43)	24 (62)	0.028	2.13 (1.07- 4.26, 0.03)	3.57 (1.50- 8.54), 0.004
Median log HIV RNA, ns (IQR)	4.84 (4.03- 5.40)	5.15 (4.30- 5.88)	0.034	1.4 (0.95, 2.07), 0.08	
HBeAg+	143 (64)	11 (13)	<.0001	0.26 (0.12- 0.56), 0.001	0.52 (0.19- 1.40), 0.2
Median log HBV DNA, ns (IQR)	7.25 (4.39- 7.25)	4.61 (3.1- 7.25)	0.13		
Median months to HBV DNA suppression (IQR)	10.84 (0- 43.40)	4.93 (0-10.85)	0.02	0.97 (0.95- 0.99), 0.01	0.97 (0.95- 0.99), 03

- IQR= 25% and 75% interquartile range
- c/ml= cells per mL
- ns= non-suppressed

625 HIGH RATES OF HBV FUNCTIONAL CURE AMONG HIV/HBV-COINFECTED PATIENTS ON ART IN ZAMBIA

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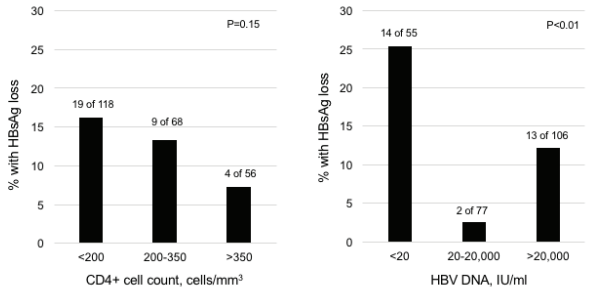
Background: Hepatitis B virus (HBV) functional cure, defined as the loss of the hepatitis B surface antigen (HBsAg), is the desired goal of HBV therapy but occurs slowly (~1%/year) in HBV monoinfection. Novel immunomodulatory therapies to augment T-cell responses are under investigation to increase rates of functional cure. In a sentinel cohort of HBV patients with HIV coinfection in Zambia, we investigated the clinical correlates of HBV functional cure during HBV-active antiretroviral (ART).

Methods: We enrolled HIV-HBV co-infected adults (≥18 years and HBsAg-positive) at two sites in Lusaka, Zambia, at start of tenofovir disoproxil fumarate-containing ART. At baseline we measured liver function tests, CD4+, and HBV DNA, and yearly thereafter we re-assessed HBV DNA and HBsAg. Negative HBsAg tests were repeated at 6 months along with surface antibody (HBsAb). After excluding those with <1 year follow-up, we analysed the proportion with HBsAg loss on ART and explored possible predictors including age, sex, baseline CD4+ categories (<200, 200-350, and >350 cells/mm^3), HBV DNA (undetectable [<20], 20-20,000, and >20,000 IU/ml), baseline ALT elevation, and 1-year change in CD4+. Logistic regression and Cuzick's non-parametric test for trend were used in statistical analyses.

Results: Among 267 patients analysed, median age was 34 years (interquartile range [IQR], 27-45), 102 (38.2%) were women, and median baseline CD4+ count was 204 cells/mm^3 (IQR, 99-341). During a median of 2.1 years on ART, 34 (12.7%) became HBsAg-negative. Most events (n=22) occurred in the initial year of therapy, 93.5% were confirmed with further testing, and 57.1% with HBsAg loss had detectable surface antibodies (HBsAb). With CD4+ <200 at ART start there was a trend towards increased HBsAg loss compared to CD4+ >350 cells/mm3 (P=0.155), but we did not find an association with age, sex, ALT elevation, or CD4+ change. Patients with either baseline undetectable or DNA >20,000 had increased HBsAg loss compared to moderate HBV VL (20-20,000 IU/ml; P<0.01; Figure 1).

Conclusion: A high proportion of HIV-HBV patients in Zambia experienced HBV functional cure on ART relative to what occurs in HBV monoinfection. Robust ART-induced immune reconstitution in the setting of high HBV antigen load may enhance anti-HBV immune responses in the liver. A better understanding of this mechanism could inform immunomodulatory therapies to increase HBV functional cure.

Figure. HBsAg loss among HIV-HBV coinfected Zambian patients, by initial CD4+ count and HBV DNA at start of antiretroviral therapy



626 HEPATITIS B VIROLOGIC FAILURE OF TENOFOVIR-BASED THERAPIES IN PATIENTS WITH HIV/HBV

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Background: A subset of patients coinfected with HIV and hepatitis B virus (HBV) exhibits persistent HBV viremia or viral breakthrough despite HIV suppression while on combination antiretroviral therapy (cART) that includes tenofovir (TFV). The current literature supports several etiologies for this phenomenon, most commonly suboptimal cART adherence. In this study, we determined tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) concentrations in dried blood spots (DBS) as novel measures of cumulative and recent adherence, respectively, among HIV/HBV coinfected patients on TFV.

Methods: In this ongoing case-control study, HIV/HBV coinfected adults on a stable tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)-based cART regimen with 1) HBV breakthrough: HIV viral suppression (<50 copies/mL) for >6 months and prior HBV viral suppression (HBV DNA < lower limit of quantification [LLOQ]) with new HBV DNA >LLOQ or 2) persistent HBV viremia: HIV viral suppression for >24 months and failure to achieve HBV DNA 6 months and HBV viral suppression on most recent assay. A 3mm DBS punch obtained at time of consent was used for analysis. Simultaneous quantification of TFV-DP and FTC-TP levels in DBS were performed using validated liquid chromatography/tandem mass spectrometry methods. Bivariate analysis was performed using Wilcoxon rank-sum test.

Results: To date, 6 men (83% Black) with persistent HBV viremia and 9 men (44% Black) with HBV viral suppression have enrolled (Table). Among those on TDF, TFV-DP levels were lower among unsuppressed (n=4) than suppressed (n=5) patients with median (range) levels of 516 (215-1176) and 1456 (1089-3108) fmol/punch, respectively (p=0.03). Among those on TAF, TFV-DP levels were 84.4 and 428 among unsuppressed patients (n=2) and median (range) of 144 (55.7-279) fmol/punch among suppressed patients (n=4). FTC-TP levels were detectable among 4 of 6 unsuppressed and all suppressed patients.

Conclusion: Median TFV-DP in DBS arising from TDF/FTC, reflecting cumulative drug exposure, was nearly 3-fold lower among HBV unsuppressed patients than suppressed patients. In contrast, the majority of both groups had detectable FTC-TP, reflecting recent adherence relative to the clinic visit. Interim findings of this ongoing study support the concern that poor long-term adherence to TFV therapy may underlie the phenomenon of concurrent HBV viremia and HIV viral suppression.

HBV status	Age (years)	Race	cART Regimen	HBV Viral Load	HBV Resistance Genotype	TFV-DP (fmol/punch)	FTC -TP (pmol/punch)
Unsuppressed	46	Black	TDF/FTC; Darunavir/ritonavir; Maraviroc	20,000 IU/mL	TFV sensitive	299	BLQ
Unsuppressed	54	Caucasian	TDF/FTC; Abacavir; Raltegravir	300,000 copies/mL	TFV sensitive	215	0.227
Unsuppressed	56	Black	TDF/FTC; Efavirenz	262 IU/mL	TFV sensitive	1176	0.195
Unsuppressed	59	Black	TDF/FTC; Maraviroc; Raltegravir	23 IU/mL	TFV sensitive	734	0.184
Suppressed	55	Caucasian	TDF/FTC; Etravirine; Raltegravir			1089	0.321
Suppressed	54	Caucasian	TDF/FTC; Efavirenz			1177	0.238
Suppressed	53	Caucasian	TDF/FTC; Darunavir/cobicistat; Dolutegravir			1456	0.146
Suppressed	76	Black	TDF/FTC; Darunavir/cobicistat			1897	0.311
Suppressed	58	Black	TDF/FTC; Darunavir/ritonavir; Etravirine			3108	0.406
Unsuppressed	63	Black	TAF/FTC; Lopinavir/ritonavir	107 IU/mL	NA	428	0.229
Unsuppressed	58	Black	TAF/FTC; Dolutegravir	21,500 IU/mL	TFV sensitive	84.4	BLQ
Suppressed	56	Caucasian	TAF/FTC; Dolutegravir			279	0.279
Suppressed	60	Black	TAF/FTC; Elvitegravir/cobicistat			55.7	0.341
Suppressed	52	Black	TAF/FTC; Raltegravir			196	0.145
Suppressed	69	Caucasian	TAF/FTC; Dolutegravir			91.8	0.299

627 HIV LATE PRESENTATION AND ITS IMPACT ON HBV SEROCONVERSION IN HBV/HIV

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Background: Several cohorts have shown that successful long-term tenofovir (TDF)-containing combination antiretroviral therapy (cART) leads to HBsAg loss in 5-15% of HBV HIV coinfected patients. However, data on determinants of HBsAg loss in this setting remain sparse. Here we evaluate factors associated with HBV seroconversion under HBV active ART in a large German multi-center cohort with a median follow-up of at least 10 years.
Methods: Non-interventional retrospective cohort of 7 German HIV care centres assessing rates of HBV seroconversion defined as HBsAg loss in 359 HBV/HIV coinfected patients under HBV active (TDF or tenofovir alafenamide (TAF) containing) cART. Fisher's exact, chi-square and Mann-Whitney U test were used for statistical analysis.
Results: In total, 359 patients were included. 90% patients were male, median age was 41 years (IQR 41-43). 83% were of Caucasian, 14% of African and 3% of Asian descent. Main routes of HIV transmission were MSM (74%), origin from high prevalence country (9%) and heterosexual intercourse (9%). CDC stage at HIV diagnosis was C3 in 13% followed by A2 (12%), CD4 nadir 251/ul (211-296). 61% were ART-naïve when TDF or TAF containing cART was initiated (baseline). Median CD4 cell count at baseline was 359/ul (321-404). 59% were HBeAg positive at baseline. 90% were HBV-DNA positive (limit of detection <10 IU/ml) at baseline. 73% received TDF/FTC, 18% TDF/3TC and 3% TAF/FTC at baseline. 53% were switched to TAF during follow-up. 44% received a boosted protease inhibitor, 41% NNRTI and 10% an integrase inhibitor. Median follow-up was 11 years (10-12), median CD4 gain was 188/ul (130-229). Overall, HBsAg loss occurred in 66/359 (18.4%) patients. Median time to HBsAg loss was 41 months (33-60). There was no correlation between HBsAg loss and gender (p=0.551), age (p=0.307), country of origin (p=0.269), CD4 cell count (p=0.639), CD4 nadir (p=0.364), HBeAg (p=0.712), ART class (p=0.818), or switch to TAF (p=0.267). However, patients with stage CDC C (p≤0.001), lower CD4 gain (p=0.043) and not receiving TDF/FTC (p=0.008) were less likely to lose HBsAg.
Conclusion: While long-term TDF-containing cART leads to higher rates of HBsAg loss when compared to published data for HBV monoinfected subjects, late presentation for HIV and poor immune recovery significantly impair HBV seroconversion rates in HBV/HIV coinfected patients.

628 ABSENCE OF HBV REACTIVATION IN HIV/HCV/HBCAB COINFECTED PATIENTS TREATED WITH DAA

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Background: HBV reactivation during HCV direct-antiviral agents (DAA) therapy has been described in individuals with positive hepatitis B (HB) core antibodies (anti-HBc) in the absence of HB surface antigen (sAg) prior to HCV treatment. This is the consequence of the disinhibition of HBV replication following HCV eradication. Despite some antiretroviral agents (ART) are effective on both HIV and HBV, little data of HBV reactivation exist in people living with HIV treated for HCV with DAA.
Methods: In order to determine the prevalence of occult HBV reactivation we retrospectively enrolled ART-treated HIV/HCV co-infected individuals who completed DAA interferon-free regimens between April 2015 and August 2018 in a large centre in London. Demographic characteristics, HBV markers, antiretroviral treatment, ART switch to prevent HBV (adding tenofovir disoproxil fumarate, TDF or tenofovir alafenamide, TAF plus emtricitabine, FTC) and addition of HBV prophylaxis (entecavir, ETV) prior to start DAA were collected. Subjects were followed up with alanine aminotransferase (ALT) at two to four weekly intervals during treatment and at week 4, 12, 24 and 48 after the end of treatment. HBV reactivation was defined as ALT elevation of 2 or more times above the upper limit of normal (ULN) in combination with molecular HBV reactivation.
Results: 274 HIV-infected subjects were treated for HCV with DAA. At baseline, 87/274 (32%) were HBs-Ag negative/anti-HBc positive, 6/274 (2%) were HBsAg positive and 141/274 (51%) were anti-HBs positive/anti-HBc negative. Results of anti-HBc positive subjects are shown in Table 1. Of all 87 HBsAg negative/anti-HBc positive subjects at risk of HBV reactivation, 85/87 (98%) received at least one anti-HBV active agent as a part of ART for at least 3 months before baseline. Six/87 (7%) commenced prophylaxis with ETV as receiving either only lamivudine (3TC) (5/6) or no anti-HBV ART (1/6). Four/87 had deranged ALT during DAA therapy or at following visits but no molecular HBV reactivation. All HBsAg positive subjects were on TDF/FTC and did not meet study criteria of HBV reactivation.
Conclusion: Almost one-third of our HIV/HCV cohort was HBcAb positive prior to DAA initiation. The absence of HBV reactivations in our cohort where 98% of anti-HBc positive subjects were on an at least one HBV-active drug prior to DAA initiation suggests that this is an effective strategy to prevent it. However, further studies are warranted to assess the role of anti-HBV prophylaxis during DAA treatment.

	HBsAg positive (n=6)	HBsAb<10 IU/l (n=28)	HBsAb 10-100 IU/l (n=23)	HBsAb>100 IU/l (n=36)	P value
Male gender, n (%)	6 (100)	24 (86)	19 (83)	36 (100)	0.06
Age, years, median (IQR)	52 (46-56)	50 (44-55)	54 (46-58)	50 (44-55)	0.4
Cirrhosis, n, (%)	3 (50)	9 (32)	3 (13)	6 (17)	0.004
BL HIV-RNA <50 c/ml, n	5 (83)	26 (93)	22 (92)	35 (97)	0.53
BL CD4 T-cell/mmc, median (IQR)	347 (58-669)	598 (451-803)	542 (437-923)	662 (501-824)	0.17
HBV-DNA performed at BL, n (%)	6 (100)	9 (32)	6 (26)	5 (14)	0.0002
BL HBV-DNA<20 IU/l, n (%)	5 (83)	9 (100)	6 (100)	5 (100)	0.3
ART including anti-HBV agent, n (%)	6 (100)	27 (96)	18 (100)	35 (97)	0.7
ART switch to prevent HBV reactivation	0	0	0	1 (3)	0.7
ETV prophylaxis added, n (%)	0	3	2	1(3)	0.5
Timing of ETV prophylaxis discontinuation	n/a	1/3 :at EOT 2/3: at SVR4	1/2: 2 weeks[a] 1/2: at SVR4	1/1: at SVR4	n/a
ALT deranged >2 ULN	0	2	2	0	0.3
HBV-DNA >20 IU/L (HBV-DNA available)	n/a	0 (1)	0 (2)	n/a	ns

a. Interrupted for liver toxicity two weeks after baseline
Legend: HB, hepatitis B; HBcAb, HB core antibodies; HBsAg, HB surface antigen; HBsAb, HB surface antibodies; IQR, interquartile range; IU, international units; DAA, direct-acting antiviral treatment; ART, antiretroviral treatment; ETV, entecavir; ALT, alanine aminotransferase; ULN, upper limit of normal; EOT, end of treatment; SVR, sustained virological response; BL, baseline

629 HEPATITIS B VIRUS DNA LEVEL CHANGES IN HBEAG+ PREGNANT WOMEN RECEIVING TDF FOR PMTCT

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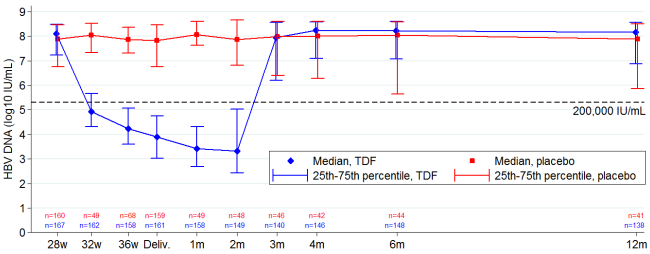
Background: High hepatitis B virus (HBV) DNA plasma levels and hepatitis B e antigen (HBeAg) carriage are the main risk factors of mother-to-child transmission (MTCT) of HBV. Antivirals can decrease HBV DNA levels and prevent HBV MTCT. Current guidelines recommend initiating antiviral prophylaxis when maternal HBV DNA level is above 200,000 IU/mL (5.3 log IU/mL); however, the optimal duration of treatment is unknown. Within a randomized trial, we assessed the changes of HBV DNA levels in HBeAg+ pregnant women receiving either tenofovir disoproxil fumarate (TDF) or placebo during pregnancy through the early postpartum period.
Methods: HBV DNA was retrospectively quantified in HBsAg and HBeAg positive and HIV-negative pregnant women enrolled in a phase III, placebo-controlled, double-blind, randomized clinical trial assessing the efficacy and safety of TDF 300 mg once daily versus placebo from 28 weeks' gestation through 2 months post-partum (NCT01745822). Samples were selected from all women assigned to the TDF arm and a randomly selected subset of women on placebo. HBV DNA plasma levels were measured at baseline (28 weeks), during the TDF course at weeks 32 and 36, delivery, and months 1 and 2 postpartum, and after TDF discontinuation at 3, 4, 6 and 12 months postpartum. HBV DNA levels were measured blind to the randomized arm using the RealTime HBV assay (Abbott Molecular Inc., IL, USA).
Results: Of 331 women enrolled, 168 were randomized to TDF and 163 to placebo. Median HBV DNA levels in women on TDF decreased from 8.1 log IU/mL at baseline to 4.9 log IU/mL at 32 weeks, 4.2 at 36 weeks, 3.9 at delivery, 3.4 at 1 month and 3.3 at 2 months post-partum. After discontinuation of TDF, median HBV DNA level returned to baseline levels within one month. In the placebo arm median HBV DNA levels were unchanged during pregnancy and the postpartum period. In the TDF arm, 99 of 162 women (61%, exact 95% confidence interval [CI] 53% to 69%) had HBV DNA <200,000 IU/mL at 32 weeks, 133 of 158 (84%, CI 78% to 89%) at 36 weeks and 142 of 161 (88%, CI 82% to 93%) at delivery.
Conclusion: In our study, more than 85% of pregnant women receiving TDF from 28 weeks' gestation achieved HBV DNA levels below 200,000 IU/mL prior to delivery.



630 A LONG-ACTING 3TC NANOFORMULATION SUPPRESSES HBV REPLICATION IN HUMANIZED MICE

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Background: Despite the success of existing antiretroviral therapy (ART) in controlling hepatitis B virus (HBV) infection, treatment requires life-long adherence to medicines. Compliance to ART can be compromised by frequency of dosing and adverse drug reactions. To this end, lamivudine (3TC), a nucleoside analog inhibitor of HBV and human immunodeficiency virus (HIV) infections, was modified into a lipophilic monophosphorylated prodrug (P3TC) to extend the apparent drug half-life, improve potency and facilitate access to viral replication sites. Lipid coated P3TC nanocrystals (NP3TC) were prepared to further improve drug biodistribution and longevity.
Methods: 3TC was modified and formulated into long acting lipid nanocrystals by high-pressure homogenization. Cellular drug uptake and retention was conducted in human monocyte-derived macrophages (MDM). To evaluate anti-HBV activity, TK-NOG mice were transplanted with human hepatocytes, and after confirmation of human albumin (Alb) concentration in peripheral blood (1.1 ± 0.2 mg/ml), animals were infected intravenously with patient-derived sera samples containing ~106 HBV DNA. Following confirmation of HBV DNA in peripheral blood, five animals were administered a single intramuscular dose of 75 mg/kg 3TC equivalents of NP3TC and controls (n=3) kept without drug. Levels of HBV DNA and HBsAg in plasma were monitored over the four-week experiment duration. At the end of the study, liver tissues were analyzed for histopathology, HBV DNA and RNA by ddPCR, and staining for human cells and viral proteins.
Results: NP3TC nanocrystals had average particle sizes of 250-300 nm, polydispersity index of <0.2 and drug loading capacity of > 70%. NP3TC was readily taken up by MDM with sustained drug levels for up to 30 days; whereas native 3TC was eliminated within a day. In efficacy studies, single administration of NP3TC reduced HBV DNA from 4.38 ± 3.39 to 3.27 ± 2.75 log10 copies/ml and 3.38 ± 2.45 log10 copies/ml at two and four weeks post drug treatment, respectively, without loss of human cells or Alb levels. The results paralleled sustained drug levels in NP3TC treated animals.
Conclusion: A long acting potent 3TC ProTide formulation was developed and preliminary studies showed sustained anti-HBV activity in humanized mice for weeks after single dosing. These results are promising for development of a long-acting potent formulation of 3TC for the treatment and prevention of HBV and HIV infections.

631 ANTI-INFLAMMATORY IL-10 IS INVERSELY RELATED TO CORONARY ATHEROSCLEROSIS IN HIV

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Background: IL-10 is an anti-inflammatory cytokine secreted by monocytes, T cells, dendritic cells and other immune cells in response to systemic inflammation and is implicated in HIV viral persistence. However, IL-10 is thought to be protective against atherosclerosis, but this has not yet been studied in people with HIV (PWH). Therefore, we sought to understand the relationship of IL-10 with coronary atherosclerosis in PWH.
Methods: Serum levels of the anti-inflammatory cytokine IL-10 were measured by ELISA (Invitrogen, MA) in a well-phenotyped observational study of men and women with HIV and matched HIV-negative controls, who were all asymptomatic and without known cardiovascular disease. Quantification of coronary plaque and plaque characteristics were obtained by coronary computed tomography angiography.
Results: Among PWH, IL-10 inversely correlated with coronary segments with noncalcified plaque (rho=-0.24, p=0.004) and with coronary segments with any type of plaque (rho=-0.19, p=0.02), but not with segments with calcified plaque (rho=-0.009, p=0.92). Among HIV-negative controls, a similar directionality of relationships was seen for IL-10 and non-calcified plaque or any plaque, but the relationships were not statistically significant. Among PWH, no relationships were observed between IL-10 and several inflammatory markers known to be related to atherosclerosis in HIV (MCP-1, sCD163, sCD14, and IL-6). In logistic regression modeling adjusting for HIV RNA, CD4+ cells, total Framingham point score, BMI, race, MCP-1 and sCD163, lower IL-10 remained significantly related to presence of plaque (p=0.008).
Conclusion: Higher IL-10 confers a lower risk of coronary plaque (and specifically non-calcified plaque) even when controlling for traditional cardiovascular risk factors, HIV RNA, CD4+ cells, and pro-inflammatory markers. The effects of IL-10 in HIV may be both protective and detrimental: while IL-10 may promote viral persistence, our study suggests that IL-10 may be involved in mitigating untoward coronary atherosclerosis.

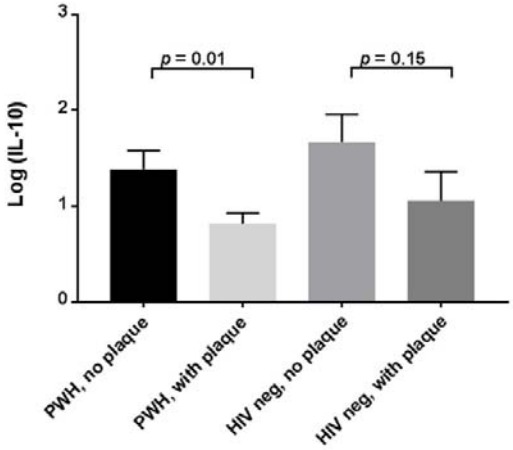

Figure: Log (IL-10) levels among people with HIV (PWH) and HIV negative controls with and without coronary plaque. Shaded bars represent the mean and error bars represent the standard error of the mean.

632 IL-32Δ AND TRAIL: NEW CARDIOVASCULAR DISEASE BIOMARKERS IN ART-TREATED HIV INFECTION

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Background: We recently demonstrated that enhanced expression of IL-32δ, a regulatory isoform of the proinflammatory cytokine IL-32, positively correlates with the coronary artery atherosclerotic total plaque volume (TPV), a subclinical cardiovascular disease (CVD) marker in HIV+ individuals receiving anti-retroviral therapy (ART). Here, we screened for new biomarkers associated with subclinical CVD that in combination with IL-32δ may serve to better predict CVD susceptibility/progression.

Methods: Plasma was collected from n=52 ART-treated aviremic HIV+ male participants with no clinical CVD from the Canadian HIV and Aging Cohort Study and n=23 age-matched uninfected controls. Participants prospectively underwent contrast-enhanced cardiac computed tomography and TPV measurement. HIV+ group was divided into n=30 with subclinical coronary artery atherosclerosis (TPV>0) and n=22 without (TPV=0) (median CD4 count: 593 and 581 cells/mm3 and median age: 53.3 and 50.5 years, respectively). Soluble factors were quantified by Luminex assay and selected biomarkers validated by ELISA. Expression of IL-32 mRNA was quantified by SYBRGreen RT-PCR in peripheral blood mononuclear cells.

Results: Expression of IL-32δ in HIV+ participants with atherosclerotic TPV was 1.5fold higher compared to TPVneg individuals (mean±SD: 0.038±0.017 vs 0.025±0.018, p=0.0006). Among 38 analytes measured by Luminex assays, levels of TNF-related apoptosis inducing ligand (TRAIL) and Epidermal Growth Factor (EGF) were lower in plasma from TPV+ compared to TPVneg HIV-infected individuals (68.5±24.3 vs 85.3±23.1 pg/ml for TRAIL and 694.1±269 vs 906.4±256.5 pg/ml for EGF, p=0.04 and p=0.01, respectively). Interestingly, IL-32δ mRNA expression negatively correlated with TRAIL (Spearman r=-0.30, p=0.032) and showed a trend for a negative correlation with EGF (Spearman r=-0.25, p=0.076). Similarly, plasma IL-32 levels negatively correlated with TRAIL (Spearman r=-0.31, p=0.024). Age, smoking or lipid levels did not confound these results.

Conclusion: Our study reveals that high expression of IL-32δ in blood cells of ART-treated HIV+ individuals with subclinical CVD correlated with low plasma levels of TRAIL and EGF, two emerging biomarkers of CVD that likely play atheroprotective roles. Indeed, TRAIL was shown to induce cell death of over-activated and malignant cells, whereas EGF is involved in myocardial protection from acute stress. Combination of IL-32δ with these biomarkers has the potential to better predict CVD in HIV+ individuals.

633 INFLAMMATION-RELATED GENES ARE ASSOCIATED WITH ACCELERATED AGING IN HIV

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Background: Chronic, low-grade inflammation is characteristic of both HIV disease and aging ("inflammaging"), and may contribute to the accelerated aging observed in people living with HIV (PLWH). We examined whether inflammation-related single nucleotide polymorphisms (SNPs) were risk factors for accelerated aging and HIV-associated non-AIDS (HANA) conditions among PLWH.

Methods: This was a cross-sectional, observational cohort study that examined 155 HIV+ cases (mean age=47.3, 81% male, 68% White) from the National NeuroAIDS Tissue Consortium. All cases had existing pre-mortem behavioral/medical/virologic data, post-mortem tissue samples, as well as genetic and epigenomic data. Accelerated aging was measured according to the Epigenetic Clock; a published biomarker of aging based on the relationship between chronological age and biological age as defined by DNA methylation levels of 353 CpGs. The resulting age estimate, DNA methylation age, was related to chronological age. Past or current HANA conditions including cerebrovascular disease, liver disease, kidney disease, COPD, cancer, and diabetes were determined via self-report or extrapolated from medical records. Mean age acceleration (expressed as Z-scores) and likelihood of past/current HANA conditions were compared between major allele homozygotes and minor allele carriers separately for each SNP (IL-6 -174G/C, IL-10 -592C/A, TNFα -308 G/A). Statistical analyses were adjusted for relevant demographic and clinical factors including comorbidities (HIV-associated neurocognitive disorder [HAND], lifetime major depressive disorder, substance use disorders, HIV disease characteristics, study site, and DNA methylation assay batch.

Results: IL-6 minor allele carriers and IL-10 major allele homozygotes demonstrated significantly greater accelerated aging (higher Z-scores) compared to other genotype groups. The likelihood of any past/current HANA condition did not differ between IL-10 genotype, but was 3.4 times greater in IL-6 minor allele carriers versus others. TNFα genotype was not associated with accelerated aging, nor HANA conditions.

Conclusion: SNPs in the interleukin pathway (IL-6 and IL-10) may be helpful in identifying PLWH who are at high risk for accelerated aging. These insights into pathophysiological pathways may lead to interventional approaches to treat the potential of rapid aging among persons living with HIV.

634 IMPACT OF INFLAMMATION AND GUT IMMUNITY ON CORONARY ARTERIAL WALL COMPOSITION

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Background: Factors that impact CAWC in the setting of HIV disease are poorly understood. We sought to investigate how HIV infection and associated changes in gut immunity, systemic inflammation and initiation of ART impacts coronary CT angiogram (CCTA).

Methods: 18 chronic HIV+ ART-naïve patients (pts) underwent CCTA,upper endoscopy for duodenal biopsies (gut) and phlebotomy before and 1 yr after initiating darunavir/ritovavir/ tenofovir disoproxil fumarate/ emtricitabine (ART).17 matched HIV- control (C) underwent identical procedures once. Known cardiovascular disease was exclusionary. Gut samples underwent tissue immunohistochemistry (IHC) or FACS analysis. 3D reconstruction of CCTA of 3 main arteries (RCA, LAD, and LCx) (expressed as % of total artery diameter) and Hounsfield Units using Aquarious iNutrition software.Plasma inflammatory biomarkers were measured by ELISA.Values are expressed as median values [interquartile range] and non-parametric (Spearman's Rho coefficient (SrC)) were used where appropriate.

Results: All pts and C were MSM with median age of 40.5 [31-51] (pts) and 38 [33-47] (C); p=0.674, and CD4 count of 431[272-559] pts and 958 [741-1273] (C); p<0.001. Baseline HIV load was 40,500[19,750-84,250]. Pts' 1 yr CD4 742[600-849] and all HIV load <20 cp/mL. CAW was thicker in pts vs C [57% vs 52% p=0.001]. CAWT correlated with gut IHC CD8+ T-cell density (SrC=0.701;p=0.019), but not gut CD4+T-cell IHC or any PBMC T cells or subpopulations. CAWC fat proportion was lower in HIV+ (14% vs 21%;p=0.012) and Ca proportion was higher in pts (28% vs 23%; p=0.05) than C. No differences were found in the non-fat-non-calcium proportion. Gut IHC CD8 T-cell density positively correlated with CAWC Ca (SrC 0.542;p=0.05) and negatively with fat CAWC (SrC=-0.612;p=0.021). Soluble (s) CD163 positively correlated with fat CAWC (SrC=0.651;p=0.008) and negatively correlated with sMAdCAM-1 (SrC -0.610;p=0.023) and intestinal fatty acid binding protein (SrC -0.657;p=0.01).
Conclusion: While CA thickness and calcium were higher in people with greater gut CD8 T-cell density, fat content was lower. Lower monocyte activation also correlated with less fat content yet more gut homing and intestinal turnover. Thus, gut repair may be essential for modulating the monocyte activation associated with fat infiltration of coronary arteries.

635 CONTRIBUTION OF HUMAN HERPESVIRUS 8 AND HERPES SIMPLEX 2 TO PROGRESSION OF IMT IN HIV

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Background: Several herpesviruses have been implicated in the pathogenesis of atherosclerosis, but limited information is available about their role in the progression of atherosclerosis in people living with HIV (PLWH). Human herpesvirus 8 (HHV-8) is a lymphotropic and vasculotropic herpesvirus with potential pro-atherogenic effects. However, to date no clinical studies have associated HHV-8 infection with atherosclerotic disease. We explored the influence of coinfection with HHV-8 and other herpesviruses on the rate of progression of subclinical atherosclerosis in virologically-suppresed PLWH.
Methods: Prospective study including men who have sex with men (MSM) infected with HIV. At the baseline visit, IgG antibodies against HHV-8 and other herpesviruses, highly-sensitive C-reactive protein (hsCRP) levels, and the Framingham risk score were measured. To evaluate the progression of subclinical atherosclerosis, successive carotid intima-media thickness (cIMT) measurements with high-resolution carotid artery ultrasound were performed over an eight-year period. Adjusted general linear mixed models were used to assess factors associated with faster cIMT progression.
Results: 141 participants with suppressed HIV-RNA (<200 copies/ml) at cIMT measurement during the study period were included. 46 (31.3%) were coinfected with HHV-8 and 76 (54%) with herpes-simplex virus-2 (HSV-2). Factors associated with faster cIMT progression adjusting for CD4 cell counts, time between cIMT measurements, hepatitis C, varicella-zoster virus and cytomegalovirus coinfection were seropositivity for HHV-8 (p=0.055), HSV-2+HHV-8 coinfection (p=0.028), the Framingham risk score (p=0.045) and hsCRP (p=0.023). Coinfection with HHV-8 was independently associated with higher levels of hsCRP (OR 1.09 [95% CI, 1.02-1.17], p=0.016). When hsCRP and HHV-8 were simultaneously included in the adjusted model, the relationship of HHV-8 with cIMT progression was attenuated.
Conclusion: HHV-8 contributes to progression of cIMT with a more prominent role when it coinfects with HHV-2 in virologically-suppressed PLWH, and this effect could be driven by systemic inflammation

636 HIV INFECTION AND RISK OF RECURRENT VENOUS THROMBOEMBOLISM: A NATIONAL COHORT STUDY

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Background: People with HIV (PWH) are at increased risk of a first venous thrombotic event (VTE). Whether this also translates into more recurrent VTE is unknown. We assessed VTE recurrence rates in PWH and compared these to VTE recurrence rates in HIV uninfected patients.
Methods: PWH with a first VTE between 2003-2018 were identified in the ATHENA cohort and compared to HIV uninfected patients with a first VTE in the MEGA cohort in the Netherlands. Provoked VTE were associated with cancer, major surgery, estrogen exposure, immobilization, or plaster cast use for fractures. The primary endpoint was recurrence of VTE following discontinuation of anticoagulant therapy for a first VTE. Multivariable Cox regression was used to estimate the VTE recurrence risk. Kaplan-Meier estimates (KME) of VTE recurrence accounted for death as competing risk and were stratified for provoked or unprovoked first VTE.
Results: Of 201 PWH with a first VTE in ATHENA, 153 had observations after anticoagulant therapy withdrawal. Of these, 126 (95 unprovoked) were in men and 27 events (13 unprovoked) in women. In MEGA, 4005 patients had a first VTE, including 1813 (998 unprovoked) in men and 2192 (363 unprovoked) in women. In PWH, 40 recurrent VTE occurred during 772 person years of follow up (PYFU; median 4.7 years, 5.2/100 PYFU, 95%CI 3.8-7.0). In MEGA, 635 recurrent VTE occurred during 20,215 PYFU (median 6.1 years, 3.1/100 PYFU, 95%CI 2.9-3.4). KME were higher for PWH at 1 year following anticoagulant withdrawal (13% vs 6%), attenuating at 3 (20% vs 11%) and 5 (23% vs 15%) years of follow up. PWH were at higher risk of recurrent VTE during the first year following anticoagulant withdrawal (HR 1.86, 95%CI 1.16-3.01), but not thereafter (HR 1.06, 95%CI 0.65-1.73). KME at 1, 3 and 5 years in PWH and HIV uninfected patients with unprovoked first VTE were 16% vs 9%, 24% vs 17% and 27% vs 24%. Multivariable Cox regression showed that the CD4+ T-cell increase between the first VTE and anticoagulant therapy discontinuation was an independent predictor of a lower recurrent VTE risk (HR 0.73 per 100 CD4+ T-cells increase, 95%CI 0.60-0.89).
Conclusion: PWH were at increased risk of recurrent VTE, which might be driven by HIV-related immune deficiency, inflammation, and associated hypercoagulability. The increased risk attenuated over time, possibly reflecting the gradual recovery of these factors following initiation of effective antiretroviral therapy.

637 PREDISPOSING FACTORS FOR VENOUS THROMBOEMBOLISM IN HIV-INFECTED PATIENTS

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Background: HIV is associated with chronic inflammation and immune activation and increases the risk of venous thromboembolism (VTE) events. Predisposing factors are important in the epidemiology of VTE in the general population but little is known about their presence among people living with HIV (PLWH) in the era of widespread access to antiretroviral therapy.
Methods: We included PLWH with VTE in 2005-2017 at 6 sites in the CNICS cohort. We developed a centralized adjudication approach for VTEs with ascertainment based on multiple criteria including diagnoses and procedures, followed by centralized adjudication of primary data by two expert reviewers, and a third reviewer if discrepancies occurred. VTEs were classified by type and anatomic location. Reviewers identified the presence of pre-disposing factors such as bedrest and long plane rides. This analysis included only initial VTEs for those with recurrent events.
Results: We included 318 PLWH with VTE: 181 (57%) deep venous thrombosis (DVT), 139 (44%) pulmonary embolus (PE), and 38 (12%) catheter-associated thrombosis events, including 40 (13%) with multiple types simultaneously (mostly DVT/PE). Two-hundred forty-eight (78%) patients were male; median age was 49 years old (interquartile range [IQR]: 40,55); and 134 (42%) were white, 151 (47%) black, and 26 (8%) Hispanic. Median CD4 count was 312 cells/µL (IQR: 149,548) and 31% had a detectable viral load (≥400 copies/mL). One-hundred forty-four (45%) were current smokers. Most patients had multiple predisposing factors (Table); mean 2.3 (standard deviation [SD] 1.5). Only 33 (10%) had no pre-disposing factor identified. The most common predisposing

factors identified included recent hospitalization (134, 42%), infection (133, 42%), or immobilization/bed rest (78, 25%) within the past 90 days, and current IV drug use (65, 20%). Eighty-seven (27%) had both hospitalization and infection in the past 90 days; 54 (17%) had both immobilization/bed rest and hospitalization.

Conclusion: We conducted a robust adjudication process and examined predisposing factors for VTE among PLWH in a large North American cohort. PLWH with VTE were relatively young and most had at least one identified traditional pre-disposing risk factor. In addition, non-traditional risk factors, including IV drug use and recent infection, were common. Almost one-third of patients had detectable viral loads, and almost half were active smokers, suggesting potential modifiable pro-thrombotic risk factors.

Table 1. Risk factors for venous thromboembolism in CNICS cohort.

Pre-disposing factor	Number (318 overall)	Percent
Hospitalization in the past 90 days	134	42%
Infection in the past 90 days	133	42%
Immobilization/bed rest in the past 90 days	78	25%
IV drug use	65	20%
Malignancy, active in the past year	60	19%
Surgery in past 90 days	33	10%
COPD	30	9%
Chemotherapy in the past 90 days	25	8%
Estrogen and/or progestin or anabolic steroid use in last 30 days	24	8%
Dialysis	21	7%
Inherited or acquired thrombophilia (other than malignancy)	18	6%
Heart failure prior to event	17	5%
Major trauma including fracture in past 90 days	15	5%
Pulmonary hypertension	15	5%
Transfusion in past 30 days	15	5%
Long plane ride/prolonged sitting in the past 30 days	9	3%
Nephrotic syndrome	6	2%
Current pregnancy or within 3 months post-partum	2	<1%

** Other factors: Cirrhosis (8, 3%), morbid obesity (7, 2%)*
COPD-chronic obstructive pulmonary disease; IV-intravenous

638 SHORTER ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT) IN PEOPLE LIVING WITH HIV

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Background: Altered coagulation in people living with HIV (PLWH) including higher d-dimer may contribute to the increased risk of cardiovascular disease (CVD) found in this population. While the extrinsic coagulation pathway has been studied extensively, less is known about the intrinsic pathway in PLWH. The activated partial thromboplastin time (APTT) is a measure of the intrinsic pathway and the overall speed at which blood clots and shortening of the APTT may increase the risk of thromboembolism. We aimed to investigate if the APTT in PLWH is altered compared to uninfected controls (UIC), and if HIV is an independent predictor of shorter APTT.

Methods: A total of 985 PLWH from the Copenhagen Co-morbidity in HIV infection study and 2955 uninfected controls (UIC) from the Copenhagen General Population Study matched on age and sex were included in the study. CRP (high sensitivity assay, hsCRP) and APTT were measured in all participants. Shortened and prolonged APTT was defined as below and above the reference interval (25-37 sec.), respectively. We measured height and weight and information about use of tobacco and alcohol was collected using structured questionnaires. We calculated 95% binomial confidence intervals and used logistic regression models adjusted for HIV, age, sex, smoking status, alcohol, diabetes, BMI and hsCRP to investigate the association between HIV and altered APTT.

Results: The median APTT was slightly shorter in PLWH than in UIC (27 vs 28 sec., p<.001). A higher proportion of PLWH compared to UIC had both shortened (14% [12;16] vs 8% [7;9] p = <.001) and prolonged APTT (2% [1;3] vs 1% [0.9;2] p =.044). Uni- and multivariable analyses are shown in Table 1. In multivariate analyses, HIV was independently associated with shortened APTT (adjusted odds ratio: 2.2 [95%CI: 1.8;2.9]) p<.001 (Table 1), but not with prolonged APTT (1.7 [95%CI: 0.9;3.0] p=.059). Apart from HIV, higher age, BMI > 25 and current smoking were associated with shortened APTT in adjusted analyses (Table 1).

Conclusion: Prevalence of both shortened and prolonged APTT was higher in PLWH than in uninfected controls, and HIV was an independent predictor of shortened APTT. This finding may help explain some of the increased risk of thromboembolic diseases found in PLWH. The mechanisms and etiology should be further investigated in prospective studies with cardiovascular endpoints.

Table 1:

Odds ratio for APTT below reference interval (95%CI)	Univariate Analysis	P	Multivariable Analysis* (OR)	P
HIV	1.9 (1.5;2.5)	<.001	2.2 (1.8;2.9)	<.001
Age (per 10 year increase)	1.2 (1.0;1.3)	.005	1.1 (1.0;1.2)	.045
Male/Female sex	.9 (0.7;1.2)	.401	0.8 (0.6;1.1)	.074
Current smoker	.8 (0.6;1.1)	.192	0.7 (0.5;1.0)	.034
Alcohol (u/week)		.029		.060
0 (0 g)	ref		ref	
1-7 (12g-84g)	1.2 (0.8;1.8)		1.4 (0.9;2.0)	
8->14 (84g->168g)	1.5 (1.1;2.2)		1.6 (1.1;2.4)	
BMI (kg/m^2)				<.006
BMI 18.5 – 24.9	ref		ref	
BMI <18.5	1.4 (0.5;4.0)		1.1 (0.4;3.3)	
BMI 25-29.9	1.3 (1.0;1.7)		1.5 (1.1;1.9)	
BMI >30	1.5 (1.1;2.0)		1.7 (1.2;2.4)	
Diabetes	1.4 (0.8;2.3)	.238	1.1 (0.6;1.8)	.889
hsCRP (per 10 mg/L increase)	0.9 (0.7;1.2)	.212	0.8 (0.6;1.1)	.241

*Model adjusted for HIV, age, sex, smoking status, alcohol, diabetes, BMI and hsCRP

BMI: Body mass index (kg/m^2); hsCRP: high-sensitivity C-reactive protein;

639 DUAL DRUG-MEDIATED MECHANISM FOR NRTI-ASSOCIATED PLATELET HYPERREACTIVITY

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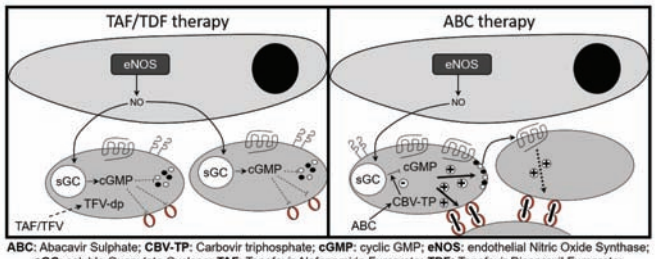
Background: Elevated cardiovascular (CV) risk in people living with HIV may be caused by multiple factors (e.g. lifestyle, HIV-associated inflammation and antiretroviral [ARV] use). Evidence suggests that some ARVs, including abacavir sulphate (ABC), increase CV risk. This is controversial and clinical studies are confounded by HIV status and previous ARV use. ABC, a guanosine analogue, has been suggested to interrupt nitric oxide (NO)–cGMP signalling, but the pharmacological mechanisms linking ARVs with platelets are unclear.

Methods: Platelets were isolated from healthy, HIV-negative and ARV naïve volunteers. Aggregation and dynamic granule release were assessed by plate-based aggregometry and flow cytometry in the presence of clinically-relevant levels of ABC, tenofovir alafenamide fumarate (TAF) or tenofovir disoproxil fumarate (TDF). In vivo platelet aggregation was assessed in mice pre-treated with ARVs.

Results: ABC, but not TAF or TDF, enhanced peak in vivo aggregation to 65U/Kg thrombin by 7.3±2.2% (P=0.02), whilst the area under the curve for 50µg/Kg collagen- and 0.4mg/Kg ADP-evoked responses were enhanced by 480.1±207.5 (P=0.04) and 160.0±45.8 (P=0.02), respectively. None of the ARVs tested affected in vitro platelet aggregation (P>0.05). Since isolated platelets do not generate NO, the pharmacological impact of ARVs was assessed in the presence of a NO donor, which reduced ADP-evoked aggregation from 48.9±5.2% to 13.0±3.4% (P<0.01). Under these conditions, the active metabolite of ABC (max aggregation: 27.3.1±7.3%, P=0.03), but not TAF/TDF (max aggregation: 13.1±5.4%, P=0.17), interrupted NO-mediated inhibition of platelet activation. Finally, we assessed platelet granule release in the absence of NO and found that ABC uniquely enhanced collagen-evoked alpha and dense granule release by 2.6±0.6- and 1.8±0.3-fold. There was no effect of any ARV on ADP- or thrombin-evoked granule release.

Conclusion: Neither TAF nor TDF had any impact on platelet activation, suggesting that these drugs may not pharmacologically interact with platelets during HIV therapy or PrEP. ABC enhanced in vivo and in vitro platelet aggregation in the presence of NO. ABC also elevated platelet granule release in a collagen-specific and NO-independent manner. Together these data suggest

that ABC impacts platelet activation independently of the issues that confound studies in patients; providing potential mechanisms for ABC-associated CV risk in patients (Fig. 1).



ABC: Abacavir Sulphate; **CBV-TP:** Carbovir triphosphate; **cGMP:** cyclic GMP; **eNOS:** endothelial Nitric Oxide Synthase; **sGC:** soluble Guanylate Cyclase; **TAF:** Tenofovir Alafenamide Fumarate; **TDF:** Tenofovir Disoproxil Fumarate; **TFV:** Tenofovir; **TFV-dp:** Tenofovir-diphosphate

640 PLATELET FUNCTION AFTER DOLUTEGRAVIR AND/OR DARUNAVIR/COBICISTAT IN HEALTHY SUBJECTS

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Background: The effects of antiretroviral combinations upon platelets and cardiovascular health remain unclear. Although data have been presented on the effect of certain nucleoside reverse transcriptase inhibitors (NRTIs), third agents have not been studied in this context in isolation. Both dolutegravir (DTG) and darunavir/cobicistat (DRV/c) are effective third agents recommended by International HIV treatment guidelines.

Methods: Platelets were isolated from two populations of HIV-negative volunteers: 1) Subjects that were not taking any medication whose platelets were pre-incubated with ARVs in vitro and 2) 21 subjects enrolled on a Phase I clinical trial (NCT03094507) who were randomised to two groups. Group one received DTG (50mg, QD), DTG plus Cobi-boosted darunavir (DRV/c; 800/150mg QD) and DRV/c for 7 d with a 14 d washout period between drugs. Group two followed the same sequence but started with DRV/c and ended on DTG. Platelets were isolated pre-dose and after achieving steady-state for each drug intervention. Intra-subject analysis was performed to compare platelet function at each time point. For in vitro studies, platelets were exposed to each drug at Cmax values derived from the clinical trial. Plate-based aggregometry and flow cytometry was used to assess platelet function.

Results: Platelet aggregation responses were reduced for subjects taking daily DTG (13.9±4.7% for 3μM ADP and 13.8±4.7% for 10μM TRAP6). This effect was lost when subjects were taking DTG/DRV/c and there was no effect of DRV on maximum platelet aggregation. Maximum aggregation values for platelets isolated from ARV-naïve volunteers were not affected by clinically-relevant concentrations of DTG or DRV. However, DTG reduced collagen-evoked alpha and dense granule release 80.6±10.1% and 71.5±13.1%, respectively. Whereas DRV increased alpha and dense granule release 2.2±0.4- and 1.2±0.2-fold, respectively.

Conclusion: The mechanism for reduced platelet activation in the presence of DTG may be explained by altered platelet granule release, that confers a potentially cardioprotective phenotype. Enhanced granule release following acute exposure to DRV may be important in the context of protease inhibitor-related cardiovascular risk. Further studies are required to correlate our basic science and clinical approaches to understand the potential impacts of alternative novel therapies upon cardiovascular health in people living with HIV.

641 DIRECT ORAL ANTICOAGULANT AND ART USAGE IN PLWH: DATA FROM THE DC COHORT

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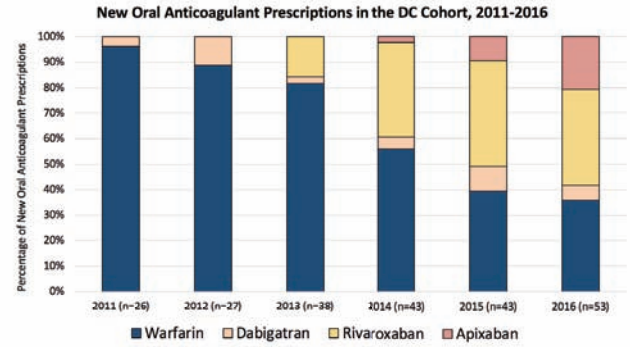
Background: People living with HIV (PLWH) may develop age-related comorbidities including venous thromboembolism (VTE). The CHEST guidelines recommend direct oral anticoagulants (DOACs) over warfarin for VTE treatment in patients without cancer due to less bleeding as well as less frequent monitoring resulting in greater patient and provider convenience. However significant drug interactions exist among DOACs and ART. Use of p-glycoprotein/CYP3A4 inhibitors such as ritonavir (RTV) or cobicistat (COBI) with rivaroxaban (RVB) is not recommended; with apixaban (APB) and dabigatran (DBG), DOAC dose reduction is needed. We characterized evolving trends in oral anticoagulant use and the prevalence of concomitant use of DOACs with RTV or COBI boosted ART among PLWH.

Methods: Established in 2011, the DC Cohort is a clinic-based, longitudinal observational cohort of PLWH. Participants from 11 sites who were prescribed anticoagulants from 1/2011-3/2017 were included. Duration of anticoagulant use was calculated. Summary statistics were generated for demographic and clinical characteristics, including concomitant ART prescriptions. Descriptive statistics of individuals prescribed DOACs and warfarin were generated.

Results: Among 8,315 PLWH enrolled during the study period, there were 239 anticoagulant prescriptions (96 DOAC, 143 warfarin) for 207 persons. PLWH prescribed anticoagulants were mostly Black (82%), male (82%), with a median age of 56 yrs. At the time of anticoagulant prescription, 95% were prescribed ART; 76% had CD4 counts >200 cells/uL and 77% had HIV RNA <200 c/ml. In 2011, DOACs accounted for 3% of total anticoagulant use, which increased to 43% in 2016. DOACs accounted for 64% of all new anticoagulant prescriptions by 2016 [Figure 1]. RVB was the most frequently prescribed DOAC (70%) in 2016, followed by APB (19%), and DBG (11%). Among PLWH on DOACs, 59% were on boosted ART prior to DOAC; 1 month after DOAC initiation, this decreased to 33%. 55% in the RVB group were receiving boosted ART prior to anticoagulant initiation. Despite the recommendation to avoid concomitant use, 29% still received boosted ART 1 month after RVB initiation. Dose adjustments for APB and DBG when given with interacting ART could not be assessed.

Conclusion: In this cohort, DOAC use increased significantly over time. Although RVB is not recommended with RTV or COBI, concomitant use was frequently seen. Feedback should be provided to clinicians on DOAC utilization trends and potential ART drug interactions.

Figure 1



U.S. FDA Approval Dates: Dabigatran 2010, Rivaroxaban 2011, Apixaban 2012
n reflects total number of new oral anticoagulant starts per year

642 VIRAL PERSISTENCE IS INDEPENDENTLY PREDICTIVE OF ATHEROSCLEROSIS IN TREATED HIV

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Background: Persons with HIV have an increased risk for cardiovascular disease, and inflammation is thought to underlie this excess risk. The impact of viral persistence and the reservoir on atherosclerosis has not been described. We hypothesized that higher levels of viral persistence would be associated with atherosclerosis as assessed by carotid artery intima-media thickness (IMT) progression over time and that viral persistence levels would be associated with markers of chronic inflammation and higher mortality.

Methods: IMT, a validated marker of atherosclerosis, was assessed over time in a cohort of treated HIV-infected adults enrolled in the SCOPE cohort. Levels of cell-associated HIV RNA (assessment of reservoir size) and DNA (ongoing level of viral replication) were isolated from cryopreserved peripheral blood

mononuclear cells. We examined associations of viral persistence with IMT after adjusting for traditional risk factors, inflammatory markers, and HIV-related features. Our secondary objectives were to examine associations of viral persistence with inflammatory markers and mortality.

Results: We studied 152 individuals (mean age 48.5 years, median CD4 count 461 cells/mm3, 92% male). The mean duration of followup was 4 years. Older age, smoking, and higher LDL were predictive of baseline mean IMT (p<0.01 for all), while viral persistence measurements were not. HIV-associated DNA was significantly associated with subsequent IMT progression (difference in CIMT: 0.015mm per doubling HIV DNA, p=0.043), and both HIV RNA (OR: 1.85 per doubling HIV RNA, p=0.003) and HIV DNA (OR: 1.60 per doubling HIV DNA, p=0.002) were predictive of incident plaque, which remained significant after adjusting for traditional risk factors, CD4 count, and CD4:CD8 ratio. In adjusted models, higher hsCRP was predictive of higher HIV RNA (p=0.012), whereas higher sCD14 was associated with HIV DNA (p=0.029). Higher RNA/DNA ratio was predictive of mortality (HR 1.66, p=0.024), along with higher IL6 (HR 2.1, p=0.002) and mean IMT (HR 8.47, p=0.015).

Conclusion: Measurements of viral persistence in the setting of treated HIV are independently predictive of IMT progression and incident plaque. Furthermore, IL-6 and RNA/DNA ratio were associated with worse survival. The size of the reservoir during ART as estimated by HIV RNA and DNA measurements may be important contributors to HIV-associated atherosclerosis and mortality.

Table: Associations of viral persistence with baseline IMT and IMT progression

		HIV RNA (per doubling) Estimate (95%CI)	HIV DNA (per doubling) Estimate (95%CI)	RNA/DNA tertile 2 Estimate (95%CI)	RNA/DNA tertile 3 Estimate (95%CI)
Baseline IMT	Unadjusted percentage difference	0.8% (-0.7%, 2.4%), p=0.303	0.4% (-1%, 1.9%), p=0.588	2% (-9.2%, 14.7%), p=0.738	-2.1% (-12.9%, 10.1%), p=0.727
	Adjusted percentage difference *	-0.4% (-1.8%, 1.1%), p=0.627	-0.8% (-2.3%, 0.7%), p=0.308	9.3% (-1.5%, 21.3%), p=0.096	7.5% (-3.3%, 19.6%), p=0.184
IMT progression	Unadjusted difference in carotid IMT (mm)	0.017 (0.007, 0.028), p=0.001	0.019 (0.010, 0.028), p=0.000	-0.061(-0.137,0.014), p=0.114	-0.106(-0.181,-0.031), p=0.006
	Adjusted difference in carotid IMT (mm) *	0.001 (-0.017, 0.018), p=0.946	0.015 (0.001, 0.029), p=0.043	-0.102 (-0.213, 0.009), p=0.076	-0.137 (-0.244, -0.030), p=0.014
Incident plaque	Unadjusted odds ratio	1.92 (1.29, 2.85), p=0.001	1.53 (1.20, 1.96) p=0.001	0.80 (0.24, 2.63), p=0.713	0.16 (0.03, 0.88), p=0.035
	Adjusted odds ratio *	1.85 (1.23, 2.79), p=0.003	1.60 (1.18, 2.17), p=0.002	0.60 (0.15, 2.48), p=0.484	0.23 (0.04, 1.36), p=0.105
Mortality	Unadjusted hazard ratio	1.14 (0.96, 1.34). p=0.133	1.03 (0.90, 1.18), p=0.662	0.94 (0.29, 3.10), p=0.920	1.46 (0.52, 4.09), p=0.477
	Adjusted hazard ratio *	1.16 (0.92, 1.47), p=0.221	0.85 (0.69, 1.04), p=0.120	1.92 (0.36, 10.14), p=0.442	5.26 (1.24, 22.27), p=0.024

* adjusted models control for age, sex, race, traditional cardiovascular risk factors, HIV-related factors

643 VALGANCICLOVIR REDUCES STNF-R2 AND VASCULAR DYSFUNCTION MARKERS IN TREATED HIV

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Background: Valganciclovir reduced T cell activation (but not IL-6, D-dimer, or sCD14) in an earlier trial of HIV/CMV co-infected individuals with incomplete antiretroviral therapy (ART)-mediated CD4 recovery, but its impact on vascular dysfunction and biomarkers that more consistently predict morbidity and mortality remain uncertain.

Methods: Plasma was assessed from a placebo-controlled trial of valganciclovir (900mg daily for 8 weeks) among 30 HIV/CMV co-infected individuals with incomplete ART-mediated CD4 recovery and high CD8+ T cell activation (>10% CD38+HLA-DR+ CD8+ T cells). sTNF-R2, IP-10, sICAM-1, sVCAM-1 (by ELISA), kynurenine/tryptophan (KT) ratio (by LC-MS), and HIV RNA levels (by single-copy assay, SCA, for values <75 copies/ml) were assessed every 4 weeks. Changes from baseline at each timepoint were compared between arms with linear mixed models, log10-transforming variables and normalizing to the baseline interquartile range (IQR) to facilitate comparisons between biomarkers.

Results: Among 14 valganciclovir-treated and 16 placebo-treated participants, most (93%) were men, 9 (30%) had detectable plasma HIV RNA levels, and median CD4 count was 190 cells/mm3. Baseline sTNF-R2 levels were highly correlated (rho) with KT ratio (0.80), %CD38+HLA-DR+ CD8+ T cells (0.66), IP-10 (0.52), sVCAM-1 (0.72), sICAM-1 (0.52, all P<0.01), and plasma HIV RNA levels (0.45, P=0.015), but not sCD14 (-0.01, P=0.98). Compared to those on placebo, valganciclovir-treated participants had a mean -55% of an IQR greater decline from baseline in sTNF-R2 levels at week 4 (P=0.006) and -45% at week 8 (P=0.041). Similar effects on sICAM-1 were observed. Higher plasma HIV RNA levels remained associated with higher plasma sTNF-R2 (P=0.002) across all timepoints. After adjustment for plasma HIV RNA levels, valganciclovir-treated participants continued to have a greater mean reduction in sTNF-R2 and sICAM-1 levels than placebo at weeks 4 and 8 (-49% to -53% of IQR, P≤0.034 for all). Adjustment for sTNF-R2 levels also abrogated the impact of valganciclovir on sICAM-1 levels.

Conclusion: Treating asymptomatic CMV in HIV-infected individuals with incomplete ART-mediated CD4 recovery reduces a biomarker of TNF signaling - that strongly predicted cardiovascular events, Type 2 diabetes, and mortality in prior studies - and a soluble marker of vascular dysfunction. Longer trials of safer anti-CMV agents are needed to assess if treating asymptomatic CMV durably decreases vascular inflammation and cardiometabolic risk.

	Relative Difference in Change from Baseline in Valganciclovir vs. Placebo Per Interquartile Range (IQR) in Baseline Level (95% CI)		
Plasma Biomarker	Week 4	Week 8	Week 12 (off drug)
sTNFR2	0.45 (0.25-0.80)	0.55 (0.31-0.97)	0.71 (0.41-1.25)
sICAM-1	0.48 (0.26-0.88)	0.58 (0.32-1.06)	0.61 (0.34-1.11)
sVCAM-1	0.78 (0.47-1.29)	0.91 (0.55-1.49)	1.01 (0.62-1.65)
KT ratio	0.55 (0.29-1.04)	0.91 (0.48-1.73)	0.90 (0.48-1.70)
IP-10	1.07 (0.45-2.56)	0.75 (0.32-1.77)	0.63 (0.27-1.49)
HIV RNA level	0.91 (0.65-1.27)	1.35 (0.97-1.89)	0.99 (0.71-1.38)

644 PLASMA TISSUE FACTOR AND MCP-1 PREDICTS CIMT PROGRESSION IN TREATED HIV

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Background: Chronic inflammation plays a key role in the development of cardiovascular disease (CVD) among persons living with effectively treated HIV infection and likely occurs early in the disease process. We evaluated the role of biomarkers of immune activation with carotid artery intima-media thickness (CIMT) progression in treated, virologically suppressed individuals.

Methods: We measured biomarkers of immune activation at baseline in 118 HIV-infected individuals with viral load <75 copies/mL from the SCOPE study, using cryopreserved mononuclear cells and plasma. CIMT was measured at baseline and longitudinally in the common, bifurcation and internal carotid artery regions using high resolution ultrasound. Plaque was defined as any focal measurement >1.5mm. Multivariable linear and logistic regression models controlled for demographics, CVD risk factors, and baseline CD4+ T cell count. The final model retained only biomarkers showing significant associations with CIMT.

Results: The median age was 49 yrs and 91% were male, 36% had hypertension, 25% were smokers, and 5% had diabetes. The median duration of follow-up was 2 years. The overall median rate of CIMT progression for the mean of the 3 regions was 6.0%/yr. Progression was faster in the bifurcation (5.6%/yr, p=0.006) and internal (6.5%/yr, p=0.0008) than common carotid regions (4.3%/yr). Incident plaque occurred in 13 of 52 individuals. After multivariable adjustment, doubling in plasma tissue factor and MCP-1 were associated with faster common CIMT progression, 0.058mm/year (p=0.0004) and 0.067mm/year (p=0.017) respectively. Doubling in CD8+ T cell count and percentage of CD38+HLA-DR+CD8+ T cells were associated with faster internal CIMT progression, 0.10mm/yr (p=0.008) and 0.054mm/yr (p=0.045), respectively. Doubling in CD8+ T cell count was also associated with 0.068mm/yr (p=0.011) faster overall mean CIMT progression. Each 10% increase in CD4+ T cell count at baseline was associated with reduced odds of plaque progression [OR 0.66, 95% CI (0.47 to 0.93), p=0.018].

Conclusion: Residual immune activation and plasma tissue factor are independently predictive of CIMT progression in treated HIV infection. Tissue factor plays a key role in the extrinsic pathway of the coagulation cascade and is thought to underlie plaque thrombogenicity. Therapeutic interventions which target the coagulation and inflammatory pathways in HIV merit additional investigations to reduce CV risk.

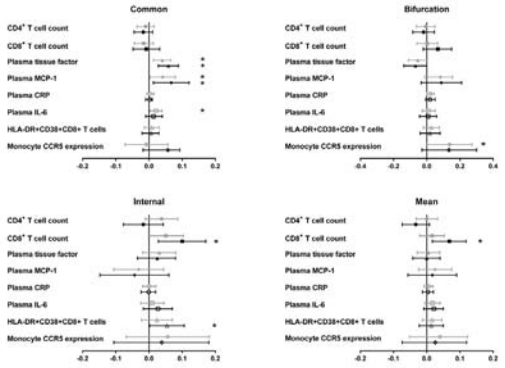

Figure 1. Factors associated with carotid artery intima-media thickness (CIMT) progression at the common, bifurcation, internal carotid artery and overall mean CIMT. Unadjusted analysis is in gray and adjusted analysis is in black. Symbols depict estimates of differences in progression (mm/yr) and error bars depict 95% confidence interval per doubling of each marker. * indicates p<0.05

645 SOCIOECONOMIC STATUS ASSOCIATES WITH ARTERIAL INFLAMMATION IN HIV

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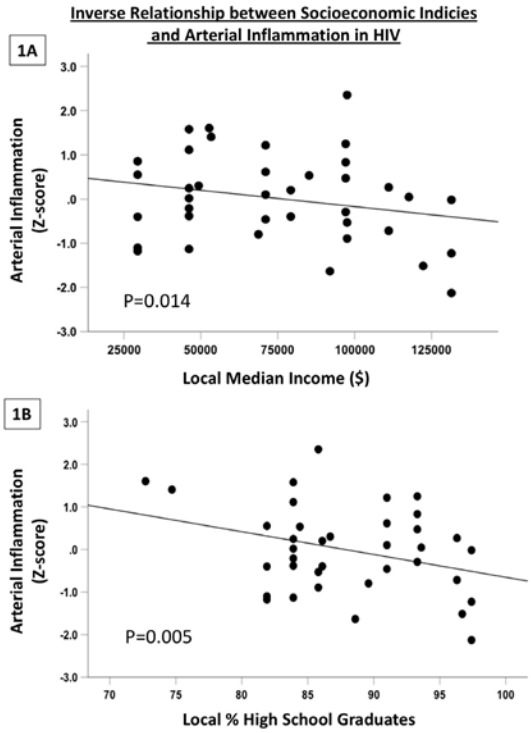
Background: Socioeconomic status (SES) is associated with higher mortality among individuals living with HIV. In the general population, lower SES associates with higher arterial inflammation (a key driver of atherosclerotic disease), and a greater cardiovascular disease risk. While higher arterial inflammation has been reported in treated HIV, the relationship between SES and arterial inflammation has not been studied.

Methods: Men living with HIV were recruited from the SCOPE (Observational Study of the Consequences of the Protease Inhibitor Era), a clinic-based cohort of individuals receiving care in San Francisco. Arterial inflammation was measured using 18F-fluorodeoxyglucose (FDG-PET) positron emission tomography, as the uptake of FDG in the wall of the ascending aorta corrected for background. Zip-code-level SES measures were derived from the U.S. Census Bureau. Multivariable linear regression was utilized to assess the association between SES and arterial inflammation; mediation analysis was used to test whether systemic inflammation mediated that relationship.

Results: Thirty-nine virologically-suppressed men living with HIV were studied (mean age of 50.5±11.1 years). The median CD4 count was 663cells/mm3 (IQR: 399- 922); 82% were receiving antiretroviral therapies. Local median income inversely associated with arterial inflammation (standardized β [CI]:-0.400 [-0.757, -0.091], p=0.014, Fig 1A) after multivariable adjustment (age, Framingham risk score, statin use, antiretroviral use, current and nadir CD4 count). Similarly, after multivariable adjustment, % high school graduates inversely associated with arterial inflammation (-0.465 [-0.808, -0.161], p=0.005, Fig 1B) and CRP (-0.400 [-0.757, -0.091], p=0.014). Mediation analysis demonstrated the impact of SES on arterial inflammation is mediated by heightened systemic inflammation, namely: ↓ SES (as graduation rate)→↑CRP → ↑arterial inflammation accounting for 44% of the total effect (p<0.05).

Conclusion: In individuals living with HIV, community-level SES factors associate significantly with arterial inflammation, independently of traditional risk factors, statin therapy, and level of HIV disease control. The link between lower SES and arterial inflammation appears to be mediated by increased systemic inflammation. Strategies to recognize SES as a CV risk factor in HIV as well as targeted interventions may be helpful in reducing HIV-associated arterial inflammation as well as clinical CV events.



646 INFLAMMATORY PHENOTYPES PREDICT PULSE WAVE VELOCITY CHANGE ON ART IN MALAWIAN ADULTS

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Background: Inflammation has been linked to vascular dysfunction and increased risk of cardiovascular disease. In low-income settings, drivers of inflammation are multiple, with infectious and environmental factors contributing. We hypothesise that adult people living with HIV (PLWH) in sub-Saharan Africa starting ART with advanced immunosuppression can be stratified into inflammatory phenotypes that predict changes in vascular dysfunction on ART, as measured by pulse wave velocity(PWV).

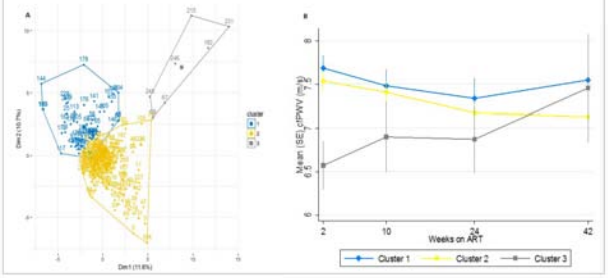
Methods: We recruited PLWH with CD4<100 cells/ul two weeks after starting ART in the REALITY trial (NCT01825031). PWV was recorded 2, 10, 24 and 42 weeks post ART. We measured markers of cell surface immune activation by flow cytometry and plasma inflammation markers by electrochemiluminescence at week 2. We identified inflammatory phenotypes using principle components analysis of 22 different markers, using linear mixed models to explore associations between inflammation clusters and change in PWV with ART.

Results: In 260 of 279 PLWH with available biomarker data we identified three clusters representing 59 (cluster 1), 194 (cluster 2) and 7 (cluster 3) subjects (Figure 1A). Cluster 1 showed markedly higher CD4 and CD8 T cell expression of HLADR and PD1 vs clusters 2 and 3 (HLADR: CD4 86% vs 69%, CD8 84% vs 72%; PD1: CD4 69% vs 39%, CD8 54% vs 33% respectively; all p<0.0001). Although small, subjects in cluster 3 had significantly higher levels of inflammatory cytokine pathways (IL6, IFNγ, IP10, IL1RA, IL10), chemotaxis (IL8), systemic and vascular inflammation (CRP, ICAM1, VCAM1) and SAA (all p<0.001); and marginally lower pre-ART CD4 (17 vs 42 cells/mm3, p=0.08). Baseline PWV was statistically lower in cluster 3 (6.3m/s vs 7.6, p=0.009), but increased over 42 weeks (log change 0.1m/s vs -0.5, p=0.07, Fig 1B). In mixed models, IL1RA was independently associated with lower baseline PWV (log -0.32m/s per pg/ml higher, p=0.02) and attenuated decline in PWV by week 24 (change in log slope +0.39m/s per pg/ml higher, p=0.01). Cluster 3 also had lower adjusted baseline

PWV (log -0.13m/s, p=0.005) but no adjusted change in PWV over time (log +0.23m/s, p=0.13).

Conclusion: In PLWH from low income settings with high pre-ART T cell activation, PWV improves (declines) on ART. However, we identified a cluster with a hyper-inflamed biological profile in whom PWV increased, with IL1RA a potential marker of this hyper-inflamed state and vascular dysunction. The clinical implications of this phenotype require further research.

Figure 1. A) Cluster map of 22 inflammatory biomarkers for 260 HIV-infected adults initiating ART with CD4<100 cells/ul. **B)** Mean Pulse Wave Velocity (m/s) over 42 weeks of ART according to inflammatory biomarker cluster.



647 TOCILIZUMAB ALTERS LIPIDS IN HIV+ INDIVIDUALS IN A RANDOMIZED, DOUBLE-BLIND STUDY

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Background: Cardiovascular disease (CVD) risk is increased in HIV infection, despite suppressive antiretroviral therapy (ART). Increased IL-6 levels are linked to CVD, and are predictive of morbidity and mortality in HIV infection. Tocilizumab (TCZ), a monoclonal antibody that inhibits IL-6 activity, can reduce inflammation and improve disease outcomes in individuals with rheumatoid arthritis (RA). Increased serum lipids (total cholesterol, HDL, LDL) were observed following TCZ treatment, but were not significantly linked to CVD risk in the RA population. The effects of TCZ on inflammation, lipid profiles, and clinical outcomes in HIV+ individuals is not known.

Methods: This was a phase I/II double-blind, placebo controlled, crossover trial of TCZ administered intravenously (IV) every 4 weeks for 3 doses. Male and female ART-treated HIV+ study participants were randomized to receive either TCZ or placebo followed by a 12 week washout period and treatment crossover. At each study visit, lipid panels and detailed lipidomics analyses, measuring ~1200 lipid species across 13 classes, were performed by mass spectrometry.

Results: Traditional lipid measurements for total cholesterol, LDL, and VLDL levels were increased following TCZ treatment (p<0.01 for all). Plasma concentrations of total lipids (p=0.0001), and concentrations of the lipid classes, CE, CER, DAG, FFA, HCER, LPC, LPE, PC, PE, SM, TAG, were increased following TCZ treatment compared to baseline and placebo (p<0.05 for all). We also measured significant changes in concentrations of 129 individual lipid species (p<0.05). Additionally, fatty acid composition was altered among lipid species; TCZ treatment reduced the proportion of free saturated fatty acids (SaFAs) (47% vs 43%, p=0.05), and increased the proportion of free monounsaturated fatty acids (MUFAs) (32% vs. 35%, p=0.06) and polyunsaturated fatty acids (PUFAs) (21% vs 22%). In vitro exposure of PBMCs to SaFAs induced inflammatory cytokine production and monocyte activation.

Conclusion: TCZ therapy alters lipid profiles in HIV+ individuals on ART. The concentrations of multiple lipid classes increased during TCZ treatment, however, the SaFA/UFA ratio was improved for some classes. IL-6 blockade may reduce some indices of inflammation in HIV+ individuals, but also exacerbates lipid levels, potentially limiting benefits in this population. Further study is needed to determine the consequences of TCZ-mediated lipidome alterations on CVD risk.

648 HDL CHOLESTEROL EFFLUX CAPACITY AND INCIDENT ASCVD IN HIV: IMPACT OF HAART

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Background: The mechanism(s) beyond traditional risk factors driving the increased atherosclerotic cardiovascular disease (ASCVD) risk among people with HIV (PWH) are unclear. In the general population, incident ASCVD events are associated with impaired macrophage HDL cholesterol efflux capacity (CEC), a derangement previously reported among PWH. We hypothesized that impaired CEC is associated with incident ASCVD events among PWH receiving ART. Additionally, we evaluated whether impaired CEC contributes to the differential ASCVD event rates reported for certain ARVs.

Methods: We selected participants from the AIDS Clinical Trials Group (ACTG) Longitudinally Linked Randomized Trials (ALLRT) cohort with samples available after 48 weeks of ART who experienced an ASCVD event (acute myocardial infarction or stroke) and matched them 5:1 in a case-cohort study design with participants who remained free of ASCVD. We measured macrophage-specific CEC to apolipoprotein B-depleted plasma from cases and controls at week 48 following ART initiation and evaluated the association of CEC with incident ASCVD event, controlling for ASCVD risk factors Finally, we compared CEC in participants randomized to ATV vs. Darunavir (DRV), Efavirenz (EFV) or Raltegravir (RAL), and to ABC vs. Tenofovir (TDF).

Results: We included 1024 participants (114 cases and 910 randomly selected controls); Mean age 41 y, 80% Male, 47% Black, 29% current smokers, mean SBP 121, mean total cholesterol 191, mean BMI 27, viral suppression was 90% at week 48. In a fully adjusted model that included traditional risk factors, HDL cholesterol , and virologic suppression status at week 48, hazard ratio for ASCVD per 1 SD increase in CEC was 0.86 (95% CI: 0.70 – 1.06). CEC was not higher in participants who had achieved virologic suppression (VL<50 copies/mL; n=817): p=0.19. ATV was associated with a higher CEC when compared to other "third" drugs (DRV, EFV or RAL). There was a trend toward lower CEC with ABC compared to TDF. Table 1 summarizes the models.

Conclusion: Unlike data from the general population, we did not observe an inverse association of CEC with risk of ASCVD among HIV-infected participants on ART. ATV use was associated with less impaired CEC than DRV, EFV and RAL, but not with lower risk of incident ASCVD events. There was a trend for lower CEC with ABC vs. TDF exposure. Larger studies will be required to fully evaluate whether certain ARVs alter CEC and its role in ASCVD progression.

Table 1. HDL Cholesterol Efflux Capacity (CEC) in Specific Antiretrovirals (ARVs) and HR for ASCVD events in the fully adjusted model.

		Comparative Effects of Antiretrovirals Drugs on CEC		HR for ASCVD Associated with Exposure to Specific Antiretrovirals
Antiretroviral	**N**	**Mean CEC (SD)**	**CEC Comparison**	**HR for ASCVD (95% CI, p value)**
"Third" Drugs			**(vs. ATV)**	
Atazanavir (ATV)	187	0.95 (0.30)	Ref.	0.88 (0.49 – 1.60; p=0.68)
Darunavir (DRV)	82	0.82 (0.21)	**p<0.001**	1.03 (0.32 – 3.40; p=0.96)
Efavirenz (EFV)	378	0.88 (0.30)	**p=0.01**	0.67 (0.44 – 1.04; p=0.07)
Raltegravir (RAL)	88	0.87 (0.26)	**p=0.05**	0.60 (0.14 – 2.52; p=0.48)
NRTIs			**(vs. ABC)**	
Abacavir (ABC)	236	0.86 (0.30)	Ref.	0.91 (0.58 – 1.42; p=0.67)
Tenofovir (TDF)	431	0.89 (0.26)	P=0.06	0.83 (0.32 – 2.97; p=0.75)

649 EVIDENCE FOR PLEIOTROPIC EFFECTS OF LIPID-LOWERING DRUGS DURING SUPPRESSIVE HAART

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Background: Statin use in HIV-infected patients is associated with improved virologic control, with decreased all-cause mortality, and decreased rates of non-AIDS defining conditions (NADC) like cancer and liver fibrosis. This has

not been well studied for other preventive medications, including other lipid-lowering (LL) drugs.

Methods: We compared ongoing and past use of statins and other preventive drug classes for their association with death, cancer, severe infection (excluding bronchitis, cellulitis, and urinary infections), and cardio- or cerebrovascular (ASCVD) events identified by ICD-9 code. We included all HIV infected US Veterans from 1995-2011 after their 1st undetectable HIV viral load on HAART and used Cox models with inverse probability weighting (IPW) for treatment and censoring. We built time-updated drug exposure models from pharmacy outpatient refill and inpatient prescription data and categorized drug exposure on a weekly basis. We defined ≥75% drug use in the past month as current use, ≥98% use in the past year as consistent use, and last drug exposure >1 year ago as remote use. We calculated propensity scores (PS) for each exposure category using multivariable generalized linear models of main effects and 2-way interactions of the following parameters: calendar year, VA station size, follow-up frequency, demographics, comorbidities including smoking and drug use, HAART-type and -adherence rate, degree of virologic suppression, CD4 counts, liver and kidney function, hemoglobin, body mass index, systolic blood pressure as well as total and HDL cholesterol.

Results: We followed 23,267 patients for a median of 5.2 years (IQR: 2.5-9.2). Median age at inclusion was 53 years (IQR 46-60). 97% of patients were male, 46% black, 37% white, and 56% ever smoked. 36% had an exposure to statins, but only 16% of follow-up years were classified as ongoing statin exposure. Hazard ratios with 95% confidence intervals for death and NADC are shown in the table.

Conclusion: We show a protective effect of statins and other LL drugs on death and NADC which had not been described for other LL drugs. The statin mortality benefit may be reflective of the reduced rates for cancer and infections and was seen despite their positive association with ASCVD events that remained after IPW. This association was weaker for other LL drugs, possibly explaining their greater mortality benefit. Of note, use of cardiac aspirin was not only associated with an increased risk of death but also cancer and infection.

Exposure Category		Patient Years	Death	Cancer	Infection	ASCVD Event
p<0.05* p<0.001*		140,130	n=4,622	n=3,469	n=6,618	n=4,027
				consistent use		
Lipid Lowering Agents (Ref: never)						
Statins	remote	8,765	0.97 (0.85-1.11)	0.78* (0.65-0.94)	0.88 (0.77-1.00)	1.21 (1.04-1.41)
	current	21,780	0.53*(0.46-0.62)	0.73*(0.58-0.91)	0.72*(0.64-0.81)	1.59*(1.41-1.79)
Fibrates	remote	6,942	0.91 (0.77-1.07)	0.78*(0.64-0.97)	0.93 (0.79-1.10)	1.19 (0.99-1.42)
	current	7,558	0.37*(0.26-0.52)	1.03 (0.65-1.63)	0.90 (0.72-1.14)	1.07 (0.84-1.36)
FishOil/Niacin/Ezetimibe	remote	4,771	0.85 (0.68-1.06)	0.72*(0.55-0.93)	0.77*(0.62-0.96)	0.96 (0.77-1.19)
	current	7,558	0.34*(0.22-0.54)	0.80 (0.48-1.34)	0.83 (0.61-1.12)	1.35 (1.01-1.80)
Antihypertensives (Ref: never)						
Angiotensin Antagonists	remote	10,238	1.86*(1.63-2.13)	0.87 (0.74-1.02)	1.12 (1.00-1.26)	1.51*(1.31-1.74)
	current	24,982	1.16*(1.02-1.33)	0.97 (0.82-1.15)	1.11*(1.01-1.22)	2.03*(1.82-2.26)
Calcium Channel Blockers	remote	12,390	1.84*(1.62-2.08)	1.00 (0.86-1.17)	1.16*(1.04-1.29)	1.65*(1.44-1.88)
	current	12,075	1.23*(1.06-1.44)	1.30 (0.94-1.80)	1.16*(1.03-1.30)	1.98*(1.72-2.27)
Cardiac Aspirin (Ref: never)	remote	16,659	1.12*(1.00-1.24)	0.97 (0.85-1.11)	1.07 (0.98-1.18)	1.37*(1.22-1.53)
	current	10,451	1.22*(1.07-1.39)	1.62 (1.01-2.59)	1.14*(1.02-1.28)	2.98*(2.63-3.37)
Vitamin D (Ref: never)	remote	3,299	1.23 (1.01-1.48)	0.98 (0.74-1.28)	0.90 (0.72-1.14)	0.92 (0.73-1.18)
	current	4,672	0.99 (0.81-1.21)	1.00 (0.44-2.27)	1.21 (0.99-1.49)	1.11 (0.87-1.41)

650 PCSK9 AND HIV INFECTION: CORRELATION WITH DYSLIPIDEMIA, INFLAMMATION, AND HAART

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Background: Lipid profile is generally deranged in antiretroviral (ART)-naïve HIV+ patients due to HIV infection severity and immunodeficiency state. Proprotein convertase subtilisin/kexin type 9 (PCSK9), a major regulator of cholesterol metabolism, is induced in some inflammatory states with a trend toward an increase in plasma levels in HIV untreated/treated patients compared to healthy controls. Whether plasma PCSK9 levels may decrease after ART initiation is not established. We measured plasma lipid and PCSK9 levels in ART-naïve HIV+ patients and investigated the impact of ART initiation on these parameters

Methods: This is a longitudinal study of 82 HIV+ ART-naïve patients not receiving any lipid-lowering treatment. At baseline and after three and six months of ART plasma total cholesterol (TC), low density lipoprotein (LDL)-C, high density lipoprotein (HDL)-C, triglyceride, lipoprotein(a), PCSK9 and high-sensitivity C-reactive protein (hsCRP) levels were evaluated

Results: At baseline plasma PCSK9 levels were significantly associated with CD4 T cell count (rho=-0.52, p=0.001), HIV-1 RNA viral load (rho=0.44, p<0.001), body mass index (rho=-0.33, p=0.002) and HDL-C (rho=-0.41, p<0.001), whereas no association was found with LDL-C and hsCRP. Initiation of ART was associated with a significant increase in TC, LDL-C, HDL-C and lipoprotein(a) levels and a significant decrease in PCSK9 and hsCRP levels. These changes were consistent for different ART regimens. TC and HDL-C but not LDL-C variations were associated with PCSK9 variation (Table 1).

Conclusion: Baseline PCSK9 levels are related to immuno-virological parameters but appear uncoupled from LDL-C levels. A complex lipid profile perturbation, including also a PCSK9 reduction, follows ART initiation

Effects of ART on lipids and inflammation

	Baseline	3 months	6 monhts	P
Total cholesterol, mg/dL	149 ± 37	167 ± 37	173 ± 41	,000
LDL cholesterol, mg/dL	88 ± 27	98 ± 28	100 ± 33	,003
HDL cholesterol, mg/dL	38 ± 12	42 ± 9	45 ± 11	,000
Triglycerides, mg/dL	91 (72-140)	115 (73-171)	107 (74-154)	,088
Lipoprotein(a), mg/dL	7.3 ± 9.1	9.6 ± 12.2	11.2 ± 15.5	,000
PCSK9, ng/mL	429 ±(201-832)	273 ±(157-446)	261 ±(137-442)	,000
hs-CRP, mg/L	2.1 ± (0.8-6.6)	1.3 ±(0.7-2.7)	1.1 ± (0.7-2.5)	,000

Predictors of Δ-PCSK9 levels

Dependent variable:	β	P
Δ-PCSK9 levels		
CD4 cell count, cell/µL	0.157	,195
HIV RNA, copies/mL	-0.073	,487
LDL cholesterol, mg/dL	0.113	,326
HDL cholesterol, mg/dL	0.058	,654
Triglycerides, mg/dL	-0.018	,885
hs-CRP, mg/L	-0.436	,001

651 LIPID CHANGES ASSOCIATED WITH TAF ARE REVERSIBLE BY SWITCHING BACK TO TDF

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Background: Switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) has shown worsening of lipid profile in people living with HIV (PLWH), but there is little data exploring changes in lipid profile in PLWH switching back from TAF to TDF.

Methods: This analysis consists of a retrospective data collection on effectively suppressed HIV-positive patients who were initially switched from TDF to TAF-based antiretroviral treatment (ARVT) due to medical or economic reasons or as a result of optimization of therapy in a single site(Center for HIV and Hepatogastroenterology). After generics of TDF were introduced a substantial proportion of patients were switched back from TAF to TDF. This analysis includes patients switched back from TAF to TDF. All components of ARVT for all patients analysed were maintained the same with the single initial substitution of TDF to TAF, and subsequent substitution of TAF to TDF. Only patients on stable lipid lowering therapy were included. We previously reported increase in total and LDL-cholesterol in patients switched from TDF to TAF. This analysis includes patients switched back to TDF after at least of 60 weeks of exposure to TAF in regular clinical care. Lipid profile was measured at 12 weeks intervals.

Results: 385 virologically suppressed PLWH were initially included. Duration of TDF exposure before switching to TAF was 350(SD±201) weeks. 72 were switched back from TAF to TDF after mean duration of 87 weeks (SD±22) on TAF. Median age of 50 (SD ±12) years, 88% were male, 93% Caucasian, with a median BMI of 23.85 sqm/kg (SD ±3.9), all patients had well controlled HIV, with mean CD4 cell count of 714/µl (SD±272). After the initial switch from TDF to TAF after 12 and 24 weeks total cholesterol (TC) had increased by + 17 (SD±24) and + 14 (SD±27)mg/dl (p<0.001) Mean triglycerides had increased by + 39 (SD±94) and + 25 (SD±94) mg/dl (p<0.001). At switching, median TC was 187 mg/dl (SD ±33). Switching back from TAF to TDF led to TC decrease at week 12 by -24 mg/dl (SD ±23) (p<0.001). TC improved in 35% of patients after switching back to TDF. Triglycerides improved by -23 mg/dl (SD ±101) (p=0.009).

Conclusion: The results of our study confirm a reversible, pharmacological effect on lipid profile of a switch from TDF to TAF and back. This effect is not a universal phenomenon, but observed in about a third of the cohort. Clinical relevance of these findings requires further investigation in particular identifying patients at risk.

652 CHANGES IN LIPIDS AFTER A DIRECT SWITCH FROM TDF TO TAF

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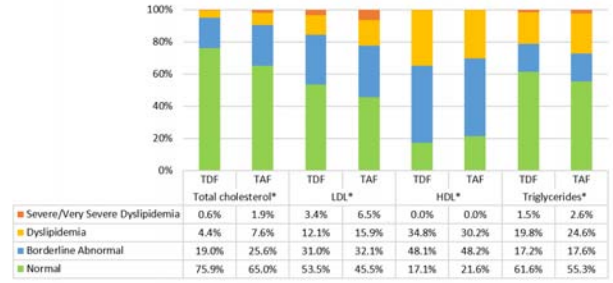
Background: Use of tenofovir disoproxil fumarate (TDF) has been associated with lower lipid levels in people living with HIV (PLWH). With the recent introduction of tenofovir alafenamide (TAF), the real-world impact on lipids of switch from TDF to TAF has not been extensively studied.
Methods: Adult PLWH prescribed TDF for ≥4 weeks who switched to TAF with ≥1 lipid measure on TDF ≤6 months prior to switch and ≥1 lipid measure ≥7 days after switch to TAF were identified in the OPERA® database (main population). Pre- and post-switch lipid levels were compared: total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and triglycerides (TG). NCEP ATPIII cut-offs defined lipid levels (mg/dL) as normal (TC <200; LDL <100; HDL ≥60; TG <150), borderline abnormal (TC ≥200 to <240; LDL ≥100 to <130; HDL ≥40 to <60; TG ≥150 to 200), dyslipidemia (TC ≥240 to <280; LDL ≥130 to <160; HDL <40; TG ≥200 to <500) or severe/very severe dyslipidemia (TC ≥280; LDL ≥160; HDL: NA; TG ≥500). Stratification by boosting agent use pre- and post-switch was performed. A sensitivity analysis included PLWH with TDF to TAF switch and no change in other ART components. Data are presented as percent changes (95% CI) and pre/post comparison of lipid categories (Pearson's Chi-square test).
Results: In the main population, 6,423 PLWH switched from TDF to TAF (84% male, 33% African American, 29% Hispanic, 43% aged ≥50 years, 91% HIV RNA <200 copies/mL at switch). After switch, lipids increased on average by TC=7.9% (95% CI: 7.4, 8.3), LDL=11.1% (9.2, 12.9), HDL=7.1% (6.2, 8.0) and TG=23.8% (22.0, 25.5). In the sensitivity analysis (n=4,305), lipids increased on average by TC=9.0% (8.5, 9.6), LDL=12.2% (9.6, 14.9), HDL=8.1% (6.9, 9.2) and TG=25.8% (23.7, 28.0). After switch to TAF, the proportion of individuals with abnormal TC, LDL and TG increased and with abnormal HDL decreased in both the main (Fig 1A) and sensitivity analyses (Fig 1B). Similar patterns were observed in percent change and pre/post lipid categories after stratification of the main population by boosting agent use.
Conclusion: In this large, diverse population of PLWH in the US, switching from TDF to TAF was associated with development of less favorable lipid profiles. These differences persisted in analyses regardless of boosting agent use and in those whose only ART change was TDF to TAF, suggesting the changes arose as a direct result of switch from TDF to TAF.

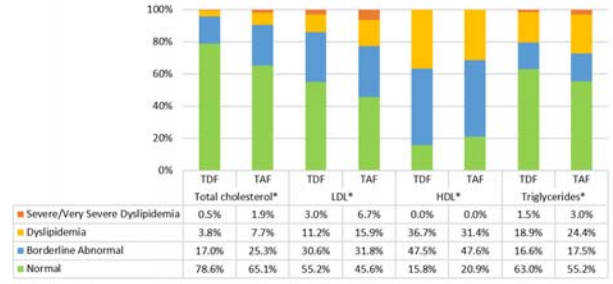
Figure 1. Lipids before and after switch from TDF to TAF

A. Complete Study Population (N=6,423)



	TDF	TAF	TDF	TAF	TDF	TAF	TDF	TAF
	Total cholesterol*		LDL*		HDL*		Triglycerides*	
Severe/Very Severe Dyslipidemia	0.6%	1.9%	3.4%	6.5%	0.0%	0.0%	1.5%	2.6%
Dyslipidemia	4.4%	7.6%	12.1%	15.9%	34.8%	30.2%	19.8%	24.6%
Borderline Abnormal	19.0%	25.6%	31.0%	32.1%	48.1%	48.2%	17.2%	17.6%
Normal	75.9%	65.0%	53.5%	45.5%	17.1%	21.6%	61.6%	55.3%

B. Population without any changes in other ARVs (N=4,305)



	TDF	TAF	TDF	TAF	TDF	TAF	TDF	TAF
	Total cholesterol*		LDL*		HDL*		Triglycerides*	
Severe/Very Severe Dyslipidemia	0.5%	1.9%	3.0%	6.7%	0.0%	0.0%	1.5%	3.0%
Dyslipidemia	3.8%	7.7%	11.2%	15.9%	36.7%	31.4%	18.9%	24.4%
Borderline Abnormal	17.0%	25.3%	30.6%	31.8%	47.5%	47.6%	16.6%	17.5%
Normal	78.6%	65.1%	55.2%	45.6%	15.8%	20.9%	63.0%	55.2%

* p-value for the pre-post switch comparison <0.0001

653 HIV-1 GP120 AND TAT-INDUCED MICROPARTICLES IMPAIR ENDOTHELIAL CELL FUNCTION

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Background: The aim of this study was to determine whether: 1) human immunodeficiency virus (HIV)-1 gp120 and Tat stimulate the release of microparticles from endothelial cells; and 2) viral protein induced EMPs are deleterious to endothelial cell function: inducing endothelial cell inflammation, oxidative stress and senescence, and increasing apoptotic susceptibility.
Methods: Human aortic endothelial cells (HAECs) were treated with recombinant HIV-1 proteins Bal gp120 (R5), Lav gp120 (X4) or Tat. Endothelial microparticles (EMPs) released in response to each viral protein were isolated and quantified. Fresh HAECs were treated with EMPs generated under control conditions and from each of the viral protein conditions for 24 h.
Results: EMP release was higher (P<0.05) in HAECs treated with R5 (141±21 MP/µL), X4 (132±20 MP/µL) and Tat (130±20 MP/µL) compared with control (61±13 MP/µL). Viral protein EMPs induced significantly higher endothelial cell release of pro-inflammatory cytokines and expression of cell adhesion molecules than control. Reactive oxygen species production was more pronounced (P<0.05) in the R5-, X4- and Tat-EMP treated cells. In addition, viral protein-stimulated EMPs significantly augmented endothelial cell senescence and apoptotic susceptibility. Concomitant with these functional changes, viral-protein stimulated EMPs disrupted cell expression of microRNAs: 34a, 126, 146a, 181b and 221 (P<0.05).
Conclusion: These results demonstrate that HIV-1 gp120 and Tat stimulate microparticle release from endothelial cells and these microparticles confer pathologic effects on endothelial cells by inducing inflammation, oxidative stress and senescence as well as enhancing susceptibility to apoptosis. Viral protein-generated EMPs may contribute to the increased risk of vascular disease with HIV-1.

654 HIV-1, CIRCULATING MICROPARTICLES, AND ENDOTHELIAL CELL DYSFUNCTION

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Background: Circulating microparticles have emerged as biomarkers and effectors of vascular disease. Elevated rates of cardiovascular disease are seen in HIV-1-seropositive individuals. The aims of this study were to determine: 1) if circulating microparticles are elevated in antiretroviral (ART)-treated HIV-1-seropositive adults; and 2) the effects of microparticles isolated from ART-treated HIV-1-seropositive adults on endothelial cell function, in vitro.
Methods: Circulating levels of endothelial (EMP)-, platelet (PMP)-, monocyte (MMP)- and leukocyte (LMP)-derived microparticles were determined by flow cytometry in plasma from 15 healthy and 15 ART-treated HIV-1-seropositive men. HUVECs were treated with microparticles from individual subjects for 24 h; thereafter, endothelial cell inflammation, oxidative stress, senescence and apoptosis were assessed.
Results: Circulating concentrations of EMPs, PMPs, MMPs and LMPs were significantly higher (~50-140%) in the HIV-1-seropositive compared with healthy men. Microparticles from HIV-1-seropositive men induced significantly greater endothelial cell release of IL-6 and IL-8 (~20% and ~35%, respectively) and NF-κB expression while suppressing anti-inflammatory miR-146a and miR-181b. Intracellular reactive oxygen species production (ROS) and expression of ROS-related Hsp70 were both higher in cells treated with microparticles from the HIV-1-seropositive men. In addition, the percentage of senescent cells was significantly higher and SIRT1 expression lower in cells treated with HIV-1-related microparticles. Finally, caspase-3 was significantly elevated by microparticles from HIV-1-seropositive men.
Conclusion: Circulating concentrations of EMPs, PMPs, MMPs and LMPs were higher in ART-treated HIV-1-seropositive men and adversely affect endothelial cells promoting cellular inflammation, oxidative stress, senescence and apoptosis. Circulating microparticles may contribute to the vascular risk associated with treated HIV-1 infection.

655 ENDOTHELIAL DYSFUNCTION IS COMMON IN EARLY HIV INFECTION AND IS REVERSIBLE WITH ART

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Background: Endothelial dysfunction is an important mechanism for cardiovascular diseases (CVD); however, the prevalence of endothelial dysfunction during early HIV infection and its reversibility with early antiretroviral therapy (ART) is unknown. Endothelial dysfunction can be reliably assessed by noninvasive measurement of peripheral arterial tonometry using the reactive hyperemia index (RHI). We evaluated RHI in ART-naïve early HIV seroconverters and after early ART.

Methods: RHI determinations (using EndoPAT 2000) were made in US Air Force members diagnosed with HIV infection between September 1, 2015 and September 30, 2017 (n=61); ART was initiated immediately after RHI testing. Log-transformed RHI values of <0.51 and ≥0.51 were defined as abnormal or normal, respectively. A subgroup of patients (n=41) had repeat RHI assessments 6.44 (IQR, 5.98-7.82) months after diagnosis.

Results: Patients were mostly younger males (males, 95.1%; African American, 57.4%; median age at diagnosis 27 years) enrolled on average within 12 months of the estimated date of seroconversion; they had fewer CVD risk factors and relatively preserved CD4+ counts (approximately 500 cells/mm3) (Table). At HIV diagnosis, 14 (23.0%) had an abnormal RHI. Age (per 10 year increase) was associated with an abnormal RHI (odds ratio=2.15; P=0.089) while other demographic features, CVD profiles, or HIV disease characteristics were not significant. Forty patients received integrase inhibitor-based regimens; one patient declined ART. Early ART was associated with a significant increase in RHI (n=40; mean (±SD) increase of 0.13 (±0.33; P=0.021); the mean (±SD) increase in RHI was greater in those with an abnormal compared with normal RHI at HIV diagnosis (0.33 [±0.34] vs 0.05 [±0.30]; P=0.03). Of the 11 persons with an abnormal RHI at diagnosis and a follow-up RHI assessment, 8 (72.7%) had normalized RHI. The patient who declined ART converted from a normal (0.60) to abnormal (0.11) RHI after 8.3 months of follow-up.

Conclusion: In young, recent HIV seroconverters with low CVD risk, nearly 25% had endothelial dysfunction by RHI assessment. Endothelial dysfunction could not be attributed to HIV disease characteristics (i.e., low CD4, high viral load). Endothelial dysfunction was reversible with early ART in the majority of patients. Conceivably, persistent endothelial dysfunction and associated CVD complications during HIV infection may relate to delayed ART.

Characteristics	Normal RHI at HIV Diagnosis (n=47)	Abnormal RHI at HIV diagnosis (n=14)	P-value
Log-transformed RHI at HIV diagnosis	0.82 (0.20)	0.30 (0.18)	<0.001
CD4 count at HIV diagnosis (cells/mm^3)	530 (436-673)	574 (483-670)	0.980
Viral load at HIV diagnosis (log_{10}c/ml)	4.37 (0.82)	4.61 (0.51)	0.204
Time from last negative HIV test to first positive HIV test (months)	16.76 (7.97-24.30)	22.77 (17.11-24.57)	0.396
Time from estimated date of seroconversion to baseline RHI (months)	10.05 (5.04-13.11)	12.11 (9.39-13.36)	0.346
Body mass index (BMI)(kg/m^2)	25.96 (4.31)	26.90 (2.59)	0.321
Diabetes mellitus type II	0 (0%)	0 (0%)	N/A
Hypertension	3 (6%)	1 (7%)	>0.999
Low-density lipoprotein (LDL)(mg/dL)	91 (78-125)	107 (86-138)	0.387
Tobacco dependence	9 (19%)	3 (21%)	>0.999
Estimated date of seroconversion defined as midpoint from last HIV negative test to first HIV positive test; Values are number (%), mean (±standard deviation), or median (interquartile range)			

656 ADVANCED GLYCATION END PRODUCTS, INFLAMMATION, AND ENDOTHELIAL DYSFUNCTION IN HIV

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Background: HIV-infected individuals are at an increased risk of premature aging and comorbidities. The mechanisms underlying these complications remain poorly understood. Advanced glycation end products (AGEs) are produced with aging and are increased in inflammatory and oxidative stress conditions. Elevated AGEs are associated with the progression of different pathological conditions such as diabetes and renal diseases. Their role in HIV remains unknown.

Methods: This is a cross-sectional study involving 90 individuals (68 HIV+ and 22 healthy controls matched by age and sex). AGEs levels were assessed using three different modalities: five different AGEs were measured in the serum; skin AGEs were determined with a non-invasive reader; dietary AGEs were estimated using 24-hour dietary recalls. Markers of inflammation, immune activation, and endothelial dysfunction (by pulse wave velocity and peripheral arterial tonometry) were also measured. Classical t-test and chi-square tests were used to compare AGEs between groups. Spearman correlations were used to explore relationships between variables and were then assessed while adjusting for demographics, BMI, CD4, and viral load.

Results: Overall, 71% were male, 68% were African American, with a mean age of 53 years. Among HIV-infected individuals, all participants were on ART by design and most participants (78%) had an undetectable HIV-1 RNA level (≤20 copies/ml). Skin and serum AGEs were significantly higher in HIV-infected participants compared to uninfected controls (p<0.01), while no differences in dietary AGEs were found between groups(p=0.2). In the HIV-infected group, but not in controls, skin and circulating AGEs were significantly associated with inflammatory and oxidative markers, and with endothelial dyfunction (table). These associations remained significant after adjusting for clinically relevant factors.

Conclusion: For the first time, we found higher levels of serum and skin AGE despite similar dietary AGE, in HIV infected individuals, suggesting intrinsic producton of AGE. The relationship between serum/skin AGE and inflammatory, oxidative and cardiovascular markers highlight the potential implications of AGEs in chronic inflammation, oxidative stress, and endothelial dysfunction in HIV, suggesting a new potential target for HIV-associated heightened inflammation and cardiovascular risk.

Table: Correlations of AGEs with selected markers of inflammation, oxidative stress, and endothelial function in the HIV-infected group (selected markers shown due to space limitation).

	Skin AGE	3DGHI	CML	CEL	GH1	MG-H1	Diet AGE
Oxidative markers							
MetSO	0.1	-0.03	**0.2***	0.2	**0.4***	**0.2***	0.2
2-AAA	0.1	0.01	**0.3***	0.2	0.1	0.01	**0.2***
Inflammatory markers							
sTNF-RI	0.2	**0.2***	**0.3***	**0.3***	**0.4***	**0.3***	-0.1
sTNFR-II	0.06	**0.2***	**0.3***	**0.3***	**0.2***	**0.2***	-0.1
d-dimer	0.1	0.1	**0.2***	0.2	0.1	**0.3***	-0.2
sCD163	**0.4***	-0.01	0.1	0.1	0.2	0.1	-0.02
Cardiovascular risk assessment							
RHI	0.01	-0.2	**-0.3***	**-0.3***	-0.2	**-0.3***	-0.01
AI	**0.4***	-0.1	-0.2	-0.1	-0.02	-0.1	-0.2
PWV	**0.3***	0.2	-0.1	-0.01	-0.1	-0.1	0.1

** Denotes p-value<0.05. AGEs: Advanced glycation end products; MetSO: methionine sulfoxide 2-AAA: 2-aminoadipic acid; 3DGHI: 3-deoxyglucosone hydroimidazolone; CML: Carboxymethyl lysine; CEL: Carboxyethyl lysine; GH1, glyoxal hydroimidazolone; MG-H1: Methylglyoxal hydroimidazolone; sTNF-RI and -RII: soluble tumor necrosis factor receptors I and II; sCD163: soluble markers of monocyte activation CD163; RHI: reactive hyperactive index; AI: augmentation index; PWV: pulse wave velocity.*

657 CUMULATIVE ART EXPOSURE IS ASSOCIATED WITH ENDOTHELIAL AND IMMUNE ACTIVATION IN HIV

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Background: Immune activation and inflammation persist in people living with HIV (PLWH) despite ART-mediated HIV suppression. Whether ART exposure is associated with residual inflammation remains unclear. We aimed to assess the association of cumulative ART exposure, quantified using tenofovir diphosphate (TFV-DP) in dried blood spots (DBS), with biomarkers of inflammation and immune activation in chronically-treated PLWH with viral suppression.

Methods: DBS and plasma were collected at two time points (6 months apart) in PLWH taking a tenofovir disoproxil fumarate (TDF)-based regimen

who were virologically-suppressed (<50 copies/mL) for ≥12 months. TFV-DP in DBS was quantified using a validated LC-MS/MS assay, and concentrations of 17 biomarkers of inflammation and immune activation were measured by electrochemiluminescence or ELISA. Log-transformed TFV-DP concentrations were analyzed using a mixed-effects model, providing estimates of percent change in plasma biomarker concentrations for every ½ $\log_e$ increase in TFV-DP in DBS. Data are presented as median [Q1, Q3] or geometric mean [95% confidence interval].

Results: A total 123 visits from 69 participants (14 women, 19 Black, 8 Hispanic) with virologic suppression were analyzed. Median age and duration of HIV suppression were 48 [41, 57] and 4 [3, 7] years, respectively. Median time between visits was 6 [4, 8] months. The geometric mean TFV-DP for all visits was 1704 [1495, 1943] fmol/punch. After adjusting for age, gender, race, body mass index, tobacco use and statin use, TFV-DP in DBS was directly associated with biomarkers of inflammation (interleukin-8, tumor necrosis-α, serum amyloid A protein), monocyte activation (soluble CD14), T-cell activation (soluble CD27), and soluble intercellular and vascular cell adhesion molecules (sICAM-1 and sVCAM-1), as noted in the Table.

Conclusion: In PLWH with long-term viral suppression on TDF-based ART, high TFV-DP in DBS was associated with higher biomarkers of endothelial activation, immune activation and inflammation. In contrast to the decrease in systemic inflammation/immune activation observed in viremic PLWH who initiate ART, these findings suggest that higher ART exposure could have a different effect in biomarkers of inflammation in chronically-suppressed individuals. Conversely, immune activation and inflammation could also influence TFV-DP in DBS. Further research is required to elucidate the mechanism and clinical significance of these findings.

Table. Percent difference in plasma concentrations of biomarkers of endothelial activation, immune activation and inflammation according to TFV-DP in DBS.

Biomarker	Unadjusted			Adjusted*		
	Percent change for every ½ log increase in TFV-DP**	95% CI	p-value	Percent change for every ½ log increase in TFV-DP**	95% CI	p-value
sVCAM-1	10.2	(5.6, 15.1)	<0.001	6.6	(3.7, 9.6)	<0.001
sICAM-1	9.8	(4.3, 15.7)	<0.001	7.2	(4.0, 10.5)	<0.001
sCD27	8.9	(3.3, 14.8)	0.002	6.0	(0.4, 11.9)	0.038
sCD14	7.7	(2.6, 13.0)	0.003	8.4	(2.8, 14.2)	0.003
IL-8	9.7	(-0.4, 20.8)	0.060	9.7	(0.8, 19.5)	0.033
TNF-α	6.7	(-1.4, 15.5)	0.106	7.6	(2.3, 13.1)	0.005
SAA	8.7	(-14.8, 38.7)	0.498	27.9	(4.8, 56.1)	0.016

*Adjusted for age, gender, race, body mass index, tobacco use and statin use. **A ½ $\log_e$ increase in TFV-DP fmol/punch provided a meaningful increase in TFV-DP: 350 vs. 577, 500 vs. 825, 750 vs. 1237 and 1000 vs. 1649 fmol/punch. Not significant: interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-13, interferon-γ, C-reactive protein, and sCD163 (p>0.05). TNF-α: tumor necrosis factor alpha; SAA: serum amyloid A protein.

658 TRANSCRIPTOMIC BIOMARKERS OF HEART FAILURE IN PEOPLE LIVING WITH HIV

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Background: Compared to HIV-uninfected controls, people living with HIV (PLHIV) have a 25-80% higher risk of heart failure (HF), including both reduced ejection fraction HF (HFrEF) and preserved ejection fraction HF (HFpEF). HF is therefore a prevalent condition in HIV that may increase substantially as the HIV-infected population ages. However, very little is known about HF risks in the current ART treatment era and the goal of this study was to identify a peripheral immune cell transcriptomic signature of HF in PLHIV. Our hypothesis is that functional genomic variation related to chronic inflammatory responses may drive HF risk in PLHIV.

Methods: As part of a case-control study within the Case Center for AIDS Research prospective clinical cohort (AIDS 125; UH IRB 01-98-55), we performed total RNA sequencing and immunophenotyping of PBMCs and classical monocytes obtained from (a) 10 HIV+ subjects with adjudicated incident HFrEF; (b) 6 HIV+ subjects with adjudicated incident HFpEF; and (c) 16 age- and gender-matched control subjects without HF. Low input libraries were generated using Kapa RNA Hyper kits and sequenced on an Illumina NextSeq 550 (75 bp, paired-end, 30 million reads/sample). Differentially expressed genes were found by two-group t test (P≤0.05) and organized into top pathways by P value (P≤0.05) via gene set variation analysis (GSVA).

Results: RNASeq analysis of PBMCs revealed enrichment of potentially therapeutically targetable pathways in PLHIV and HF, including adipogenesis and hypoxia, IL1 signaling, TGFB and CTLA4 signaling, and the fibrin-collagen formation system. RNASeq of classical monocytes revealed enrichment of additional pathways in PLHIV and HF, including hypoxia signaling, PI3K AKT MTOR activation, CXCR4 signaling, relaxin signaling, and TNFA/TGFB signaling. Our immunophenotyping analysis found that PLHIV with HF have significantly higher expression of CD57, a marker of senescence, on their CD4 T cells compared to non-HF PLHIV (p=0.01). Linear regression modeling integrating both data types identified upregulation of EGF/TGFB family genes as significantly associated with higher expression of CD57 on CD4 T cells.

Conclusion: We have identified proinflammatory gene expression signatures that correlate with HF in PLHIV and constitute candidate biomarkers of HF in HIV alongside our immunophenotyping data. Our data provide a platform for future investigation of the inflammatory factors associated with chronic HIV infection over time and those that may promote HF risk.

659 HIV/HCV-SPECIFIC MARKERS AND ECHOCARDIOGRAPHIC PULMONARY ARTERY SYSTOLIC PRESSURE

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Background: Pulmonary hypertension is associated with increased mortality in those with HIV compared to matched, uninfected controls. In small cohorts, hepatitis C virus (HCV) co-infection appears to increase pulmonary hypertension risk. We hypothesized that markers of HIV/HCV disease activity would be associated pulmonary artery systolic pressure (PASP).

Methods: We performed a cross-sectional study of participants from the Veterans Aging Cohort Study (VACS) enrolled April 2003 through October 2015 referred for an echocardiogram to examine the association between markers of HIV/HCV viral status and PASP. We performed multiple linear regression analysis to determine whether HIV/HCV mono-infection or coinfection were associated with higher PASP, adjusting for comorbidities with known PH associations and HIV/HCV status. We performed subset analyses, including markers of disease severity as follows: 1) restricted to HIV+ subjects to assess the association of HCV coinfection, higher HIV viral load, lower CD4+ T-cell count, and antiretroviral therapy (ART) with PASP levels and 2) restricted to those with chronic HCV infection to determine whether higher HCV viral load or interferon use was associated with higher PASP.

Results: Among the 8,226 subjects in our sample, 2,194 (27%) had HIV only, 540 (7%) had HCV only, and 637 (8%) were HIV-HCV coinfected. In adjusted analyses, we did not observe an association between HIV mono-infection ($\hat{\beta}$=0.19, 95% CI -0.52, 0.90), HCV mono-infection ($\hat{\beta}$=0.04, 95% CI -1.19, 1.26), or HIV/HCV co-infection ($\hat{\beta}$=0.71, CI -0.47, 1.88) with PASP. We observed a modest inverse association between CD4+ T-cell count and PASP (Table). Neither HIV nor HCV viral loads were associated with PASP. Those on "Other" ART regimens (i.e. not on NRTI+NNRTI or NRTI+PI) demonstrated reduced PASP. Interferon exposure was not associated with PASP among HCV-infected individuals.

Conclusion: Contrary to reports from smaller, selected populations we did not observe an independent association between infection with HIV and/or HCV and higher PASP. Our sample of coinfected individuals is roughly six times larger than prior published cohorts. Lower absolute CD4+ T-cell count was inversely associated with PASP suggesting that a more intact adaptive immune system has a greater impact on PASP than viral replication. ART regimens may have variable effects on PASP, which requires further study.

Table: Association of HIV/HCV Viral Markers and Medication Regimens with PASP (mmHg)

Variables* Among All HIV Cases	β-estimate (mmHg) [95% CI]	P-value
HCV positive status	0.47 [-0.86, 1.80]	0.4908
HIV viral load (10,000 copies/mL)	-0.007 [-0.03, 0.02]	0.6052
CD4+ T-cell count (200 cells/mm^3)	-0.47 [-0.86, -0.08]	0.0191
ART Regimen		
NRTI+NNRTI vs. NRTI+PI	-0.93 [-2.76, 0.90]	0.3208
Other vs. NRTI+PI	-2.08 [-3.45, -0.71]	0.0030
No ART vs. NRTI+PI	-0.49 [-2.16, 1.17]	0.5617
Variables Among All HCV Cases	**β-estimate [95% CI]**	**P-value**
HIV positive status	-0.08 [-1.92, 1.75]	0.9289
HCV viral load (10,000 copies/mL)	0.001 [-0.002, 0.003]	0.1004
Interferon exposure	0.13 [-5.60, 5.85]	0.9653

*Adjusted for: age, gender, race, hypertension status, diabetes status, dyslipidemia status, smoking status, estimated glomerular filtration rate, body mass index, hemoglobin concentration, FIB-4 (fibrosis-4) score, alcohol status, cocaine status, chronic obstructive pulmonary disease status, left ventricular ejection fraction, stroke history, heart disease history, and antiretroviral regimen (ART).

660 EVIDENCE OF PRECLINICAL MYOCARDIAL FIBROSIS IN ART-TREATED PLWH IN SOUTH AFRICA

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Background: Cardiovascular disease (CVD) risk is higher among persons living with HIV (PLWH), based on data from U.S. and Europe showing excess risk for atherosclerotic coronary heart disease. In sub-Saharan Africa, hypertension and heart failure are the predominant CVD manifestations, where the influence from ART-treated HIV disease remains less clear.
Methods: Asymptomatic PWLH on ART and uninfected controls, both without known heart failure, were enrolled in Khayelitsha, Cape Town, South Africa. Roche immunoassays estimated biomarker levels for myocardial injury (high sensitivity troponin T [cTnT] via 5th Gen) and dysfunction (NT-pro brain natriuretic peptide [NTproBNP]). PLWH then had BNP levels measured by point of care (POC) Abbott iSTAT ELISA, and cardiac magnetic resonance (CMR) imaging was performed. Biomarker elevations were defined using thresholds of: >6.0ng/L for cTnT (i.e., a detectable level), and >100pg/mL for NT-proBNP (90% sensitive for dysfunction among those <70 years old) and POC BNP (manufacturer threshold). Linear and log binomial regression was used to assess associations between biomarkers, HIV status, and CMR measures.
Results: Among 49 PLWH and 57 uninfected controls, respectively, median (IQR) age was 46 (43-53) and 50 (45-57), 61% and 63% were women, and 33% and 37% were hypertensive. Among PLWH, median (IQR) CD4+ count was 515 cells/μL (334-677), and 78% had HIV RNA <50 copies/mL. No participants had evidence of ischemic disease on ECG (Q-waves or LBBB). PLWH, versus uninfected controls, had a higher proportion with NT-proBNP levels >100pg/mL (33% vs. 19%; p=0.04) but differences in detectable cTnT were not statistically significant (45% vs. 32%; p=0.15). The proportion of PLWH with POC BNP >100pg/mL was 14%, and NT-proBNP and POC BNP levels were highly correlated (r=0.89; p<0.0001). The data table reports associations for cardiac biomarkers and CMR measures among PLWH. Elevated NT-proBNP and POC BNP levels tended to be associated with parameters reflecting myocardial inflammation and fibrosis (i.e., ECV, LGE, native T1), some measures of diastolic dysfunction, (i.e., strain rates) but not systolic dysfunction (i.e., EF).
Conclusion: These pilot data suggest that PLWH in South Africa may have ongoing myocardial inflammation and fibrosis and pre-clinical myocardial dysfunction. Future research should focus on understanding the mechanisms and clinical relevance of HIV-associated myocardial injury in sub-Saharan Africa.

Table: Estimated Difference* (95% CI) in CMR measures among PLWH on ART with High vs. Low Myocardial Biomarker Levels (n=49)

CMR Measures	cTnT > vs. ≤ 6 ng/L		NT-proBNP > vs. ≤ 100pg/mL		POC BNP > vs. ≤ 100pg/mL	
LV mass index, g/m^2	9.1 (2.5, 15.8)	p=0.01	-1.2 (-9.0, 6.6)	p=0.76	5.8 (-4.4, 15.9)	p=0.26
LV EF, %	-1.9 (-6.3, 2.6)	p=0.41	-2.2 (-7.1, 2.6)	p=0.36	2.2 (-4.2, 8.6)	p=0.50
Peak circumferential diastolic strain rate, s^{-1}	-0.1 (-0.3, 0.2)	p=0.64	-0.2 (-0.4, 0.1)	p=0.17	0.1 (-0.2, 0.5)	p=0.41
Peak longitudinal diastolic strain rate, s^{-1}	-0.0 (-0.3, 0.2)	p=0.78	-0.2 (-0.5, 0.1)	p=0.14	0.0 (-0.3, 0.4)	p=0.91
Peak radial diastolic strain rate, s^{-1}	-0.0 (-1.0, 1.0)	p=0.95	-0.9 (-1.9, 0.1)	p=0.08	-1.9 (-3.2, -0.6)	p=0.01
Average native T1 value, ms	11.6 (-18.4, 41.5)	p=0.44	32.6 (1.7, 63.5)	p=0.04	34.3 (-7.2, 75.9)	p=0.10
LV LGE volume fraction	-3.1 (-7.0, 0.8)	p=0.11	4.1 (0.0, 8.2)	p=0.05	1.8 (-3.6, 7.3)	p=0.50
Average ECV value	0.7 (-1.5, 2.8)	p=0.54	1.5 (-0.7, 3.8)	p=0.18	2.7 (0.0, 5.6)	p=0.05
Average T2 value, ms	-0.7 (-2.4, 1.1)	p=0.44	1.5 (-0.3, 3.3)	p=0.10	1.1 (-1.3, 3.5)	p=0.37

*Difference adjusted for age and sex; LV=left ventricle; EF=ejection fraction; LGE=late gadolinium enhancement; ECV=extracellular volume

661 HIV IS ASSOCIATED WITH LUNG-FUNCTION IMPAIRMENT IN THE MULTICENTER AIDS COHORT STUDY

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Background: HIV is an independent risk factor for chronic obstructive pulmonary diease (COPD), a major cause of death and disability worldwide. Although studies have measured lung function in persons living with HIV (PLWH), major limitations have included small samples, lack of HIV-negative controls or limited lung function assessment. We addressed these weaknesses by collecting spirometry (both pre- and post-bronchodilation) and single-breath diffusing capacity for carbon monoxide (DLCO) in a multicenter cohort of men who have sex with men (MSM), both HIV-positive and HIV-negative.
Methods: We included participants in the Multicenter AIDS Cohort Study seen between April 2017 - March 2018. Spirometry and DLCO were measured using standardized equipment, according to published standards, centrally reviewed for quality, and normalized (calculation of %predicted values) using published population-based equations. We tested the effect of HIV status on %predicted post-bronchodilator forced expiratory volume in 1s (FEV1) and DLCO, both as continuous outcomes and as categorical outcomes (<80% of predicted). Multivariable models were adjusted for cigarette smoking, illicit drug use, and co-infection with hepatitis B or C.
Results: Among 1305 participants who attended research visits, 1176 (90.1%) completed lung function testing. Quality control standards were met for 1126 spirometry tests and 1094 DLCO tests. PLWH were younger, less likely to be Caucasian, reported more illicit drug use, and more commonly had hepatitis co-infection (each p<0.01). We observed no difference in FEV1 %predicted by HIV status (adjusted difference of 0.9% of predicted; 95%CI: -3.1% to +1.2%; p=0.40), but DLCO %predicted was significantly lower in PLWH (adjusted difference of -2.5% of predicted; 95%CI: -4.4 to -0.6%; p=0.009) (Table). PLWH were more likely to have DLCO <80% of predicted (OR 1.56; 95%CI: 1.17 to 2.09; p=0.003). Among the HIV-positive participants, lower DLCO values were correlated with lower nadir CD4+ T-cell count (adjusted β = 0.27; p=0.016) and borderline for increasing years of ART exposure (adjusted β = -1.2; p=0.063).
Conclusion: Compared to HIV-negative MSM, HIV-positive MSM are at higher risk for impaired DLCO, but not airway obstruction. While mechanisms of DLCO impairment in PLWH are unclear, worse DLCO in PLWH has been linked to mortality and decreased functional status, suggesting it is an important health issue in this population.

Table. Comparisons of forced expiratory volume in 1 second (FEV_1) and single-breath diffusing capacity for carbon monoxide (D_LCO) among HIV-negative and HIV-positive men in the Multicenter AIDS Cohort Study. Sample sizes varied by specific lung function measures (for FEV_1 %predicted: HIV-negative n=505 and HIV-positive: n=619; for D_LCO HIV-negative n=489 HIV-positive n=602).

	HIV-negative	HIV-positive	Unadjusted Difference (95%CI) p-value	Adjusted[1] Difference (95% CI) p-value
Continuous Variable Analyses				
FEV_1 %predicted (IQR)	97 (86-107)	97 (87-107)	-0.2% (-2.2 to +1.7) p= 0.82	-0.9% (-3.1% to +1.2%) p=0.40
D_LCO %predicted (IQR)	86 (77-98)	85 (75-94)	-1.5% (-3.3% to -0.2%) P=0.086	-2.5% (-4.4 to -0.6%) p=0.009
Categorical Variable Analyses[2]				
FEV_1 <80% of predicted	15.4%	14.1%	OR 0.90 (0.65 to 1.25) p=0.54	OR 0.67 (0.67 to 1.40) p=0.85
D_LCO <80% of predicted	34.0%	39.4%	OR 1.26 (0.99 to 1.62) p=0.065	OR 1.56 (1.17 to 2.09) p=0.003

1: Adjusted for smoking status (current/former/never), illicit drug use, and hepatitis B or C co-infection. Age not included in these models, as age is included in calculations of predicted values.
2: Presented as odds ratios

662LB HIV IS NOT ASSOCIATED WITH SLEEP-DISORDERED BREATHING

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Background: Sleep-disordered breathing (SDB) and related intermittent hypoxaemia are associated with increased risk of cardiovascular disease, cognitive dysfunction, malignancy, and impaired quality of life. Although high SDB prevalence has been reported in persons living with HIV (PLWH), studies have been small, lacked relevant HIV-negative controls, relied on risk scores or self-reported sleep apnoea rather than objective testing, and/or selectively enrolled PLWH with sleep symptoms potentially biasing findings. We compared overnight oximetry measures in PLWH and HIV-negative persons with similar lifestyles participating in the POPPY study.
Methods: We recruited a subset of POPPY participants (PLWH ≥50 y/o, PLWH <50 y/o, and HIV-negative controls ≥50 y/o) without regard to sleep symptoms or sleep apnoea risk. Participants undertook overnight finger pulse oximetry with centralized quality control, with oxygen desaturation index (ODI) defined as number of oxyhaemoglobin desaturation events ≥4% per hour of sleep and SDB as >5 ODI events per hour. Associations between HIV status and ODI were assessed using linear regression; multivariable models included HIV-status/group, age, race, body mass index (BMI), marital status and hypertension.
Results: 453 of 475 (95%) participants provided analysable data: 231 older PLWH (median age 60y), 102 older HIV-negative (60y) and 120 younger PLWH (45y). SDB was present in 42%, 41% and 28% of the groups, respectively. Older PLWH had a median (IQR) ODI of 3.7/h (1.8, 7.5), which was similar to that of the older HIV-negative group (4.2/h [2.1, 7.9]; p=0.76) but higher than that of the younger PLWH (2.7/h [1.5, 5.7]; p=0.02). In multivariable analysis (Table), increased ODI was associated with higher BMI, older age, and marital status, but not HIV status (difference in ODI of -0.02/h [95%CI: -1.4 to +1.4; p=0.97]).
Conclusion: SDB is prevalent in older individuals, both with and without HIV. More severe overnight hypoxaemia is associated with expected risk factors such as obesity and older age, but not with HIV status. Further research will determine the effect of SDB and hypoxaemia on relevant HIV outcomes such as cognition, systemic inflammation, and immune activation.

Table: Multivariable linear regression model of relationship between covariates and oxygen deaturation index (ODI).

Variable	Increase/decrease in ODI (95% CI)	p-value
HIV-status		
PLWH vs HIV-negative	-0.02 (-1.41 to 1.36)	0.97
Male vs female	1.53 (-0.19 to 3.25)	0.08
Age [per 5-year]	0.34 (0.02 to 0.66)	0.04
Black-African vs white	1.56 (-0.60 to 3.73)	0.16
BMI [per 5 kg/m^2]	1.77 (1.11 to 2.42)	<0.001
Marital status		0.04
Single vs. Married/In a partnership	-0.27 (-1.46 to 0.92)	0.66
Divorced vs. Married/In a partnership	1.89 (-0.51 to 4.29)	0.12
Widow/Widower vs. Married/In a partnership	5.05 (0.59 to 9.52)	0.03
Hypertension	1.00 (-0.48 to 2.48)	0.18

663 SEX-SPECIFIC PATTERNS IN HIV-ASSOCIATED CARDIOVASCULAR MORTALITY IN NEW YORK CITY

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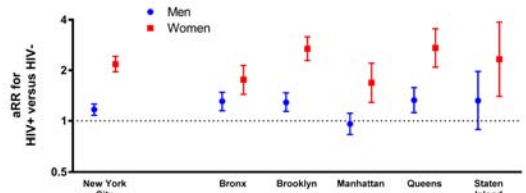
Background: We previously identified more pronounced associations between HIV status and cardiovascular disease mortality in women than men in New York City. However, because socioeconomic status may confound this relationship and New York City contains both some of the highest and lowest income counties in the nation, we re-analyzed this data restricted to the Bronx, which is both a high HIV prevalence and lower income borough/county.
Methods: We included all residents age 13+ reported with HIV to the population-based New York City HIV Surveillance Registry and living between 2007 and 2012. Surveillance data were linked with the city Vital Statistics Registry and National Death Index. Residents without HIV living in each borough, including the Bronx, were enumerated using modified US intercensal estimates after subtracting the surveillance-based counts of those with HIV. We examined sex-specific rates of death due to major cardiovascular diseases (ICD-10 codes I00-I78). Using log-linear models, we determined the association of HIV serostatus with cardiovascular disease mortality rates by sex within each borough, and compared this to the relationship across all New York City residents.
Results: There were 1,673 deaths attributed to cardiovascular disease as the underlying cause among HIV+ New Yorkers between 2007 and 2012, with 376 of these occurring among Bronx residents. In the Bronx, the age-adjusted cardiovascular disease mortality rate was 3.33/1,000 person-years (95% confidence interval [CI] 2.45-4.21) among HIV+ men and 2.47/1,000 (95% CI 1.42-3.51) among HIV+ women. In analyses of the entire city, the relative rate of cardiovascular disease mortality attributed to HIV serostatus was almost twice as high in women (rate ratio [RR] 2.18, 95% CI 1.96-2.42) than men (RR 1.17, 95% CI 1.08-1.26, P for interaction <0.001) (Figure). A similar disparity was also observed in each of the five boroughs except for the Bronx, where differences by sex were substantially attenuated (RR 1.76, 95% CI 1.44-2.14 in women vs. RR 1.31, 95% CI 1.15-1.48 in men, P for interaction 0.25).
Conclusion: After accounting for socioeconomic status through restriction, we found that sex differences in the association of HIV with cardiovascular disease mortality were attenuated. More work is needed to better characterize how socioeconomic and biological factors related to sex may affect cardiovascular disease in people living with HIV.

Figure. Adjusted cardiovascular disease mortality rate ratios (aRRs) for HIV+ versus HIV- New Yorkers, 2007-2012, by sex and borough

aRRs adjusted for age, race/ethnicity, calendar time, and in New York City overall model, borough.



	New York City		Bronx		Brooklyn		Manhattan		Queens		Staten Island	
	M	W	M	W	M	W	M	W	M	W	M	W
N CVD deaths, HIV+	746	431	270	106	316	185	266	66	139	59	25	15
Age-adj. rate per 1,000, HIV+	2.86	3.20	3.33	2.47	2.88	3.74	2.28	2.01	2.89	4.34	4.20	2.78
aRR for HIV+ vs HIV-	1.17	2.18	1.31	1.76	1.29	2.69	0.96	1.69	1.33	2.72	1.32	2.33
W:M ratio of aRRs	1.9		1.3		2.1		1.8		2.0		1.8	
P for interaction	<0.001		0.25		0.003		<0.001		0.001		0.15	

664 DIFFERENCES IN TYPES OF MYOCARDIAL INFARCTIONS AMONG PATIENTS AGING WITH HIV

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Background: The Universal Definition classifies MI by type according to the mechanism of myocardial ischemia. Type 1 MI (T1MI) result spontaneously from atherosclerotic plaque instability. Type 2 MI (T2MI) are secondary to other causes such as sepsis and cocaine-induced vasospasm resulting in oxygen demand-supply mismatch. We previously demonstrated that, in contrast to the general population, almost half of MIs among people living with HIV (PLWH) are T2MI. We conducted this study to compare MI rates by type and age among PLWH. We hypothesized that increases in rates with older age would differ by MI type, and that in contrast to the general population, T2MI would be more common in younger individuals, but there would be a measurable rate of T1MI even among 18-30 year-old PLWH.

Methods: Potential MI events were identified in the centralized data repository at 6 CNICS sites. Case identification criteria included MI diagnoses and cardiac biomarkers to optimize ascertainment sensitivity. For each potential MI, sites assembled de-identified packets with physician notes, ECGs, procedure results, and lab results. Two experts reviewed each packet followed by a 3rd if discrepancies occurred. Reviewers categorized each MI by type and identified causes for T2MI. By decade of age, we calculated T1 and T2MI rates and confidence intervals (CI) per 1000 person-years of follow-up. Rate ratios were calculated for rates of T2MI vs. T1MI per decade of age.

Results: We included 564 T1MI (54%) and 483 T2MI (46%). T1MI rates increased with older age although T1MI occurred in all decades including young adults (Table). T2MI rates were significantly higher than T1MI rates for PLWH under 40 and increased with age among those over 40 (Table). T1MI rates were similar or higher than T2MI rates among those over 40 (significantly higher for those 61-70 years of age). Of note, there were differences in causes of T2MI among those at younger vs. older ages with cocaine-induced vasospasm more common in younger PLWH while causes such as hypertensive urgency and arrhythmia were more common in older PLWH.

Conclusion: We found that among PLWH rates of T2MI were higher than T1MI until age 40 differing from what is seen in the general population, but rates of both were very high among older PLWH. Causes of T2MI differed by age with substance use prominent at younger ages and cardiovascular-related risk factors common at older ages. These results highlight the importance of evaluating MI by type among PLWH.

Table. Rates of Type 1 and Type 2 myocardial infarctions per 1000 person-years of follow-up

Age category	Rate (CI) Type I MI	Rate (CI) Type 2 MI	Rate ratio (CI) Type 2 vs Type 1 MI, p-value
18-30	0.2 (0.1-0.6)	1.1 (0.7-1.8)	5.7 (1.6-30.2), 0.002
31-40	0.6 (0.4-0.8)	1.0 (0.7-1.3)	1.7 (1.0-2.9), 0.03
41-50	2.1 (1.8-2.5)	1.7 (1.5-2.1)	0.8 (0.6-1.1), 0.1
51-60	3.3 (2.9-3.9)	2.8 (2.3-3.3)	0.8 (0.7-1.1), 0.1
61-70	4.3 (3.3-5.6)	2.9 (2.1-4.0)	0.7 (0.4-1.0), 0.05
≥71	10.5 (6.9-16.1)	9.0 (5.7-14.3)	0.9 (0.4-1.7), 0.6

CI: confidence interval; MI: myocardial infarction

665 ALCOHOL USE AND RISK OF MYOCARDIAL INFARCTION (MI): DOES MI TYPE MATTER?

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Background: People living with HIV (PLWH) are at increased MI risk. MIs are classified into type 1 (T1MI) due to atherothrombotic coronary plaque rupture and type 2 (T2MI) from supply-demand mismatch such as with sepsis. Data on alcohol and MIs in HIV are limited, conflicting and do not distinguished MI types. Understanding the relationship between alcohol use and MI by type may clarify differences in prior study findings.

Methods: PLWH in care from 6 sites completed tablet-based assessments ~every 6 months including alcohol use (AUDIT-C). Alcohol severity was defined by AUDIT-C score (0-12 points); alcohol and binge frequency were defined as number of drinking and binge days/month. Alcohol categories were none, mild and hazardous (AUDIT-C score of ≥5 for men, ≥4 for women). MIs were centrally adjudicated and categorized by type. Alcohol associations were examined using Cox models, adjusted for age, sex, race/ethnicity, hepatitis C, smoking, diabetes, hypertension, dyslipidemia, and kidney disease. All models adjusted for CD4 cell count and viral load as time-varying variables. We repeated models using time-updated alcohol use but as sensitivity models given the potential moderating effects. Due to prior studies identifying a high prevalence of "sick quitters" among non-drinkers, we repeated analyses among those with some alcohol use.

Results: Among 12,800 PLWH, 64% drank alcohol, and there were 134 T1MI and 112 T2MI during follow-up. In adjusted analyses, those reporting higher baseline alcohol scores and frequency of alcohol use had lower T1MI risk; this association was not seen for binge drinking frequency or T2MI (Table). In analyses limited to those reporting alcohol use, associations were non-significant. In analyses of alcohol use categories, a significant protective association was seen for mild alcohol use vs. no use (0.54, 95% confidence interval 0.32-0.89, 0.02) and T1MI, but not for hazardous alcohol use. Sensitivity analyses with time-updated alcohol use showed similar results for alcohol severity although alcohol frequency was no longer significant for T1MI.

Conclusion: These findings suggest a J-shaped curve for alcohol associations with T1MI for PLWH with some protective association seen for mild alcohol use although potentially driven by "sick-quitters". They highlight the influence of different alcohol definitions and the importance of carefully considering the impact of "sick quitters". These same associations were not seen for T2MI highlighting the benefits of adjudicating MIs.

Table. Associations between patterns of alcohol use and type 1 and type 2 myocardial infarction in adjusted analyses

Alcohol use definition	Type 1 MI	95% CI	P value	Type 2 MI	95% CI	P value
Alcohol score	0.9	0.8-1.0	0.03	1.0	0.9-1.1	0.5
Alcohol use frequency (days per month)	0.9	0.9-1.0	0.008	1.0	1.0-1.0	0.9
Binge frequency	1.0	0.9-1.1	0.4	1.0	1.0-1.1	0.5

** All models adjusted for age, sex, race/ethnicity, Hep C, smoking, diabetes, treated hypertension, treated dyslipidemia, eGFR <30. All models adjusted for CD4 cell count and viral load as time-varying variables*

666 CARDIOVASCULAR RISK MANAGEMENT AMONG PLWH: DOES PROVIDER SPECIALTY MATTER?

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Background: Although persons living with HIV (PLWH) are known to be at increased risk for major atherosclerotic cardiovascular disease (ASCVD) events, the impact of provider specialty managing ASCVD risk in this population remains unclear.

Methods: We conducted a retrospective analysis of PLWH with a diagnosis of hypertension (HTN) and/or hyperlipidemia (HLD) (by ICD9/10 code) receiving care at 2 major academic health systems in the Southeast between 2013 and 2017. Clinical data were obtained from the Carolinas Collaborative Research Database for all PLWH with HTN and/or HLD and without previous diagnosis of ASCVD (defined as acute coronary syndrome, stroke, coronary artery intervention or peripheral vascular disease) prior to study period. Responsible provider for HTN/HLD management were defined by medication prescription (anti-HTN or statins) and classified into 5 groups: 1) infectious diseases (ID) provider only (≥ 3 prescriptions from ID without evidence of prescription entry by other provider), 2) non-ID primary care provider (PCP) only, 3) co-managed by ID and PCP (≥3 ID prescriptions and ≥1 PCP prescription), 4) medication prescribed by other provider, 5) no prescription found. Cohort members were followed until 1st ASCVD event, death, or end of study period (12/31/17). The primary HTN outcome was meeting 8th Joint National Commission's (JNC 8) blood pressure (BP) goal of 140/90 at end of observation. The primary HLD outcome was end observation low density lipoprotein (LDL). Risk factors for failure to meet BP goals were defined using logistic regression.

Results: Of 1458 PLWH included in the analysis, 1077 (73%) had a diagnosis of HTN and 614 (42%) had HLD (see Table 1). Of persons with HTN (n = 1077), 223 (21%) were managed by ID exclusively, 184 (17%) by PCP only, 37 (3%) by both and 40% had no anti-HTN prescribed. Overall, 616 (57%) met JNC 8 BP goal. Risk factors associated with not meeting JNC 8 goals were Black race (Odds ratio (OR) 0.68, 95% CI 0.50-0.91) and exclusive management by ID (OR 0.66 (95% CI 0.48-0.91), Table 1). Of persons with HLD (n =614), the mean end observation LDL-c was 109.8 mg/dL. On regression analysis, HLD managed exclusively by ID provider was associated with a 11.8 mg/dL (95% CI 1.9-21.3) in end observation LDL-c compared to the rest of the cohort.

Conclusion: PLWH with HTN or HLD do not meet evidence-based treatment goals consistently, and provider specialty may play a role in these outcomes. Further study of optimal ASCVD care models in PLWH is needed.

Table 1. Cohort Demographics (n = 1458) and Point Estimates for Hypertension and Hyperlipidemia Outcomes

Characteristic	Number of Patients (%) (n = 1458)
Male	989 (68)
Black	913 (62)
Hispanic	50 (3)
Mean Age at Start of Observation (SD)	52.6 (7.7)
Diagnosis	
Hypertension only	839 (57)
Hyperlipidemia only	376 (26)
Hypertension and Hyperlipidemia	238 (16)
Diabetes	109 (7)
All Three Diagnoses	26 (2)
CVD Events	80 (5)
Acute Coronary Syndrome	17 (1)
Coronary Intervention w/o ACS	6 (<1)
Stroke	34 (2)
Peripheral Vascular Disease	23 (1)
Deaths	149 (10)

Variable	aOR (95%CI) for Failure to meet JNC 8 Target	Adjusted Change in (mg/dL) End Observation LDL (95%CI)*
Female	1.12 (0.85-1.47)	11.5 (1.9,21.3)
Black	**0.68 (0.50-0.91)**	2.8 (-6.3,12.0)
Hispanic	0.79 (0.30-2.11)	-8.2 (-31.8,15.5)
Age (per 1 year increase)	1.005 (0.99-1.02)	-0.3 (-0.88,0.28)
Medicaid/Medicare	0.87 (0.26-2.88)	-4.9 (-46.1,36.3)
Self Pay	0.80 (0.23-2.64)	-11.1 (-51.1,28.9)
ID Physician Managing Hypertension	**0.66 (0.48-0.91)**	**11.8 (2.8,20.8)**

667 INCREASED PREVALENCE OF PROLONGED QTC IN PERSONS LIVING WITH HIV COMPARED TO CONTROLS

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Background: An abnormal electrocardiogram (ECG) is associated with increased risk of arrhythmias and sudden cardiac death (SCD). We aimed to investigate the prevalence and associated risk factors of major ECG abnormalities, prolonged QTc and prior myocardial infarction (MI), in persons living with HIV (PLWH) and uninfected controls.

Methods: PLWH aged ≥40 were recruited from the Copenhagen comorbidity in HIV infection (COCOMO) study and matched on sex and 5-year age strata to uninfected controls from the Copenhagen General Population Study. Blood pressure, lipids, glucose and hsCRP were measured. Questionnaires were used to obtain data on smoking history and medication. ECGs were recorded on the same CardioSoft electrocardiograph and categorized according to The Minnesota Code Manual of ECG Findings definition of major abnormalities. A QT interval corrected for heart rate (QTc) >440 ms in males and >460 ms in females was considered prolonged. Prior MI was defined as major Q-wave abnormalities. We calculated binomial proportion confidence intervals (95% CI) and assessed factors associated with ECG abnormalities using a logistic regression model adjusted for age, sex, smoking, dyslipidemia, diabetes, hsCRP and hypertension.

Results: An ECG was available for 740 PLWH and 2,955 controls. PLWH were younger (median 52 vs 54), fewer had hypertension (48 % vs 63%), but more were current smokers (26% vs 12%) compared to controls. Prolonged QTc was more prevalent among PLWH (11% [9-13]) than among controls (8% [7-9]), p=.005. Prior MI was also more common in PLWH (6% [5-8]) than in controls (4% [4-5]), p=.04, but there was no difference in prevalence of major ECG abnormalities between PLWH and controls (12% [10-14]) and 12% [11-14], respectively), p=.992 (Table). In adjusted analyses, HIV was independently associated with prolonged QTc (adjusted odds ratio:1.6 [95%CI:1.2-2.1]) but not with other ECG abnormalities. Among PLWH, use of protease inhibitors, previous AIDS, CD4 count, intravenous drug use or methadone treatment were not independently associated with prolonged QTc or major abnormalities.

Conclusion: Prevalence of prolonged QTc was higher among PLWH compared to uninfected controls, and HIV remained associated after adjustment for cardiovascular risk factors. Although evidence indicated more ischaemic changes in PLWH, the risk seemed to be associated mainly with an adverse risk profile. These data suggest that continued awareness of QTc may be important in lowering the excess risk of SCD among PLWH.

Electrocardiographic abnormalities

	PLWH 740	Controls 2,955	*P*-value
Heart Rate, bpm (SD)	69 (12)	66 (11)	<.001
QTc, median ms (SD)	424 (24)	422 (22)	.024
• Prolonged*	81 (11)	229 (8)	.005
• >480ms	14 (2)	32 (1)	.076
Major Abnormalities, n (%)**	**88 (12)**	**351 (12)**	**.992**
• Major Q/QS waves (Old MI), n (%)	45 (6)	127 (4)	.04
• Minor Q/QS with ST-T (Possible old MI), n (%)	6 (1)	12 (0.4)	.157
• Intraventricular block, n (%)	34 (5)	141 (5)	.839
• RBBB with left anterior hemiblock, n (%)	2 (0.3)	10 (0.3)	>.999
• Brugada pattern, n (%)	0	0	-
• LV-hypertrophy plus ST-T, n (%)	3 (0.4)	23 (0.8)	.458
• Major QT prolongation, n (%)	9 (1)	32 (1)	.757
• Atrial fibrillation / flutter, n (%)	4 (1)	28 (1)	.377

Bpm: Beats per minute; LV: Left ventricle; MI: Myocardial Infarction; n: number; QTc: QT corrected for heart rate using Bazett's formula; RBBB: Right Bundle Branch Block; SD standard deviation

*QTc > 450ms for men and >460ms for women (only where heart rate <100 bpm)
** Major abnormalities according to Minnesota code manual for ECG findings

668 HYPERTENSION CONTROL IN INTEGRATED HIV/NCD CLINICS IN THE SEARCH STUDY

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Background: There has been a call for integration of non-communicable disease (NCD) care within HIV services and across to HIV-uninfected populations but little data. In the SEARCH study (NCT01864603) where existing HIV chronic care systems are leveraged to provide care for persons with hypertension, with or without HIV, we sought to assess the feasibility, effectiveness, and systems factors that influence hypertension control in HIV-infected and uninfected persons.

Methods: Following population screening of HIV and hypertension (HTN) in 34,704 adults living in ten communities in rural Uganda, individuals with either or both diseases were referred to an integrated chronic disease clinic. Based on Uganda treatment guidelines follow-up visits were scheduled every 4 weeks when blood pressure was uncontrolled (SBP > 140 mmHg or DBP > 90 mmHg) and every 12 weeks when blood pressure was controlled. Drug stock-outs sometimes required more frequent visits. We assessed visit interval (whether more or less frequent than clinical indication) and HTN outcomes for HIV-infected and uninfected patients with HTN who linked to NCD care over 3 years of follow-up. We describe univariate distributions of demographic and clinical variables among HIV-infected and uninfected individuals. We then used multilevel mixed-effects logistic regression to evaluate predictors of HTN control.

Results: Within 1 year 2,038 participants (89 HIV+ and 1,949 HIV-) with HTN linked to care and contributed 15,653 follow-up visits over 3 years. Median duration of follow-up was 583 days and 742 days among HIV-infected and HIV-uninfected respectively. HTN control was achieved at 46% (44-48%) of follow-up visits. 20% of visits among those with HTN control were scheduled at 4-8 weeks (vs 12 weeks) due to drug shortages. In multivariate analysis adjusting for HTN stage, medication prescription at the previous visit, HIV status, and clinic site, scheduled visit interval more frequent than clinical indication for patients with controlled HTN was associated with lower HTN control (aOR = 0.88; 95% CI 0.77-0.98). HIV-infected patients were more likely than uninfected patients to have controlled blood pressure (aOR 1.33; 95% CI 1.00-1.77).

Conclusion: HTN control in an integrated NCD/HIV model was higher than previously reported in SSA and control was more likely among HIV-infected. Similar to HIV care, visit frequency determined by drug supply chain rather than clinical indication is associated with worse HTN control.

	Adjusted OR (95% CI) for HTN control	*p* value
Hypertension Stage at previous visit		
0	1.0	
1	0.54 (0.47, 0.63)	<0.001
2	0.26 (0.22, 0.31)	<0.001
Medication prescribed at previous visit		
Yes	1.25 (1.09, 1.44)	0.002
No	1.0	
HIV Status		
Infected	1.33 (1.00, 1.77)	0.05
Uninfected	1.0	
Scheduled visit interval		
Per HTN treatment guidelines	1.0	
More frequently than guidelines	0.88 (0.77, 0.98)	0.03
Less frequently than guidelines	0.83 (0.71, 0.97)	0.02
Clinic		
Bugamba	0.72 (0.58, 0.89)	0.001
Kameke	3.38 (2.61, 4.36)	<0.001
Kamuge	1.45 (1.20, 1.74)	<0.001
Kazo	1.39 (1.05, 1.83)	0.011
Merikit	1.60 (1.28, 2.02)	<0.001
Mitooma	1.0	
Muyembe	1.73 (1.39, 2.17)	<0.001
Nankoma	1.85 (1.43, 2.39)	<0.001
Rubaare	1.13 (0.87, 1.47)	0.37
Ruhoko	1.23 (0.79, 1.21)	0.12

*Guidelines are to schedule follow-up visit 4 weeks later for patients with uncontrolled hypertension (stage 1 or stage 2) and every 3 months for patients with controlled hypertension (stage 0) at previous visit. More frequently than guidelines is a scheduled follow-up visit <84 days when blood pressure is controlled (SBP < 140 and DBP < 90) and less frequently than guidelines is a scheduled follow-up visit > 30 days when blood pressure is uncontrolled (SBP >= 140 or DBP >= 90)

669 RISK FACTORS FOR EXCESS WEIGHT GAIN FOLLOWING SWITCH TO INTEGRASE INHIBITOR–BASED ART

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Background: Weight gain following antiretroviral therapy (ART) initiation occurs with all modern regimens. Recent real-world reports from small studies suggest that integrase strand transfer inhibitor (INSTI)-based ART may be associated with excess weight gain. We assessed weight gain following switch to INSTI-based ART among AIDS Clinical Trials Group (ACTG) participants in ACTG protocols A5001 and A5322, which provided long-term observational follow-up of individuals enrolled in randomized interventional trials.

Methods: A5001 and A5322 participants in follow-up from 1997-2017 who switched to INSTI were included. Within-person weight and waist circumference trajectories were generated, allowing participants to serve as their own controls for estimation of background/age-related weight gain. Piecewise linear mixed effects models adjusting for age, sex, race/ethnicity, parent study baseline BMI and their interactions, nadir CD4+ T cell count, smoking, diabetes and percent follow-up time with suppressed (<200 copies/mL) HIV-1 RNA examined weight and waist circumference change before and after first switch to INSTI. Linear spline models with a single knot accounted for non-linear trends.

Results: Adults (n=972) who switched to INSTI (68% from PI, 31% NNRTI, 2% other non-INSTI at median 7.8 years after parent trial entry) were 81% male and 50% non-white. Median age at switch was 50 years, CD4+ T cell count 511 cells/μL and BMI 26.4 kg/m2; 539 switched to RAL, 222 to EVG and 211 to DTG. When restricted to persons with suppressed HIV-1 RNA at switch (n=691), women, blacks and persons age ≥60 experienced significantly greater weight gain in the 2 years following switch to INSTI vs 2 years prior to switch; men and persons age <40 experienced less weight gain. In adjusted models, white or black race, age ≥60 and BMI ≥30 kg/m2 were associated with greater weight gain following switch among women, whereas age ≥60 was the greatest risk factor among men. Trends for waist circumference were similar (data not shown).

Conclusion: Yearly weight gain increased following switch to INSTI. These increases were particularly significant for women, blacks and persons age ≥60. When compared to pre-switch weight changes on stable suppressive ART and given concomitant increases in waist circumference, these data suggest increases in weight/fat mass greater than expected for age. The cardiometabolic implications of increased weight gain following switch to INSTI need to be established.

Weight change in kg/year (p value) for 2 years before and after switch to INSTI in virologically-suppressed adults (n=691).

	All	Women	Men	White race*	Black race	Age <40**	Age ≥60	BMI <18.5 kg/m²**	BMI >30 kg/m²
Pre-INSTI	0.4 (<0.0001)	0.3 (0.05)	0.5 (<0.0001)	0.4 (<0.0001)	0.3 (0.04)	1.1 (<0.0001)	-0.03 (0.85)	0.8 (0.7)	0.02 (0.89)
Post-INSTI	0.6 (<0.0001)	1.6 (<0.0001)	0.4 (0.0009)	0.4 (0.002)	1.2 (<0.0001)	-0.3 (0.42)	1.2 (<0.0001)	1.4 (0.03)	0.5 (0.05)
Pre-post Difference	0.2 (0.22)	1.3 (0.0003)	-0.1 (0.57)	0.01 (0.97)	0.9 (0.002)	-1.4 (0.01)	1.2 (0.001)	0.5 (0.58)	0.5 (0.20)

*Results for Hispanic ethnicity similar to white race
**No significant change in slope of weight gain among persons 40-60 years of age or for BMI 18.5-30 kg/m²

670 GREATER WEIGHT GAIN AMONG TREATMENT-NAIVE PERSONS STARTING INTEGRASE INHIBITORS

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Background: Obesity among persons living with HIV (PLWH) has steadily increased in the era of combination antiretroviral therapy (ART), and some PLWH experience substantial weight gain after initiating ART that may lead to metabolic comorbidities and poorer survival. To assess the influence of antiretroviral class and integrase strand transfer inhibitors (INSTI) on this phenomenon, we compared weight changes after initiating ART among treatment-naïve PLWH in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

Methods: Adult, treatment-naïve PLWH in NA-ACCORD initiating INSTI, protease inhibitor (PI), and non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based ART regimens after 01/01/2007 were included and followed through 12/31/2015. We used multivariate linear mixed effects models to generate marginal predictions of weights over time, adjusting for age, sex, race, cohort site, HIV acquisition mode, ART initiation year, and baseline weight, HIV-1 RNA, and CD4+ cell count. We used restricted cubic splines to relax linearity assumptions, multiple imputation for missing values, and bootstrapping to generate 95% confidence intervals. Predicted weights by ART class were reported at years 2 and 5. Due to shorter follow-up for newer INSTI drugs, predicted weights for raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG) were reported at years 1 and 2.

Results: Among 21,886 participants, 4,112 initiated INSTI-based regimens (2106 RAL, 1510 EVG and 477 DTG), 87% were male, and 43% were white. At ART initiation median age was 42 years, BMI was 25 kg/m^2, and CD4+ count was 303 cells/mm^3. Weight gain was highest among PLWH starting INSTI (Figure1, A). At 2 and 5 years, PLWH on INSTI gained 4.4 and 5.8 kg, respectively, compared to 3.3 and 4.1 kg for NNRTI ($p<0.001$), and 4.3 and 5.0 kg for PI($p=0.68$). Among PLWH starting INSTI, weight gain at year 2 was 5.6 kg for DTG, 5.4 kg for RAL, and 3.4kg for EVG ($p=0.03$ compared to RAL). By year 2, PLWH starting RAL ($p<0.001$) and DTG ($p=0.01$) gained significantly more weight compared to NNRTI, while those starting EVG ($p=0.03$) gained significantly less weight than PI (Figure1, B).

Conclusion: Treatment-naïve PLWH starting INSTI, especially DTG and RAL, are at higher risk of weight gain compared to older NNRTI-class regimens. This is clinically important as INSTI-based regimens are now recommended first line ART and PLWH are at increasing risk for obesity, metabolic comorbidities, and cardiovascular disease.

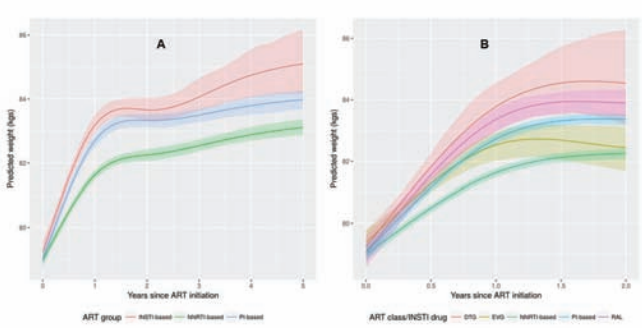

Figure. Predicted weights over (A) 5-years by ART class and (B) 2-years by ART class and INSTI drug

671 WEIGHT GAIN DURING TREATMENT AMONG 3,468 TREATMENT-EXPERIENCED ADULTS WITH HIV

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Background: Weight gain is a known complication of HIV treatment. However, the specific risk factors and magnitude are not well understood, especially after the initial treatment period. The objectives of this study were (1) to describe the demographic, clinical, and treatment characteristics of treatment-experienced adults with virally-suppressed HIV that had ≥3% annual weight gain in recent years (2013 to 2018) and (2) to identify variables independently associated with such gain.

Methods: EMR and prescription data were collected for the most recent ART exceeding 1 year in length for 3,468 previously-treated adult patients with continued HIV suppression. Patients resided in 21 States + DC and were in care at 6 HIV treatment centers. Data inclusion required ≥1 BMI at ARV prescription and ≥1 BMI during treatment but after 365 days up to 730 days. The resultant observation window was Aug 2013 to Aug 2018 and represented 5,459 patient years. Bivariate comparisons were made using chi-square or Fisher's tests followed by independent variable assessment via logistic regression (LR).

Results: Among the 3,468 adults, annualized weight gain was ≥3% for 1,045 (30%). Compared to those with <3% weight gain, the group with ≥3% gain had higher proportions of underweight and normal BMI at baseline, female, age <50, and psychiatric disorders and lower rates of comorbidities CKD, CVD, DM, hyperlipidemia, and hypogonadism. [TABLE] The weight gain patients were less commonly treated with PI-containing ART and more commonly treated with InSTI-containing ART. Factors identified as negatively associated with weight gain via LR were overweight or obese at baseline, hypogonadism, and use of PI-containing therapies. Psychiatric disorders were positively associated with weight gain via LR. InSTI-containing ART was not significantly associated with weight gain in the LR.

Conclusion: Weight gain in the treatment-experienced population with continued HIV suppression was primarily associated with lower BMI, reduced proportion of hypogonadism, increased proportion of psychiatric disorders, and non-PI-containing regimens. The association between InSTI-based ART and weight gain, which reached significance in bivariate analyses, did not remain significant in LR, suggesting that in this population, weight changes are primarily driven by other factors.

	Weight Gain < 3% n = 2423	Weight Gain ≥ 3% n = 1045	Total Population n = 3468	Univariate P-Value*	Multivariate† Odds-Ratio (95% CI)
Baseline BMI				<0.001	
Underweight (< 18.5)	25/2423 (1%)	18/1045 (1.7%)	43/3468 (1.2%)		1.77 (0.9-3.4), p=0.091
Normal (18.5-24.9)	847/2423 (35%)↓	450/1045 (43.1%)↑	1297/3468 (37.4%)		*multivariate base case*
Overweight (25-25.9)	986/2423 (40.7%)↑	371/1045 (35.5%)↓	1357/3468 (39.1%)		**0.69 (0.6-0.8), p=<0.001**
Obese (> 30)	565/2423 (23.3%)↓	206/1045 (19.7%)↓	771/3468 (22.2%)		**0.62 (0.5-0.8), p=<0.001**
Patient Age Group				0.001	
Age < 30	156/2368 (6.6%)↓	98/1022 (9.6%)↑	254/3390 (7.5%)		1.16 (0.9-1.6), p=0.346
Age 30-49	1124/2368 (47.5%)↓	526/1022 (51.5%)↑	1650/3390 (48.7%)		*multivariate base case*
Age ≥ 50	1088/2368 (45.9%)↑	398/1022 (38.9%)↓	1486/3390 (43.8%)		0.84 (0.7-1), p=0.051
Patient Gender				0.030	
M	2005/2323 (86.3%)↑	820/984 (83.3%)↓	2825/3307 (85.4%)		*multivariate base case*
F	317/2323 (13.6%)↓	162/984 (16.5%)↑	479/3307 (14.5%)		1.25 (1-1.6), p=0.055
Non-Binary	1/2323 (0%)	2/984 (0.2%)	3/3307 (0.1%)		1.0 (0.0-inf), p=0.957
InSTI	1527/2423 (63%)↓	704/1045 (67.4%)↑	2231/3468 (64.3%)	0.014	0.95 (0.7-1.3), p=0.740
NNRTI	696/2423 (28.7%)	278/1045 (26.6%)	974/3468 (28.1%)	0.202	0.79 (0.6-1.1), p=0.125
PI	534/2423 (22%)↑	151/1045 (14.4%)↓	685/3468 (19.8%)	<0.001	**0.58 (0.4-0.7), p=<0.001**
Comorbidities					
CKD	231/2423 (9.5%)↑	76/1045 (7.3%)↓	307/3468 (8.9%)	0.032	0.81 (0.6-1.1), p=0.168
CVD	308/2423 (12.7%)↑	104/1045 (10%)↓	412/3468 (11.9%)	0.021	0.88 (0.7-1.1), p=0.315
Diabetes	223/2423 (9.2%)↑	67/1045 (6.4%)↓	290/3468 (8.4%)	0.006	0.85 (0.6-1.2), p=0.310
Hyperlipidemia	890/2423 (36.7%)↑	342/1045 (32.7%)↓	1232/3468 (35.5%)	0.024	0.96 (0.8-1.2), p=0.682
Hypertension	659/2423 (27.2%)	264/1045 (25.3%)	923/3468 (26.6%)	0.237	1.15 (0.9-1.4), p=0.148
Hypogonadism	487/2423 (20.1%)↑	160/1045 (15.3%)↓	647/3468 (18.7%)	<0.001	**0.81 (0.6-1), p=0.050**
Psychiatric Disorder	353/2423 (14.6%)↓	187/1045 (17.9%)↑	540/3468 (15.6%)	0.013	**1.28 (1-1.6), p=0.020**

*Pearson's Chi-Square Test except where >20% of samples had n ≤ 5 and Fisher's Exact Test was used. †Logistic Regression with 'Weight Gain ≥ 3%' as the dependent variable. Note: ↑ or ↓ signifies statistical significance (at a = 0.5) on a z-test of that group's standardized Pearson residual.

672 INTEGRASE STRAND TRANSFER INHIBITORS ARE ASSOCIATED WITH WEIGHT GAIN IN WOMEN

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Background: Integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy (ART) is recommended first line for HIV treatment. Studies have suggested individuals who switch to INSTI-ART experience increase in body weight. These changes may be more prominent in women. We evaluated the effect of INSTI use on body weight and measurements in HIV+ women.

Methods: Data were collected from 2008-2017 from HIV+ women enrolled in the Women's Interagency HIV Study (WIHS) with viral load <1000 copies/mL on ART. Women who switched to or added an INSTI to ART (SWAD group) were compared to women who remained on non-INSTI ART (STAY group). Outcomes included changes in body weight; body mass index (BMI); percentage body fat (PBF); circumference of waist, hip, arm, and thigh; blood pressure (BP); and incident diabetes mellitus (DM). Outcomes were measured 6-12 months before and 6-18 months after INSTI switch/add in the SWAD group with comparable time points in the STAY group. Baseline demographic and clinical characteristics for STAY and SWAD groups were compared. Linear regression models compared change over time in each outcome by STAY/SWAD group, adjusted for age, race, WIHS site, education, income, smoking status, and baseline ART regimen. Changes in outcomes were also stratified by INSTI type (dolutegravir or raltegravir/elvitegravir).

Results: 1118 WIHS participants (884 STAY and 234 SWAD) were followed for average 2.0 (+/- 0.1) years; mean baseline age was 48.8 (+/- 8.8) years, 61% were Black, and mean CD4 669 (+/- 294) cells/mm3. At baseline, women in SWAD group were more likely to be on protease inhibitor-ART but did not differ from STAY by demographics or body measurements. Compared to the STAY group, the SWAD group experienced 2.14 kg greater increase in weight, 0.78 kg/m^2 greater increase in BMI, 1.35% greater increase in PBF, and 2.05, 1.87, 0.58, and 0.98 cm greater increases in waist, hip, arm, and thigh circumference, respectively (Table 1). Women in SWAD also had 2.24 and 1.17 mmHg greater change in systolic and diastolic BP. New-onset DM occurred in 4.5% (n=8) in SWAD and 2.2% (n=15) in STAY, p=0.11. No significant differences in outcomes were observed by INSTI type.

Conclusion: In a longitudinal study of HIV+ women on ART, a switch to INSTI was associated with significant increases in body weight and measurements, body fat, and blood pressure compared to those remaining on non-INSTI ART. Further research is urgently needed for prevention and management of metabolic effects with INSTI use.

Table 1 : Model-adjusted change over time in outcome variables in SWAD and STAY groups

Outcome Variable	Mean (SD) SWAD Baseline	Mean (SD) STAY Baseline	Mean (95% CI) Change in SWAD[a]	Mean (95% CI) Change in STAY[a]	Difference Between Means, SWAD-STAY (95% CI)[a]
Mean Weight (kgs)	80.84 (25.66)	80.84 (23.02)	2.36 (1.45, 3.26)	0.21 (-0.37, 0.79)	+2.14 (1.21, 3.08)****
Mean BMI (kg/m^2)	30.56 (8.86)	30.95 (8.25)	0.94 (0.60, 1.27)	0.15 (-0.04, 0.35)	+0.78 (0.42, 1.14)****
Mean Body Fat (%)[b]	33.95 (11.53)	35.04 (11.61)	1.84 (1.04, 2.65)	0.49 (0.02, 0.96)	+1.35 (0.49, 2.22)**
Body Measurements					
Waist Circumference (cm)	99.19 (17.07)	99.57 (16.23)	2.62 (1.69, 3.55)	0.57 (0.03, 1.12)	+2.05 (1.06, 3.04)****
Hip Circumference (cm)	104.48 (15.53)	106.29 (14.90)	1.68 (0.86, 2.51)	-0.19 (-0.67, 0.30)	+1.87 (0.99, 2.75)****
Arm Circumference (cm)	32.84 (6.64)	33.01 (6.37)	0.72 (0.41, 1.03)	0.14 (-0.04, 0.32)	+0.58 (0.25, 0.91)***
Thigh Circumference (cm)	53.11 (10.64)	54.06 (9.91)	1.04 (0.49, 1.58)	0.06 (-0.26, 0.38)	+0.98 (0.39, 1.56)**
Mean Systolic BP (mmHg)	119.06 (14.22)	120.84 (16.21)	4.47 (2.52, 6.43)	2.23 (1.09, 3.38)	+2.24 (0.14, 4.35)*
Mean Diastolic BP (mmHg)	73.20 (8.19)	74.19 (9.03)	1.65 (0.61, 2.69)	0.48 (-0.13, 1.09)	+1.17 (0.05, 2.29)*

[a] From models adjusted for age, site, race/ethnicity, income, smoking status, education, baseline antiretroviral therapy (ART)
[b] Using Bioelectrical Impedance Analysis [(body fat/ weight_kg)*100] = (%)
Abbreviations: STAY, women on non-integrase strand transfer inhibitor (INSTI) ART; SWAD, women switching/adding INSTI to ART; SD, standard deviation; BMI, body mass index; BP, blood pressure; CI, confidence interval
* P<0.05, **P<0.01, ***P<0.001, ****P<0.0001

673 THE IMPACT OF WEIGHT GAIN AND SEX ON IMMUNE ACTIVATION FOLLOWING INITIATION OF ART

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Background: Immune activation persists despite suppressive antiretroviral therapy (ART) and may be affected by sex or body composition. We hypothesized that weight gain, sex and BMI would be associated with changes in immune activation following ART initiation and explored these relationships in a selected subset of women and men initiating ART in two large randomized ACTG trials (A5202 and A5257).

Methods: A purposeful sampling design selected participants who achieved virologic suppression on ART and either maintained weight within +/- 0.5 kg/m2 ("maintainers") or gained 2.6-6.4 kg/m2 ("gainers") from baseline to 96 weeks. We measured IL-6, sTNF-RI and II, IP-10, hsCRP, sCD14 and sCD163 at weeks 0 and 96. Multivariable linear regression explored associations of weight gain (gainers vs maintainers), sex, and pre-ART BMI with outcomes of pre-ART biomarker concentrations and changes from baseline to week 96, adjusting for baseline age, race/ethnicity, ART regimen, CD4 count and HIV-1 RNA.

Results: 340 participants were selected; median pre-ART age 42 years, CD4+ cell count 273 cells/mm3, HIV-1 RNA 4.7 log10 copies/mL; 49% were women, 33% white, 42% black, and 24% Hispanic. Pre-ART biomarker concentrations were similar in women and men (data not shown). While pre-ART BMI was similar between gainers and maintainers (overall and within sex), gainers had significantly lower pre-ART CD4 vs maintainers. In adjusted models among those with normal pre-ART BMI, pre-ART IL-6, sTNF-RII, IP-10, and sCD163 were higher for gainers versus maintainers. Association of weight gain on week 96 changes of these 4 biomarkers differed by sex; women who gained weight had smaller declines in biomarkers compared to men who gained (see Table). For IL-6, for women, gaining weight was associated with attenuating changes by 0.05 (difference between model-based means), whereas for men, gaining weight was associated with increasing changes by 0.13. For sTNF-RII, the association between weight gain and changes in sTNF-RII also varied by pre-ART BMI.

Conclusion: Higher pre-treatment immune activation markers are significantly associated with weight gain following ART initiation even after controlling for pre-ART CD4 counts. Weight gain attenuates the decline in several immune activation markers following ART initiation among women; thus, women may be at increased risk for complications of weight gain. Identifying individuals at risk of weight gain may allow for targeted investigation of preventive interventions.

Total sample (n=340)	Gained Weight (n=196) (+2.6 - 6.4 kg/m²)	Maintained Weight (n=144) (+/- 0.5 kg/m²)	Women (n=166)		Men (n=174)		p-values (weight gain, and weight within sex)
			Gained weight (n=96)	Maintained weight (n=70)	Gained weight (n=100)	Maintained weight (n=74)	
Median **Pre-ART BMI** (kg/m²)	25.4	25.9	27.1	27.7	24.1	24.2	≥ .70
Median **Pre-ART CD4** (cells/mm³)	195	344	219	328	174	361	< .01

	Gaining weight vs Maintaining weight					Sex by weight gain interaction p-values
	Pre-ART concentrations	Changes from baseline by sex [model based means]				
	Adjusted differences (95% CI)					
IL-6 (log_{10} pg/mL)	0.26 (0.17, 0.35)	-0.11 normal 0.02 overwt 0.08 obese	-0.16 -0.03 0.03	-0.25 -0.13 -0.07	-0.12 0.01 0.07	.004
sCD163 (log_{10} ng/mL)	0.08 (0.02, 0.14)	-0.17	-0.25	-0.23	-0.21	<.001
sTNF-RII (log_{10} pg/mL)	0.12 (0.07, 0.16)	-0.26 normal -0.20 overwt -0.18 obese	-0.24 -0.25 -0.25	-0.30 -0.24 -0.22	-0.21 -0.22 -0.22	.021
IP-10 (log_{10} pg/mL)	0.19 (0.11, 0.27)	-0.47	-0.50	-0.53	-0.41	.004

674 WEIGHT GAIN AMONG VIRALLY SUPPRESSED PERSONS WHO SWITCH TO InSTI-BASED ART

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Background: INSTI-associated weight gain has been described among ART-naïve persons initiating INSTI-containing ART, but not among virally suppressed (VS) persons whose first INSTI exposure is via a switch regimen. We evaluated changes in weight (CW) among such persons in the HIV Outpatient Study (HOPS).

Methods: We analyzed medical record data of patients from nine United States HIV clinics who were INSTI-naive and VS for >1 year on non-INSTI-based ART, and switched to INSTI-based ART and remained VS. Participants received INSTI-based ART for >6 months, had >2 weights recorded in the year prior to switch and >1 after. We evaluated CW over time, overall and stratified by demographics, pre-switch body mass index (BMI) and ART use, CD4 at ART start, and INSTI received. We used multivariable random regression mixed model to estimate factors associated with CW.

Results: Among 437 patients (median age 51 years, interquartile range 44.5, 57.5), 86 (19.6%) were women, 107 (24.5%) were non-Hispanic Black (NHB). Pre-INSTI regimens often included an NNRTI (193 [44.1%]) or PI (185 [42.0%]) with >1 NRTI (402 [91.5%]). INSTI regimens included raltegravir (236 [54.0%]), elvitegravir (89 [20.4%]), or dolutegravir (112 [25.6%]). Mean CW in the year prior to INSTI was -0.2 kg (95% confidence interval [CI]: -0.6, 0.2). Mean duration of INSTI use was 2.9 years (max=9.7 years). Mean CW on INSTI was 1.2 kg (CI 0.6, 1.9), did not differ by INSTI drug used (p>0.2) and was greater for persons with pre-INSTI BMI < 25 (2.2 kg, CI 1.5, 3.0) than 25-29.9 (0.5 kg, CI -0.5, 1.4) or >30 (0.4 kg, CI -1.7, 2.6), p=0.03; NHB than Non-Hispanic whites, 2.7 kg (CI 1.3, 4.1) vs 1.0 kg (CI 0.2, 1.7), p=0.02; and persons whose pre-INSTI ART did not include an NRTI vs those whose did, 4.5 kg (CI 1.8, 7.3) vs. 0.9 kg (CI 0.3, 1.6), p<0.01. Duration of INSTI use was not associated with CW: mean 1.0 kg (CI 0.5, 1.4) for 6-<12 months (mos), 1.2 kg (CI -0.5, 2.9) for 12-<24 mos, 1.3 kg (CI 0.7, 1.9) for 24-<60 mos, 1.2 kg (CI 0.5, 2.0) for ≥60 mos, p=0.7. In multivariable models NHB race, and no pre-INSTI NRTI use remained associated with greater percent change in weight (p<0.05) while lower pre-INSTI BMI was borderline significant, p=0.08.

Conclusion: We observed weight gain among VS persons who switched to INSTI-based ART that was associated with NHB race, no pre-INSTI NRTI use, and lower pre-INSTI BMI .These findings of differential risk for INSTI-related weight gain require further evaluation.

675 DIFFERENTIAL BMI CHANGES FOLLOWING PI- AND InSTI-BASED ART INITIATION BY SEX AND RACE

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Background: While older protease inhibitors (PI) were more frequently associated with central fat accumulation, initiation of currently used ART regimens has been associated with increases in body mass index (BMI), particularly in women and with integrase strand transfer inhibitors (INSTI). The goal of this study was to analyze the differential effect of individual PIs and INSTIs on changes in BMI by sex and race in a large urban HIV clinic.

Methods: All patients initiating ART at the Parkland Health and Hospital System in Dallas, TX from 2009 to 2017 were included in the analysis. Exposure to ART was defined as concurrent receipt of at least two nucleoside reverse transcriptase inhibitors (NRTI) and at least one PI, Non-nucleoside reverse transcriptase inhibitor (NNRTI) or INSTI. In regression analysis, we compared yearly change in BMI (kg/m2) between men and women and between Blacks, Hispanics and Non-Hispanic Whites following initiation of PIs (Atazanavir [ATV], Darunavir [DRV] or Lopinavir [LPV]) or INSTI (Raltegravir [RAL], Elvitegravir [EVG] or Dolutegravir [DTG]). We controlled for year of HAART initiation, baseline CD4 count and HIV-1 RNA, and whether patients achieved virologic suppression on HAART.

Results: We included 4,048 patients, 69% male, 53% Black, 28% Hispanic, and 16% non-Hispanic Whites. Mean age was 46.3 years (SD 11.9). Mean baseline BMI was 27.0 kg/m2 (6.4). Median follow-up time on HAART was 6.7 years (IQR 2.8 – 11.2). Cumulative exposure to NNRTI, PI, and INSTI-based HAART were 3546, 6184, and 3090 person-years, respectively. The BMI slope per year on NNRTI, PI and INSTI were 0.22, 0.24 and 0.32, respectively. BMI slopes for individual PI- and INSTI-based regimens by sex, race and ethnicity are presented in Table 1. There was no significant interaction between sex and race/ethnicity on BMI gains. Proportion of overweight /obese (BMI, ≥ 25) increased from 51% at HAART initiation to 65% at year 3 (p<0.001).

Conclusion: We observed a differential effect of individual INSTI and PI-based HAART regimens on BMI changes by sex. All PIs were associated with greater BMI gain in women than in men, but with no difference by race/ethnicity. LPV-based ART was associated with relatively smaller BMI gains. Among INSTIs, while EVG appeared to be associated with greater BMI gains overall, the effect did not vary or by sex or race/ethnicity. DTG and RAL are associated with greater BMI gains in women, and DTG with greater gains in Blacks & Hispanics.

Table 1: BMI Slopes by Year on HAART

	All Patients		By Race/Ethnicity				By Sex		
	N	Slope	B	H	NHW	P value	Men	Women	P value
All	4048	0.26	0.28	0.26	0.19	**0.03**	0.23	0.30	**0.008**
ATV	780	0.24	0.29	0.13	0.20	0.24	0.17	0.36	**0.03**
DRV	1278	0.18	0.17	0.19	0.14	0.89	0.10	0.29	**0.007**
LPV	223	0.06	0.05	0.09	-0.05	0.79	0.03	0.32	**0.03**
RAL	591	0.16	0.16	0.06	0.25	0.40	0.08	0.30	**0.03**
EVG	405	0.39	0.33	0.42	0.52	0.74	0.35	0.43	0.72
DTG	2037	0.23	0.34	0.27	0.12	**0.02**	0.12	0.44	**<0.001**

676 LONG-LASTING ALTERATIONS IN FAT DISTRIBUTION IN PLWH EXPOSED TO THYMIDINE ANALOGUES

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Background: Thymidine analogues (TA) and didanosine (ddI) have been associated with redistribution of body fat from subcutaneous (SAT) to visceral (VAT) adipose tissue, which, in turn, is a risk factor for cardiovascular disease (CVD). We explored differences in adipose tissue distribution between people living with HIV (PLWH) with/without prior exposure to TA and/or ddI and uninfected controls and the association with CVD risk factors.

Methods: 761 PLWH from the COCOMO study aged > 40 and 2,283 age- and sex-matched uninfected controls from the GCPS study were included. PLWH were stratified according to prior exposure to TA and/or ddI. VAT and SAT were determined by abdominal CT-scan. Hypotheses were tested by linear and

logistic regression analyses adjusted for age, sex, origin, smoking, physical activity, and BMI.

Results: Age and sex distribution were similar in PLWH and uninfected controls (54.2 vs 54.4 years and 85.5% vs 85.5% male). 451 (60.5%) PLWH had exposure to TA and/or ddI. Of those, 6 (1.4%) were still exposed. Mean cumulative exposure was 6.6 (SD, 4.2) years and time since discontinuation was 9.4 (SD, 2.7) years. After adjustment, prior exposure to TA and/or ddI was associated with 21.6 cm2 larger VAT (13.8 –29.3) compared to HIV infection without exposure and HIV-negative status was associated with similar VAT compared to HIV infection without exposure (Table 1). After adjustment, HIV infection with exposure to TA and/or ddI was associated with 14.8 cm2 smaller SAT compared to HIV infection without (-23.3 - -6.3) (Table 1). HIV-negative status was associated with 13.0 cm2 larger SAT compared to HIV infection without exposure (5.8 - 20.3) (Table 1). Cumulative exposure to TA and/or ddI (3.7 cm2 per year [2.3 - 5.1]), but not time since discontinuation (-1.1 cm2 per year [-3.4 – 1.1]), was associated with VAT. In PLWH, after adjusting for confounders prior exposure to TA and/or ddI was associated with excess risk of hypertension (aOR 1.62 [1.13 - 2.31]), hypercholesterolemia (aOR 1.49 [1.06 - 2.11]), and low HDL (aOR 1.40 [0.99 – 1.99]).

Conclusion: Prior exposure to TA and/or ddI was associated with long-lasting alterations in abdominal fat distribution, persisting after TA and/or ddI discontinuation, which may be involved in the excess risk of hypertension, hypercholesterolemia, and low HDL found in PLWH with prior exposure to TA and/or ddI. Our findings may help to identify a subgroup of PLWH who may benefit from more intensive monitoring and cardiovascular prevention interventions.

Table 1. Linear Regression Model predicting the degree of change (with 95% CI) in cm^2 of VAT and SAT according to the exposure to TA and/or ddI

	Visceral adipose tissue				Subcutaneous adipose tissue			
	Unadjusted β* [95% CI]	p-value	Adjusted β* [95% CI]	p-value	Unadjusted β* [95% CI]	p-value	Adjusted β* [95% CI]	p-value
Study Group								
PLWH **without** exposure to TA/ddI	Ref		Ref		Ref		Ref	
Uninfected controls	17.6 [9.5;25.7]	< 0.0001	0.2 [-6.4;6.8]	0.9319	34.2 [24.1;44.3]	< 0.0001	13.0 [5.8;20.3]	0.0004
PLWH **with** exposure to TA/ddI	26.6 [16.8;36.3]	< 0.0001	21.6 [13.8;29.3]	< 0.0001	-15.6 [-27.8;-3.4]	0.0122	-14.8 [-23.3;-6.3]	0.0006
Age, per 5 years	10.6 [9.3;11.9]	< 0.0001	7.3 [6.31;8.4]	< 0.0001	-2.6 [-4.3;-0.9]	< 0.0001	-2.9 [-4.05;-1.7]	< 0.0001
Sex, male	43.9 [37.2;50.7]	< 0.0001	34.9 [29.3;40.5]	< 0.0001	-56.5 [-65.1;-47.9]	< 0.0001	-58.5 [-64.4;-52.5]	< 0.0001
BMI, per unit	9.1 [8.6;9.7]	< 0.0001	8.7 [8.2;9.2]	< 0.0001	14.8 [14.3;15.4]	< 0.0001	14.5 [13.9;15.0]	< 0.0001

*β coefficients represent the degree of change in cm^2 of VAT and SAT for every 1-unit of change in the explanatory variables.
Abbreviations: visceral adipose tissue, VAT; subcutaneous adipose tissue, SAT; people living with HIV, PLWH; thymidine nucleoside analog reverse-transcriptase inhibitors, TA; didanosine, ddI; body mass index, BMI; confidence interval, CI
Multivariable models were adjusted for: age, sex, origin, physical activity, BMI, and study group

677 HIGH PREVALENCE OF CENTRAL OBESITY IN HIV-INFECTED & HIV-UNINFECTED ADULTS, BOTSWANA

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Background: Central obesity is a major risk factor for cardiovascular disease, and treated HIV infection has been associated with central obesity in some but not all studies. The prevalence of central obesity among HIV-infected and –uninfected individuals in a community setting in high HIV-prevalence settings in Africa is not well described.

Methods: We enrolled a random sample of ~20% of adults in 30 rural communities in Botswana as part of a community-randomized HIV prevention trial. During the final household survey, we conducted a one-time central obesity assessment, including waist and hip circumference measurements, in participants in 20 of the communities from February 2017-March 2018. Central obesity was defined using World Health Organization-recommended sex-specific thresholds: waist circumference (WC) > 88 cm and 102 cm for women and men respectively, and waist-hip ratio (WHR) > 0.85 and 0.90 for women and men respectively. Crude and adjusted prevalence ratios for central obesity were estimated using Poisson regression.

Results: Among 2,039 participants assessed, 586 (29%) were HIV-infected, 1,369 (67%) were female, and median age was 35.3 years (IQR=26.3-48.3). Six hundred and seventy three (33%, 95% CI 30-36%) met the criteria for central obesity using WC criteria versus 879 (43%, 95% CI 40-47%) by WHR criteria. Using WHR criteria, similar proportions of HIV-positive and HIV-negative adults met criteria for central obesity (48% and 42%, respectively, p=0.0003). However, using the WC criteria, significantly more HIV-positive participants met criteria for central obesity compared to HIV-negative participants (35% versus 32%, p=0.87). After adjustment for age and gender, significantly fewer HIV-infected persons has central obesity according to the WC criteria (aPR; 0.85; 95%CI: 0.78-0.93), but not when using WHR criteria (aPR: 0.99; 95%CI: 0.90-1.09).

Conclusion: Up to two-fifths of adults in peri-urban and rural Botswana have central obesity, with WHR defining a larger proportion with central obesity than WC. HIV was associated with a lower risk for central obesity by WC but no risk by WHR criteria in this community-based cohort with very high ART coverage. More studies are needed to clarify appropriate cut-off points and risk factors for central obesity in this setting.

Percentage of participants meeting the definition of central obesity, using either waist circumference or waist-hip ratio and World Health Organization-recommended cut-off points

	HIV-infected Women (n=446)	HIV-infected Men (n=140)	ALL HIV-infected (n=586)	HIV-uninfected Women (n=917)	HIV-uninfected Men (n=536)	All HIV Uninfected (n=1453)	All Participants (n=2,039)
Waist Circumference	44%	5%	35%	47%	6%	32%	33%
Waist-Hip Ratio	50%	39%	48%	45%	36%	42%	43%

678 SLEEVE GASTRECTOMY VS ROUX-EN-Y BYPASS ON WEIGHT AND METABOLIC COMPLICATIONS IN HIV

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Background: Obesity and associated metabolic complications remain a major issue in the HIV population. The efficacy and safety of bariatric surgery in HIV-infected individuals remain poorly understood; and the differential effect of different types of surgeries on weight loss and associated comorbidities is unclear.

Methods: We retrospectively reviewed a database of all HIV-infected patients who have undergone bariatric surgery at the University Hospitals Cleveland Medical Centers and MetroHealth Medical Center. We included data from 2010 to 2018; 24 patients were identified (6 underwent Roux-en-Y gastric bypass [GB], and 18 had a sleeve gastrectomy [SG]). All included patients met US criteria for bariatric surgery including BMI >35 kg/m2 with ≥2 comorbidities or BMI > 40. Our primary outcome was weight loss. Secondary outcomes included changes in viral load, CD4 count, and metabolic complications. Outcomes were collected 6 months after surgery and then yearly, up to 6 years after the procedure. General linear models were used to compare outcomes between the procedures while adjusting for age, sex, race and baseline weight.

Results: 68% were female; mean age was 48 years, CD4 count 771 cells/mm3 and preoperative BMI 47 kg/m2. All patients were on ART at the time of surgery, and 96% had undetectable viral load. The mean follow-up duration was 37 months (range 3 – 91). Overall, weight loss was maintained up to 6 years following surgery [mean(SD) 62.3 (33) lbs]. Early on, the mean reduction in weight did not differ between GB and SG procedures (66.6 vs. 61.4 at 6 months, and 83 vs. 76 at year 1; p>0.05) after adjustment. However, GB was more effective, with a mean reduction in weight of 98 lbs for GB vs. 62 for SG at year 2; 114 vs. 64 at year 3; 113 vs. 66 at year 4; and 94 vs. 43 at year 5 (all p<0.03 after adjustment). No changes in CD4 count or viral load were observed after either procedure. Patients with diabetes (n=8) had normalization of their HbA1c after surgery, except for one patient who underwent SG. Among 17 hypertensive patients, 4 showed remission after the surgical procedure (3 of them had GB)

Conclusion: While the obesity surgery field is moving towards SG predominance, our results suggest greater weight loss and improvement of obesity-related comorbidities with GB compared to SG in HIV-infected obese

patients. Further studies are needed to determine whether alterations in gut integrity and microbiota with GB play a role in these improvements.

679 DOLUTEGRAVIR AND INSULIN RESISTANCE

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Background: HIV infection has been independently associated with insulin resistance (IR), potentially through chronic immune activation/inflammation, however this effect is not necessarily mitigated through successful antiretroviral therapy (ART). ART has been associated with IR through varying mechanisms, however, in the context of combination ART, increased obesity, and an aging HIV-infected population, these potential associations are difficult to interpret. We investigated potential risk factors associated with HOMA-IR (homeostasis model of assessment – insulin resistance) and the potential effect of dolutegravir (DTG) on IR over time.

Methods: Data from 4 DTG clinical trials (SPRING-1, STRIIVING, SWORD-1 and -2) with fasting insulin and glucose measurements available, were included; subjects with diabetes were excluded. IR was determined by HOMA mathematical model and defined as a HOMA-IR value ≥ 2; additional cut-offs of 3 and 4 were also explored. Analysis of relationship between baseline (BL) risk factors and HOMA-IR was completed. Change in HOMA-IR over time and relative to controls were assessed with logistic regression and ANCOVA models, respectively.

Results: HOMA-IR data was available at BL, week 24 and week 48 for 824, 304 and 543 DTG-exposed subjects and 713, 219 and 460 control subjects, respectively. At BL, subjects were mostly male (81%), white (76%) and had a median age of 43yrs; 50% were overweight/obese; 70% had a HOMA-IR>2. Results are shown in the table. There were similar modest increases in HOMA-IR between DTG and control groups over time (24 and 48 weeks). Overall, there was no difference in the odds of HOMA-IR>2 between treatment groups at 48 weeks. An association between BL HOMA-IR and increasing age, geographic region, increased BMI/weight, the presence of metabolic or cardiac disorders, lipids, and elevated liver function tests (ALT, ALP and albumin) was observed. Risk factors for IR (HOMA-IR>2) at week 48 were BL HOMA-IR, Sex, BMI, AIDS CDC category, smoking history, and elevated ALT.

Conclusion: There was no association between treatment and insulin resistance observed in this analysis over a 48 week period, however IR modestly increased over time in all groups. In general, risk factors identified as being associated with IR at Week 48 were consistent with known risk factors for diabetes/IR. These results should be interpreted with caution as the studies were not primarily designed to assess effects of DTG exposure on insulin resistance.

			ANCOVA Analysis			Logistic Regression Analysis		
Analysis		**n**	**LS Means Est(se)[1]**	**Geometric LS mean ratio (95%CI)[2]**	**P-value**	**HOMA-IR) >2/n**	**Odds ratio (95% CI)**	**P-value**
Overall Week 48[a]	Control	460	1.18(0.024)			360 /460		
	DTG	543	1.16(0.022)	0.98(0.92, 1.04)	0.497	413 /543	0.81 (0.57, 1.14)	0.222
SPRING1 Week 24	Control[b]	35	1.07(0.090)			29/35		
	DTG	125	1.02(0.047)	0.95(0.77, 1.16)	0.583	98/125	0.46 (0.12, 1.45)	0.215
SPRING1 Week 48	Control[b]	38	1.06(0.092)			29/38		
	DTG	123	1.13(0.050)	1.07(0.86, 1.32)	0.546	99/123	0.20 (0.03, 1.16)	0.086
STRIIVING Week 24[d]	Control[c]	184	0.97(0.046)			131/184		
	DTG	179	1.05(0.046)	1.07(0.95, 1.22)	0.273	147/179	1.86 (1.08, 3.23)	0.027
SWORD 1 and 2 Week 48	Control[c]	422	1.21(0.024)			331/422		
	DTG	420	1.15(0.024)	0.95(0.89, 1.02)	0.161	314/420	0.78 (0.55, 1.11)	0.167

n= Number of subjects with evaluable HOMA-IR data at baseline and analysis time point, CI=95% Confidence interval, Est= estimates, ls= least squared, se= standard error and is based on log scale. HOMA-IR = [Insulin (µU/ml × glucose (mmol/L)/22.5].

[1] Geometric LS mean ratio estimates least squared ratio at the analysis time point over baseline values. The following baseline risk factors were selected from the final ANCOVA model as potential risk factors for the development of insulin resistance at week 48: baseline HOMA-IR, female gender, bodyweight, immune disorder at baseline, and an increase in triglycerides, ALT and viral load.

[2] The following baseline risk factors were selected from the final logistic model as potential risk factors for the development of insulin resistance at week 48: baseline HOMA-IR, female gender, BMI, smoking history, immune disorder at baseline, ALT and viral load.

[a] includes SPRING1 and SWORD studies, [b] Efavirenz, [c] Current antiretroviral therapy (boosted PI, INSTI, NNRTI, NRTI), [d] only Week 24 data is presented as all subjects switched to DTG after this timepoint.

680 LOWER CARDIOVASCULAR DISEASE RISK ASSOCIATED WITH INTEGRASE INHIBITORS

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Background: Several antiretroviral therapy (ART) classes have been associated with increased myocardial infarction (MI) risk. No studies have examined cardiovascular disease (CVD) in people living with HIV (PLWH) on integrase strand transfer inhibitors (INSTI). We examine the risk of CVD in PLWH on INSTI-based regimens.

Methods: Using Truven Health Analytics MarketScan® databases for commercially insured and Medicaid covered adults, we identified PLWH newly initiated on ART between Jan 1, 2008 and Dec 30, 2015. New users were those without ART claims in the 6 months prior to study inclusion. The primary outcome, major adverse cardiac event (MACE), was a composite of acute MI, ischemic stroke, coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) assessed through Dec 30, 2016. We excluded PLWH with MACE events 6 months prior to the first stable regimen start. We identified cardiac outcomes and covariates associated with risk of cardiac events using ICD-9-CM diagnosis and procedure codes and CPT-4 codes. Calendar-time specific inverse-probability-weighted Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for association between INSTI use and MACE. Propensity score models included potential predictors of CVD and INSTI use. Censoring occurred for the earliest of MACE events during the first 6 months of a stable regimen, 90 days post-ART switch, health plan disenrollment, death and study end.

Results: 20,459 new ART initiators were identified. 5,128 (25%) PLWH initiated INSTI-based regimens (raltegravir 33%, elvitegravir 49%, dolutegravir 18%). 11,191 (55%) initiated non-nucleoside reverse transcriptase inhibitors and 4,145 (20%) protease inhibitors. Median duration of follow-up was 561 (348, 985) days. Mean age was 40.6 years, 79% were male, and 17% were Medicaid insured. Hypertension was present in 9.5% of INSTI users vs 7.4% non-users; lipid lowering treatment in 19.8% vs 17.9%; diabetes in 6% vs 4.8% and smoking in 13.5% vs 10.2%. 161 MACE events occurred; acute MI 11 (0.21%) vs 55 (0.36%), stroke 14 (0.27%) vs 48 (0.31), CABG 1 (0.02%) vs 6 (0.04%), PCI 5 (0.1%) vs 21 (0.14%) of INSTI users vs. non-users. INSTI-based ART was associated with significantly lower risk of MACE events (HR 0.57; 95% CI 0.45, 0.73) compared to non-INSTI based regimens.

Conclusion: INSTI-based regimens were associated with a 43% decreased risk of CVD in this cohort. Validation of these findings in cohorts with longer follow up is needed.

681 CHANGES IN FAT DENSITY AFTER ART INITIATION

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Background: Adipose tissue (AT) disturbances are common in people living with HIV (PLWH), and changes in AT quality may occur independently of changes in AT quantity. Decreases in AT density, a marker of AT quality, suggest disrupted adipocyte function and lipid accumulation. We previously reported that subcutaneous AT (SAT) density on computed tomography (CT) reflects biopsy-quantified SAT adipocyte size in PLWH, and that AT quantity increases on antiretroviral therapy (ART). In this exploratory analysis, we assessed changes in AT density after ART initiation and associations with immuno-metabolic parameters.

Methods: ACTG A5257 randomized ART-naïve, adult PLWH to raltegravir (RAL) or ritonavir-boosted atazanavir (ATV/r) or darunavir (DRV/r), each with tenofovir disoproxil fumarate and emtricitabine, for 96 weeks. The subset with Weeks 0 and 96 (W0 and W96) abdominal CT scans and W96 HIV-1 RNA <50 copies/mL were included. Linear regression models compared W0, W96 and 96-week changes in SAT and visceral AT (VAT) density (in Hounsfield units, HU), adjusting for AT area and clinical/demographic parameters. Partial Spearman's correlations adjusting for AT area assessed relationships between AT density and immuno-metabolic parameters.

Results: Median age was 36 years, CD4+ T cell count 344 cells/μL and BMI 24.5 kg/m2; 89% were male and 56% non-white. W0 median SAT and VAT density were -99 and -80 HU, respectively. Over 96 weeks, SAT and VAT HU decreased in all arms (Table). In adjusted models, female sex and higher W0 HIV-1 RNA were independently associated with greater declines in AT density (women: SAT -4.8 and VAT -4.0 HU greater than men; per log10 HIV-1 RNA copies/mL: SAT -2.3 and VAT -2.7 HU). Statistically different effects of ART type were not seen (p>0.13), though variability was high. W96 SAT and VAT HU correlated (p<0.05) positively with HDL cholesterol and adiponectin levels (r=0.19 to 0.30) and negatively with IL-6, non-HDL cholesterol, triglyceride, leptin and HOMA-IR (r=-0.23 to -0.68) even after adjusting for baseline CD4+ T cell count, HIV-1 RNA and AT area.

Conclusion: VAT and SAT density decreased following ART initiation. Women and PLWH with higher HIV-1 RNA had greater decreases. Following virologic suppression, lower AT density was associated with greater systemic inflammation, lipid parameter disruption and insulin resistance independent of AT area. These findings suggest that changes in fat tissue during ART may have adverse health consequences.

Table. Median (interquartile range) absolute 96-week changes in VAT and SAT density.

	All (n=228)	DRV/r (n=74)	ATV/r (n=75)	RAL (n=79)	Men (n=204)	Women (n=24)
Change in SAT density (HU)	-1.9 (-6.9, 2.2)	-3.2 (-10.5, 1.0)	-1.6 (-5.8, 3.5)	-2.0 (-7.1, 2.2)	-1.9 (-7.4, 2.3)	-1.6 (-6.8, 1.3)
P value	<0.001	<0.001	0.06	0.006	<0.001	0.05
Change in VAT density (HU)	-3.2 (-8.9, 2.0)	-4.0 (-10.5, 3.0)	-2.3 (-6.5, 1.5)	-4.7 (-10.5, 3.01)	-2.9 (-8.7, 2.3)	-4.1 (-11.7, -1.8)
P value	<0.001	0.003	0.004	<0.001	<0.001	<0.001

*p-value based on sign-ranked test.

682 DUAL-ENERGY X-RAY ABSORPTIOMETRY (DXA) POORLY APPROXIMATES VISCERAL FAT IN HIV

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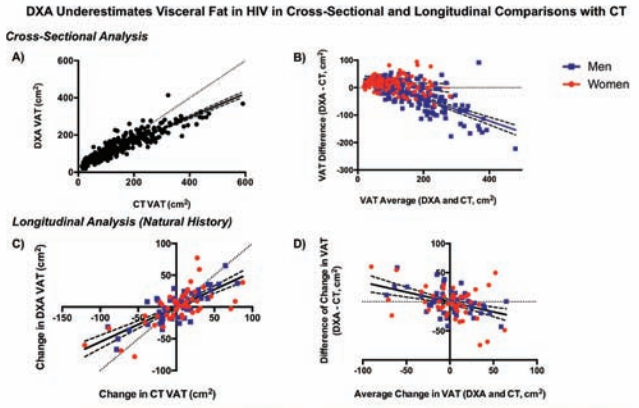
Background: People living with HIV (PLWH) are prone to visceral fat accumulation, which predisposes to comorbidities including dyslipidemia and coronary artery disease. Given the importance of visceral fat to cardiometabolic health in HIV, techniques to allow for its safe and affordable measurement are critically needed. Dual-energy x-ray absorptiometry (DXA) is an inexpensive modality that uses minimal radiation to quantify body composition. Recently, advanced software has allowed visceral fat to be ascertained from standard DXA, although this has never before been validated in HIV. Here, we investigated the accuracy of DXA in the measurement of visceral fat in comparison to computed tomography (CT) as the gold standard.

Methods: We pooled data from 5 prior studies of PLWH and uninfected controls in which paired DXA and CT scans were available. For this purpose, DXA (Hologic) was re-analyzed to quantify visceral fat using APEX 6.6.0.5 software. In a cross-sectional analysis, L4-L5 visceral fat cross-sectional area (VAT) as measured by DXA and CT were compared in PLWH (n=313) and controls (n=144). In longitudinal analyses, the accuracy of DXA with respect to changes in VAT over time was assessed (1) among PLWH (n=106) and controls (n=80) on no intervention for 12 months, and (2) among PLWH on tesamorelin (n=23) – an FDA-approved medication known to reduce VAT in HIV – or placebo (n=20) for 6 months. Bland-Altman plots were used to compare DXA with CT.

Results: In HIV, DXA-VAT and CT-VAT were strongly correlated (r=0.91, P<0.0001). However, the measurement bias (DXA – CT) became progressively more negative with greater VAT (P<0.0001). In this regard, whereas the bias was -9±47 cm2 overall, it was -61±58 cm^2 among those with VAT≥200 cm^2. Sex modified the inverse relationship between VAT and measurement bias (P<0.0001) such that it was particularly pronounced in men rather than women. Longitudinally, in the natural history analysis, DXA underestimated changes in VAT, irrespective of sex, with the largest bias at the extremes of VAT gain or loss (P<0.0001). DXA similarly underestimated changes in VAT among PLWH treated with either tesamorelin or placebo (P=0.004). Analogous cross-sectional and longitudinal findings were seen among uninfected controls.

Conclusion: DXA underestimated VAT compared to CT in HIV-infected men with visceral fat accumulation. DXA also underestimated changes in VAT over time in both men and women with HIV. DXA-VAT should be used with caution in HIV and non-HIV alike.



A) In HIV, CT-VAT and DXA-VAT were highly correlated (*P*<0.0001), though the linear regression line deviated below the line of unity (*P*<0.05). **B)** The underestimation of VAT by DXA became progressively larger with increasing VAT (*P*<0.0001), particularly in men with HIV. **C)** In HIV, DXA underestimated changes in VAT as measured by CT irrespective of sex (*P*<0.05). **D)** The underestimation of VAT changes by DXA was most pronounced at the extremes of VAT gain or loss. For all panels, the linear regression line with 95% confidence bands are shown.

683 UNIQUE MIRNA SIGNATURE IN HIV LIPODYSTROPHY WITH REDUCED ADIPOSE DICER EXPRESSION

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Background: Suppression of Dicer, an endoribonuclease that regulates microRNAs (miRNA), has evolved as a viral mechanism to enhance host HIV infectivity and may have unintended metabolic consequences. Animal knockout models of adipose-specific dicer (ADicer) acquire lipodystrophy accompanied by severe metabolic abnormalities. Data show adipose is a source of exosomal miRNAs, which function as adipokines influencing metabolic homeostasis. We hypothesized a unique miRNA profile among individuals well-phenotyped for HIV lipodystrophy and reduced ADicer expression.

Methods: We evaluated >1000 miRNAs from exosomes derived from sera among the 27 male individuals [9 HIV lipodystrophy (HIV/lipo), 9 HIV without lipodystrophy (HIV/non-lipo), 9 non-HIV] whom we previously showed variations in ADicer: most suppressed among HIV lipo, followed by HIV non-lipo and non-HIV (2.49[0.02,4.88] vs. 11.20[4.83,21.45] vs. 17.69[10.72,47.91], P=.002). To estimate miRNA abundance, data was normalized to the average expression of all measured miRNAs. Student's T-test for 2 group comparisons and a false discovery rate analysis (FDR) was applied. Using target prediction databases (TargetScan, miRDB, Diana), we identified genes related to fat biology and lipid metabolism via a conservative approach (presence in all 3 databases + target score of >85%) with clinical relevance to lipodystrophic phenotypes.

Results: HIV/lipo individuals (mean age 56±3 years, BMI 30±1 kg/m2, duration HIV 24±2 years, duration ART 20±2 years, CD4+ count 482±90 cells/μl, undetectable VL 67%) were similar to HIV/non-lipo (age 52±3 years, BMI 30±1 kg/m2) and non-HIV (age 55±3 years, BMI 30±1 kg/m2) individuals. Reduced ADicer expression was significantly related to reduced CD4+ count (r=0.55, P=.02), duration ART use (r=-0.70, P=.001) and duration PI use (r=-0.71, P=.03) and tended to be related to duration HIV (r=-0.44, P=.07) and reduced CD8+ count (r=0.42, P=.08). Accounting for the FDR, we detected miRNA-20a-3p (P=.0026), 324-5p (P=.0059), and 186-5p (P=.0977) were expressed differentially in HIV/lipo vs. non-HIV and 324-5p(P=.0348) in HIV/lipo vs. HIV/non-lipo. Relevant target genes per individual miRNA include: 20a-3p (EBF1, EHMT1, EZH2, NF1, PCNA, RAB4A, SPRY1, TDG), 324-5p (VDAC1), and 186-5p (MYT1L, NEGR1, NFAT5, PDE10A, PID1).

Conclusion: These novel data enhance our understanding by which altered ADicer expression and specific exosomal miRNAs may affect gene expression of regulators important to fat biology and metabolic homeostasis in HIV.

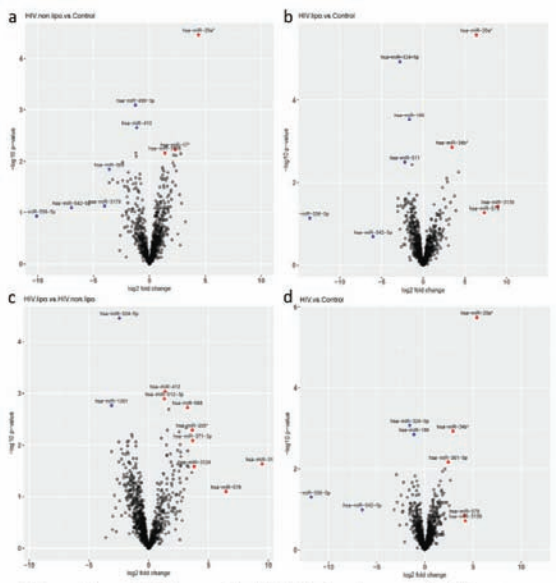

Figure Legend: Volcano plot highlighting the most significant miRNAs in the comparison according to p-value and fold change among (a) HIV/non-lipo vs. non-HIV, (b) HIV/lipo vs. non-HIV, (c) HIV/lipo vs. HIV/non-lipo and (d) HIV (both HIV/lipo and HIV/non-lipo) vs. non-HIV.

684 ADIPOSE TISSUE CD4+ AND CD8+ T-CELL PROFILES DIFFER BY GLUCOSE TOLERANCE IN HIV

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Background: T lymphocytes play a central role in modulating adipose tissue inflammation and, by extension, adipocyte function. We hypothesized that greater adipose tissue T-cell activation in persons living with HIV (PLWH) may contribute to higher rates of diabetes.

Methods: We compared CD4 and CD8 T-cell subsets in the subcutaneous adipose tissue (SAT) and blood of 9 non-diabetic (fasting blood glucose [FBG]<100mg/dL), 8 pre-diabetic (FBG=100-125 mg/dL) and 9 diabetic (FBG>=126mg/dL) PLWH, in addition to 8 pre-diabetic, HIV-negative [HIV(-)] controls. SAT was collected by liposuction and T cells extracted by collagenase digestion. The proportion of naïve (TN) CD45RO-CCR7+, effector memory (TEM) CD45RO+CCR7−, central memory (TCM) CD45RO+CCR7+, and effector memory revertant RA+ (TEMRA) CD45RO-CCR7− CD4 and CD8 T cells were measured by flow cytometry. T cell subsets were compared by Wilcoxon signed-rank (paired blood and adipose), Mann-Whitney (between groups), and linear regression tests according to glucose tolerance.

Results: Age, race and sex were similar across groups. Compared to HIV(−) controls, SAT from PLWH with similar glucose tolerance had significantly higher CD8 T cells (49% vs 19%, p<0.01) and lower CD4 T cells (47% vs 65%, p<0.01). The distribution of SAT CD4 and CD8 memory subsets did not differ by HIV status, except for higher CD4 TCM (p<0.01) and lower CD4 TEM (p<0.05) in the PLWH. SAT was enriched for CD4 TEM compared to blood (45 vs. 15%, p<0.0001) and TEMRA (8 vs. 2%, p<0.0001), depleted in TN (16 vs. 29%, p<0.001) and TCM (15 vs. 26%, p<0.001). These findings were similar for CD8 T cell subsets. While the relative proportions of SAT CD4 and CD8 TCM, TEM, and TEMRA cells were similar regardless of glucose tolerance status in PLWH, expression of CD69 - a marker of activation and tissue resident cells - on CD4 T cells rose with progressive insulin resistance (see Table, p=0.004), which was robust to adjustment for BMI (p=0.03). Among CD4 T cell subsets, progression from non-diabetic to diabetic groups was accompanied by increased CD69 on TCM, TEM, and TEMRA cells.

Conclusion: This study is the first to characterize SAT CD4 and CD8 memory T cell subsets in PLWH. SAT from PLWH is enriched for TEM and TEMRA CD4 and CD8 compared to blood, which could contribute to tissue inflammation. Increased insulin resistance in PLWH is associated with increased CD69 on SAT CD4 T cells, potentially reflecting a link between accumulation of adipose resident CD4 cells and metabolic disease.

Table: Mean CD4+ T cell CD69 expression according to glucose tolerance

T cell subset	Non-diabetic	Pre-diabetic	Diabetic	p-value*
Total CD4+ T cells	7.5%	10.9%	17.2%	p=0.004
T_{NAIVE}	0.4%	1.1%	2.3%	p=0.03
$T_{CENTRAL\ MEMORY}$	4.6%	7.3%	13.6%	p=0.02
$T_{EFFECTOR\ MEMORY}$	12.4%	16.9%	25.9%	p=0.04
$T_{EFFECTOR\ MEMORY\ RA+}$	4.7%	8.4%	7.9%	p=0.04
*Linear regression				

685 FIBROBLAST GROWTH FACTOR 21 (FGF21) IS ELEVATED IN HIV AND AFFECTED BY INFLAMMATION

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Background: FGF21 is a relatively recently identified endocrine hormone that appears to have beneficial metabolic effects, including promoting weight loss, improving glucose metabolism and decreasing inflammation. In obesity, diabetes and metabolic syndrome, FGF21 levels are paradoxically increased, suggesting an FGF21-resistant state. Levels in HIV have been related to metabolic abnormalities, but little is known about FGF21 and its relationship to HIV-specific vs. non-HIV factors.

Methods: HIV+ subjects on antiretroviral therapy (ART) or naïve to therapy were prospectively enrolled, along with healthy controls and underwent a comprehensive clinical and laboratory assessment. Body composition was assessed by dual-energy x-ray absorptiometry. Fasting lipids, insulin, glucose, and inflammatory markers were measured. Plasma FGF21 levels were assessed in duplicate by ELISA and log-transformed to achieve a normal distribution.

Results: 150 HIV+ (119 on ART; 31 ART-naïve) and 29 controls were enrolled. There was no significant difference in age-adjusted log FGF21 (pg/mL) between subjects on ART vs. ART-naïve (5.4 vs. 5.3; P=0.68), so groups were combined and compared to controls. There was no difference between HIV+ and controls in sex, race, alcohol use, body mass index (BMI), trunk fat, and HDL-C, but HIV+ were older with more smokers and higher waist-to-hip ratio (WHR), waist circumference (WC), HOMA-IR, LDL-C, and triglycerides (TG). Unadjusted log FGF21 was higher in HIV+ vs. controls (5.4 vs. 4.8; P=0.003). After controlling for age, smoking and alcohol use, log FGF21 remained higher in HIV+ (5.3 vs. 4.9; P=0.04). In HIV+, variables most associated with higher FGF21 in bivariate analyses included older age, smoking, alcohol use, increased trunk fat, WHR, WC, TG, HOMA-IR, IL-6, sTNFR-I, viral load >200 copies/mL, and lower LDL-C. Other HIV variables (nadir/current CD4, HIV duration, ART duration/type), BMI, sex, and race showed no relationship to FGF21. In stepwise regression models, variables that affected FGF21 most significantly were smoking, higher IL-6 and TG, and lower LDL-C.

Conclusion: People with HIV, regardless of treatment, have increased circulating FGF21 compared to healthy controls. Inflammation appears to play a significant role in affecting FGF21 in HIV, whereas other aspects of HIV/ART do not. Further research is needed to determine the role that inflammation plays in FGF21 pathways and whether increased FGF21 levels are due to a resistant state or reflect a compensatory response.

686 HAART IS ASSOCIATED WITH REDUCED RISK OF OSTEOPOROSIS-RELATED FRACTURES

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Background: People living with HIV (PLWHIV) face a higher risk of osteoporosis-related fractures (ORF) compared with HIV-negative individuals. HIV-related systemic inflammation and antiretroviral therapy (ART), particularly tenofovir disoproxil fumarate (TDF), have been associated with reduced bone mineral density; however, there is no clear association between ORF and these factors. We investigated the association of HIV-related factors including viral suppression and ART exposure with the risk of ORF among PLWHIV in British Columbia, Canada (BC).

Methods: Our study uses data from the Comparative Outcomes and Service Utilization Trends (COAST) study, a population-based retrospective cohort study

examining health outcomes and service use of PLWHIV and a 10% sample of HIV-negative individuals in BC. Wrist, humerus, vertebrae and hip fractures were considered as ORF and were assessed using physician and hospital-based administrative data and ICD-9/10. The effect of the variables on the risk of ORF was assessed by logistic generalized estimating equation model. Sex, age at ART initiation, previous injuries, history of injection drug use (IDU), ART initiation era and viral suppression were covariates. The effect of ART drug classes was analyzed in a univariate model including data after ART initiation. TDF was studied separately and considered only data after TDF was available in BC.
Results: A total of 6,846 PLWHIV and 514,619 HIV negative individuals were included in the incidence analysis. ORF occurred in 416 PLWHIV and 28,028 HIV-negative individuals (6.08% versus 5.45% p=0.02). Among PLWHIV, 63% of the first ORF occurred before the age of 50 years of age, while only 34% occurred before age 50 in the HIV negative group (p<.0001). In a multivariate analysis, female sex, older age at ART initiation, IDU and previous injuries were associated with increased risk of ORF; while later ART initiation era and higher proportion of viral suppression were associated with reduced likelihood of ORF. ART drug classes and TDF were negatively associated with having an ORF. (Table 1).
Conclusion: Higher incidence of ORF was found in PLWHIV versus HIV negative individuals at an earlier age. In our population, viral suppression and length of time on ART were associated with reduced risk of ORF, including ART regimes containing TDF, which in previous studies have been shown to be associated with bone toxicity. Our study indicates that early initiation of ART may reduce the risk for ORF in PLWHIV.

Table 1

Variable	Odds Ratio	95% Confidence Interval	
Multivariate Model			
Sex			
Male [ref]	1.00		
Female	1.46	1.11	1.93
IDU			
No [ref]	1.00		
Yes	2.08	1.58	2.73
Age at ART initiation (10 Years)	1.53	1.36	1.72
Any injuries except falls before ORF*			
No [ref]	1.00		
Yes	3.88	2.99	5.03
ART initiation era			
<=1999 [ref]	1.00		
2000-2003	0.78	0.59	1.04
2004-2007	0.53	0.39	0.72
>=2008	0.20	0.14	0.30
Proportion of VL <500 copies/ml until ORF(10%)	0.96	0.93	1.00
Univariate Model			
Length of time on ART until ORF (1 year)*	0.92	0.89	0.94
Length of time on NRTI (not include TDF) until ORF (1 year)*	0.89	0.8642	0.9184
Length of time on NNRTI until ORF (1 year)*	0.92	0.88	0.96
Length of time on PI until ORF (1 year)*	0.96	0.93	0.99
Length of time on TDF until ORF (1 year)*	0.85	0.79	0.92

Note

Only fractures occuring among PLWHIV after ART initiation were included
For TDF, only people who initiated ART after 01 December 2001 were considered.
IDU: Intravenous Drug Use
ART: Antiretroviral Therapy.
ORF: Osteoporosis-related Fracture.
VL: plasma HIV-1 RNA viral load.
TDF: tenofovir disoproxil fumarate
NRTI: Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
PI: Protease Inhibitors.
Injuries include motor vehicle collision, land transportation injuries, self harm and assault.
** Are time-varying variables.*

687 EFFECTS OF ERADICATION OF HCV ON BONE MINERAL DENSITY IN HIV/HCV-COINFECTED PATIENTS

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Background: HCV infection has been associated with increased risk of bone loss and fracture in HIV-infected persons. Little is known, however, about the effects of eradication of HCV on bone mineral density (BMD) in HIV/HCV-coinfected persons.
Methods: We performed a multicenter prospective study (Feb 2012 to Mar 2014) to analyze BMD at baseline and 96 wk after initiation of anti-HCV Rx in HIV/HCV-coinfected persons. BMD was assessed by dual-energy X-ray absorptiometry (DXA) at the lumbar spine and femoral neck. Definitions: osteoporosis, T score, ≤−2.5 SD; osteopenia, T score, −1 to −2.5 SD. As different densitometers were used, standardized BMD (sBMD) was calculated using published equations for the femoral neck (J Bone Mineral Research 1997;12:1463) and lumbar spine (Osteoporosis International 2001;12:438).
Results: Paired determinations of BMD were made in 160 patients in 13 centers using Hologic® (n=113), Lunar® (n=30), and Norland® (n=17). Median age was 49 y. Men accounted for 74.4%, and prior IDU for 73.8%. Cirrhosis was detected in 46.3%, smokers accounted for 68.1%, and 2.5% of patients had a high alcohol intake. Anti-HCV Rx included pegylated interferon + ribavirin (PR) in 35%, PR + a first-generation HCV protease inhibitor in 44%, sofosbuvir + R in 12.5%, and PR + daclatasvir in 8.1%. A total of 102 patients (64%) achieved a sustained viral response (SVR). Statistically significant differences between responders and nonresponders were found in baseline HCV-RNA and type of anti-HCV Rx. At baseline, sBMD values (g/cm2) were similar between responders and nonresponders in the lumbar spine (median [95%CI] 1.02 [0.89-1.14] vs 1.00 [0.92-1.11], P=0.739); however, a trend towards higher sBMD was found in the femoral neck in responders compared with nonresponders (median [95% CI] 0.85 [0.75-0.94] vs 0.78 [0.72-0.87], P=0.06). No differences in sBMD changes from baseline to wk 96 were found between responders and nonresponders in the lumbar spine (median [95% CI] −0.01 [−0.03 to 0.03] vs −0.01 [−0.03 to 0.03], P=0.76) or femoral neck (median [95% CI] −0.02 [−0.06 to 0.01] vs −0.02 [−0.05 to 0.01], P=0.97). No statistically significant differences were found in the proportion of patients with changes in the BMD categories (normal, osteopenia, osteoporosis) from baseline to week 96 at the lumbar spine or femoral neck (Table).
Conclusion: Our data suggest that, in the medium term, eradication of HCV following anti-HCV Rx in coinfected patients is not associated with significant changes in BMD.

Table. Changes in BMD categories from baseline to week 96 in patients with and without SVR

	SVR N=102			Non-SVR N=58		
	Baseline n (%)	96 wk n (%)	P	Baseline n (%)	96 wk n (%)	P
Lumbar spine			0.846			0.091
Normal	52 (51.0)	50 (49.0)		27 (46.6)	24 (41.4)	
Osteopenia	29 (28.4)	31 (30.4)		21 (36.2)	27 (46.6)	
Osteoporosis	21 (20.6)	21 (20.6)		10 (17.2)	7 (12.1)	
Femoral neck			0.123			0.174
Normal	54 (53.5)	45 (44.6)		20 (35.7)	18 (32.1)	
Osteopenia	40 (39.6)	47 (46.5)		32 (57.1)	31 (55.4)	
Osteoporosis	7 (6.9)	9 (8.9)		4 (7.1)	7 (12.5)	

688 HIV-ASSOCIATED HYPOPARATHYROIDISM: RESULTS FROM A GERMAN HIV COHORT

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Background: Parathyroid hormone (PTH) secretion in response to hypocalcemia was reported to be blunted in individual people living with HIV (PLWH). HIV-infection has therefore been acknowledged to be an infrequent cause of hypoparathyroidism (hypoPT). Population data are, however, missing. We evaluated the prevalence and characteristics of hypoPT in PLWH in a single-center cohort in Munich,
Methods: Single-center substudy of the German multi-center ArcHIV Cohort Study. PLWH with available measurements of PTH and calcium levels in two

consecutive years (2016 and 2017) for diagnosis of hypoPT were included in the study. HypoPT was defined as confirmed PTH <65 pg/mL and albumin-corrected calcium <2.12 mmol/L.

Results: In total, 496 PLWH were included; median age was 47 (IQR, interquartile range: 40-54 years), 393 (79.2%) were male. TDF was used by 51.8% and 39.9% of PLWH in 2016 and 2017, respectively. Laboratory criteria for hypoPT was met in 15.3 % of PLWH (76/496) in 2016 and in 8.3 % (41/496) in 2017. 14/496 PLWH (2.8 % [95% CI: 1.6-4.7]) presented with confirmed hypoPT. Characteristics of PLWH with and without confirmed hypoPT are shown in Table 1. Univariate associations between potential covariables and confirmed hypoPT were as follows in crude analysis: male sex (OR 1.0 [95% CI: 0.3-3.5]; P = 0.95), age ≥55 years (OR 0.3 [95% CI: 0.0-1.9]; P = 0.19), average cystatin c ≥1.0 mg/dl (OR 0.4 [95% CI: 0.1-1.8]; P = 0.22), being vitamin D deficient in both years (OR 0.2 [95% CI: 0.0-1.8]; P = 0.16), and use of tenofovir disoproxil fumarate (TDF) in both years (OR 4.3 [95% CI: 1.3-14.1]; P = 0.01). TDF remained significantly associated with hypoPT after adjusting for sex, age (≥55 years), and vitamin D deficiency (OR 4.2 [95% CI: 1.3-13.9]; P = 0.02).

Conclusion: Prevalence of hypoPT was unexpectedly high in our cohort of PLWH with 2.8% compared to 0.01-0.04 % as reported in general populations. TDF containing therapy was the only factor significantly associated with hypoPT. This is consistent with a much higher prevalence of hypoPT in 2016, before the more wide-spread use of tenofovir alafenamide starting end of 2016 (proportion of PLWH on TAF were 18.6% and 30.0% (P<0.001) in 2016 and 2017, respectively). Although our results on hypoPT seem to be in contrast to previous findings of high PTH levels in PLWH on TDF, a possible link might be hypocalcemia resulting in secondary hyperparathyroidism in some, and hypoPT in other PLWH, that have HIV-associated impaired PTH-secretion.

Table 1: Characteristics of HIV-infected patients with laboratory constellation of HypoPT and HIV-infected controls.

	Units	Patients without HypoPT (N = 482)	Patients with HypoPT (N = 14)	P-value
Median Age	Years (IQR)	48 (40-54)	45 (39-51)	0.321
Male patients	N (%)	11 (2.8)	3 (2.9)	0.951
Creatinie*	mg/dL (IQR)	0.97 (0.87-1.08)	0.94 (0.80-1-14)	0.726
Cystatine C*	mg/dL (IQR)	0.94 (0.85-1.01)	0.95 (0.79-0.98)	0.528
Alkaline phosphatase*	U/L (IQR)	78 (65-93)	83 (58-92)	0.736
β-crosslaps *	ng/mL (IRQ)	0.31 (0.23-0.42)	0.29 (0.19-0.43)	0.633
Phosphate*	mg/dL (IQR)	3.4 (3.1-3.6)	3.2 (2.9-3.6)	0.091
Patients with at least one episode of low phosphate	N (%)	7 (2.1)	7 (4.5)	0.125
HIV-RNA*	/mL	< 20	< 20	0.110
CD4 cell count (absolute)*	/µL (IQR)	692 (522-890)	567 (436-805)	0.157
Patients with CD4 cells <450 copies/µL	N (%)	63 (13.1)	4 (28.6)	0.094
Patients with 25(OH)D < 20 ng/mL in both years	N (%)	120 (24.9)	1 (7.1)	0.127
Patients on TDF-containing ART in both years	N (%)	176 (36.5)	10 (71.4)	***0.008***

* = Median of individual average values of available measurements throughout both years.

689 IMPACT OF RENAL TUBULE FUNCTION ON BONE MINERAL DENSITY IN OLDER PEOPLE WITH HIV

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Background: Whether renal tubule dysfunction (RTD), common in people with HIV (PWH), contributes to low bone mineral density (BMD) remains controversial. We studied the relationship between RTD and BMD in a cross-sectional study (GS-US-104-0423) in a group of older (men >50 years and post-menopausal women) PWH on stable antiretroviral therapy (ART) that had always or never contained tenofovir (TDF), with or without exposure to protease inhibitors (PI) for the past three years.

Methods: We analysed stored urine for albumin:creatinine (ACR) and retinol-binding protein:creatinine (RBPCR) ratio, and fractional excretion of phosphate (FE-PO4) and urate (FE-urate). BMD at the lumbar spine (LS) and femoral neck (FN) was measured by dual X-ray absorptiometry (expressed in g/cm2). ART exposure was stratified into four groups (no-TDF/no-PI, no-TDF/PI, TDF/no-PI, TDF/PI). We used linear regression models to assess associations between tubular markers and BMD, adjusting for clinical characteristics and ART exposure.

Results: 228 individuals (median [IQR] age 57 [53, 64] years, 47% female, time on ART 10 [6, 16] years, CD4 643 [473, 811] and 98% with VL <200 c/mL) contributed to the analyses. The prevalence of osteoporosis (T score <-2.5) at LS and FN ranged from 21-30% and 14-28% in the four ART exposure groups, respectively (p=0.24 and p=0.08). In univariate analysis, lower LS-BMD was associated with female sex and lower BMI but not with RBPCR (p=0.673), and lower FN-BMD with older age, female sex, lower BMI and higher RBPCR (β -0.014 [95%CI -0.025, -0.002], p<0.0001); neither BMD at LS or FN was associated with eGFR, ACR, FE-PO4, FE-urate or ART exposure group. In multivariable models adjusting for age, gender and BMI, RBPCR was no longer associated with BMD-FN (Table, Model 1). Further adjustment for TDF exposure fully attenuated the relationship between RBPCR and FN BMD (Model 2). Using no TDF/no-PI as the ART reference group, exposure to no-TDF/PI and TDF/no-PI was associated with lower LS BMD, and exposure to TDF/no-PI and TDF/PI with lower FN BMD.

Conclusion: In this cohort of older PWH with a high prevalence of osteoporosis, RBPCR was the only marker of RTD associated with BMD, but the association lessened with demographic adjustment and was fully abrogated after adjustment for TDF exposure. Continuous TDF exposure was associated with significantly lower BMD at the femoral neck.

Table: Factors associated with BMD lumbar spine and BMD femoral neck

	LS-BMD: Model 1 β (95% CI)	P	LS-BMD: Model 2 β (95% CI)	P	FN-BMD: Model 1 β (95% CI)	P	FN-BMD: Model 2 β (95% CI)	P
Age per year	-		-		-0.003 (-0.006, -0.001)	0.011	-0.004 (-0.006, -0.001)	0.005
Female sex	-0.073 (-0.124, -0.022)	0.005	-0.085 (-0.137, -0.032)	0.002	-0.053 (-0.091, -0.016)	0.005	-0.053 (-0.091, -0.014)	0.007
BMI (per 1 unit)	0.008 (0.002, 0.014)	0.009	0.009 (0.003, 0.016)	0.003	0.011 (0.007, 0.015)	<0.0001	0.010 (0.006, 0.142)	<0.0001
RBPCR (log transformed)	0.003 (-0.012, 0.019)	0.662	0.007 (-0.009, 0.023)	0.409	-0.005 (-0.016, 0.006)	0.359	-0.001 (-0.012, 0.011)	0.932
ART: No TDF/No PI	-		1		-		1	
ART: No TDF/PI	-		-0.084 (-0.016, -0.012)	0.022	-		-0.046 (-0.097, 0.006)	0.083
ART: TDF/No PI	-		-0.078 (-0.015, -0.010)	0.025	-		-0.074 (-0.012, -0.026)	0.001
ART: TDF/PI	-		-0.057 (-0.013, 0.017)	0.131	-		-0.062 (-0.114, -0.011)	0.019

690 GENETIC AND CLINICAL RISK FACTORS FOR CHRONIC KIDNEY DISEASE IN HIV

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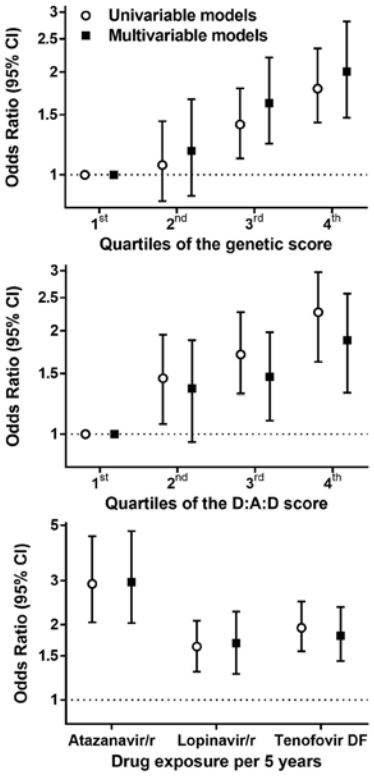
Background: In the general population, 53 common single nucleotide polymorphisms (SNPs) have been found to associate with chronic kidney disease (CKD) through genome-wide association studies (GWAS). The relative contribution of genetic background, HIV-related factors, antiretroviral medications, and traditional risk factors to CKD has not been evaluated in the setting of HIV infection.

Methods: We performed genome-wide genotyping in HIV-positive, white Swiss HIV Cohort Study participants with normal baseline estimated glomerular filtration rate (eGFR >90 mL/min/1.73 m2). We applied a 1:1 case-control design with incidence density matching. Since we had more cases than controls, we repeated the matching process 2000 times with random resampling from cases and controls. The averaged odds ratio (OR) of CKD from conditional logistic regression analyses was calculated as the antilog of the mean of the 2000 log-transformed ORs and the 95% confidence interval (CI) was based on the 2.5 and 97.5 percentiles. We present uni- and multivariable analyses of CKD and the effects of genetic background, clinical D:A:D CKD risk score, and potentially nephrotoxic antiretrovirals.

Results: We included 754 cases with CKD defined as confirmed eGFR drop to <60 mL/min/1.73 m2 (n=144) or eGFR drop of >25% (n=610), and 323 controls with eGFR drop of <15%. A genome-wide genetic risk score built from

CKD-associated SNPs significantly contributed to CKD in uni- and multivariable analysis (Figure). In the final multivariable model, participants in the 3rd and 4th genetic score quartiles had a CKD OR of 1.62 (95% confidence interval, 1.23–2.21) and 2.01 (1.47–2.81), compared to the 1st quartile (most favorable genetic background). In comparison, persons in the 3rd and 4th quartile of the D:A:D CKD risk score had CKD OR of 1.47 (1.09–1.98) and 1.88 (1.32–2.57), compared to the most favorable 1st quartile. Cumulative exposure per 5 years to atazanavir/ritonavir, lopinavir/ritonavir, and tenofovir disoproxil fumarate were associated with CKD OR of 2.96 (2.03–4.74), 1.69 (1.27–2.26), and 1.81 (1.43–2.36), respectively.

Conclusion: The effect of an unfavorable genetic background on CKD risk in HIV-positive persons was similar to the effect of the established D:A:D clinical risk score, and similar to 5-year exposure to nephrotoxic antiretrovirals. Genetic testing may provide prognostic CKD information complementary to clinical and antiretroviral risk factors.



691 LYSOSOMAL TOXICITY AS A NOVEL MECHANISM IN TENOFOVIR-ASSOCIATED NEPHROTOXICITY

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Background: Tenofovir disoproxil fumarate (TDF) treatment can lead to renal impairment. Experimental data suggest that tenofovir (TFV)-mediated mitochondrial toxicity contributes to tubular cell damage. We hypothesized that tenofovir induces lysosomal hyper-activation and destabilization, which compromises renal proximal tubular function and viability.

Methods: The aim of the study was to assess the effects of TFV and TDF on autophago-lysosomal homeostasis, autophagic flux, lysosomal mass, lysosomal membrane composition, acidity, cathepsin activity and kidney cell viability in organic anion transporter 1 (OAT1) expressing (OAT1-HEK-293) and parental WT-HEK-293 kidney cells. Analyses were performed using immunostaining, calorimetric measurements, flow cytometry, real-Time PCR and confocal microscopy.

Results: TFV incubation of OAT1-HEK-293 cells resulted in increased autophgic flux (99.4 ± 5.8% change to control; P<0.001), lysosomal hyper-activation, increased lysosomal mass (74.2 ± 7.0% change to control; P<0.001) and acidity (31.5 ± 1.3% change to control; P<0.001) and higher activity of the lysosomal cell death executors cathepsin B and L (75.7 ± 5.2% and 76.2 ± 3.6% change to control; P<0.001). These changes were associated with decreased membrane stability, decreased relative abundance of lysosomal stabilizing proteins LAMP1 and 2 (-33.2 ± 2.7% and -45.7 ± 2.2 change to control; P<0.05, P<0.001) loss of lysosomal integrity (Control 20.6 ± 1.2% vs TFV 43.2 ± 2.2%; P<0.001) and compromised cell viability and were related to intracellular TFV amount. Importantly, inhibition of lysosomal activity using ammonium chloride (NH4Cl) or chloroquine (CQ) counteracted cell toxicity and rescued cell viability (Cell death without NH4Cl/CQ 180.2 ± 23.2% change to control vs plus NH4Cl -16.5 ± 6.9 % or plus CQ -55.4 ± 3.7%; P<0.001).

Conclusion: Intracellular accumulation of TFV induces lysosomal toxicity as demonstrated by organelle hyper-activation and membrane destabilization ultimately leading to compromised kidney cell viability. Our results contribute to a better understanding of the long-term side effects of this commonly used antiviral agent.

692 DYNAMICS OF E-FGR WITH ONE OR MORE ANTIRETROVIRALS THAT INHIBIT CR TUBULAR SECRETION

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Background: Cobicistat (C), dolutegravir (DLT) and rilpivirine (RPV) all are modest antiretroviral drugs that inhibit proximal tubular creatinine secretion and hence a moderate and early non progressive creatinine estimated glomerular filtration (Cr-eGFR) reduction has been observed in clinical trials. Neither in vitro, nor clinical trials have explored whether combination of these drugs may have an additive effect in the inhibition of creatinine secretion.

Methods: Cr-eGFR changes after starting Darunavir (DRV)/c alone or in combination with DTG and/or RPV were assessed in a nation-wide retrospective cohort study of consecutive HIV-infected patients initiating DRV/c from June/2014 to March/2017. The eGFR was calculated with Cr-CKD-EPI in mL/min/1.73m2. The relationship between Cr-eGFR change over time and the use of DRV/c alone or in combination with DTG and/or RPV adjusted by different factors that might influence Cr-eGFR such as HIV patient´s characteristics, socio-demographics, HIV severity, use of TDF, and concomitant medication other than ARV was explored. Ethics approval was obtained and patients signed informed consent.

Results: There were 761 patients (85% men, 91% Caucasian, 99% antiretroviral-experienced, 34% HCV coinfected, 80% on prior DRV/ritonavir, 32% prior AIDS, 84% HIV RNA < 50 copies/mL, 88% ≥200 CD4/mm3) from 21 Spanish HIV Units. Thirty-six (5%) patients were excluded due to the lack of Cr-eGFR data. Mean baseline (SD) Cr-eGFR was 94 (19) and 5% had eFGR below 60, increasing to 8% at 48 week. Only 6 (1%) patients had DRV/c switched DRV/c due to renal adverse effects. Higher significant decreases in Cr-eGFR were observed in patients taking two or more Inhibitors of Tubular Cr Secretion at week 24, and a strong trend at week 48 (Figure). In multivariate analysis in patients receiving DRV/c, female sex was associated with a significant improvement of Cr-eGFR adjusted median difference (AMD) 2.5±1.3 CI 95% (0.4; 5.1) P=0.047, while the combination of DRV/c with either RPV or DTG or both decreases Cr-eFGR AMD 3.5±1.6 CI 95% (-6.6 ; -0.3); p= 0.032.

Conclusion: The concomitant use of Darunavir/cobicistat plus other known inhibitors of tubular creatinine secretion (dolutegravir, Rilpivirine or both) produced an additive effect in the expected Cr-eGFR decrease.

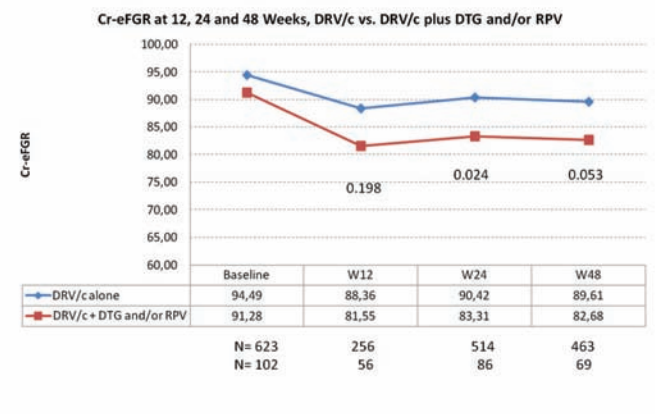

Table 1. Adjusted IRR (Incidence rate ratio) from Poisson regression analysis of eGFR recovery to pre-TDF values (model A) and of change from G2 to G1 eGFR category in CKD (model B). *eGFR in model A was calculated at baseline pre-TDF and in model B at switch; n.e.=variable not entered in the model. Significant values are reported in bold.

	Model A			Model B		
	aIRR	95%CI		aIRR	95%CI	
Age, (10 yrs older)	n.e.			0.80	0.65	0.99
Years of HIV infection, (per 1 yr more)	1.01	0.98	1.03	n.e.		
CDC stage C va A/B	1.17	0.80	1.70	n.e.		
Nadir CD4<=200 cell/mmc vs >200	0.85	0.62	1.17	n.e.		
CD4 at BL>=350 cell/mmc vs <350	1.29	0.82	2.02	n.e.		
CD8 at BL>=800 cell/mmc vs <800	**1.50**	**1.19**	**1.90**	n.e.		
Number of previous regimen (per 1 more)	0.97	0.90	1.06	n.e.		
eGFR*, (per 10 mL/min higher)	**0.87**	**0.82**	**0.93**	**2.41**	**1.73**	**3.37**
Years of TDF exposure (per 1 yr more)	0.99	0.94	1.04	1.03	0.95	1.11
Unboosted third drug vs boosted	**1.35**	**1.07**	**1.71**	1.29	0.86	1.93

693 EVOLUTION AND REVERSIBILITY OF RENAL FUNCTION AFTER SWITCH FROM TDF TO TAF REGIMENS

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Background: Tenofovir alafenamide (TAF) benefits over Tenofovir disoproxil fumarate (TDF) on renal function has been consistently demonstrated mainly as change of renal filtrate in randomized clinical trials. However, a recent meta-analysis has shown a significant advantage of TAF (in term of discontinuations for renal events) only if combined with a boosted third drug. Aim of the study was to evaluate size of improvement and reversibility of renal function in patients (pts) previously exposed to TDF who switched to TAF.
Methods: HIV+ pts from the Icona Foundation Cohort switching from a TDF- to a TAF-containing regimen, maintaining the same third drug were included. Outcomes: a) difference in estimated glomerular filtration rate (eGFR, by CKD-EPI formula) at 3-6 months (the later measurement); b) proportion of pts with recovery of eGFR to the baseline before TDF introduction (± 5%); c) change of eGFR category in CKD (from G2 60-89 ml/min/1.73 m2 to G1≥90). T-test for paired and unpaired samples was used to analyze eGFR change and Poisson regression analysis for predictors for all the two categorical outcomes.
Results: 947 pts were included: 504 in unboosted regimen (75% NNRTI as third drug, 25% INI), 443 in boosted one (21% PI, 79% INI); 793 (84%) males, median age 44 (36-52) years, eGFR 93 (81-105) ml/min/1.73 m2 at baseline (BL, time of switch to TAF), eGFR 109 (98-118) before TDF introduction, TDF exposure 3 (2-5) years. Mean change in eGFR after 3-6 months (data available for 627 pts) was +1.2 ml/min/1.73 m2 in the overall population (p=0.007), and +1.7 and +0.6 in unboosted and boosted, respectively (p=0.19). An eGFR recovery to pre-TDF values was observed in 302/896 (33.7%) pts; higher eGFR pre-TDF was associated to a lower probability of recovery, while higher CD8 values and being on a unboosted regimen predicted greater probability of recovery (Table 1). A change from G2 to G1 eGFR category in CKD was observed in 96/394 (24.4%), the use of booster did not seem to affect this outcome (Table 1).
Conclusion: After switching from TDF to TAF, only a small even statistically significant improvement in eGFR was observed and a complete recovery of renal filtrate or a transition to normal CKD category occurred in less than half of cases over a median of 1 year of observation. Unboosted regimens seem to be associated with a higher probability of regaining renal filtrate. These data may be useful for selecting in which patients to maintain TDF without jeopardizing renal function.

694 GLOMERULAR FILTRATION RATE RECOVERY AFTER A SWITCH FROM TDF TO TAF OR ABC

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Background: Tenofovir-disoproxil fumarate (TDF) containing cART can be associated with an accelerated decline of the estimated glomerular filtration rate (eGFR). Limited data are available on the extent of the reversibility of this eGFR decline and whether using T-alafenamide (TAF) is non-inferior to abacavir (ABC) regarding eGFR recovery after TDF discontinuation.
Methods: The BACTAF-studies are 2 multicenter studies; an ongoing prospective randomized study (NCT02957864) and a retrospective cohort study. Both have similar goals; 1. Evaluate the reversibility of TDF-associated eGFR decline and 2. Compare the eGFR recovery in pts switching to TAF or ABC. Pts were included if they had switched from TDF to TAF or ABC for a significant eGFR-decline, defined as a decline of >3mL/min/yr during ≥5yrs of TDF use **or** an eGFR decline >25% **or** an eGFR<70mL/min with eGFR>90mL/min at TDF initiation. Pts with detectable HIV-RNA, diabetes, history of cardiovascular disease, uncontrolled hypertension, use of >1 antihypertensive drug, use of potentially nephrotoxic medication, ABC resistance, HBV/HCV coinfection or another diagnosed kidney disease that may partially explain the eGFR-decline were excluded to increase the likelihood of TDF-relatedness of the eGFR decline. An eGFR recovery of >50% at week 48 after TDF discontinuation was considered successful and defined the primary endpoint.
Results: Of the 215 pts included, 114 switched to TAF and 101 to ABC. eGFR had declined by a mean of 5.1mL/min/yr and 6.7 mL/min/yr during a median of 7 and 5yrs of TDF use respectively. The mean eGFR was 73mL/min at TAF and 67mL/min at ABC initiation, and 22% and 33% had an eGFR<60 mL/min. Week 48 eGFR results were available for 187 pts and showed significant increases by 6.7mL/min with TAF and 6.5mL/min with ABC (p<0.001 compared to baseline for both, p>0.1 for TAF versus ABC). A >50% eGFR recovery was observed in 28/100 (28%) and 23/85 (27%) respectively (p>0.1). In 23 of 46 patients with w48 results available and eGFR<60 at TDF discontinuation, a recovery to >60ml/min was observed. Overall, more pts discontinued ABC than TAF (11% vs 2%, p=0.008) and this was mostly driven by discontinuations for drug-related AE (10% vs 2%, p=0.014). HIV-RNA remained suppressed in all but 2 pts.
Conclusion: Although a modest improvement in eGFR was observed after TDF discontinuation, few patients recovered >50% of their eGFR. The recovery rate in patients that switched to TAF and ABC was comparable.

695 SUBCLINICAL TUBULAR IMPAIRMENT IS COMMON IN ART-TREATED HIV+ PATIENTS IN UGANDA

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Background: Tenofovir disoproxil fumarate (TDF) has been associated with low bone mineral density and renal tubular impairment. As nephrotoxicity in HIV+ patients is poorly documented in resource-limited settings (RLS), where the use of TDF still represents a cornerstone of antiretroviral treatment (ART), we aimed to assess the prevalence of proximal tubular dysfunction in HIV+ Ugandan patients on long-term ART.

Methods: We conducted a cross-sectional study at the Infectious Diseases Institute, Kampala, Uganda. We included adult HIV+ individuals on continuous ART that had undergone DXA scan during the previous 12 months; subjects with known renal impairment or diabetes were excluded. Urine samples were collected for dipstick analysis, urine creatinine and retinol binding protein (uRBP); uRBP/Cr normality ranges were <130 and <172 µg/g (patients aged <50 or ≥50 years, respectively). Non-parametric tests were used for all analyses; a multivariate binary logistic regression was performed including age, gender, BMI and nadir CD4 cell count in those receiving and not receiving TDF.

Results: We enrolled 101 participants. Median age and BMI were 37.9 years (IQR 31-41) and 23 kg/m^2 (IQR 20.5-25.9); 47.5% were male. Median ART duration was 12.2 years (IQR 10.6-13.1) and 61% were on TDF. 80 subjects (79.2%) had a HIV RNA <20 cp/mL; median current and nadir CD4 cell count were 468 (IQR 326-674) and 48 (IQR 12-139) cells/mcL. Median uRBP/Cr was 119.9 µg/g (IQR 80-216.3), with 47 individuals (47%) having abnormal values. In univariate analyses, male gender (p=0.044), low BMI (p=0.046) and longer TDF exposure (p=0.002) were associated with abnormal uRBP/Cr. In multivariate analyses, PI use (p=0.007, aOR 7.54, 95% CI 1.74-32.76) and years of TDF exposure (p=0.028, aOR 1.31, 95% CI 1.03-1.68) were independent predictors in TDF-recipients; no factor was identified in participants not receiving TDF. We observed a significant inverse correlation between uRBP/Cr and DXA T-scores [lumbar (p=0.031), femoral neck (p>0.001) and total hip (p=0.002)]; an abnormal uRBP/Cr was associated with greater odds of having a lumbar T-score <-1 (OR 2.35, 95% CI:1.01-5.35).

Conclusion: We found a high prevalence of subclinical tubular impairment in a Ugandan cohort of HIV+ patients on long-term ART. These data highlight the importance of expanding access to TDF-sparing regimens (eg. TAF) in RLS, where the HIV infected population is progressively ageing and facing an increase in non-communicable diseases.

696 ALOPECIA AFTER SWITCH TO TENOFOVIR ALAFENAMIDE IN 5 AFRICAN AMERICAN WOMEN

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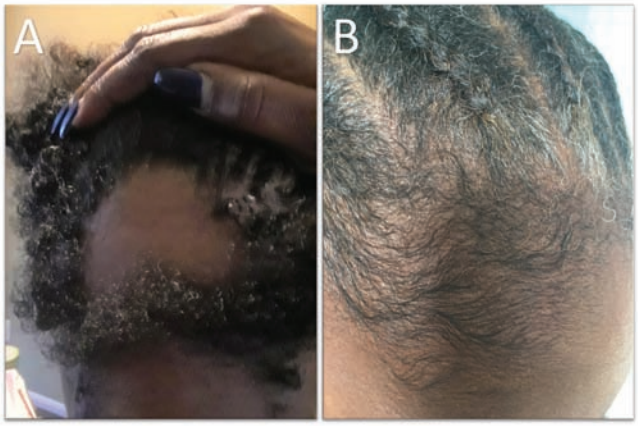
Background: Adverse drug reactions have been reported with all antiretroviral drugs and have been a major cause for non-compliance with antiretroviral therapy. Alopecia is a rare but known side effect of some antiretroviral therapies (ART), however, no cases of TAF-induced alopecia have been reported in the literature.

Methods: This is a case series reported from an academic outpatient HIV practice located in Detroit Michigan comprised of 5 patients identified between 2017 and 2018. Informed oral consent was obtained from patients for the use of photographs

Results: We report 5 cases of alopecia in HIV- infected African American female patients that started after switching TDF to TAF containing regimens. Their age ranged between 40 and 49 years. Hair loss was severe, diffuse and involved the scalp in all patients (Fig. 1A and B). One patient initially had diffuse hair loss that later became patchy, involving the back of the head and forehead. Time-to-onset of alopecia after switching to TAF ranged between 2 months and 1 year, but 4 out of 5 patients reported hair loss after 2-3 months. No pain, pruritus or tenderness were present and there was no evidence of scarring or inflammation on physical exam. All patients had sustained viral suppression and had no clinical evidence of active infections. A basic metabolic panel including liver function tests, complete blood count, sexually transmitted diseases workup, CD4 T-lymphocyte count and HIV viral load were non-revealing. Concomitant use of other medications could not explain the alopecia.

Conclusion: Most clinical trials show very low rates of recruitment of African American patients, therefore, some of the side effects of this novel combination might be underreported in this patient. This report aims to raise awareness among healthcare practitioners about alopecia as a potential distressing adverse effect of TAF that could predominate in certain underrepresented patient populations. Increased representation of African American women in HIV/AIDS clinical trials is important to identify issues that may be unique to some populations. Further investigations are needed to determine causality.



697 IMPACT AND DETERMINANTS OF COMORBIDITY CLUSTERS IN PEOPLE LIVING WITH HIV

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Background: Comorbidities in people living with HIV (PLWH) may occur in clusters, potentially affecting quality of life and general health in different ways. We explored associations of risk factors and patient reported health outcomes with common clusters of co-occurring comorbidities.

Methods: We considered 65 comorbidities reported by PLWH via a structured interview with trained staff. Principal component analysis was used to identify non-random clusters of co-occurring comorbidities and obtain a score for each cluster proportional to the number of comorbidities included in the cluster and present in an individual. Cluster scores were standardised (mean=0, SD=1), with higher scores indicating a greater number of comorbidities characterising a cluster. Multivariable median regression was then used to investigate associations of sociodemographic, lifestyle and HIV-specific factors with each cluster score. Multivariable linear regression was used to evaluate associations of cluster scores (independently of each other) with physical and mental health summary scores (obtained from SF-36 questionnaire, range 0-100).

Results: In 1073 PLWH (85% male, 84% white ethnicity, median (IQR) age 52 (47-59) years) we identified 6 comorbidity clusters (Table). "CVDs", "metabolic" and "chest/other infections" scores were independently associated with older age and longer time since HIV diagnosis (all p's<0.001). Higher body-mass index was associated with higher scores in the "CVDs" (p=0.009), "cancers" (p=0.03) and "metabolic" clusters (p=0.006). PLWH with prior AIDS events had higher scores than PLWH without prior AIDS events for all clusters (p<0.05) except "STDs". Associations with smoking and alcohol consumption were weak across all clusters (all p's>0.05). Higher scores in the "mental health" and "chest/other infections" clusters were independently associated with poorer SF-36 physical (p's<0.001) and mental health scores (p<0.001 and p=0.03, respectively - Table). "CVDs" and "cancers" scores were associated with poorer physical (p=0.02, p=0.03) but not mental health (p's>0.05).

Conclusion: Comorbidity clusters in PLWH are associated with different demographic, lifestyle and HIV-related factors, and significantly impact on quality of life, particularly physical functioning. Identifying common comorbidity clusters in PLWH may help prioritise interventions for those at risk for poorer health outcomes and focus research to understand common pathophysiological pathways contributing to comorbidities in treated PLWH.

Table: Comorbidity clusters and their association with physical and mental health scores (reported as regression coefficients from multivariable linear regression associated with a unit increase in the standardised cluster score)

Cluster	Key comorbidities included in the cluster	Physical health		Mental health	
		β (95% CI)	p-value	β (95% CI)	p-value
"CVDs"	Angina, CABG, MI, Heart failure, Hypertension, PVD, Renal disorders	-0.88 (-1.60, -0.16)	0.02	0.33 (-0.35, 1.01)	0.34
"STDs"	Gonorrhoea, Syphilis, LGV, Chlamydia, Hepatitis C	1.40 (0.75, 2.05)	<0.001	-0.12 (-0.73, 0.50)	0.71
"Mental health"	Depression, Anxiety, Panic attacks	-2.25 (-2.92, -1.58)	<0.001	-4.69 (-5.32, -4.06)	<0.001
"Cancers"	Haematological cancer, Skin cancer, Solid organ cancer	-0.78 (-1.46, -0.09)	0.03	0.46 (-0.19, 1.10)	0.17
"Metabolic"	Dyslipidaemia, Lipodystrophy/Lipoatrophy, Hypertension	0.74 (0.05, 1.43)	0.04	0.70 (0.05, 1.35)	0.04
"Chest/other infections"	CMV, Pneumonia, Dizziness/Vertigo, Asthma/Bronchitis/COPD, Chest infection	-2.37 (-3.05, -1.71)	<0.001	-0.69 (-1.32, -0.60)	0.03

CABG: coronary artery bypass grafting; MI: myocardial infarction; PVD: peripheral vascular disease; LGV: lymphogranuloma venereum; CMV: Cytomegalovirus; COPD: Chronic obstructive pulmonary disease.

698 WIDESPREAD PAIN AND ASSOCIATIONS WITH HIV-RELATED FACTORS IN PEOPLE WITH HIV

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Background: Widespread and burdensome pain is frequently reported by PWH, although associations with HIV factors, particularly in those on current antiretroviral (ART) regimens, have not been determined. We investigated the prevalence of widespread pain and its associations with HIV factors among PWH in the POPPY study.

Methods: PWH on ART were included. Self-reported pain information was collected from 2013-2015 via self-completed questionnaires and through a pain mannikin identifying affected body sites (19 distinct sites). Associations between extent of pain (widespread [>6 affected sites], non-widespread [1-6 sites], none) and HIV factors (current/nadir CD4, total ART drugs received, current/cumulative exposure to each ART class, and previous exposure to stavudine, didanosine or zalcitabine ('D' drugs, associated with neuropathy)) were investigated using ordinal logistic regression adjusted for age and gender.

Results: The 522 PWH were mainly male (86.0%), white (87.7%) with median (interquartile range [IQR]) age 53 (47-59) years. Median (IQR) exposure to NRTIs, PIs and NNRTIs was 8.5 (4.4-14.1), 1.9 (0-7.6) and 3.5 (0.1-8.9) years, respectively with 83.5%, 43.5% and 46.6% currently receiving each class; 14.4%/10.5% had ever/were currently receiving an INSTI. PWH had received 6 (4-9) ART drugs and 169 (32.4%) had received a d-drug. Median current/nadir CD4 counts were 620 (472-800) and 210 (100-300) cells/mm3. Pain was reported by 341 (65.4%), with most commonly affected sites being the lower (31.0%) and mid (22.4%) back, knees (33.1%), ankle/foot (26.3%), shoulders (23.0%) and neck (14.9%). The median (range) number of sites causing pain was 2 (0-17); 74 (14.2%) and 267 (51.2%) reported widespread and non-widespread pain, respectively. Widespread pain was more common in those with longer exposure to NRTIs, longer exposure to PIs, those currently receiving NNRTIs, those exposed to a greater number of ART drugs, those previously exposed to D-drugs and those with a higher current CD4 count (Table), with only exposure to D-drugs remaining associated with widespread pain after adjusting for other factors (aOR 2.09).

Conclusion: Widespread pain reported in PWH is commoner in those with prior exposure to D-drugs, likely representing a legacy of prior ART-induced neuropathy. Although we found no other associations with any of the studied HIV-related factors in PWH on virally-suppressive ART, further analyses will investigate drug and immunosuppression associations in more depth.

Table: Associations between ART and immunosuppression factors and the extent of pain (no pain, non-widespread or widespread)

	OR (95% CI)	p-value
Cumulative exposure to NRTIs (/year)	1.06 (1.03-1.10)	0.0001
Currently receiving NRTIs	0.93 (0.60-1.45)	0.75
Cumulative exposure to PIs (/year)	1.05 (1.01-1.09)	0.006
Currently receiving PIs	0.81 (0.58-1.13)	0.21
Cumulative exposure to NNRTIs (/year)	1.01 (0.98-1.05)	0.43
Currently receiving NNRTIs	1.44 (1.03-2.01)	0.03
Cumulative exposure to INSTIs (/year)	1.06 (0.92-1.22)	0.45
Currently receiving INSTIs	1.13 (0.66-1.93)	0.65
Ever received a d-drug	2.09 (1.44-3.01)	0.0001
Total ART drugs received (/drug)	1.10 (1.05-1.16)	0.0003
Current CD4 count (/50 cells/mm^3 higher)	1.03 (1.00-1.06)	0.04
Nadir CD4 count (/50 cells/mm^3 higher)	0.99 (0.94-1.04)	0.69

IQR: inter-quartile range; OR: odds ratio; CI: confidence interval; NRTIs: nucleoside reverse transcriptase inhibitors; PIs: protease inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors; INSTIs: integrase strand transfer inhibitors. Each estimate is derived from a separate logistic model which also includes adjustment for age and gender

699 MOOD DISORDERS & INCREASED RISK OF NONCOMMUNICABLE DISEASES IN ADULTS AGING WITH HIV

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Background: Mood disorders of major depression and bipolar affective disorder have been associated with systemic inflammation and non-communicable disease (NCD) risk. They are also prevalent among persons living with HIV (PLWH), though whether they are associated with NCDs in PLWH has not been well described.

Methods: PLWH attending the Vanderbilt Comprehensive Care Clinic from 1998-2015 and ≥1 year of follow-up contributed data. Mood disorder exposure was based on diagnoses one year after clinic entry date (baseline) to mitigate imprecise onset date. NCDs were: coronary artery disease, chronic kidney disease, cerebrovascular disease, diabetes, dementia, hepatic disease, hyperlipidemia, hypertension, obesity, peripheral vascular disease, and non-AIDS-defining cancers. Multimorbidity was the accumulation of ≥2 NCDs. Metabolic syndrome was ≥3 of hypertension, hyperlipidemia, diabetes, or obesity. Multivariable competing risk (death) models yielded cumulative incidences and subhazard ratios (sHR) of incident NCDs and multimorbidity. Cox regression yielded hazard ratios (HR) for mortality after multimorbidity. Adjusted models included sex, race, prevalent NCD, hepatitis C status, substance use, tobacco use, alcohol use, and time-updated CD4 cell count (CD4), CD4/CD8 ratio, and HIV RNA. Age was the time metric for all models.

Results: Of 4,140 adults, 999 (24%) had a mood disorder. Mood disorder patients were significantly older at baseline (40 vs. 39 years) and more likely to be female (27 vs. 22%), white (68 vs. 48%), have a history of injection drug use (12 vs. 10%), and have any tobacco use ever (62 vs. 47%). Baseline CD4 and CD4/CD8 ratio were similar; mood disorder patients were less likely to have HIV RNA <400 copies/mL (57 vs. 61%) and more likely to have ≥1 NCD (57 vs. 48%). A higher proportion of mood disorder patients died (15 vs. 13%). Mood disorders were associated with incident NCDs and multimorbidity in models (Figure). Mood disorders were also significantly associated with metabolic syndrome, which persisted even after adjusting for psychiatric medication use. Increased mortality risk after ≥2 NCDs by mood disorder status was not significant (adjusted HR=1.11, 95% confidence interval: 0.78-1.59).

Conclusion: PLWH with mood disorders are at increased risk of incident NCDs and multimorbidity, particularly metabolic syndromes. Focused prevention and treatment of NCDs in PLWH with mood disorders may reduce the burden of multimorbidity in this high-risk group.

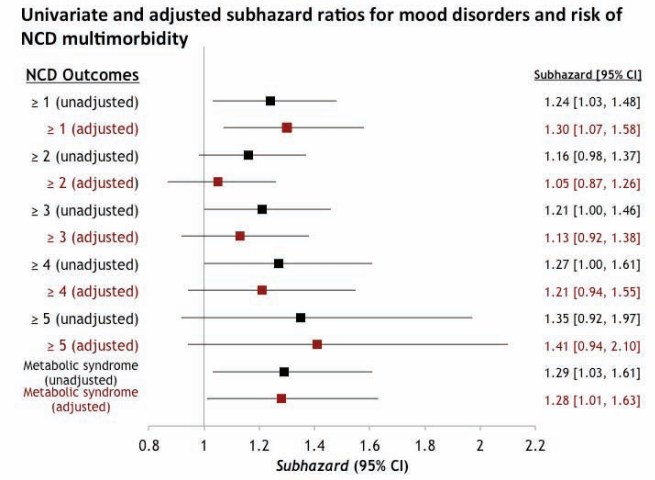

Table 1. Associations between treated and untreated psychiatric disorders and time with HIV viral load ≥200 copies/mL.

	Adjusted Rate Ratio (95% CI)	p
Major depressive disorder		
Treated	1.11 (0.95, 1.29)	0.17
Untreated	1.21 (1.06, 1.38)	**0.0041**
Bipolar disorder		
Treated	1.17 (0.96, 1.43)	0.12
Untreated	1.39 (1.16, 1.68)	**0.0005**
Anxiety disorder		
Treated	0.69 (0.49, 0.99)	**0.045**
Untreated	0.86 (0.71, 1.03)	0.11
Stress-/trauma-related disorder		
Treated	1.09 (0.78, 1.52)	0.61
Untreated	0.86 (0.69, 1.07)	0.17
Psychotic disorder		
Treated	1.03 (0.77, 1.38)	0.83
Untreated	0.87 (0.67, 1.14)	0.33

700 TREATMENT OF PSYCHIATRIC DISORDERS AND TIME WITH HIV VIRAL LOAD ≥200 COPIES/ML

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Background: Psychiatric disorders are common among persons living with HIV (PLWH) and can negatively impact HIV outcomes. We examined the impact of treatment of psychiatric disorders by assessing whether various psychiatric disorders, both treated and untreated, were associated with duration of time with VL ≥200 copies/mL.

Methods: Clinical data from electronic medical records were collected between Jan 2011-Mar 2018 for adult PLWH enrolled in the DC Cohort, a multisite observational study of persons receiving HIV care in Washington, DC. Among PLWH ≥18 years old who received primary care at their clinic site, we assessed diagnoses and drug treatment prescriptions for mood, anxiety and stress-/trauma-related, and psychotic disorders. We assessed associations between time-updated measures for psychiatric disorders/medication prescriptions and the proportion of estimated subsequent days with VL ≥200 copies/mL (out of total days) using multivariable Poisson regression with generalized estimating equations, adjusting for socio-demographic, behavioral, and HIV-related factors.

Results: Among 5,904 participants (median age 51; 70% male; 82% Black), 45% had ≥1 psychiatric disorder, including 38% with a mood disorder (26% depression; 9% bipolar), 18% with an anxiety or stress-/trauma-related disorder (12% anxiety; 8% stress-/trauma-related), and 4% with a psychotic disorder. Prevalence of drug treatment for psychiatric disorders was 55% (mood), 40% (anxiety or stress-/trauma-related), and 53% (psychotic). Untreated (vs. no) depression (aRR 1.21; 95% CI: 1.06-1.38) and untreated (vs. no) bipolar disorder (aRR 1.39; 1.16-1.68) predicted more time with VL ≥200 copies/mL; associations were attenuated for treated depression and treated bipolar disorder (Table 1). Treated (vs. no) anxiety disorder (aRR: 0.69; 0.49-0.99) predicted less time with VL ≥200 copies/mL. Covariates predictive of more time with VL ≥200 copies/mL included female sex (aRR 1.17; 1.01-1.35), Black race (aRR 1.99; 1.51-2.62), smoking (aRR 1.21; 1.05-1.35), and substance use disorder (aRR 1.21; 1.05-1.40).

Conclusion: Nearly half of PLWH in this cohort had a diagnosed psychiatric disorder. PLWH with an untreated mood disorder had a greater risk of VL ≥200 copies/mL, while those with a treated anxiety disorder had a lower risk, compared to PLWH without each disorder. The appropriate diagnosis, treatment, and monitoring of psychiatric disorders is critical for promoting sustained viral suppression among PLWH with comorbid psychiatric disorders.

701 BLUNTED MUSCLE MITOCHONDRIAL RESPONSES TO EXERCISE TRAINING IN OLDER ADULTS WITH HIV

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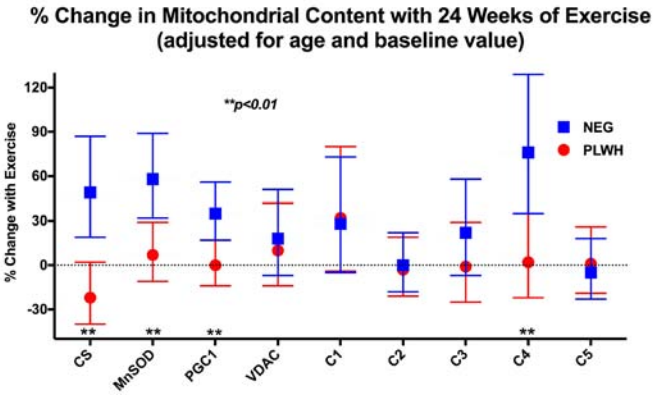
Background: HIV, antiretroviral therapy (ART), and aging have been associated with mitochondrial dysfunction in skeletal muscle, whereas exercise improves mitochondrial function. We found improved physical function with exercise training among older people living with HIV (PLWH) and thus hypothesized that exercise would increase mitochondrial marker expression in muscle.

Methods: Vastus lateralis muscle specimens were obtained by percutaneous needle biopsy before and after completing a supervised 24-week cardiovascular and resistance exercise intervention in previously sedentary, older PLWH (on ART >2 years) and uninfected controls (NEG) who were fasted and had not exercised for >24 hours. Protein expressions of complex (C) I-V, manganese superoxide dismutase (MnSOD), peroxisome proliferator-activated receptor-γ coactivator-1α (PGC1), and voltage-dependent anion channel 1 (VDAC1) in muscle lysate were measured via Western blot using commercially available antibodies and normalized to vinculin. Citrate synthase (CS) activity (colorimetric assay) was normalized to total protein. Outcomes were log-transformed and modeled with multiple linear regressions. Baseline comparisons were adjusted for age; differences due to training were also adjusted for baseline levels. Results are reported as the geometric mean [95% CI], means (±SD) or percent change from baseline.

Results: Baseline and 24-week muscle samples were provided by 40 (18 PLWH, 22 NEG), and 31 (15 PLWH, 16 NEG) participants, respectively, who were majority male (98%), white (78%) and non-Hispanic (82%). PLWH and NEG were of similar age (56 [54, 59]; 57 [54, 60] yr); PLWH had a lower BMI (25±2; 29±5 kg/m⁻2). PLWH had a CD4 count of 563 cells/μl [455, 698] and all had plasma HIV-1 RNA <50 copies/mL. 12 PLWH had prior thymidine analogue exposure. At baseline, PLWH had lower C-III (0.77 [0.58, 1.01] vs 1.15 [0.90, 1.46]) and greater VDAC1 (3.95 [2.40, 6.49]; 1.89 [1.21, 2.96]) (P<.04) compared to NEG. After 24 weeks of exercise, CS, MnSOD, PGC1, and C-IV increased in NEG (P≤.001) with no significant changes in any markers in PLWH. Exercise-induced changes in in CS, MnSOD, PGC1, and C-IV were significantly less among PLWH (P≤.01; Fig).

Conclusion: Skeletal muscle mitochondrial responses to exercise training at moderate to high intensity were blunted in PLWH compared to controls. Different types of exercise (e.g., high intensity interval) or longer training periods may be necessary to stimulate mitochondrial adaptations in older PLWH.



702 WEAK GRIP AND FRAILTY ARE ASSOCIATED WITH MTDNA HAPLOGROUP IN ADULTS WITH HIV

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Background: Mitochondrial DNA (mtDNA) haplogroups have been associated with disease risk and longevity, perhaps as a marker of mitochondrial function. Among persons living with HIV (PLWH), mitochondria may be affected by HIV itself and antiretroviral therapy; mtDNA haplogroup has been associated with AIDS progression, neuropathy, cognitive impairment, and gait speed decline. We sought to determine if haplogroup is associated with frailty and its components among older PLWH.

Methods: A cross-sectional analysis was performed of AIDS Clinical Trials Group A5322 (HAILO) participants with available genome-wide genotype and frailty phenotype assessments. Frailty included weight loss, fatigue, low activity, weakness, and slowness, and was considered as continuous (0-5) or categorical (frail [3-5 components], pre-frail [1-2], non-frail [0]). Weakness (grip) and slowness (4-meter gait) were considered separately, using sex and body mass index (grip) or height (gait) cut-points. Multivariable models adjusted for age, sex, education, smoking, hepatitis C, and prior use of didanosine/stavudine.

Results: Among 634 participants, 81% were male, 49% non-Hispanic white, 31% non-Hispanic black, and 20% Hispanic. Mean age was 51.0 (SD 7.5) years and median nadir CD4 count 212 (IQR 72, 324) cells/μL. Thirty-five (6%) were frail and 244 (39%) pre-frail; 7% had slow gait (mean speed 4.0 sec/4m) and 21% weak grip. Of 13 frail white participants, 10 were from European mtDNA haplogroup H (p=0.059); similarly, among 46 with weak grip, 30 were H (p=0.015). In adjusted analyses, PLWH with haplogroup H tended towards higher frailty score (β=0.090 points; p= 0.058) and weaker grip (β=-0.37 kg; p=0.028), but not slower gait (β=-0.022 seconds; p=0.65) compared to non-H. Among 199 black participants, haplogroups were not associated with frailty, grip strength, or gait speed. Among 125 Hispanic participants, 6 were frail and 4 had slow gait; all were from non-major Hispanic haplogroups (p=0.06 and p=0.10, respectively.)

Conclusion: In this analysis of ART-treated PLWH, European mtDNA haplogroup H was independently associated with weak grip and frailty versus with non-H European haplogroups. Mechanisms may include primary effects on mitochondrial function in skeletal muscle or indirectly through neurologic pathways, and warrants further study. This association has not been reported among people without HIV, thus could represent a unique contribution of HIV to weakness and frailty.

703 GLYCEMIC CONTROL AND COGNITION ARE INDEPENDENTLY ASSOCIATED WITH GAIT SPEED DECLINE

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Background: Neurocognitive impairment (NCI) and impaired glucose metabolism have been associated with decline in gait speed in the general population. Gait speed declines more in people living with HIV (PLWH) compared to uninfected persons, but factors related to this functional outcome are limited to a single cohort of men.

Methods: AIDS Clinical Trials Group (ACTG) A5322 (HAILO) is an observational cohort study of PLWH ≥ 40 years old that includes semi-annual laboratory tests and annual cognitive and gait speed assessments. Slowness was defined as gait speed of >4 seconds on 4-m walk. Participants who developed slowness during the first 3 years were compared to persons who maintained normal speed. We used multivariable logistic regression to assess associations between development of slowness and baseline covariates including age, sex, race, alcohol use, BMI, waist circumference, nadir CD4, history of AIDS defining illness, hemoglobin A1C (HbA1C), and NCI (≥1 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).

Results: Of 929 participants, 81% were male, 31% Black, and 20% Hispanic. Median age was 51 years (IQR 46-56). Most individuals (91.9%) had undetectable plasma HIV RNA (VL <50 copies/mL) with median CD4 count 631 cells/mm^3 (IQR 458-840) at study entry. At study entry, 7% of participants had slow gait, 16% had NCI, 12% had diabetes. Over 3 years, 6% of participants developed a slow gait and 87% maintained a normal gait. In multivariable models, HbA1C percentage, per 1% change (OR 1.40; 95% CI=1.06, 1.85; p=0.019), NCI (OR 3.38; 95% CI=1.53, 7.46; p=0.003), and black vs white race (OR 2.34; 95% CI=1.03, 5.29; p=0.042) at entry were significantly associated with increasing prevalence of slowness compared to those maintaining normal gait speed.

Conclusion: The association between baseline hemoglobin A1C and development of slow gait speed highlights an intervenable target to prevent progression of physical function limitations. Additionally, the presence of NCI among PLWH should prompt screening for and early intervention to avert declines in physical function.

704 SERIOUS INJURY AFTER A FALL: ARE THOSE WITH HIV AT GREATER RISK THAN UNINFECTED?

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Background: HIV infected (HIV+) Veterans 50+ years of age are more likely to fall than uninfected comparators. Whether they are at greater risk for serious injury after the fall is not known.

Methods: We used data from the Veterans Aging Cohort Study (VACS). The primary exposures were HIV and falls. The outcome was serious injury as identified by ICD9 codes (hip fracture, fragility fracture, joint dislocation, traumatic brain injury (TBI), and head injury). We identified medically significant falls using Ecodes and a machine learning algorithm applied to radiology reports. After verifying that associations between HIV and each type of serious injury were similar, all injuries were merged into a composite outcome. An interaction term between HIV and falls assessed whether falls had a differential impact on the risk of injury among HIV+ and uninfected participants. The analytic unit was a six-month person-interval. Covariates assessed at the beginning of the interval were evaluated for associations with occurrence of a serious injury in that interval. Multivariable logistic regression was used to evaluate the associations of HIV and falls with serious injury with adjustment for risk factors for fall-related injury identified among older adults and for disease severity with the VACS Index.

Results: Our analysis included 73,283 Veterans who were 50+ years of age, 31% of whom were HIV+. Fall incidence was 46 per 1000 person-years (95% CI 45-47 per 1000 person-years) for HIV+ and 40 per 1000 person-years (95% CI

40-41 per 1000 person-years) for uninfected. In bivariate analyses, relative to uninfected Veterans, joint dislocation and TBI were less common among HIV+ (1.2% vs 1.7%, p<0.001; and 1.2% vs 1.4%, p<0.001, respectively) whereas hip fracture and fragility fractures were more common (hip fractures: 1.3% vs 0.7%, p<0.001; fragility fractures: 8.0% vs 7.4%, p<0.001, respectively). In fully adjusted models, relative to those who did not fall, those who fell had a substantially increased risk of serious injury: HIV+ (OR 4.14; 95% CI 3.86, 4.44) and uninfected (OR 1.42; 95% CI 1.35, 1.49).
Conclusion: Among those 50+ years of age, HIV+ are more likely to fall and more likely to experience serious injury, commonly in the form of fracture, after they fall compared to uninfected individuals.

705 SCREENING AND PREEMPTIVE ANTIFUNGAL THERAPY FOR SUBCLINICAL CRYPTOCOCCAL DISEASE

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Background: Serum cryptococcal antigen (sCrAg) screening and pre-emptive antifungal treatment is recommended for individuals with HIV and CD4 ≤100 cells/µl by the World Health Organization. However the prevalence of subclinical antigenemia, optimal management of positive individuals, and outcomes following 'screen and treat' are poorly defined.
Methods: In this multicenter, prospective implementation science cohort study, HIV infected individuals with CD4 counts ≤100 cells/µl and without symptomatic meningitis, enrolled at 20 outpatient centers in Harare underwent sCrAg testing. Lumbar puncture (LP) was recommended to sCrAg positive participants. Hospitalization and treatment with intravenous (IV) amphotericin B and high dose fluconazole was recommended to cerebrospinal fluid (CSF) CrAg positive participants; sCrAg positive participants who declined LP were treated with high dose fluconazole monotherapy. ART and HIV disease management was done by the primary HIV provider. Recommendations were made to initiate ART immediately in sCrAg negative and 4 weeks after initiating antifungal therapy in sCrAg positive participants. Primary endpoints were survival at 6 and 12-months. Outcomes assessed included sCrAg seroprevalence, and prevalence of disseminated cryptococcal disease as determined by positive blood or CSF cultures.
Results: Between April 2015 and June 2016 2016, 1320 participants were enrolled; 130 (9.8%) were sCrAg positive with a median titre of 1:20. Sixty-six (50.8%) of sCrAg participants consented to an LPs; 11 (16.7%) had evidence of CNS disease dissemination. Blood cultures were positive in 10/129 (7.5%) sCrAg positive participants. Overall survival rate at 12-months was 83.9% (95% CI: 81.5-86.0) and 76.1 % (95% CI: 67.1 – 83.0; p=0.011) in sCrAg negative and positive participants respectively. Factors associated with increased mortality were positive sCrAg, positive CSF CrAg, CD4 count, and time to ART initiation in sCrAg negative. All cause mortality and sCrAg titre did not differ among sCrAg positive participants that received LPs and IV amphotericin when indicated, and those that declined LP.
Conclusion: The prevalence of subclinical antigenemia is high and a positive sCrAg remains an important risk factor for mortality. Disease dissemination is evident despite subclinical disease; however in this cohort LPs and IV therapy did not markedly improve survival compared with high dose fluconazole alone. Early initiation of ART in sCrAg negative individuals improved survival.

706 SCREENING FOR TALAROMYCES AND CRYPTOCOCCAL ANTIGENEMIA IN AIDS PATIENTS IN GUANGDONG

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Background: Talaromycosis and cryptococcosis are the leading causes of morbidity and mortality in patients with advanced HIV disease in Southern China. We conducted a prospective study using commercially available antigen detection assays in Guangdong located in Southern China to determine disease burden and clinical significance of antigenemia to inform disease control strategies.
Methods: This is an analysis of an ongoing prospective study enrolling antiretroviral-naive patients aged ≥18 with CD4 count ≤100 cells/µl who continuously registered for care in Guangzhou Eighth People's Hospital between January 2016 and December 2016. Talaromycosis was screened using a novel talaromyces Mp1p antigen enzyme immunoassay (Mp1p EIA) and an aspergillus galactomannan (GM) test. Cryptococcosis was screened using a cryptococcal antigen (CrAg) test. Management and follow up of patients were according to the standard HIV care.
Results: A total of 236 patients have been recruited: 194 (83%) were males; mean age was 41 ±13; median CD4 count was 23.5 cells/µl (IQR: 8-54.5). The number of patients with positive Mp1p, GM and CrAg tests were 46 (19.5%), 38 (16.1%), and 8 (3.4%), respectively. Mp1p and GM positivity were associated with having symptoms and a CD4 count ≤50 cells/µl (P<0.05), while CrAg positivity was not (P≥0.05) . Over a mean of 9 months of follow up, 43/44 (97.7%) Mp1p-positive and 30/38 (79.0%) GM-positive patients had culture-confirmed talaromycosis, and 5/8 (62.5%) CrAg-positive patients had culture-confirmed cryptococcosis. Meanwhile, 6/131 (4.6%) Mp1p-negative and 19/137 (13.9%) GM-negative patients had talaromycosis, and 0/186 CrAg-negative patients had cryptococcosis. The sensitivity, specificity, positive predictive value, and negative predictive value for each test are included in the Table. The mortality of cases was higher in Mp1p- or CrAg-positive patients (13.0% and 37.5%) than Mp1p- or CrAg-negative patients (4.7% and 5.3%) at one year follow-up (Chi Square P<0.05). However, the difference in mortality between GM-positive and GM-negative patients was not statistically significant (P≥0.05).
Conclusion: Talaromycosis is significantly more prevalent than cryptococcosis in patients with advanced HIV disease in southern China. Our data demonstrate that the Mp1p EIA and CrAg test are useful tools for rapid diagnose and screening for these infections and should be implemented to reduce HIV morbidity and mortality in southern China.

Index	Mp1p	GM	CrAg
Sensitivity (%)	87.8	61.2	100
Specificity (%)	99.2	93.7	98.4
Positive predictive value (%)	97.7	78.9	62.5
Negative predictive value (%)	95.4	86.1	100

707 THE COST-EFFECTIVENESS OF AMBISOME FOR ASYMPTOMATIC CRYPTOCOCCAL INFECTION

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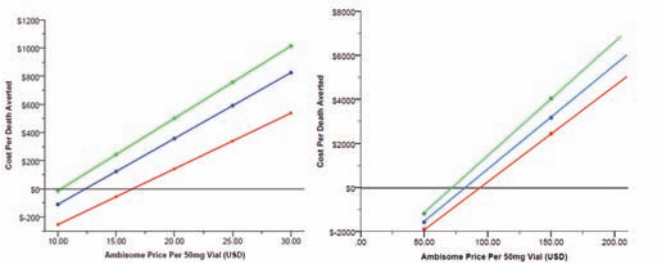
Background: Screening for cryptococcal antigen (CrAg) among those with advanced HIV disease and treating asymptomatic CrAg+ with fluconazole is lifesaving. However, fluconazole monotherapy still results in 25% mortality.1 Enhanced preemptive treatment options are being evaluated to prevent cryptococcal meningitis. Single dose Ambisome (at 10mg/kg) plus fluconazole is being prospectively evaluated for preemptive treatment in asymptomatic CrAg+. We sought to explore the threshold of efficacy and cost that would improve on current standard of care therapy in Uganda and South Africa, representing a low income setting and a middle income setting respectively. The current price of Ambisome in South Africa is $165 per vial. The anticipated discounted price for treatment of cryptococcal meningitis in resource-limited settings is $16.25 per vial.
Methods: We used a decision analytic model to evaluate CrAg screening and treatment outcomes in Uganda for those with a CD4<100 cells/µL. Costs were estimated for screening, preemptive therapy, hospitalization, and maintenance therapy. Parameter assumptions were taken from large prospective CrAg screening studies in Uganda, and clinical trials from sub Saharan Africa.2 CrAg-positive persons could be: a) asymptomatic and thus eligible for preemptive treatment with fluconazole; or b) symptomatic with meningitis with hospitalization. We varied parameters to approximate South African CrAg prevalence and hospitalization costs.
Results: At a discounted price of $16.25 per vial, assuming 95% efficacy, Ambisome would be cost-saving to the Ugandan national healthcare system, primarily in meningitis hospitalization costs averted. At the same cost, but assuming 85% efficacy, the cost is $195 to save one life. In South Africa, at the current price of $165 per vial, if assumed to have 95% efficacy, the cost is $3090 to prevent one death from cryptococcal meningitis. At the same price, but assuming 85% efficacy, it would cost $4817 to prevent one death (Figure). If

Ambisome was priced at $72 per vial or less, this would be cost saving if efficacy is 85% or more. At a discounted price of $16.25 per vial and 85% efficacy, the health care system would save $2949 for every death averted from cryptococcal meningitis.

Conclusion: Single dose Ambisome for asymptomatic cryptococcal infection given at 10mg/kg once in conjunction with fluconazole has potential to save lives and save costs, if proven effective.



708 CRYPTOCOCCAL ANTIGENEMIA IN HIV PATIENTS WITH VIROLOGIC FAILURE IN UGANDA

Edward Mpoza[1], David Meya[1], Maria S. Nabaggala[1], Lillian Tugume[1], Kenneth Ssebambulidde[1], Joshua Rhein[2], David R. Boulware[2], Radha Rajasingham[2]
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Background: Cryptococcal antigen (CrAg) precedes fulminant cryptococcal meningitis, and preemptive treatment of those CrAg positive before development of meningitis is life-saving. The World Health Organization recommends screening and preemptive treatment for those with a CD4<100 cells/μL who are initiating ART. However, the proportion of patients presenting with fulminant cryptococcal meningitis is increasingly ART-experienced. It is not clear if there is a role for CrAg screening among ART-experienced persons with virologic failure. We evaluated CrAg prevalence among ART-experienced persons with suspected virologic failure in Uganda, and present 6-month survival and incidence of meningitis among CrAg-positive persons.

Methods: We retrospectively performed CrAg testing on plasma samples of adults with virologic failure (HIV viral load >1000 copies/mL) between September 2017 and January 2018. For those CrAg-positive, ART history, incidence of cryptococcal meningitis, and 6-month survival were obtained from retrospective medical chart review.

Results: We tested 1186 plasma samples of patients with viral loads >1000 copies/mL and found 35 CrAg-positive (prevalence of 2.95%). Of the 35 CrAg-positive persons, median ART duration was 42 months (IQR 14 to 78 months). We obtained 6-month outcome data on 21 CrAg-positive patients. Of these, 15 were alive, and 6 were dead. Five survivors were known to have received fluconazole. Two patients developed meningitis and survived with treatment. Thus, meningitis-free survival at 6-months was 13/21 (62%). Median viral load for CrAg negative was 11,650 copies/mL (IQR: 3,465 to 54,950), whereas median viral load for CrAg positives was 53,700 copies/mL (IQR: 17,513 to 163,500), (p<0.0001). Overall, 91% (32/35) of CrAg-positive persons had viral loads >5000 copies/mL compared with 64% (735/1149) of CrAg-negative (Odds Ratio = 6.0; 95%CI, 1.8 to 19.7, P=0.001). CrAg prevalence increased among higher viral loads with 4.2% (32/768) CrAg-positivity among those with >5000 copies/mL and 0.9% (5/553) CrAg-positivity among those with <5000 copies/mL

Conclusion: CrAg prevalence was ~3% among ART-experienced persons with virologic failure, and median viral load was higher in CrAg positives compared to CrAg negatives. Meningitis-free survival was 62% at 6-months. Further studies to evaluate the potential benefit of CrAg screening in the ART-experienced population are warranted.

709 CYTOMEGALOVIRUS VIREMIA ASSOCIATED WITH MORTALITY IN CRYPTOCOCCAL MENINGITIS

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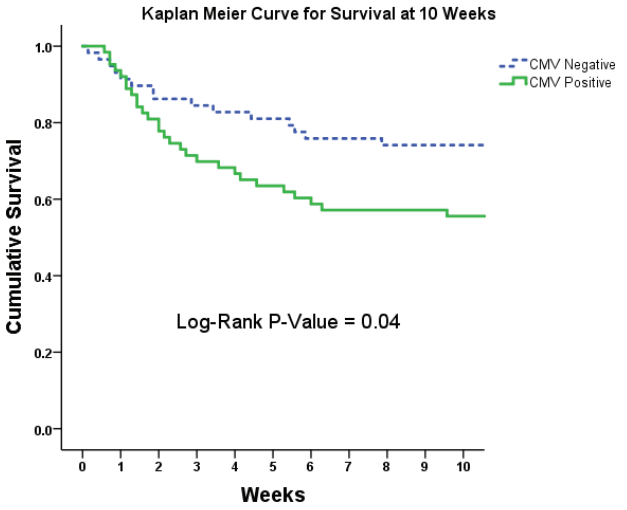
Background: Cryptococcal meningitis and tuberculosis are both major causes of morbidity and mortality in persons with advanced HIV disease. Cytomegalovirus (CMV) viremia may be associated with increased mortality in HIV-infected persons with tuberculosis. It is not known if CMV viremia is associated with mortality in other AIDS-related opportunistic infections.

Methods: We prospectively enrolled HIV-infected Ugandans with cryptococcal meningitis from 2010-2013 and cryopreserved plasma samples. Subsequently, we analyzed 121 randomly-selected, stored baseline samples for CMV DNA. We compared CMV viremia versus 10-week survival by time-to-event analysis.

Results: Of 121 plasma samples tested, 63 (52%) had detectable CMV DNA (median viral load 298 copies/mL [IQR, 150 to 1630]). The median age was 36 years (IQR, 30 to 41), and the median CD4+ T cell count was 20 cells/μL (IQR, 9 to 72). A total of 43 deaths occurred. The mortality was 44% (28/63) in the CMV-positive group and 26% (15/58) in the CMV-negative group by 10-weeks (Hazard Ratio = 1.93; 95%CI, 1.02-3.61; P=0.04). Median CD4 counts did not differ between CMV-positive and CMV-negative groups (20 [IQR, 9 to 54] vs. 23 [IQR, 10 to 76] cells/μL, respectively; P=0.47). There was no association between the presence of CMV viremia and HIV RNA levels (P=0.71). Every 2-fold increase in IL-2 blood levels was associated with a lower probability of being CMV-positive (Odds Ratio = 0.74; 95%CI, 0.59-0.93; P=0.01).

Conclusion: Half of persons with advanced AIDS and cryptococcal meningitis had CMV viremia. The presence of CMV viremia was significantly associated with mortality in persons with cryptococcal meningitis. It remains unclear if the relatively low level CMV viremia in the setting of high baseline mortality due to cryptococcal meningitis contributes to this mortality or may reflect underlying immune dysfunction (i.e. cause vs. effect). Further investigation is warranted. Ultimately, a randomized clinical trial of CMV treatment in advanced AIDS population would be needed to definitively answer if CMV viremia is a modifiable risk factor for mortality.



710 ASYMPTOMATIC TALAROMYCES MARNEFFEI ANTIGENEMIA AND MORTALITY IN ADVANCED HIV DISEASE

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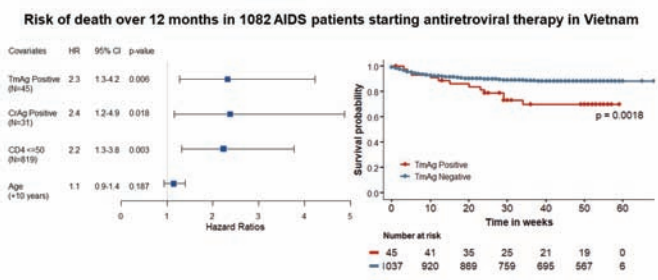
Background: Talaromyces marneffei (Tm) is a leading cause of HIV-associated infection with a mortality of 30% in SE Asia. Delay in culture diagnosis is associated with death. We have demonstrated in large cohorts that a novel Mp1p antigen detection assay is more sensitive than blood culture (90% vs. 70%) and is 98% specific in detecting Tm. We hypothesize that the test can

detect pre-clinical disease in patients with advanced HIV disease, and Tm antigenemia (TmAg) is associated with higher mortality.
Methods: We retrospectively tested for TmAg in stored baseline plasma samples from patients aged ≥18 years with CD4 count of ≤100 cells/μL who were newly enrolled in care at 22 HIV clinics across Vietnam and participated in the Vietnam Cryptococcal Retention in Care Study (CRICS), August 2015 to April 2017. We excluded 34 patients with a talaromycosis diagnosis at enrollment. We investigated the risk factors for TmAg using multiple logistic regression analysis and investigated the association between TmAg and time to death over 12 months with Cox regression analysis, adjusting for age (+10 years), baseline CD4 counts (≤ or> 50 cells/μL), and cryptococcal antigenemia (CrAg). Future analyses will take potential within-clinic correlation into account.
Results: Baseline plasma samples were available for 1082/1174 patients: 74.2% were male; median age was 35 years (IQR: 31-41), and median CD4 count was 36 cells/ μL (IQR: 15-62). TmAg was detected in 45 (4.2%) patients (95% CI: 3.1%-5.6%) and was non-overlapping with CrAg (prevalence=2.9%). TmAg prevalence was higher in northern (33/497; 6.6%) than southern (12/585; 2.1%) Vietnam, Chi Square p<0.001. TmAg was independently associated with CD4 count ≤50 cells/μL (OR=3.5, 95% CI: 1.4-11.8, p=0.006) and residency in highland regions (OR=3.4, 95% CI: 1.8-6.3, p<0.001). Overall the probability of death was 12.7% (95% CI: 10.6-14.7), and was higher in TmAg-positive (30.0%; 95% CI: 14.0-43.1) than TmAg-negative (11.9%; 95% CI: 9.8-13.9) patients, Log-rank p=0.002. In multivariable survival analysis, TmAg was an independent predictor of death, hazard ratio =2.3, 95% CI: 1.3-4.2, p=0.006.
Conclusion: CD4 count of less than 50 cells/μL and living in highland regions are independent risk factors for TmAg, and asymptomatic TmAg is an independent risk factor of death. The M1p1 antigen assay is therefore a useful tool to screen for asymptomatic talaromycosis for pre-emptive antifungal therapy. This has the potential to substantially reduce HIV mortality in Southeast Asia.



711 PREDICTIVE MODELING OF MORTALITY IN INVASIVE TALAROMYCOSIS IN HIV PATIENTS

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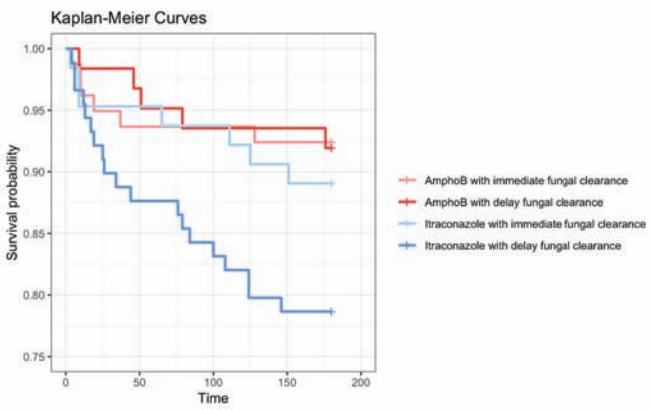
Background: Talaromycosis (formerly penicilliosis) is an invasive fungal infection endemic in Southeast Asia, and is a leading cause of death in patients with advanced HIV disease. We have demonstrated in the recent IVAP trial the superiority of Amphotericin B over Itraconazole with regard to mortality, clinical response, and blood fungal clearance. Here, we investigated if early fungicidal activity in blood is a useful surrogate endpoint for all-cause mortality for HIV-associated talaromycosis.
Methods: IVAP trial enrolled 440 patients across 5 hospitals in Vietnam from October 2012 to December 2016. 391 (87%) patients who had at least 3 measurements of blood fungal load (in colony forming units [CFUs] per ml) during the first 2 weeks were included in the analysis. We used nonlinear regression to characterize individual fungal clearance dynamics with single and double exponential curves that were best fitted to the data. Individual parameters estimated from the model fit include: peak value of log fungal count (a), time to reach peak fungal load (c, days), and rate of fungal decline (br, log fungal count/ml/day). The parameters were used in a multivariate survival analysis to predict the risk of death over 6 months using Cox proportional hazard model, adjusting for age, antifungal treatment, antiretroviral status, intravenous drug use, baseline CD4 count, log fungal count at enrollment, and dyspnea requiring oxygen.
Results: The median adjusted R^2 of the fitted curves is 0.94 (IQR: 0.79-1.00); 74.4% of fitted curves had an adjusted $R^2 > 0.8$. In the multivariate Cox regression model, older age (+5 years) and time to reach peak blood fungal load were independent predictors of death, HR=1.25, 95% CI: 1.07-1.47, p=0.005 and HR=1.23, 95% CI: 1.07-1.41, p = 0.002, respectively. The risk of death due to a delay in fungal clearance (of > 0 day)was statistically significant in patients who received Itraconazole, (HR=1.31, 95% CI: 1.12-1.53, p<0.001) but not in patients receiving Amphotericin B (HR=1.17, 95% CI: 0.86-1.58, p=0.313) (Figure).
Conclusion: Time to initiation of blood fungal clearance is an independent predictor of 6-month mortality and can potentially be used as an outcome measure for early phase clinical trials to efficiently assess novel therapeutic strategies for HIV-associated talaromycosis.



712 WITHHOLDING PCP PROPHYLAXIS IN VIRALLY SUPPRESSED HIV PATIENTS FROM COHERE

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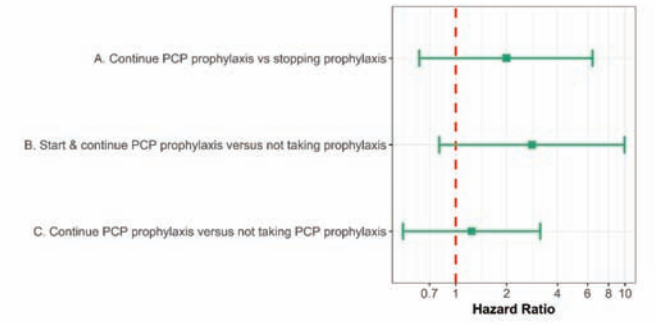
University Hospital of Bern, Bern, Switzerland

Background: Analyses using COHERE data previously suggested (Clin Infect Dis 2010:51:611) that primary Pneumocystis Pneumonia (PcP) prophylaxis could be withdrawn in patients with CD4 counts of 100-200 cells/μL if HIV-RNA is suppressed, suggesting HIV replication as major risk factor for PcP. Given the wealth of new data available in COHERE we investigated whether prophylaxis might be withheld or stopped in all patients on antiretroviral therapy with suppressed plasma HIV RNA (<400c/mL) irrespective of CD4 count.
Methods: We estimated the risk of primary PcP in COHERE patients on cART including time-updated CD4 counts, HIV-RNA and use of PcP prophylaxis. We emulated a hypothetical randomised trial using established causal inference methods in which inverse probability (IP) weighting adjusts for censoring selection bias. Eligibility criteria were plasma HIV RNA (<400c/mL) and CD4 counts ≤200 cells/μL. We emulated three trials comparing the effect of A.) continue PCP prophylaxis versus stop prophylaxis, B.) start and then continue PCP prophylaxis versus not starting prophylaxis, and C.) taking PCP prophylaxis versus not taking PCP prophylaxis, irrespective of PCP prophylaxis status at baseline. In each case, we estimated the hazard ratio (HR) fitting a pooled logistic model which included baseline characteristics (CD4, RNA, gender, age, transmission, geographical origin calendar year), used restricted cubic splines to capture CD4/RNA trajectories, and included polynomial time for modelling the baseline hazard.
Results: There were 9,743 patients eligible for the emulated trials with a total of 18,550 person years followed-up during 1998-2015. The unadjusted incidence rate of PCP diagnosis was 1.5 per 1000py on PCP prophylaxis compared to 2.8 off PCP prophylaxis. The HR estimates for the PCP outcome from the 3 emulated trials were 2.0 ([0.61 6.4], p=0.3) for Trial A, 2.8 ([0.8 9.9], p=0.1) for Trial B, and 1.2 ([0.5, 3.2], p=0.8) for Trial C (see Figure).
Conclusion: In virologically suppressed patients, irrespective of CD4 levels, the risk of PcP appears to be low, and similar for individuals on and off prophylaxis, although the precision of the results was limited due to the overall low incidence of PCP. This suggests that primary PcP prophylaxis might be withheld in this patient group.

Figure: Adjusted hazard ratios for risk of PCP diagnosis for Trials A, B and C;
HR > 1 means risk for PCP is higher for those off prophylaxis.



Multivariate Cox Regression Analysis for risk factors associated with IPD in HIV-infected patients

Variable	Adjusted hazard ratio (95% confidence interval)	*P*
Pneumococcal Vaccination	0.64 (0.33-1.25)	.191
AIDS-defining condition	2.82 (1.26-6.33)	.012
Charlson Comorbidity Index*	1.23 (1.14-1.33)	.0001
Plasma HIV RNA<1,57 log	0.44 (0.22-0.86)	.016

*excluding AIDS

713 PNEUMOCOCCAL VACCINATION IN HIV+ ADULT PATIENTS ON SUPPRESSIVE ART, 2010-2017

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Background: There is little information on the efficacy of the pneumococcal vaccines (PV), especially of the pneumococcal conjugate vaccines (PCV), in successfully treated patients in the modern ART era.
Methods: Case-control study in a tertiary, University Hospital in Madrid. Cases were HIV-patients admitted to the hospital (2010-2017) with a microbiologically confirmed infection due to S. pneumoniae (from a normally sterile site and/or a positive urinary antigen). Controls (HIV-infected patients without IPD) were selected by random sampling matched with cases by gender and year of HIV diagnosis. The selection was blind for the study factor (vaccination). Sample size was estimated (61 cases and 183 controls). We performed comparisons to vaccine exposure and outcome associations using time-dependent covariates in a Cox proportional-hazards regression model.
Results: The population of study included 256 subjects, 64 cases and 192 controls. Male 77%, median age 29, previous AIDS 43%, median Charlson Comorbidity Index 6. 115 (45%) patients had been vaccinated. Median CD4-cell count at the time of administration of the PV was 518 (318-733) cells/mL, 79% with HIV RNA<50. In a multivariate logistic regression analysis, risk factors associated with IPD were the Charlson Comorbidity Index (HR 1.23 95%CI 1.14-1.33 P=0.0001) and previous diagnosis of AIDS (HR 2.82 95%CI 1.26-6.33 P=0.012), while plasma HIV RNA <50 copies/mL (HR 0.44 95%CI 0.22-0.86 P=0.016) was protective. PV was not associated with IPD after adjusting in the multivariate model with time protection as a dependent covariate (HR 0.64, 95% CI 0.33-1.25 P=0.191). We also investigated the influence of different PV schedules. In univariate analysis, compared to no vaccine, no significant protection was found in patients who received only PPSV-23 or only a conjugate vaccine (PCV-7 or PCV-13), while two vaccines given in series (PCV13- PPSV-23 or PPSV23-PCV13) showed protection (HR 0.3 95% CI 0.11-0.77 p=0.012). However, in an adjusted model we found no evidence of protection by double PV schedules (HR 0.44 95%CI 0.17-1.14 p=0.09).
Conclusion: In this case-control study, different schedules of pneumococcal vaccination did not show protection against IPD. As only plasma HIV RNA <50 copies/mL was found to be a protective factor, early ART initiation could ensure the protection in most patients. As with HIV-uninfected persons, the pneumococcal vaccination should then be individualized in HIV-infected patients based on traditional risk factors for IPD.

714 DIGITAL CHEST RADIOGRAPHY OPTIMISES TB SCREENING OF SOUTH AFRICAN CLINIC ATTENDEES

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Background: In 2016, it is estimated that approximately 165 000 Tuberculosis (TB) cases were missed in South Africa. Optimising TB screening is imperative in meeting national and global TB targets, including identifying 90% of all TB cases. Digital CXR (d-CXR) provides a quick, reproducible technique incurring low marginal costs, reduced radiation exposure and improved portability for TB screening. We assessed whether d-CXR screening with Computer-Aided Detection for Tuberculosis (CAD4TB) would improve TB yield when combined with the World Health Organisation (WHO) TB 4-question symptom screening tool.
Methods: A systematic sample of adult patients attending three public health clinics for any reason (excluding ante-natal care) in the Free State Province, South Africa, were screened for TB between November 2017 and June 2018 using d-CXR and the WHO TB symptom tool. Patients <18 years, pregnant, currently receiving or received anti-tuberculosis treatment within the past two years were ineligible for participation. Two spot sputum were collected for Xpert MTB/RIF Ultra assay (Xpert Ultra) and MGIT culture from attendees with ≥1 TB symptom and/or a CAD4TB score of ≥60. All participants were offered HIV testing. TB yield was compared between screening strategies and the number needed to test (NNT) determined.
Results: We approached 4352 clinic attendees, 3.8% refused participation, 26.3% were ineligible and 3,041 participants were screened (2,005 female [65.9%], mean age 45 years (SD 15.2), HIV prevalence 36.3% [1,030/2,837]). The proportion of attendees screened by d-CXR, symptoms and d-CXR/symptoms requiring TB investigations was 19% (573/3041), 36% (1109/3014) and 45% (1356/3041) respectively. The yield of TB (Xpert Ultra/culture positive) for d-CXR, symptom and d-CXR/symptom screen was 2.2%, 2.3% and 2.8% and the NNT was 8.7, 15.4 and 16.1 respectively.
Conclusion: A high proportion of clinic attendees had symptoms suggestive of TB. The addition of d-CXR to symptom screening improved TB yield with a modest increase in the number requiring TB investigations. D-CXR alone compared to symptom screening alone had a similar yield of TB and almost halved the number requiring TB investigations. D-CXR screening alone is potentially a cost effective TB screening strategy.

Table 1: Diagnostic yield of TB using different screening modalities

	Screening n = 3,041		Confirmatory testing (Xpert Ultra and Culture) on those screened positive				Yield (n=3,041)	NNT
	Positive	Negative	Positive	Negative	No sputa produced	Lab error		
*d-CXR	573 (19%)	2454 (81%)	66 (12%)	325 (57%)	181 (32%)	1 (0%)	2.2% (66/3041)	8.7 (573/66)
Symptom screen	1109 (36%)	1932 (64%)	72 (6%)	592 (53%)	443 (40%)	2 (0%)	2.3% (72/3041)	15.4 (1109/72)
d-CXR + symptom screening	1356 (45%)	1685 (55%)	84 (6%)	710 (52%)	560 (41%)	2 (0%)	2.8% (84/3041)	16.1 (1356/84)

*14 d-CXR not done

715 DIAGNOSIS OF LATENT TUBERCULOSIS AMONG US-BORN PEOPLE LIVING WITH HIV

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Background: Persons living with HIV (PLWH) are a priority for latent tuberculosis infection (LTBI) screening due to the risk of progression to active tuberculosis (TB). Studies of LTBI diagnostic test characteristics are conflicting and limited by the lack of a gold standard.

Methods: The TB Epidemiologic Studies Consortium is conducting a multicenter prospective cohort study to evaluate the performance of the tuberculin skin test (TST), QuantiFERON Gold In-Tube (QFT) and T-SPOT.TB (TSPOT). We analyzed US-born PLWH >5 years old who had valid results for all three tests and were enrolled from 18 clinics during September 2012- April 2017. We estimated LTBI prevalence and test characteristics, using Bayesian latent class analysis models with varying cutpoints. Sensitivity and specificity were used to quantify the under- and overdiagnosis of LTBI per 1000 persons screened with varying LTBI prevalence.

Results: Among 1510 participants, median age was 49 years (interquartile range [IQR] 42-55), 1073 (71%) were male, 1057 (70%) were black; 945 (62.6%) had a self-reported CD4+ count (median 532 cells/mm3, IQR 355-764). LTBI prevalence was estimated at 5.1% (95% credible interval [95CrI] 3.4 to 7.0%) overall (range 0.8-14.5% by site). Table 1 describes test characteristics. Using the standard US cutpoints, the QFT had higher sensitivity (Sn) than the TST (difference [diff] 16.0%, 95CrI 2.3 to 30) and TSPOT (diff 15.4%, 95CrI 0 to 30.8%). The difference in the Sn was 0.6% (95CrI -12.6 to 14.6) for the TSPOT compared to TST. The TSPOT had higher specificity (Sp) than the TST (diff 2.6%, 95CrI 1.6 to 3.8) and QFT (diff 2.9%, 95CrI 1.7 to 4.2). The difference in the Sp was 0.3% (95CrI -1.2 to 1.7) for the TST compared to QFT. The difference in positive predictive value (PPV) was 4.2% (95CrI -9.0 to 17.8) for the QFT compared to TST; TSPOT had higher PPV than TST (diff 37.1%, 95CrI 20.8 to 52.3) and QFT (diff 32.9%, 95CrI 15.4 to 49.2%).

Conclusion: Using the standard US cutpoints and 5% LTBI prevalence, Sn was highest for QFT; Sp and PPV were highest for TSPOT. Both the international (>6 spots) and US (>8 spots) TSPOT cutoffs resulted in more LTBI under- than overdiagnosis, regardless of LTBI prevalence. For the TST and the QFT, the US cutoffs (5mm for TST and 0.35 IU/mL for QFT) resulted in more LTBI over- than underdiagnosis in a population with medium LTBI prevalence (5.1%); however, the optimal cutoff of the TST and QFT varied depending on LTBI prevalence.

Table 1. Estimated test characteristics and frequency of under/overdiagnosis of LTBI using varying LTBI prevalence and test cutoffs

	TST (mm induration)			QFT (IU/mL)			TSPOT (spots)			
	5	10	15	0.35	0.70	1.00	5	6	7	8
Sensitivity (%)	50.0	43.4	26.9	74.4	55.3	49.0	57.2	54.0	50.8	48.5
Specificity (%)	97.0	97.8	99.4	96.7	98.1	98.4	99.1	99.6	99.6	99.8
1% LTBI Prevalence										
PPV (%)	14.4	16.6	31.2	18.5	22.7	23.6	14.6	57.7	56.2	71.0
Underdiagnosed (n)	5.0	5.7	7.3	2.6	4.5	5.1	4.3	4.6	4.9	5.1
Overdiagnosed (n)	29.7	21.8	6.0	32.7	18.8	15.8	8.9	4.0	4.0	2.0
5% LTBI Prevalence										
PPV (%)	26.7	50.9	70.2	54.3	60.5	61.7	77.0	87.7	87.0	92.7
Underdiagnosed (n)	25.0	28.3	36.6	12.8	22.3	25.5	21.4	23.0	24.6	25.7
Overdiagnosed (n)	28.3	21.0	5.7	31.4	18.1	15.2	8.6	3.8	3.8	1.9
15% LTBI Prevalence										
PPV (%)	74.6	77.7	88.8	79.9	83.7	84.4	91.8	96.0	95.7	97.7
Underdiagnosed (n)	75.0	85.0	109.7	38.4	67.0	76.5	64.2	69.0	73.8	77.2
Overdiagnosed (n)	25.5	18.7	5.1	28.1	16.2	13.6	7.7	3.4	3.4	1.7

Abbreviations: PPV, positive predictive value; LTBI, latent tuberculosis infection; TST, tuberculin skin test; QFT, QuantiFERON Gold In-Tube; TSPOT, T-SPOT.TB; mm, millimeters; IU, International Units; mL, milliliter
Underdiagnosed LTBI cases: Number of LTBI diagnoses missed per 1000 screened
Overdiagnosed LTBI cases: Number of LTBI misdiagnoses per 1000 screened

716 QUANTIFICATION OF CD64: A PREDICTIVE BIOMARKER FOR PROGRESSION TO ACTIVE TUBERCULOSIS

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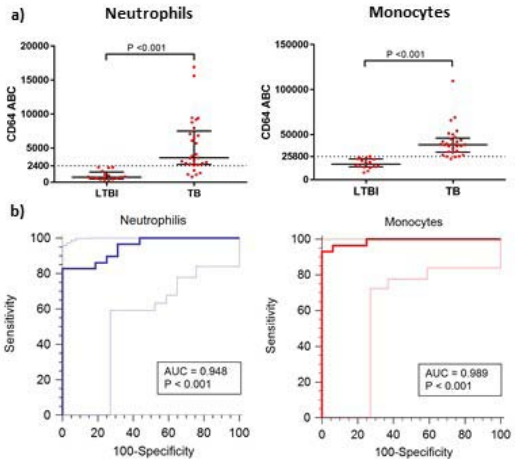
Background: To reach the goal of end-Tuberculosis strategy, new biomarkers are needed to identify active tuberculosis (TB). Currently, only QuantiFERON® TB assay (QTF) is used in peripheral blood for screening tuberculosis infection. However, this method cannot distinguish active from latent TB infection (LTBI). Recent studies show a transcriptional increase of several genes, including CD64, which code for a high affinity Fc receptor I involved in inflammatory reactions. In addition, Neutrophils (NE) and Monocytes (MO) exert bactericidal responses by producing inflammatory proteins caused by infection with *M. Tuberculosis* (MBT). The purpose of this study was to quantify CD64 expression on the surface of NE and MO as a predictive biomarker of progression from LTBI to active TB in QuantiFERON® (QTF) positive or indeterminate patients

Methods: Patients were enrolled with positive and indeterminate QTF. Non-systemic infections were documented. Flow cytometric quantitative expression of CD64 was evaluated from peripheral blood samples and expressed in ABC (Antibody Binding Capacity) units, with NE normal range <1000 ABC and MO normal range 15000-20000 ABC. MTB cultures from respiratory specimens were also performed.

Results: Of the 45 positive QTF cases, 25 MTB cultures were positive and 16 were negative. The positive QTF with negative MTB cultures were considered LTBI. The median of NE CD64 ABC and MO CD64 ABC was significantly higher ($p<0.001$) in MTB positive cultures (NE 3593 ABC; MO 38757 ABC) than in MTB negative cultures (NE 724 ABC; MO 17151 ABC) (Fig. a). The NE CD64 and MO CD64 AUC-ROC values were 0.948 (95% CI 0.838-0.992) and 0.989 (0.901-1.000), respectively (Fig. b). By establishing the NE CD64 value of >2400 ABC or the MO CD64 value of >25800, the sensitivity increased to 95.5% (82.2-99.9) with 100% specificity and 100% Positive Predictive Values (PPVs) (Fig. c). Of the 6 indeterminate QTF enrolled, the 4 with MTB positive cultures showed NE CD64 >2400 ABC or MO CD64 value >25800 ABC and the 2 with MTB negative cultures showed NE CD64 <1000 ABC or MO CD64 <23000 ABC.

Conclusion: The quantification of NE and MO CD64 expression is a powerful diagnostic tool in discriminating between active TB and LTBI and may be used as predictive biomarker of active TB in patients with a positive QTF test. Providing a fast diagnostic solution, this may address the limitation of current tuberculosis diagnostics. Further studies with a larger patient cohort are needed to validate our preliminary data.



c)

	Sensivity % (CI 95%)	Specificity % (CI 95%)	PPV %
CD64 NE > 2400 ABC	82.76 (64.23-94.15)	100.00 (79.41-100.00)	100.00
CD64 MO >25800 ABC	93.10 (77.23-99.15)	100.00 (79.41-100.00)	100.00
CD64 NE > 2400 ABC OR CD64 MO >25800 ABC	96.55 (82.24-99.91)	100.00 (79.41-100.00)	100.00
CD64 NE > 2400 ABC AND CD64 MO >25800 ABC	79.31 (60.28-92.01)	100.00 (79.41-100.00)	100.00

717 ORAL SWAB ANALYSIS (TB-OSA) FOR NON–SPUTUM-BASED TB DIAGNOSIS IN KENYA

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Background: Despite recent advances in rapid TB diagnostics, sample collection remains challenging in those unable to produce sputum. In published proof-of-concept data, oral swab analysis (OSA) detected M. tuberculosis in 90% of HIV-negative Xpert+ adult TB cases in South Africa, with 100% specificity in negative controls. A larger, follow-on evaluation in the same South African population found 92% sensitivity and 92% specificity relative to sputum Xpert. We evaluated OSA performance in HIV-infected and HIV-uninfected TB suspects in Kenya.

Methods: One hundred Kenyan TB suspects (cough >2 weeks, plus >1 additional symptom of fever, night sweats, or weight loss) >13 years of age had oral swabs then sputum for Xpert and culture collected at enrollment and consecutive morning visit. Cryopreserved swabs underwent Mtb DNA extraction and qPCR analysis targeting IS6110 insertion sequence. A predetermined threshold Cq <38 was considered positive (lower Cq indicating a stronger more positive signal). OSA performance was assessed compared to a reference of Xpert or culture. OSA mean Cq values were compared using t-tests.

Results: Of 94 participants enrolled with oral swab results, median age was 38 years (IQR 29-44), 48.9% were female, 54.3% were HIV-infected, and 20.1% with history of TB. Among 51 HIV+, 86.3% were on ART and 9.5% had ever received isoniazid preventive therapy (IPT). Nineteen TB cases were identified (18 Xpert/culture+, 1 culture+ only). OSA sensitivity was 68.4% (13/19) with 82.7% (62/75) specificity overall, and 83.3% (5/6) sensitivity and 75.6% (34/45) specificity among HIV-infected. Performance improved on subsequent morning visit samples compared to Xpert alone (sensitivity 80.0% [12/15], specificity 92.3% [60/65]. Mean OSA Cq was stronger (indicated by lower Cq) among Xpert+ vs. Xpert- participants (35.1 +0.8 vs. 37.9 +1.0 SD, p=0.05) and at subsequent morning vs. enrollment visit among OSA+/TB+ (32.5 +2.4 vs. 34.9 +2.6 SD, p=0.008).

Conclusion: In this analysis, performance appeared reduced compared to previous analyses, possibly due to differences in setting, population, and/or study design. Despite the lower performance compared to sputum-testing methods, OSA provides a promising means of TB detection for populations that are unable to produce adequate sputum including those who are HIV-infected.

718 QUANTIFICATION OF CIRCULATING ANTIGENS ENABLES A RAPID BLOOD TB TEST

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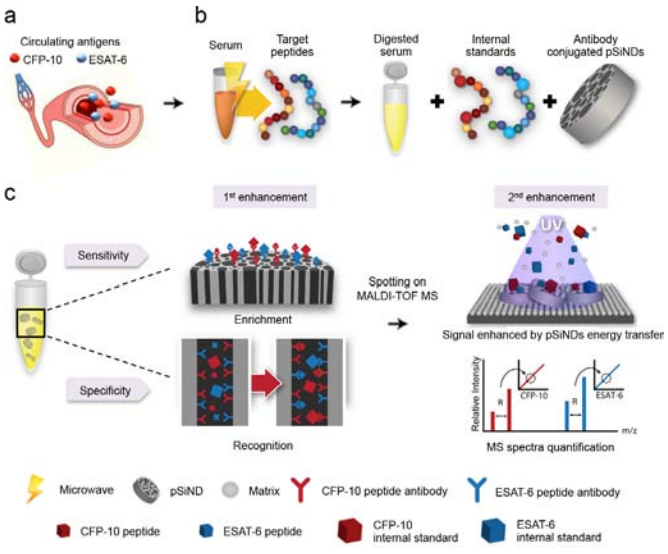
Background: Most TB cases are diagnosed by slow and somewhat non-specific microbiological methods. PCR-based GeneXpert MTB/RIF, introduced to improve speed and specificity, has poor sensitivity at low bacterial loads, cannot distinguish live and nonviable bacilli, and has reduced performance in HIV and TB co-infected patients. Serum-based detection of Mtb virulence factors offers direct evidence of TB, but current methods lack adequate sensitivity and specificity. We have developed a rapid blood-based diagnostic method independent of mycobacterial isolation to quantify the low molecular-weight Mycobacterium tuberculosis (Mtb) antigens (CFP-10 and ESAT-6). Our strategy combines energy mediating porous silicon nanodisks, functionalized with customized antibodies highly specific to Mtb antigen peptides, and high-throughput mass spectrometry (NanoDisk-MS) for dual enhancement of sensitivity and specificity.

Methods: Serum samples are subjected to microwave-assisted tryptic digestion and mixed with functionalized NanoDisks and stable isotope-labeled internal standard peptides. The antibody-conjugated nanodisks performs the recognition and enrichment of target peptides and stable isotope-labeled internal standard peptides, following with a Matrix Assisted Laser Deposition Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) analysis. A NanoDisk effect to enhance MALDI-TOF MS signal allows quantification of target peptide at low concentrations, determined by MS intensity ratio of target and isotope-labeled internal standard peptides.

Results: We evaluated our platform with 385 adult and 720 pediatric patients and controls chosen from five highly relevant cohorts (active TB, HIV/TB co-infection, pediatric TB, latent TB, and non-TB mycobacterial infection), provided by multiple institutes worldwide. Sensitivities and specificities of adults (92.1% / 98.2%) and children (89.0% / 97.5%) were achieved in active TB identification. Absolute quantification of circulating antigens was informative in detecting treatment response four days after anti-mycobacterial initiation.

Conclusion: Our NanoDisk-enabled TB detection assay addresses sensitivity and speed shortcomings associated with active TB diagnosis, and meets several criteria for a WHO-mandated noninvasive TB assay. Based on our preliminary studies, we are confident that this diagnostic system will benefit the global tuberculosis control effort by improving the personalized management of TB.



719LB BD MAX™ MDR-TB ASSAY FOR DETECTION OF TUBERCULOSIS AND DRUG RESISTANCE

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Background: Tuberculosis (TB) control among people living with HIV requires accurate, rapid diagnostic tests to identify Mycobacterium tuberculosis complex (MTBc), and detect isoniazid (INH) and rifampin (RIF) resistance. We evaluated the performance of the BD MAX™ MDR-TB (BD MAX) assay, which tests up to 24 specimens at once.
Methods: Outpatient adults with signs and/or symptoms of active pulmonary TB were enrolled in South Africa, Uganda, India, and Peru. A single collected sputum was split into 2 portions. Smear microscopy and BD MAX were performed on the raw portion. The other portion was processed using NALC-NaOH, and tested using culture (MGIT™), phenotypic drug susceptibility testing, Xpert® MTB/RIF (Xpert), BD MAX, and microscopy.
Results: 1053 participants (47% female, 32% HIV-infected) with presumptive TB were enrolled. The majority (94%) of HIV-infected participants were enrolled from high HIV/TB burden sites (Uganda and South Africa) with median CD4 of 367 (IQR 228-536). Overall BD MAX test sensitivity was 93% (262/282 [95% CI 89,95]) among microbiologically confirmed TB participants, and specificity was 97% (593/610, [96,98]) among participants with negative cultures. Among 273 HIV-infected participants, sensitivity was 86% (44/51 [74,93]), and specificity was 98% (217/222 [95,99]) When stratified by ZN smear microscopy status, sensitivity of BD MAX for detection of HIV-associated TB was 100% (22/22, [85, 100]) for smear-positive, and 76% (22/29, [58, 88]) in smear-negative HIV/TB patients. Among TB patients with both BD MAX and Xpert results, sensitivity was 82% (41/50, [69, 90]) for both assays. BD MAX sensitivity for detection of any drug resistance (INH and/or RIF) was 100% (4/4 [51,100]), with specificity among those with drug-susceptible TB of 100% (30/30 [89,100]) when compared to MGIT DST among HIV/TB participants. Sensitivity and specificity for detection of INH resistance was 100% (3/3 [44, 100]) and 100% (35/35, [90, 100]), respectively. Sensitivity for RIF resistance was 100% (2/2, [34,100]). One participant had RIF resistance by BD MAX, but was considered susceptible on MGIT DST and bi-directional sequencing, resulting in an overall specificity of 97% (34/35, [85,99]).
Conclusion: The BD MAX MDR-TB assay has high sensitivity and specificity for detection of MTBc, and rifampin and isoniazid drug resistance in settings of high HIV/TB burden and may aid in the rapid detection of tuberculosis and MDR-TB.

720 THE EFFECTIVENESS OF VARIOUS SYMPTOM-BASED ALGORITHMS FOR TB SCREENING AT HIV TESTING

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Background: It is essential to screen for TB prior to ART initiation in TB endemic settings. Algorithms are needed to identify low-risk patients for immediate ART initiation, and high-risk patients who merit TB testing prior to ART initiation. If TB screening is conducted at the time of HIV testing, symptomatic patients may also be tested for TB, even if they test negative for HIV. We conducted a retrospective analysis to evaluate the diagnostic yield of five different symptom screening strategies among patients who presented for HIV testing in Haiti.
Methods: From October 1, 2015 to March 31, 2016, the first 20 patients who presented for HIV testing each day at GHESKIO were queried regarding TB symptoms, and received AFB smear, GeneXpert testing, and chest x-ray, regardless of symptoms. TB symptom screening algorithms were evaluated based on the total proportion of TB cases diagnosed and the number of missed TB cases, stratified by HIV status.
Results: 1,108 individuals received diagnostic testing for both HIV and TB. 48% were female, median age was 33 (27-44) and 216 (19%) tested positive for HIV, with median CD4 count of 364 cells/mm3 (IQR: 210-563). 59 patients (5%) were diagnosed with TB; 55 (93%) of these were bacteriologically confirmed, and 4 (7%) were diagnosed based on symptoms and chest x-ray. Among the 216 persons who tested positive for HIV, 13 (21%) of those who reported cough of any duration were diagnosed with TB (Table 1). Of non-coughing patients with HIV, 2 (1%) were diagnosed with TB; these patients also did not report fever, night sweats, or weight loss. Among the 892 patients who tested negative for HIV, 36 (16%) of those who reported cough of any duration were diagnosed with TB. Among HIV-negative patients without cough, 8 (1%) were diagnosed with TB; 3 of these patients reported fever, night sweats or weight loss in the absence of cough.
Conclusion: Testing for TB in patients who do not report cough at HIV testing is low yield in Haiti, regardless of HIV test results; ART can generally be initiated in patients who do not report cough without further TB testing. Patients who report cough of any duration at HIV testing should be evaluated for TB, regardless of HIV test results. Patients newly diagnosed with HIV should be screened for cough of any duration, and those reporting cough should be tested for TB prior to ART initiation.

Table 1. Performance of Different TB Symptom Screening Algorithms at HIV Testing (N=1108)

Symptom[1]	No. Diagnosed with TB/No. Tested for TB	No. of Missed TB Cases/Total Patients	Total Proportion of TB Cases Diagnosed
Persons Diagnosed with HIV (n=216)			
Cough ≥2 weeks	11/53=21%	4/216=2%	11/15=73%
Cough any duration	13/62=21%	2/216=1%	13/15=87%
Any TB symptom ≥2 weeks	13/98=13%	2/216=1%	13/15=87%
Any TB symptom any duration	13/124=10%	2/216=1%	13/15=87%
All patients regardless of symptoms	15/216=7%	0/216=0%	15/15=100%
Persons Testing Negative for HIV (n=892)			
Cough ≥2 weeks	35/201=17%	9/892=1%	35/44=80%
Cough any duration	36/227=16%	8/892=1%	36/44=82%
Any TB symptom ≥2 weeks	38/315=12%	6/892=1%	38/44=86%
Any TB symptom any duration	39/374=10%	5/892=1%	39/44=89%
All patients regardless of symptoms	44/892=5%	0/892=0%	44/44=100%

Notes:
[1] TB symptoms include weight loss, cough, fever and night sweats. Any TB symptoms ≥2 weeks was defined as any weight loss and/or cough, night sweats or fever ≥2 weeks.

721 OPTIMIZING DIAGNOSTIC ALGORITHMS FOR ACTIVE PULMONARY TUBERCULOSIS IN HIV CLINICS

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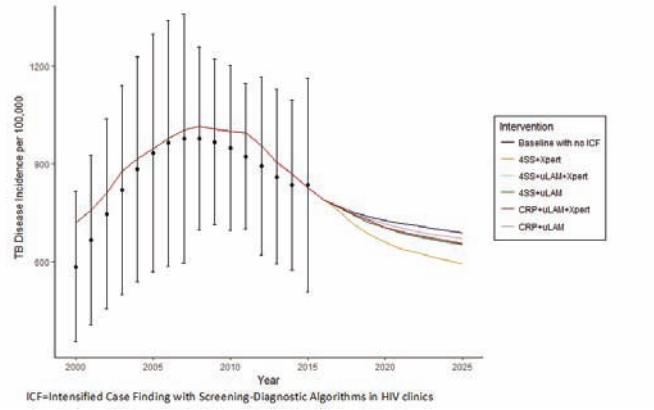
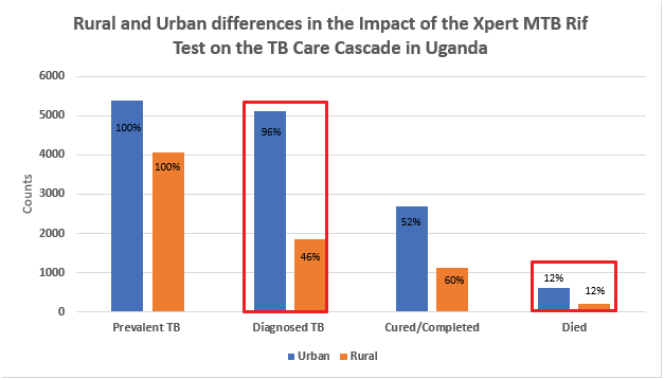
Background: Most TB deaths are preventable with early diagnosis and treatment among people living with HIV (PLHIV). Current testing algorithms rely on symptom screening and sputum-based diagnostic tests, which are less sensitive among PLHIV and often result in treatment delays and loss to follow-up; nearly 20% of TB cases go undiagnosed in South Africa. Point-of-care (POC) testing in HIV clinics may improve case-detection, thereby reducing TB disease incidence and mortality.
Methods: We used EMOD-TB, an individual-based TB transmission model, to estimate the impact of HIV clinic-based screening-diagnostic algorithms on rates of TB disease incidence and mortality in South Africa. The model accounted for the natural history of TB and HIV, disease progression, the TB care cascade, and historical estimates of country-level disease incidence and mortality. The model assumes each algorithm is offered to all clinic attendees beginning in 2016 when receiving HIV testing and annually thereafter. Test sensitivities and specificities differed by HIV status and CD4 count. The five algorithms, with each test based on a preceding positive result, were: 1) Four TB symptom screening (4SS)+GeneXpert (Xpert); 2) 4SS+urine lipoarabinomannan (uLAM)+Xpert (to reduce testing costs); 3) 4SS+uLAM; 4) C-reactive protein (CRP)+uLAM+Xpert; and 5) CRP+uLAM.
Results: Incorporating intensified TB case finding into routine HIV testing resulted in a reduction in predicted TB incidence and mortality. The algorithm of 4SS+Xpert yielded the greatest overall decline in TB burden with an estimated additional reduction of 12% (11-13%) in incidence and 16% in mortality (15-17%) from 2016 to 2025 compared to baseline trends. Both 4SS+uLAM and CRP+uLAM+Xpert resulted in reductions of an additional 4% in TB incidence (3-5%) and 6% in TB mortality (7-10%) compared to baseline trends. Administering uLAM before confirmatory testing resulted in a 90% reduction in the number of Xpert tests ordered in the HIV clinic.
Conclusion: Incorporating 4SS+Xpert testing into HIV care would significantly reduce TB disease incidence and mortality in South Africa. We predict that HIV clinic-based testing algorithms that incorporate CRP and uLAM would result in smaller declines in burden, however uLAM testing would have a greater relative impact on mortality among PLHIV with lower CD4 counts. HIV clinic-based testing algorithms that incorporate CRP and uLAM should be evaluated in prospective clinical trials with respect to improving TB outcomes among PLHIV.

Figure 1. Mean TB disease incidence per 100,000 by year and HIV clinic-based screening algorithm: A population-level mathematical modeling analysis in South Africa



ICF=Intensified Case Finding with Screening-Diagnostic Algorithms in HIV clinics



722 RURAL AND URBAN DIFFERENCES IN THE IMPACT OF THE XPERT MTB/RIF TEST ON TB CARE

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Background: Since 2014, utilization of the Xpert MTB/Rif test (Xpert) for diagnosis of Tuberculosis (TB) has increased compared with smear microscopy in Uganda. In 2016, more than half of the health facilities with onsite Xpert were rural. However, the impact of the increased uptake of Xpert on the care cascade and health outcomes for TB patients remains unclear. We hypothesized that the care cascade for HIV-associated TB in rural health facilities with onsite Xpert would be similar to that of urban health facilities with onsite Xpert.

Methods: We retrieved electronic data on health facility outpatient attendance, number of TB patients diagnosed, treated, and their outcomes from the national HMIS database (June 2016 to July 2017), and rural versus urban placement status of Xpert from the National TB Reference Laboratory reports. We estimated prevalent TB using the total number of outpatients with a diagnosis of any cough or pneumonia. Based on review of local and regional literature, we assumed that 2% of individuals with any cough had TB while 12% of individuals with pneumonia had TB. Of the total prevalent TB, we assumed that 42% had TB/HIV co-infection based on the national TB report of 2016. We computed the absolute counts and percentages for each of the following steps of the TB care cascade: number of prevalent TB patients at the health facility, number of diagnosed TB patients, number of TB patients cured or completed treatment and number of TB deaths.

Results: Data was obtained from a total of 758,823 patients from 106 health facilities with onsite Xpert of which 57/106 (54%) were rural. Rural health facilities had 299,643 patients (39%) with any cough and 30,197 patients (4%) with pneumonia, while urban facilities had 386,293 patients (51%) with any cough and 42,690 patients (6%) with pneumonia. Rural facilities diagnosed 1,855/4039 (46%) of the estimated prevalent TB/HIV cases versus 5,101/5397 (95%) at urban facilities. Treatment cure/completion was 60% for rural facilities versus 52% for urban facilities ($p<0.001$). Mortality was similar in rural and urban health facilities (12% rural versus 12% urban).

Conclusion: Despite increased placement of Xpert in rural health facilities, they detected less than half of their prevalent TB cases compared with urban health facilities. Rural facilities had better cure/completion treatment outcomes however, mortality was similar in both settings. Focused interventions are required to address these distinct quality gaps in TB care.

723 TB PREVENTIVE THERAPY UPTAKE IS HIGH WITH COMMUNITY ART DELIVERY IN SOUTH AFRICA

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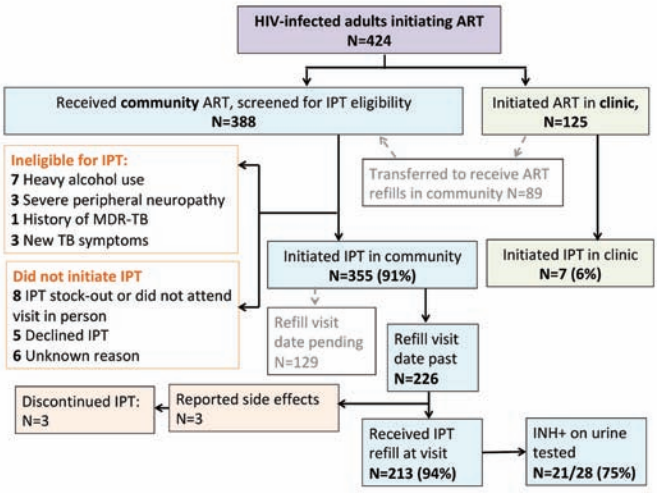
Background: Isoniazid (INH) preventive therapy (IPT) reduces mortality and tuberculosis (TB) in persons with HIV and is recommended for all HIV+ persons in high TB prevalence settings, including South Africa, but uptake is low. Barriers to IPT include lack of provider education and prioritization, screening with non-specific TB symptoms, IPT provided separately from HIV services, and monthly clinic visits for refills. Our objective was to increase uptake of IPT for HIV-infected persons newly initiating ART.

Methods: IPT was integrated into community-based ART in the DO ART Study in peri-urban communities in KwaZulu-Natal, South Africa. DO ART is an ongoing randomized clinical trial with intervention arms providing community-based ART delivery, quarterly refills, mobile monitoring, and access to facility-based services only as needed. Between 7/2017-9/2018, 388 HIV-infected adults (149 (38%) men) received care in the community-based arms including ART initiation and at least one follow-up visit. Participants were screened by lay health workers for TB symptoms and contraindications to IPT at every visit. Eligible participants were offered IPT starting 1 month after ART initiation. IPT refills were quarterly and synchronized with ART. We assessed IPT acceptance, refusal, and receipt of a first refill as indicators of feasibility and acceptability. In 7/2018, we began testing urine for INH metabolites at community IPT refill visits to confirm self-reported IPT adherence.

Results: 388 participants who received community-based ART were screened for IPT eligibility. 355 (91%) were eligible and initiated IPT. There were 10 refusals, 5 of whom initiated IPT at a subsequent visit. 99% participants reported no side effects or toxicities. 3 persons self-discontinued IPT due to side effects. Self-reported adherence was high. 94% completed a first refill visit and received an indicated IPT refill. Urine testing confirmed presence of INH in 21 of 28 (75%) persons spot-tested for adherence. Among 125 participants who initiated ART at a clinic, 7 (6%) reported receiving IPT. No incident TB cases were reported.

Conclusion: High levels of IPT uptake and continuation were achieved in a community-based ART project, and demonstrated feasibility, high safety, adherence, and acceptability in South Africa. Community-based IPT can be effectively provided in a differentiated HIV care model with infrequent clinic contacts, and may have better uptake than clinic-based IPT. Urine testing can complement self-reported adherence.

Figure 1. IPT in clinic vs. community-based ART delivery in the DO ART study



724 EVALUATION OF PULMONARY TUBERCULOSIS FOLLOWING IPT IN KENYAN ADULTS LIVING WITH HIV

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Background: Isoniazid preventive therapy (IPT) is a proven intervention to reduce tuberculosis (TB)-related morbidity and mortality among people living with HIV (PLHIV). The World Health Organization (WHO) recommends a symptom screen to rule-out TB prior to administering IPT. Previous studies have shown decreased sensitivity of the symptom screen in ART-treated individuals. TB incidence following IPT administered under programmatic conditions has not been well-described. We performed a study in Kenya to assess the incidence of TB in IPT-naïve and -treated individuals receiving ART and to assess the accuracy of the WHO symptom screen and other tests for the rule-out of TB disease.
Methods: We enrolled PLHIV at two HIV care clinics in Nyanza region, Kenya. Patients who were IPT-naïve or had completed IPT at least 6 months prior to enrollment were eligible. We collected demographic, clinical, and laboratory data including blood for potential TB biomarkers (C-reactive protein [CRP], HIV viral load, CD4 count, monocyte:lymphocyte ratio, platelets, hemoglobin), and sputum sample for AFB-smear, -culture, and GeneXpert MTB/RIF (Xpert) testing. In bivariate analyses, we assessed the relationship between TB (culture-positive), and clinical characteristics (body mass index [BMI], antiretroviral therapy [ART]), WHO TB symptom screen, and potential TB biomarkers.
Results: Between March 2017 and June 2018, we enrolled 389 participants (Table). 87.8% of participants had previously received IPT (median days since IPT completion=394 [280-539 IQR]). TB was diagnosed in 5 participants (1.3%, 95% confidence interval [CI] 0.4–3.0%), and was higher among IPT-naïve (4.3%, 95% CI 0.5-14.5%) than IPT-treated (0.9%, 95% CI 0.2-2.6%) participants. The rate of TB following completion of IPT was 0.8 per 100 person-years (95% CI 0.3 – 2.4). Among the 3 participants with post-IPT TB, 2 had a prior history of treated TB disease. One participant was diagnosed with INH-resistant TB. All participants diagnosed with TB had negative WHO symptom screens, negative AFB-smears, and 4 of 5 had negative Xpert testing. The sensitivity of all candidate biomarkers for TB was poor including CRP >8 mg/L (40%); hemoglobin <10g/dl had the best performance (60% sensitivity, 86% specificity).
Conclusion: IPT provided under programmatic conditions is effective. The WHO symptom screen and candidate tests were insensitive for TB disease in PLHIV on ART. A positive history of TB may be a risk factor for TB after IPT.

725 THE IMPACT OF HIV-COINFECTION ON THE EVOLUTION OF MYCOBACTERIUM TUBERCULOSIS

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Background: HIV is fuelling the resurgence of human tuberculosis (TB) in many parts of the world. Adequate T-cell responses, in particular CD4+ T-cells that are preferentially infected by HIV, are essential for providing protective immunity against Mycobacterium tuberculosis (Mtb) infection, but also act as drivers of lung pathology and mediators of TB transmission. For most of its evolutionary history, Mtb has evolved in the absence of HIV co-infection. We thus hypothesize that the immunocompromised human host environment affects Mtb fitness, both by altering the immune environment within host and by altering transmission dynamics.
Methods: We collected Mtb isolates and clinical data from HIV co-infected (HIV+) and HIV uninfected (HIV-) adults with pulmonary TB in nine high-burden countries in Africa, Asia and Latin America, as well as Switzerland. We inferred phylogenetic reconstruction by maximum likelihood methods and compared terminal branch lengths by HIV status and CD4 cell counts. We also compared the genetic diversity of human T-Cell epitope regions in HIV+ and HIV- patients.
Results: Out of 908 Mtb strains, 458 came from HIV+ and 450 from HIV- patients. Isolates from all four main Mtb lineages (L1, L2, L3 and L4) responsible for the global TB epidemic are represented in our dataset, although L4 was the most frequent (62%). The phylogenetic tree of all isolates revealed no particular subdivision by HIV status (Figure 1). Terminal branches of the phylogenetic tree contained more mutations in HIV+ patients than in HIV- (p-value <0.001). This indicates that Mtb isolated from HIV+ individuals have a higher number of mutations that are not shared by other isolates in the population, possibly reflecting a lower transmission potential of HIV co-infected patients. The human T-cell epitopes of Mtb are known to be hyper-conserved compared to the rest of the genome, suggesting that immune recognition is required for successful Mtb transmission. We find the human T-cell epitopes of Mtb/HIV+ individuals harboured more mutations than Mtb/HIV- individuals, indicating less stringent purifying selection.
Conclusion: Our study is consistent with findings from epidemiologic studies indicating reduced transmission of Mtb from HIV+ patients. The findings also reinforce our current understanding of epitope conservation in Mtb and brings new insights which could be used in the design of TB vaccines in HIV co-infected population.

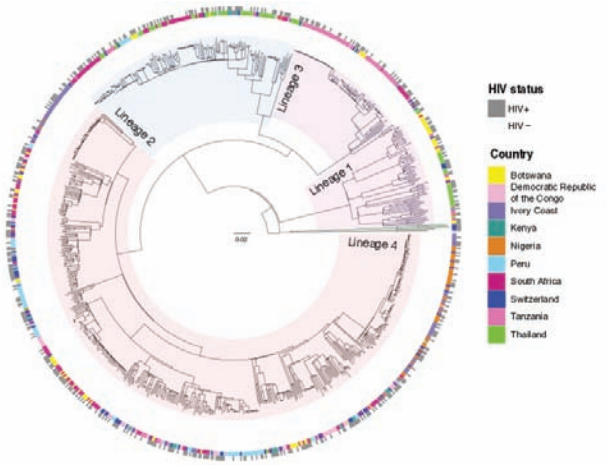

Figure 1: Maximum likelihood phylogenetic tree inferred from 908 *M. tuberculosis* genomes. HIV status of the host is indicated in the outer ring and country of isolation of the isolate is indicated on the inner ring

726 MYCOBACTERIUM TUBERCULOSIS COINFECTION INCREASES HIV RESERVOIR SIZE

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Background: Tuberculosis (TB) is the most frequent opportunistic infection among people living with HIV. The contribution of Mycobacterium tuberculosis (Mtb) co-infection in HIV reservoir establishment and maintain is not clear, hindering HIV/TB co-infected persons benefit from HIV cure strategy.

Methods: We prospectively enrolled 38 HIV-infected participants with culture-confirmed TB and 35 participants with HIV mono-infection naïve to therapy. Participants received antituberculosis and/or antiretroviral therapy (ART) accordingly. Blood samples were collected from all the participants prior to therapy and after a median of 12 months of ART. Total HIV-DNA in peripheral blood mononuclear cells (PBMC) were quantified by real-time PCR. Plasma levels of interleukin-7 (IL-7), the key cytokine in the development and hemostasis of T cells, were measured by ELISA.

Results: Levels of total HIV-DNA among participants with HIV/TB co-infection was significantly higher than that in HIV mono-infected participants at pre-ART (3.34 ± 0.42 log10/106 PBMC vs 2.70 ± 0.45 log10/106 PBMC, P<0.001). M.tb co-infection was identified as the only predictor of high HIV DNA level (Table). After 12 months of ART, the HIV reservoir size decreased significantly, which was positively correlated with their pre-ART level. HIV/TB co-infected participants, who had already been cured for TB, maintained a larger reservoir size compared to HIV mono-infection participants (2.86± 0.36 log10/106 PBMC vs 2.09 ± 0.60 log10/106 PBMC, P< 0.001). Multiple linear regression analysis showed that M.tb co-infection contribute to HIV-DNA independent of pre-ART HIV DNA level (P=0.033). Mechanically, plasma levels of IL-7 was significantly higher in HIV/TB co-infected participants than that in HIV mono-infection participants at both pre-ART (20.94±10.13 pg/ml vs 9.10±7.05 pg/ml, P<0.001) and on-ART(16.26±9.54 pg/ml vs 7.35± 5.36 pg/ml, P=0.004). Level of IL-7 was positively correlated with HIV-DNA level (R= 0.33, P< 0.01).

Conclusion: M.tb co-infection contributes to a larger size of HIV reservoir in HIV infection. Interventions targeting IL-7 may reducing HIV reservoir size in this population and warrant further investigations.

Multiple linear regression analysis for predictors of total HIV DNA in PBMC

	Pre-ART HIV DNA		On-ART HIV DNA	
	Coefficient	*P*-value	Coefficient	*P*-value
Age	-0.001	0.878	<0.001	0.951
Male	-0.181	0.214	--	--
Mtb co-infection	0.511	**0.001**	0.347	**0.033**
CD4 T cell counts(cells/ml)	<0.001	0.764	-0.001	0.488
CD8 T cell counts(cells/ml)	<0.001	0.841	<0.001	0.052
CD4/CD8 ratio	-0.493	0.320	-0.092	0.823
Pre-ART total HIV DNA(log_{10} copies/10^6 cells)	--	--	0.459	**<0.001**
Duration of ART(Month)	--	--	0.006	0.626

* For the overall model, the adjusted R^2 were 0.36 and 0.60 for pre and on-ART HIV DNA respectively, both *P*<0.0001.

727 FUNDAMENTAL SHIFTS IN HIV POPULATION STRUCTURE AFTER TB-IRIS

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Background: Tuberculosis (TB) is the most common coinfection in HIV-infected people. Those with advanced HIV/AIDS and TB who initiate antiretroviral therapy (ART) are at risk for potentially lethal immune reconstitution inflammatory syndrome (IRIS), characterized by exuberant expansions of TB-specific CD4+ T cells. HIV infected CD4+ T cells also undergo clonal expansion during ART, which has profound effects on HIV population structure. The effects of the combination of IRIS and ART on HIV population structure remain unknown. Thus we hypothesized that TB-IRIS drives fundamental changes in the size and structure of HIV populations.

Methods: Subjects with advanced HIV/AIDS were enrolled in a prospective study of IRIS. Plasma and peripheral blood lymphocytes were collected at pre-, early (2-14w) and prolonged (44-200w) ART from subjects with TB-IRIS (n=9), TB/no IRIS (n=8) and no TB/no IRIS (n=9). Cell-associated (CA) HIV DNA and RNA were assessed by qPCR. HIV populations were characterized by single genome sequence (SGS) analysis of HIV pro-pol from plasma RNA and CA DNA. SGSs were evaluated with phylogenetic and population genetic analyses; clonal prediction scores for identical HIV sequences were determined (Laskey et al. PLOS Path 2016). Population parameters were compared with Fisher-Exact and Mann-Whitney tests.

Results: Study subjects had a median CD4 count of 34 cells/μl and significant declines in HIV CA RNA and DNA after starting ART (pre- vs on-ART p<0.0001). No differences in CA HIV RNA, DNA or RNA:DNA ratios were detected on ART between groups (for all p>0.05). TB-IRIS subjects had higher CA HIV DNA diversity than no TB/no IRIS subjects pre-ART (1.2% vs. 1.9% p=0.03) and during IRIS (1.1% vs 1.9% p=0.03). After prolonged ART, HIV population shifts (pre-ART RNA vs. CA DNA on ART) were detected in 6/9 TB-IRIS subjects but only in 3/17 subjects without IRIS (p=0.03) when identical sequences were collapsed. Identical HIV DNA SGSs emerged during ART in all groups and were probable clones (p<0.05). However after 144w ART, probable clones were less frequent in TB-IRIS than in non-IRIS groups (p=0.0001).

Conclusion: Despite broad immune activation, TB-IRIS did not drive elevated levels of CA HIV RNA. Clonal expansion of HIV infected cells results in profound differences in HIV populations after prolonged ART between IRIS and non-IRIS groups. This data highlights the role of inflammation in reshaping HIV populations and the HIV reservoir.

728 TB-SPECIFIC CD4+ T CELLS ARE ASSOCIATED WITH PULMONARY INFLAMMATION ON ART IN HIV/TB

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Background: Initiation of antiretroviral therapy (ART) in HIV-infected patients with pulmonary tuberculosis (TB) is associated with rapid reconstitution of CD4+ T cells, which may lead to expansion of Th1-type responses and respiratory compromise via TB-immune reconstitution inflammatory syndrome (TB-IRIS). Mechanisms driving pulmonary inflammation in HIV/TB are unclear. We hypothesized that rapid recovery of antigen (Ag)-specific CD4+ T cell responses on ART are associated with worsening pulmonary inflammation and lung function.

Methods: We enrolled a cohort of HIV-infected, ART-naïve adults with pulmonary TB in Tembisa, South Africa. Lung inflammation was assessed using 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) at baseline (ART initiation) and four weeks following ART initiation to measure lung total glycolytic activity [TGA]. Changes in lung function were assessed using spirometry (% predicted forced expiratory volume in 1 second [FEV1%]) at both time points. Intracellular cytokine staining and flow cytometry were used to determine the frequency of CD4+ T cells expressing IFN-γ, IL-2 and/or TNF-α in response to PPD. Wilcoxon rank-sum test was used to compare functional responses at baseline, week 4, and change from baseline to week 4 among participants who had increase versus decrease in 1) lung TGA and 2) FEV1% on ART. P values were corrected for multiple comparisons.

Results: Thirty subjects, with a mean age of 38 years (range 27-49), a median CD4 count of 112 (IQR 48-294), of whom 15 (50%) were females, completed both FDG PET-CT scans. Those with increases in lung TGA had similar baseline, but markedly greater increases from baseline to week 4 post-ART initiation in total IFN-γ+ and TNF-α+ (Figure 1A), as well as dual IFN-γ+/TNF-α+ and TNF-α+ monofunctional CD4+ T cells (Figure 1B) (all p< 0.01). Similarly, subjects with an incident FEV1% drop on ART (median drop of -9% (IQR -14 to -4) had similar baseline, but greater changes and week-4 levels of TNFα+ monofunctional CD4+ T cells (all p<0.03) versus participants whose FEV1% did not drop.

Conclusion: Rapid increases in TB-specific CD4+ T cells expressing IFN-γ and/or TNFα soon after ART initiation in HIV/TB co-infected participants is associated with incident pulmonary inflammation and decreased lung function. New

approaches to dampening pathologic inflammation mediated by Th1 immune recovery may improve treatment outcomes in HIV/TB.

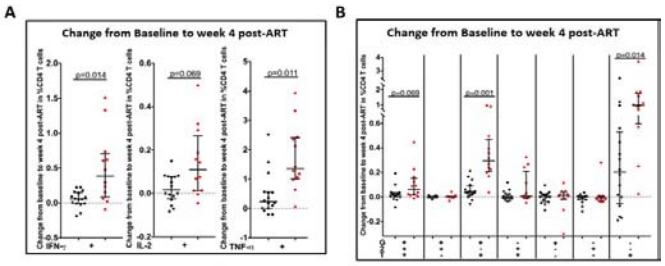

Figure 1: Changes in PPD-specific CD4+ T cell responses from baseline (ART initiation) to week 4 of ART in HIV/TB co-infected participants, organized by whether or not lung inflammation on FDG PET-CT increased (red) or did not increase (black) on ART. (**A**) Changes from baseline to week post-ART initiation in the percent of CD4+ T-cells positive for IFN-γ, IL-2, or TNF-α after stimulation with PPD among participants with increasing (n=12, red) vs. unchanged or decreasing lung TGA (n=18, black). (**B**) Changes from baseline to week 4 post-ART initiation in the percent of CD4+ T-cells expressing each of seven possible combinations of IFN-γ, IL-2, and TNF-α after stimulation with PPD.

729 HIV TEST YIELD AND REASONS FOR UNKNOWN HIV STATUS AMONG TB PATIENTS: THE KOPANYO STUDY

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Background: Botswana is approaching global targets for testing, treatment and viral suppression for HIV. With fewer people living with unknown HIV status, it is more difficult and costly to find and test the remaining few that could benefit from HIV treatment. Based on PEPFAR program reports, the overall yield of HIV testing activities in Botswana was about 5% in 2017. Testing tuberculosis (TB) patients for HIV is a high-yield activity. Our objective was to examine HIV test yield among TB patients never tested previously or with undocumented HIV status and the reasons for unknown HIV status at the start of anti-TB treatment among patients enrolled in a multiyear, population-based TB transmission study in Botswana – the KOPANYO study.
Methods: During September 2012 – March 2015, all persons registered with TB in Gaborone and Ghanzi Districts, Botswana were eligible for the study. At enrollment, all TB cases were offered HIV testing in accordance with national guidelines, except those previously documented positive and tested negative within 90 days before enrollment. HIV test results were recorded. The reasons for no results were documented.
Results: Among 4331 TB patients enrolled, 14% (623/4331) never tested previously nor had documented HIV status at the start of anti-TB treatment. Of these, 77% (480/623) were tested for HIV during the course of treatment - including 23% (110/480) patients newly diagnosed with HIV. Of all participants, for 3% (143/4331) their HIV status remained unknown to the end of the study. Of these 143 patients, 65% (93) outright refused HIV testing without providing reasons; while 35% (50) did not refuse, but had no test results. The reasons for unknown status among non-refusals included: 29% (16/50) unspecified; 22% (12/50) no test kit was available; 22% (12/50) tested at a different facility with no documented HIV results, and 18% (10/50) agreed to test but deferred for a later time.
Conclusion: In this analysis, we found that among the TB patients with unknown HIV status, HIV testing yield was 23%, 4 times higher than other HIV-testing activities in Botswana (5%); however, an unacceptable proportion of HIV status results remained unknown due to patient refusal, or logistical reasons. Further research is needed to understand why patients refuse testing.

730 TIMING AND INCIDENCE OF HIV-ASSOCIATED TUBERCULOSIS: A 4-COUNTRY STUDY

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Background: Scale up of combination antiretroviral therapy (cART) has a profound impact on the risk of developing tuberculosis (TB) in persons with HIV, both in low and high TB burden countries. Nonetheless, TB remains a major cause of morbidity and mortality in persons with HIV. Knowledge of timing and determinants of TB risk is essential to designing strategies to address this issue.
Methods: The study was conducted in four countries with different TB burden (Uganda, Peru ,Mexico, and Italy). We analyzed data of persons enrolled in HIV observational cohorts (one multicenter cohort ICoNA – Italy and 3 single institution cohorts: INNSZ-Mexico, IMTAvH-Peru and IDI-Uganda) from 2006-2016. Cases of TB diagnosed at first presentation (within 3 months of HIV diagnosis/initiation of HIV care) or during follow-up, before and after cART initiation, were considered. Factors associated with the risk of having TB at enrollment were identified by multivariable logistic regression. Incidence rates of TB from enrollment were calculated, and Poisson regression model was used to identify factors associated with the incidence of TB in the study population
Results: The analyzed cohort included 24,043 persons of whom 2,455 (10.2%) were diagnosed with TB. TB was diagnosed at first presentation in 1763 (72%), in 260 (11%) at least 3 months after presentation and before cART start, and in 432 (18%) after cART initiation. Proportion of cases diagnosed at first presentation ranged from 69.9% in Uganda to 82% in Mexico. Presentation for HIV care with low CD4 cell count was a strong risk factor for TB in all countries. Preventive therapy was infrequently reported in these patients (<2%). Incidence of TB after cART initiation ranged from 13.3 per 1000 person-years in Uganda to 0.83 in Italy. Incidence declined rapidly during the first year of treatment in all countries. After 12 months of treatment however, it remained higher than the background incidence in each country (Table).
Conclusion: Timing of TB diagnosis among persons with HIV was remarkably similar in all four countries despite different TB burdens. More than three-quarters of cases were diagnosed upon presentation to HIV care and were associated with low CD4 cell count. Early HIV diagnosis and immediate initiation of cART may be the most important intervention to further decrease the risk of HIV-associated TB. Additional prevention interventions, such as preventive therapy, may be needed, however, in particular during the first year of cART.

Table. Timing and incidence of tuberculosis (TB) among persons enrolled in HIV observational cohorts in four countries

Country (TB incidence in general population)*	Uganda (2.01)	Peru (1.16)	Mexico (0.22)	Italy (0.07)
Persons enrolled	12238	3562	655	7648
Timing of TB occurrence n. (%)				
At first presentation	1245 (69.9)	321 (72.0)	51 (82)	105 (83.3)
Before ART start	223 (12.5)	33 (7.4)	0	4 (3.2)
After ART start	312 (17.5)	92 (20.6)	11 (18)	17 (13.5)
Incidence before ART start†	21.71 (18.99 – 24.82)	17.85 (12.69-25.11)	----	1.03 (0.28-2.63)
Incidence after ART start†				
Overall	13.34 (11.87 – 15.00)	9.23 (7.52-11.33)	4.40 (2.43-7.95)	0.83 (0.48-1.33)
0 – 3 months since start	45.52 (36.85 – 56.23)	46.13 (33.42-63.67)	38.41 (17.25 - 85.51)	1.97 (0.74, 5.25)
4 – 12 months since start	20.63 (16.23-25.86)	9.99 (6.02-16.58)	12.87 (4.83 - 34.31)	2.26 (1.18, 4.34)
>12 months since start	7.72 (6.46 – 9.24)	5.22 (3.83-7.12)	0.49 (0.07 - 3.50)	0.28 (0.10, 0.74)

* Rate per 1,000 population per year; Global tuberculosis report 2018 –WHO
† Rate per 1,000 person-years (95% confidence intervals)

731 HIGH INCIDENCE OF TUBERCULOSIS AMONG HIV+ PATIENTS TREATED WITH HAART IN ZAMBIA

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Background: Tuberculosis (TB) is the leading cause of morbidity and mortality among Human Immunodeficiency Virus (HIV+) patients. The risk of TB among HIV+ patients on combination Anti-Retroviral Therapy (cART) is heterogenous depending on the timing of cART. However, it is not known whether there are differences in the risk of TB among HIV+ patients accessing cART in rural and urban health settings in sub-Sahara Africa. In urban settings, high TB incidence is sustained by the high HIV prevalence and crowded living conditions. Rural settings have distinct challenges which drive the TB and HIV epidemic. These

include poor health care access, lack of diagnostics and severe shortage of health care providers. Therefore, it is important to understand differences in the risk of TB between these 2 populations. To address this knowledge gap, we evaluated the risk of TB among HIV+ patients on cART.

Methods: We performed a retrospective cohort study on a sample of HIV patients who started cART between 2005 and 2014 within the Zambia National ART Program. We estimated the Incidence Rates (IR) of TB were person-time at risk of TB was accrued from the date of starting cART until diagnosis of TB. To assess the risk factors associated with incident TB, Cox proportion hazard regression was performed.

Results: Overall 1,518 patients met the eligibility criteria (rural: 33%; urban:67%). At the time of initiating cART 82 patients (5.4%) were diagnosed with prevalent TB. New cases of TB were diagnosed for 44 patients (2.4%) over 21,209 person-years of observation (PYO). The overall IR was 2.07/1000PYO (95% CI: 1.8–3.7). The IR was 2.6/1000PYO (95% CI: 1.6–4.4) in urban health settings and 1.9/1000PYO (95%: 1.3–2.7) in the rural health settings. Within the first year of cART the IR was 7.6/1000PYO (95% CI: 5.3–10.7), 1.9/1000PYO (95% CI: 0.8– 4.2) in the second year and 0.43/1000PYO (95% CI: 0.2–1.1) after 5 years. In the adjusted analysis, the incidence of TB was not associated with rural/ urban health care setting (aHR =0.9, 95% CI: 0.4 – 1.7) (table 1). As compared to patients with prevalent TB, patients not diagnosed with TB at the start of cART were 90% more likely to be diagnosed with TB during follow up on cART (aHR = 1.9, 95% CI: 1.1 – 2.7).

Conclusion: Incidence of TB is substantially high in both rural and urban HIV care settings especially during the first year of cART. HIV treatment programs must develop effective TB screening mechanisms and robust use of isoniazid prophylaxis when TB has been ruled out.

Table: Risk factors for incidence of TB among HIV+ individuals on cART in Zambia: Crude Hazard Ratio, adjusted Hazard Ratio.

Variable	Category	# of new cases	PYO	Crude HR (95% CI)	Crude HR (95% CI)
Urban/rural setting	Rural	14	21209	1.0	1.0
	urban	30	5313	1.1 (0.5-2.0	0.9 (0.4-1.7)
Treatment of TB at cART initiation	Yes	37	13905	1.0	1.0
	No	7	7304	3.2 (1.4-7.1)	1.9 (1.1-2.7) *
Cotrimoxazole prophylaxis	No	4	20107	1.0	1.0
	Yes	40	1102	0.5 (0.1-1.4)	0.6 (0.2-1.7)
Disclosure	No	12	2256	1.0	
	Yes	32	15890	0.9 (0.4-1.8)	
Sex	Female	27	13045	1.0	
	Male	17	1102	1.1(0.4-2.7)	
WHO staging of HIV at cART initiation	stage 1	2	1026	1.0	
	stage 2	3	3312	3.1(0.5-18.5)	
	stage 3	38	1683	7.0 (1.6-28.9)	
	stage 4	1	41	2.7(0.2-30.2)	
Body Mass Index	under weight	17	8316	1.0	
	normal weight	24	7527	0.7(0.3-1.3)	
	obese	1	2719	1.5 (0.1-11.3)	
CD4 count at start of cART	0 - 200	30	14222	1.0	
	>200 cells/mm³	14	6987	0.8 (0.4-1.6)	
TB symptom screening at cART initiation	No	34	16151	1.0	
	Yes	10	5058	0.9 (0.4-1.9)	
Presence of 1 or more symptoms suggestive of TB	Yes	23	1316	1.0	
	No	21	8046	1.3 (0.7-2.3)	

* Statistically significant

732 COMMUNITY ART REFILL GROUPS AND TUBERCULOSIS RATES IN ZIMBABWE

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Background: Community ART Refill Groups (CARGs) are an antiretroviral (ART) differentiated service delivery model in which stable clients on ART form into groups, with a single individual collecting ART for all group members. In focus group discussions, healthcare workers suggested that CARGs may reduce rates of diagnosed tuberculosis (TB) either due to reduced frequency of TB screening by healthcare workers or through reduced transmission with clients no longer gathering at the clinic. We evaluated if facilities with a larger proportion of clients in CARGs had fewer ART clients initiating TB treatment.

Methods: This analysis used data from two six-month time periods: October 2016 to March 2017 and October 2017 to March 2018. The exposure of interest was the proportion of ART clients at each facility who were in CARGs. The outcome was the number of ART clients who started TB treatment in the six-month period, and the number of ART clients at each facility was used as an offset to estimate rates. To evaluate the association, we used a mixed-effects generalized linear model with random effects for each facility, a negative binomial family, log link, and robust standard errors.

Results: 181 facilities were included in the analysis. In the earlier 6-month period 2.0% (3,401/170,114) of ART clients were in CARGs compared to 14.6% (28,595/195,443) in the later 6-month period, and 0.6% (2,016/365,557) of ART clients started TB treatment per 6-month period. We found that within any given site, the rate at which ART clients initiated TB treatment when the site had 10-30% of ART clients in CARGs was 0.85-times (95% CI, 0.62-1.15) the rate compared to having <10% of clients in CARG. When any given site had more than 30% of its ART clients in CARGs, it had 0.54-times (95% CI, 0.36-0.79) the rate compared to having <10% of clients in CARGs. This multivariable model adjusted for facility type, facility size, and time period.

Conclusion: Sites with a larger proportion of ART clients in CARGs experienced a lower rate of ART clients starting TB treatment. This may reflect a decline in active TB cases among CARG members due to improved ART adherence and/ or reduced TB exposure at clinic waiting areas. However, it is also possible that reduced frequency of clinic visits among CARG members is resulting in undiagnosed TB cases. Community-level TB screening among CARG members may be one solution to address this possibility.

733 INCIDENCE OF TUBERCULOSIS IN THE BOTSWANA NATIONAL ARV PROGRAMME

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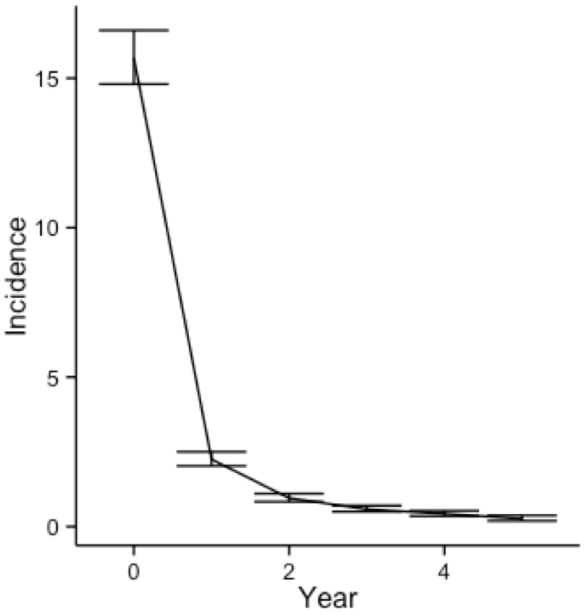
Background: We previously reported a high incidence of TB in a small cohort of HIV-infected patients initiating antiretroviral therapy (ART) and sought to examine whether TB incidence remains high among a national sample of HIV-infected patients receiving ART in Botswana

Methods: We analyzed a dataset of 66,382 adult patients (≥18years) who initiated ART between 2011 and 2016. We estimated the incidence and risk factors for TB using Kaplan-Meier survival curves and Cox regression analysis adjusting for gender, age and baseline CD4+ T-cell counts

Results: We excluded records from 8098 patients with missing ART initiation dates. Of 58,284 patients, 65% were women with a median age of 37 years (IQR 31-45) and baseline CD4+ T-cell count of 272cells/µl (IQR 146-403). Two thousand and eleven patients developed TB over a median of 1.9 years (IQR 0.6-3.5) of follow-up (IR 2.02 per 100py; 95% CI 1.94-2.11). The risk of TB was greatest in the first 6months of ART (IR 31.36/100py; 95%CI 29.43-33.42) and decreased to 3.08/100py and 0.90/100py by 18 and 36 months post ART initiation respectively. When we excluded cases occurring within 6 months, the overall incidence rate decreased to 1.09/100py (95% CI 1.03-1.17). The risk of TB was high in men, adjusted hazard ratio 2.78 (95% CI 1.84-4.18), and low in those with high baseline hemoglobin levels [aHR 0.83 (95% CI 0.78-0.90)] and formal employment [aHR 0.97 (95% CI 0.67-1.40)].

Conclusion: TB incidence is highest in the first 6 months of ART suggesting a need for active TB case finding and a possible utility for the use of preventative therapy during this time period.



734 HIGH RATES OF TB IN THE FIRST 6 MONTHS OF DOLUTEGRAVIR-BASED ART IN BOTSWANA

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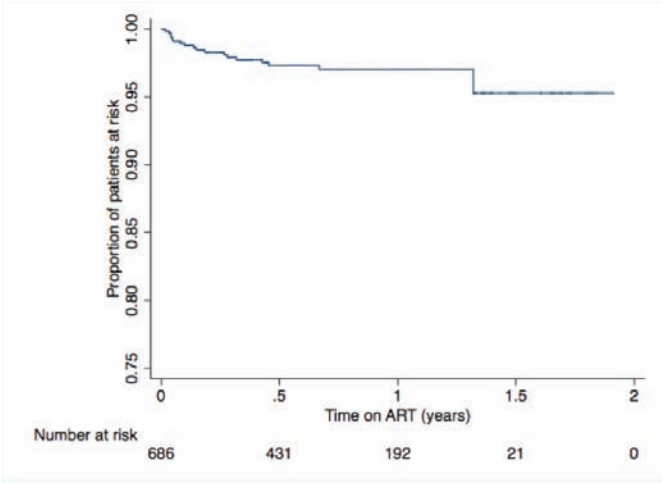
Background: Tuberculosis (TB) remains a major problem among HIV-infected persons in sub-Saharan Africa with most cases of unmasking TB occurring within the first few months of antiretroviral therapy (ART) initiation. As one of the first countries in sub-Saharan Africa to roll out dolutegravir (DTG)-based ART as first line therapy, we sought to determine the incidence of TB in patients initiating DTG-based ART between March 2016 and June 2018 in Gaborone, Botswana.

Methods: The Botswana Epidemiological ART Treatment (BEAT) Cohort is an operational research cohort study that was established in 2017 to determine DTG-vs-Efavirenz (EFV) based ART treatment efficacy, monitor drug resistance and the implementation of the Treat All Strategy. Trained research assistants abstracted data from electronic and manual patient records of those initiating ART at five clinics in Gaborone.

Results: We analyzed data from 737 patients with a median time on ART of 7 months (interquartile range [IQR]; 3, 12), mostly female (60%). Among those with baseline CD4+ T-cell count data (n=219, (30%)), the median count was 387cells/µl (IQR; 219, 577). At ART initiation, 1% (n=10) of the patients had an active TB diagnosis. By 3 months on ART, 97% (n=265/273) of the patients had undetectable viral loads. 686 patients contributed 481 person-years of follow-up for an incident rate of 3.75/100py (95% CI: 2.36-5.94). Most (89%) of the TB cases occurred within the first 6 months of initiation (IR= 26.42/100py, 95%CI 16.18-43.12) with only one case occurring post one year of ART (Figure 1). Neither older age (HR 1.03, 95%CI: 0.95-1.11) nor male gender (HR 0.47, 95% CI: 0.08-2.62) predicted TB incidence.

Conclusion: We found high rates of TB within the first six months of initiating DTG-based ART, which suggests that most TB cases are due to missed diagnosis or unmasking of subclinical TB. Improved screening strategies for TB prior to ART initiation are needed to reduce the burden of TB in ART programmes.



735 KIDNEY DISEASE IN AFRICANS WITH HIV AND TUBERCULOSIS

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Background: Tuberculosis (TB) is common in Africans with HIV. TB, HIV and the drugs to treat these infections may all have acute or chronic effects on the kidney although this has not been well studied. We investigated kidney function and kidney pathology in Africans with HIV/TB in three cohorts.

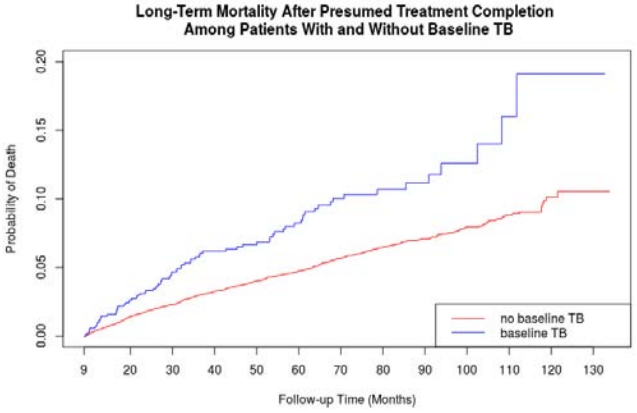
Methods: We studied kidney function over 12 months from TB diagnosis in consecutive HIV/TB patients in South London (UK, 2004-2016), and kidney pathology in consecutive HIV/TB autopsies performed in Abidjan (Cote d'Ivoire, 1991) and in consecutive HIV/TB kidney biopsies performed in Cape Town (South Africa, 2014-2017). Acute kidney injury (AKI) was defined by KDIGO stages 2/3, chronic kidney disease (CKD) by estimated glomerular filtration rate (eGFR) <60 (mL/min/1.73m2) for >3 months and severe CKD by eGFR <30. The amount of chronic damage in kidney biopsies was assessed as mild (<25%), moderate (25-50%) or severe (>50%). In the Cape Town cohort, predictors of recovery of kidney function at six months were assessed using Cox regression.

Results: In the London cohort (median [IQR] eGFR at TB diagnosis: 118 [88-129]), the incidence of moderate/severe AKI was 15.1 (95%CI 8.6-26.5) per 100 person-years, and the prevalence of CKD and severe CKD 13.7% and 7.4% respectively. Pathologically-confirmed HIV-associated nephropathy (HIVAN) was diagnosed in 6.3% of patients in London and 6.0% of autopsies in Abidjan. Renal tuberculosis was present in 60% of autopsies in Abidjan. Patients in the Cape Town cohort had severe kidney failure (median eGFR: 9), with often multiple renal pathologies on biopsy: 59% had renal TB, 43% HIVAN and 64% acute tubular necrosis (ATN). The majority of biopsies showed mild (61%) or moderate (23%) chronic damage, and substantial recovery of kidney function was noted at six months with 36%, 53% and 35% of those with HIVAN, ATN and renal TB having eGFR >60 and a further 28%, 19% and 21% having eGFR 30-59. ART status, CD4 count, eGFR at biopsy and renal pathology were not predictive of eGFR recovery (>60 or >30).

Conclusion: Acute and chronic kidney disease was common in Africans with HIV/TB. HIVAN, ATN and renal TB were common aetiologies, and improvement of kidney function was frequently observed irrespective of the severity of renal impairment or kidney disease aetiology. Close monitoring of kidney function and provision of renal replacement therapy to those with severe kidney failure is warranted in African patients with HIV/TB.

Table: Clinical characteristics

	London cohort (n=95)	Abidjan cohort (n=100)	Cape Town cohort (n=58)
Age, mean (SD)	37.8 (10.4)	36.4 (10.2)	38.4 (9.8)
Female, n (%)	49 (52)	23 (23)	26 (45)
Black African, n (%)	95 (100)	100 (100)	58 (100)
CD4 count, median (IQR)	90 (26-199)	Not available	70 (28-201)
Log HIV RNA, median (IQR)	5.1 (4.0-5.7)	Not available	2.8 (1.5-4.6)
eGFR, median (IQR)	118 (88-129)	Not available	9 (5-18)
Kidney pathology (n, %)			
-HIVAN	6/7	6 (6)	25 (43)
-Interstitial nephritis	2/7	31 (31)	8 (14)
-TB (granulomas/AFB)	0/7	60 (60)	34 (59)
-Acute tubular necrosis	0/7	5 (5)	37 (64)



736 MORTALITY AFTER PRESUMED TB TREATMENT COMPLETION IN PERSONS WITH HIV IN LATIN AMERICA

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Background: Several studies in HIV-negative cohorts have suggested that the risk of mortality is increased after tuberculosis (TB) cure, compared to individuals without TB. Data are limited on long-term survival after TB cure among people living with HIV (PLWH).

Methods: The study cohort included PLWH who were ≥18 years of age and who were ART-naïve at first clinic visit at a CCASAnet clinical site in Brazil, Chile, Haiti, Honduras, Mexico, or Peru from 2006 to 2015. Baseline TB was defined as TB diagnosed within 30 days before or after enrollment. Follow-up started at 9 months after enrollment or date of TB diagnosis, as a proxy for TB treatment completion in those with baseline TB. We compared time to death among patients with and without baseline TB, using Kaplan-Meier analysis and the log-rank test. We estimated predictors of mortality with univariable and multivariable Cox models, stratified by site and adjusting for baseline TB, sex, mode of transmission, education, age, year of enrollment, and CD4 count.

Results: Of 19,197 patients, 1306 (6.8%) were diagnosed with TB at baseline. Of these, 15,999 patients remained in care 9 months after enrollment and were included in the analysis; 1051 (6.6%) had baseline TB. Patients with TB were more likely to be male, older, less educated, with lower CD4 counts, and residing in Haiti or Peru. Starting 9 months after enrollment (Figure 1), patients with a history of baseline TB had higher long-term mortality compared with those without baseline TB (p-value <0.001). The unadjusted 5-year mortality (measured from 9 months after enrollment) was 10.0% for patients with baseline TB vs. 5.6% in those without baseline TB; 10-year mortality was 19.1% vs. 10.5%, respectively. In multivariable Cox models, increased mortality was associated with baseline TB (hazard ratio [HR]=1.53, 95% confidence interval [CI]: 1.21-1.93), lower CD4 count (100 vs. 350 cells/mm3: HR=1.59, 95% CI: 1.45-1.76; 500 vs. 350 cells/mm3: HR=0.89, 95% CI: 0.81-0.99), older age (age 55 vs. 35: HR=1.52, 95% CI: 1.29-1.79), and lower education (none vs. at least secondary: HR=1.21, 95% CI: 0.90-1.64).

Conclusion: PLWH who present with baseline TB have an elevated risk of long-term mortality, even after TB treatment completion. Further study is necessary to understand the long-term clinical impact of TB disease in PLWH.

737LB WITHDRAWN / INTENTIONALLY UNASSIGNED

738 RIFAMPIN-RESISTANT TUBERCULOSIS IN THE UNITED STATES, 1998–2014

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Background: Rifampin is the backbone of the standard regimen for tuberculosis. Monoresistance to rifamycins necessitates longer and more toxic regimens and is a precursor to multidrug resistance. We examined characteristics and mortality associated with rifampin-monoresistant TB (RMR) in the United States.

Methods: We analyzed Mycobacterium tuberculosis culture-positive cases reported to the National TB Surveillance System (excluding California because HIV infection of TB cases was not reported to CDC during 2005-2010) between 1998 and 2014. We defined: (1) RMR-TB found on initial drug susceptibility testing, and (2) possible acquired rifampin-resistantTB (ARR). We assessed temporal trends in RMR-TB. We calculated adjusted risk ratios (adjRR) and 95% confidence intervals (CI) for social and clinical characteristics associated with RMR-TB, mortality with RMR-TB, ARR-TB, and mortality with ARR-TB compared to drug susceptible TB (DS) in multivariable models. Time to sputum culture conversion was assessed using medians and interquartile ranges (IQR).

Results: Of 180,329 TB cases, 136,561 (76%) were eligible for analysis, with 359 (0.26%) of eligible cases reported as RMR. Similar to the decline in HIV/TB over the period, the percentage of RMR cases with HIV declined significantly over time. Persons with HIV and prior TB were more likely to have RMR (adjRR=8.8, CI=5.2-14.8) as were persons with HIV and no prior TB (adjRR=3.1, CI=2.4-4.1), versus those without either characteristic, controlling for age ≥ 65 (adjRR=0.4, CI=0.3-0.6) and black race (adjRR=0.7, CI=0.5-0.9). RMR cases had significantly greater mortality (adjRR=1.4, CI=1.04-1.8), controlling for HIV (adjRR=2.9, CI=2.7-3.0), directly observed therapy (DOT; adjRR=0.79, CI=0.76-0.82), and other variables. Persons with HIV also had greater risk of ARR than persons without HIV (adjRR=9.6, CI=6.9-13.3). ARR was also associated with increased mortality (adjRR=2.4, CI=1.8-3.4), controlling for DOT (adjRR=0.5, CI=0.4-0.6) and other variables. There was a significant (P<0.01) delay in sputum culture conversion for RMR cases (median 60 days, IQR 38-95 days) compared with median time for DS cases (49 days, IQR 26-77 days), and for ARR cases (median 190 days, IQR 75-362 days) compared with that of rifampin- and isoniazid-susceptible cases (median 76, IQR 53-110 days).

Conclusion: All forms of rifampin resistance were positively associated with HIV co-morbidity, delayed culture conversion, and increased mortality (controlling for HIV, and age, and DOT).

739 GLOBAL DISPARITIES IN PRICES OF KEY MEDICINES FOR MULTIDRUG-RESISTANT TUBERCULOSIS

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Background: Worldwide, 245,000 people with HIV died from TB coinfection in 2016, with 30,000 of those deaths due to drug-resistant TB. Multidrug-resistant (MDR) TB is increasing in prevalence, but only 54% of notified MDR-TB cases are

treated and cured, and <25% of those who could benefit from newer MDR-TB treatments receive them.

Methods: We compared prices for 7 medicines prioritized in current WHO guidelines: bedaquiline, delamanid, linezolid, moxifloxacin, levofloxacin, cycloserine, and amikacin. Price data were gathered from national price sources for 41 countries in North America, Europe, the Middle East, South East Asia, India, and South Africa, and converted to the price for a monthly of treatment at standard doses. For all medicines except amikacin, only solid oral forms were used.

Results: Monthly prices of MDR-TB medicines are displayed in the Table, for selected countries. As context, we include estimates of generic prices calculated in a previous analysis, based on analysis of the wholesale prices of the active pharmaceutical ingredients and other costs of production. For moxifloxacin, levofloxacin, linezolid, and amikacin, price data were available for more than 30 of the 47 countries. Data were limited for the other medicines, with prices of bedaquiline available only for 15 countries, cycloserine 9, and delamanid 4. Prices for a month of treatment ranged $94-5,273 for bedaquiline, $3,070–6,614 for delamanid, $7–4,856 for linezolid, $4–3,526 for amikacin, $48–2,501 for cycloserine, $1–674 for levofloxacin, and $4–206 for moxifloxacin. These were in most cases significantly higher than previously estimated generic prices (e.g. $8-17/month for bedaquiline, $5-16/month for delamanid).

Conclusion: Prices of key MDR-TB medicines remain very high in many countries. The low availability of pricing data for bedaquiline, delamanid, and cycloserine may reflect unavailability in many countries. Global price differences are large for MDR-TB medicines, both for patented medicines (bedaquiline and delamanid, with linezolid recently off-patent) and to a lesser extent generics (all others). Attention is drawn to the high prices charged in ex-Soviet bloc countries that, despite now being classed as high-income countries or upper-middle-income in the case of Bulgaria, have relatively underresourced health systems and high burdens of MDR-TB (e.g. Bulgaria, Latvia, Lithuania, Slovenia).

Country	bedaquiline	amikacin	levofloxacin	linezolid	moxifloxacin
US	$4,097	$340	$22	$191	$70
Canada (Quebec)		$3,526	$31	$1,693	$35
UK	$3,252	$785	$33	$624	$55
Bulgaria	$1,790	$139	$17	$1,637	$34
Turkey	$2,006	$64	$19	$490	$28
Russia	$201	$22	$25	$1,409	$34
South Africa	$94	$35	$6	$150	$12
India		$9	$1	$7	$4
Cost-based estimated price	$8–17	$8–54	$7–17	$4–9	$4–8

740 DEVELOPMENT AND VALIDATION OF A PREDICTIVE MODEL FOR AMINOGLYCOSIDE OTOTOXICITY

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Background: Individuals treated for drug-resistant tuberculosis (DR-TB) with aminoglycosides (AGs) in resource-limited settings often experience permanent hearing loss, but there is no practical and cost-effective means to identify those at higher risk. We sought to develop a prediction model of AG-induced hearing loss among patients initiating DR-TB treatment in South Africa.

Methods: We nested this analysis within a cluster randomized trial of nurse-led case management in 10 South African TB hospitals. All participants ≥13 years old received kanamycin or amikacin. We performed clinical and audiometric evaluations at treatment initiation. Hearing loss was defined as a poorer hearing threshold compared to baseline. We developed the model using data from 265 patients at hearing frequencies from 250Hz to 8kHz and validated the model using data from 114 separate patients at both 250Hz-8kHz and ultrahigh frequencies (9-16kHz). We estimated standardized weekly AG exposure as: {prescribed daily AG dose (mg) x frequency of dosing per week} ÷ weight (kg). Cox proportional hazard and logistic regression were used for multivariable adjustment.

Results: Of 936 participants, 54% were male; mean age was 36 years; and 75% were HIV coinfected at baseline. Comparing patients with high (≥75 mg/kg/week) versus low (<75 mg/kg/week) AG exposure, the adjusted hazard (aHR) of regimen cessation due to ototoxicity was 1.33 (p=0.006), and for audiometric hearing loss was 1.34 (p=.038). Baseline hearing loss (aHR=1.71, p<.001) and age (aHR=1.02, p=.031) were also associated with increased hazard of hearing loss. Predictors of ototoxicity in the final prediction model included: standardized weekly AG exposure, HIV status, CD4 count, age, serum albumin, BMI, and baseline hearing loss. This model demonstrated moderate discrimination (AUC=0.72) and good calibration (χ2[8]=6.10, p=.64) at normal frequencies and better discrimination (AUC=0.81) at ultrahigh frequencies that might represent early manifestations of AG ototoxicity. Discrimination for AG regimen cessation due to ototoxicity (among 671 patients without baseline audiometric data) was weaker (AUC=0.60). Using a cutoff of 85% predicted probability of hearing loss, the positive predictive value was 100%, and the negative predictive value was 41%.

Conclusion: This model identifies patients at high risk for AG-induced hearing loss and may inform clinical guidelines regarding which patients to prioritize for injectable-free regimens.

Table. Multivariate Logistic Regression Model Predicting AG-induced Hearing Loss

Predictors	Adjusted OR (95% CI)	P Value
Age (years)	1.04 (1.01-1.08)	.014
BMI (kg/m^2)		
< 18.5	1 [Reference]	
18.5-24.9	0.38 (0.18-0.82)	.014
≥ 25	0.28 (0.09-0.87)	.028
Standardized weekly AG exposure (mg/kg/week)		
< 60	1 [Reference]	
60-74.9	0.66 (0.26-1.69)	.386
≥ 75	1.31 (0.52-3.33)	.569
HIV status & CD4 count (cells/mm^3)		
HIV negative	1 [Reference]	
HIV positive with CD4 ≥ 200	1.69 (0.68-4.22)	.261
HIV positive with CD4 < 200	2.02 (0.82-5.01)	.127
Serum Albumin (g/L)	1.02 (0.97-1.08)	.486
Baseline hearing loss	1.17 (0.55-2.46)	.685

Full model

Log odds of hearing loss = 0.045 (age) – 0.96 (BMI: 18.5-24.9) – 1.27 (BMI: ≥ 25) – 0.41 (weekly AG exposure: 60-74.9) + 0.27 (weekly AG exposure: ≥ 75) + 0.53 (HIV+ with CD4 ≥ 200) + 0.71 (HIV+ with CD4 < 200) + 0.02 (serum albumin) + 0.15 (baseline hearing loss) – 1.61

Abbreviations: AG= aminoglycoside; BMI= body mass index; CD4= cluster of differentiation 4; CI= confidence interval; HIV= human immunodeficiency virus; OR= odds ratio

741 RIFAMPICIN RESISTANCE ACCURATELY IDENTIFIED BY CLUSTERING ULTRA MELTING TEMPERATURES

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Background: South Africa (SA) has performed >1.2 million GeneXpert(Gx) MTB/RIF Ultra(Ultra) tests since October 2017 in the national tuberculosis(TB) program. All Ultra test results are stored in a central data warehouse and all operational data is accessible through C360(supplier dashboard) installed on each Gx. Ultra applies melting curve analysis (Tm) to differentiate wild type from rifampicin resistance (RR) mutations with 97% unambiguity on well characterised strains. This analysis describes that only using the Tm can accurately identify the RR conferring mutation obtained from Ultra test results.

Methods: Ultra test results with rpoB Tm's were extracted between October2017 to April2018 and k-means was used to cluster Tm's into different RR mutation groups. Random forest(RF) imputation was applied to the wild type and RR Tm's to assign probable Tm's to incomplete values (1 to 3 rpoB probe values missing) thus optimizing clustering performance. K-means was applied to RR Tm's and then to resulting clusters, labelled according to known Tm profiles and visualised with t-distributed stochastic neighbour embedding(t-

SNE). Algorithm performance was determined using root mean square error (RMSE), where a minimum Tm shift to identify a mutation is 2.3°C.
Results: A total 52431 tests were extracted, 5354 positive(10.2%), 18(0.3% hetero resistant and excluded from analysis), 339 (6.3%) RR and 37(0.7%) were RR indeterminate. 121 RR results had incomplete Tm values. The attached figure shows clustering of RR Tm's: mutations(n=280); potential wild types (n=5 to 24 owing to skewing by RF) and unknown (n=35). Average RMSE was 0.3 °C for known Tm profiles.
Conclusion: Ultra and Xpert are clinically used as a qualitative diagnostic for TB and screen for RR. Ultra generates additional information over Xpert through Tm's which can definitively identify RR conferring mutations and thus provide valuable information for individual patient care and population based surveillance. The algorithm tested here shows good accuracy (<="" div="">

742 THE COST AND IMPACT OF MDR-TB TREATMENT GUIDELINE CHANGES IN SOUTH AFRICA

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Background: The current standard regimen for treating multi-drug and rifampicin-resistant tuberculosis (MDR/RR-TB) in South Africa is 24 months, requires daily injectable aminoglycoside (IA) treatment during the first 6 months, has significant side-effects, and poor treatment outcomes. Recent evidence supports the use of a shortened regimen (9-12 months), as well as the replacement of the IA with the well tolerated, higher-cost, oral bedaquiline (BDQ). To determine affordability of a switch in the MDR/RR-TB regimen for the South African Government, we compared the budgetary impact of the use of BDQ in the current MDR/RR-TB regimen or in the shortened regimen.
Methods: We developed a Markov model to analyze the impact of changes in the treatment regimens on patient outcomes and total costs over a five-year time horizon (2019-2023). The model utilized the South African RR-TB case register (EDRweb) from 2013-2015 to define treatment outcomes. The standard regimen scenario allows for switching (14% in the first month) to BDQ when toxicity to the IA occurs, as per current practice. Costs were estimated from the provider perspective using costs incurred by 137 MDR-TB patients at Helen Joseph Hospital in Johannesburg and included laboratory tests, staff, consumables, equipment, overhead, and 2018 drug prices. Improvement in mortality and successful outcomes were assumed for those receiving BDQ. Results are reported as the cost of reaching a successful outcome (cured or completed treatment), calculated as total cost/successful outcomes and expected budget impact as a result of the introduction of the shortened/BDQ MDR-TB regimen in South Africa.
Results: By 2023, an annual estimated 5791, 6489, and 6670 patients will be successfully treated under the standard, standard/BDQ, and shortened/BDQ regimens, respectively. The cost/successful outcome for the standard regimen will be $8327 (annual $48million nationally). Introducing BDQ to standard-length treatment results in a similar cost per successful treatment ($8372), but higher total annual costs due to BDQ price ($54million/year). This increase in total cost can be offset by a simultaneous switch to a BDQ containing shortened regimen, $5232/treatment success, and impose an annual cost of $35million (28% savings compared to standard length therapy).
Conclusion: Despite the increased cost of BDQ, the move from a 24-month to a 9-12 month regimen is predicted to result in a net decrease in cost along with improved outcomes for MDR/RR-TB patients in South Africa.

Table 1. The total cost, number of successful treatments and cost per successful treatment of standard and shortened MDR-TB treatment with and without the use of bedaquiline in 2023

	Successful treatments	Cost per successful treatment (USD)
*Standard regimen (Baseline)	5,791	8,327
†Standard regimen + BDQ	6,489	8,372
% change over baseline		*1%*
‡Shortened regimen + BDQ	6,670	5,232
% change over baseline		*-37%*
Annual costs (USD millions)		
Standard regimen (Baseline)		48.22
Standard regimen + BDQ		54.32
% change over baseline		*13%*
Shortened regimen + BDQ		34.90
% change over baseline		*-28%*

*Standard regimen = 24-month regimen with 6 months injectable aminoglycoside
† Standard regimen + BDQ = 24-month regimen with BDQ as a substitute for injectable aminoglycoside
‡ Shortened regimen + BDQ = 9-12 month regimen with BDQ as a substitute for injectable aminoglycoside

743 NEURAL TUBE DEFECTS, HIV, AND ANTIRETROVIRALS: BIRTH-DEFECT SURVEILLANCE IN UGANDA

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Background: Neural tube defects (NTDs) are one of the most common congenital malformations affecting births worldwide. The estimated NTD prevalence in Africa is 12 per 10,000 live births [95% confidence interval (CI) 5-75]; but data are limited. The impact of antiretroviral therapy (ART) during pregnancy on the risk for birth defects is unknown; therefore, ongoing surveillance is needed for pharmacovigilance.
Methods: A hospital-based surveillance program was established at four hospitals in Kampala, Uganda to provide estimates of the baseline prevalence of selected birth defects and assess potential associations with HIV status and ART use. All live births and stillbirths, regardless of gestational age, were included. Data were collected from hospital records, maternal interviews, photographs, and narrative descriptions of birth defects (BD). Births were examined by trained midwives and confirmed by a BD specialist. Prevalence (Wilson 95% CI) and adjusted odds ratio (AOR) estimates for potential risk factors of NTDs using logistic regression with site as an effect modifier are reported for births from August 2015-December 2017.
Results: A total of 69,767 births were included in surveillance. Median maternal age was 26 years (IQR=22-30), 51.3% had their first antenatal visit after the first trimester, 9.6% (6,725/69,767) were HIV-infected with 95.2% (6,399/6,725) on ART. The majority of HIV-infected women were on an efavirenz-based ART (80%), 16% on nevirapine-based ART and 4% received other ART regimens. Overall, 62 births were affected with NTDs, giving a prevalence of 8.9 (6.8-11.4) per 10,000 live births. Spina bifida (n=34) was the most common type of NTD with prevalence (95%CI) of 4.9 (3.4-6.8) per 10,000 live births, followed by anencephaly (n=16) with 2.3 (1.3-3.7) and encephalocele (n=12) with 1.7 (0.9-3.0). There was no significant difference in NTD prevalence (95%CI) among HIV-infected [5.9 (0.1-11.8)] and HIV un-infected women [9.2 (6.8-11.6)]; AOR 0.75 (95% CI:0.2-2.2), p= 0.61. NTDs were not significantly associated with maternal age, HIV status, ART, or parity. Anencephaly was more common among females

compared to males with site as an effect modifier [AOR of 5.9 (95%CI:1.9-17.9), p=0.002].
Conclusion: NTDs are a common congenital malformation affecting births in Kampala. These findings are similar to the current estimates for Africa. ART was not associated with an increased risk for NTDs. With the introduction of new ART regimens during pregnancy, ongoing BD surveillance is critical.

744 NO INCREASE IN BIRTH DEFECTS IN INFANTS EXPOSED TO INTEGRASE INHIBITORS AT CONCEPTION

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Background: Integrase inhibitors (InSTI) are increasingly used by HIV-infected women during pregnancy. Following an alert on the association of dolutegravir with neural tube defects, we evaluated the risk of birth defects in case of exposure to this antiretroviral class.
Methods: The French Perinatal Cohort is a multicenter national cohort including all HIV-infected women in 90 maternities. We studied all mother-infant pairs exposed to InSTI, categorized into 3 groups: (G1) ongoing at conception, (G2) initiated during pregnancy, as first-line regimen, and (G3) initiated during pregnancy, as 2nd-line regimen. Within each group, we matched 1:1 to an InSTI-unexposed infant according to other drugs, ethnicity, center, year of delivery, and gestational age at ART-initiation. InSTI exposed women who did not receive PI or NNRTI were matched to women receiving darunavir, with the same other drugs. We compared birth defect rates between the 3 InSTI-exposed groups and, for each group, with the respective matched group, using chi2 and McNemar tests.
Results: Overall, 309 infants were exposed to InSTI at conception (G1): 224 to raltegravir, 41 to dolutegravir, and 44 to elvitegravir. Birth defects rates for InSTI-exposed infants at conception (G1: 5.5% 17/309) did not significantly differ from those of InSTI-exposed infants of the two other groups: 2.7% (5/184) in G2 and 3.0% (10/329) in G3, p=0.18. There was no neural tube defect among infants exposed to InSTI at conception, and only two birth defects among the 41 infants exposed to dolutegravir (a case of Down syndrome, and a persistant ductus arteriosus). When restricting to matched infants, birth defect rates in G1 were not significantly different from the matched InSTI-unexposed group (6,3%, 12/189 vs 3,7%, 7/189, respectively, p=0.26). The EUROCAT types of birth defects were similar for InSTI-exposed at conception and matched infants. There was no difference in stillbirth rates (1.8% vs 0.4%, p=0.37), nor in preterm birth rates (14.3% vs 10.8%, p=0.29) between pregnancies exposed at conception and the matched pregnancies. Among women exposed at conception, 65% were still receiving InSTI at delivery. Similarly, there was no difference in birth defect rates between InSTI-exposed infants in G2 and G3 and the matched unexposed infants.
Conclusion: We found no evidence of a higher birth defect rate among 309 infants exposed to InSTI at conception, mostly exposed to raltegravir, however in the current context, surveillance must be pursued for this class of ART.

745 EVALUATION OF NEURAL TUBE DEFECTS AFTER EXPOSURE TO RALTEGRAVIR DURING PREGNANCY

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Background: The purpose of this comprehensive review is to evaluate the risk of neural tube defects (NTDs) after exposure to raltegravir during pregnancy.
Methods: Exposures to raltegravir during pregnancy reported cumulatively through 31-May-2018 to the company safety database were reviewed. This database includes all reports of pregnancy from Merck-sponsored clinical trials, spontaneous post-marketing and non-interventional data sources, including the Antiretroviral Pregnancy Registry (APR). Reports were classified as prospective (exposure report prior to knowledge of pregnancy outcome) or retrospective (report after knowledge of pregnancy outcome). Pregnancy reports were further reviewed to identify cases of NTDs. We also reviewed data from two ongoing pregnancy cohorts.
Results: A total of 2426 pregnancies with reported outcomes were identified among women exposed to raltegravir: 1238 from the Merck safety database and 1188 from United Kingdom/Ireland and French pregnancy cohorts. Among all 2426 pregnancy reports, 1991 were prospective. No cases of NTDs were identified among the prospective pregnancy reports, of which 767 were first trimester, including 456 in the periconception period (at or within 28 days after conception). Among the 435 retrospective reports, four NTD cases per APR criteria were identified, of which only one (myelomeningocele) was among exposures in the periconception period. Given the inherent limitations and bias of retrospective reports, it is not appropriate to calculate an incidence rate.
Conclusion: Prospectively collected pregnancy outcome data do not suggest an association between raltegravir exposure in the periconception period and NTDs.

746 REPORTS OF NEURALTUBE DEFECTS FOR 8 ARTS, IN FDA, WHO, EMA, AND UK SAFETY DATABASES

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Background: The Botswana TSEPAMO study reported neural tube birth defects (NTDs) in 4/596 (0.67%) infants of women receiving dolutegravir (DTG) antiretroviral therapy (ART) preconception vs 14/11,300 (0.12%) receiving preconception non-DTG ART. Further data are required to confirm or refute this potential safety signal. Pregnant women were excluded from Phase 3 randomised DTG trials and data from other observational studies of DTG in pregnancy are currently limited. Clinicians, patients and pharmaceutical companies can report adverse drug reactions (ADRs) to pharmacovigilance (PV) databases, which could be used to assess potential safety signals.
Methods: 4 PV databases with online data availability were analysed for NTD reports for 4 integrase inhibitors (DTG, raltegravir, elvitegravir, bictegravir), two protease inhibitors (darunavir, atazanavir) and two non-nucleosides (nevirapine, efavirenz): 1. Food and Drug Administration FAERS database (USA) 2. World Health Organisation VigiAccess (WHO) 3. European EudraVigilance (EU), 4. UK Medicines Health Regulatory Authority (MHRA). ADR reports in the System Organ Class (SOC) "Congenital or Familial Disorders" were searched for NTDs using the search terms Neural Tube Defect, spina bifida, meningocele, meningomyelocele, anencephaly, iniencephaly, and encephalocele
Results: NTDs were reported for all drugs except bictegravir. The number of reported NTD cases with DTG exposure were similar in the FDA and WHO databases, but no cases were reported to EU and UK MHRA (Table 1). Since ART consists of multiple drugs, NTDs could be reported for multiple drugs and from multiple sources for the same patient; for example, for one patient in the FDA database, there were 91 NTD reports for the same patient who received 7 different drugs
Conclusion: PV databases included reports of NTDs for pregnant women taking a wide range of ARVs. These databases have many limitations – there is no denominator for patient exposure to the drug, reporting is not systematic, there is overlap in reports for multiple drugs given combination ART, duplicate cases are difficult to identify, and results differ between the databases. Given widespread use of multiple new ARVs worldwide, and anticipated use of new drugs (e.g. TAF, bictegravir cabotegravir), prospective follow up of pregnant women and birth surveillance studies such as Tsepamo are critically needed for a wide range of ARVs. In addition, pregnant women should be enrolled in Phase 3 trials where regulations allow.

Table: Neural Tube Defect cases reported to regulatory authorities and WHO

Database	FDA	WHO	EU	UK MHRA
DTG	6	8	0	0
RAL	5	17	4	2
ELV	1	1	0	0
BIC	0	0	0	0
DRV/r	3	16	3	3
ATV/r	6	9	2	0
NVP	14	30	6	3
EFV	13	28	9	0

747 InSTI EXPOSURE AND NEURAL TUBE DEFECTS: DATA FROM ANTIRETROVIRAL PREGNANCY REGISTRY

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Background: Dolutegravir (DTG) is an integrase strand transfer inhibitor (InSTI) with once-daily dosing, good viral efficacy, high barrier to resistance, and good tolerability. Preliminary data from the NIH-supported Botswana birth defects surveillance project (Tsepamo study) reported a potential increased risk of neural tube defects (NTD) in infants born to HIV-positive women receiving DTG-based antiretroviral therapy (ART) prior to conception, compared to non-DTG ART or to uninfected women (0.9%, 0.1% , and 0.09%, respectively). Using data from the Antiretroviral Pregnancy Registry (APR), a voluntary, international, prospective exposure-registration cohort study with independent Advisory Committee oversight, we describe central nervous system (CNS) defects and NTD in infants born to women receiving InSTIs.
Methods: Data on prospectively enrolled pregnancies through 31Jan2018 with birth outcome are summarized. Birth defects are reviewed by a dysmorphologist, coded according to modified Metropolitan Atlanta Congenital Defects Program criteria, classified by organ system and assigned timing of exposure to each InSTI (DTG, elvitegravir [EVG], raltegravir [RAL]). Birth defects within the CNS organ system include both NTDs and encephalocele, which is reported separately from NTD.
Results: A total of 19,688 pregnancies resulted in 20,026 fetal outcomes including 18,685 live births. APR reports come from North America (75%), Europe (8%), Africa (7%), South America (6%) and Asia (4%). There were 1,021 live births with an InSTI exposure at any time during pregnancy, of which 507 had ongoing exposure at conception, including 121 DTG, 155 EVG, and 231 RAL live birth outcomes. There were no NTD or other CNS birth defects among prospective cases for any InSTI drug (Table).
Conclusion: No occurrences of CNS defects or NTDs were observed among 1,021 prospective live birth outcomes with InSTI exposure at any time. This frequency is consistent with the observed low prevalence of NTD in developed countries (~0.1%), as most APR reports (83%) come from North America and Europe where food is supplemented with folate, which reduces NTD prevalence. However, InSTIs are a newer class of ARVs and the number of pregnancies with InSTI exposure in the APR to date is insufficient to draw definitive conclusions about a potential association between DTG and NTD, or to look at specific geographic regions. Healthcare providers are encouraged to continue to report pregnancies with prospective antiretroviral exposures to the APR.

Table: Frequency of CNS and NTD defect cases by InSTI drug and timing of earliest exposure, APR, Jan 2018

	Live Births N=18,658	Central Nervous System[1,2]	Neural Tube[1]	Encephalocele[2]
Any InSTI Exposure				
Ongoing at Conception	507	0	0	0
First Trimester	111	0	0	0
Second/Third Trimester	403	0	0	0
Any Dolutegravir Exposure				
Ongoing at Conception	121	0	0	0
First Trimester	40	0	0	0
Second/Third Trimester	94	0	0	0
Any Elvitegravir Exposure				
Ongoing at Conception	155	0	0	0
First Trimester	25	0	0	0
Second/Third Trimester	52	0	0	0
Any Raltegravir Exposure				
Ongoing at Conception	231	0	0	0
First Trimester	60	0	0	0
Second/Third Trimester	278	0	0	0

[1]Neural tube cases are a subset of CNS defects and are counted in both columns

[2]Encephalocele cases are a subset of CNS defects and are counted in both columns

748 UGANDAN CLINIC EXPERIENCE FOLLOWING POTENTIAL TERATOGENICITY ALERT FOR DOLUTEGRAVIR

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Background: In 2017, the Infectious Disease Institute (IDI) introduced dolutegravir (DTG)-based regimens in its Kampala clinic in Uganda. In May 2018, the WHO and international regulators released warnings on a possible increased risk of neural tube defects in infants born to women taking DTG at the time of conception. In response, IDI implemented a process to inform and support women already on DTG to make informed treatment choices.
Methods: A clinic response plan was developed in the first week following the alert and clinic staff were trained on safety guidance. All women <55 years on DTG were identified from the clinic database and contacted by phone for earlier appointments. From May-June, group counselling sessions (<15 women/group) were held. Non-menopausal and non-surgically sterilized women were referred for urine pregnancy testing, evaluation of pregnancy intentions in next 12 months and effective family planning was offered (preferably condoms plus implants, IUDs, depo-provera or pills). Pregnancies were confirmed by ultrasound and obstetrician review. Women intending to conceive were offered efavirenz (EFV)-based regimens. Women that chose to remain on DTG without effective family planning signed a declaration of informed choice. We used modified Poisson regression to determine factors associated with switching off DTG.
Results: 9% (692/7963) were identified to be on DTG and 95% (658/692) were reviewed by September 2018. 22% (146/658) were menopausal or surgically sterilized. 510 women were of reproductive potential with median age (IQR); 37 (30 - 42) and mean duration (SD) on DTG of 4.26 months (1.63). 5% (23/510) were HCG positive and all initial ultrasound reports revealed no deformities. 21% (108/510) had intentions to conceive and opted to be switched off DTG with 90% (97/108) switched to EFV. 79% (402/510) opted to stay on DTG. However only, 40% (160/402) chose effective contraceptives methods and 60% (242/402) opted for condoms only/no contraceptive method. Factors associated with switching off DTG were younger age (Prevalence Ratio (PR) 0.96 [95% CI: 0.94, 0.99, p=0.002]) and not using effective contraception (PR 0.04 [95% CI: 0.01,0.15, p<0.001]).

Conclusion: A rapid well-coordinated response ensured prompt communication of the DTG safety warning. Women made informed decisions with most opting to stay on DTG however effective contraception uptake was low. While a patient-centered approach was feasible in this clinic, ongoing monitoring for DTG pregnancy exposures is needed.

749 SERUM FOLATE AND BIRTH OUTCOMES: DTG VS EFV TRIAL EVIDENCE IN SOUTH AFRICA

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Background: Dolutegravir (DTG) exposure was associated with a 5.4 fold higher risk of neural tube defects (NTDs) in the Botswana Tsepamo study. The mechanism underlying this potential association is unknown. Potentially, effects of DTG on folate metabolism, especially a lowering of levels, could account for these findings. We hypothesized that antiretroviral regimen could affect serum folate concentrations, and evaluated this in the ongoing South African ADVANCE trial (NCT03122262).
Methods: In ADVANCE, 1053 treatment-naïve patients were randomised to start treatment with DTG-tenofovir alafenamide fumarate-emtricitabine (DTG-TAF-FTC), dolutegravir-tenofovir-emtricitabine (DTG-TDF-FTC) or efavirenz-tenofovir-emtricitabine (EFV-TDF-FTC). Preconception serum folate concentrations were measured in a subcohort (n=486) of female participants at weeks 0, 12 and 24 after enrolment. We compared changes in mean serum folate concentrations and the occurrence of marginal serum folate deficiency (<14.0 nmol/L) between study groups. We also describe birth outcomes in women who became pregnant during the trial. These women were on ART at conception, had a gestational age assessment (ultrasound and date of last menstrual period) and congenital foetal anomaly screen.
Results: Mean serum folate concentrations were balanced across the treatment arms at baseline (Table 1). However, at weeks 12 and 24, mean serum folate was lower in women on EFV-TDF-FTC (p<0.001), and 30% of these women had marginal serum folate deficiency, compared to 13.7% in the DTG-TDF-FTC arm, and 5.4% in the DTG-TAF-FTC group (p<0.001) at week 24. No declines in serum folate concentrations in either DTG arms were noted. To date, 59 women have become pregnant; 19 in DTG-TAF-FTC; 20 on DTG-TDF-FTC; and 20 on EFV-TDF-FTC. Among pregnant women, those in the EFV-TDF-FTC arm had lower mean serum folate concentrations at week 12 (p<0.001) and differences were detected in marginal folate deficiency at week 24. There have been 16 live births; 1 infant death; 1 spontaneous abortion; 2 congenital anomalies (naevus flammeus and umbilical hernia), and 19 elective terminations, and 23 pregnancies are ongoing.
Conclusion: In this randomised study, first-line treatment with EFV-TDF-FTC was associated with decline in folate over 24 weeks and with significantly lower serum folate concentrations than in women treated with DTG-TDF-FTC or DTG-TAF-FTC. DTG does not appear to alter folate metabolism, but effects of EFV on folate raise important concerns.

Table 1: Serum folate concentrations (nmol/L) in women participating in the ADVANCE trial: measures in all women and those who had a pregnancy

Variable	DTG-TAF-FTC Total n=173 *	DTG-TDF-FTC Total n=159 *	EFV-TDF-FTC Total N=153*	P**
Age, mean (sd)	31.6 (7.7)	31.4 (7.1)	32.4 (6.6)	0.32
Folate week 0 (all women) mean (sd)	23.0 (8.7)	24.1 (9.1)	23.6 (7.7)	0.53
Folate week 12 (all women) mean (sd)	26.8 (8.5)	22.5 (9.0)	17.5 (7.6)	**<0.001**
Folate week 24 (all women) mean (sd)	28.3 (8.0)	23.9 (8.8)	18.9 (8.1)	**<0.001**
Folate week 0 (pregnant women) mean (sd)	25.1 (8.0)	27.9 (8.0)	23.3 (7.1)	0.23
Folate week 12 (pregnant women) mean (sd)	30.0 (7.6)	26.2 (9.5)	15.7 (6.1)	**<0.001**
Folate week 24 (pregnant women) mean (sd)	30.2 (8.6)	26.8 (7.8)	20.6 (9.5)	0.059
Marginal folate deficiency week 0 (all women) n (%)***	29 (17.3)	23 (14.8)	16 (10.8)	0.26
Marginal folate deficiency week 12 (all women) n (%)	9 (5.4)	32 (21.1)	57 (40.1)	**<0.001**
Marginal folate deficiency week 24 (all women) n (%)	8 (5.4)	19 (13.7)	41 (29.9)	**<0.001**
Marginal folate deficiency 0 (pregnant women) n (%)	0 (0)	1 (5.6)	2 (12.5)	0.31
Marginal folate deficiency week 12 (pregnant women) n (%)	1 (5.9)	2 (11.1)	5 (33.3)	0.08
Marginal folate deficiency week 24 (pregnant women) n (%)	1 (6.3)	0 (0)	5 (38.5)	**0.005**

*Number of pregnant women overall=59; 19 (32.2%) on DTG-TAF-FTC; 20 (33.9%) on DTG-TDF-FTC; 20 (33.9%) on EFV-TDF-FTC
**Significance determined P<0.05
***Marginal folate deficiency = <14nmol/L

750 FETAL BIOMETRY SIMILAR WITH DOLUTEGRAVIR OR EFAVIRENZ EXPOSURE

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Background: Pregnant women living with HIV (PWLHIV) are increasingly receiving dolutegravir (DTG) worldwide and in Botswana. Few studies have assessed fetal biometry in PWLHIV on DTG-based antiretroviral therapy (ART).
Methods: We evaluated fetal biometry via ultrasound in PWLHIV and HIV-uninfected (HIV-U) pregnant women enrolled in the Tshilo Dikotla cohort in Botswana. PWLHIV enrolled between 16-36 weeks gestational age (GA) and received tenofovir + emtricitabine and either DTG or efavirenz (EFV). Pregnancies with multiple gestations or ending in fetal demise were excluded. Head circumference (HCZ), biparietal diameter (BPDZ), abdominal circumference (ACZ), and femur length (FLZ) Z scores were calculated using Intergrowth-21st references. Linear regression models were fit to assess the association of in utero HIV/ART exposure with each fetal biometric Z score, and among PWLHIV, the association of DTG vs EFV exposure with fetal biometry.
Results: Of 435 pregnant women, 176 received DTG-based ART, 92 efavirenz (EFV)-based ART, and 167 were HIV-U. PWLHIV were older (28.9 vs 24.5 years, p=<0.01) higher in gravidity (3 vs 1, p<0.01), and less likely to have completed tertiary education (9.3% vs 31.1%, p<0.01) than HIV-U women. GA at ultrasound was higher in PWLHIV than HIV-U women (28 vs 26 weeks, p=0.01). Among PWLHIV, women on DTG were younger (28.2 vs 30.5 years, p=0.01) with shorter ART duration prior to ultrasound (15.3 vs 27.6 weeks, p<0.01) than those on EFV. In unadjusted analyses, median HCZ, BPDZ, ACZ, and FLZ did not differ between fetuses of PWLHIV vs HIV-U women (-0.30 vs -0.26, p=0.15; 0.09 vs 0.07, p=0.22; 0.00 vs 0.00, p=0.57 and 1.45 vs 1.24, p=0.22 respectively). This relationship persisted after adjusting for maternal age, height, education level, gravidity and alcohol use in pregnancy. There were no differences in fetal biometry between fetuses exposed to DTG vs EFV (HCZ: -0.39 vs -0.62, p=0.15, BPD: 0.14 vs 0.34, p=0.27, ACZ: 0.31 vs 0.34, p=0.15, FLZ: 1.42 vs 1.49, p=0.24). This relationship remained after adjusting for the same variables above as well as CD4 count. (Table)
Conclusion: In this small Botswana cohort, there does not appear to be a substantial association between in utero HIV/ARV exposure and fetal biometry or between in utero DTG vs EFV exposure and fetal biometry. While these results are reassuring and support continued use of these regimens in pregnancy, larger studies with serial ultrasounds are needed to validate these findings.

Table. Linear Regression Models for Fetal Biometric Measurement Outcomes Comparing Maternal HIV Infection vs Non-Infection and TDF/FTC/DTG vs TDF/FTC/EFV Exposures

	HCZ		BPDZ		ACZ		FLZ	
Exposure of Interest	Coefficient	p value	Coefficient	p value	Coefficient	p value	Coefficient	p value
Maternal HIV infection vs. non-infection *	-0.11	0.32	-1.68	0.15	-0.19	0.30	0.14	0.32
TDF/FTC/DTG vs TDF/FTC/EFV ^	0.14	0.29	0.21	0.22	-0.21	0.33	-0.13	0.42

ACZ = abdominal circumference z score, BPDZ = biparietal diameter z score, DTG = dolutegravir, EFV = efavirenz, FLZ = femur length z score, HCZ = head circumference z score, TDF = tenofovir, FTC = emtricitabine
**Model adjusted for maternal age, gravidity, education level, height, and alcohol use in pregnancy.*
^Model adjusted for maternal age, gravidity, education level, height, alcohol use in pregnancy, and CD4.

751 SIMILAR BIRTH ANTHROPOMETRICS WITH IN UTERO EXPOSURE TO DOLUTEGRAVIR OR EFAVIRENZ

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Background: Prior to a policy of lifetime antiretroviral treatment (ART) for all pregnant women living with HIV (WLHIV), some studies reported lower HIV-exposed uninfected (HEU) infant birth anthropometrics compared to HIV-unexposed uninfected (HUU) infants. We quantified birth anthropometrics by infant HIV exposure status in two Botswana prospective studies, where HEU infants were exposed to either dolutegravir (DTG)- or efavirenz (EFV)-based regimens.

Methods: WLHIV and HIV-uninfected (HIV-U) women enrolled in the Tshilo Dikotla study between 16-36 weeks gestation and the Infant Gut Microbiome study between 36 weeks gestation and 3 days post-delivery. All WLHIV received a backbone of tenofovir + emtricitabine, and either DTG or EFV. Birth anthropometrics for singleton infants were abstracted from hospital records. Intergrowth21 was used to derive birth weight-for-age (WAZ) and length-for-age (LAZ) z-scores, adjusting for delivery gestational age and sex. Mean birth WAZ and LAZ was compared between HEU and HUU infants using a Student's t-test. Among HEU infants, we also compared birth WAZ and LAZ by in utero exposure to either a DTG- vs EFV-based regimen.

Results: Data from 463 infants were analyzed, including 275 (59%) HEU infants, with 158 (57%) DTG-exposed and 117 (43%) EFV-exposed. ART exposure from conception occurred among 39 (25%) DTG-exposed and 89 (76%) EFV-exposed infants (p<0.001). WLHIV were older than HIV-uninfected women (29.7 vs 25.3 years; p<0.01). Gestational age at delivery did not differ between HEU and HUU infants (39.0 vs 39.6; p=0.15). Mean birth WAZ and LAZ did not differ by infant HIV exposure status [WAZ: HEU -0.13 (95% Confidence Interval (CI) -0.25, -0.01) vs HUU 0.00 (CI -0.16, +0.16); p=0.20]; [LAZ: HEU +1.07 (95% CI +0.87, +1.26) vs HUU +1.17 (+0.93, +1.41); p=0.51]. Among HEU infants, birth WAZ and LAZ did not differ by DTG vs EFV exposure [WAZ: DTG -0.09 (95% CI -0.26, +0.09) vs EFV -0.18 (95% CI -0.36, 0.00); p=0.45]; [LAZ: DTG +1.16 (95% CI +0.89, +1.43) vs EFV +0.95 (95% CI +0.66, +1.23); p=0.28].

Conclusion: We found no significant difference in birth WAZ or LAZ between HEU and HUU infants or between HEU infants exposed in utero to DTG-based versus EFV-based regimens. Our findings require validation in larger birth cohorts.

752 ADVERSE BIRTH OUTCOMES AMONG PRENATALLY VS SEXUALLY HIV-INFECTED WOMEN IN BOTSWANA

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Background: Adverse birth outcomes among perinatally HIV-infected women (PHIV) may be increased compared with sexually HIV-infected women, but comparisons are potentially subject to bias from use of older ART regimens or other factors. The purpose of this study was to compare birth outcomes among (PHIV) and sexually HIV-infected women in a large dataset from Botswana.

Methods: Data were compiled from an ongoing birth outcomes surveillance study at eight government delivery sites in Botswana from July 2014 to June 2018. Pregnant women diagnosed with HIV before their 11th birthday were classified as PHIV; all other women were categorized as sexually HIV-infected. Birth outcomes included small for gestational age (SGA) (<10th percentile weight for GA), preterm delivery (PTD) (<37 weeks GA), stillbirth (SB), and neonatal death (ND). Chi-square and Fisher's exact tests were conducted comparing birth outcomes among all PHIV women with sexually HIV-infected women within the same age range (15-27 years). Crude and adjusted risk ratios (RR) for maternal age, initial ART regimen prescribed or continued during pregnancy, gravida, education, and occupation were determined using log-binomial regressions.

Results: Of 22,761 HIV+ women who delivered during the study period, a total of 255 (1%) PHIV women were identified and were compared with 6,773 sexually HIV-infected women in the same age range. The median age of HIV diagnosis was 7 years for PHIV women and 21 years for sexually HIV-infected women. PHIV women were more likely to have a secondary or equivalent level of education (86% vs. 77%, p=0.03). PHIV were more likely to use nevirapine (NVP)-based ART (42% vs. 6%, p<0.0001). The prevalence of adverse birth outcomes for PHIV women was 25% SGA, 23% PTD, 2% SB, and 0.8% ND, compared with a prevalence for sexually HIV-infected women of 19% SGA, 21% PTD 3% SB, and 2% ND. Univariate models produced null findings except for SGA (RR=1.33 95% CI:1.07-1.65, p=0.009) and for any adverse outcome (RR=1.23 95% CI:1.08-1.41, p<0.01). Multivariate models produced null findings for all adverse birth outcomes. Use of NVP-based ART accounted for the strongest association with any adverse birth outcome in the multivariate model (Table 1).

Conclusion: After adjustment for use of NVP-based ART, a known risk for adverse birth outcomes, there was no difference in adverse birth outcomes between perinatal and sexual HIV transmission. Updating ART regimens may improve birth outcomes for all HIV-infected women.

Table 1. Crude and Adjusted Risk Ratios for All Adverse and Severe Adverse Outcomes

	[1]All Adverse Outcomes		[2]Severe Adverse Outcomes	
	RR (95% CI)	aRR(95% CI)	RR(95% CI)	aRR(95% CI)
PHIV (n=255)	**1.23(1.08, 1.41)**	1.13(0.97, 1.32)	1.01(0.74, 1.40)	0.81(0.57, 1.15)
Age		1.00(0.99, 1.02)		1.03(0.99,1.06)
[3]Initial ART Regimen				
NVP-Based ART		**1.33(1.19, 1.49)**		**1.95(1.63, 2.39)**
Other		Reference		Reference
Gravida				
≥3		0.86 (0.77, 0.94)		0.68(0.55, 0.83)
2		0.88(0.81, 0.96)		0.72(0.61, 0.86)
1		Reference		Reference
Education				
Standard/Primary		1.20(0.86, 1.68)		1.17(0.61, 2.27)
Secondary or Equivalent		1.08(0.79, 1.49)		1.03(0.56, 1.91)
Tertiary or University		1.04(0.74, 1.45)		0.86(0.45, 1.67)
None		Reference		Reference
Occupation				
Student		0.83 (0.70, 0.98)		1.02(0.75, 1.38)
Salaried		0.89(0.82, 0.96)		0.79(0.67, 0.94)
Housewife or None		Reference		Reference

[1]All adverse outcomes include preterm delivery, small for gestational age, neonatal death, and stillbirth

[2]Severe adverse outcomes include very preterm delivery (<32 weeks GA), very small for gestational age (<3rd percentile GA), neonatal death, and stillbirth

[3]Other ART Regimen includes any LPV, EFV, or DTG-based ART

753 ADVERSE PREGNANCY OUTCOMES IN HIV-POSITIVE PREGNANT WOMEN ON ART IN KENYA

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Background: While antiretroviral treatment (ART) is essential for the elimination of mother-to-child transmission (MTCT) and improved health outcomes for women living with HIV (WLWH) globally, adverse pregnancy outcomes (APO) among pregnant women on life-long ART are a growing concern.

Methods: A total of 1225 pregnant WLWH enrolled in the Mother-Infant Visit Adherence and Treatment Engagement (MOTIVATE) study from 24 clinics in a high HIV prevalence region in southwestern Kenya between January 2015 to January 2018 were included. MOTIVATE is a cluster-randomized trial testing the impact of two behavioral interventions (community mentor mothers (CMMs) and text messaging) on retention in care and antiretroviral treatment (ART) adherence among HIV-positive pregnant/postpartum women. Women with an APO (miscarriage, stillbirth, neonatal death, infant death, preterm delivery, low birth weight) were compared with women with live birth at least 30 days postpartum without APO. Maternal deaths were excluded from analysis. Multivariable logistic regression was conducted including multiple predictors of APO, accounting for clustering by site.

Results: Among 1225 HIV-positive pregnant women of median age 30.5 years (IQR 26.2 – 34.2), 440 women (35.9%) experienced an APO, including 333 (27.2%) preterm deliveries, 54 (4.4%) low birthweight infants, and 80 (18.2%) fatal adverse outcomes (including stillbirths, miscarriages, and maternal,

neonatal or infant deaths). Women receiving the text message intervention [adjusted odds ratio (aOR) 0.60, 95%CI (0.45-0.80)] and those who received both text messages and the CMM intervention [aOR 0.68 (0.55-0.86)] had lower odds of having an APO when compared to the control group. (Table1) Women on non-nucleoside reverse transcriptase inhibitors (NNRTI) based ART were less likely to experience an APO when compared to those on protease inhibitors (aOR 0.43, 95%CI 0.21-0.88). Women receiving Tenofovir were twice as likely to experience an APO when compared to women on Zidovudine (aOR 2.00, 95%CI 1.28-3.10). Other factors associated with increased odds of APO included age (aOR 1.14 per 5 years, 95%CI 1.01-1.29) and time on ART.

Conclusion: This cohort of pregnant women on ART experienced high rates of adverse pregnancy outcomes, which were associated with age, type of ART, and duration on ART. Further understanding of the impact of ART and possible mitigating interventions to reduce adverse pregnancy outcomes in this population are needed.

Table 1. Associations with Adverse Pregnancy Outcomes among women on ART in Kenya

	No Adverse Pregnancy Outcome N (%)/median	Adverse Pregnancy Outcome N (%)/median	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Age in years (per 5 years)	30.2	31.2	1.134 (1.013-1.27)	**0.029**	1.137 (1.007-1.285)	**0.038**
Baseline_hemoglobin (hgb) g/dl	10.2	9.4	0.954 (0.929-0.981)	**0.001**	0.97 (0.936-1.006)	0.096
Parity	2	2	1.059 (0.963-1.165)	0.236	0.981 (0.89-1.081)	0.695
Gestational period (weeks)	24.0	26.0	1.014 (1.002-1.027)	**0.027**	1.012 (0.998-1.026)	0.088
County						
Homabay	162 (20.3%)	113 (24.5%)	Ref		Ref	
Kisumu	307 (38.5%)	140 (30.3%)	0.654 (0.451-0.947)	**0.024**	0.775 (0.55-1.09)	0.143
Migori	329 (41.2%)	209 (45.2%)	0.911 (0.623-1.331)	0.629	0.891 (0.662-1.199)	0.446
Intervention						
Control	184 (23.1%)	125 (27.1%)	Ref		Ref	
CMM and Text msg	183 (22.9%)	141 (30.5%)	1.134 (0.858-1.499)	0.377	0.684 (0.546-0.858)	**0.001**
CMM only	215 (26.9%)	102 (22.1%)	0.698 (0.522-0.935)	**0.016**	0.813 (0.634-1.042)	0.102
Text msg only	216 (27.1%)	94 (20.3%)	0.641 (0.502-0.817)	**<0.001**	0.599 (0.451-0.796)	**<0.001**
ART Timing						
Pre-conception	563 (71.8%)	336 (73.5%)	Ref		Ref	
Post-conception	221 (28.2%)	121 (26.5%)	0.917 (0.698-1.205)	0.536	1.155 (0.83-1.609)	0.392
Time on ART (months)	45.0	46.6	1.003 (1-1.007)	0.053	1.006 (1.002-1.011)	**0.006**
ART combination						
PI-based	38 (4.8%)	26 (5.6%)	Ref		Ref	
NNRTI-based	760 (95.2%)	436 (94.4%)	0.838 (0.406-1.73)	0.634	0.426 (0.207-0.879)	**0.021**
ART combination						
AZT-based	90 (11.6%)	42 (9.3%)	Ref		Ref	
TDF-based	683 (88.4%)	408 (90.7%)	1.28 (0.936-1.751)	0.123	1.994 (1.284-3.097)	**0.002**
CD4						
<200	66 (9.7%)	45 (11.3%)	Ref			
200-499	316 (46.3%)	176 (44.1%)	0.817 (0.59-1.132)	0.224		
≥500	300 (44.0%)	178 (44.6%)	0.87 (0.621-1.219)	0.419		
Viral Load						
<=1000 copies	564 (92.2%)	279 (88.0%)	Ref		Ref	
>1000 copies	48 (7.8%)	38 (12.0%)	1.6 (1.032-2.483)	**0.036**	1.601 (0.968-2.649)	0.067

754 TIMING OF MATERNAL ANTIRETROVIRAL THERAPY INITIATION AND STILLBIRTH IN MALAWI

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Background: Studies on the use of antiretroviral therapy (ART) during pregnancy in HIV-infected women suggest that in-utero ART exposure may be associated with adverse birth outcomes, including stillbirth, preterm delivery, and being small for gestational age. Despite efforts to understand the effect of ART exposure on birth outcomes in prevention of mother-to-child transmission programs, the association remains unclear in resource-limited settings. We assessed the association between timing of maternal ART initiation and stillbirth among HIV-infected pregnant women in Malawi's Option B+ program.

Methods: We conducted a cross-sectional study using routine program data from maternity registers at 20 large health facilities. We included all women with data on maternal age and timing of ART initiation who delivered singleton live births or stillbirths at ≥28 weeks of gestation between January 1, 2012 and June 30, 2015. We defined stillbirth as an infant born with no sign of life at ≥28 weeks of gestation. We reported proportions of stillbirth by timing of maternal ART initiation (never initiated ART; before pregnancy; during 1st or 2nd trimester; during 3rd trimester or labor). We used logistic regression with cluster-based robust standard errors to account for clustering of women within health facilities to investigate the association between timing of ART initiation and stillbirth.

Results: Of 10,558 mother-infant pairs, 8,994 (85.2%) met the inclusion criteria. The overall stillbirth rate was 25 per 1,000 deliveries (95% confidence interval 22–28). We found no significant association between timing of maternal ART initiation and stillbirth. Older maternal age, male sex of the infant, breech vaginal delivery, delivery at <34 weeks of gestation, and having any maternal obstetric complication were associated with increased odds of stillbirth. Delivery at a mission hospital or health center were associated with lower odds of stillbirth than deliveries at a central hospital.

Conclusion: Pregnant women's exposure to ART, regardless of time of initiation, was not associated with an increased risk of stillbirth. This finding suggests that any negative effects of antiretroviral drug exposure to the infant may be compensated by the benefit of ART on the health of the mother.

755 PRETERM BIRTH AMONG WOMEN WITH ULTRASOUND-BASED GESTATIONAL DATING IN PROMISE 1077BF

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Background: The PROMISE trial found antiretroviral therapy (ART) to be associated with preterm birth (PTB) compared to zidovudine (ZDV) alone. PROMISE used newborn clinical exam to define PTB, since gold-standard ultrasound (US) dating was not universally available. We analyzed the association between ART and PTB in a subset of participants in whom fetal US was available.

Methods: This analysis is restricted to singleton liveborn pregnancies with pre-randomization fetal US biometry. Our outcomes were PTB<37 weeks and <34 weeks. Exposures of interest were antiretroviral regimens in the trial's 3 randomization groups: ZDV-alone, ZDV-based ART, and tenofovir (TDF)-based ART. We fit multivariable logistic regression models, adjusting for maternal characteristics, obstetric history, and HIV disease severity. Since earlier ultrasound dating is more accurate, we conducted a sensitivity analysis of women with US<24 weeks. For comparison, we also present results of an earlier analysis of all trial participants (Chi et al., CROI 2016).

Results: Among 3,423 trial participants, 724 (21%) singleton pregnancies had gestational age dating by both newborn exam and fetal US. The median gestational age at US was 24.0 weeks (IQR: 19.0, 28.8); 99% were from Uganda, South Africa, or India. Overall, 46% of women were randomized to ZDV-alone, 44% to ZDV-based ART, and 10% to TDF-based ART (a lower proportion because of a mid-trial protocol change). PTB<37 weeks was 20% and PTB<34 weeks was 6%. In multivariable analysis, women receiving either ART regimen had significantly higher odds of PTB at both <37 and <34 weeks compared to ZDV-alone. Findings were similar when restricted to 353 women with US<24 weeks. The odds of PTB<37 weeks by randomization arm was generally consistent with prior analyses where gestational age was defined by newborn exam. However, our results differed when examining the PTB<34 outcome in this smaller subset: the association between ZDV-based ART and PTB < 34weeks became stronger, while a previously detectable difference between the two ART arms disappeared (Table).

Conclusion: A subset analysis of PROMISE 1077BF among women with US dating reconfirmed a significant association between ART started in pregnancy and PTB. A significantly increased risk of PTB<34 weeks with ART was observed with US dating but not with newborn exam. This may be attributable to reduced misclassification with more accurate US gestational dating and warrants further research.

Table. Analysis of antiretroviral treatment strategy and PTB <37 and <34 weeks gestation (defined by ultrasound and newborn exam) comparing women with any dating ultrasound (N=724), dating ultrasound <24 weeks gestation (N=353), and the PROMISE 1077BF trial (N=3,333)

	Frequency by treatment arm			Multivariable analysis comparing treatment arms		
Study outcomes	**ZDV-alone**	**ZDV-ART**	**TDF-ART**	**ZDV-ART vs. ZDV-alone Adjusted odds ratio, AOR (95% CI)ϕ**	**TDF-ART vs. ZDV-alone Adjusted odds ratio, AOR (95% CI)ϕ**	**TDF-ART vs. ZDV-ART AOR (95% CI)ϕ**
PTB <37 weeks defined by ultrasound						
Any OB US (N=724)	46/334 (13.8)	66/320 (20.6)	21/70 (30.0)	1.67 (1.09 – 2.55)	2.72 (1.40 – 5.31)	1.65 (0.87 – 3.12)
OB US <24 weeks (N=353)	20/158 (12.7)	35/164 (21.3)	10/31 (32.3)	2.02 (1.07 – 3.80)	4.60 (1.61 – 13.08)	2.00 (0.77 – 5.22)
PTB <37 weeks defined by newborn exam						
Current study sample (N=724)	35/334 (10.5)	64/320 (20.0)	12/70 (17.1)	2.19 (1.38 – 3.46)	3.10 (1.37 – 6.99)	1.32 (0.62 – 2.77)
Clinical trial (N=3,333)*	190/1467 (13.0)	289/1454 (19.9)	78/412 (18.9)	1.75 (1.42 – 2.17)	1.70 (1.24 – 2.33)	0.97 (0.72 – 1.32)
PTB <34 weeks defined by ultrasound						
Any OB US (N=724)	8/334 (2.4)	23/320 (7.2)	7/70 (10.0)	3.41 (1.48 – 7.86)	6.00 (1.77 – 20.34)	1.73 (0.66 – 4.56)
OB US <24 weeks (N=353)	5/158 (3.2)	17/164 (10.4)	3/31 (9.7)	5.00 (1.64 – 8.69)	3.22 (0.52 – 19.67)	0.71 (0.15 – 3.30)
PTB <34 weeks defined by newborn exam						
Current study sample (N=724)	5/334 (1.5)	8/320 (2.5)	2/70 (2.9)	1.73 (0.55 – 5.42)	1.95 (0.35 – 10.98)	1.13 (0.27 – 7.51)
Clinical trial (N=3,333)*	37/1467 (2.5)	43/1454 (3.0)	25/412 (6.1)	1.14 (0.71 – 1.85)	2.93 (1.66 – 5.16)	2.56 (1.47 – 4.46)

* These results are from a prior analysis of the clinical trial (Chi et al, CROI, 2016) that included 3,333 of 3,425 enrolled women, and excluded 90 singleton pregnancies whose fetus was stillborn (n=84) or a spontaneous abortion (n=6).
ϕIn the current analysis, multivariable models adjusted for: antiretroviral regimen, maternal age, body mass index, country, baseline plasma viral load, and number of prior preterm births. In the prior analysis (Chi et al, CROI 2016), multivariable models adjusted for the above variables as well as: baseline CD4 cell count, history of alcohol use, gestational age at entry, multiple gestation, and the following obstetrical complications: abruptio placenta, chronic hypertension, pregnancy-induced hypertension, oligohydramnios, intrauterine growth restriction, premature labor, premature rupture of membranes, urinary tract infection, and vaginal bleeding.

756 LOPINAVIR (AN HIV PROTEASE INHIBITOR) IMPAIRS UTERINE REMODELING DURING PREGNANCY

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Background: Exposure to protease inhibitor (PI) based combination antiretroviral therapy (cART) during pregnancy; especially Lopinavir (LPV) based cART during periconception, increases the prevalence of preterm delivery and low birth weight. PIs may contribute to these adverse events by lowering progesterone (P4) levels. P4 plays a central role in uterine preparation for pregnancy, and a critical P4-dependent process in early pregnancy is remodeling of the uterine endometrium to form the decidua. The key events of this process include decidualization of endometrial stroma, and remodeling of decidual spiral arteries into highly dilated vessels to adequately supply maternal blood to the placenta and fetus. As PI-cART causes P4 dysregulation, we hypothesized that decidualization and spiral artery remodeling are likely to be impaired upon exposure to LPV based cART. Hence we investigated the effects of PIs on the decidua.
Methods: Human HIV-negative decidua and placenta tissue was collected from elective first trimester terminations. The placenta-decidua co-culture model was used to investigate the effects of PIs on spiral artery remodeling by immunohistochemistry. The placental villous explant culture was used to study extravillous trophoblast (EVT) invasion across matrigel. A primary decidual cell culture system was used to assess PI-induced changes in soluble and intracellular protein factors using ELISA and multiplex approaches. Flow cytometry was used to examine the viability of various decidual cell types.
Results: Treatment with LPV impaired the EVT outgrowth as well as remodeling of decidual spiral arteries. A dysregulation of decidualization was observed, marked by reduced stromal expression of prolactin and IGFBP1, the key biomarkers of decidualization. The viability of uterine NK (uNK) cells was affected, concomitant with changes in the secretion profile of uNK and stroma cell specific growth-factors and cytokines/chemokines such as VEGF, PlGF, IL-15, MMP-9 and CXCL16. The effects of LPV treatment could be attributed to a decrease in the expression of transcription factor STAT3, known to regulate decidualization.
Conclusion: Overall, our data reveal that LPV based cART causes dysregulation of decidualization and impairment of spiral artery remodeling, thereby possibly contributing to inadequate placentation and poor birth outcomes. Our findings suggest a possible mechanism to explain why LPV exposure from conception may be associated with higher rates of adverse birth outcomes.

757 POPULATION PK OF DOLUTEGRAVIR IN PLASMA, CORD, AND BREASTMILK: RESULTS FROM DOLPHIN-1

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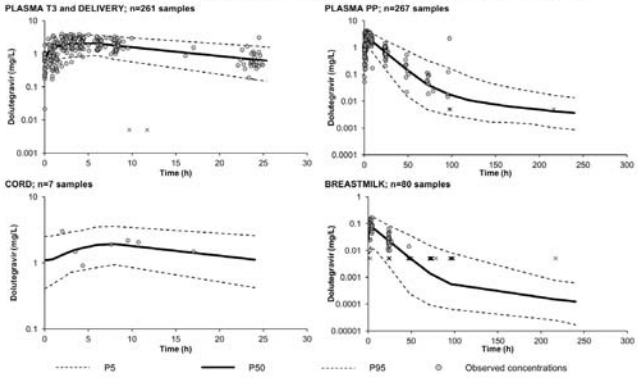
Background: Women diagnosed with HIV late in pregnancy (≥28wks) require safe and effective treatment to quickly reduce viral load and prevent neonatal transmission. DolPHIN-1 (NCT02245022) examined the PK and safety of dolutegravir (DTG) in pregnant women and their infants presenting with untreated HIV late in pregnancy (28-36wks gestation).
Methods: Women recruited from Uganda and South Africa (SA) were randomised to receive DTG-based therapy (50mg OD) or efavirenz-based standard of care (SoC). DTG PK sampling (0-24h) was undertaken 14days after therapy initiation (third trimester; T3) and within 2wks of delivery (postpartum; PP). Where possible, matched maternal and cord samples were taken at delivery. Breastmilk (BM) was sampled PP, 2-6h and 24h post-dose. After PP sampling, patients switched to SoC and a plasma and BM sample was taken 1-3days post-switch. Nonlinear mixed effects (NONMEM v. 7.3) was used to describe DTG PK in maternal plasma, cord and BM. Covariates included maternal age, weight, pregnancy (T3 *vs.* PP), gestational age, delivery (vaginal *vs.* C-section), site (Uganda *vs.* SA) and wks PP. Model evaluation was performed by visual predictive check (VPC).
Results: Twenty-eight women [14 Uganda, 14 SA; median (range) age, weight: 27yr (19-42), 67kg (44-160), respectively] contributed 528 plasma, 7 cord and 80 BM samples to the model; 27 had paired T3/PP visits [gestational age: 39wks (35-43)]. A 2-compartment model described DTG in plasma, which was linked to a fetal compartment of negligible volume and a BM compartment of fixed volume (0.125L) by first-order processes. Apparent oral clearance (CL/F) was higher than previously reported for HIV+, treatment-naïve patients (1.47 *vs.* 0.90L/h) but not significantly different between T3 and PP. Model VPC and measured DTG are shown (Figure). Median (range) simulated cord AUC_{0-24} was 37.7mg.h/L (27.7-6.9; n=7) and was 107% (105-112) that of plasma. BM AUC_{0-24} was 1.13mg.h/L (0.64-4.22; n=27) and was consistently 3% (2-7) that of plasma when simulated 48-240h post-switch. BM C_{av} was 0.047mg/L (0.027-0.18) corresponding to a relative infant dose (RID) to that of the mother of 0.26% (0.11-0.97).
Conclusion: Rich and sparse data collection allowed estimation of DTG disposition in maternal plasma, cord and BM by population PK modelling. RID of DTG from BM was within the suggested safety threshold of 10%, although accumulation in the infants was observed, potentially due to delayed excretion.

Figure. Dolutegravir VPC (90% prediction interval; P5, P50, P95) in plasma, umbilical cord and breastmilk generated from 1000 simulations using the model estimates. Observed dolutegravir are superimposed. Samples below assay LLQ (x) are presented as LLQ/2 (0.005mg/L).



758 DOLUTEGRAVIR PHARMACOKINETICS DURING PREGNANCY AND POSTPARTUM

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Background: Although dolutegravir (DTG) should be avoided around conception and until the first 8 gestational weeks due to potential neural tube defects, a place for DTG remains in the treatment of pregnant women thereafter in several scenarios, such as late presentation or as salvage regimen. Adequate antiretroviral (ARV) exposure is important to prevent the development of resistance and mother-to-child transmission of HIV. However, pregnancy-

related physiological changes may alter ARV exposure. As limited data are available on PK of DTG during pregnancy, we present data on 3rd trimester DTG exposure in HIV-positive pregnant women.
Methods: Multi-centre phase IV study in HIV infected pregnant women recruited in European HIV treatment centers. Patients treated with DTG 50mg QD during pregnancy had 24-hour PK profiling in the 3rd trimester (T3) and 3-7 weeks postpartum (PP). Paired cord (CB) and maternal (MB) blood samples were taken at delivery. Safety and virological data were collected. DTG plasma concentrations were determined with a validated LC-MS/MS method (LLOQ of 0.01mg/L). Geometric mean ratio (GMR) T3 PK versus PP with 90% confidence interval (CI) was calculated for AUC0-24h, Cmax and Ctrough.
Results: 14 patients (10 black, 4 white/other), median (range) age 32 (21-42) yrs were included. 5 patients did not attend at postpartum, 1 patient was excluded from PK analysis because of invalid plasma concentrations. Median (range) GA at delivery was 39 wks (34-40); birth weight was 3258 gr (2120-4040). Peri-delivery all patients had HIV VL<50cps/mL. 10 children were HIV un-infected (4 unknown status).One intrauterine fetal death (34 weeks GA) occurred due to cholestasis pregnancy syndrome, 1 infant had hypospadia, 1 had polydactily (as other members of her family). Two maternal hospital admissions occurred to exclude pre-eclampsia. Ratios T3/PP (GMR (90%CI), n=8) were: 0.88 (0.67-1.16) for AUC0-24h; 0.94 (0.75-1.18) for Cmax; 0.74 (0.50-1.09) for Ctrough. One patient had a subtherapeutic Ctrough (<0.3 mg/L) in the T3 of pregnancy. Median (range) CB:MB ratio was 1.4 (1.1-1.8; n=8).
Conclusion: Although variability is high, DTG AUC0-24h seems similar in pregnancy and postpartum. In T3 DTG plasma Ctrough was above the efficacy level of 0.3 mg/L in all but one patient. These findings, coupled with the undetectable viral loads at delivery, support standard dosing of DTG during pregnancy.

759 PREGNANCY ASSOCIATED WITH DECREASED SERUM ISONIAZID LEVELS IN WOMEN LIVING WITH HIV

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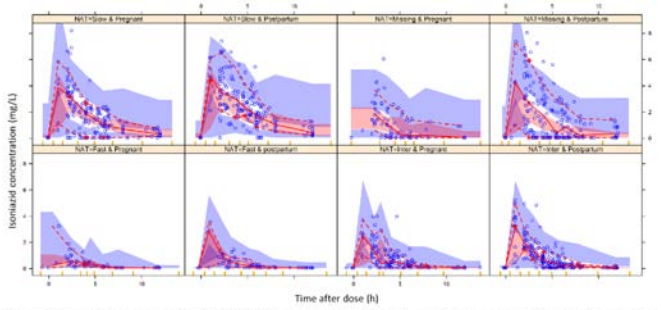
Background: World Health Organization guidelines recommend that all people living with HIV from low- and middle-income countries (LMIC) where TB is endemic receive > 6 months of isoniazid (INH) preventive therapy, including pregnant women. INH plasma concentrations during pregnancy have not been well described.
Methods: Pregnant women living with HIV infection (WLWH) at 14 to 34 weeks of gestation and on or starting ART were recruited from 8 LMIC into a phase IV randomized double-blind placebo-controlled multicenter international trial (IMPAACT P1078). The study had two arms: Arm A (immediately started on INH 300 mg daily for 28 weeks, then placebo) and Arm B (started on placebo, then switched to INH 300 mg daily at 12 weeks postpartum). A subset of women underwent intensive PK sampling (before INH dosing,1, 2, 4, 6, 8 and 12 h after), while the remaining women underwent sparse PK sampling (approximately 2 h after dose). Sampling occurred once at ≥ 2 weeks after recruitment and again at 12-21 weeks after delivery. NAT2 acetylator status was determined. INH PK was described by a two-compartment disposition model and elimination with a well-stirred liver model. Allometric scaling based on total body weight was applied on clearance, volume parameters, and hepatic plasma flow.
Results: INH concentrations from 32 intensively and 752 sparsely-sampled women were included. 748 WLWH were on efavirenz-based ART. The median weight, age, and gestation at study entry were 67 (range 38,166) kg, 29 (18, 45) years, and 28 (14-34) weeks, respectively. After including NAT2 genotype, the model predicted a 67-kg woman to have clearance of 13.5, 38.3, and 71.3 L/h if slow, intermediate, or fast acetylator, respectively. After adjusting for these factors, pregnancy was found to increase INH clearance by 23% (p<0.001) compared with postpartum, i.e. a 67-kg NAT2 intermediate acetylator would have an area under the time-concentration curve of 6.70 h.mg/L during pregnancy and 7.84 to during postpartum.
Conclusion: INH exposure was decreased during pregnancy, likely due to increased clearance. Overall, INH clearance in all three NAT2 acetylator groups was higher compared to historical nonpregnant ranges, regardless of pregnancy. The consequences of this reduction in exposure on the safety and effectiveness of INH preventive therapy is being further investigated.



Visual predictive check of the final model, stratified by *NAT2* genotype and pregnancy status. The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observed data, while the shaded areas represent the 95% confidence intervals for the same percentiles, as predicted by the model. An appropriate model is expected to have all observed percentiles within the simulated confidence intervals.

760 VIROLOGICAL RESPONSE OF RAL-BASED REGIMEN AMONG HIV-INFECTED PREGNANT WOMEN IN BRAZIL

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Background: Antiretroviral therapy (ART) led to important declines in the likelihood of HIV perinatal transmission. In 2017, Brazil implemented 3TC-TDF-RAL as the preferred regimen for HIV-infected pregnant women (HIPW), replacing 3TC-TDF-EFV. Our study aims to identify treatment-related factors associated with the virological response of RAL-based regimens compared with other regimens in HIPW on ART in Brazil, from January/2016 to June/2018.
Methods: We analyzed programmatic data from HIPW aged 15 and over who had at least one antiretroviral prescription between January/2016 and June/2018, and had at least one viral load (VL) measurement between 60-180 days after this prescription. Logistic regression models were used to assess the likelihood of achieving viral load suppression (VLS), defined as last viral load (VL) count <50copies/mL within 60-180 days after first prescription during pregnancy.
Results: A total 8,539 HIPW aged 15+ were included - median age 29 (IQR: 23–34) - of whom 948 (11%) were using TDF+3TC+RAL. Approximately 38% of HIPW were treatment naïve (63% among HIPW using RAL-based and 49% among those on EFV-based regimen) and 42% were on ART for over two years. Overall VLS after 60-180 days after first prescription during pregnancy was 77% (82% among HIPW using TDF+3TC+RAL, 81% among those using TDF+3TC+EFV and 71% among those using TDF+3TC+LPV/r; p-value<0.001). In multivariable analysis, compared to HIPW using TDF+3TC+EFV, odds of VLS were 36% (aOR=1.358; CI95%: 1.105-1.668) higher among those using TDF+3TC+RAL and 49% lower among those using TDF+3TC+LPV/r (aOR=0.516; CI95%: 0.401-0.664). Other factors that increased the odds of achieving VLS were higher baseline CD4, lower baseline VL, lower time on ART, older age, and higher educational level.
Conclusion: This study revealed the significant superiority of TDF+3TC+RAL compared to other regimens in suppressing viral load among HIPW. This superiority remains after controlling for certain sociodemographic and clinical characteristics, such as age and baseline CD4. Therefore, RAL-containing regimens are an important tool for the reduction of mother-to-child transmission.Interestingly, lower time on ART showed higher odds of achieving VLS, suggesting that non-naïve HIPW may have been on suboptimal ART before or during pregnancy. Further research is needed to elucidate these findings.

Results of the univariate and multivariate logistic regression models for achieving virological suppression after 2-6 months of treatment. Brazil, 2016-2018.

Caractheristics	N	%	VL<50cp/ml[1]		Achieve VLS			
			%	p-value	OR	CI95%	aOR	CI95%
Total	8.539	100,0%	77,2%	-				
Regimen at first dispensation as pregnant								
TDF+3TC+EFZ	3.279	38,4%	80,5%	<0.001	1,000		1,000	
3TC+AZT+LPV/r	1.972	23,1%	72,6%		0,640	(0,561-0,73)	0,575	(0,495-0,667)
TDF+3TC+RAL	948	11,1%	81,9%		1,092	(0,906-1,316)	1,358	(1,105-1,668)
TDF+3TC+ATV/r	1.015	11,9%	76,3%		0,777	(0,657-0,92)	0,705	(0,58-0,858)
TDF+3TC+LPV/r	471	5,5%	71,1%		0,596	(0,48-0,741)	0,516	(0,401-0,664)
Other	854	10,0%	74,4%		0,702	(0,588-0,837)	0,604	(0,49-0,745)
Time on ART (days)								
Naive	3.210	37,6%	76,7%	<0.001	1,000		1,000	
Up to 180	669	7,8%	83,6%		1,541	(1,237-1,921)	1,123	(0,875-1,441)
180-364	353	4,1%	83,6%		1,543	(1,151-2,068)	0,728	(0,518-1,023)
365-729	686	8,0%	81,9%		1,375	(1,113-1,697)	0,667	(0,521-0,853)
730 and over	3.621	42,4%	74,9%		0,905	(0,81-1,011)	0,505	(0,437-0,583)
Baseline CD4[2]								
0-99	192	2,3%	49,0%	<0.001	1,000		1,000	
100-199	458	5,4%	57,2%		1,394	(0,994-1,954)	1,136	(0,777-1,661)
200-349	1.125	13,2%	70,0%		2,427	(1,78-3,311)	1,744	(1,23-2,475)
350-499	1.371	16,1%	75,8%		3,263	(2,396-4,441)	2,113	(1,489-2,997)
500+	3.278	38,4%	84,4%		5,632	(4,18-7,589)	2,660	(1,886-3,752)
NA	2.109	24,7%	77,6%		3,615	(2,675-4,884)	2,266	(1,546-3,32)
Baseline VL[3]								
0-49	2.821	33,0%	92,1%	<0.001	7,347	(6,211-8,691)	8,794	(7,123-10,858)
50-199	510	6,0%	82,9%		3,081	(2,398-3,959)	3,204	(2,426-4,232)
200-999	837	9,8%	73,0%		1,713	(1,429-2,054)	1,694	(1,384-2,072)
1000-9999	1.444	16,9%	73,1%		1,719	(1,476-2,001)	1,638	(1,383-1,939)
10000+	1.686	19,7%	61,2%		1,000		1,000	
NA	1.241	14,5%	70,3%		1,503	(1,286-1,758)	1,580	(1,221-2,046)
Year of dispensation								
2016	3.859	45,2%	74,9%	<0.001	1,000			
2017	3.395	39,8%	78,4%		1,216	(1,09-1,356)		
2018	1.285	15,0%	80,9%		1,423	(1,216-1,665)		
Age group (years)								
15-24	2.708	31,7%	71,2%	<0.001	1,000		1,000	
25-29	2.114	24,8%	79,0%		1,519	(1,329-1,736)	1,521	(1,308-1,769)
30-39	3.129	36,6%	80,3%		1,647	(1,459-1,86)	1,577	(1,371-1,813)
40+	588	6,9%	81,5%		1,775	(1,418-2,22)	1,672	(1,294-2,159)
Race/color								
White/yellow	3.490	40,9%	78,6%	0.017	1,000			
Black	3.498	41,0%	76,0%		0,000	0,000		
Indigenous	13	0,2%	76,9%		0,000	0,000		
Missing	1.538	18,0%	76,9%		0,000	0,000		
Education (years)								
0-7	2.275	26,6%	74,0%	<0.001	1,000		1,000	
8-11	2.469	28,9%	79,7%		1,375	(1,201-1,575)	1,269	(1,088-1,478)
12+	677	7,9%	82,6%		1,663	(1,335-2,071)	1,322	(1,037-1,685)
Missing	3.118	36,5%	76,4%		1,134	(1,001-1,285)	1,094	(0,95-1,26)
Social vulnerability index								
Very low, low	4.689	59,9%	77,9%	0.017	1,267	(1,067-1,504)		
Medium	2.342	29,9%	76,3%		1,157	(0,963-1,39)		
High, very high	802	10,2%	73,6%		1,000			

Notes: (1) Last VL measured after 60 up to 180 days of ART initiation during pregnancy; (2) CD4 up to 6 months before first dispensation during pregnancy; e (3) VL up to 6 months before first dispensation during pregnancy.

761 SEARCH INTERVENTION INCREASES VIRAL SUPPRESSION AMONG PREGNANT & POSTPARTUM WOMEN

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Background: Achieving viral suppression (VS) with antiretroviral therapy (ART) in HIV+ women of child-bearing age is critical to maternal health and reducing mother-to-child transmission. Gains in VS among pregnant and post-partum women of universal "test and treat" approaches above and beyond "Option B+" (ART initiated during pregnancy) are unknown.

Methods: The SEARCH trial (NCT:01864603) compared an intervention of annual population testing via multi-disease campaigns and universal ART via patient-centered care to an active control of baseline population testing with ART by country standard, including Option B+, in 32 communities in Kenya and Uganda over 3 years. HIV+ women were asked about current pregnancy and live births over prior year and had viral load measured at baseline and after 3 years in control communities, and annually in intervention communities. Between arms, we compared population-level VS estimates (adjusting for incomplete viral load measurement) among all HIV+ women (15-45 years, including in-migrants) reporting a current pregnancy or live birth in the preceding year. In intervention, we also assessed annual impact of incident pregnancy on maintaining or achieving VS, if suppressed or non-suppressed 1-year prior, respectively, as some prior studies have found increased risk of non-suppression post-partum

Results: At trial baseline (2013-14), 92% and 93% of 15-45 year-old women tested for HIV, with HIV prevalence of 12.7% and 12.3%, in intervention and control communities, respectively (Table). Among women reporting a current pregnancy or live birth in prior year, population-level VS estimates were 44% and 50% at baseline, and 82% and 77% (p=0.03) at year 3 in intervention and control, respectively. Among women not reporting pregnancy/live birth, population-level VS was also higher at year 3 in intervention (85%) vs. control (75%; p<0.001). Incident pregnancy did not affect proportion maintaining viral suppression (96% if pregnant vs. 97% if not, RR: 1.0 [95% CI: 0.96-1.03]) or achieving viral suppression (77% vs. 74%, RR: 1.04 [0.95-1.13]) at year 1 in intervention communities.

Conclusion: The SEARCH "test and treat" strategy resulted in significantly higher levels of VS among HIV+ pregnant and post-partum women compared to a control that followed Option B+, suggesting a positive impact of annual population testing and patient-centered care. Post-partum women were as likely to maintain or achieve VS as women who did not experience incident pregnancy in intervention communities.

Baseline	Intervention (16 communities) Women (15-45 yrs) N=32,954	Control (16 communities) Women (15-45 yrs) N=29,112
HIV Tested	30,154 (92%)	26,935 (93%)
HIV+	3,852 (12.7%)	3,315 (12.3%)
HIV+ AND currently pregnant or live-birth in preceding year	1,252 (33%)	1,081 (33%)
% Viral suppression, HIV+ and pregnant/live birth (adjusted for incomplete VL measurement)	44% (95% CI: 39-49%)	50% (95% CI: 47-54%)
3-Year Follow Up	**Women (15-45 yrs) N=41,433**	**Women (15-45 yrs) N=36,179**
HIV Tested	33,821 (82%)	30,697 (85%)
HIV+	4,035 (11.9%)	3,501 (11.4%)
HIV+ AND currently pregnant or live-birth in preceding year	481 (12%)	488 (14%)
% Viral suppression, HIV+ and pregnant/live birth (adjusted for incomplete VL measurement)	82% (95% CI: 80-85%)	77% (95% CI: 73-81%)

762 IDENTIFYING WOMEN LIVING WITH PERINATAL HIV INFECTION AT RISK OF POSTPARTUM VIREMIA

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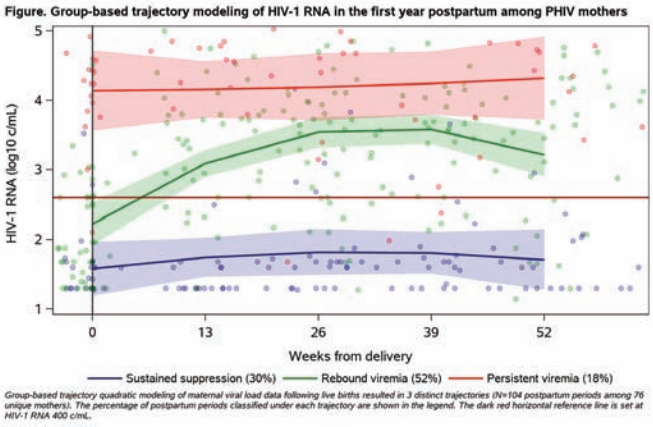
Background: Previous studies have observed worse postpartum outcomes among women living with perinatal HIV infection (WLPHIV) compared to women who acquired HIV later in life. We characterized postpartum viral load trajectories among WLPHIV and evaluated factors that may identify those at risk for postpartum viremia.

Methods: PHACS AMP Up is a longitudinal cohort of young adults aged ≥18 years living with perinatal HIV from 14 sites in the United States and Puerto Rico. Lifetime HIV disease characteristics and pregnancy history were abstracted from clinical charts. Group-based trajectory modeling (GBTM) was used to identify trajectories of viral load in the first year postpartum for all pregnancies that resulted in a live birth. Sociodemographic and clinical factors were compared across identified trajectories using generalized estimating equations (GEE) regression models for nominal multinomial responses.

Results: Of 276 WLPHIV in AMP Up, 86 had 124 pregnancies resulting in a live birth. 104/124 (84%) of these pregnancies (among 76 women) had postpartum viral loads available for trajectory analysis. The average age at conception of these pregnancies was 21.2 years and 63% were first pregnancies. 19% of births were preterm and there was one second-generation perinatal HIV transmission. GBTM identified three distinct postpartum viral load trajectories as the optimal fit of the data (Figure). These trajectories were classified as reflecting sustained suppression, rebound viremia, and persistent viremia, with 31 (30%), 55 (52%), and 18 (18%) pregnancies included in each group, respectively; viremia was defined as ≥400 copies/mL. Pregnancies of women with sustained postpartum suppression tended to be conceived at older ages than those with rebound or persistent postpartum viremia (mean: 22.5 vs. 20.8 and 20.2 years respectively). Pre-pregnancy viremia also predicted postpartum viremia: 72% of pregnancies with persistent postpartum viremia had all viral loads ≥400 copies/mL in the one year prior to conception, compared to 36% and 3% of pregnancies with postpartum rebound viremia and sustained suppression, respectively.

Conclusion: We observed that only 30% of pregnancies among WLPHIV achieved sustained suppression in the first year postpartum. Pregnancies conceived at younger ages and those with pre-pregnancy viremia tended to predict postpartum rebound or persistent viremia, helping identify potential candidates for postpartum adherence interventions.



763 LONG-TERM OUTCOMES OF AN INTEGRATED MATERNAL AND CHILD HIV CARE TRIAL IN SOUTH AFRICA

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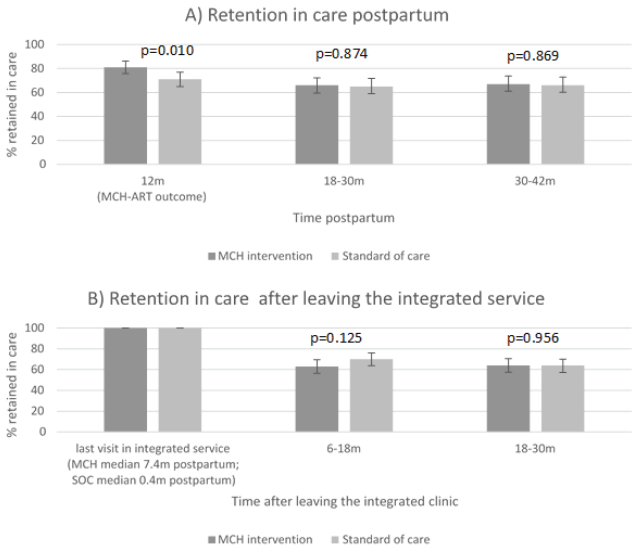
Background: The MCH-ART trial demonstrated that co-located maternal HIV and routine paediatric care, integrated in maternal and child health (MCH) services through weaning, increased retention in care and viral suppression (VS) through 12m postpartum. Long-term outcomes after leaving integrated services are not known.

Methods: To assess long-term outcomes in the MCH-ART cohort, an additional study visit was conducted at 36-60m postpartum including interviews and viral load (VL) testing. Provincial electronic health records were accessed to ascertain deaths and retention regardless of attending the additional visit. The primary outcomes were: 1) retention (any ART visit, pharmacy dispensing, CD4 count or VL test) and 2) VS (<50 copies/mL), in the 12m prior to the study visit or prior to the median time postpartum at the study visit for women who did not attend. Predictors of retention and VS were assessed using Poisson regression reported as adjusted risk ratios (aRR) with 95% confidence intervals (CI).

Results: Of 471 women enrolled in MCH-ART (Jun 2013-Dec 2014), 450 (96%) were followed in routine medical records (11 withdrew from MCH-ART or refused further follow-up; 10 deaths were ascertained) and 353 (75%) completed the additional study visit (May 2017-Apr 2018; median 44m postpartum). Of 450 women followed, 63% were retained in HIV care; among 368 women with either study or routine VL available, 56% had VS. The MCH-ART intervention effect observed at 12m postpartum did not persist at 24m and 36m postpartum; loss from care appeared similar in both trial arms after the last visit in the integrated clinic (Figure). The risk of non-retention was increased by nadir CD4 cell count >350 cells/μL (vs ≤200; aRR 1.43 95% CI 0.97-2.12) and late gestation at presentation for antenatal care in MCH-ART (>20 vs ≤20 weeks; aRR 1.36 95% CI 1.05-1.76). The risk of VL≥50 was increased by late gestation at presentation (aRR 1.27 95% CI 1.00-1.62) and increasing log VL at delivery (aRR 1.25 95% CI 1.13-1.38); findings persisted in sensitivity analyses assuming all missing VLs were VS or not.

Conclusion: This long-term follow-up of the MCH-ART trial suggests that the benefits of integrated postpartum MCH care attenuate rapidly after postpartum transfer and are lost by 36-60m postpartum. The substantial non-retention and loss of VS observed in this cohort is concerning and interventions to support women on ART beyond pregnancy and breastfeeding are urgently needed.



764 EVALUATION OF GUIDELINES FOR VL MONITORING IN PREGNANCY & BREASTFEEDING: A SIMULATION

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Background: There are global concerns about adherence to ART in pregnant and breastfeeding (P&BF) women and subsequent elevated viral load (eVL) and MTCT risk. Intensified VL monitoring for P&BF women has been proposed in guideline recommendations but not evaluated systematically.

Methods: We developed a stochastic individual patient simulation of VL in 10000 P&BF women, modelled weekly from conception through 2y postpartum. Parameters were from published evidence and model outputs were calibrated against data from studies of ART in P&BF (PROMISE, PROMOTE, MmaBana and MCHART). Simulation settings were that 50% of women initiated ART in pregnancy (median 22w gestation (IQR, 16-28)) and 50% were on ART prior to conception (86% <50 c/mL at 1stANC) with modelled ART adherence. Delivery was at median 38w (IQR, 37-40); breastfeeding was for median 40w (IQR, 29-49). We applied to the same simulated population 5 different guidelines for VL monitoring, including adaptations for P&BF women when stated. Guidelines were compared on coverage of VL testing in P&BF, the proportion of eVL in the simulation successfully detected, and the cumulative VL experienced by the time of detection.

Results: Coverage of VL monitoring in P&BF varied widely by guidelines (Table). By 24m postpartum, 92% of women initiating ART achieved VL<50 c/mL, and 18% of these subsequently experienced transient or extended eVL >1000 c/mL. Specific recommendations for testing at either a fixed gestation (WHO) or a fixed period after initiation (PHS) achieved >95% testing in pregnancy; other guidelines led to 59-83% antenatal testing; and with no special stipulation only 16% of women received an antenatal test under Malawian guidelines. Guidelines calling for monitoring in BF (SA, Kenya) had >70% testing during BF compared to 30-40% among guidelines that did not (WHO, Malawi). Only a small proportion of simulated episodes of eVL>1000 c/mL were successfully detected by monitoring (range, 11-29%); guidelines with more frequent testing in P&BF led to shorter delays from the onset of eVL to detection as well as lower cumulative VL before detection. In sensitivity analyses, findings were robust to realistic variations in the simulated population.

Conclusion: Without guidance specific to P&BF women, <1 in 5 women would receive antenatal or postnatal VL monitoring. However even with specific guidance, current guidelines yield suboptimal detection of eVL. Further research

is needed to optimize the timing of monitoring in P&BF women to improve outcomes.

Table. Results of simulation of guidelines for viral load (VL) monitoring in pregnant and breastfeeding women

	Guideline	WHO 2016	USPHS 2018	South Africa 2015	Malawi 2016	Kenya 2018
Guideline summary	Women initiating ART in pregnancy	@4m post initiation, 12m, every 12m; plus test at 34w gestation	1st ANC then every 1m; move to every 3m if VS<50 c/mL; plus test at 34w gestation	@1m, 4m post initiation, then every 6m until end BF	@4m post initiation, then every 24m	@4m post initiation, then every 6m until end BF
	Women continuing ART into pregnancy	Every 12m	As above	@1st ANC then every 6m until end BF	Every 24m	@1st ANC then every 6m until end BF
Simulated population	% women with VL<1000 c/mL before delivery	79.3	79.5	79.4	79.4	79.4
	% women with VL >1000 c/mL after initial VS	18.4	18.2	17.7	17.9	17.7
Characteristics of VL monitoring	Median number of VL tests per woman	2 (1, 2)	14 (13, 16)	3 (2, 3)	1 (1, 1)	2 (2, 3)
	Median weeks to 1st VL (among initiating ART in pregnancy)	14 (8, 19)	3 (2, 4)	12 (12, 12)	29 (26, 31)	29 (26, 31)
	Median weeks to 1st VL (among continuing ART into pregnancy)	10 (5, 16)	0 (0, 0)	0 (0, 0)	28 (12, 42)	0(0, 0)
	% women with ≥1 VL in pregnancy	96.6	100	83.2	16.5	58.4
	% women with ≥1 VL in BF	37.2	50.1	71.2	47.4	84.1
Outcomes of VL monitoring	% women detected at time of VL>1000 c/mL	11.3	29.1	24.9	11.3	28.3
	Weeks elapsed from start of VL >1000 c/mL until VL monitoring or end of BF	17 (2, 20)	3 (0, 20)	14 (3, 42)	19 (4, 40)	18 (5, 30)
	Cumulative viral load from 1st ANC until detection of VL>1000 cpy/mL or 2y PP (if not detected) (log_{10} c/mL*years)	1.08 (0.4, 2.3)	0.25 (0.1, 0.9)	0.87 (0.3, 2.0)	1.08 (0.6, 2)	1.1 (0.5, 1.7)

Acronyms: World Health Organization (WHO); United States Public Health Service (US PHS); viral load (VL); antiretroviral therapy (ART); antenatal care (ANC); breastfeeding (BF); copies/mL (c/mL); VS (viral suppression)

765 MOBILITY AND THE 1-YEAR POSTPARTUM MATERNAL MORTALITY IN HIV-POSITIVE PREGNANT WOMEN

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Background: There is increasing evidence that mobile population living with HIV might experience disengagement from health services and worse health outcomes. We sought to characterize pregnant women's mobility patterns and its association with maternal mortality.

Methods: All pregnant women aged ≥15 years were followed up to 1 year after delivery using one of Africa's largest ongoing population-based cohorts between January 2003 and December 2016 in rural KwaZulu-Natal, South Africa. Changes in residency and household membership were recorded during biannual household surveys. External migration was defined as moving-in or -out of the surveillance area during pregnancy or in the first-year postpartum period. Maternal death was ascertained with the closest care giver via verbal autopsy based on the INDEPTH/WHO questionnaire. Of those with unknown HIV status, women whose death were attributable to AIDS or TB were considered as HIV-positive and the others as HIV-negative in a sensitivity analysis. Multiple cox regression models were used.

Results: Of 30,291 pregnant women, 3,339 were HIV-positive while 10,958 were HIV-negative and 15,994 had unknown HIV status at delivery. There were 27 unique mobility patterns- 64% and 13% of women always resided inside or outside of the study area, respectively. Of 23% women who had externally migrated at least once, 39% delivered outside the study area. The overall maternal death rates were 0.6/1000 person-years (PY) among HIV-negative postpartum women. Of HIV-positive postpartum women, maternal mortality rates were 7.5/1000 PY among who always resided within the study area, compared to 22.6/1000 PY among those who externally migrated and delivered outside the area ($p<0.001$). HIV-positive pregnant women who externally migrated and delivered outside the study area had a 2.82 times higher hazard of maternal mortality (95% CI: 1.04-7.69) after adjusting for age, parity, time period (before or after 2010) and other sociodemographic factors. In the sensitivity analysis, HIV-positive women who had external migration had a six times higher hazard of mortality than HIV-negative women who always resided within the study area, adjusting for maternal HIV status.

Conclusion: A substantial portion of peripartum women moved within-country around the time of delivery and experienced a significantly higher risk of mortality, likely due to disengagement from health services. Interventions to address linkage to and retention in care among migrating pregnant women are urgently needed.

766 TENOFOVIR HAIR LEVELS RISE OVER THE POSTPARTUM PERIOD AND HIGHLY PREDICT VIRAL LOADS

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Background: Adherence to antiretroviral therapy (ART) throughout pregnancy and breastfeeding is crucial for both maternal health and prevention of perinatal and sexual transmission. Tenofovir (TFV) concentrations in hair, reflecting long-term cumulative exposure, have been examined as an adherence metric for PrEP but have not yet been examined among persons living with HIV. We examined hair TFV levels in breastfeeding women on TFV disoproxil fumarate (TDF)/emtricitabine (FTC)-based ART over time, predictors of these levels, and the association of hair levels with viral suppression.

Methods: Women in the IMPAACT PROMISE 1077BF Study who were on ART during both pregnancy and breastfeeding are included in this analysis. From 2013-2016, hair samples were collected at 1 week (6-14 days) postpartum, 6, 14, 26 weeks and every 3 months through breastfeeding up to 18 months. For women on TDF/FTC ≥30 days, hair TFV levels were measured by liquid chromatography/tandem mass spectrometry. Using generalized estimating equations, we estimated the impact of hair TFV levels on viral suppression (plasma HIV RNA <400copies/mL) over time via logistic regression and assessed predictors of hair TFV levels via linear regression.

Results: Hair TFV levels were measured at 374 visits in 71 women who breastfed a median of 14 months (interquartile range [IQR] 12-15). Median weeks on ART at delivery was 12 (IQR 7-17); median age 26 years (IQR 22-30). After ≥90 days on ART, 18/69 (26%) ever experienced viremia (median 8907 copies/mL, range 444-244,984); 8 (12%) had >1 measure ≥400. Each doubling of TFV level was associated with 2.53 times the odds of viral suppression (95%CI: 1.51-4.25, p=0.0004), adjusted for age and time since delivery. The strongest predictor of hair TFV levels was time since delivery. Compared to 0-3 months postpartum, TFV levels were 1.38 fold higher (95%CI 1.09-1.76) in months 3-6, 1.65 fold higher (95%CI 1.31-2.07) in months 6-12 and 1.45 fold higher (95%CI 1.12-1.89) after 12 months (Figure). We did not identify other factors meaningfully associated with TFV levels.

Conclusion: We present the first report examining hair TFV levels among people living with HIV on TDF/FTC-based ART, here in breastfeeding women up to 18 months postpartum. Hair TFV levels strongly predicted viral suppression. Average hair TFV levels were lowest in the first 3 months postpartum, suggesting the need for intensified adherence support in this major transition period to preserve maternal health and prevent perinatal transmission.

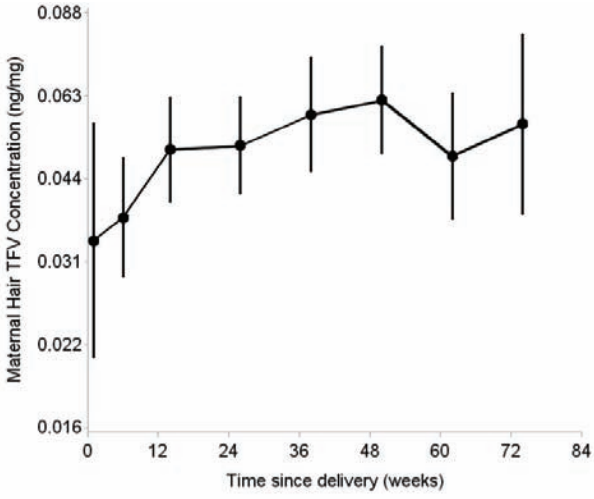

Figure. Hair TFV concentrations by time since delivery, geometric mean and 95% CI

767 POSTPARTUM DEPRESSIVE SYMPTOMS IN WOMEN LIVING WITH HIV IN BOTSWANA

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Background: Postpartum depression (PPD) is associated with poor maternal and child health outcomes. Few studies have evaluated PPD in women living with HIV (WLHIV) in Botswana, a high prevalence HIV setting.

Methods: Using the Edinburgh Postnatal Depression Scale (EPDS), we evaluated PPD symptoms at 2, 6, and 12 months (mo) postpartum in WLHIV and HIV-uninfected (HIV-U) women enrolled in the Tshilo Dikotla cohort study in Botswana. Women scoring ≥10 on the EPDS or reporting thoughts of self-harm were defined as at risk for ongoing PPD symptoms. Secondary outcomes included: EPDS score ≥10, EPDS score ≥13, and EPDS score ≥13 or reporting thoughts of self-harm. Generalized estimating equation models were fit to assess the association of maternal HIV infection with risk of PPD symptoms in the first year postpartum. Subgroup analyses in WLHIV were performed to assess factors associated with risk of PPD symptoms.

Results: Of 321 women enrolled, 195 were WLHIV. WLHIV were older (28.9 vs 24.4 years, p<0.01) with higher gravidity, (3 vs 1, p<0.01) and were less likely to complete tertiary education (7% vs 31%, p<0.01) compared to HIV-U women. Among WLHIV, 45% had a CD4 count >500 cells/mm3 and 93% had an HIV RNA level <40 copies/mL at enrolment; median years since HIV diagnosis was 1.6. All WLHIV received a backbone of tenofovir + emtricitabine and either dolutegravir (DTG) or efavirenz (EFV). At 2, 6, and 12 mo postpartum, 301, 233, and 103 women, respectively, completed the EPDS. At 2 mo, 4 WLHIV and 6 HIV-U met the criteria for being at risk for PPD symptoms. At 6 mo and 12 mo, 6 and 4 WLHIV respectively met the criteria for being at risk for PPD symptoms, whereas no HIV-U women met the criteria. After adjusting for age, gravidity, education level, marital status, and employment, WLHIV were at increased risk for PPD symptoms compared to HIV-U women (adjusted Odds Ratio: 3.37, 95% Confidence Interval: 1.14-10.02). Findings were similar in models evaluating secondary outcomes. (Table 1) Among WLHIV, no associations were seen between age, gravidity, employment, CD4, years with HIV, timing of ART initiation, or ART regimen and PPD symptoms.

Conclusion: Despite overall low rates of PPD symptoms in this small Botswana cohort, WLHIV may be at higher risk for experiencing PPD symptoms in their first year postpartum compared to HIV-U women. Screening WLHIV for PPD symptoms and providing support during the postpartum period are an important part of routine postpartum care for this vulnerable population.

Table 1. Adjusted Generalized Estimating Equation Models of the Association between Maternal HIV Infection and Depressive Symptoms in the First Year Postpartum

Outcome	Adjusted Odds Ratio	95% Confidence Interval
Edinburgh score ≥ 10 or report of thoughts of self- harm	3.37	1.14 – 10.02
Edinburgh score ≥ 10	3.57	1.26 – 10.08
Edinburgh score ≥ 13 or report of thoughts of self- harm	5.16	1.24 – 21.40
Edinburgh score ≥ 13	4.57	1.13 – 18.54

All models adjusted for age, gravidity, highest education level, marital status, and employment.

768 TOWARDS EMTCT IN ZIMBABWE: SERVICE UPTAKE AND IMPACT OF OPTION B+ ON MTCT, 2012-2018

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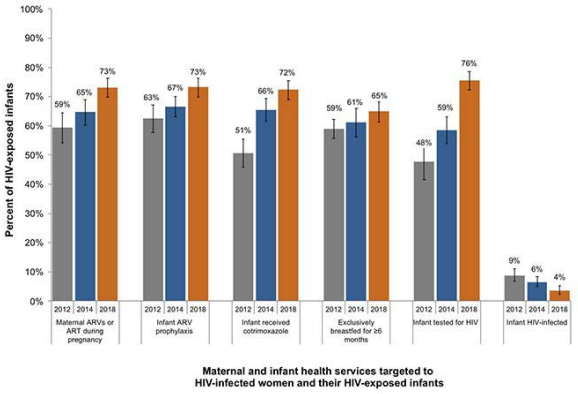
Background: WHO revised treatment recommendations for pregnant women in 2013, and Zimbabwe began to place all pregnant women on HIV treatment for life (Option B+) in January 2013. We examined trends in the uptake of maternal PMTCT services and MTCT among women with a recent birth in Zimbabwe from 2012-18.

Methods: We analyzed serial cross-sectional serosurvey data collected in 2012 (n=8800), 2014 (n=10,404), and 2018 (n=7361) from the evaluation of Zimbabwe's Accelerated PMTCT Program. Using multi-stage cluster sampling, we randomly sampled mother-infant pairs each survey year from catchment areas (CAs) of 157 facilities. Eligible women were ≥16 years old and biological mothers of infants (alive or deceased) born 9 to 18 months before the interview. Participants were tested for HIV and interviewed about health service utilization during pregnancy and breastfeeding.

Results: In 2018, of 7361 women surveyed, 6816 (92.6%) attended ≥1 antenatal care (ANC) visit, 5196 (70.6%) attended ≥4 ANC visits, 6872 (93.4%) were tested for HIV and received their results, and 6290 (85.5%) delivered in a health facility. The uptake of services targeted to all women was relatively stable from 2012-2018. In contrast, utilization of services targeted to HIV-infected women and their infants increased (Figure, maternal HIV prevalence in 2012: 12.4%, 2014: 13.4%, 2018: 10.6%). Uptake of both maternal antiretroviral therapy (2012: 59.4%, 2014: 64.7%, 2018: 73.2%; p<0.01) and infant ARV prophylaxis (2012: 62.6%, 2014: 66.5%, 2018: 73.3%; p<0.01) significantly increased from 2012-2018. Of infants born to HIV-infected mothers, 8.8%, 6.7%, and 3.6% were HIV infected in 2012, 2014, and 2018, respectively. In the 128 CAs with data on HIV exposed infants before and after implementation of Option B+, mean decrease in CA level MTCT was -6.4 percentage points (95% CI -9.3, -3.5) and the proportion of CAs with no transmissions increased from 55% in 2012 to 82% in 2018. CA level MTCT in 2018 varied by province between 1.3% and 9.5%.

Conclusion: Zimbabwe has made remarkable progress increasing coverage of PMTCT services and reducing MTCT. Coverage of services for women living with HIV increased significantly, and an overall MTCT decreased to below the 5% threshold for virtual elimination. However, MTCT rates varied across provinces, and a minority of women living with HIV still did not receive PMTCT services. This highlights the need for continued efforts to simulate demand and overcome barriers to health services.

Figure. Prevention of mother-to-child HIV transmission (PMTCT) cascade in Zimbabwe, 2012–2018. The percentages at each step are the proportion of the total number of HIV-infected women and their HIV-exposed infants in the survey receiving each service. Analysis restricted to biological mothers and their eligible infants (9-18 months of age).



769 HIV DRUG RESISTANCE AT PERINATAL TRANSMISSION AND ACCUMULATION DURING BREASTFEEDING

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Background: HIV drug resistance (DR) can undermine antiretroviral treatment (ART). We examined risks of maternal DR on perinatal transmission (PT) in a case-control study, and infants' acquisition of DR during breastfeeding (BF) in the PROMISE 1077BF trial.

Methods: 85 HIV-infected infants and their transmitting mothers were compared to 254 HIV-infected, non-transmitting control mothers. PT was categorized by time of diagnosis: in utero (IU) at ≤2 weeks or during BF at >2 weeks of age. Controls for each PT category were matched for date of delivery and site. Plasma from infant's date of HIV diagnosis, ART initiation, and last study visit, and mother's plasma ≥40c/mL from the nearest date proximate to PT (or their matching case's time of PT for controls) were genotyped by consensus sequencing (CS) of HIV pol. Infants and mothers were categorized as wild-type (WT) or DR based on major DR mutations (DRM) defined by the Stanford Database. Maternal viral loads (VL) and DR rates were independently compared using Mann-Whitney and Fisher's Exact tests. Adjusted analyses used logistic regression.

Results: Proximate to infant diagnosis, case mothers had higher median VL vs. controls (4.28 vs. 3.86 log10 c/mL, p<0.0001). DR was significantly higher in transmitting vs. control mothers (15.8% vs. 7.6%, p=0.048). DR was more prevalent in mothers who transmitted via BF compared to IU (29.7% vs. 4.4%; p=0.002). In a logistic regression adjusted for VL, antepartum (AP) treatment arm, and clinical site, DR was no longer associated with PT (p=0.618), while VL increased (p<0.0001) and AP triple ARV decreased (p=0.021) risk of PT. Of 75 infants with CS, 5/40 (12.5%) with IU vs. 19/35 (54.3%) with BF transmission had DRM at diagnosis (p<0.001). Of the 24 DR infants, 58.3% had 1 NNRTI DRM, 25% had ≥2 NNRTI DRM, 12.5% had 1 NRTI DRM, and 4.2% had dual-class DRM. Among 72 mother-infant pairs genotyped, 46 (64%) were concordant for WT, 7 (9.7%) concordant for DR and 19 (26.3%) were discordant (17 (89.5%) WT mothers had DR infants). Among 46 infants with longitudinal genotypic data, 8/13 (62%) WT infants at diagnosis in the IU cohort and 1/6 (17%) WT infants in the BF cohort acquired DRM resulting in 33/75 (44%) DR infants.

Conclusion: DR was frequently detected among women with PT during BF. However, in this study, DR does not appear to be a driver of PT. DR was less prevalent in infants with IU vs. BF PT, and accumulated during early infancy, suggesting that exploration of additional prophylactic regimens is warranted.

Table 1: Maternal viral load (ranges) and genotype by perinatal transmission type

		Cases			Controls			Case vs Control
		Genotype		Total	Genotype		Total	p-value
		Wild-Type	Drug-Resistant		Wild-Type	Drug-Resistant		Univariate Analysis
IU/Peripartum	Number of Women	43 (95.6%)	2 (4.4%)	45	117 (95.1%)	6 (4.9%)	123	1.0000
	Median VL (Log10), range	4.00 (2.61-6.18)	4.10 (3.60-4.60)	4.00[a] (2.61-6.18)	3.77 (2.35-5.45)	4.05 (3.42-5.26)	3.79[a] (2.35-5.45)	0.1471[a]
Breast-feeding	Number of Women	26 (70.3%)	11 (29.7%)	37	91 (89.2%)	11 (10.8%)	102	0.0155
	Median VL (Log10), range	4.73 (2.64-6.00)	4.75 (2.91-5.82)	4.73[b] (2.64-6.00)	3.91 (1.84-5.65)	3.47 (2.73-5.22)	3.91[b] (1.84-5.65)	<0.0001[b]
Overall	Number of Women	69 (84.1%)	13 (15.8%)	82	208 (92.4%)	17 (7.6%)	225	0.0481
	Median VL (Log10), range	4.20 (2.61-6.18)	4.66 (2.91-5.82)	4.28[c] (2.61-6.18)	3.87 (1.84-5.65)	3.83 (2.73-5.26)	3.88[c] (1.84-5.65)	<0.0001[c]

[a,b,c] Denote which variables were compared and their corresponding p-value.

770 GP41 ECTODOMAIN-SPECIFIC IGG IS ASSOCIATED WITH INCREASED VERTICAL HIV-1 TRANSMISSION

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Background: Studies of the epitope specificity of maternal antibodies in relation to reduced risk of mother-to-child transmission (MTCT) have identified correlates of protection in some studies. However, there is little consistency between results across studies. In addition, few studies have investigated pre-existing passively-acquired HIV-specific antibody responses in infants, which are most relevant because they are present prior to HIV exposure through breastfeeding. We hypothesized that pre-existing passively-acquired antibodies that target specific epitopes confer protection against MTCT of HIV-1.

Methods: We performed binding antibody multiplex assays to measure IgG binding against a cross-clade panel of 19 HIV-1 antigens in a cohort of 72 breastfeeding Kenyan mother-infant pairs enrolled during the pre-ART era. Infant plasma from the first week of life (before infection) and paired maternal plasma were screened for binding. IgG binding of the non-transmitting vs transmitting maternal samples (or uninfected vs infected infant samples) were compared by a logistic regression analysis adjusting for maternal viral load.

Results: IgG binding to two antigens, a gp41 ectodomain protein and gp140 monomer, which contains the gp41 ectodomain, was significantly higher for transmitting mothers compared to non-transmitting mothers (ectodomain p=0.005; gp140 p=0.021), with a similar trend for maternal IgG binding to a gp41 full length protein (p=0.0501). Passively-acquired IgG binding for infected infants compared to uninfected infants also showed trends in the same direction for these antigens (ectodomain p=0.058; gp140 p=0.071; gp41=0.080). None of the gp120-only antigens or the envelope SOSIP trimer, where the gp41 ectodomain is present but partially buried, showed a difference in binding between the transmission groups for either maternal or passively-acquired IgG.

Conclusion: These data suggest that in this cohort, IgG targeting the gp41 ectodomain is associated with increased odds of MTCT. This suggests that some antibody responses may be detrimental in terms of MTCT risk. Determining whether gp41 antibodies directly affect transmission or whether their presence reflects a redirecting of the responses toward epitopes exposed on non-native envelope may help better define protective antibody responses need to prevent MTCT.

771 EPITOPE TARGETS OF ADCC-MEDIATING ANTIBODIES AND THEIR RELATION TO MTCT OF HIV-1

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Background: We previously reported that passively-acquired antibody-dependent cellular cytotoxicity (ADCC) in infants is associated with improved survival of infected infants and a trend towards protection against mother-to-child transmission (MTCT) of HIV-1. However, the epitopes of these beneficial ADCC-mediating antibodies have not been investigated. Because CD4-incudible (CD4i) epitopes are a common target of antibodies elicited by natural infection, we hypothesized that ADCC targeting these CD4i epitopes may contribute to improved infant survival.

Methods: LALA variants to 3 CD4i antibodies, A32, C11, and 17b, were used as inhibitors in a competition rapid and fluorometric ADCC assay to measure CD4i epitope-specific ADCC of plasma samples from a cohort of 72 breastfeeding Kenyan mother-infant pairs enrolled during the pre-ART era. Infant plasma from the first week of life (pre-infection) and paired maternal plasma were tested. A32-like, C11-like, and 17b-like ADCC of the non-transmitting vs transmitting maternal plasma (or uninfected vs infected infant plasma) were compared using logistic regression adjusted for maternal viral load. The effect of ADCC targeting CD4i epitopes on infected infant survival was assessed by Cox-proportional hazards models.

Results: A32-like and C11-like ADCC were common in this cohort but were not associated with MTCT (Table 1). A32-like ADCC was not associated with infected infant survival, but maternal C11-like ADCC was associated with a trend towards increased mortality of infected infants (HR=1.062; p=0.09; Table 1). Surprisingly, 17b-like ADCC was negative in the majority of samples, indicating that 17b-LALA mediated an enhancement of plasma ADCC. This enhancement was not associated with MTCT but was associated with increased infected infant mortality (Table 1). Enhancement with 17b-LALA was inversely correlated with total ADCC (Pearson R: -0.72), indicating that the negative association of enhancement with infant outcome may be due to lower total ADCC, consistent with our previous report.

Conclusion: While CD4i-epitope-specific ADCC antibodies were elicited in this cohort, they likely are not responsible for improved infant outcome seen with higher passively-acquired ADCC. As suggested by the trend with maternal C11-like ADCC, C11-like ADCC may actually be associated with worse infant outcome, although further investigation is necessary.

Table 1

	Maternal Plasma (N=72; 51 NT, 21 T)				Infant Plasma (N=71; 51 HEU, 20* HIV+)			
	A32-like ADCC	C11-like ADCC	17b-like ADCC	Enhancement by 17b-LALA[a]	A32-like ADCC	C11-like ADCC	17b-like ADCC	Enhancement by 17b-LALA[a]
Mean Ab-like ADCC activity (entire cohort)	+37.21%	+13.59%	-45.15%[b]	+45.15%[b]	+39.47%	+11.88%	-42.02%[b]	+42.02%[b]
Effect on transmission (N=72 or 71[c])								
Mean difference of Ab-like ADCC between transmission groups (NT-T or HEU-HIV+)	-10.51	-1.65	-11.08	+11.08	-8.22	+9.36	+8.72	-8.72
Logistic regression adj. for maternal VL (aOR (p))[d]	1.010 (0.34)	1.001(0.85)	1.010 (0.11)	0.990 (0.11)	1.005(0.60)	0.991(0.33)	1.003(0.58)	0.997 (0.58)
Effect on infected infant survival (N=21 or 20*)								
Cox proportional hazards model (HR (p))[e]	1.009(0.57)	1.062(0.09)	0.987(0.08)	1.013 (0.08)	1.019(0.27)	1.004(0.80)	0.992(0.03)*	1.009(0.03)*

Antibody-like ADCC was calculated as 100%-(ADCC in the presence of LALA antibody/total ADCC without competition), averaged from two biological replicates. Within each biological replicate, samples with total ADCC without competition below our limit of detection (pre-specified as 2*total ADCC without competition of negative control influenza antibody) were excluded from this analysis. 7 maternal samples (5 NT, 1T) and 6 infant samples (5 HEU, 1 HIV+) met this exclusion criteria for at least 1 replicate.
a: Plasma from one HIV+ infant was no longer available.
b: Negative 17b-like ADCC activity indicates enhancement of ADCC by the 17b-LALA antibody. Enhancement = (ADCC in the presence of 17b-LALA/total ADCC without competition)-100%.
c: Effect of antibody-like ADCC on odds of MTCT was assessed by logistic regression adjusted for maternal viral load
d: only HIV-infected infants were included in the Cox proportional hazards model
*statistical significance: p<0.05
Abbreviations: Ab, antibody; NT, non-transmitter; T, transmitter; HEU, HIV-exposed uninfected; HIV+, HIV-infected; VL, viral load; adj., adjusted; aOR, adjusted odds ratio

772 ABUNDANT EXPRESSION OF CCR5 ON EARLY HOFBAUER CELLS MAY INCREASE HIV-1 SUSCEPTIBILITY

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Background: Even with optimal adherence, maternal antiretroviral therapy reduces, but does not eliminate, vertical transmission of HIV-1. Placental macrophages (Hofbauer cells, HCs) are thought to be key mediators of in utero HIV-1 transmission to the fetus. Previous studies have demonstrated that HIV-1 replication of HCs can be regulated by cytokines and interferons (IFNs) (Cobos Jimenez, Booiman et al. 2012), and that certain maternal coinfections (such as HCMV) (Johnson, Boggavarapu et al. 2018) can enhance HC susceptibility and viral replication in vitro by altering HC polarization. Early gestation placental tissue has yet to be evaluated in the context of HIV-1 permissivity.

Methods: Here, we determined the levels of expression of HIV-1 co-receptors CCR5 and DC-SIGN on HCs isolated from fresh placentae throughout gestation (12 weeks to term) and evaluated expression of HIV-1 restriction factors SAMHD1, Tetherin, Trim5α, TREX-1, and APOBEC3G. To determine if HC polarization and activation state differentially modify HIV-1 permissivity throughout gestation, HCs were subjected to polarizing conditions (LPS+IFN-γ, IL-10) or IFNs (IFN-α A/D, IFN-λ1), and changes in receptor and restriction factor expression were determined at the protein and RNA level.

Results: Basal CCR5 expression levels significantly differed throughout gestation; while only 50% of term HCs expressed CCR5, 100% of early gestation HCs were positive for this receptor. Surface expression of CCR5 remained stable at the protein level and was increased at the RNA level. HIV-1 restriction factors were present at baseline and were upregulated in HCs as a result of treatment. Upregulation of restriction factors in HCs isolated from early gestation matched or exceeded that of term samples, suggesting a level of innate immune protection from vertical transmission even in early pregnancy. Interestingly, IFN-λ1, which is strongly produced by placental trophoblasts, did not affect the expression of HIV-1 restricting factors, suggesting a limited role in controlling HIV-1 replication in HCs.

Conclusion: Placental macrophages in early pregnancy may be susceptible to HIV-1 infection due to abundant expression of CCR5, as compared to term samples. Co-receptor expression may be counterbalanced by robust basal and cytokine-induced expression of key HIV-1 restriction factors in HCs, offsetting in utero transmission early in gestation.

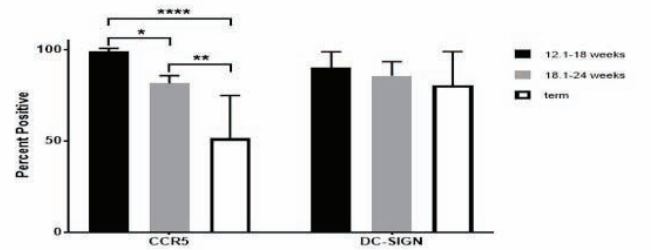

Figure 1: HIV-1 coreceptor expression in placental macrophages. Freshly isolated HCs were stained with antibodies against CCR5 and DC-SIGN, and analyzed with flow cytometry. Results are given as percent of total live, CD14+ cells. Means of each marker were calculated and compared between different macrophage populations using two-way ANOVA with Tukey's correction for multiple comparisons. *p<0.05, **p<0.01, ****p<0.0001

773 INCIDENT HIV INFECTION AMONG PREGNANT WOMEN IN BOTSWANA

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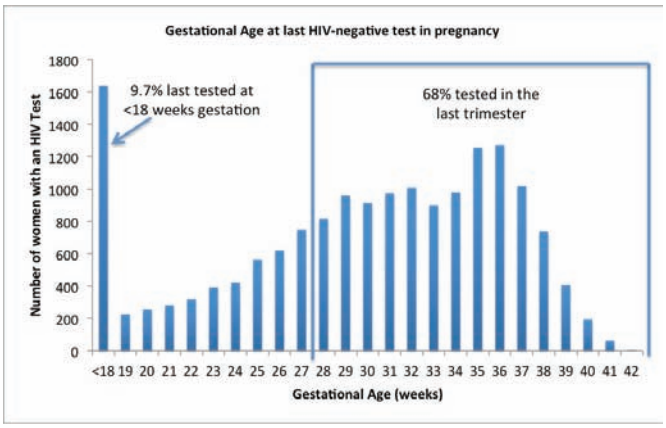
Background: In Botswana, >90% of HIV+ women receive ART in pregnancy. An increasing proportion of MTCT may occur among women with incident undiagnosed HIV infection during pregnancy. Botswana guidelines recommend repeat HIV testing every 3 months in pregnancy, with at least 1 in the 3rd trimester. We evaluated the rate of antenatal repeat HIV testing and estimated HIV incidence during pregnancy.

Methods: In the Tsepamo Study, we abstracted HIV test dates and results from obstetric records of all women who delivered in 8 maternities across Botswana between May 2017 (when abstraction of these data were added) and Sept 2018. This analysis includes women not known to be HIV+ at the start of pregnancy. We defined seroconversion as an initial negative or indeterminate HIV test in pregnancy, followed by a positive test. The incidence rate (IR) of seroconversion was calculated among women with >= 2 known testing dates during pregnancy. Missed seroconversions were estimated among women without a test in the 3rd trimester by applying the IR to the time after their last HIV test until delivery.

Results: Among 28,999 women delivering, 5724 (20%) were known to be HIV+ prior to pregnancy 1,758 (6.1%) tested HIV+ at first test in pregnancy, 229 (0.8%) had no HIV test in pregnancy, 57 (0.2%) were unknown, and 21,231 (73%) tested HIV-negative at first test in pregnancy. Of women who initially tested negative, 5321 (25%) had 1 test, 12225 (58%) had 2 tests, and 3678 (17%) had 3 tests during pregnancy. The median gestational age at first HIV test was 16 weeks (IQR 12,21) and median gestational age at last HIV test was 31 weeks [IQR 26,35], with 68% tested in the 3rd trimester (Figure 1). Older women, women with more education, and primigravid women had more HIV tests. The proportion with only one test also differed by site (range 11%-50%). There were 39 seroconversions identified among 15,940 pregnancies (2.4/1000 pregnancies) with at least 2 HIV tests, yielding an IR of 6.5/1000 person-yrs. Among 5547 women without an HIV test in the 3rd trimester, we estimate approximately 10 seroconversions may have been missed because of a lack of repeat testing.

Conclusion: In pregnancy, HIV incidence after an initial negative test was low and the majority of women tested in the 3rd trimester. However lack of re-testing in the 3rd trimester led to an estimated 20% decrease in detection of seroconversions. To reach the goal of zero new pediatric HIV infections, Botswana will need to intensify identification of incident HIV.



774 HETEROGENEITY OF HIV RETESTING DURING PREGNANCY AND POSTPARTUM IN KENYA

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Background: HIV retesting during pregnancy/postpartum is crucial for early detection and treatment of incident maternal HIV infection, and to

achieve elimination of mother-to-child HIV transmission (MTCT). Kenyan guidelines recommend retesting peripartum HIV negative women but data on implementation are lacking. We measured the frequency of HIV retesting during pregnancy, delivery, and postpartum and correlates of postpartum retesting.
Methods: HIV-seronegative women seeking maternal and child health (MCH) services were enrolled in a cross-sectional study in rural Kenya at the Ahero County and Bondo sub-County Hospitals at one of the following time points: pregnancy; delivery; 6 weeks, 6 months, or 9 months postpartum. Data on programmatic retesting was abstracted from MCH booklets to ascertain retesting during pregnancy and/or postpartum prior to the study visit. Retesting was defined as any HIV test after the initial antenatal care (ANC) test or after pregnancy if testing was not done in ANC. Poisson regression, clustered by site, was used to identify correlates of retesting among women enrolled at 9 months postpartum.
Results: Among 1919 women enrolled, the median age was 23 years, 63% were married and the median number of times tested for HIV in the most recent pregnancy/postpartum period was 1 (interquartile range [IQR]: 1-2). Overall, 659 women were enrolled in the 3rd trimester, 128 within 48 hours after delivery, 387 at 6 weeks postpartum, 412 at 6 months postpartum, and 333 at 9 months postpartum. Prevalence of any programmatic HIV retesting was significantly higher at 6 weeks postpartum (46%) than in the 3rd trimester (23%), at delivery (5%), and at 6 months postpartum (28%) ($p<0.001$ for all). By 9 months postpartum, HIV retesting was associated with prior sexually transmitted infection (STI) diagnosis (Prevalence Ratio [PR]:1.28, 95% Confidence Interval [CI]:1.06-1.56; $p<.001$), higher gravidity (PR:1.05 per pregnancy, 95% CI:1.04-1.06; $p<.001$), and being an orphan (PR:1.02, 95% CI:1.01-1.02 $p=.02$). Results were similar in a multivariable analysis of cofactors significant in the univariate model.
Conclusion: Prevalence of retesting was higher in the early postpartum period and more common among women who had a history of STIs and higher gravidity. Strategies to offer retesting to all peripartum women in high prevalence regions could help identify incident maternal HIV and maximize prevention of MTCT efforts.

775 PRIMARY HIV PREVENTION IN PREGNANT AND LACTATING UGANDAN WOMEN: A RANDOMIZED TRIAL

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Background: The 'Primary HIV Prevention among Pregnant and Lactating Ugandan Women' (PRIMAL) study aimed to assess the effectiveness of enhanced counseling for preventing HIV acquisition among HIV-uninfected pregnant women throughout the breastfeeding period.
Methods: We conducted an unblinded randomized control trial between 02/2013 and 04/2016 to assess the effectiveness of enhanced counseling to prevent primary HIV infection among HIV-uninfected pregnant and lactating women in Uganda. HIV-uninfected pregnant women aged 15-49 were enrolled individually or in couples, randomized 1:1 to an intervention or control group, and followed up to 24 months postpartum or the end of breastfeeding, whichever came first. Both groups were tested for STIs and HIV at enrollment, delivery, 3 and 6 months postpartum and every 6 months thereafter until the end of follow-up. The intervention group received enhanced HIV prevention counseling every 3 months throughout follow-up. The control group received standard counseling at the time of HIV retesting.
Results: We enrolled 820 HIV-uninfected pregnant women individually (n=410) or in couples (n=410 women and 410 partners) in one urban and one rural public Ugandan hospital. 675 (76%) women completed follow-up per protocol representing 1,439 women-years of follow-up. Although the frequency and proportion of condom use in the last 3 months or at last vaginal sex increased over follow-up, there were no statistically significant differences between the study arms. During follow-up, <2.1% of women tested positive for either syphilis, gonorrhea, C. trachomatis or T. vaginalis at any follow-up visit, while four women (two per arm) and no enrolled men became infected with HIV, for an overall HIV incidence rate of 0.186 per 100 person-years. There were no statistically significant differences between study arms
Conclusion: A sustained enhanced HIV prevention counseling intervention for up to 2 years postpartum among pregnant and breastfeeding women did not have a statistically significant effect on condom use or HIV incidence among these women. However, in both study arms, condom use increased over follow-up while STI and HIV incidence remained very low, suggesting that repeat HIV testing during breastfeeding, whether with standard or enhanced counseling, could be an effective strategy for the primary prevention of HIV among pregnant and lactating women in high HIV prevalence settings. Further research is needed to verify this hypothesis.

776 MODELING THE IMPACT OF PrEP FOR PREGNANT AND BREASTFEEDING WOMEN IN SOUTH AFRICA

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Background: HIV-uninfected pregnant and breastfeeding women are at high risk of HIV acquisition, contributing to persistent high levels of MTCT. Pre-exposure prophylaxis (PrEP) is safe and effective in preventing HIV acquisition in pregnancy, but PrEP in pregnancy is not policy in many countries including South Africa (SA). We examined the potential impact of providing PrEP for SA pregnant and breastfeeding women.
Methods: We used the Thembisa model, an established SA model to estimate the potential effect of introducing PrEP for pregnant and breastfeeding women. The model divides the SA population by key demographic factors and, among sexually active individuals, into high-risk (individuals with a propensity for concurrent partners and/or commercial sex) and low-risk individuals. We consider two scenarios for modelling PrEP uptake during pregnancy and breastfeeding: (1) a conservative scenario with model assumptions to match the experience reported in the Kenyan PrEP program for pregnant women (uptake probability=32% and 11% in high-risk and low-risk women, respectively); (2) an optimistic scenario with PrEP initiated by 80% of all pregnant women (high-risk and low-risk). PrEP in pregnant/breastfeeding women scenarios were compared with PrEP for female sex workers (FSWs), men who have sex with men (MSM), and adolescent girls and young women (AGYW). PrEP efficacy was assumed to be 65% throughout.
Results: Between 2020-2030, providing PrEP to pregnant and breastfeeding women would reduce new HIV infections in SA by 2.5% (95%CI:2.4-2.6%) in the conservative scenario and 7.2% (95%CI:6.8-7.5%) in the optimistic scenario (Figure). This is similar to the FSW and MSM PrEP scenarios (1.9% and 3% respectively). Without PrEP, 76,000 (95% CI: 64,000-90,000) new cases of MTCT are expected over 2020-2030; PrEP provision may reduce these infections by 13% (95% CI: 13-14%) in the conservative scenario and 41% (95% CI: 39-44%) in the optimistic scenario. Under the optimistic scenario PrEP would have a proportionally greater impact on breastfeeding transmission (47% reduction, 95% CI: 44-49%) vs. in utero and intrapartum transmission (23% reduction, 95% CI: 18-27%).
Conclusion: High levels of uptake of and adherence to PrEP among pregnant and breastfeeding women could fundamentally alter MTCT in SA. There is an urgent need for implementation research to identify interventions that will facilitate PrEP use during pregnancy and breastfeeding in this setting.

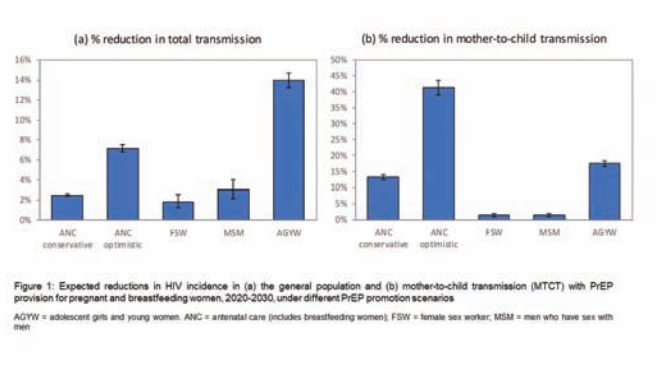

Figure 1: Expected reductions in HIV incidence in (a) the general population and (b) mother-to-child transmission (MTCT) with PrEP provision for pregnant and breastfeeding women, 2020-2030, under different PrEP promotion scenarios

AGYW = adolescent girls and young women. ANC = antenatal care (includes breastfeeding women); FSW = female sex worker; MSM = men who have sex with men

777 PREFERENCES FOR HOME VS CLINIC AND BLOOD VS SALIVA HIV RETESTING IN PREGNANCY

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Background: HIV retesting during pregnancy and postpartum is critical to reduce mother-to-child HIV transmission (MTCT) due to incident maternal infections. However, widespread scale-up of this policy may confer additional strain on health systems. HIV self-testing may be an innovative solution for maternal retesting by addressing client access barriers and staffing shortages.
Methods: HIV-negative pregnant women were enrolled between November 2017 and August 2018 in Nyanza and Nairobi regions in Kenya. At enrollment, retesting preferences were assessed for location (clinic or home), test type (saliva- or blood-based rapid), and test performer (self or provider). Reasons for preferences were assessed and women were asked to select a test strategy for retesting during the current pregnancy: blood-based testing by a provider in clinic (clinic-based testing [CBT]) or self-testing at home using a saliva-based test (home-based testing [HBT]). Chi-squared and t-tests were used to compare reasons for choice. Generalized linear models (log link, binomial family) were used to assess cofactors for testing strategy.
Results: Overall, 1,000 pregnant women were enrolled, with a median gestational age of 28 weeks (Interquartile range [IQR]: 22-32) and median age 24 years (IQR: 21-27). More women elected CBT (665 [67%]) than HBT (335 [34%]) for retesting ($p<0.001$). Later gestational age was associated with lower likelihood of electing HBT (PR per week: 0.99, 95%CI: 0.98-1.0, $p=0.04$). Maternal age, parity, income, education, same day HIV testing, marital status, relationship duration, and partner testing history were not associated with choice ($p>0.05$ for all). Preferences for test location (33% home vs 67% clinic), test operator (31% self vs 69% provider), and test type (32% saliva vs 68% blood) mirrored choice of HBT or CBT. Women who elected HBT were more likely to report being unavailable during clinic hours than women who elected CBT (18% vs 10%, $p<0.001$) and report longer clinic wait times (73 vs 53 minutes, $p<0.001$).
Conclusion: While pregnant women generally preferred CBT for HIV retesting, HIV self-testing at home was preferred by one-third of women, particularly those with challenges accessing health centers. As HIV retesting scales up in pregnancy and postpartum, HBT may reduce burden on health systems, increase retesting rates, and facilitate efforts to eliminate MTCT.

778 CHALLENGES OF POTENTIALLY FALSE-POSITIVE HIV TESTS IN PREGNANT WOMEN IN THE PrEP ERA

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Background: HIV testing, done repeatedly over time, is a cornerstone of both antenatal care (ANC) and PrEP care. In many settings, HIV rapid tests are done in sequence to confirm infection, but discrepant results (i.e. one positive, one negative) can occur. Guidelines are lacking for how to make treatment decisions after discrepant rapid results in the context of pregnancy and PrEP where urgent antiretroviral treatment (ART) to prevent mother-to-child transmission could be indicated but inappropriate ART may have negative psychosocial, interpersonal, and health systems impacts.
Methods: In a cluster randomized trial in Kenyan public health programs (NCT03070600), PrEP is offered to HIV seronegative women at ANC. Repeat HIV testing is done at each follow-up visit (monthly in pregnancy, tri-monthly in postpartum). The Kenyan national HIV testing algorithm indicates that if one rapid (Determine) is reactive, a second (First Response) is performed; if discrepant, both tests are repeated by a separate provider and a DNA PCR is performed using standard of care national referral systems.
Results: Among 2,231 women enrolled during pregnancy and followed for postpartum care, 3,135 repeat HIV tests have been performed, 7 of which had discrepant rapid results (0.22%, 95% CI: 0.09-0.46%) among 5 individuals. DNA PCR samples were collected on the same day as discrepant results; median time to receipt of PCR results was 22 days (range 16-37). In all 5 initial cases, DNA PCR was negative and none of the women were initiated on ART. Two of 5 women subsequently had repeat discrepant rapid results with repeat negative PCRs, one of whom had subsequent concordant positive rapid results (PCR pending) at delivery and declined ART due to disbelief in rapid test results.
Conclusion: False positive results are expected to occur at a low frequency with repeated rapid testing. For individuals who are pregnant or using PrEP, positive results demand urgent ART, but false results could trigger inappropriate ART. As repeat HIV testing during pregnancy and PrEP monitoring expands, the volume of discrepant rapid test results will increase. Our data provide evidence that discrepant results are more likely false positive than true positive. Management of discrepant results needs to balance benefits of rapid ART for PMTCT among true positives, with specific counseling about temporary ART and "disclosure" among women with false positive results. Expedited point-of-care HIV PCR could prevent unclear diagnosis, messaging, and treatment.

First test	Second test	Third test	Fourth test	Fifth test	Days to PCR results	PrEP user	Final HIV Status
Reactive (D)	Non-reactive (FR)	Reactive (D)	Non-reactive (FR)	Negative DNA PCR (FP)	28	No	Negative*
Reactive (D)	Non-reactive (FR)	Reactive (D)	Non-reactive (FR)	Negative DNA PCR (FP)	37	No	Negative
Reactive (D)	Non-reactive (FR)	Reactive (D)	Non-reactive (FR)	Negative DNA PCR (FP)	21	No	Negative
Reactive (D)	Non-reactive (FR)	Reactive (D)	Non-reactive (FR)	Negative DNA PCR (FP)	22	No	Negative**
Non-reactive (D)	Reactive (HIV & Syphilis dual test)	Negative (FR)	Negative DNA PCR (FP)		16	No	Negative

(D) Determine; (FR) First Response; (FP) Filter paper
* Repeat discrepant at next visit but PCR negative; concordant rapid positive at 3rd visit (PCR results pending)
** Repeat discrepant at next visit, no PCR taken

779 PILOTING POINT-OF-CARE HIV TESTING AT BIRTH AND 6 WKS POSTNATAL IN 4 KENYAN HOSPITALS

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Background: Point-of-care (POC) testing can expedite HIV diagnosis and treatment among HIV-exposed infants, particularly if performed at birth. Repeat testing at 6 wks is needed to detect intrapartum infections.
Methods: A non-blinded pilot study was conducted at 4 Kenyan hospitals with randomly assigned POC technologies (n=2 GeneXpert, n=2 Alere q). Implementation was tailored to a hospital's layout, departmental collaborations, and patient flow. Exposed infants enrolled in the study were targeted for POC testing at birth (0 to <2 wks) and the 6-week period (4-8 wks). We report preliminary results for median age at birth and 6-week POC testing for 434 infants born November 3, 2017 to July 5, 2018, uptake of the POC test at both stages, and median age at ART initiation and drug resistance (DR) status for HIV+ infants.
Results: Of 434 infants, 358 (82.5%) received POC testing at any timepoint; 219 (61.2%) of these received a POC test within the birth window. Infants tested with POC at birth included 100 (45.7%) tested in Maternity (≤2 d of age) and 119 (54.3%) tested on a return visit (3-14 d of age). The median age at birth POC was 0.4 wks (IQR, 0.1-1.3). An additional 52 (14.5%) infants received a first POC test in the near-birth (2 to <4 wks) period, at median age 2.5 wks (IQR, 2.1-3.0). In the 6-wk window 257 (71.8%) received a POC test, at median age 6.1 wks (IQR, 6.0-6.3). Among infants receiving an initial POC test at or near-birth, 170 (62.7%) returned for a repeat test in the 6-wk period. The optimum test sequence (first at 0-2 wks, then at 4-8 wks) was achieved for 144 (40.2%) infants. A total of 91 missed opportunities for POC were due to machine breakdown (12: all Alere q),

machine errors (44: 42 Alere q, 2 GeneX) or cartridge stock-out (35: 14 Alere q, 21 GeneX).

Conclusion: POC testing at birth and 6 wks requires collaboration among departments and cadres of personnel, yet is feasible in government hospitals in Kenya. Patient education and provider sensitization are needed to support POC at birth, repeat testing at 6 wks, and immediate ART initiation to realize the full benefit of POC technologies.

780 ROUTINE POINT-OF-CARE HIV TESTING AT BIRTH: RESULTS FROM A 1-YEAR PILOT IN ESWATINI

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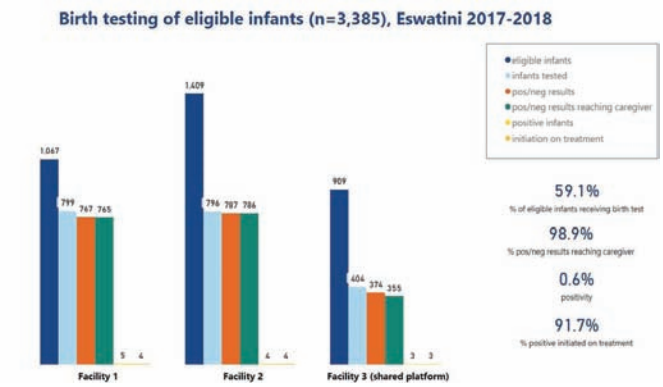
Background: In 2017, point of care (POC) birth testing was introduced into routine care at the 3 highest volume maternity sites in Eswatini. POC birth testing was offered to HIV-exposed infants born at, or presenting to, the maternities within 3 days of birth. Two of the POC platforms were used only for birth testing; one was shared with another hospital unit. National guidance states that infants testing negative at birth should return for a 6-week test; infants testing positive at birth should start nevirapine (NVP) immediately and return at 14 days of life to begin a lopinavir/ritonavir regimen (LPV/r).

Methods: Prospective data were collected on tests occurring 1 Aug 2017-1 Aug 2018. Variables included number of infants eligible for birth testing, percentage of infants tested, turnaround time from sample collection to receipt of results, positivity, percentage of infected infants initiated on treatment, turnaround time from sample collection to treatment initiation, and percentage of infants testing negative at birth who received a subsequent test at 6 weeks.

Results: Of 3385 eligible infants, 1999 (59.1%) received a birth test. Of those producing a positive or negative result (n=1928; 96.4%), 98.9% (n=1906) reached the caregiver. Median turnaround time from sample collection to caregiver receipt of results was 0 days (range 0-31; IQR 0-0). Testing uptake was lower, but turnaround time to result receipt was not longer for the shared platform. 12 HIV-infected infants were identified (yield = 0.6%) and 11 were initiated on treatment (91.7%); 3 on day 14 after diagnosis, 4 after 15 days, and 4 after 60 days. The median time from sample collection to initiation on treatment for positive infants was 32 days (range 14-124; IQR 16-65). One infant died after diagnosis but prior to initiation. Analysis of subsequent tests of infants who tested negative at birth is ongoing (and will be available to be presented at CROI).

Conclusion: POC EID at birth is a feasible strategy in this setting. However, not all eligible infants were tested, possibly due to staff shortages or queues for platform use. In practice, infants received no treatment until they returned to begin LPV/r. Same-day pediatric treatment initiation is uncommon in Eswatini due to caregiver desire to consult with male family members. Policymakers may consider better promotion of NVP at birth, the introduction of new pediatric formulations that can be used at birth and beyond, and/or better linkage to care to ensure timely initiation on treatment.



781 EARLY INFANT DIAGNOSIS OF HIV USING DNA PCR CT VALUE AND REPEAT TESTING ALGORITHM

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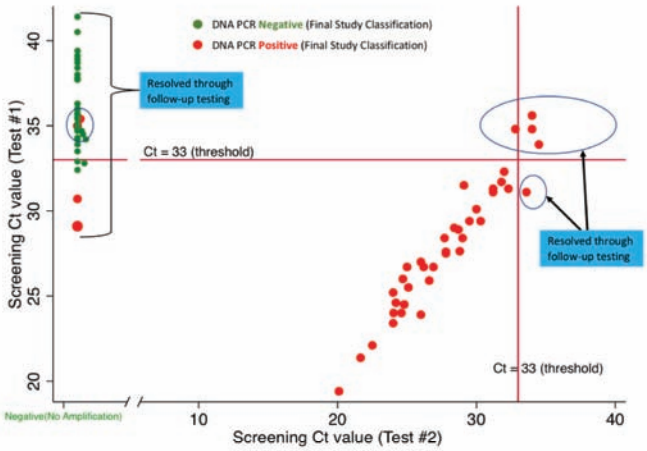
Background: Early infant diagnosis (EID) of HIV immediately after birth allows for rapid initiation of treatment in HIV+ infants, limiting disease progression and restricting viral reservoir seeding. However, no standardized testing algorithm is currently recommended.

Methods: From April 2015-July 2018, the Early Infant Treatment Study (EIT) screened HIV-exposed infants in Botswana < 96 hours from delivery by Roche TaqMan qualitative DNA PCR. A negative DNA PCR test was defined as no HIV DNA amplification (target not detected) at initial dried blood spot screening; a positive as two concordant spots from same sample with target detected at any cycle threshold (Ct) value; and indeterminate as discordant spots (target detected/target not detected) from same sample. Repeat blood draw occurred for initial positive and indeterminate results. Quantitative HIV-1 RNA testing occurred for those presumptively enrolled in the study. We compared Ct values by the ultimate HIV status of the child (as confirmed by subsequent HIV-1 DNA, and when possible DNA/RNA, testing).

Results: Of 10622 HIV-exposed infants screened, 10549 (99.3%) tested negative, 42 (0.4%) tested positive, and 31 (0.3%) tested indeterminate at the first HIV screening test. On repeat testing, 40 (95.2%) of the initial 42 positive infants remained positive and 2 (4.8%) tested negative. Of the 31 indeterminates, repeat testing confirmed 29 (93.5%) as negative and 2 (6.5%) as positive. Confirmatory testing of all positives and indeterminates re-classified 4 (5.5%) infants in total; 1 (1.4%) of the indeterminates required further HIV RNA testing to become reclassified as positive. Median DNA PCR Ct value at screening was 28.1 (IQR 19.8, 34.8) for all positive results and 35.5 (IQR 32.8, 41.4) for indeterminates (p<0.0001). Only 6 (8.2%) infants with final HIV+ status had Ct value > 33 at first screen, and only 2 (6.5%) with indeterminate result and Ct value < 33 at first screen had a final negative HIV status.

Conclusion: Using a standard cycle threshold of 33 and a confirmatory second blood draw for HIV DNA and RNA, our test algorithm appeared to eliminate the risk for false positive HIV results in the first week of life. Infants with Ct >33 should be re-tested with follow-up sampling, to minimize the risk for false positive testing.

Figure 1: Comparison of Ct values for the initial screening DNA PCR test performed within 96 hours of delivery in Botswana*



*Note: Initial screening consisted of dried blood spot testing on a single spot (Test#1), with a second spot (Test #2) performed for all instances of HIV DNA target detection at any cycle threshold. Follow-up testing (results not shown) was performed on a second blood sample (using dried blood spot or plasma).

782 DIAGNOSTIC ACCURACY OF HIV ORAL RAPID TESTS VS BLOOD-BASED RAPID TESTS AMONG CHILDREN

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Background: Gaps persist in HIV testing globally for children who missed testing in prevention of mother to child transmission of HIV programs. Oral mucosal transudate rapid HIV tests (OMT) have been shown to be highly sensitive in adults but their performance has not been established in children. We validated the OraQuick ADVANCE Rapid HIV-1/2 Antibody test against blood based rapid diagnostic testing (BBT) in children aged 18 months to 18 years in Kenya and Zimbabwe.
Methods: ART naïve children were tested for HIV using a series of rapid OMT and BBT. BBT followed the Kenyan and Zimbabwean national algorithms (Determine, followed by First Response [3rd generation] if Determine was reactive). The Determine test used in Zimbabwe was 4th generation, detecting antibodies and antigen; the Determine test used in Kenya was 3rd generation, detecting antibodies only. OMT samples were collected and interpreted by research staff; BBT were performed and interpreted by clinic or research staff. Sensitivity and specificity were calculated using the national algorithms as gold standard; secondary analysis excluded 2 cases where OMT was positive but national algorithm was initially falsely negative. Binomial distribution was used for 95% confidence intervals [95%CI].
Results: A total of 1,622 children were enrolled, median age was 7 years (IQR: 4,12); 2 (0.1%) were 18-24 months; 1310 (80.8%) were 2-12 years; 301 (18.6%) were 13-18 years. Among the 56 children positive by BBT, 56 (sensitivity: 100% [97.5%CI: 93.7-100%]) were positive by OMT. Among the 1566 children negative by BBT, 1564 (specificity: 99.9% [95%CI: 99.5-100.0%]) were negative by OMT. Due to clinical presentation and OMT results, the 2 children who initially tested BBT negative and OMT positive were subsequently confirmed positive within 1 week by further tests; one (9 years) by ELISA and the second (2 years) by First Response and a third test, INSTI. Excluding these 2 children, the sensitivity and specificity of OMT compared to BBT were each 100% (97.5%CI: 93.7-100% and 99.8-100%, respectively).
Conclusion: When compared to the national algorithms, OMT did not miss any positive children. This data suggests that OMT tests are valid in this age range and may be useful for facility or community-based use. Future research should explore the acceptability and uptake of OMT use by caregivers and health care workers in diverse settings to improve pediatric HIV testing coverage globally.

Table 1: Performance of OMT vs BBT for HIV diagnosis

		BBT		
		Positive	Negative	Total
OMT	Positive	56	2*	58
	Negative	0	1564	1564
	Total	56	1566	1622

**subsequently tested positive*

Sensitivity	100%
Specificity (including 2 discrepant)	99.9%
Specificity (excluding 2 discrepant)	100%

783 FINDING THE MISSING CHILDREN WITH HIV: INDEX-LINKED TESTING IN CLINICS & COMMUNITIES

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Background: HIV prevalence is much lower in children than in other age groups but the proportion undiagnosed is significantly higher. Therefore, innovative and targeted strategies are required to improve uptake and yield of HIV testing among children. We evaluated the effectiveness of index-linked HIV testing implemented in clinic and community-based settings in children aged 2-18 years living in the household of an HIV-infected individual in urban and rural settings in Zimbabwe.
Methods: Individuals attending for HIV care at 3 urban and 3 rural primary care clinics in western Zimbabwe who had children (2-18 years) of unknown HIV status living in their households were offered 3 options for their children to access HIV testing and counselling (HTC): 1) Clinic-based HTC 2) Home-based HTC by community health workers 3) Testing performed by caregivers using an oral mucosal test (assisted self-testing) Demographic data was collected from consenting caregivers who were followed up over 2 months to ascertain testing outcomes.
Results: We recruited 2813 people living with HIV (median age 38, IQR 32-46 years) who had 3431 children eligible for testing (median age 9, IQR 6-13 years). HTC was accepted for 2757 (80.4%) eligible children. Overall, 74.7% selected clinic-based testing, 19.2% opted for community-based testing and 6.1% for assisted self-testing, with no difference in trend by rural or urban setting. Among the 2757 children for whom HTC was accepted, 1977 (71.7%) completed testing. Those who selected community-based testing were more likely to complete the test than those who selected clinic-based testing (OR=1.69 95%CI:1.3-2.2, p<0.001) or assisted self-testing (OR=2.38 95%CI:1.0-2.3, p=0.04). Overall HIV prevalence was 1.4% but the prevalence among 12-18 year olds was 2.5% and 81% of those diagnosed were >7 years. HIV yield was 0.8% overall. Previously undiagnosed HIV was strongly associated with older age (OR=3.54, 95%CI:1.1-11.1, p=0.03) comparing 13-18 years to 2-5year olds and with single or double orphanhood (OR=3.10, 95%CI:1.4-6.9, p=0.005). All 28 HIV positive children were linked to care within 2 weeks.
Conclusion: Index-linked testing is a feasible HTC strategy for children in Zimbabwe. However, while clinic-based testing has the highest uptake, children were more likely to be tested in community settings. Older children and orphans are at increased risk of undiagnosed HIV. Strengthening of HTC strategies to target this age group are required.

784 EARLY CHILD DEVELOPMENT OF HIV-EXPOSED UNINFECTED CHILDREN IN RURAL ZIMBABWE

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Background: Maternal HIV exposure may affect early child development (ECD), but studies comparing developmental outcomes between HIV-exposed uninfected (HEU) and HIV-unexposed children have had heterogeneous findings. We compared ECD outcomes between HEU and HIV-unexposed children recruited to the SHINE trial in rural Zimbabwe.
Methods: SHINE was a community-based cluster-randomized trial of infant and young child feeding (IYCF) and water, sanitation and hygiene (WASH) interventions in two rural Zimbabwean districts (ClinicalTrials.gov/NCT01824940). We assessed ECD outcomes at 24 months of age using the Malawi Developmental Assessment Tool (MDAT, assessing motor, cognitive, language and social development); MacArthur-Bates Communication Development Inventory (CDI) (assessing vocabulary and grammar); A-not-B test (assessing object permanence); and a self-control task. All tools were designed for use in sub-Saharan Africa, and specifically adapted for Shona-speaking households. We used generalized estimating equations to compare ECD scores between HEU and HIV-unexposed children. We included only those randomized to the standard-of-care arm to evaluate children in the absence of trial interventions.

Results: 63 HEU and 373 HIV-unexposed children were evaluated at 24 months of age. Mean total MDAT score was 0.2 standard deviations (SD) lower in HEU compared to HIV-unexposed children (90.7 versus 92.7; mean difference -1.8; 95%CI -3.7, 0.1), driven mainly by lower gross motor scores (difference -0.8; 95%CI -1.5, -0.1). MacArthur-Bates CDI vocabulary scores were also 0.2 SD lower in HEU compared to HIV-unexposed children (56.9 versus 61.3 words; mean difference -4.2, 95%CI -8.3, -0.2). There was no evidence of a difference in object permanence or self-control scores between groups (Table).
Conclusion: ECD outcomes at 2 years of age differed between HEU and HIV-unexposed children in some but not all measures. There was some evidence that HEU children had lower total developmental scores, including lower language scores as assessed by a tool specifically adapted for Shona-speaking households. However, there was no evidence of differences in object permanence or self-control. Longer-term studies are needed to evaluate whether relatively small differences in motor and cognitive outcomes at age 2 years translate into meaningful differences in school attainment at older ages.

		HEU	HIV-unexposed		
		Mean score (SD)		Difference (95% CI)	P
MDAT	*Total score*	90.7 (8.1)	92.7 (9.5)	-1.8 (-3.7, 0.1)	0.06
	Gross motor	23.0 (2.6)	23.8 (3.3)	-0.8 (-1.5, -0.1)	0.02
	Fine motor	22.9 (2.4)	23.4 (2.7)	-0.4 (-1.0, 0.1)	0.11
	Language	20.7 (3.8)	21.4 (4.2)	-0.6 (-0.7, 0.4)	0.24
	Social	24.1 (2.1)	24.2 (2.1)	0.0 (-0.5 0.4)	0.95
MacArthur-Bates CDI vocabulary score		56.9 (18.3)	61.3 (18.7)	-4.2 (-8.3, -0.2)	0.04
A-not-B test		7.8 (1.3)	7.8 (1.3)	0.0 (-0.4, 0.4)	0.94
		Percentage		Risk ratio (95%CI)	P
Self-control task (hidden)		72.9	64.9	1.32 (0.87, 2.00)	0.19
Self-control task (unhidden)		53.4	47.3	1.14 (0.85, 1.51)	0.39

Table: Early child development in HIV-exposed uninfected and HIV-unexposed children at 24 months of age. HEU: HIV-exposed uninfected; MDAT: Malawi Developmental Assessment Tool; CDI: Communication Development Inventory; 95%CI: 95% confidence interval.

785 NEURODEVELOPMENT IN INFANTS OF WOMEN WITH PERINATALLY VS NONPERINATALLY ACQUIRED HIV

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Background: The neurocognitive and psychosocial impact of lifelong HIV and antiretroviral therapy (ART) may confer neurodevelopmental (ND) risk on offspring of women with perinatally acquired HIV infection (PHIV). No studies have assessed whether maternal PHIV is associated with early infant ND outcomes.
Methods: Using the Bayley Scales of Infant and Toddler Development, 3rd Ed. (Bayley-III), we compared ND outcomes at 1 year of age in HIV-exposed uninfected (HEU) infants born to women with PHIV vs. non-perinatally acquired HIV (NPHIV) enrolled in the Surveillance Monitoring for ART Toxicities (SMARTT) study. Eligible HEU infants included those with valid Bayley-III data at 1 year of age and mothers born after 1982. Cognitive, language, and motor domains were assessed as continuous composite scores. The proportion with a composite score <78 in each domain was also evaluated. Maternal PHIV status was identified by self-report and medical record review. Due to the clustering effect of siblings, linear mixed effects models were fit to estimate the mean difference in Bayley-III scores in each domain, comparing infants of women with PHIV vs. NPHIV, adjusting for potential confounders.
Results: 550 WLHIV gave birth to 678 HEU children (125 and 553 born to women with PHIV and NPHIV respectively). Women with PHIV were younger (median age 23 vs 25, p<0.01), more likely to be Hispanic (24% vs 12%, p<0.01), have a CD4 count <200 cells/mm^3 (21% vs 10%, p<0.01), and receive ≥3 classes of antiretrovirals (ARVs) in pregnancy (18% vs 3%, p<0.01). In addition, women with PHIV had higher median Wechsler Abbreviated Scale of Intelligence (WASI) scores (91 vs 86, p<0.01). Mean scores and the proportion with an abnormal score for each of the Bayley-III domains were not significantly different between infants born to women with PHIV vs NPHIV in unadjusted models. After adjustment for maternal age, race/ethnicity, WASI score, CD4 in pregnancy, and presence of mental health condition, as well as infant English monolingual environment and in utero exposure to ≥3 ARV classes, infants of women with PHIV had lower language (91.8 vs 94.8, p=0.04) and motor (93.7 vs 96.8, p=0.03) composite scores but no differences in cognitive composite scores.
Conclusion: Cognitive outcomes of infants born to women with PHIV vs NPHIV are reassuring. Differences in language and motor functioning, while of limited clinical significance, highlight the importance of long-term monitoring of neurodevelopment in children born to PHIV women.

Table. Adjusted mean Bayley Scales composite scores comparing infants of women with perinatally vs. non-perinatally acquired HIV

Bayley Scales III Domain	Mean Estimate		*p* value
	Infants of Women with PHIV	Infants of Women with NPHIV	
Neurocognitive	100.1	102.5	0.13
Language	91.8	94.8	0.04
Motor	93.7	96.8	0.03

**Models adjusted for maternal age, race/ethnicity, WASI score, CD4 in pregnancy, and presence of mental health condition, as well as infant English monolingual language environment and in utero exposure to ≥3 ARV drug classes. NPHIV=non-perinatally acquired HIV, PHIV=perinatally acquired HIV*

786 NEURODEVELOPMENTAL OUTCOMES FOLLOWING IN UTERO EFAVIRENZ EXPOSURE AMONG HEU CHILDREN

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Background: A large and increasing number of women with HIV infection conceive while taking efavirenz (EFV)-based antiretroviral treatment (ART) globally. Despite concerns regarding potential adverse neurologic outcomes, few studies have evaluated child neurodevelopment following in utero exposure to EFV-based maternal ART. We hypothesized that (a) HEU children with fetal EFV exposure would exhibit worse neurodevelopmental and social-emotional outcomes than HEU children with fetal exposure to non-EFV-based antiretroviral (ARV) regimens, and (b) among EFV-exposed children, initial exposure beginning at conception or during the first trimester would be associated with worse outcomes than exposure beginning later in gestation.
Methods: 24-month old HEU children whose mothers took EFV-based ART (EFV-exposed) were recruited from May 2016 to May 2017. Their neurodevelopmental outcomes were compared to those from a previously-tested cohort of 24-month old HEU children exposed to non-EFV-based ARVs (non-EFV-exposed). The testing protocol included the Bayley Scales of Infant Development: Third Edition (BSID-III) adapted for use in Botswana; and the Developmental Milestones Checklist (DMC), and Profile of Social Emotional Development (PSED), both developed in Africa. General linear models were used to compare mean outcomes, adjusting for maternal health and child sociodemographic cofounders; mean differences were expressed using Cohen's d effect sizes.
Results: Our analysis included 493 HEU children (126 EFV-exposed, 367 EFV-unexposed). Adjusted mean scores for the EFV-exposed group were lower (worse) than the EFV-unexposed group on the BSID-III Receptive Language scale (adjusted means=21.5 vs 22.5, p = 0.05), DMC Locomotor (30.7 vs 32.0, p<0.01), and Fine Motor scales (17.8 vs 19.2, p<0.01); higher (better) on the DMC Language scale (17.6 vs 16.5, p=0.01); and higher (worse) on the PSED (11.7 vs 9.9, p=0.02). Effect sizes for these differences ranged from 0.24 – 0.50 (see Table 1). Children with fetal EFV exposure during the first trimester (n = 53) had worse scores on the BSID-III Receptive Language scale than children with later gestational exposure (n = 73; EFV mean = 20.7 vs non-EFV mean = 22.2, p=0.02).

Conclusion: HEU children with fetal EFV-exposure may be at higher risk for delays in some neurodevelopmental and social-emotional domains than HEU children with fetal exposure to non-EFV-based ARVs.

Table 1: *Neurodevelopmental and social-emotional outcomes by EFV-exposure group*

		Unadjusted Analyses				Adjusted* Analyses		
Neurodevelopmental Assessment		EFV+ (n = 126)	EFV- (n = 367)	p-value	Cohen's d	EFV+ (n = 126)	EFV- (n = 367)	p-value
BSID-III	Cognitive	56.2 (3.9)	56.4 (4.4)	0.65	-0.05	56.3 (0.5)	56.4 (0.2)	0.86
	Receptive Language	21.5 (3.5)	22.5 (3.1)	0.006	-0.30	21.5 (0.4)	22.5 (0.2)	0.05
	Expressive Language	26.7 (4.8)	27.0 (4.7)	0.62	-0.06	27.0 (0.6)	26.8 (0.3)	0.86
	Fine Motor	38.1 (3.7)	38.5 (3.3)	0.24	-0.11	37.9 (0.4)	38.6 (0.2)	0.19
	Gross Motor	55.4 (6.1)	53.7 (3.9)	0.002	0.33	54.9 (0.6)	53.9 (0.3)	0.17
DMC	Locomotor	31.2 (3.4)	31.9 (2.4)	0.02	-0.24	30.7 (0.3)	32.0 (0.2)	0.001
	Fine Motor	18.5 (2.7)	18.9 (2.3)	0.06	-0.16	17.8 (0.3)	19.2 (0.1)	<0.001
	Language	17.8 (2.7)	16.4 (2.9)	<0.001	0.50	17.6 (0.3)	16.5 (0.2)	0.01
	Personal-Social	45.6 (3.5)	46.7 (4.7)	0.02	-0.27	45.7 (0.5)	46.6 (0.3)	0.13
Profile of Social Emotional Development		12.1 (5.5)	9.8 (5.2)	<0.001	0.43	11.7 (0.6)	9.9 (0.3)	0.02

Note. Unless otherwise noted, values are M(SD) for unadjusted analyses, M(SE) for adjusted analyses. EFV+ = efavirenz-exposed; EFV- = efavirenz-unexposed; BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; DMC = Developmental Milestones Checklist.
*Adjusted models included as covariates child age, child sex, infant feeding method, and ART initial exposure timing (conception/1st trimester vs. 2nd/3rd trimester), as well as other medical/sociodemographic factors found to be associated with outcomes at p ≤ 0.20 in univariate analyses.

787 HIV-EXPOSED UNINFECTED INFANT GUT MICROBIOME EVOLUTION IN THE FIRST YEAR OF LIFE

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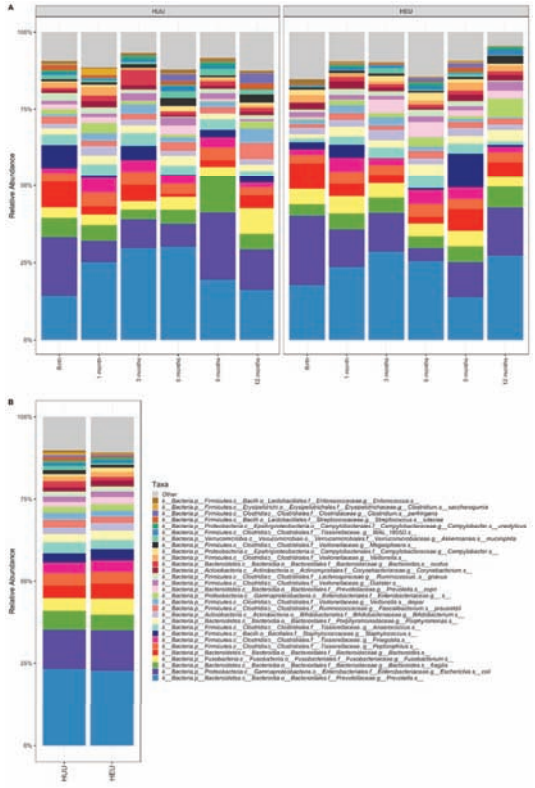
Background: HIV-exposed uninfected (HEU) infants experience higher infectious morbidity than HIV-unexposed uninfected (HUU) infants. Infant commensal gut microbiome influences the developing infant immune system, with dysbiosis associated with immune activation. We compared gut microbiome evolution in the first year of life and hospitalizations between HEU and HUU infants Botswana.
Methods: Women living with HIV (WLHIV) and HIV-uninfected (HIV-U) women were enrolled in the Infant Gut Microbiome Study between 36 weeks gestation and 3 days post-delivery. Study eligibility required vaginal delivery of a full-term (≥ 37 weeks gestation), singleton infant, with commitment to exclusively breastfeed (EBF) for six-months. WLHIV had to be on first line efavirenz-containing antiretroviral treatment regimen ≥ six weeks prior to delivery. Infant rectal swabs were obtained at delivery, 1, 3, 6, 9, and 12 month study visits. DNA extracted from rectal swabs was used to perform 16S rRNA gene sequencing, amplicon data processing, taxonomic profiling, and downstream biostatistical analysis.
Results: Longitudinal gut microbiome was analyzed from 315 rectal swabs contributed by 58 infants, 34 (59%) of whom were HEU. Median EBF duration did not differ between HEU and HUU infants, (5.65 vs 5.70 months (mos); p=0.36). Total breastfeeding duration was shorter among HEU infants (6.0 vs 9.0 mos; p=0.02). Significant differences were observed across time from birth to 12 months in both HEU and HUU subsets (filtered terminal taxa relative abundance Bray-Curtis dissimilarity PERMANOVA; $p < 0.05$). Terminal taxa differences can be seen among time points (Figure 1A), whereas HUU and HEU compositions showed no significant differences averaged across all time points (Figure 1B). Only 4 infants hospitalizations occurred, 3 among HEU infants without differences in microbiome between hospitalized and non-hospitalized infants.
Conclusion: Significant changes in the gut microbiome of both HEU and HUU infants in the first year of life were noted, as would be expected. However, we did not observe differences in the 30 most prevalent taxa between HEU and HUU infants, or differences between hospitalized and non-hospitalized infants. Given the small number of hospitalizations, we were underpowered to detect such a difference. Further studies are needed to better understand how differences in breastfeeding duration influence gut microbiome and immune system phenotype and function of HEU infants.



788 DIFFERENCES IN GUT MICROBIOME IN HIV-INFECTED VERSUS HIV-EXPOSED, UNINFECTED INFANTS

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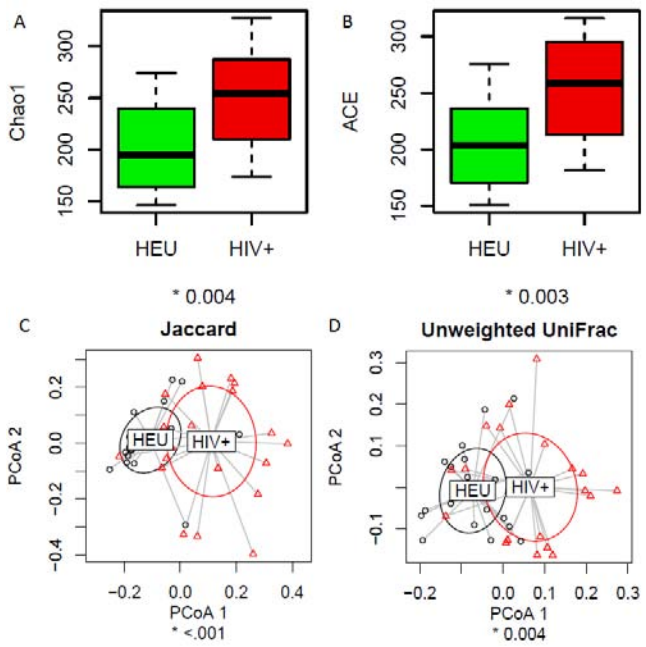
Background: Gut dysbiosis is observed in adults with HIV compared with uninfected adults and implicated in persistent inflammation (IF) and immune activation (IA). Little is known about the gut microbiome in HIV-infected (HIV+) infants, who also have persistent IF and IA compared with HIV-exposed uninfected (HEU) infants. The gut microbiome in breastfed (BF) and non-breastfed (NBF) HIV+ and HEU infants was assessed.
Methods: 40 (20 HIV+ and 20 HEU) infants on co-trimoxazole prophylaxis were selected from a clinical trial (IMPAACT P1072/NWCS 612) of rotavirus vaccine (RotaTeqTM) based on stool availability, having age-matched (3 mos.) and breastfeeding-matched HEU control infants. 16S rRNA (V3V4) sequences from stool DNA were assigned organizational taxonomic units with QIIME. α- (Chao1, abundance coverage estimator (ACE), Shannon, Simpson) and β- (Bray-Curtis, Jaccard, unweighted and weighted UniFrac) diversity, and differentially abundant taxa (linear discriminant analysis effect size (LEfSe)) were analyzed. Multivariate analysis was performed, adjusting for HIV status, breastfeeding and gender. Microbiome regression-based kernel association test was used for multivariate analysis of β-diversity.
Results: An HEU NBF infant was excluded for low read count. There were more females in the HIV+ than HEU (80% vs. 47.4%; p=0.048) group; HIV+ infants had lower mean CD4% (32.6 vs 39.9; p=0.032) and WHO weight-for-age Z score (-1.1 vs -0.5; p=0.042) than HEU. HIV+ infants had higher α-diversity (Chao1 p=0.004; ACE p=0.003; Fig. A, B) and differed significantly by β-diversity (Jaccard $p<0.001$, unweighted UniFrac p=0.004; Fig. C, D) compared with HEU; even after adjusting for breastfeeding and gender. LEfSe showed taxa differences between HIV+ and HEU from phylum to genus level, with enrichment of Veillonella and Klebsiella genera in HIV+, and Actinomyces, Alloiococcus, Akkermansia, Weeksellaceae genera in HEU. BF infants had significantly lower α-diversity and differed by β-diversity (all measures $p<0.05$ after adjusting for HIV infection status and gender) compared with NBF infants.

Conclusion: The gut microbiota differs significantly at three months of age in bacterial composition and diversity by HIV infection and breastfeeding status, with higher α-diversity and differing β-diversity with HIV infection, and lower α-diversity and differing β-diversity with breastfeeding. The impact of these differences on systemic IF and IA in HIV+ infants requires further study.



789 COMPLETE MITOCHONDRIAL GENOME IN HIV-INFECTED CHILDREN AND MOTHER-CHILD PAIRS

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Background: Antiretroviral therapy (ART) is universally recommended for HIV-infected children and HIV-infected pregnant women; HIV-exposed uninfected (HEU) infants are also exposed to ART during pregnancy. Current ART combinations include two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs); the association between the latter and mitochondrial DNA (mtDNA) depletion has been well documented. Whether mutational changes rely at the basis of such mtDNA depletion and whether 1st generation NRTIs (zidovudine, didanosine and stavudine) are more mutagenic than the rest of NRTIs (2nd generation: lamivudine/emtricitabine, tenofovir, abacavir) are questions that remain unclear. We aimed to assess the presence of mutations and depletion of mtDNA in 3 groups of patients exposed to either 1st or 2nd generation NRTIs: HIV-infected children, HIV-infected pregnant women and their HEU infants, and equivalent groups of HIV-uninfected ART-unexposed healthy controls.
Methods: Cross-sectional study. Peripheral blood mononuclear cells (PBMC) were obtained simultaneously 6 weeks after birth from the mothers and their HEU infants and at a mean±SD age of 12.5±4.3 years in HIV-infected children. PBMCs were isolated through a Ficoll's gradient. mtDNA depletion was determined through multiplex PCR (Applied Biosystems 7500 Real Time PCR System) in 96 well plates with the simultaneous determination of the mitochondrial 12S ribosomal RNA (mt12SrRNA) gene and the constitutive nuclear RNAseP gene (nRNAseP). To study heteroplasmic variants the whole mitochondrial genome was amplified by long range PCR. Sample libraries were prepared with Nextera XT kit (Illumina) and sequencing proceeded in the MiSeq. Row data were analyzed using MiSeq Reporter Software. Funded by ISCIII, Spain (PI13/01738).
Results: None of the patients presented with clinical manifestations and/or analytical disorders consistent with mitochondrial dysfunction at assessment. MtDNA depletion was confirmed in HIV-infected mothers and their HEU infants, but not in HIV-infected children. No significant differences were observed in the number of mtDNA mutations among the diverse groups of patients that were analyzed.
Conclusion: Our results suggest that the mtDNA depletion in HIV-infected pregnant women and their HEU infants exposed to 1st generation NRTIs is not associated to increased mutagenesis. We observed no differences in mitochondrial parameters between patients exposed to 2nd generation NRTIs and healthy controls in either of the groups.

		1stgNRTIs	2ndgNRTIs	p[1]	Controls	p[2]
		n=39	n=31		n=25	
Children	mtDNA content (median, IQR)	53.9 (27.5-75.7)	53.8 (40.5-76.8)	0.302	50.7 (19.8-70.5)	0.751
	mtDNA heteroplasmic variants (mean, SD)	7.9±12.5	5.9±5.5	0.410	6.0±5.4	0.476
		n=34	n=14		n=29	
Pregnant women	mtDNA content (median, IQR)	48.9 (19.1 – 71.8)	101.1 (58.8 – 161.1)	0.031	72.6 (64.2 – 85.3)	0.004
	mtDNA heteroplasmic variants (mean, SD)	4.3±3.7	3.2±2.8	0.326	3.3±3.2	0.403
		n=29	n=14		n=29	
HEU infants	mtDNA content (median, IQR)	47.4 (22.9 – 72.0)	94.2 (77.7 – 215.6)	0.024	78.1 (59.9 – 108.5)	0.002
	mtDNA heteroplasmic variants (mean, SD)	3.7±3.5	3.0±2.1	0.418	2.9±3.2	0.426

([1], 1stgNRTIs vs 2ndgNRTIs; [2], 1stgNRTIs vs controls)

790 SURVIVING AND THRIVING? OUTCOMES OF HIV-EXPOSED CHILDREN IN RURAL ZIMBABWE

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Background: Prevention of mother-to-child transmission (PMTCT) programs have reduced the number of children acquiring HIV. However, the impact of PMTCT programs on mortality and growth of HIV-exposed children in sub-Saharan Africa is uncertain.
Methods: SHINE was a community-based cluster-randomized trial of infant and young child feeding (IYCF) and water, sanitation and hygiene (WASH) interventions in two rural Zimbabwean districts with 15% HIV prevalence (ClinicalTrials.gov/NCT01824940). The trial did not administer PMTCT, but promoted early antenatal booking, uptake of PMTCT through local clinics, exclusive breastfeeding for 6 months, and prolonged breastfeeding to 24 months. Children were followed from birth and had longitudinal HIV testing. We used generalized estimating equations to compare mortality and growth between HIV-exposed and HIV-unexposed children through 18 months.
Results: There were 738 HIV-exposed and 3989 HIV-unexposed live births between 2012-2015. 81% of HIV-positive mothers had documented ART use during pregnancy, and mean (SD) CD4 count was 473 (221) cells/μL. Overall, cumulative mortality in HIV-exposed children was 39% higher than HIV-unexposed children through 18 months (risk ratio 1.39; 95%CI 1.02, 1.89; P=0.04). 25 of 738 children (3%) were known to be HIV-infected by 18 months, 596 (81%) were HIV-exposed uninfected, and 117 (16%) children had an unknown HIV status. Among children confirmed to be HIV-exposed uninfected (HEU) at 18 months, mean length-for-age Z-score was -0.34 (95%CI -0.44, -0.25) lower than in HIV-unexposed children (P<0.001), and stunting prevalence was 46% versus 31% (risk ratio 1.48; 95%CI 1.34, 1.64; P<0.001). There were also significant differences between groups in weight-for-age, weight-for-height and head circumference; HEU children had almost 2-fold higher prevalence of underweight, wasting and microcephaly (Table). Among 738 HIV-exposed births, only 320 were known to be alive, HIV-free and non-stunted at 18 months.
Conclusion: In the current PMTCT era, mortality and growth failure are higher among HIV-exposed compared to HIV-unexposed children in rural Zimbabwe; almost half of all HEU children were stunted by 18 months. As HIV transmission continues to decline, we propose the composite status of "Alive, HIV-free and non-stunted" as the long-term goal of PMTCT programs. Our findings highlight the ongoing poor outcomes of HEU children despite PMTCT, and the need for additional interventions to ensure that HIV-exposed children survive and thrive.

	HEU	HIV-unexposed	Comparison	
18 month outcomes	Mean Z-score (standard deviation)		Difference between means	P
LAZ	-1.86 (1.10)	-1.50 (1.07)	-0.34 (-0.44, -0.25)	<0.001
WAZ	-0.94 (1.08)	-0.68 (1.01)	-0.25 (-0.35, -0,15)	<0.001
WHZ	-0.08 (1.09)	0.05 (1.06)	-0.13 (-0.23, -0.04)	0.006
HCZ	-0.50 (1.11)	-0.22 (1.07)	-0.28 (-0.37, -0.18)	<0.001
	Percentage		Risk ratio (95% CI)	P
Stunting	45.9	30.7	1.48 (1.34, 1.64)	<0.001
Underweight	17.4	9.2	1.88 (1.53, 2.31)	<0.001
Wasting	4.7	2.5	1.90 (1.29, 2.81)	0.001
Microcephaly	9.5	5.0	1.88 (1.42, 2.50)	<0.001

Table: Growth outcomes of HIV-exposed uninfected children compared to HIV-unexposed children at 18 months of age. HEU: HIV-exposed uninfected (confirmed HIV-negative at ≥ 18 months); LAZ: length-for-age Z-score; WAZ: weight-for-age Z-score; HCZ: head circumference-for-age Z-score; stunting: LAZ < -2; underweight: WAZ < -2; wasting: WHZ < -2; microcephaly: HCZ < -2; 95%CI: 95% confidence interval.

791 IMPACT OF IMPROVED NUTRITION/SANITATION ON STUNTING AND ANEMIA IN HIV-EXPOSED INFANTS

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Background: Stunting (linear growth failure) is associated with child mortality and neurodevelopmental impairment. Anemia often co-exists with stunting and is a further driver of impaired neurodevelopment. HIV-exposed children have a high prevalence of stunting and anaemia, with few effectiv¬¬¬e preventive interventions. We hypothesized that improved infant and young child feeding (IYCF) and improved water, sanitation and hygiene (WASH) would reduce stunting and anemia in HIV-exposed children.

Methods: We conducted a cluster-randomised 2x2 factorial trial in rural Zimbabwe, testing the impact of improved IYCF and improved WASH on child linear growth and hemoglobin (ClinicalTrials.gov NCT01824940). Pregnant women were eligible if they lived in study clusters allocated to standard-of-care (SOC; 52 clusters); IYCF (20g Nutributter/day from 6-18mo, complementary feeding counseling; 53 clusters); WASH (pit latrine, 2 hand-washing stations, liquid soap, chlorine, play space, hygiene counseling; 53 clusters); or IYCF+WASH (53 clusters). Masking of participants and fieldworkers was not possible. Intention-to-treat analyses were stratified by maternal HIV status. Primary outcomes were length-for-age Z-score (LAZ) and hemoglobin among HIV-exposed children at 18 months. Secondary outcomes include stunting, anemia and diarrhea.

Results: From 726 HIV-positive pregnant women, 668 children from 181 clusters were evaluated at 18 months (147 from 46 SOC clusters; 147 from 47 IYCF clusters; 184 from 43 WASH clusters; 190 from 45 IYCF+WASH clusters). 22 (3%) were HIV-positive, 594 (89%) HIV-exposed uninfected, and 52 (8%) HIV-unknown at 18 months. 2.8% live-born infants were lost to follow-up. IYCF increased mean LAZ by 0.26 (95%CI 0.09, 0.43) and hemoglobin by 0.29g/dL (95%CI 0.09, 0.49), reducing stunting prevalence from 50.2% to 40.5% (absolute reduction 9.7%, 95%CI 2.1, 17.2) and anaemia from 14.1% to 24 7.3% (absolute reduction 6.8%, 95%CI 2.1, 11.6). There was no evidence of an impact of WASH on length or hemoglobin. There was no evidence of an effect of either intervention on diarrhea. There were no trial-related adverse/serious adverse events.

Conclusion: Among HIV-exposed children, improved complementary feeding reduced stunting and anaemia, while there was no evidence of an impact of improved WASH. Delivered at scale, IYCF interventions would have substantial benefit in areas with high antenatal HIV prevalence.

792 EXTENDED PROPHYLAXIS WITH NEVIRAPINE DOES NOT AFFECT GROWTH IN HIV-EXPOSED INFANTS

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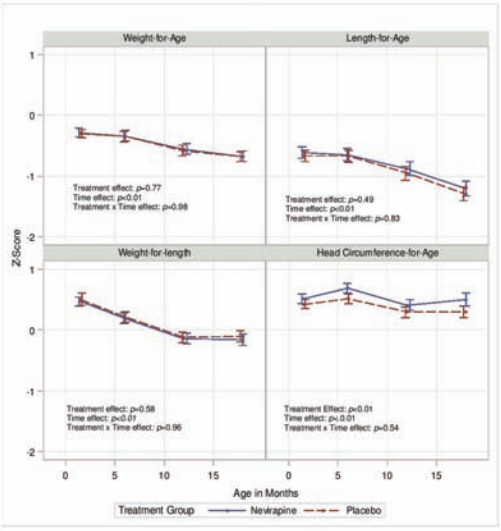
Background: Effects of prolonged nevirapine prophylaxis exposure on growth among high risk HIV exposed-uninfected (HEU) infants are unknown. The objective of this secondary data analysis was to examine the impact of extended nevirapine prophylaxis from six weeks to six months on the growth of HEU infants followed for 18 months in the HPTN 046 trial. Correlates of incident wasting, stunting, underweight, and lower head circumference were also determined.

Methods: Intention-to-treat analysis examined the effect of extended nevirapine exposure on growth outcomes: weight-for-age Z-score (WAZ), length-for-age Z-score (LAZ), weight-for-length Z-score (WLZ) and head circumference-for-age (HCZ). Linear mixed effects models were used to compare the rate of change in infant growth outcomes (WAZ, LAZ, WLZ, and HCZ) between the two study arms. Each infant was modeled as a random effect nested within treatment group. Time was modeled as a continuous variable. Multivariable Cox proportional hazard models were used to determine correlates of incident growth faltering outcomes.

Results: Extended course of prophylactic nevirapine given daily from six weeks to six months did not adversely affect growth (WAZ, LAZ, WLZ, HCZ) in HEU breastfeeding infants (treatment x time effect: p>0.05) when compared with placebo. However, overall growth declined over time (time effect: p<.01) when compared to WHO general population norms. Overall prevalence and incidence did not differ between study groups but male sex, short duration of breastfeeding, and lack of maternal ART exposure were associated with higher risk of growth faltering outcomes (p<.05).

Conclusion: It is re-assuring that prolonged exposure to nevirapine for prevention of maternal to child HIV transmission does not appear to restrict growth. However, targeted interventions that support normal growth among at-risk HIV-exposed uninfected infants are needed to curtail the risk of growth faltering outcomes.

Figure: Average Trends in Growth Outcomes: Weight for Age, Length for Age, Weight for Length and Head Circumference for Age



*Maternal ART exposure did not modify treatment effects on growth outcomes (Maternal ART x treatment: p>0.05). Maternal ART Strata, therefore combined in plots above

793 GROWTH PATTERNS IN CHILDREN OF WOMEN WITH PERINATALLY VS NON-PERINATALLY ACQUIRED HIV

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Background: Increasing numbers of women with perinatally acquired HIV (PHIV) are reaching reproductive age and having children. Few studies have evaluated the long-term growth of HIV-exposed uninfected (HEU) children born to these women, which may vary by race and sex.
Methods: We compared growth trajectories from birth to age 7 years (yrs) in HEU infants born to women with PHIV vs non-perinatally acquired HIV (NPHIV) in the Surveillance Monitoring for ART Toxicities (SMARTT) study, a U.S.-based cohort study enrolling since April 2007. Infants of women born after 1982 were eligible. Z-scores were calculated using U.S. growth references for weight (WTZ) and height (HTZ) from birth, weight-for-length (WLZ) up to 36 months (mos), and body mass index-for-age (BMIZ) from 36 mos onward. Mixed effects models were fit stratified by race and sex to assess differential growth patterns by maternal PHIV status, and included an interaction term for child age by maternal PHIV status along with inverse probability weights to account for administrative censoring.
Results: 1236 infants had height and weight measured from birth (252 and 984 were born to women with PHIV vs NPHIV, respectively). Women with PHIV were younger (23 vs 25 yrs, p<0.01), had lower median CD4 count (386 vs 496 cells/mm^3, p<0.01), and were more likely to have HIV RNA level > 400 copies/mL at delivery (25% vs 12%, p<0.01). A smaller percentage of infants born to women with PHIV were black (63% vs 74%, p<0.01). In the model limited to black female children (n=415), those born to women with PHIV had lower birth WTZ (mean difference: -0.22 [95% confidence intervals (CI): -0.41, -0.03]) and similar WTZ trajectories from 0-3 yrs (slope difference: -0.06 [95% CI: -0.16, 0.04]), but more rapid weight gain after 3 yrs (slope difference: 0.10 [95% CI: 0.00, 0.19]) than those of women with NPHIV; the overall mean difference (PHIV vs NPHIV) between 0-7 years was -0.30 (95% CI: -0.50, -0.09). (Figure 1) Within the other race and sex strata, no differences in overall WTZ or WTZ trajectories were found in HEU children of women with PHIV vs NPHIV. The growth trajectories of HTZ and WLZ/BMIZ over time, as well as overall means, did not differ between children of women with PHIV and NPHIV.
Conclusion: In general, children of women with PHIV had similar growth compared to those of women with NPHIV, which is reassuring. However, black female children of women with PHIV vs NPHIV may be at increased risk for lower weight through early childhood.

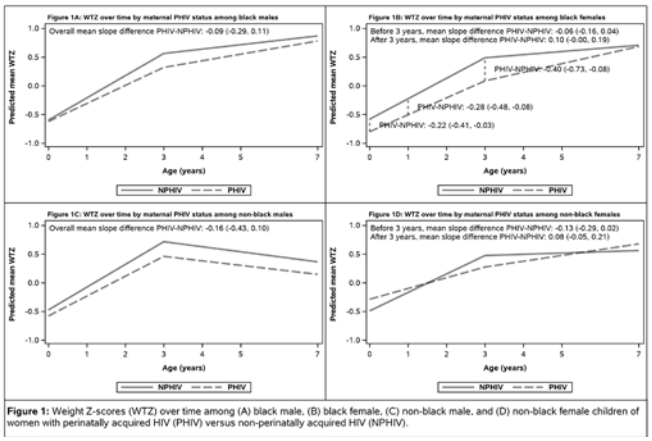

Figure 1: Weight Z-scores (WTZ) over time among (A) black male, (B) black female, (C) non-black male, and (D) non-black female children of women with perinatally acquired HIV (PHIV) versus non-perinatally acquired HIV (NPHIV).

794 POSTNATAL GROWTH IN CHILDREN EXPOSED OR UNEXPOSED TO HIV: A NATIONWIDE COHORT STUDY

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Background: Studies mainly from resource-limited settings have shown impaired growth among HIV-exposed uninfected (HEU) children. We aimed to compare anthropometric outcomes of Danish HEU children to a matched control group of children not exposed to HIV in the first 5 years of life.
Methods: In a nationwide register-based study we included all singleton HEU children born in Denmark, 2000-2016. HEU children were individually matched by parity, maternal age at birth, maternal ethnicity and child sex to five singleton controls born to HIV uninfected mothers. Weight-for-age (WAZ), length-for-age (LAZ) and BMI-for-age (BMI) z-scores were generated according to the WHO standards and the Fenton growth chart for prematurity for infants born <37 week. Differences in WAZ, LAZ and BMI z-scores were analyzed using linear mixed models, adjusting for maternal smoking and total number of growth measurements.
Results: In total, 493 HEU children and 2.495 controls were included, with a mean of 5 growth measurements in each group (range: 1-23). HIV-infected mothers were more likely to smoke during pregnancy (11% vs. 7%) and their infants were more likely to be born preterm (<37 weeks) (11% vs 5%) and to be delivered by Caesarean Section (66% vs. 27%). Most HIV-infected mothers were fully suppressed at the time of delivery with HIV RNA levels <50 copies/mL (87%). Overall, both HEU and control group children had normal growth with z-scores close to or above the average population mean of 0 (Figure 1). Compared to controls, HEU children were smaller at birth with a difference in mean WAZ and LAZ scores of -0.26 (95%CI -0.40:-0.13; p=<0.001) and -0.44 (95%CI -0.69:-0.29: p=<0.001), respectively. Over time, there was a trend towards increasing WAZ and LAZ in HEU children, and there was no significant difference in WAZ z-scores by age 12 months (-0.10 (95%CI -0.26:0.06: p=0.22) and no significant difference in LAZ z-scores by age 24 months (-0.13 (95%CI -0.32; 0.04: P=0.15). There was no difference in BMI-for-age between the two groups at any age. A sensitivity analysis limited to children with information on breastfeeding did not change results significantly.
Conclusion: In a high-resource setting, exposure to HIV and/or antiretroviral therapy does not seem to be adversely associated with infant and child growth. Compared to a matched control group, HEU children were smaller at birth, but this difference decreased with time and is not considered to have a negative impact the overall health and well-being of HEU children.

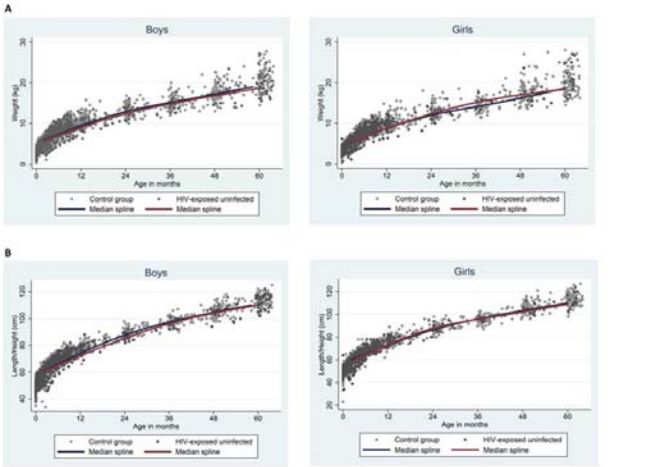

Figure 1: Weight by age (A) and Length/height by age (B). Raw data with median spline for control group (blue) and HEU children (red)

795 IN UTERO HIV EXPOSURE IS LINKED TO OBESITY AND REACTIVE AIRWAY DISEASE IN ADOLESCENCE

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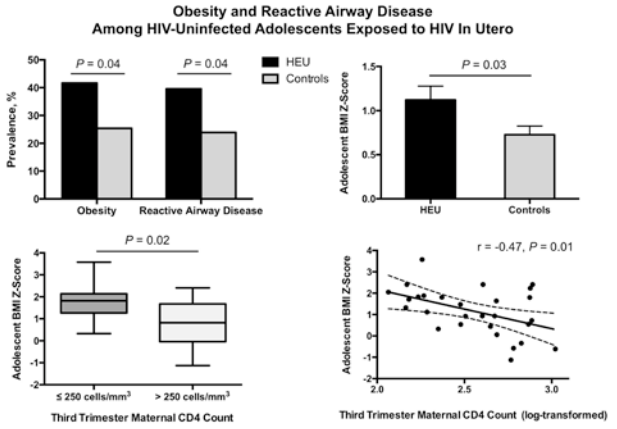
Background: With the implementation of prenatal ART, 98% of individuals born to mothers with HIV are HIV-exposed but uninfected (HEU). HEU infants

and children exhibit impaired growth, mitochondrial toxicity, and immune dysregulation compared to their HIV-unexposed peers. However, the long-term sequelae of in utero HIV and ART exposure, particularly in resource-adequate settings, has not been well examined. We hypothesized that metabolic and immune abnormalities entrained by in utero HIV exposure may predispose to obesity and reactive airway disease (RAD) later in life.

Methods: We leveraged the Partners HealthCare Research Patient Data Registry (RPDR, Boston) to compare long-term health outcomes among HEU adolescents and matched controls, and to determine maternal factors associated with adverse HEU outcomes. An RPDR search was performed to identify HEU individuals born since 1990 with medical records available at age ≥13 y. Over 200,000 controls also were retrieved from RPDR and matched up to 3:1 on birthdate (±5 y), age of last encounter (±2 y), sex, race, and zip code (SAS 9.4). Charts were manually reviewed to confirm HEU status and to extract medical information. BMI was standardized for age and sex using CDC growth charts. Obesity was defined as BMI ≥30kg/m^2 or ≥95 percentile. RAD was by clinical report.

Results: 50 HEU young adults (18 [15,20] y, 54% male) and 141 matched controls (19 [16,21] y, 55% male) were compared. Mothers of HEU adolescents were aged 30±4 y with HIV for 4 [1,7] y. CD4 count was 405 [222,615]/mm^3 with 93% receiving prenatal ART. Obesity was seen in 42% of HEU adolescents compared to 25% of controls (P=0.04). BMI z-score was higher in HEU than controls (1.1±1.1 vs. 0.73±1.1, P=0.03). The prevalence of RAD also was higher in HEU than controls (40% vs. 24%, P=0.04). Within the HEU group, there was a strong inverse correlation between log-transformed maternal third-trimester CD4 and adolescent BMI z-score (r= -0.47, P=0.01). This relationship persisted upon adjustment for prenatal maternal factors including age, BMI, ART, and HIV duration (P<0.05). Prenatal maternal CD4 nadir, peak HIV viral load, HIV duration, and ART were not associated with adolescent BMI z-score. Unlike obesity, maternal factors did not relate to RAD among HEU.

Conclusion: In utero HIV exposure and maternal immune dysregulation may predispose to obesity and RAD in adolescence. To our knowledge, this cohort represents the oldest group of HEU individuals to be compared to general population controls.



Top left: *P*-value was determined with chi-square test. ***Top right:*** Mean and SEM are shown. *P*-value was determined with t-test. ***Bottom left:*** Boxes show median and interquartile range, whereas whiskers span from min to max. *P*-value was determined with Wilcoxon rank-sum test. ***Bottom right:*** Linear regression with 95% confidence bands are shown.

796 DETECTION HIV DNA BY DDPCR BEFORE VIREMIA IN INTRAPARTUM & AT BIRTH IN IU INFANTS

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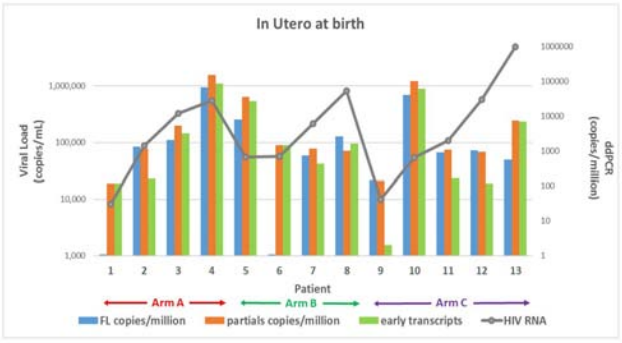
Background: HIV MTC Transmission occurs during gestation in utero (+ at birth),or intrapartum IP(HIV- at birth) and positive 4-6 wks of life or later if breast- fed. Using ddPCR as a sensitive method of quantitating proviral HIVDNA including full length(FL)/partial transcripts(PT), we assessed early events in IP infected infants prior to detectable viremia and HIV proviral DNA as a measure of viral reservoirs in in utero infected infants including FL transcribed HIV DNA and PT compared to plasma HIV RNA

Methods: As part of a trial of infant HIV prophylaxis to prevent IP MTCT a subset of non breast-fed HIV infants defined as IP(14) or IU(13)by - HIV DNA /RNA or + at birth (resp).Infants with adequate samples birth,2,4-6,12, and 24 wks were chosen.Genomic DNA isolated with phenol/chloroform from PBMCs and HIV-1 DNA quantified by ddPCR.cp/million/PBMC Primer/probe pairs targeted full-length HIV reverse transcripts at the LTG-gag junction (SR1/M661/ZXF-FAM) and partials(SR1/AA55/ZXF-FAM) run in parallel with cellular beta-Globin (BGF1/BGR1/BGX1-HEX). Unintegrated HIV cp/ per million were calculated by the difference of full length and partials.

Results: We assessed PT and FL HIV DNA by ddPCR in 14 IP infected infants at birth,2,4-6,12 and 24 wks and found that 12/14 (85%) had P/FL or both prior to HIV RNA detection. 8 were detectable at birth and 5/6 who received 6 wks ZDV prophylaxis group A had detection at birth, the remainder became positive by 2 +wks. In IU (13) infected infants, we found both FL HIV DNA (0-68,000 cp/million),Partials (142-154,000 cp/million)which include FL and early transcripts as cp/millionPBMC and the difference which is early transcripts(2-86,000)as seen in Figure . FL (includes integrated HIV DNA) ranged from 1% to 100% of detectable HIV DNA. HIV RNA ranged from (8,000-5million cp/ml). Surprisingly, there was no clear relationship between HIV DNA levels and HIV RNA at birth. Most infants already had detectable HIV reservoirs at birth although the percentage of FL and early transcripts varied.

Conclusion: Early detection of HIV proviral DNA by ddPCR in IP infected infants at birth or weeks prior to viremia has important implications for pathogenesis especially with enhanced 2NVP/ZDV and 3(NFV,3TC ZDV) drug ARV prophylaxis which reduced postpartum transmission by 50% .Likewise the quantity / differentiation of full lengthHIV DNA (including integrated)vs early transcripts at birth is an important measure of HIV reservoirs for early treatment CURE / Remission protocols



797 MATERNAL HIV RNA AFTER DELIVERY IS CORRELATED WITH INFANT PRETREATMENT HIV RNA

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Background: Detectable maternal HIV RNA at delivery is a strong risk factor for in utero mother-to-child HIV transmission (MTCT), but the impact of maternal HIV RNA level near delivery (in the setting of effective maternal antiretroviral treatment [ART]) on the early viral burden of HIV+ infants is not well studied.

Methods: We enrolled 40 HIV+ mother-infant pairs in the Early Infant Treatment Study (EIT) in Botswana, at < 7 days from delivery. All infants had received prophylactic single-dose nevirapine and twice daily zidovudine per government protocol, up until HIV diagnosis by DNA PCR using the Roche TaqMan. HIV RNA was performed using Abbott HIV-1 m2000rt with a lower detectable limit of 40 copies/ml. Baseline HIV RNA for enrolled infants was compared with maternal HIV RNA values collected on the same day, as well as maternal ART regimen and duration of ART in pregnancy. Spearman's correlation

was used to evaluate associations and Kruskal Wallis test to compare infant HIV RNA by maternal ART regimen.
Results: Among 40 mother-infant pairs, 35 (87.5%) women and 39 (97.5%) infants had a detectable HIV RNA at a median of 2 days post-delivery (range 1, 5 days). Median enrollment HIV RNA was 11,335 copies/ml (range <40, >1,000,0000 copies/ml) for infants and 24,789 copies/ml (range <40, 491,512 copies/ml) for women. Fourteen (35%) enrolled infants were not exposed to any ART in utero, 14 (35%) were exposed to EFV-based ART, 10 (25%) to DTG-based ART, and 2 (5%) to LPV/r-based ART. Median duration of in utero ART exposure was 2.5 weeks (range 0, 40 weeks). Maternal HIV RNA had a strong positive correlation with infant pre-treatment HIV RNA (rs = 0.63, p < 0.001) (Table 1). The duration of ART exposure in utero did not correlate with infant HIV RNA (rs= -0.039, p = 0.81). The median HIV RNA values for infants with either no ART exposure, exposure to EFV, or exposure to DTG were 19,246 copies/mL, 2,491 copies/mL, and 346 copies/mL, respectively; this difference was non-significant (p=0.19), although small numbers were available for these comparisons.
Conclusion: Higher maternal HIV RNA post-delivery correlated with higher pre-treatment infant HIV RNA. Effective ART to reduce maternal HIV RNA in pregnancy may also reduce viral burden among infants with in utero HIV acquisition, beginning the beneficial early treatment process and potentially reducing viral reservoir.

Table 1. Correlation between maternal and infant HIV RNA, by ART exposure

ART exposure *in utero*	Median Duration of in-utero ART exposure (weeks) / [range]	Median Maternal HIV RNA (copies/ml) / [range]	Median Infant HIV RNA (copies/ml) / [range]	Correlation* r-value / p-value
No ART exposure (n=14)	NA	55,589 [547, 374341]	19,246 [<40, >10000000]	0.28 / 0.33
EFV-based ART (n=14)	14 [0, 40]	23,638 [<40, 491512]	2,491 [276, >10000000]	0.70 / 0.005
DTG-based ART (n=10)	8.5 [1, 25]	325 [<40, 85697]	346 [79, 389270]	0.88 / <0.001
LPV/r-based ART (n=2)	NA#	29,085 [23912, 34257]	80,430 [17244, 143616]	NA#
Total (n=40)	**2.5 [0, 40]**	**24,789 [<40, 491512]**	**11,335 [<40, >10000000]**	**0.63 / <0.001**

* by Spearman's correlation
# not applicable because of small sample size (n=2).

798 EARLY ART START IN CHILDREN IS ASSOCIATED WITH MORE RAPID DECAY OF HIV-1 DNA

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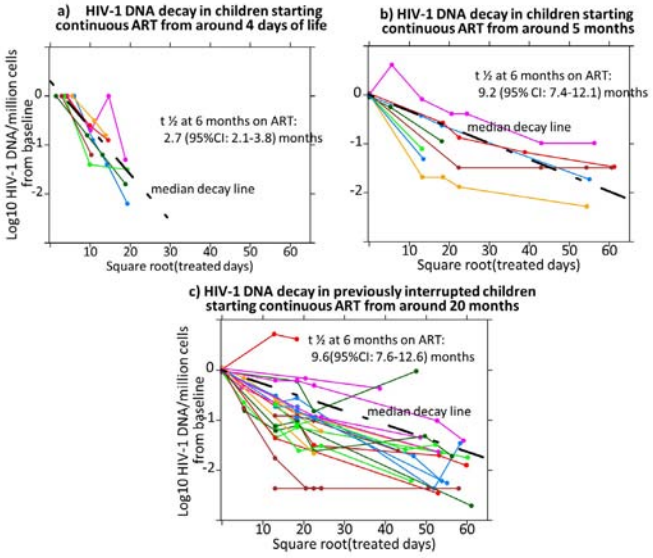
Background: There is limited information on whether the age at ART initiation, duration of the initial treatment phase and subsequent ART interruption influences the persistence of HIV-1 infected cells in children.
Methods: We investigated HIV-1 DNA decay in 3 groups of children on ART (ART regimens excluded InSTIs): group-1 were 7 starting at a median of 4 days of life and continuing uninterrupted; group-2 were 8 starting at a median of 5 months and continuing uninterrupted; and group-3, 23 on ART from a median of 1.8 months for either 40 or 96 weeks, then interrupting ART for a median of 7 months, and restarting based on CD4 criteria. Total HIV-1 DNA was assayed with a sensitive HIV-1 subtype C adapted quantitative PCR for a conserved integrase sequence. Goodness of fit of the decay curves within each group was assessed with conditional R^2. Duration of treatment was square root transformed to fit with the observed deceleration in decay rate. For each group, the point estimates of decay rates were determined at 6 months on continuous ART or 6 months after reinitiating ART. For groups-2 and 3 combined (n=31) a mixed effect regression model was used to investigate covariates of decay rate; with the square root of time, baseline variables and prior interruption as fixed effects, and patient as the random effect.
Results: The conditional R^2 (95% CI) values for the HIV DNA decay curve was 0.82 (0.65-0.93) for group-1 (early start), 0.85 (0.67-0.94) for group-2 (late start) and 0.79 (0.68-0.86) for group-3 (interrupted). At 6 months on continuous suppressive ART: the HIV-1 DNA t½ in months (95% CI) was shorter in group-1; 2.7 (2.1-3.8), compared to 9.2 (7.4-12.1) in group-2; and 9.6 (7.6-12.6) in group-3 (Figure). In the multivariable model, HIV-1 DNA concentration before treatment (p<0.001) and the change in HIV-1 DNA during interruption (p<0.01) were independent significant predictors of slower subsequent HIV-1 DNA decay. In contrast, children who received prolonged initial treatment for 96 weeks had a faster decay after reinitiating than those interrupting after 40 weeks (p=0.02).
Conclusion: Rapid HIV-1 DNA decay in very early treated children suggests that ART can prevent persistence of long-lived infected cells. Delaying or interrupting ART is associated with longer persistence of infected cells. Further studies are needed to study the unintegrated fraction of HIV-1 DNA in early treated children, the proportions of integrated proviruses that are defective or intact; and InSTI-containing regimens.



799LB VIROLOGIC RESPONSE TO VERY EARLY ART IN NEONATES WITH IN UTERO HIV: IMPAACT P1115

Deborah Persaud[1], Ellen G. Chadwick[2], Camlin Tierney[3], Bryan Nelson[3], Mark Cotton[4], Anne Coletti[5], Theodore Ruel[6], Mutsa Bwakura-Dangarembizi[7], Macpherson Mallewa[8], Kimesh L. Naidoo[9], Christina Reding[10], Rohan Hazra[11], Patrick Jean-Philippe[12], Yvonne Bryson[13], for the IMPAACT P1115 Study Team
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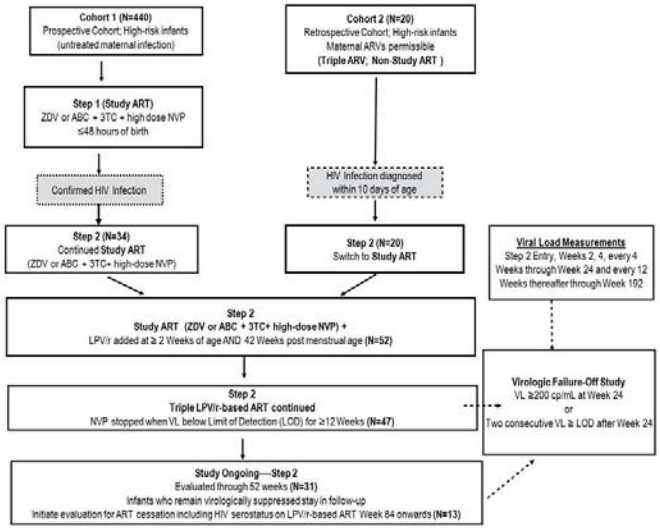
Background: Perinatal HIV infection treated ≤48 hours of birth (very early ART [VE-ART]) limited HIV reservoirs and provided 27 months of undetectable viremia off ART in the "Mississippi baby". IMPAACT P1115 is an ongoing prospective phase I/II proof-of-concept study of VE-ART of in-utero infected infants. We report on the completed viral load (VL) response and safety follow-up through 52 wks.
Methods: Newborns enrolled into two cohorts (Fig.1). Cohort 1 (N=440) was treated within 48 hrs of life (Step 1) due to high-risk HIV exposure from untreated maternal infection. 34 had confirmed infection and moved to Step 2. Cohort 2 (N=20) received non-Study triple ARVs ≤48 hrs of life, and directly enrolled into Step 2 with confirmed infection before age 10 days. LPV/r was added to the Step 2 regimen at 42 wks postmenstrual age and NVP stopped with specified virologic criteria (Fig.1). VL was frequently monitored (Fig.1). Virologic failure (VF) was defined as VL ≥200 cp/mL at wk 24, and confirmed VL≥ limit of detection (LOD) at later visits. Probabilities (95% CI) of sustained viral suppression (no VF) were estimated by Kaplan-Meier method. Grade 3 and 4 safety events were assessed for relation to Study ART. Median (Q1, Q3) are presented.

Results: 54 HIV-infected infants (61% girls) enrolled from 11 countries; 81.5% breast-fed. Median study enrollment age in Cohort 1 was 22 hrs and 8 days in Cohort 2. For Cohorts 1 and 2 median age at ART initiation was 7.3 (1.8, 21.0) and 33 (0.4, 40.1) hrs, and median earliest VL was 4.9 (4.0, 5.3) and 4.1 (3.2, 5.2) log10 cps/mL, measured at a median of 1 (0,1.0) and 6.5 (2.0, 8.0) days of age; loss to follow-up was 3% and 15%. Estimated probability of sustained viral suppression through 52 wks on Step 2 was 50% (32%, 66%) and 67% (37%, 85%) in Cohorts 1 and 2, respectively; 47/52 who started LPV/r met virologic criteria to stop NVP at median age 29.4 (25.0, 37.7) wks. Grade 3 or 4 related events that were reversible occurred through 52 wks in 15 (44%) and 7 (35%) infants from Cohorts 1 and 2, and were mostly hematologic. There was one death in each cohort, neither related to Study ART. Among infants followed through wk 84, 5/8 and 4/5 in Cohorts 1 and 2 are HIV-seronegative.
Conclusion: VE-ART for infants with in-utero HIV-infection results in moderate rates of strict virologic control through 52 wks. More effective VE-ART regimens are needed to achieve high rates of sustained virologic suppression in infants with in-utero HIV infection



800 SHIV CH505 T/F RESERVOIR AND REBOUND IN INFANT AND ADULT RHESUS MACAQUES

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Background: Each year >150,000 infants get infected with HIV, ~50% infections occurring during breastfeeding. While lifelong ART results in effective viral suppression, these infants are predisposed to long-term metabolic consequences and development of drug-resistant viral strains. Therefore, a functional cure is required to attain an ART-free life of sustained viral remission. The primary barrier for a cure is the ability of HIV to establish persistent viral reservoirs, immediately upon infection. Therefore, strategies to reduce viral reservoirs are urgently needed to delay viral rebound, and attain prolonged viral remission. For that, it is critical to monitor establishment of HIV reservoirs and kinetics of viral rebound.
Methods: In this pilot study, 6 SHIV.C.CH505 T/F infected infants and 6 adult rhesus macaques (RMs) were used to characterize viral replication and establishment of reservoirs upon ART initiation at 12 wpi. After 8 wk of ART, the kinetics and anatomic distribution of viral rebound upon ART interruption was measured using ddPCR and co-culturing mononuclear cells with Tzm-bl reporter cells.
Results: Plasma viral RNA (vRNA) in infants and adults peaked at 2 wpi (infant mean: 6.9e6 vRNA copies/ml; adult mean:4.2e6 vRNA copies/ml). While both groups demonstrated similar viral load kinetics until ART initiation at 12 wpi, 33% infants showed pre ART control. Cell-associated viral DNA (vDNA) in PBMCs were comparable at 6 wpi in infant (Mean: 1.5e7 copies/million CD4+ T cells) and adult (Mean: 2.1e7 copies/million CD4+ T cells) RMs. Upon initiation of ART, plasma vRNA suppressed below levels of detection within 2-4 wk. Interestingly, ART-suppressed RMs showed similar frequencies of cell-associated vDNA in naïve, Tfh and memory CD4+ T cell populations in LNs. (Range: undetectable-2.6e4 copies/million CD4+ T cells). Upon ART interruption, 5/6 infants and 3/6 adult RMs rebounded to >150 vRNA copies/ml of plasma. Plasma VL at ART initiation was a predictor of time to viral rebound, and infants had more variability in time to rebound. While all the adults controlled systemic virus within 3-4 wk of rebound, only 3/5 infants demonstrated post-rebound viral control. Oral LNs were a primary site of vRNA and infectious virus in both adults and infant RMs.
Conclusion: Using a RM model of postnatal infection, we have characterized SHIV.C.CH505 reservoirs and rebound kinetics, which can inform correlates of viral rebound, and design immune-based interventions to reduce pediatric HIV reservoirs.

801 HIV-SPECIFIC ANTIBODY LEVELS CORRELATE WITH TFH MATURATION IN EARLY TREATED INFANTS

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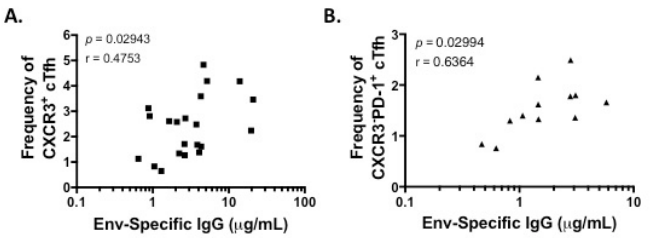
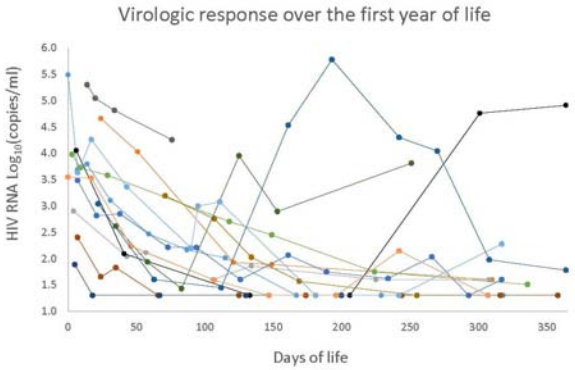
Background: Though they have a developing immune system, infants develop potent HIV-specific antibodies. To understand the B cell response that develops after early ART, we measured the circulating T follicular helper cell (cTfh) frequencies and HIV-specific antibody production in early treated infants.
Methods: Eighty-two Thai infants living with HIV were included. Samples were taken from viremic infants at baseline (median 2.3 mo old, range 0.8-6.6 mo; n=59), and virally-suppressed infants after a median 12.6 months of ART (range 10.8-16.6 mo; n=50) or a median 24.5 months of ART (range 20.7-26.4 mo; n=25). CD19+CD20+ B cells and CD4+ T cells were analyzed by flow cytometry. Plasma Env-specific IgG and IgM levels were measured by ELISA. Plasma levels of CXCL12, CXCL13, and soluble CD40 ligand (sCD40L) were measured by Luminex.
Results: At baseline, very low Env-specific IgM levels were detected in the plasma of infants with HIV (median 1.4µg/mL). Env-specific IgM levels correlated with viral load ($r=0.75$, $p<0.001$), as well as plasma levels of the stimulatory molecule sCD40L ($r=0.43$, $p=0.03$) and CXCL13, a biomarker of germinal center activity ($r=0.63$, $p<0.001$). Though infant Env-specific IgG levels could not be measured due to the presence of maternal antibodies, the frequency of cTfh (CXCR5+CD45RA–CD4+ T cells) correlated with the frequency of IgG+ B cells ($r=0.55$, $p=0.04$) at baseline. Baseline frequencies of IgG+ B cells and cTfh in the blood negatively correlated with plasma levels of CXCL12 ($r=-0.62$ $p=0.03$; $r=-0.66$ $p=0.01$), suggesting these cells are exiting the blood through high endothelial venules. The levels of Env-specific IgM increased after 1 year of ART (median 2.4µg/mL, $p<0.001$). Env-specific IgG levels decreased as maternal antibodies waned, and remained stable between 1 and 2 years of ART (median 2.4 vs 1.5µg/mL). After 1 year of ART, Env-specific IgG levels correlated with the frequency of Th1-biased cTfh expressing CXCR3 (Fig 1A; $r=0.48$, $p=0.03$). In contrast, after 2 years of ART Env-specific IgG levels correlated with the frequency of CXCR3–PD-1+ cTfh, which provide better B cell help (Fig 1B; $r=0.64$, $p=0.03$).
Conclusion: During early infection, viremic infants produce low levels of Env-specific IgM. Though early treated infants had low levels of Env-specific IgG after ART, antibody levels correlated with the maturing cTfh populations. These data suggest that effective elicitation of HIV-specific antibodies in infants will depend on therapeutic targeting of proper cTfh populations.

Figure 1. Env-specific IgG levels correlate with cTfh population frequencies.





802 OUTCOMES OF NEONATES WITH RAPID HIV TREATMENT IN US: TREATING INFANTS EARLY STUDY

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Background: While several international trials are testing strategies of early antiretroviral therapy (ART) for infants with HIV, little is known about the outcomes of perinatally infected infants in clinical (non-research) settings, in which neonatal ART options are limited. The Treating Infants Early Study (TIES) is an observational cohort study that aims to describe the management, safety, efficacy of ART initiated at < 6 weeks of life in communities throughout the USA.

Methods: Informed consent was obtained by phone or in person, with paper or electronic documentation. Eligibility criteria were HIV diagnosis, age < 2 years, and ART start at < 6 weeks of life. Maternal, birth and ART history, and clinical outcomes were abstracted from medical records, collected periodically during follow up. Descriptive statistics were used for this analysis.

Results: Among 38 infants screened from Dec. 2015 to Sept. 2018, 15 enrolled, providing median (range) follow-up of 19(1-32) months; one was excluded from analysis due to prior research participation. Infants were born at 37(28-40) weeks gestation weighing 2.7 (1.1-3.9) kg to mothers 24 (15-36) years old, 6(43%) of whom were diagnosed with HIV in labor. Infants received zidovudine (ZDV)(n=2), ZDV + 3 doses nevirapine(NVP) with(n=7) or without(n=2) lamivudine (3TC), or ZDV/3TC+NVP twice daily at treatment doses(n=2) prior to HIV diagnosis. ART as treatment was initiated at 8.5 (0-36) days of life: ZDV/3TC + NVP(n=12) or lopinavir/ritonavir(n=2). First CD4 count was 2,390(231-4,190) cells/μl, CD4% was 46(10-66) and HIV RNA was 3.7(1.9-5.0) log10 copies/ml. While 8(53%) and 5(33%) were diagnosed with anemia and neutropenia respectively, ART was never interrupted, and regimens were later changed for anticipated efficacy and tolerance, but not toxicity. With heterogeneity in baseline plasma HIV RNA level and initial response (figure), suppression (RNA 200 c/ml, at 295 days), but many had early and prolonged suppression (e.g. 66 through 958 days of life).

Conclusion: Most infants with HIV in this cohort had initiated ART before 9 days old, underscoring the need for potent and safe ART options in the neonatal period. With rapid and durable virologic suppression, some perinatally infected infants treated in community settings are likely to have low reservoir levels and be good candidates for future studies of remission strategies

803 HIV PERSISTS IN DIFFERENTIATED MEMORY CD4 T CELLS IN ART-SUPPRESSED CHILDREN

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Background: HIV primarily persists in memory CD4 T cells in adults on antiretroviral therapy (ART). However, less is known about the HIV distribution in the pediatric population. We sought to identify the main cellular reservoirs for HIV in ART-suppressed Thai children and assess the inducibility of these genomes by evaluating their ability to produce viral proteins upon stimulation.

Methods: Enriched CD4 T cells from 5 vertically infected, early treated children (ART initiation within 3.5 months of life and median age of 2.5 years) were stimulated with PMA/ionomycin in the presence of brefeldin A to maintain the expression of cell surface markers. After 24h, naïve (CD45RA+CCR7+CD27+), central memory (CM, CD45RA-CCR7+CD27+), transitional memory (TM, CD45RA-CCR7-CD27+) and effector memory (EM, CD45RA-CCR7-CD27-) cells were sorted by flow cytometry. Integrated HIV DNA was quantified in the sorted subsets by real-time PCR. The frequency of cells producing the HIV protein Gag was measured by flow cytometry using a novel assay detecting p24 expression with high specificity.

Results: We first measured the frequency of each subset within the CD4 compartment. As expected, naïve cells represented the vast majority of CD4 T cells (median frequency of 84%), whereas CM, TM and EM were underrepresented (10%, 2% and 1%, respectively, Table 1). In spite of their high frequencies, naïve cells were rarely infected (median 45 [0-103] HIV DNA copies/106 cells). Most proviruses were detected in memory subsets, particularly in the EM subset which included the highest levels of cells harboring integrated genomes (median 10,943 [3,398-162,594] copies/106 cells) followed by TM and CM subsets (median 1,253 [172-11,571] and 206 [132-9,806] copies/106 cells, respectively). Although EM cells represented a small fraction of all CD4 T cells, their contribution to the HIV reservoir was higher than CM and TM cells (median 54%, 30% and 4%, respectively). Despite these high levels of HIV DNA, p24-producing cells were not detected in any of the pediatric samples tested upon stimulation. In contrast, p24+ events were detected in CD4 T cells from suppressed adults with comparable HIV DNA levels.

Conclusion: In vertically infected children on ART, the large naïve compartment minimally contributes to the HIV reservoir. Although high levels of HIV DNA are present in memory cells, these proviruses did not produce detectable levels of p24 protein, suggesting that the latent reservoir is poorly inducible in ART-suppressed children.

Table 1: Integrated HIV DNA and contribution of each subset to the pool infected cells in early treated ART-suppressed children

	% of CD4 T cells	Frequency of integrated HIV DNA (copies/10^6 cells)	Contribution of each subset to the HIV reservoir
Total CD4		575 [50-864]	
Naive	84% [75-87]	45 [0-103]	1% [0-5]
CM	10% [7-13]	206 [132-9,806]	30% [10-51]
TM	2% [1-5]	1,253 [172-11,571]	4% [2-36]
EM	1% [1-2]	10,943 [3,398-162,594]	54% [14-88]

median [IQR]

804 IMMUNO-VIROLOGICAL IMPACT OF EARLY VS LATE ART INITIATION IN CHILDREN AND ADOLESCENTS

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Background: Few data are available on the long-term benefit of early cART initiation for children and adolescents. The ANRS-EP59-CLEAC study aimed to assess the immunological and virological characteristics of HIV-1-infected children and adolescents who achieved initial virological suppression, according to the age at cART initiation (<6 months vs ≥24 months of age).
Methods: Patient recruitment was conducted in the Paris area in 2016 - 2018. PBMC-associated total HIV-1 DNA was quantified using ultrasensitive qPCR (adapted from Biocentric, France). CD4 and CD8 CD45RA+CCR7+ naive T lymphocytes were quantified in fresh blood by flow cytometry. Parameters of early- (E-Ch)/late- (L-Ch) treated children (5-12 years) and early- (E-ado)/ late- (L-ch) treated adolescents (13-17 years) were compared with Wilcoxon test.
Results: We prospectively enrolled in the early-cART group 27 children and 9 adolescents, and in the late-cART group, 19 children and 21 adolescents. At the time of the study, all patients were receiving ART, 83% had plasma HIV-RNA <50 copies/mL, and the median CD4 T-cell count was 856 [IQR: 676 - 1236] cells/µl. In multivariate analysis, early cART and longer duration of viremia <50 cp/mL during the 2 previous years were strongly associated with lower HIV-DNA levels (respectively, p<0.0001 and p=0.0067). Restricting the analysis to the 63 patients with current viral suppression, early cART was associated with lower HIV-1 DNA levels (p<0.0001). Aviremic E-ado had very low HIV-DNA levels (median 1.42 [IQR: 1.08-2.25] log cp/10e6 PBMC). E-Ch had higher median percentages of naïve CD8 T lymphocytes than L-Ch (49 versus 31%; p<0.0007). Conversely, in adolescents, early cART was associated with lower percentage of naïve CD4 T lymphocytes (39 versus 52%, p=0.05), even when restricting the analysis to patients with current viral suppression.
Conclusion: An immunological benefit of early cART initiation on naïve T lymphocytes was suggested in children. Further investigations are pending to explore if the high levels of thymic activity observed in adolescents may compensate for the deleterious effects of long duration of HIV replication. Early cART initiation during infancy is associated with lower short- and long-term total HIV-DNA levels, as targeted in HIV-1 remission strategies. Interestingly, aviremic E-Ado had HIV-DNA levels comparable to those observed in adults with spontaneous or post-treatment HIV control.

805 LONG-TERM PERSISTENCE OF HIV-INFECTED CELL CLONES IN CHILDREN TREATED EARLY

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Background: Integration site analysis has shown extensive clonal expansion of HIV-1 infected cells in adults. We know that infected clones arise early, persist for many years, and that there is selection for cells with proviruses integrated in BACH2, MKL2, and STAT5B. However, little is known about the behavior of infected cells in children treated shortly after birth. We characterized clones of infected cells in a cohort of perinatally-infected and early-treated children.
Methods: PBMC samples were obtained from the Children with Early HIV Antiretroviral therapy (CHER) cohort prior to ART and after 6 to 9 years of continual suppression on ART. We determined the integration sites in samples taken at both time points and compared the data to integration site data from PBMCs infected ex-vivo and adults who initiated ART in either early or chronic infection.
Results: Integration sites were obtained from 11 children who initiated ART at a median age of 5.1 months (range: 1.8-17.4 months). We obtained a median of 701 integration sites per child (range: 204-1482) pre-ART and 128 on-ART (range: 94-454). We found clones of infected cells in pre-ART samples from 8 children, including 2 who started ART before 3 months of age, and in all 11 children after 6-9 years on ART. In 6 children, some of the clones detected pre-ART persisted for at least 6 years on ART and in 1 child for 9 years on ART. We quantified the fraction of integration sites detected in clones and found no significant difference between children (24%) and adults treated either in early infection (N=14; 16%) (p=0.08) or in chronic infection (N=9; 22%) (p=0.66). We also compared the fraction of integration sites in individual genes in the on-ART samples to a library prepared from ex-vivo infected PMBCs and, as in adults, we found strong selection for proviruses integrated in BACH2 (p=2*10^-11) and STAT5B (p=1*10^-23).
Conclusion: Although the numbers of T cells and their population dynamics are different in children and adults, the timing of establishing HIV-1 infected cell clones, the frequency of infected clones, and the selection for some infected clones appears similar in children and adults, even in children who initiated ART before 3 months of age. Our findings indicate that clonal expansion of infected cells occurs very early after infection in children, as in adults, and that clonal expansion of infected cells is a major mechanism for persistence of HIV-1 despite long-term ART.

806 INTACT HIV PROVIRUSES ARE DETECTABLE 7-9 YEARS LATER WHEN ART STARTS AFTER 3 MONTHS

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Background: In adults starting ART in acute infection only 2-5% of proviruses are intact. However, no intact full length proviral sequences were detected in a cohort of early treated, long-term suppressed children. We sought to characterize proviral sequences in another cohort of early treated children after 6-9 years on suppressive ART.
Methods: PBMC samples from perinatally infected children in the CHER study were analyzed. Single, near full length proviral amplification and sequencing (NFL-PAS) was performed at one time point after 6-9 years of suppressive ART. Amplicons with large internal deletions were excluded (<9kb on gel electrophoresis). All amplicons ≥9kb were sequenced (Sanger and Illumina) and analysed through an 'Intactness bio-informatic pipeline' to detect indels, frameshifts, inactivating point mutations and/or hypermutations that would render the proviruses defective.
Results: In 9 children who started ART at a median age of 2.3 (range: 1.7 – 11.1) months, 738 single NFL-PAS amplicons were generated. Of these, 553 (74.9%) had large internal deletions, 175 (23.7%) had hypermutation, 3 (0.4%) had deletions in the packaging signal and major splice donor site, and 7 (1%) were intact. These 7 intact sequences were from 3 children who initiated ART after 8 months of age; of whom one had two identical and intact sequences, suggestive of a cell clone harbouring a replication-competent provirus. No intact provirus was detected in 5 children who initiated ART before 2.3 months of age.

Conclusion: Rare, intact proviruses could be detected in the blood of children who initiated ART after 2.3 months of age. The frequency of intact proviruses is similar to that reported for adults treated during early HIV infection.

PID	Age ART start (months)	Treatment History and Longitudinal viral loads	Duration of ART at sample (years)	Number of Sequences with large internal deletions	Number of 9kb Sequences with hyper-mutations and stop codons	Number of sequences with packaging signal/MSD defects	Number of intact proviruses	Total number of single genomes
333676	1.7	Interrupted ART after 9months; reinitiated after 3.6yr; viremic until after re-initiation	8.6	4	1	0	0	5
360806	2.0	Continuous therapy; Delayed suppression for first 6 months on ART, good suppression thereafter	9.13	68	19	0	0	88
341622	2.16	Interrupted ART after 9.9months; reinitiated after 13months; viremic until after reinitiation	6.9	30	4	0	0	34
341862	2.2	Continuous therapy; Detectable viral load after 2.2yrs on ART, supressed 5 months later and good suppression thereafter	6.96	89	101	0	0	190
333716	2.3	Interrupted ART after 2yrs; blip 4months after interruption; reinitiated 4months after interruption; viremic until after reinitiation	8.55	18	3	0	0	21
339606	8.5	Continuous therapy	7.93	27	9	1	2	39
340116	9.23	Continuous therapy	7.31	207	23	2	1	233
339266	9.32	Continuous therapy	8.2	56	15	0	4	75
334436	11.1	Poorly suppressed for first 2.5yrs on ART	8.82	54	0	0	0	54
Total	Median= 2.3		Median = 8.2	553 (74.9%)	175 (23.7%)	3 (0.4%)	7 (1%)	738

807 POORER CONTROL OF VIRAL LOAD IN PATIENTS INFECTED PERINATALLY VERSUS DURING ADULTHOOD

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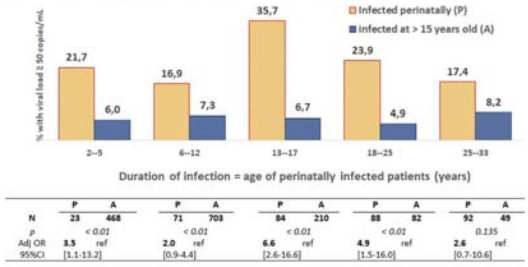
Background: Combined antiretroviral treatment (cART) allows most HIV-infected infants to reach adulthood. We studied whether the current virological response of perinatally-infected children and young adults to cART was similar to that of patients infected during adulthood, with a similar duration of infection and treatment history.

Methods: Data from 5 ongoing French national ANRS cohorts were pooled: 1) patients diagnosed at < 13 years of age, followed as children (EPF-CO10), or as adults (COVERTE-C019); 2) patients diagnosed at ≥ 15 years of age, included at the time of primary HIV infection (PRIMO-C06), or diagnosis (COPANA-C09, SEROCO-CO2). Here we retained all patients diagnosed in the two years following birth for perinatally infected patients or following seroconversion for patients infected during adulthood, under cART for ≥ 6 months at last evaluation, between 2012 and 2017 (respectively: n = 358 and n = 1512). We distinguished 5 strata for the duration of HIV infection, based on relevant time-points for perinatally infected patients: 2-5, 6-12, 13-17, 18-24, and 25-32 years. The main outcome was detectable viral load (HIV RNA ≥ 50 cp/ml) at last evaluation. A multivariate logistic regression was conducted for each stratum to adjust for gender, birth country, and treatment history.

Results: At last visit, most patients had been receiving the same cART regimen for six months or more. The use of new-generation drugs varied with age and period of acquisition. The proportion of detectable VL was significantly higher in the youngest children and in the adolescents and young adults infected since birth than in patients infected during adulthood with a similar duration of infection; the difference was lower for perinatally-infected patients ≥25 years (Fig 1). The findings were similar after multivariate analysis (AOR in Fig 1) and when restricting the analyses to patients with no changes in treatment regimen during the previous six months.

Conclusion: Among cART-treated patients diagnosed soon after birth or seroconversion, young patients infected perinatally had much poorer viral control than adults with a similar duration of infection, not explained by treatment history, including the number and type of drugs in the context of a European country with universal free access to care. These results may reflect the difficulties of drug administration to younger children and of maintaining adherence during adolescence and young adulthood. The long-term impact of viral replication should be studied.

Fig 1. % of no virological control (CV≥ 50cp/mL) at last evaluation, between HIV-treated patients infected perinatally (P) or at adulthood (A), according to five periods of infection duration (=age of perinatally infected).
National EPF, COVERTE, PRIMO, COPANA, SEROCO cohorts – 2012-2017



	P	A	P	A	P	A	P	A	P	A
N	23	468	71	703	84	210	88	82	92	49
p	< 0.01		< 0.01		< 0.01		< 0.01		0.135	
Adj OR	3.5	ref	2.0	ref	6.6	ref	4.9	ref	2.6	ref
95%CI	[1.1-13.2]		[0.9-4.4]		[2.6-16.6]		[1.5-16.0]		[0.7-10.6]	

808 SLOW CD4/CD8 RATIO RECOVERY AMONG CHILDREN AND ADOLESCENTS DESPITE VIRAL SUPPRESSION

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Background: There are limited data describing long-term outcomes of young adults living with HIV who are successfully treated with combination antiretroviral therapy (cART). We investigated the recovery rates of CD4/CD8 ratio, a suggested marker for chronic immune activation, among Thai children and adolescents after they initiated cART.

Methods: This study was carried out in an ongoing HIV Thai cohort that includes children and adolescents (both perinatally [PaHIV] and behaviorally [BaHIV] acquired HIV infections) who had started cART at 5 years of age. CD4/CD8 normalization was defined as two consecutive values of the ratios ≥1. Participants were eligible for inclusion in this analysis if they achieved and maintained viral suppression at <50 copies/mL after starting cART, and if CD4/CD8 ratio at first viral suppression was <0.8. Follow-up was censored once participants had viral rebound after achieving suppression.

Results: A total of 138 children and adolescents (101 PaHIV and 37 BaHIV) aged <25 years old met inclusion criteria. Among 37 BaHIV adolescents, 27 (73%) were men who have sex with men. Median (interquartile range, IQR) age at ARV initiation was 10.6 (8.1-16.3) years old with median (IQR) baseline CD4 and CD8 cell counts of 178 (37-320) cells/mm^3 and 964 (616-1332) cells/mm^3, respectively. Median duration of cART was 9.3 years (10.6 for PaHIV and 2.4 for BaHIV) and median duration of virological suppression was 3.1 years (4.7 for PaHIV and 1.8 for BaHIV). Overall CD4/CD8 ratio of children and adolescents at first virological suppression was 0.47 (0.29-0.62). Over 559 person years of follow-up (PYFU), the incidence of CD4/CD8 ratio normalization among children and adolescents <25 years old was 4.1 per 100 PYFU (95% confidence interval [CI]: 2.7-6.2). Using the Kaplan-Meier method, the probabilities of normalization at 2, 5 and 10 years after virological suppression were 5.2%, 22.6% and 35.6%, respectively. After 2 years of virological suppression, the normalization probability of PaHIV children and adolescents was higher but not significantly different than that of BaHIV (11.1% vs. 6%).

Conclusion: CD4/CD8 ratio recovery was slow among children and adolescents after initiating cART, despite persistent virological suppression. The clinical consequences of ongoing immune activation among children and adolescents on suppressive cART without CD4/CD8 normalization needs further investigation.

809 UNDERSTANDING THE IMPACT OF ART INTERRUPTION ON THYMIC OUTPUT AND TCR REPERTOIRE

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Background: Antiretroviral therapy (ART) interruptions in adults lead to decreases in CD4+ T cells and an increase in mortality and morbidity. ART

interruptions in children also cause a rapid reduction in CD4+ T cells but with less clinical impact and with good CD4+ T cell restoration following ART reintroduction. In contrast to adults, who predominantly reconstitute their T cells from the peripheral cell population, children have a great capacity for immune reconstitution mainly from the thymus. In this study, we have investigated ART interruption in children with HIV to determine the impact on thymic output, peripheral T cell proliferation, TCR diversity and clonality.
Methods: TCR repertoire and TCR clonotypes was estimated by Next Generation Sequencing techniques in purified naive CD4+ T cells and memory CD8+ T cells. Thymic output was measured using a mathematical model, combining naive CD4+ T-cell proliferation rates with DNA PCR quantification of TCR excision circles, and IL-8, a chemokine released from naive T cells. Samples from 8 HIV-infected children were available for this study from a randomized controlled trial where one cohort remained on ART and the other had treatment withdrawn for 48 weeks.
Results: Thymic output was found to increase rapidly when ART was stopped. The increase in thymic output was associated with increased peripheral T cell proliferation, both returning to pre-interruption levels when the children re-started ART. TCR repertoire diversity and clonotype profiles appeared to be similar before treatment interruption and 3 years after ART re-introduction in both naive CD4+ T cells and memory CD8+ T cells. Specific clonotypes were seen to expand and being highly shared in the naïve CD4+ T cell population in response to ART interruption. There was no difference observed in these immune parameters in the HIV children receiving continuous treatment between baseline and end of study.
Conclusion: Importantly we found that thymic output, peripheral cell expansion, TCR repertoire and clonotypic profiles return to pre-interruption levels. This indicates that the high levels of thymic output in children may be sufficient to reverse the impact of ART cessation.

810 HIGH CMV DNAAEMIA ASSOCIATES WITH STUNTING AND CHRONIC LUNG DISEASE IN HIV+ CHILDREN

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Background: Long-term survival of children with perinatally acquired HIV (PHIV) - even in those stable on antiretroviral therapy (ART) - is associated with significant health problems that are not typical of HIV-associated opportunistic infections or AIDS-defining illnesses. In sub-Saharan Africa, older children and adolescents with PHIV experience a range of chronic complications including growth impairment, chronic lung disease (CLD), cardiac abnormalities, pubertal delay and neurocognitive disorders. Moreover, the beta herpes virus, cytomegalovirus (CMV), is ubiquitous in Africa, infecting all children by age 18 months. We hypothesised that CMV reactivation might play a role in the poor health of older children with PHIV and we examined the associations between uncontrolled co-infection with CMV and comorbidities including lung function and growth.
Methods: Plasma samples were isolated from two cohorts of older children and adolescents aged 6-16 years with PHIV (n=394) and HIV negative controls (n=224). The HIV-infected children were either newly diagnosed (hence untreated), or known to be HIV-infected and stable on antiretroviral therapy (ART). CMV DNA-aemia was measured using quantitative polymerase chain reaction (qPCR). We used longitudinal mixed-effects logistic regression to model CMV DNA-aemia as a time-varying outcome.
Results: At enrolment, CMV DNA-aemia ≥1000 copies/ml (defined as "clinically significant") was detected in 5.8% of uninfected children, 14.1% of HIV-infected participants stable on ART and 22.5 % of the HIV-infected ART-naïve children (Chi2 = 23.4, p<0.001). The prevalence of clinically significant CMV DNA-aemia was associated with CD4 count below 350 cells/µl. Amongst HIV-infected ART-naïve children, CMV DNA-aemia ≥1000 copies/ml was independently associated with reduced lung function (adjusted odds ratio aOR=3.15, 95%CI: 1.20-8.28, p=0.02). Amongst ART-treated children, stunting was associated with CMV DNA-aemia ≥1000 copies/ml (aOR=2.79, 95%CI: 0.97-8.02, p=0.057).
Conclusion: Clinically significant CMV DNA-aemia was common in older children and adolescents with PHIV, even amongst those stable on ART, suggesting a role for inadequately controlled CMV infection in the pathogenesis of the chronic complications of PHIV in Africa.

811 IMMUNE IMBALANCE IS ASSOCIATED WITH IMPAIRED SPIROMETRY IN PERINATALLY ACQUIRED HIV

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Background: Chronic lung disease (CLD) is increasingly recognized among youth living with perinatally-acquired HIV (PHIV) worldwide. Yet, pathophysiologic mechanisms of CLD in PHIV youth are largely unknown. We hypothesized that immune imbalance and activation based on a high CD8 T-cell count and low CD4/CD8 ratio are associated with impaired lung function in PHIV, and explored whether lung function differed between youth living in a high-income and a low-and-middle-income setting.
Methods: We performed a cross-sectional analysis of PHIV youth (10-21 years old) in the U.S. Pulmonary Complications in the Pediatric HIV/AIDS Cohort (PCPA) Study (n=188) and Kenyan BREATHE I Study (n=49). Sociodemographic, clinical, immune function, and spirometry data were ascertained within 3 months of enrollment. In U.S. and Kenyan youth combined, we estimated Spearman partial correlations of CD8 and CD4/CD8 with pre- and post-bronchodilator (BD) %-predicted forced expiratory volume in one second (FEV1%), adjusted for age and sex. We also fit linear regression models to evaluate mean differences (95%CI) in FEV1% by study site, adjusted for age, sex, and CD8 (or CD4/CD8 in separate models).
Results: Kenyan youth were younger, and a higher percent had prior pulmonary infections and passive cigarette smoke exposure (Table). Although Kenyan youth had later antiretroviral therapy (ART) initiation, Kenyan and U.S. youth had similar distributions of ART use and recent CD4. Nonetheless, Kenyan youth had significantly higher CD8 and lower CD4/CD8 ratio. Overall, correlations of CD8 with pre- and post-BD FEV1% were -0.25 (p<0.001) and -0.22 (p<0.001), and correlations of CD4/CD8 with pre- and post-BD FEV1% were 0.28 (p<0.001) and 0.26 (p<0.001). In adjusted linear regression models, pre-BD [-9.6 (95%CI -15.4, -3.8); p=0.001] and post-BD [-8.3 (95%CI -14.0, -2.7); p=0.004] FEV1% were lower in Kenyan compared to U.S. youth. These differences were attenuated in models also adjusting for CD8 (pre-BD: [-5.2 (95%CI -11.6, 1.2); p=0.11]; post-BD: [-4.5 (95% CI -10.7, 1.8); p=0.16]); associations were similar in models adjusted for CD4/CD8.
Conclusion: High CD8 and low CD4/CD8 were associated with greater spirometry impairment. Further, Kenyan PHIV youth had lower lung function measures than U.S. PHIV youth, and this association was attenuated by adjusting for CD8 or CD4/CD8. Our findings suggest that chronic immune imbalance and activation may contribute to CLD in PHIV despite ART use with associated CD4 reconstitution.

Table. Select characteristics of U.S. and Kenyan youth living with perinatally-acquired HIV

Characteristics		U.S. PCPA (N=188)	Kenya BREATHE I (N=49)	P-Value
Age at spirometry (years)	Mean (SD)	16.7 (2.8)	13.8 (3.3)	< 0.001
Male sex	N (%)	79 (42%)	25 (51%)	0.26
CD4 T-cell count (cells/µL)	Median (Q1, Q3)	635 (458, 783)	667 (453, 834)	0.45
CD8 T-cell count (cells/µL)	Median (Q1, Q3)	722 (514, 930)	1,098 (849, 1,473)	< 0.001
CD4/CD8 ratio	Median (Q1, Q3)	0.91 (0.55, 1.25)	0.65 (0.42, 0.94)	0.004
Currently receiving antiretroviral therapy	N (%)	165 (89%)	46 (94%)	0.33
Age at antiretroviral therapy initiation (years)	Median (Q1, Q3)	3 (1, 5)	8 (5, 11)	<0.001
Active or passive smoking	N (%)	34 (19%)	11 (22%)	0.60
History of prior pulmonary infection	N (%)	87 (46%)	27 (55%)	< 0.001
FEV_1 %-predicted, pre-bronchodilator	Median (Q1, Q3)	98 (85, 109)	86 (76, 100)	0.003
FEV_1 %-predicted, post-bronchodilator	Median (Q1, Q3)	100 (88, 113)	93 (83, 104)	0.006

812 ENDOTHELIAL DYSFUNCTION IN SOUTH AFRICAN YOUTH WITH PERINATALLY ACQUIRED HIV ON ART

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Background: Evidence in adult populations shows that HIV and antiretroviral therapy (ART) confer cardiovascular (CV) risk. Few studies have assessed endothelial dysfunction (ED), an early marker of subclinical CV risk, in youth living with perinatally acquired HIV (YLPHIV).

Methods: Using Peripheral Arterial Tonometry (endoPAT), we compared endothelial function in YLPHIV and age-matched HIV-uninfected (HIV-U) youth enrolled in the Cape Town Adolescent Antiretroviral cohort (CTAAC) in South Africa. A reactive hyperaemic index (RHI) <1.35 was defined as ED. Eligible participants included those aged 9-14 years and on ART >6 months at enrolment. Body mass index z scores (BMIZ) were calculated using WHO references, abnormal lipids were defined as >95th percentile using references from the United States (U.S.) National Health and Nutrition Examination Survey (NHANES), and elevated blood pressure (BP) were defined as >90th percentile for age, sex and height using U.S. standards. Modified Poisson regression models were fit to assess the adjusted association of HIV infection with ED. Subgroup analyses were performed to assess predictors of ED among YLPHIV.

Results: Overall 431 YLPHIV and 93 HIV-U youth were included. YLPHIV had lower BMIZ (-0.2 vs 0.4, p<0.01) but higher rates of hypercholesterolemia (10% vs 1%, p=0.01) compared to HIV-U youth. No differences in age, sex, Tanner stage, elevated BP or tobacco use were found. Among YLPHIV, mean log viral load (VL) was 4.83 copies/ml with 21.7% harboring a CD4 count <500cell/mm3 and median duration on ART was 9.8 years with 38% initiating at <2 years of age. YLPHIV had higher rates of ED compared to HIV-U youth (50% vs 34%, p=0.01); this relationship persisted after adjusting for age, sex, BMIZ, elevated BP, and hypercholesterolemia (RR 1.43, p=0.02). Among YLPHIV CD4 count >500 cell/mm3 (RR 1.04, p=0.76), VL (RR 1.01, p=0.78) and current ART class (protease inhibitor-based vs non-nucleoside inhibitor-based ART, RR 0.90, p=0.186) were not associated with ED after adjusting each model for age, sex, BMIZ, elevated BP, and hypercholesterolemia.

Conclusion: Even after adjusting for physiologic differences, YLPHIV appear to be at increased risk for ED compared to age-matched HIV-U youth in South Africa. Further longitudinal studies are required to explore risk of developing CV disease in YLPHIV.

813 EARLY CARDIAC DYSFUNCTION IN HIV-INFECTED CHILDREN AND ADOLESCENTS IN WESTERN KENYA

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Background: HIV-associated cardiac dysfunction has severe consequences, and traditional measures of echocardiography underestimate the true burden of dysfunction. Novel echocardiographic measures may detect early disease in time for possible intervention. The aims of this study are to define the prevalence of early cardiac dysfunction in children living with HIV and the relationships between cardiac function and same-day HIV RNA and soluble inflammatory marker levels.

Methods: Using a cross-sectional study design, perinatally HIV-infected children and adolescent at Moi Teaching and Referral Hospital in Eldoret, Kenya underwent an echocardiogram and provided a blood sample. Early cardiac dysfunction was defined as left ventricular global longitudinal strain (LVGLS) z-score < -2 or myocardial performance index (MPI) ≥ 0.5. Comparisons between those with early cardiac dysfunction and those with normal cardiac function were made using Chi square, Fisher's Exact, or Wilcoxon Rank Sum tests, as appropriate. Regression models were used to assess the relationship between measures of cardiac function and potential predictors.

Results: 643 children and adolescents (mean age 14.1±5.2 years, range 1-25 years) with perinatally acquired HIV were enrolled. The average time on antiretroviral treatment was 6.8±3.6 years. 296 participants (46.0%) had documented exposure to AZT as a part of their treatment regimen. 288 of 638 (45.1%) had detectable HIV RNA levels. 178 of 643 (27.7%) children and adolescents met study criteria for early cardiac dysfunction (176, 98.9%, by the MPI criteria). Early cardiac dysfunction was associated with older age (15.3 vs 13.5 years, p<0.001), higher percentage of detectable HIV RNA levels (52.5% vs 41.7%, p=0.018), and higher median level of plasma IL-6 concentrations (1.00 vs 0.88, p=0.011). In adjusted models, ejection fraction was negatively associated with detectable same-day HIV RNA level (β -0.28; 95%CI -0.56, -0.003) and AZT exposure (β -2.05; 95%CI -3.48, -0.61), and ejection fraction was positively associated with higher proportion of life on ART

Conclusion: Nearly one quarter of these children and adolescents demonstrated evidence of early cardiac dysfunction, based primarily on MPI measurements. This finding was associated with older age, higher percentage of detectable HIV RNA, and elevated IL-6 levels. Further investigation is needed into the clinical significance of these findings as abnormal MPI is predictive of mortality in inflammation mediated cardiac dysfunction.

814 WEIGHT IS AN INDEPENDENT RISK FACTOR IN INSULIN RESISTANCE IN HIV+ UGANDAN CHILDREN

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Background: HIV-infection has become a chronic disease in pediatric patients with potential for long-term survival. The risk of cardiometabolic complications in HIV+ and exposed uninfected children (HEU) and their relationship to systemic inflammation is not well established. Our objective was to focus on how insulin resistance is associated with HIV related factors and markers of inflammation, immune activation and gut integrity.

Methods: This is a cross-sectional study in HIV+, HEU and HIV unexposed uninfected (HIV-) children aged 2-10 years old enrolled in Uganda. HIV+ children were on stable ART with HIV-1 RNA< 400 copies/mL. Participants were age, body mass index (BMI) and gender matched 1:1:1. Insulin resistance was assessed by homeostasis model assessment of insulin resistance (HOMA-IR). We measured markers of systemic inflammation, monocyte activation and gut integrity. Kruskal-Wallis tests were used to compare markers by HIV status, and Pearson correlation and multiple linear regressions were used to assess associations of HOMA-IR with biomarkers.

Results: Overall, 172 participants were enrolled (57 HIV+, 59 HEU and 56 HIV-). Mean age was 7 years, 55% were females and mean BMI was 15. Among HIV+ children, mean CD4 was 34%, 93% had viral load ≤ 20 copies/mL, 77% were on a non-nucleotide reverse transcriptase regimen. Among traditional cardiovascular disease risk factors, HIV+ participants, compared to HEU and HIV- children, had higher waist hip ratio; HDL cholesterol, triglycerides and levels of HOMA-IR (figure). Four HIV+ participants had insulin resistance (HOMA> 2.5). sCD14, beta d glucan (a marker of fungal translocation) and zonulin (a marker of intestinal permeability) were also higher in the HIV+ group (p≤0.01). Factors associated with HOMA-IR included higher BMI, HDL (r≥0.09, p≤0.01), and lower sTNFRI (r=-0.19, p=0.02). HIV related factors were not associated with HOMA-IR (p≥0.08). After adjusting for age, gender, sTNFRI and family history of diabetes, BMI remained independently associated with HOMA-IR (β=0.14, p<0.01).

Conclusion: Despite viral suppression, HIV+ Ugandan children have disturbances in glucose metabolism, immune activation and gut integrity. However, higher BMI, and not immune activation, is associated with insulin resistance in this population. With obesity becoming more frequent in the HIV population, our findings support the need for preventive interventions aimed at weight control in the HIV population, including in children.

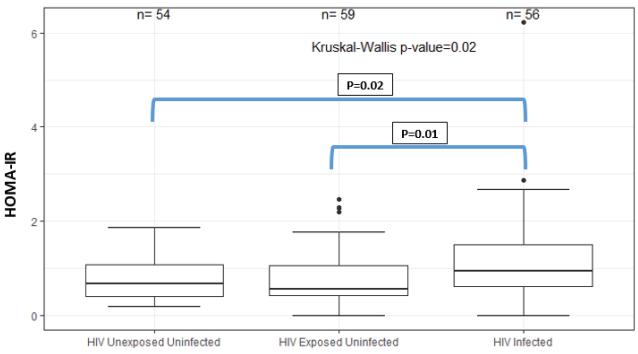

Figure: Box plots of insulin resistance (HOMA-IR) between the groups

815 GROWTH AND METABOLIC CHANGES AFTER ANTIRETROVIRAL START IN SOUTH AFRICAN CHILDREN

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Background: High viral load (VL) associated with delays in antiretroviral therapy (ART) initiation has been linked to poor outcomes in children living with HIV (CLHIV). Fewer studies have assessed the impact of VL at initiation on growth and metabolic changes of CLHIV on optimal ART. We assessed longitudinal alterations in growth and lipid metabolism in CLHIV <12 years old initiating 1st-line ART in South Africa (SA) from 2012 to 2015.

Methods: Per SA national ART guidelines, CLHIV <3 years were initiated on lopinavir/ritonavir (LPV/r)-based and those ≥3 years on efavirenz (EFV)-based ART (both regimens included abacavir+lamivudine). Length-for-Age (LAZ), Weight-for-Age (WAZ), and Body Mass Index-for-Age (BMIZ) z scores were calculated using World Health Organization reference standards. Lipids [Total Cholesterol (TC), Low-Density Lipoprotein (LDL), and High-Density Lipoprotein (HDL)] were measured at enrollment, 6, 12, and 24 months. Mixed effects models were fit to assess the association of VL at initiation with each z-score and lipid subfraction over time. Interaction terms to evaluate the effect of VL on rates of change in each outcome were dropped where p-value>0.05. CLHIV<3 years on LPV/r-based ART were analyzed separately from those ≥3 years on EFV-based ART.

Results: Of 283 CLHIV, 172 <3 years started LPV/r-based ART and 111 >3 years started EFV-based ART. At enrollment, younger CLHIV on LPV/r and older CLHIV on EFV had a median age at ART start of 10 months and 8 years, log VL of 6.1 and 5.2, and CD4% of 19% and 14%, respectively. Among younger CLHIV, higher VL at ART initiation was associated with persistently lower mean differences over time in LAZ (ß:-0.32, p=0.02), WAZ (ß:-0.34, p=0.01), TC (ß:-6.65, p=0.05) and LDL (ß:-7.26, p<0.01), but was not associated with slope changes in any of the outcomes after adjustment (Table 1). Among older CLHIV, higher VL at enrollment was associated with significantly lower mean LAZ (ß:-0.27, p=0.05) and borderline significantly lower WAZ (ß:-0.32, p=0.06) as well as with more rapid increases in LAZ (ß:0.14, p=0.01) and WAZ (ß:0.19, p=0.04). No associations were found between VL and lipids among older CLHIV.

Conclusion: High viral load at ART initiation was associated with persistently lower growth and lipid outcomes over time among younger CLHIV on LPV/r-based ART. Further research is needed to understand the impact of this trend in lipids on the long term cardiometabolic health of young CLHIV with high viral burden at ART initiation.

Effect of Log Viral Load at ART Initiation on Mean Anthropometric and Lipid Subfraction Outcomes Over Time in Two Cohorts After Initiating Antiretroviral Therapy

	Younger CLHIV initiating ABC/3TC/LPV/r		Older CLHIV initiating ABC/3TC/EFV	
Anthropometric Outcome[a]	**Estimate**	***p*-value**	**Estimate**	***p*-value**
LAZ	-0.32	0.02	-0.27[c]	0.05[c]
WAZ	-0.34	0.01	-0.32[c]	0.06[c]
BMIZ	-0.09	0.45	-0.03	0.81
Lipid Subfraction Outcome[b]	**Estimate**	***p*-value**	**Estimate**	***p*-value**
TC	-6.65	0.05	-2.85	0.35
LDL	-7.26	<0.01	-4.02	0.14
HDL	-0.96	0.41	0.49	0.57

3TC=lamivudine, ABC=abacavir, ART=antiretroviral therapy, BMIZ=Body Mass Index Z-score, CLHIV= children living with HIV, EFV=efavirenz, HDL=high density lipoprotein, LAZ=Length-for-age Z-score, LDL=low density lipoprotein, LPV/r=lopinavir/ritonavir, TC=total cholesterol, WAZ=Weight-for-age Z-score.

[a] Adjusted for age, sex, log HIV viral load, caregiver, and wealth index.
[b] Adjusted for age, sex, log HIV viral load, caregiver, wealth index, BMIZ, and skinfold ratio.
[c] Model included interaction term of (log HIV viral load)*(time)

816 LOWER BONE STRENGTH BY PERIPHERAL QUANTITATIVE CT IN CHILDREN LIVING WITH HIV

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Background: Most prior studies demonstrating compromises in bone mass among children living with HIV (CLWH) used dual x-ray absorptiometry (DXA). DXA, in contrast to peripheral quantitative computed tomography (pQCT), estimates areal (2D) rather than volumetric (3D) bone mineral density (vBMD), is unable to distinguish between cortical and trabecular bone, and does not provide an estimate of bone strength. The aim of this study is to compare bone structure and strength in school-aged CLWH and controls.

Methods: This study included 172 CLWH on ART and 99 controls without HIV enrolled in the CHANGES Bone Study at the Empilweni Services and Research Unit in Johannesburg, South Africa. Peripheral quantitative computed tomography (pQCT) scans (Stratec XCT-2000) of the non-dominant radius (4% slice for trabecular) and tibia (38% slice for cortical) were performed at the MRC/WITS Developmental Pathways for Health Research Unit. Measurements included trabecular area and vBMD, as well as cortical area, thickness, and vBMD. Bone strength was estimated by the polar strength strain index (SSI), a validated measure of fracture risk.

Results: At the time of pQCT scan, CLWH (51% male) and controls (63% male) were an average of 10.9 and 10.2 years of age, respectively. Mean ART duration for CLWH was 9.5 years, with 121 (70.4%) on a LPV/r-based, 49 (28.5%) on an EFV-based regimen, and 2 on another regimen. The CLWH had a lower radial length (208 vs. 217 mm, p<0.01), tibial length (299 vs. 328 mm, p<0.01), trabecular area (95 vs. 112 mm^2, p<0.01), and cortical area (157 vs. 185 mm^2, p<0.01) than controls. No difference in trabecular vBMD or cortical vBMD was observed in CLWH compared to controls after adjustment for sex, age, and radial or tibial length. Polar SSI was lower in CLWH than controls (778 vs. 962 mm^3, p<0.01); this finding was consistent in boys and girls. In addition, CLWH on a LPV/r-based regimen had lower trabecular (199 vs. 220 mg/cm^3, p<0.02) and cortical vBMD (1076 vs. 1092 mg/cm^3, p=0.017) than those on an EFV-based regimen. No difference in polar SSI was observed between treatment groups.

Conclusion: Reduced bone strength was observed in well-suppressed CLWH on ART, placing them at a higher risk for fracture. In addition, lower vBMD was found in CLWH on a LPV/r-based regimen compared to EFV-based regimen. Bone outcomes are an important consideration for treatment guidelines.

817 HIV AND CANCER RISK IN ADOLESCENTS AND YOUNG ADULTS IN SOUTH AFRICA, 2004-2014

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Background: The risk of developing cancer is increased amongst Adolescents and Young Adults (AYA) living with HIV compared to uninfected AYA. Low retention in care, poor virologic control, low CD4 counts and a high prevalence of other oncogenic viruses may further increase cancer risk in AYA living with HIV. We aimed to determine the association between cancer and HIV as well as the spectrum of cancers amongst AYA living with and without HIV.
Methods: This was a record linkage study of all AYA aged between 10 and 25 who had a cancer diagnosed between 2004 and 2014 in the South African public health sector laboratories. HIV data were retrieved from the National Health Laboratory Service and linked using probabilistic methods to cancer records in the South African National Cancer Registry database. The linkage variables included names, surnames, age and gender. We further extracted additional HIV data from the clinical history section of the cancer pathologists' report using text searching methods. To determine the association between HIV status (infected vs uninfected) and different cancers in AYA , we fitted logistic regression models adjusting for age (adolescents vs young adults), gender (as appropriate), ethnicity (black vs non-black) and calendar period (early vs mid vs late-ART).
Results: From 2004 to 2014, 8,472 AYA were diagnosed with incident cancer. The HIV status was known for 45% (n=3,812) of the AYA cancer population and the remainder was not tested for HIV. About half of those with a known HIV status were HIV positive (n=1,853; 48.6%). Female AYA with cancer were more frequently HIV positive as compared to male AYA with cancer and black AYA with cancer more frequently than non-black ethnic groups. Young adult cancer patients were more frequently HIV-positive compared to adolescent cancer patients. Adjusted odds ratios for AYA living with compared to only those without HIV were 219 (95% CI 90-530) for Kaposi sarcoma, 2.18 (95% CI 1.23-3.88) for cervical cancer, 2.09 (95% CI 1.66-2.63) for non-Hodgkin's lymphoma and 2.73 (95% CI 1.27-5.86) for anogenital cancers other than cervix.
Conclusion: The elevated risk of different AIDS defining and non AIDS defining cancers in this age group points to a possible gap in the ART programme for AYA living with HIV. The elevated risk for cervical cancer in young women indicates the need for enhanced continuous screening for pre-cancerous cervical lesions amongst AYA living with HIV as well as improved primary prevention strategies.

Table 1: Cancer risk amongst AYA living with HIV compared to AYA without HIV in the South African Public Health Sector.

Cancer Diagnosis	Cancer proportions		Overall	Adolescents (10-19)	Young Adults (20-24)
	HIV +, n=1853	HIV-, n=1959	OR (95% CI)	OR (95% CI)	OR (95% CI)
Kaposi's sarcoma	786	5	219 (90-530)	152 (47.9-440)	322 (79.7-1303)
Cervix	76	18	2.18 (1.23-3.88)	3.63 (0.70-18.9)	2.03 (1.11-3.72)
NHL	204	150	2.09 (1.66-2.63)	3.11 (2.30-4.20)	1.29 (0.93-1.79)
Burkitt's lymphoma	61	33	2.65 (1.65-4.28)	2.36 (1.32-4.21)	3.39 (1.33-8.60)
non-Hodgkin, NOS	37	12	4.28 (2.06-8.91)	4.13 (1.67-10.2)	4.51 (1.25-16.2)
DLBCL, NOS	95	68	1.99 (1.39-3.88)	3.45 (2.18-5.44)	0.95 (0.56-1.59)
DILBCL, NOS	26	8	4.54 (1.90-10.8)	10.8 (2.96-39.4)	1.64 (0.53-5.16)
Hodgkin's lymphoma	119	243	0.61 (0.47-0.79)	0.73 (5.00-1.06)	0.54 (0.38-0.77)
NOS	36	43	0.89 (0.53-1.49)	0.77 (0.35-1.69)	1.00 (0.49-2.06)
Mixed cellularity, NOS	28	29	2.02 (1.11-3.71)	2.09 (0.99-4.42)	2.00 (0.71-5.60)
Lymphocyte depletion, NOS	5	7	1.04 (0.31-3.52)	0.60 (0.12-2.93)	-
Anogenital cancers other than cervix	40	11	2.73 (1.27-5.86)	2.00 (0.50-7.99)	3.14 (1.17-8.45)
Leiomyosarcoma	6	2	2.13 (0.38-11.9)	3.50 (0.31-39.5)	1.32 (0.14-12.5)
Liver	10	38	0.28 (0.13-0.61)	0.38 (0.11-1.32)	0.25 (0.10-0.64)

HIV+= HIV positive. HIV-= HIV negative. n= total number of laboratory confirmed HIV positive/negative AYA in the entire dataset. NHL= non-Hodgkin's lymphoma. NOS=Not otherwise specified. DLBCL= Diffuse large B-cell lymphoma. DILBCL= Diffuse immunoblastic large B-cell lymphoma. Anogenital cancers other than cervix includes cancers of the anus, vulva, penis and vagina. OR= Odds Ratio. Logistic regression models used to determine the relative risk of cancer presented as Odds ratios. Models adjusted for gender (male and female), ethnicity (black and non-black) and ART period (early ART, mid-ART and late ART).

818 CANCER INCIDENCE IN YOUNG PEOPLE WITH HIV: PRIVACY-PRESERVING RECORD-LINKAGE STUDY

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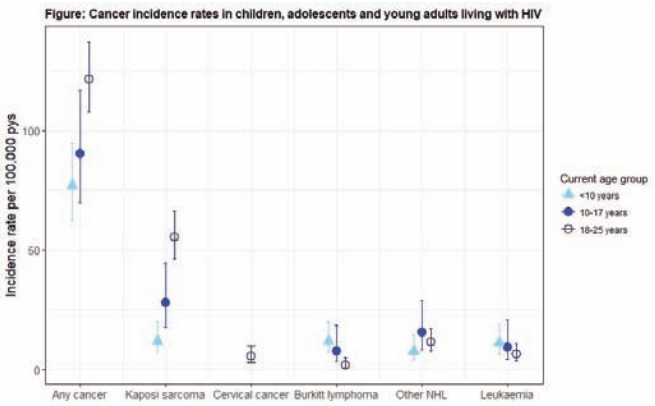
Background: Data on cancer incidence in children and young people living with HIV are sparse. We used laboratory test records to create a cohort of children, adolescents and young adults who received public sector health care in Gauteng province, South Africa, and assessed cancer incidence.
Methods: We retrieved laboratory records for HIV and CD4 tests from the National Health Laboratory Service for the years 2004-2014. We used privacy preserving probabilistic record linkage using names, date of birth/age, sex, and facility information as linkage variables to identify records belonging to the same person. Next, we linked the cohort to records of the National Cancer Registry using similar methods. We included children, adolescents and young adults with ≥2 HIV-related laboratory test records in the analysis. We estimated cancer incidence rates per 100,000 person-years (pys), stratified by current age group (<10, 10-17, and 18-25 years). Time at risk was calculated from the 1st positive HIV test or CD4 measurement to 6 months after the last laboratory test record or to cancer diagnosis.
Results: Based on 907,171 laboratory records we created a cohort of 49,946 children (<10 years), 17,707 adolescents (10-17 years) and 120,706 young adults aged 18-25 years at their 1st HIV-related laboratory test. Half (51%) of children, 70% of adolescents and 89% of young adults were female. Median 1st CD4 count in children ≥5 years, adolescents, and young adults was 349 cells/µl (IQR 210-521); in children <5 years, median 1st CD4% was 9% (IQR 5-15). Over 576,389 pys 414 incident cancer cases were recorded. Median follow-up time was 2.3 years (IQR 1.0-4.6). Overall cancer incidence rates per 100,000 pys increased with current age group from 77 (95% confidence interval [CI] 63-94) in children, 90 (95% CI 70-117) in adolescents to 121 (95% CI 108-137) in young adults (Figure). In children, cancer-specific incidence rates were similarly high for Kaposi sarcoma (KS), Burkitt lymphoma, other non-Hodgkin Lymphoma (NHL), and leukemia. KS incidence rates increased with age. Specific incidence rates were higher for KS than for other cancers in adolescents and young adults.
Conclusion: Record linkage methods using laboratory test records can facilitate the assessment of cancer risk in children and young people living with HIV in South Africa. Incidence rates for cancers increased with age which was mainly driven by cancers associated with oncogenic viruses. Dedicated prevention strategies are required.



819 YOUTH PSYCHIATRIC TRAJECTORIES PREDICT PERINATALLY HIV INFECTED YOUNG-ADULT VIREMIA

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Background: Little is known about the relationship between patterns of psychiatric functioning over time and HIV outcomes, especially among perinatally HIV-infected (PHIV) adolescents and young adults (AYA).
Methods: Using data from one of the few cohort studies of PHIV AYA, we identified longitudinal trajectories of psychiatric disorders among 130 PHIV AYA living in New York City, and examined their associations with sociodemographic factors at enrollment and experiencing a viremic event in young adulthood. Psychiatric disorders (mood, anxiety, behavioral, substance use) were assessed using the Diagnostic Interview Schedule for Children at enrollment (ages 9-16) and 4 follow-up (FU) visits. At last FU (ages 18-28), a viremic event was defined as any past year viral load >200 copies/mL. Multivariate longitudinal latent class

analysis was used to identify co-occurring trajectories of psychiatric disorders, and multinomial logistic regression was used to examine sociodemographic predictors of the trajectories. A log-binomial model was used to examine the association between trajectories and a viremic event.
Results: We identified 3 psychiatric trajectories spanning a median of 10 years. 1) AYA with "consistent low disorder" (63%) had no mood or behavioral disorders, few and decreasing anxiety disorders, and increasing but relatively few substance use disorders. 2) AYA with "persistent anxiety" (26%) had persistent anxiety disorders, low and decreasing behavioral disorders, and low but increasing mood and substance use disorders. 3) AYA with "escalating comorbidity" (11%) had substantial comorbidity at enrollment, with increasing substance use disorders, anxiety and mood disorders over time. At last FU, more than half (62%) of AYA had a viremic event. Compared to AYA with "consistent low disorder," AYA with "escalating comorbidity" were significantly older (OR=1.62; 95% CI=1.26-2.10), reported higher neighborhood stress at enrollment (OR=4.28; 95% CI=1.67-11.0), and had 51% higher risk of a viremic event (RR=1.51; 95% CI=1.08, 2.12), while AYA in the "persistent anxiety" trajectory were more likely to be female (OR=2.05; 95%CI=1.17-3.61) and had 26% higher risk of a viremic event (RR=1.26; 95% CI=0.93, 1.72).
Conclusion: PHIV AYA are at high risk for mental health and substance use problems, with more comorbidity over time associated with a viremic event. Addressing the substantial and evolving mental health challenges among AYA is critical to meeting 90-90-90 treatment goals.

820 TRAJECTORY ANALYSIS OF COGNITIVE OUTCOMES IN CHILDREN WITH PERINATAL HIV

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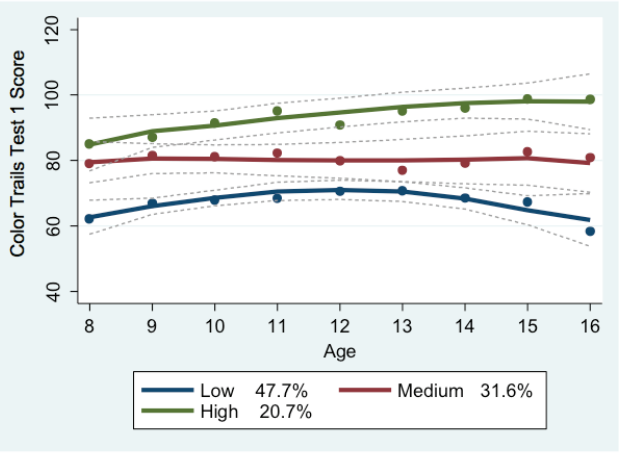
Background: Cognitive impairment is common in children with perinatal HIV (pHIV). HIV-related neuropathogenesis may produce distinct cognitive phenotypes as children age. We used trajectory modeling to identify clusters of children with pHIV following unique developmental trajectories and identified predictors of belonging to select cognitive trajectory groups.
Methods: Participants included Thai and Cambodian children with pHIV enrolled in the PREDICT study. Children ages 4 to 12 years, with CD4% between 15-24% and no history of AIDS defining illnesses were included. Cognitive measures included intelligence tests, Children's Color Trails, and Beery-Buktenica Developmental Test of Visual-Motor Integration and were conducted annually with a minimum follow-up of 3 years (median 5 years). Children with similar cognitive trajectories were classified using maximum likelihood estimation and Bayesian Information Criterion. Joint estimation was used to assess the influence of time varying co-variates of treatment initiation and viral suppression on trajectory course. Multiple logistic regression was employed to identify baseline factors (age, household income, parent as a caregiver, CD4 nadir, and treatment arm) associated with trajectory group membership.
Results: At baseline assessment, 286 children had a median age of 8 years, median CD4% of 20%, and 51% were on ART. Trajectory analyses revealed a 3-cluster classification for cognitive data representing high, medium and low scoring groups. Figure 1 shows an example of trajectory groups for Children's Color Trails 1. Scores in the low and medium trajectory groups were stable across adolescence. In contrast, the highest scoring group demonstrated a 10-point increase in scores from baseline. Children in the lowest scoring trajectory groups were more likely to enroll at an older age (p=0.01) and report lower household income (p<0.005). Neither CD4 nadir nor treatment arm (immediate versus deferred until immunosuppression ART initiation) was associated with cognitive trajectory status.
Conclusion: Trajectory modeling succinctly classifies cohort heterogeneity in cognitive outcomes in pHIV. Most trajectory scores remained stable across age suggesting that cognitive potential is likely determined at an early age with the exception of a subgroup of children who experienced developmental gains in select cognitive domains. Poverty and longer duration of untreated HIV may predispose children with pHIV to an increased risk of suboptimal cognitive development.

Figure 1: Children's Color Trails Test 1 Trajectory Groups



821 FOCUSED COGNITIVE FUNCTION TESTING IN YOUNG PEOPLE WITH PERINATAL HIV IN ENGLAND

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Background: We previously reported that cognitive performance in young people with perinatal HIV (PHIV+) without a CDC C diagnosis (PHIV+/no C) was similar to a comparable group of HIV-negative (HIV-) young people in England, but poorer than normative data, most noticeably in the domains of learning and memory. Here, we assess cognitive performance in the same cohort 2 years later, with expanded testing of these specific cognitive domains.
Methods: 234 PHIV+ and 68 HIV- young people completed 9 tests: 5 NIH Toolbox tests measuring executive function (Flanker inhibitory control/attention, dimensional change card sort), speed of information processing (pattern comparison), and memory (list sorting, picture sequence); 2 Hopkins Verbal Learning Tests (HVLT-R) (learning (L) (sum of 3 trials), delayed recall (R)); and 2 verbal language measures (Weschler Individual Achievement Test word reading (WIAT-II)), British Picture Vocabulary Scale). Z scores for each test were calculated using normative data, adjusted for age (and sex, ethnicity, and education for NIH Toolbox), and averaged by domain where appropriate. Chi squared, Wilcoxon rank sum and ANOVA tests compared proportions, median and means respectively, by HIV and CDC C status.
Results: 139(59%) and 48(71%) of PHIV+ and HIV- were female (p=0.09), 202(86%) and 52(76%) were black (p=0.05), and median age was 19[17,21] and 18[16,21] years (p=0.45) respectively. 55(24%) of PHIV+ had a CDC C diagnosis (PHIV+/C). For HVLT-R, PHIV+/C participants had lower mean z scores (L -2.8 (95% CI -3.3, -2.2), R -2.6 (-3.1, -2.0)) than PHIV+/no C (L -2.0 (-2.3, -1.8), R -1.9 (-2.1, -1.6)) and HIV- participants (L -1.7 (-2.1, -1.3), R -1.5 (-1.9, -1.0)), and all were <1 SD below the reference mean (Figure). However, 292(97%) improved their score over the learning trials, and this was seen in all groups (p=0.62). PHIV+/C had poorer scores than the other 2 groups for verbal language measures, however mean scores were within 1 SD below the reference mean for all groups indicating mild impairment. NIH Toolbox executive function, speed of information processing and memory tests were similar for all 3 groups.
Conclusion: Cognitive function was similar between PHIV+ and HIV- young people in most domains/tests. However, performance in verbal learning and recall fell below population normative scores, and was more pronounced in PHIV+/C, supporting wider findings that earlier ART initiation may protect aspects of cognitive development.

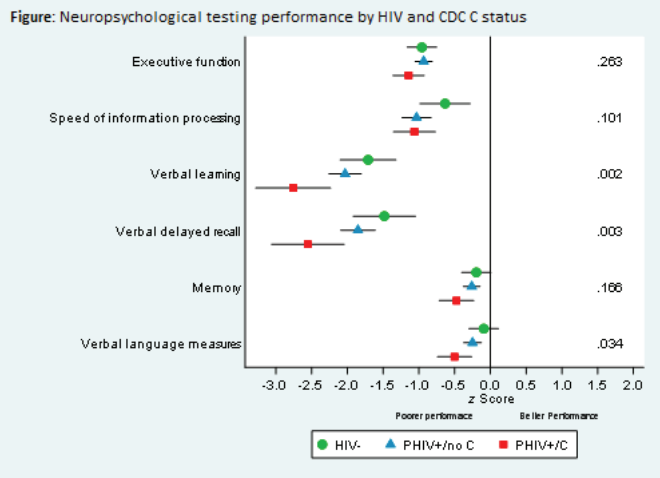

Figure: Neuropsychological testing performance by HIV and CDC C status

822 SYSTEMIC INFLAMMATION AND STRUCTURAL BRAIN CHANGES IN PERINATALLY HIV+ ADOLESCENTS

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Background: Neurological impairments despite ART are well documented in perinatally-infected HIV+ adolescents (PHIV) but the mechanisms that drive this are not well defined. Systemic inflammation may be one mechanism but this has not been investigated in adolescence when the brain is undergoing rapid development.

Methods: Baseline data were drawn from the Cape Town Adolescent Antiretroviral Cohort (CTAAC). PHIV on ART >6m at public sector facilities completed a comprehensive neurocognitive test battery assessing function in 10 cognitive domains. Diffusion tensor imaging and structural brain magnetic resonance imaging (MRI) was done to determine fractional anisotropy (FA), mean diffusivity (MD), axial diffusion (AD), radial diffusion (RD) gray and white matter volumes, cortical thickness and cortical surface area. In analysis we examined how neurocognitive and neurostructural measures were associated with concurrently measured markers of systemic inflammation including hs-CRP and fasting low density lipoprotein-cholesterol (LDL-C).

Results: Overall 204 PHIV ages 9-12 years (mean CD4 cell count 953 cells/μL and 85.3% VL<50 copies/mL) and 44 age-matched HIV- controls completed all assessments. PHIV had higher hs-CRP (p<0.001) and LDL (p=0.06) vs controls. Among PHIV, hs-CRP negatively correlated with multiple neurocognitive measures including general intelligence (p=0.005), attention (p=0.015), working memory (p=0.003), visual space acuity (p=0.005), processing speed (p<0.001), and executive function (p=0.002); LDL-C negatively correlated with Language (p=0.048); however none of these correlations were apparent among controls. In measurements of the fornix and internal capsule FA, AD, MD and RD all increased with higher hs-CRP values (p<0.005 for all associations). Higher MD and RD are suggestive of inflammation and myelin loss. There were no associations in PHIV or controls between hs-CRP and global brain measures (total grey matter, total white matter, mean cortical thickness), but whole brain mean cortical thickness increased with higher levels of LDL-C in PHIV (p=0.027).

Conclusion: Markers of systemic inflammation appear associated with both neurocognitive impairment and structural brain changes in PHIV. While further investigation including long-term follow-up is required, this provides novel evidence that inflammatory mechanisms may drive persistent neurological impairment in PHIV.

823 GENOMICS LINKS AUTOPHAGY WITH NEUROCOGNITIVE IMPAIRMENT IN HIV-INFECTED CHILDREN

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Background: HIV associated neurocognitive impairment (NCI) is a common complication of perinatal HIV infection and is associated with elevated markers of inflammation. Here we identified host genetic variants associated with NCI in HIV-infected children (2 mo-18 yrs).

Methods: Whole exome sequencing was performed on 195 HIV-infected children with NCI (standardized global cognitive score for age (CSA) <70) and 211 infected controls matched for age, CD4+ count and viral load without NCI evaluated prior to the start of ART (P152/P300-Discovery Cohort [DC], mean age: 2.7 yrs). SNPs identified in DC were evaluated in 2 validation cohorts (VC): PHACS AMP (CSA <70: n=61; >70: n=306; mean age: 11.6 yrs): a contemporary longitudinal study of perinatal HIV-infected children; and P338/P377 (CSA <70: n=54; >70: n=303, mean age: 6.8 yrs) consisting of children stable on NRTI therapy prior to treatment with either ritonavir (P338) or nevirapine, nelfinavir or ritonavir (P377). Logistic regression was used to estimate adjusted odds ratios (OR). The combined, across study, OR estimate was computed using inverse variance weights. P-values <.05 were considered to be statistically significant.

Results: 22 SNPs with >5 subjects/SNP in 19 genes reaching p <0.001 and OR >1.5 for each comparison of cognitively impaired group to controls with >70, >85 and >100 CSA were identified in the DC. The 22 SNPs were evaluated by PCR in the PHACS Adolescent Master Protocol cohort and identified 3 SNPs, CCRL2 (rs3204849), FAM134B [RETREG1] (rs61733811) and YWHAH [14-3-3 proteins] (rs73884247) comparing CSA 70 with similar 95% confidence interval (CI) for the OR. These 3 SNPs were further evaluated in a second VC from PACTG 338/377. Only the OR for rs73884247 was in the same direction (OR >1.0). However, the overall 95% CI for the ORs excluded the null hypothesis, indicating that the overall difference is statistically significant (rs3240849: p<.0001, rs6173381: p<.0001, rs73884247: P<.001; Figure).

Conclusion: Using whole exome sequencing and two VCs, we have identified three genetic variants that are associated with NCI in HIV-infected children. Since YWHAH and CCRL2 binding to chemerin both affect mTORC1 phosphorylation and FAM134B plays a role in autophagosome formation, a potential common mechanism for these three genetic variants is the modulation of autophagy leading to altered inflammation affecting neurocognitive function.

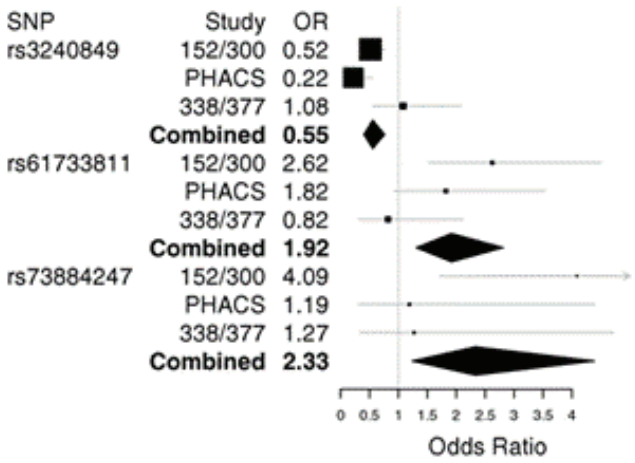

Figure: Combined and study specific Odds Ratios by SNP

824 HIGH PRESCRIPTION ERROR RATES AMONG CHILDREN ON ANTIRETROVIRAL THERAPY IN KENYA

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Background: Access to life saving antiretroviral therapy (ART) in many resource-limited settings has increased, yet more than 30% of children on ART do not achieve viral suppression. Infants and children require continuous medication dose adjustments in response to changing pharmacodynamics, and inappropriate dosing may contribute to viral non-suppression. This study sought to determine the magnitude of prescription dosing errors and associated factors.

Methods: We conducted a cross sectional study among HIV Infected children aged ≤11 years in four public health facilities in Nairobi, Kenya. Demographic, clinical and prescription data for the last clinical visit were abstracted from the medical charts of children receiving ART at the time of study. Descriptive statistics were used to summarize participant characteristics and prescription errors. Logistic regression was conducted to determine factors associated with dosing errors.

Results: A total of 196 children were included in the study; among these, 53% were male and the median age was 7.9 years (Interquartile range [IQR] 4.8, 10.0). The most commonly used ART regimens were abacavir/lamivudine/lopinavir/ritonavir taken by 61 (31%) children, followed by zidovudine / lamudivine /nevirapine with 43 (22%) children, and abacavir/ lamivudine/ nevirapine taken by 36 (18%) children. Overall, 85 (44%), 90 (46%) and 92 (47%) children lacked data on the antiretroviral (ARV) drug formulation, dosage, and frequency of dosing respectively, translating into almost half of children having prescription errors from the outset. Among 104 (53%) children with complete formulation, dosage and frequency of dosing prescription information, 38 (37%) had at least one prescription dosing error. In a multivariable model, being on non-nucleoside reverse transcriptase inhibitors was independently associated with an increased likelihood of a dosing error (adjusted odds ratio 8.8; 95% confidence interval 2.1-36.3).

Conclusion: Almost half of children receiving antiretroviral therapy had inadequate prescription information and among those with adequate information, one third had prescription dosing errors. These findings call for urgent measures to address health care workers prescribing practices and knowledge, particularly on documentation and appropriate dosing including weight based dose adjustments. In addition, further evaluation should be conducted to determine association of prescription errors with viral suppression.

825 EFFECT OF ANTITUBERCULOSIS THERAPY ON NEVIRAPINE PHARMACOKINETICS IN YOUNG CHILDREN

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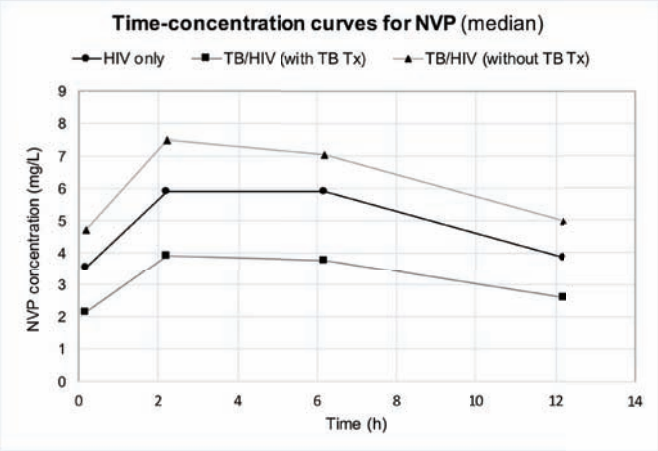
Background: Nevirapine (NVP)-based antiretroviral therapy (ART) is one of the limited options in children younger than 3 years old with TB/HIV coinfection. Given the scarce data, we examined the effect of first-line TB therapy on NVP pharmacokinetics (PK) in Ghanaian children.

Methods: ART-naïve HIV-infected children aged 3–35 months with and without TB were treated with NVP 200 mg/m2 twice daily plus two NRTIs. The new WHO recommended higher dosages of rifampin and isoniazid were used. After 4 weeks of ART, PK samples were collected at 0, 2, 6, and 12 hours post-dose to measure NVP plasma concentrations, using a validated LC/MS/MS assay. In the co-infected patients, sampling was repeated after 4 weeks off TB therapy. PK parameters were calculated using noncompartmental analysis and were compared between groups using Wilcoxon Rank-sum test and within group using Signed-rank test.

Results: Of the 53 patients, 23 (43%) had TB coinfection, of whom 15 completed PK sampling on (PK1) and off (PK2) anti-TB therapy. Baseline characteristics were similar in the two groups except co-infected children had lower median height-for-age-Z-score. Median NVP concentrations were lowest in the children with TB/HIV coinfection on TB therapy, followed by HIV infection only and highest in the co-infected off TB therapy (Figure). Median NVP Cmax, Cmin and AUC0-12h were not significantly different between children with HIV and those with TB/HIV on or off anti-TB therapy. In multivariate analysis, TB therapy and CYP2B6 516G>T genotype status were joint predictors of NVP PK. Among children with CYP2B6 516GG genotype, NVP exposure was significantly lower in the TB co-infected compared to HIV-infected group; this difference was not seen in children with GT or TT genotypes. The proportion of children with NVP Cmin <3 mg/L was 61% in the co-infected group and 30% in the HIV group (P = 0.03). Among the TB/HIV co-infected children with paired samples, geometric mean ratio (90% CI) PK1/PK2 of NVP Cmax, Cmin and AUC0-12h were 0.68 (0.55–0.85), 0.84 (0.51–1.38) and 0.71 (0.56–0.91). Nine (41%) of 22 children with viral load data at 6 months had HIV RNA >200 copies/mL.

Conclusion: First-line TB therapy reduced NVP plasma exposure in young HIV-infected children, especially those with CYP2B6 516GG genotype. Given that NVP dose optimization with TB therapy may require a genotype-guided approach, evaluation of more compatible alternatives to NVP is needed in young children with TB coinfection.



826 SAFETY AND EFFICACY OF STARTING ANTIRETROVIRAL THERAPY IN THE FIRST WEEK OF LIFE

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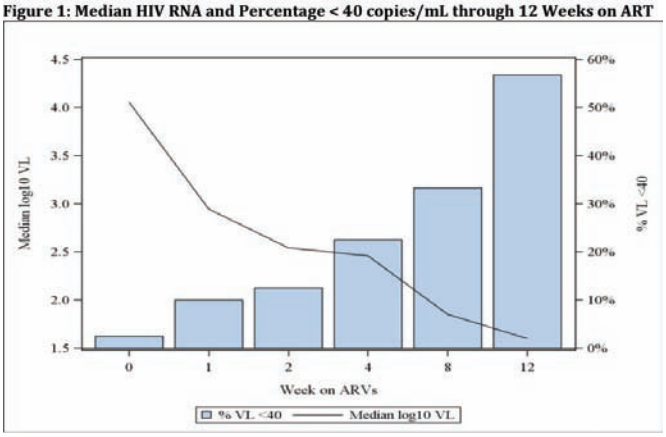
Background: Antiretroviral treatment (ART) started in the first week of life may limit HIV viral reservoir and improve treatment outcomes, but little information is available about safety, viral efficacy, and pharmacokinetics (PK) of ART in early infancy.

Methods: HIV+ infants <7 days of age, >35 weeks gestation, and >2000g were offered enrollment in the Early Infant Treatment Study (EIT) in Botswana and started on treatment doses of NVP (6mg/kg BID), ZDV, and 3TC as initial ART, and changed to LPV/r, ZDV, 3TC after 2-5 weeks (when >2 weeks of life and >40 weeks gestational age equivalent). Study visits and HIV RNA testing occurred at weeks 0, 1, 2, 4, 8, 12. PK testing of NVP trough values occurred at weeks 1 and 2. Comparisons were by Wilcoxon rank sum testing and Spearman correlations.

Results: From April 2015-July 2018, 40 HIV+ infants were enrolled; 37 (93%) had reached 12 wks on ART as of 20 September 2018. Median age at screening was 1 day after birth (range 0, 4), and median age at ART initiation was 2 days after birth (range 1, 5). Median change from NVP-based to LPV/r-based ART was after 2.7 wks (range 2.3, 4.4 wks). No deaths or loss to follow-up occurred in the first 12 wks, and no modification of ART for toxicity occurred. Only 1 grade 3/4 neutropenia and no grade 3/4 anemias were reported through 12 wks. HIV RNA declined from a median of 4.05 log copies/mL at baseline (IQR 2.79, 4.86 log copies/mL) to 2.54 log copies/mL at 2 wks (IQR 1.86, 3.21) and <1.60 log copies/mL at 12 wks (IQR <1.60, 1.89 log copies/mL) (Figure 1), and did not differ by infant HIV RNA at baseline (p=0.10). At 12 wks of ART, 21 (57%) of 37 had HIV RNA < 40 copies/mL, and only 3 (8%) were > 400 copies/mL. However, 9 (22.5%) infants had transient increases in HIV RNA in the 4-wk period following

transition to LPV/r-based ART, thought to be adherence-related. Median NVP trough concentration at 1 and 2 wks was 3.01 mcg/mL (at median 15 hrs); 48% of concentrations were below the therapeutic target of 3.0 mcg/mL (including 10% BQL, indicating non-adherence); concentrations did not correlate with the magnitude of decline in HIV RNA log copies/mL at either 2 or 4 wks.
Conclusion: NVP, ZDV, 3TC started in the first week of life was safe and effective, even among infants with NVP levels below the ideal therapeutic PK target. Although poor tolerability often led to transient viral rebound following transition to LPV/r-based ART, almost all children were able to achieve HIV RNA declines to < 400 copies/mL by 12 weeks of life.

Figure 1: Median HIV RNA and Percentage < 40 copies/mL through 12 Weeks on ART



827 IN SILICO PREDICTION OF DOLUTEGRAVIR PHARMACOKINETICS & DOSE OPTIMISATION IN NEONATES

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Background: Dolutegravir (DTG) is a selective and potent HIV-1 integrase inhibitor and has potential for treatment of neonates with HIV infection and use as prophylaxis of perinatal transmission. Safety and pharmacokinetics (PK) of DTG have previously been studied in pediatric patients and current studies are investigating the appropriate dose in infants aged > 4 weeks. Dose optimisation in neonatal patients is complex and physiologically-based pharmacokinetic (PBPK) modelling may help inform knowledge gaps in the absence of empirical data. The aim of this study was to simulate the PK of DTG in neonates to help identify an appropriate dosing regimen using PBPK modelling.
Methods: The PBPK model was designed in Simbiology (MATLAB R2018a) incorporating neonatal maturation characteristics and a description of physiological and anatomical growth data from various sources. Experimental *in vitro* data for DTG was integrated into the model to aid prediction of DTG PK in the neonatal population. DTG is predominantly metabolised by UGT1A1 and CYP3A4 and the PBPK model was qualified using clinical data from the surrogate substrates raltegravir (UGT1A1) and midazolam (CYP3A4) in neonates. Additionally, DTG adult and paediatric clinical data were used for the validation of the PBPK model. The model was assumed to be qualified if the simulated values were within 0.5-1.5 fold of the mean reported values as per convention for the approach.
Results: A combination of different DTG single and multiple dose strategies were simulated in 100 healthy neonates with the aim of achieving plasma exposure comparable to therapeutic levels observed in paediatric patients (C_{trough}: 0.90 mg/L and AUC_{24}: 46 mg.h/L). The PK parameters are summarised in Table 1. Regimens 1-3 result in PK parameters comparable to those in paediatric patients, with convenient dosing schedules.
Conclusion: Due to the lack of clinical PK data, neonates represent a vulnerable population. Clinical trials in neonates are extremely difficult to conduct and dose prediction is therefore beneficial to inform trial design. The combination of rapid development and immature ontogeny make it difficult to easily scale existing doses. PBPK modelling allows these changes to be represented mathematically, and should result in more accurate predictions. The presented data can be used to inform neonatal clinical trials to help accelerate dose optimisation in this population.

Table 1: Pharmacokinetic properties of dolutegravir (DTG) in neonates

Regimen	Dose (mg/kg)	C_{max} (mg/L)	AUC_{24} (mg.h/L)	AUCav (mg.h/L)	C_{trough} (mg/L)
1	Day 1 = 4.5; Day 4-30 = 1.0 QD	3.37	65.70	41.76	0.90
2	Day 1 = 3.0; Day 2-10 = 1.0 QD; Day 11-30 = 1.5 QD	2.23	43.38	49.68	1.27
3	Day 1 = 3.0; Day 3-30 = 1.5 QD	2.24	43.97	57.83	1.39
4	Day 1 = 2.5; Day 3-30 = 1.5 QD	1.85	36.13	51.98	1.22
5	Day 1 = 2.0; Day 2-30 = 1.0 QD	1.50	28.78	40.62	0.92
6	Day 1 = 2.5; Day 2-14 = 1.0 QD; Day 15-30 = 1.5 QD	1.88	36.81	47.43	1.32

AUC_{av}, Average area under curve over 30 days; AUC_{24}, Area under curve over 24 hours; C_{max}, Maximum plasma concentration; C_{trough}, Trough plasma concentration; QD, Once daily.

828 SIMILAR EFFICACY AND SAFETY OF DOLUTEGRAVIR BETWEEN AGE GROUPS OF PEDIATRIC PATIENTS

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Background: Dolutegravir (DTG)-based cART are now approved for use in HIV+ children aged ≥6 years in many countries worldwide. However, published data about its efficacy and its safety profile in the pediatric population are scarce, especially in youngest children. This retrospective monocentric study compared data about safety and efficacy of DTG in patients followed in a French pediatric unit and divided into three groups of age at the time of DTG initiation: 5-12 (Group 1), 12-18 (Group 2) and ≥ 18 year old (Group 3).
Methods: Clinical and biological data from 109 patients, who initiated DTG-based cART between January 2014 and December 2017 were retrospectively analysed: 33 in Group 1, 51 in Group 2 and 25 in Group 3. 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: Most of the individuals were antiretroviral experienced (91.7%) and 12 (11%) were previously exposed to INSTI. INSTI-associated resistance associated mutations (RAMs) were previously isolated in 4 patients: E157Q in 2 cases, N155H in 2 individuals (who were treated with twice-daily DTG). The proportions of patients with virological suppression at baseline in each of the groups were 66.7%, 54.9% and 56.0%. Median follow-up was 24 months (range 6-54). Sustained virological success was obtained in 79.8% of patients, with similar rates observed in the 3 groups (87.9%, 72.5% and 84.0%, p=0.22). With reinforced measures to improve adherence, undetectable PVL was obtained at the last visit in 88.1% of patients, with similar proportions in the 3 groups (93.9%, 84.3% and 88.0%, p=0.51). Sustained virological success and undetectable PVL at the last visit were obtained in 91.7% and 100.0% of INSTI-experienced patients, respectively. No emergence of resistance mutation was observed in the 22 patients with virological failure. DTG was well tolerated; only 1 patient (Group 2) stopped treatment for severe drug-related side effect (dizziness, sleep disturbance). None of the three Grade 3 laboratory events were study drug related.
Conclusion: Virological efficacy and safety of DTG were similar between the 3 groups of age. Because of its high genetic barrier to resistance, DTG could be especially useful in the paediatric population, in which the risk of poor treatment adherence is high.

829LB PK AND 4-WEEK OUTCOMES OF DOLUTEGRAVIR DISPERSIBLE TABLETS IN HIV-INFECTED CHILDREN

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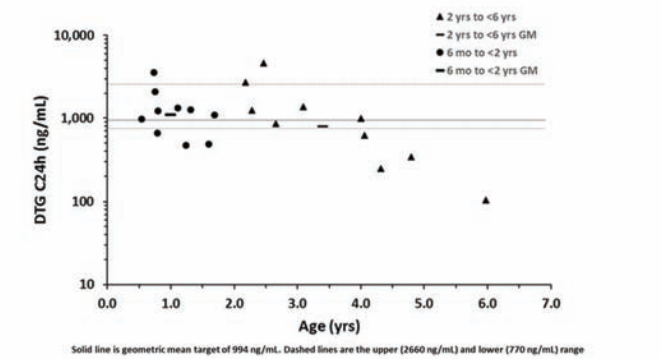
Background: Dolutegravir (DTG, S/GSK1349572) is recommended as first-line treatment for HIV-infected adults and children 6 yrs and older due to its potency, high barrier to resistance, convenience and tolerability. A 5mg dispersible tablet (DTG-DT) formulation for children is being evaluated in IMPAACT P1093 (NCT01302847), an ongoing phase I/II open-label dose-finding study. The first DTG-DT dosing tested did not meet target drug exposures. Here we present the intensive pharmacokinetic (PK), 4-week safety and efficacy data of higher dosing for DTG-DT in children ages 6 mo to <6 yr.

Methods: Enrollment was stratified into two age cohorts of 10 children (≥6 mo to <2 yr and ≥2 to <6 yr). DTG-DT was dosed once daily by WHO weight-band (6 to <10kg: 15mg, 10 to <14kg: 20mg, 14 to <20kg: 25mg). Children received DTG-DT alone or added to stable-failing or empiric initial background regimens. PK sampling was completed between days 5-10 under fasting conditions. Background regimens were optimized based on enrollment HIV genotypes. Safety, tolerability, and plasma HIV-1 RNA levels were assessed through 4 weeks. Based on adult data, exposure targets were geometric mean (GM) (range) AUC24h of 46 (37-134) mg.h/L and C24h of 995 (697-2260) ng/mL.

Results: Twenty children (10 female) with median (range) age 22 months (6, 71), and weight 9.4 kg (6.5, 17.5) were studied. Median baseline CD4+ cell % and HIV-1 RNA levels were 27.3 (IQR: 22.0, 36.9) and 4.3log10 (c/mL) (IQR: 3.3, 5.3). For age cohorts of ≥6 mo to <2 yr and ≥2 to <6 yr, the GM(CV%) AUC24h(CV%) was 70.2 (49.6) mg.h/L and 59.0 (62.2) mg.h/L, C24h was 1094(70.4) ng/mL and 791 (105) ng/mL, and Cmax was 5702(37) ng/mL and 5181 (44) ng/mL, respectively. C24h levels varied from 104 to 4579 ng/mL (figure). DTG was well tolerated, with no drug-related Grade 3 or 4 AEs or discontinuations. HIV-1 RNA levels were <400 c/mL in 16/20 and <50 c/ml in 8/20 participants after 4 weeks of treatment, with median decrease from BL of 2.38 log10 (c/mL) (IQR: 1.36, 3.11).

Conclusion: The tested dosing of DTG-DT met pre-specified AUC24h and C24h targets for age-cohorts children 6 mo to <6 yr old, even with moderate intra-participant variability. DTG was virologically potent and well tolerated through week 4. With the additional PK, long-term safety and efficacy data currently being collected, these novel results will form the basis of safe and efficacious WHO weight-band dosing recommendations for DTG-DT in children.



830LB ADULT DOLUTEGRAVIR 50MG TABLETS IN CHILDREN LIVING WITH HIV WEIGHING 20 TO <25KG

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Background: Weight band pharmacokinetic (PK) substudies within the ongoing phase III ODYSSEY-trial evaluate PK and safety of simplified weight band-based dosing of dolutegravir (DTG) for children on first-line and second-line antiretroviral therapy (ART). This substudy assessed PK and safety of DTG adult film-coated tablets (FCT) and pediatric dispersible tablets (DT) in children weighing 20 to <25kg who make up a high proportion of children living with HIV. DT have higher bioavailability compared to FCT in adults (ratio 1.5-1.8).

Methods: Steady state 24h DTG PK profiles in fasted children taking once-daily DTG 50mg FCT or 30mg DT (6x5mg) were recorded ≥7 days after switch from DTG 25mg FCT. Blood was sampled at t=0, 1, 2, 3, 4, 6 and 24h and DTG plasma concentrations were measured with a validated UPLC-MS/MS method. Non-compartmental PK analysis was performed to calculate PK parameters (WinNonlin 8.1). Results were compared to those in HIV-positive adults taking DTG 50mg FCT once/twice daily, and children 20 to <25kg on 25mg FCT once daily (Table). Safety was evaluated at 2, 4, 12, and then every 12 weeks.

Results: 15 African children were enrolled in Zimbabwe and Uganda (Table). The 50mg FCT (n=7) and 30mg DT (n=8) doses both resulted in geometric mean (GM) C_{trough} values comparable to adults on DTG 50mg FCT once-daily and were higher compared to children 20 to <25kg on 25mg FCT. GM AUC_{0-24h} for both doses was in-between values observed in adults taking DTG 50mg once daily and 50mg twice daily. GM C_{max} on both doses exceeded adult GM values for DTG 50mg once and twice daily. DTG 50mg FCT in this weight band provided a lower GM C_{max} compared to 30mg DT. After median (IQR) follow-up of 11.9 (4.0-11.9) and 5.1 (3.0-11.8) weeks on 50mg FCT and 30mg DT respectively, no children experienced grade 3/4, serious adverse events or discontinued DTG.

Conclusion: Daily DTG 50mg FCT and 30mg DT provide similar and appropriate PK profiles for children 20 to <25kg. Short-term safety data are reassuring and, provided ongoing longer-term safety is acceptable, these results support use of either 50mg FCT or DTG 30mg DT in this weight band. Adult DTG 50mg FCT could offer a practical and accessible dosing strategy for children weighing 20 to <25kg allowing rapid alignment of WHO-preferred ART regimens for adults and children ≥20kg in low- and middle-income countries.

Table Participant demographics and PK parameters by dose and formulation in children 20 to <25kg and adult reference populations.

	ODYSSEY		ODYSSEY	Reference adults	
WHO weight band	20-<25kg		20-<25kg	≥ 40kg	
Dose (mg) and formulation	30 DT	50 FCT	25 FCT[a]	50 FCT	50 FCT BID
N	8	7	14	10[b]	24[c]
Sex male, n (%)	4 (50%)	4 (57%)	7 (50%)	10 (100%)	18 (75%)
Age (years)	8.6 (6.8-11.3)	9.7 (8.1-11.7)	9.3 (7.1-11.3)	34 (22-53)	47 (33-68)[d]
Weight (kg)	21.8 (20.3-22.7)	22.4 (20.5-24.5)	23.4 (20.2-24.3)	-	-
Dose (mg/kg)	1.4 (1.3-1.5)	2.2 (2.0-2.4)	1.1 (1.0-1.2)	-	-
C_{trough} (mg/L)	0.71 (74)[e]	0.77 (51)	0.32 (94)[f]	0.83 (26)[b]	2.72 (70)[c]
AUC_{0-24h} (mg*h/L)	71.8 (28)	62.8 (30)	30.1 (41)	43.4 (20)[b]	93.4 (50)[c]
C_{max} (mg/L)	7.42 (25)	6.07 (29)	3.20 (40)	3.34 (16)[b]	5.41 (40)[c]

PK parameters are geometric means with coefficient of variation (%). Other data are mean (range) for age, dose mg/kg, and weight, unless otherwise indicated. [a]Data presented at the 10th International workshop on HIV Pediatrics, July 2018. [b]Fasted HIV-positive adults. [c]HIV-positive treatment-experienced adults, fed state not specified. [d]Data are median (range). [e]One participant had a C_{trough} of 0.30mg/L, below EC90 (0.32mg/L). [f]Ten participants had C_{trough} below EC90 (0.32mg/L).

831 RECENT HIV INFECTION SURVEILLANCE AMONG ADOLESCENT GIRLS AND YOUNG WOMEN IN MALAWI

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Background: Tests for recent infection can distinguish recent (in the last 12 months) from long-term HIV infection, and have been used to estimate HIV incidence in population-based surveys but have had limited application in programmatic settings. We implemented a novel surveillance system to detect

clusters of recent infection and estimate incidence among newly diagnosed adolescent girls and young women (AGYW) seeking antenatal care (ANC) in Malawi.

Methods: Pregnant AGYW aged 15–24, newly diagnosed with HIV at their first ANC visit in Lilongwe, Blantyre, Machinga, and Zomba districts were consecutively enrolled, completed behavioral questionnaires and provided blood samples for recency testing. Recent infection was defined as normalized optical density value of ≤1.5 or ≤2.0 on the Limiting Antigen Avidity Enzyme Immunoassay (Maxim or Sedia, respectively) and VL ≥1,000 copies/mL. We calculated the prevalence of recent infection and annualized incidence using data abstracted from ANC registers on the number and serostatus of all AGYW attending ANC. We assumed mean duration of recent infection of 161 days (95% confidence interval [CI], 145–177 days), 1% false recency rate and that previously diagnosed AGYW had long-term infections.

Results: From November 2017 to July 2018, we enrolled 610 AGYW. Over half [63.6%, (367/577)] were unaware of their partners' HIV status, 30.6% (185/605) had never been tested, 31.6% 188/595) reported sexually transmitted infection symptoms in the past year, and 25.1% (151/602) reported ever being abused by a sexual partner. HIV prevalence among pregnant AGYW in all districts was 4.3%. Of 590 AGYW with test results, 68 (11.5%) had recent infection; median VL among recently infected AGYW was 27,548 copies/mL (IQR 8,060 - 88,785 copies/mL). Overall incidence was 0.31/100 person years (py; CI 0.14-0.44): 0.25/100 py (CI, 0.12-0.38) among AGYW aged 15-19 years and 0.34/100 py (CI, 0.19-0.49) among AGYW aged 20-24 years. Incidence was significantly higher in Blantyre [0.55/100 py (CI, 0.24–0.86), P <0.001] and Lilongwe [0.37/100 py (CI, 0.21–0.53), P <0.001] relative to Machinga and Zomba [0.12/100 py (CI, 0.00–0.24)].

Conclusion: One in ten newly diagnosed pregnant AGYW was recently infected, with incidence estimates indicating ongoing transmission among AGYW in these districts. The majority had been infected >1 year ago, which may represent delayed diagnosis. Recent infection testing in ANC settings can help identify unmet needs for HIV prevention, testing, and treatment.

832 HIV SEROSTATUS CONVERSION AMONG REPEAT-TESTING FEMALE SEX WORKERS IN TANZANIA

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Background: The risk of HIV acquisition among female sex workers (FSW) across Sub-Saharan Africa is estimated to be 13x higher than other women: understanding population-specific risk factors can provide important information to guide HIV prevention interventions. Sauti is a PEPFAR/USAID-funded combination prevention project working in 14 regions in Tanzania, serving key and vulnerable populations with biomedical and structural prevention, care and treatment interventions including HIV testing. FSW are primary recipients of Sauti services, provided at brothels and other hot spots for HIV transmission. This analysis describes factors associated with HIV serostatus conversion among a cohort of FSW originally testing HIV negative and subsequently testing HIV positive during the course of attending Sauti services.

Methods: Sauti project data comprise clinical intake forms which Sauti program collects, de-identifies, enters into a database and uses for program analysis. From October 2016 to December 2017, 261,566 FSW tested for HIV. 6,892 returned for repeat testing testing for 3 months or more from the original test: these are the repeat testers cohort. All repeat tester data was analyzed to examine when re-testing occurred and understand factors which may have influenced seroconversion. We conducted multivariable logistic regression analysis to estimate odds ratios for risk factors associated with HIV seroconversion.

Results: 6,128 FSW repeat tested, testing negative for HIV at initial test. Of these 235 (3.8%) tested HIV positive upon repeat test. Having a syndromic STI (3.21, 95% CI: 2.53-8.12) and non-use of STI periodic presumptive treatment (1.34, 95% CI: 1.07-1.94) were highly predictive of HIV sero-conversion. Other predictors for included: older age 35+ years (3.10, 95%: CI: 1.97-4.85), never used condom in last three sexual intercourse (1.58, 95% CI: 1.16-3.05) and practicing anal sex (2.45, 95% CI: 1.81-3.31)

Conclusion: Our findings highlighted higher risk of sero-conversion among FSW who had a syndromic STI and/or did not have presumptive periodic treatment of STIs, as well as behavioral factors such as reporting anal sex and/or inconsistent condom use. The findings underscore the importance of provision of both biomedical and behavioral services to FSW tailored to fit their risk profile. Consistent condom use and STI/HIV prevention are important service delivery components to stress in light of these findings.

Table 1: Factors associated with HIV serostatus conversion among repeat testing FSW (N=6,128)

Risk behaviors	Total	HIV serostatus convertors	Crude analysis		Multivariable analysis	
	N	n (%)	OR [95% CI]	P-value	aOR [95% CI]	P-value
Overall	**6,128**	**235 (3.8)**				
Age						
18-24	1269	29 (2.3)	Reference		Reference	
25-34	3858	133 (3.5)	1.53 [1.03-2.29]	0.041	1.40 [0.92-2.12]	0.113
35+	1001	73 (7.3)	3.36 [2.17-5.22]	<0.001	3.10 [1.97-4.85]	**<0.001**
Condom use in last three sexual intercourse						
Always	469	10 (2.1)	Reference		Reference	
Sometimes	2235	64 (2.9)	1.35 [0.69-2.65]	0.379	1.29 [0.64-2.57]	0.489
Never	3424	161 (4.7)	2.26 [1.18-4.32]	0.013	1.58 [1.16-3.05]	**0.047**
Ever had anal sex						
No	4653	148 (3.2)	Reference		Reference	
Yes	1475	87 (5.9)	3.35 [2.01-5.57]	<0.001	2.45 [1.81-3.31]	**<0.001**
Syndromic STI screening result						
Negative	5911	185 (3.1)	Reference		Reference	
Positive	217	50 (23.0)	7.27 [4.54-13.1]	<0.001	3.21 [2.53-8.12]	**<0.001**
Provided/using STI periodic presumptive treatment						
Yes	4808	168 (3.5)	Reference		Reference	
No	1320	67 (5.1)	1.48 [1.11-1.97]	0.008	1.34 [1.07-1.94]	**0.016**

833 QUANTIFYING TRANSMISSIONS FROM AGE GROUPS IN SIMULATIONS OF HPTN071 (POPART) TRIAL

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Background: The HIV epidemic in sub-Saharan Africa (SSA) is known to be heterogeneous, contributing to the perception that preventative efforts need to be targeted to those at most risk of transmitting or acquiring the virus. The HPTN071 (PopART) trial has been testing the impact of a universally delivered combination prevention package in 21 communities in Zambia and South Africa. An individual-based simulation model (IBM) has been developed as part of the trial. Using the IBM we quantify the proportion of new infections that arise from men and women of different age groups, and the potential impact of suppressing transmissions from each of these groups.

Methods: The IBM is calibrated to trial data in each intervention community (arm A of the trial; one community shown here). Using the best-fitting parameter set, projections of the epidemics are made up to 2030, with 40 replicates. Projections beyond the end of the trial assume continuation of the PopART intervention at a national scale. We estimate the population attributable fraction (PAF), the proportion of new infections that arise from men and women of different ages over defined time-periods. PAF can be defined either as the proportion of infections where a certain group is directly the source of the infection (PAF_{direct}), or can include both direct and indirect effects by modelling the total number of HIV infections averted if a certain group were not able to transmit HIV (PAF_{total}).

Results: In all simulations, for individuals less than 25 years old (y.o.), PAF_{direct} of women was higher than men whereas, for ages greater than 25 y.o., this relationship was reversed. When considering indirect transmissions, PAF_{total} was similar in men and women across all age groups but higher in the 20-34 y.o. age group. In the first 20 years of the epidemic, the PAF_{direct} was highest in 25-29

y.o. men and in 20-24 y.o. women. Over the trial period these heterogeneities in contributions to the epidemic were increased (fig 1). Beyond the trial, PAF_{direct} of 30-34 yo men was >15% in 2023-2028, twice that of women of the same age.
Conclusion: This work illustrates the significant contribution of 25-34 y.o. men to HIV transmission in generalised HIV epidemics in SSA, and of young people when considering indirect transmissions. Future interventions that target sub-populations in SSA need to address such discrepancies. Estimates of PAF_{direct} may be complemented from phylogenetic studies.

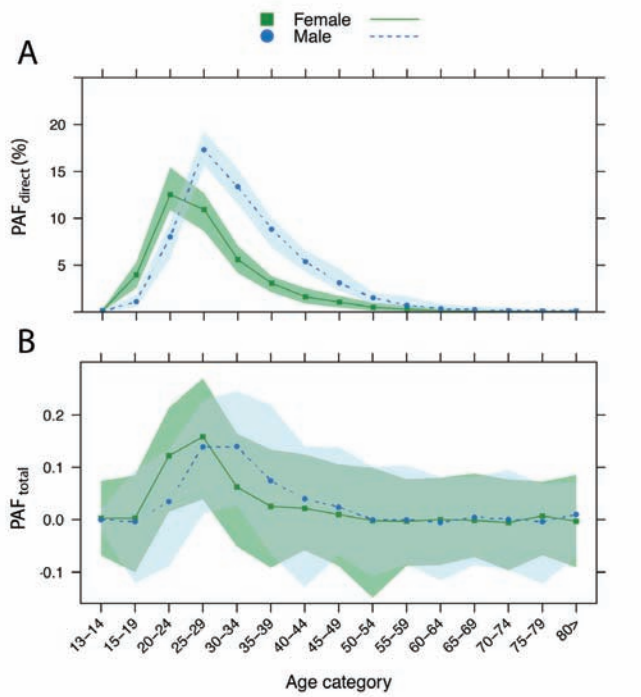

Figure 1: A) PAF direct and B) PAF total across age and sex for trial period (2014.5-2018); points are averaged across 40 model replicates; shaded area are 2.5% and 97.5% quantiles.

834 COMMUNITY PREVALENCE OF VIREMIA: A NEW STANDARD FOR BIO-BEHAVIORAL SURVEYS

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Background: Monitoring HIV programs requires estimates of HIV incidence which can be challenging to obtain. We characterize the change in HIV incidence over 4 years among people who inject drugs (PWID) and men who have sex with men (MSM) across 22 cities in India and evaluate associations with community prevalence of viremia (PV).
Methods: These data are from a cluster-randomized trial among PWID (12 clusters) and MSM (10 clusters) in India that included baseline (2012-13) and follow-up (2016-17) respondent-driven sampling surveys of ~1000/cluster. Cross-sectional HIV incidence was estimated using a validated multi-assay algorithm incorporating LAg Avidity EIA, BioRad Avidity assay, CD4+ count and HIV RNA (limit of detection>150 copies/ml). PV was estimated as the percentage of persons with detectable HIV RNA in the cluster. Cluster-level linear regression assessed the association between change in PV and change in HIV incidence over 4 years controlling for study arm and baseline PV. Multi-level Poisson regression assessed the association between baseline and follow-up PV and individual-level incident HIV risk at follow-up accounting for individual-level correlates using a risk score
Results: The median HIV incidence in PWID clusters at follow-up was 5.16% (range: 0, 18.5); the median absolute change (baseline to follow-up) in incidence was 0.1% (range: -4.55, 12.4). In MSM clusters, median HIV incidence was 1.44% (range: 0.47, 2.96) and median absolute change was 0.04% (range: -2.08, 1.94). In adjusted cluster-level analysis, a one percentage point increase in PV was associated with a 0.38 percentage point increase in HIV incidence (95% CI: 0.2, 0.6; Figure). Individual risk factors of incident HIV in PWID included age, gender, marriage, education, recent needle sharing, sex work and HCV, and among MSM included age, income, recent male and female sexual partners and injection drug use. After controlling for individual risk, PV at baseline (incidence rate ratio [IRR] per 10% increase in PV: 2.51; 95% CI: 1.53, 4.13) and follow-up (IRR per 10% increase: 2.80; 95% CI: 1.79, 4.38) were significantly associated with individual incident infections at follow-up.
Conclusion: Prior studies have demonstrated a strong cross-sectional association between community PV and HIV incidence. We provide further evidence of the role of PV as a surrogate for incidence by demonstrating that change in community PV predicts change in incidence and PV predicts future incident HIV infections independent of individual risk.

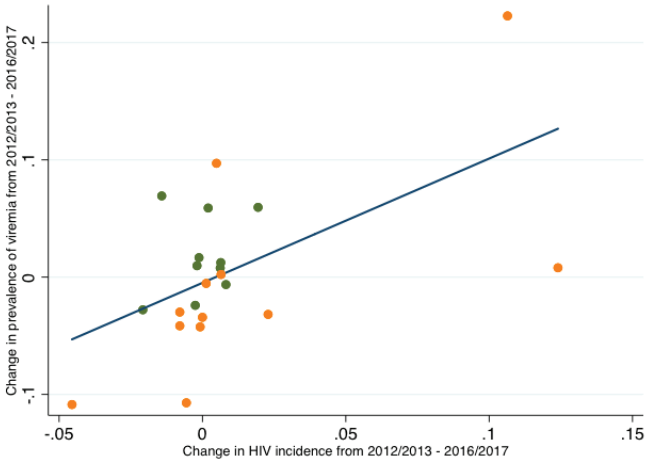

Figure: Scatterplot of change in cross-sectional incidence vs. change in community prevalence of viremia (PV) between baseline (2012-13) and follow-up (2016-17) surveys. Orange = PWID clusters; Green = MSM clusters

835 HIV EPIDEMIC IN A BRIDGE POPULATION IN UKRAINE CALLS FOR NEW PREVENTION STRATEGIES

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Background: Ukraine is experiencing one of the severest HIV epidemic in the World. From its onset in 90th it was primarily an IDU driven. The tremendous efforts that community-based organizations investing in HIV prevention slow down the disease spread among key populations (KP) including people who inject drugs (PWID). The HIV prevalence has stabilized at the level of 22% (21. 9% in 2015 and 21.6% in 2017 sentinel surveys). But when the prevalence is high there is always a risk that the disease may spread to the bridging population. To estimate the HIV burden in one of the bridge groups we conducted the survey among sexual partners of PWID.
Methods: The study population included 769 respondents from 10 cities of Ukraine recruited through a linked RDS in a period of May-August 2015. The sample included those who had sexual intercourse with the PWID in the last 90 days and haven't inject drugs for the last 30 days. All participants were confidentially interviewed to assess their HIV risk behavior. Blood samples were tested for HIV, hepatitis B, C and syphilis by rapid combo tests. The analysis were done in SPSS 21.0 and RDS-Analyst.
Results: Among all the participants 87,3% were females. Medium age – 32,2. 75,5% declared as never injected (72.4-78.5%). 97,6% were regular sex partners of their PWID-recruiters. Only 48.5% used condom during the last intercourse and 35.9% never used condom in the last 90 days. The HIV prevalence in the group of non-injecting sexual partners of PWID as high as 15,0% (12,4 – 17,5%). Among those who declared themselves as never injected – 9,2% (6,8 – 11,6%) and among those who never injected and were HCV-negative - 5,6% (4.2 – 6.8%). The prevalence of syphilis was 4,7% (3.2 – 6.2%). Only 4.6% of the respondents were clients of the HIV prevention programs; 3.6% have received

free condoms as part of prevention service in the last 12 month. 23.5% of couples were serodiscordant, in 16.9% of cases partner-PWID was HIV-positive. Only quarter of them had the HIV test in the last 12 month and knew the result. None of HIV-negative partners received PrEP.
Conclusion: The HIV epidemic in Ukraine is still in progress and it's involving people outside of KP through unprotected sex. With the understanding that the sexual behavior is hard to correct and people won't start use condoms with their regular partners if they have not done so yet - better prevention strategy is needed. In this view sexual partners of PWID should be considered as one of the priority groups for PrEP

836 LOW CROSS-SECTIONAL HIV-1 INCIDENCE AT END OF BOTSWANA "YA TSIE" PREVENTION STUDY

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Background: Botswana has one the highest HIV-1 prevalence estimates and high antiretroviral treatment (ART) coverage. We sought to measure HIV incidence cross-sectionally in the 6 Botswana communities participating in a community-wide End-of Study Survey (ESS) of the Botswana Combination Prevention Project (BCPP), "Ya Tsie."
Methods: All consenting adult residents aged 16–64 years in 6 rural and peri-urban communities were enrolled in the BCPP ESS. Data and samples from ESS were used to estimate cross-sectional HIV incidence by an algorithm that included Limiting-Antigen Avidity Assay (LAg-Avidity EIA), ART status (documented or by testing for ARV drugs in plasma) and HIV-1 RNA load. The LAg-Avidity EIA cut-off normalized optical density (ODn) was set at 1.5 and HIV-1 RNA cut-off at 400 copies/mL. The Mean Duration of Recent Infection was estimated to be 130 days and the False Recent Rate (FRR) was 0%.
Results: Among 14,125 individuals participating in the ESS, HIV status was available for 13,985 participants, 3,614 of whom were HIV positive and 3,248 were on ART. Among 366 ART-naïve participants, LAg-Avidity EIA data was generated for 345 (94%) participants with 37(11%) having ODn<1.5 and initially classified as recent infections. Among these 37, 21(57%) had an HIV-1 RNA load ≤400 copies/mL and were excluded, as potential elite/viremic controllers or undisclosed ART use. Thus, 16 LAg-Avidity-EIA-recent, ARV-naïve individuals with detectable HIV-1 RNA (>400 copies/mL) were classified as individuals with recent HIV infections. The annualized HIV incidence among 16–64 year old adults was estimated at 0.44% (95% CI 0.22–0.65%).
Conclusion: Using a cross-sectional algorithm, HIV incidence in the 6 BCPP ESS communities was less than 0.5%. The rate at ESS is lower than the BCPP baseline incidence of ~1%, which might reflect the successful scale-up of the ART program in Botswana.

837 BEHAVIORAL AND SEROLOGICAL FINDINGS OF THE KADUNA STATE AIDS INDICATOR SURVEY, 2017

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Background: Nigeria has one of the highest rates of new HIV infections in sub-Saharan Africa. Approximately three million Nigerians are living with HIV with a current adult prevalence of 3.0%. Thirty-one percent of positive adults and 21% of positive children are on Antiretroviral treatment (ART). In Kaduna state, ART coverage is estimated to be 27% for adults and 6% for children. We conducted this study to determine the prevalence of HIV and describe the demographic, socio-economic, and behavioral risk factors associated with the HIV epidemic and programmatic gaps in Kaduna State, Nigeria.
Methods: We conducted a population based, cross-sectional, two staged survey of households across the 23 Local Government Areas in the state between January to April 2017. Twenty-two thousand one hundred and ninety-four (22,194) individuals aged 0-64 years were sampled through strata allocation from 3,383 urban and rural households. Open data kits (ODK) electronics questionnaires were used to collect information about HIV, awareness of HIV status and behaviors that drives the HIV epidemic across age-groups. Blood samples were collected to determine to HIV status, CD4 count and viral load. Data was analyzed using STATA 12 software
Results: A total 22,194 individuals were interviewed with a response rate of 93.9%, 20,406 (97.9%) tested for HIV and given result. One hundred and thirty individuals tested positive. Overall HIV prevalence was 0.6%.Of the 20,406 respondents, 3,115 (15.3%) were previously tested with result and 47 (36%) self-reported being HIV positive. Ninety-six percent of those who self-reported HIV positive were positive when retested. Among all the positives, 17.6% had CD4 count ≤ 500µ/ml and 39.7% had viral load < 1000 copies/ml. Behavioral drivers of HIV were hesitation to take a HIV test 68.3% (OR 1.7 95%CI 0.9-3.2) and fear of loss of respect from others if found positive 66.4%(OR 1.0 95% CI 0.5-1.9),inconsistent condom use in the last 12 months 3.1%,(OR 0.3 95% CI 0.2-0.6), widowed 5.3%(OR 11.795% CI 4.2-32.5), unmarried but living with partner 4.9%(OR 11.195%CI 1.9-65.7)
Conclusion: Fear of stigmatization and co-habitation were found to be behavioral drivers of HIV in Kaduna state, and indicates potential for HIV transmission and spread. We recommend to the State targeted campaigns about HIV Counselling and testing services (HTS), health promotion of non-discriminatory attitudes about HIV, and health education about safer practices to reach different sectors of the population.

838 CANGO LYEC (HEALING THE ELEPHANT): HIV INCIDENCE IN POSTCONFLICT NORTHERN UGANDA

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Background: Conflict in Northern Uganda in the 2000s resulted in widespread atrocities, human rights violations and death, and saw millions flee to internally displaced people (IDP) camps. War related traumas combined with difficulties in accessing prevention and health services has led to extreme HIV vulnerability among conflict-affected people who have survived the war.
Methods: The Cango Lyec (Healing the Elephant) Project is a prospective cohort involving conflict-affected people in Nwoya, Amuru, and Gulu districts, Northern Uganda. Participants aged 13–49 at baseline were followed over 2 years and longitudinal data were collected on war-related experiences, mental health, sexual vulnerabilities, and sociodemographics. Blood samples were collected and tested for HIV at baseline and at each 12-month follow-up. Cox proportional hazard models determined factors associated with HIV incidence.
Results: In total, 1918 participants (1021 female, 897 male) who were HIV negative at baseline and had at least one follow-up, contributed a total of 3899 person years for analysis. In this study, 39 (23 female, 16 male) participants contracted HIV during follow-up. This corresponds to a combined cumulative incidence of 10.0 per 1000 person years (95%CI: 7.1-13.7). Stratified by sex, cumulative incidence was 11.0 (95%CI: 7.0-16.6) among women and 8.8 (95%CI: 5.0-14.3) among men. Adjusting for potential confounders (age, sex, marital status, district of residence, displacement status, and religion), factors associated with an increased risk of contracting HIV included: having ever been abducted (HR: 3.6; 95%CI: 1.8-7.3), experiencing war-related traumatic events (HR: 2.5; 95%CI: 1.2-5.3), suicide ideation (HR: 3.2; 95%CI: 1.1-9.2), having 2 or more sexual partners (HR: 4.0; 95%CI: 1.2-13.4), inconsistent condom use (HR: 5.6; 95%CI: 1.18-25.0), and genital ulcers (HR: 2.8; 95%CI: 1.1-7.5).
Conclusion: Conflict-affected participants who had experienced abduction and traumatic events during the war were disproportionately impacted by HIV infection in this study. Trauma-informed HIV prevention and treatment services, as well as culturally safe mental health initiatives are urgently required.

839 HIV, COINFECTIONS, AND RISK BURDEN AMONG PRISONERS AND STAFF: UGANDA NATIONAL SURVEY

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Background: Prisoners are one of five WHO-defined key populations disproportionately affected by HIV. Yet, data on prisoners from sub-Saharan Africa, the region with highest HIV burden, are sparse. The Uganda Prisons Service sero-behavioral survey 2013-14 assessed the prevalence of HIV, associated behaviors and infections including Hepatitis B (HBV), Herpes Simplex Virus type 2 (HSV2) and syphilis, among prisoners and staff of Uganda Prisons Service.

Methods: We randomly selected 117/241 prison units in a two-stage cluster sampling process with probability proportional to population size. At selected facilities, participants were randomly selected from lists of current prisoners and staff. Prisoners and staff aged ≥ 18 years who provided informed consent were included. A structured questionnaire was administered in English and six local languages, using computer-assisted technologies. Blood was collected for HIV rapid testing (national algorithm), HBV (Murex anti-HBcAb 3rd gen EIA), HSV2 (Kalon ELISA) and syphilis (rapid Taytec with Plasmatec or Human Diagnostics RPR confirmation). Participants with positive test results were referred for management. Statistical analysis factored in design effect but did not include weighting. The study was approved by Ugandan and U.S. Institutional Review Boards.

Results: Responding prisoners (n=8919) were 93.6% male with median age 31.1 years. Responding staff (n= 1687) were 63.2% male and had median age 38.1 years. HIV prevalence was 15% for prisoners (15%; 14.4% male; 24.4% female) and 12% for staff (10.5% male; 14.5% female) for staff. For prisoners and staff respectively, HBV prevalence rates were 55.7% and 38.6%, for HSV2 were 44.3% and 50%, and for syphilis were 4.2% and 1.2%.. Injection of illicit drugs was acknowledged by 2.9% and 1.1% of prisoners and staff, and among men, 6.5% of prisoners and 2.9% of staff reported sex with other men.

Conclusion: Prisoners and prison staff had double or higher the national adult prevalence of HIV (6.2%), excess burden of related infections, and higher rates of illicit drug use and MSM behavior than national estimates. Over 100,000 individuals cycle through the prison system annually in Uganda. Providing systematic HIV prevention, testing, treatment and related services tailored to the challenges of prison settings is critical to reducing new infections in prisons and communities in Uganda and other countries.

Characteristic	Prisoners (n=8919)	Staff (n=1687)
Sex (% male)	93.6%	63.2%
Median Age	31.1	38.1
Proportion circumcised (males)	49.8%	45.7%
HIV prevalence (overall; male; female)	15.0%; 14.4%; 24.4%	12.0%; 10.5%; 14.5%
HBV prevalence (overall; male; female)	55.7%; 56.0%; 51.1%	38.6%; 35.7%; 43.6%
HSV2 prevalence (overall; male; female)	44.3%; 42.6%; 69.1%	50.0%; 42.2%; 63.4%
Syphilis prevalence (overall; male; female)	4.2%; 4.1%; 6.2%	1.2%, 1.6%; 0.5%
Reported having sex with men (males only)	6.5%	2.9%
Reported ever using drugs to get high	9.8%	5.7%
Reporting ever injecting illicit drugs	2.9%	1.1%

840 QUANTIFYING DELAY IN HIV PROGRAMME ACCESS AMONG YOUNG FEMALE SEX WORKERS IN KENYA

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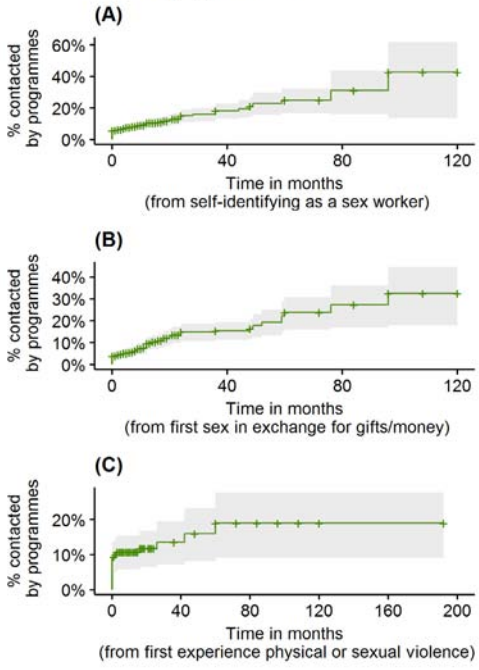
Background: Programme data in Kenya suggest that 85-90% of all female sex workers have been contacted by HIV prevention programmes. Yet missing from these data is the timing of programme access with respect to sex workers' sexual life-course – such that access delays remain unmeasured. We estimated the time from first experience of HIV-associated vulnerabilities to initial programme contact among young women engaged in sex work (YSW).

Methods: We conducted a cross-sectional bio-behavioral survey of 408 cis-female YSW (14-24 years of age) in Mombasa, Kenya in 2015, after geographical mapping and enumeration which estimated a total of 6,127 [range, 4,793 to 7,642] YSW in Mombasa. Timing of HIV-associated vulnerabilities (self-identifying as sex workers; sex in exchange for gifts/money; and physical or sexual violence) and timing of initial contact with a programme were determined by survey questions on "how many months ago" these events occurred in relation to the survey date. We conducted survival analyses to estimate the rate of initial programme contact since experiencing each HIV-associated vulnerability. We quantified access delay in the survey sample by calculating the person-years between self-identifying as a sex worker and initial programme contact, and then estimated the person-years of delay in total population of YSW in Mombasa.

Results: Among 408 YSW, 26% reported any programme contact. The median time to initial programme contact were 18 months [IQR: 8-36] and 24 months[12-36] respectively, from self-identifying as a sex worker, and from first sex in exchange for gifts/money. A total of 38% (N=154) experienced physical or sexual violence prior to programme contact, with a median of 18 months [4-36] from first experience of violence to initial programme contact. Rates of initial programme contact were 0.64 per 100 person-months (95% CI: 0.47 – 0.80); 0.52 (95% CI: 0.39 – 0.65); and 0.48 (95% CI: 0.28 – 0.69), respectively since self-identifying as a sex worker; since first sex in exchange for gifts/money; and since first experience of violence (Figure). Based on YSW population size in Mombasa, we estimated 9,268 to 14,776 person-years of access delay at the population-level.

Conclusion: Using a person-year approach, we identified a large gap in programme access among YSW in Mombasa, and among those who accessed the programme, a substantial delay in access. The findings signal an urgent need for prevention services prioritized or tailored to YSW.

Figure 1: Time from HIV-associated vulnerabilities to programme access



841 LITTLE OR NO OVERLAP OF SEXUAL NETWORKS OF TRANSGENDER WOMEN AND MSM IN LIMA, PERU

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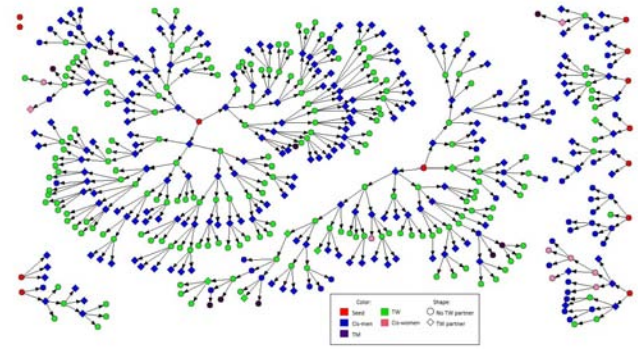
Background: Transgender women (TW) are at extremely high risk of HIV, even compared to men who have sex with men (MSM). MSM and TW and their sexual networks are often conflated in research. While studies of MSM show transmission in 'closed' networks comprised almost exclusively of MSM, sexual networks of TW have not been characterized. Understanding TW sexual networks, including identity and behavior of sexual partners of TW (PTW), is important to better explain the high HIV incidence in TW.

Methods: We used modified respondent-driven sampling to collect cross-sectional data from TW and their sex partners in Lima, Peru (February – July 2018). TW seed participants completed a survey and invited up to 3 sex partners using a WhatsApp referral system. In each wave of forward partner referral, invited partners could complete the survey and were provided referral coupons. The questionnaire assessed gender and sexual identity, sexual behavior, and self-reported HIV status. We constructed a sexual network map and characterized sociodemographics and behavior of PTW.

Results: In total, 470 eligible respondents completed the survey, including 203 PTW, defined as reporting a TW partner within 3 months. The network diagram (Figure) shows that almost all partners invited by TW were cisgender (cis-) men, who almost always invited only TW sexual partners in the next wave. In the survey, 41% of PTW reported exclusively TW partners in the previous 3 months and 52% reported both cis-women and TW partners; only 7% reported cis-male partners. TW primarily reported cis-male partners, with only 2% reporting other gendered partners. PTW reported attraction to TW (83%) and cis-women (68%), with only 9% reporting attraction to cis-men. Most PTW reported being the insertive partner in anal sex (88%); most also reported ever purchasing (78%) or selling (56%) anal sex. Condomless anal intercourse in the past 3 months was reported by 60% of PTW and 65% of TW. Over half of PTW did not know their HIV status (54%), compared to 42% of TW and 20% of other network members (primarily MSM).

Conclusion: We found almost no overlap between MSM and TW sexual networks. Nearly all PTW were bi-/hetero-sexual cis-men who partner with trans- or cis-women. Most reported HIV-risk behaviors and did not know their HIV status. Our results do not fully explain the high HIV rates in TW, but highlight the need for HIV prevention interventions specifically designed for TW and PTW, particularly in settings where interventions focus mostly on MSM.

Figure. Network diagram of recruitment into the respondent-driven sampling study categorized by gender (TW: transgender women; TM: transgender man; Cis-: cisgender)



842 FACTORS ASSOCIATED WITH HIV SEROPOSITIVITY AMONG HIGH-RISK MEN IN TANZANIA

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Background: Due to dramatically lower enrollment into HIV care and treatment, WHO identified men as highly important to reach with HIV testing services (HTS) and enrollment into treatment. Globally, only one third of all HIV tests performed are on men and 40% of men living with HIV are on ART. In Tanzania, 19% fewer men living with HIV know their status, 7% fewer use ART and 6% fewer are virally suppressed compared to women. The Sauti project is a PEPFAR/USAID-funded HIV combination prevention project providing outreach services to high-risk individuals in 14 regions of Tanzania. Biomedical services provided to men include HIV testing, linkage to care and treatment, screening for STIs and TB, alcohol and drug screening and provision of condoms. Male Sauti beneficiaries are male partners of female sex workers (PFSW), other men (OM) who visit hotspots for HIV such as bars and brothels, and men having sex with men (MSM).

Methods: Sauti project collect data through clinical intake forms, de-identifies and uses for project analysis. We conducted multi-variable regression analysis to identify factors associated with testing HIV-positive on men, with categories PFSW, OM and MSM. Data analyzed was from October 2017 to June 2018.

Results: 268,842 men were tested for HIV (n=183,936 PFSW; n=81,274 OM and n=3,632 MSM) with 3.1% testing positive (5.2% among 35+ years and 2.1% below 35). HIV infection rates were higher among men age 35 + (3.4% among men who thought they were HIV negative or didn't know their status and 5.6% newly HIV infected), compared to 1.4% and 2.1% respectively, among men <35. PFSW were 1.56, (1.48-1.64) times more likely to test positive compared to OM, and MSM were over twice as likely [2.20, (1.84-2.63)]. Behavioral and biomedical factors increasing likelihood of testing HIV positive: inconsistent condom use [1.70, (1.58-1.82), and self-reported uncircumcised [1.62, (1.54-1.69).

Conclusion: While the majority of men reached with HTS were < 35 years, a much higher proportion of men 35+ tested positive. Presumably testing the same number of older compared to younger men could have resulted in 4,526 more HIV positive men being identified and linked to treatment. Our findings support a targeted approach to creating demand among older men for HTS, and providing targeted services to men promoting condom use and circumcision. Findings were also consistent with other studies showing MSM to be at highest risk of HIV infection, and thus in need of targeted test and treat services

Table 1. Factors associated with testing HIV positive for high-risk men reached through outreach program

	Total	Tested HIV+ n (%)	aOR [95% CI]	P-value
Age				
Age below 35 years	182406	3813 (2.1)	Reference	
Age 35+ years	86436	4526 (5.2)	2.62 [2.50-2.74]	<0.001
Male beneficiary category				
Other high risk men (men attending hot spots)	81274	2260 (2.8)	Reference	
Partners of Female Sex Workers (PFSW)	183936	5938 (3.2)	1.51 [1.44-1.59]	<0.001
Men who have sex with men (MSM)	3632	141 (3.9)	2.05 [1.72-2.44]	<0.001
Self-reported c ircumcision status				
Yes	196098	5140 (2.6)	Reference	
No	72744	3199 (4.4)	1.67 [1.59-1.75]	<0.001
Know sexual partner HIV+ status				
Yes	13166	672 (5.1)	1.54 [1.42-1.67]	<0.001
No	255676	7667 (3.0)	Reference	
Self-reported c onsistent condom use				
Yes	48963	922 (1.9)	Reference	
No	219879	7417 (3.4)	1.71 [1.60-1.84]	<0.001

843 HIV EPIDEMIC POTENTIAL IN SEXUAL NETWORKS OF MSM IN SAN FRANCISCO AND ATLANTA

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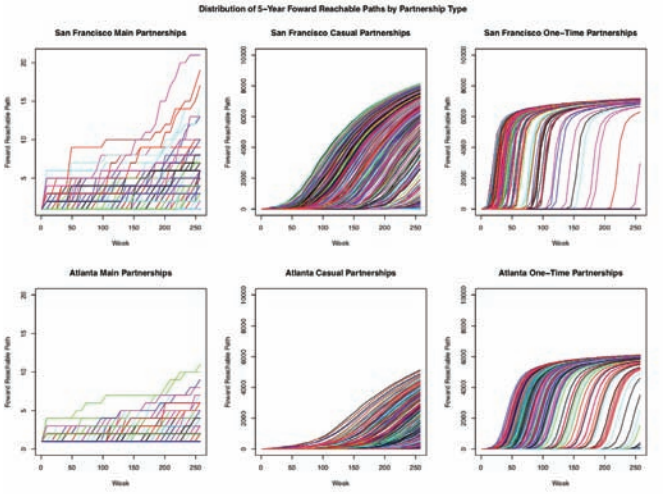
Background: Population-level HIV transmission dynamics depend on the potential speed through which HIV may circulate, which is a function of the connectivity of sexual partnership networks. Sexual network features are often characterized by cross-sectional measures such as concurrency or demographic mixing patterns, but these do not quantify the epidemic potential of HIV through a network over time. Temporal measures of connectivity in high-risk populations are needed to estimate the potential for future HIV outbreaks and optimize control efforts.

Methods: We compared the forward reachable path (FRP) of men who have sex with men (MSM) in San Francisco (SF) and Atlanta (ATL). The FRP measures the maximum number of men each MSM can reach directly, though his own partners, and indirectly, through partners of partners. Empirical data were from ART-Net, a cross-sectional study of 2176 MSM in the US, aged 15–65. Recent partnerships were categorized as main, casual (ongoing, but shorter than main), and one-time. We fit temporal exponential random graph models for each partnership type from these data. Complete MSM networks predicted from

these models were simulated for 5 years. The FRP was calculated at bimonthly intervals, by city and partnership type.

Results: Across all partnership types, the median 5-year FRP was 0.998 in SF and 0.983 in ATL. In SF, a 50% FRP was achieved by week 2, whereas in ATL this took 5 weeks. This high temporal connectivity was largely driven by one-time partnerships: a 50% FRP was met through one-time partnerships within 2.5 years in ATL and in 0.9 years in SF. In casual partnerships, the 5-year FRP in ATL never reached 50% (median FRP: 3.8%), but in SF a 50% FRP was met within 4.5 years, with a median 5-year FRP of 61.1%. The median FRP for main partnerships was <0.01% in both cities.

Conclusion: MSM in SF have higher FRPs, than do MSM in ATL, suggesting a greater epidemic potential in SF. However, SF and ATL have a similar HIV prevalence (22% and 24% in SF and ATL, respectively). Factors like differences in the use of HIV PrEP may differentially mitigate the effects of temporal network connectivity. One-time partnership networks, characterized by a high degree and short partnership duration, reached 50% of the population much faster than casual partnership networks. Focusing prevention efforts on casual partnerships, and among those with a high predicted FRP across partnerships, could be an effective disease control approach given currently available empirical data.



844 TRENDS IN HIV RISK BEHAVIORS OF HISPANIC MEN WHO HAVE SEX WITH MEN IN 19 US CITIES

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Background: In 2015, Hispanics/Latinos accounted for about 25% of all new diagnoses of HIV in the US where a large proportion of those cases were among Hispanic men who have sex with men (MSM). However, risk behaviors among Hispanic MSM can vary by nativity status (i.e., location of birth and length of time in U.S.). We conducted a trend analysis to assess differences in HIV risk behaviors among Hispanic MSM within the continental U.S. by nativity status and acculturation using the National HIV Behavioral Surveillance (NHBS) system.

Methods: MSM aged ≥ 18 years were sampled at venues in 19 U.S. cities, during 2011, 2014, and 2017. Analysis was limited to MSM who reported having ≥ 1 male sex partner within the past 12 months. Poisson regression with generalized estimating equations and clustered on recruitment event and city were conducted to assess changes in risk behaviors over time by nativity status, defined as being born in the continental U.S or not, and acculturation among foreign born, defined as residing in the U.S. more than 5 years. Estimates were adjusted for age and self-reported HIV status. Outcomes include condomless anal sex (CAS) and receiving a diagnosis of a sexually transmitted infection (STI) within the past 12 months.

Results: Among Hispanic MSM, there was an increase in condomless anal sex (63% to 74% ($p < 0.001$)) and receipt of an STI diagnosis (11% to 21% ($p < 0.001$)) from 2011 to 2017. Trends in CAS and STI by nativity status are shown in the figure. Increases in CAS were significant among U.S. born (61% to 74% ($p < 0.01$)) and acculturated foreign-born Hispanic MSM (60% to 73% ($p < 0.001$)). An increase in STI diagnosis was significant among U.S. born Hispanic MSM (11% to 23% ($p < 0.001$)).

Conclusion: While CAS increased overall and in U.S.-born and acculturated participants, the increase in STI diagnosis was only significant among U.S.-born MSM. These results suggest sexual risk among Hispanic MSM may vary by experiences within the U.S. and mechanisms for STI transmission by nativity, even after adjusting for age and HIV status. Further research is needed to better understand how changes in sexual risk associate with changes in STIs differently by nativity status. However, HIV and STI prevention strategies for Hispanic MSM should recognize nativity status as an important factor in the lives of Hispanic MSM and consider tailored approaches.

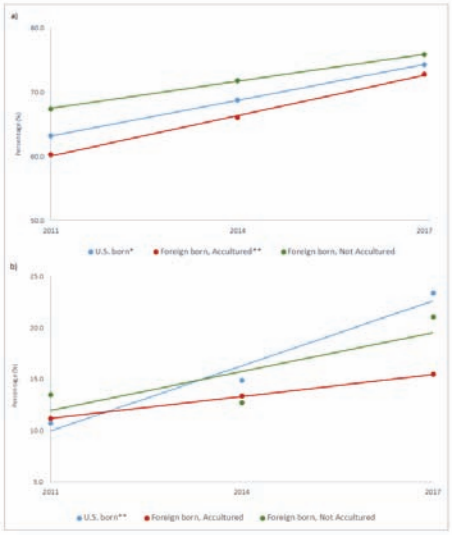

Figure 1: a) Condomless anal sex reported in the past 12 months and b) reported diagnosis of a STI in the past 12 months among Hispanic MSM by nativity status and acculturation with adjustments for age and self-reported HIV status, NHBS, 19 US Cities, 2011, 2014, 2017. *P-value < 0.01, **P-value < 0.001.

845 SUBSTANTIAL UNMET NEED FOR PrEP AMONG MSM IN HANOI

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Background: Despite increasing HIV burden in MSM in Vietnam, PrEP is not publicly available. We describe the unmet PrEP need among Hanoi's MSM using data from the Health in Men (HIM)-Hanoi Study.

Methods: HIM-Hanoi is an ongoing, observational cohort study of sexually active MSM aged ≥16 years. The first wave was recruited via time-location sampling based on comprehensive mapping of MSM venues and enrolled from 7/17-12/17. We analyzed baseline demographic, behavioral, and bacterial STI testing data of the 720 MSM who tested HIV negative to identify those having at least one 2017 CDC recommended indication for PrEP. Weighted, stratified analysis was performed, taking into account variability of the venue size and selection probability. Six month follow-up data were used to identify MSM who seroconverted.

Results: Mean age was 24.3 years[22.9-25.8], and most were employed (93.7%[88.3-96.7%]). Over half (53.7%[46.6-60.7%]) endorsed condomless anal intercourse (CAI) in the last six months. Few had recent injection drug use (2.1%[1.0-4.5%]) or a HIV-positive partner (4.4%[2.3-8.4%]). History of bacterial STI was reported by 15.3%[10.4-21.9%]; positive STI testing at baseline was common (38.1%[31.8-44.9%]). In all, 71.6%[65.9-79.7%] had at least one PrEP indication; 35.1%[28.7-42.1%] had two or more. CAI was the most common indication (48.7%[41.8-55.7%]), followed by previous or current STI (42.9%[36.1-50.0%]). Of 432 with six month follow-up data, 16(3.7%) MSM seroconverted; 13(81.3%) of these had at least one PrEP indication at baseline.

Conclusion: Nearly three-quarters of MSM accessed through venues in Hanoi have an indication for PrEP, indicating a substantial unmet need. In addition

to urgent PrEP scale-up, efforts to reduce CAI and address STIs are critical for effective HIV prevention in this population.

846 RISK FACTORS FOR HIV INFECTION AMONG MSM IN THE ANRS IPERGAY PrEP TRIAL

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Background: In the ANRS IPERGAY trial, on demand pre-exposure prophylaxis (PrEP) has been demonstrated to be highly effective in preventing HIV infection among men who have sex with men (MSM). We aimed to identify MSM who would benefit the most from PrEP by assessing baseline risk factors for HIV infection in this population.

Methods: We analyzed baseline data from participants enrolled in the placebo arm of the ANRS IPERGAY trial or infected between pre-enrollment and baseline, and who completed the online questionnaire. We analyzed socio-demographic characteristics, past use of psychoactive substances and sexual behavior as risk factors for HIV infection. HIV incidence rate ratios (RR) were estimated with their 95% Confidence Intervals (CI). Results are reported in the table.

Results: 203 MSM were included in this analysis, with a median age of 34 years (IQR: 29-42). Overall, 16 HIV infections occurred during a median follow-up of 9 months (IQR: 5-20). The number of sexual partners in prior 2 months (≥10 vs. <10) and the number of condomless receptive anal sex episodes in prior 12 months (≥6 vs. <6) were associated with a significantly increased risk for HIV infection (RR: 3.1; 95%CI [1.1-9.9] and RR: 3.3; 95%CI [1.2-10.2] respectively), whereas those with mostly insertive sexual practices were at lower risk (RR: 0.1, 95%CI: 0-0.6). A diagnosis of bacterial STI at baseline was not significantly associated with an increased risk. Participants who met casual partners in backrooms/sex-clubs or in private sex-parties were also at increased risk for HIV infection (RR: 3.9; 95%CI [1.1-26.8] and RR: 2.9; 95%CI [1.1-9.5] respectively). The use of ketamine, MDMA, GHB/GBL or drugs for erectile dysfunction in prior 12 months was associated with a significantly increased risk of HIV infection. We found no association with age, education level, having a steady partner, or tobacco, alcohol and cannabis consumption in prior 12 months, but being enrolled in Paris was associated with a significant increased risk of HIV infection (RR: 4.1; 95%CI [1.1-28.3]).

Conclusion: MSM who have frequent condomless receptive anal sex, multiple partners met in backrooms/sex-clubs or in private sex-parties, or use drugs for sex should be particularly targeted in prevention programs in particular if they live in an area with a high prevalence of HIV infection.

Baseline Characteristics	No. HIV infections/Person-Years	Rate Ratio [95%CI]	P Value
Paris (vs Montreal or other French cities)	14 / 130.9	4.1 [1.1-28.3]	0.03
≥ 10 sexual partners past 2 months (vs. <10)	11/ 87.6	3.1 [1.1-9.9]	0.03
≥ 6 episodes of condomless receptive anal intercourse past 12 months (vs.<6)	9 / 63.4	3.3 [1.2-10.2]	0.02
Mostly insertive sexual practices (vs. receptive)	1 / 84.7	0.1 [0.0 – 0.6]	0.004
Bacterial STI at screening (vs. no)	5 / 60.8	1.2 [0.4-3.2]	0.80
Met casual partners in backrooms, sex-clubs past 6 months (vs. no)	14 / 131.4	3.9 [1.1-26.8]	0.04
Met casual partners in private sex-parties past 6 months (vs. no)	11 / 88.6	2.9 [1.1-9.5]	0.04
Use of ketamine past 12 months (vs. no)	6 / 32.6	3.3 [1.1-9.1]	0.03
Use of MDMA past 12 months (vs. no)	9 / 62.4	3.1 [1.1-8.7]	0.03
Use of GHB/GBL past 12 months (vs. no)	12 / 68.3	5.9 [2-21.7]	0.001
Use of erectile drugs past 12 months (vs. no)	10 / 69.7	3.4 [1.2-10.1]	0.02

847 IMPROVED DETECTION OF ACUTE HIV IN THE UNITED STATES, 2012-2017

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Background: Timely detection of acute HIV infection (AHI) can lead to earlier treatment and prevent further transmission. In June 2014, CDC recommended use of a laboratory HIV diagnostic testing algorithm that facilitates detecting AHI. We used laboratory data reported to the National HIV Surveillance System to examine trends in and demographic associations with diagnosis of AHI.

Methods: We analyzed data from persons at least 13 years old with HIV diagnosed in 2012–2017 and reported through June 2018. Infections were classified as acute if there was a negative or indeterminate HIV-1 antibody test ≤60 days after the first confirmed positive HIV-1 test, or a negative/indeterminate antibody test or qualitative HIV-1 nucleic acid test (NAT) ≤180 days before the first positive test, if the first positive test was a NAT or detectable viral load. To accommodate reporting delay, for assessing the trend in detecting AHI, we examined data from 2012–2016. Data from 2015–2017 were used to assess characteristics associated with AHI.

Results: From 2012 to 2016, while the annual numbers of HIV diagnoses remained stable, the percentage of those that were classified as acute at diagnosis increased from 1.3% (535 of 40,939) to 4.0% (1,563/39,459); preliminary 2017 data show that 3.9% were AHI (1,484/38,182). Of the 117,465 cases diagnosed during 2015–2017, 4,251 (3.6%) were AHI. AHI was associated with all demographic characteristics examined (P<0.0001). The percentage of persons whose HIV infection was acute at diagnosis was higher among those who were white, Hispanic/Latino, or other race, aged 13-24 years, or had HIV infection attributable to both male-to-male sexual contact and injection drug use or male-to-male sexual contact alone, or when diagnoses were made in emergency departments, STD clinics, or inpatient settings (Table).

Conclusion: The increase in the percentage of persons with AHI diagnosed from 2012 to 2017 suggests that implementation of the recommended laboratory HIV testing algorithm has enhanced the ability to identify AHI in surveillance data, although increased testing early in infection may have played a role as well. Health departments should ensure complete and accurate collection of laboratory data and prompt recognition of AHI to prioritize follow-up and optimize opportunities for treatment and prevention.

Table. Number and demographic distribution of acute HIV infections among persons aged ≥13 years with diagnosed HIV, National HIV Surveillance System, 2015-2017

		No. Acute HIV Infections (Row %)		No. HIV Diagnoses (% of Total)		p-value
Race/ethnicity	Black/African American	1,575	(3.1)	51,183	(43.6)	<0.0001
	Hispanic/Latino	1,143	(4.0)	28,885	(24.6)	
	White	1,257	(4.1)	30,522	(26.0)	
	Other	276	(4.0)	6,875	(5.9)	
Age group (years)	13-24	1,364	(5.3)	25,724	(21.9)	<0.0001
	25-34	1,524	(3.9)	39,950	(34.0)	
	35-44	628	(2.8)	22,478	(19.1)	
	45-54	454	(2.5)	17,943	(15.3)	
	55+	263	(2.3)	11,370	(9.7)	
Transmission category*	Male-to-male sexual contact	3,207	(4.1)	78,153	(66.5)	<0.0001
	IDU	196	(2.9)	6,835	(5.8)	
	Male-to-male sexual contact/IDU	161	(4.2)	3,881	(3.3)	
	Heterosexual contact	683	(2.4)	28,379	(24.2)	
	Other	4	(1.8)	217	(0.2)	
Type of facility at diagnosis	Emergency department	222	(8.9)	2,486	(2.1)	<0.0001
	Inpatient	964	(5.1)	18,877	(16.1)	
	STD	352	(5.8)	6,095	(5.2)	
	Counseling and testing	262	(2.6)	10,276	(8.7)	
	Other/Unknown	2,451	(3.1)	79,731	(67.9)	

IDU: injection drug use

* Data have been statistically adjusted for missing transmission category.

848 DIAGNOSIS OF HIV INFECTION WITHIN 1 YEAR OF ACQUISITION, US, 2010-2016

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Background: Diagnosis of HIV infection soon after acquisition is important for preventing transmission and improving clinical outcomes. Data on time from HIV infection to diagnosis can be used as an indicator of success of testing programs.

Methods: We used National HIV Surveillance System data reported through June 2018 to estimate HIV incidence and number of diagnoses among persons with recent infection (<=12months) in each year from 2010-2016 using the CD4 depletion model. We then estimated the probability of receiving a diagnosis within 12 months of HIV infection and assessed trends, using estimated annual percentage change (EAPC), in the probability of receiving a diagnosis within 12 months of infection over a six-year (2010-2015) period. Trends were assessed overall and by age at HIV diagnosis, race/ethnicity, transmission category, and region of residence at diagnosis.

Results: During 2010-2015, the overall probability of HIV diagnosis within one year of acquiring infection remained stable between 35.1% and 33.9% (EAPC

= -0.75 [-1.81, 0.32]). Probabilities remained stable for all subgroups with the exception of age at infection. The probability of being diagnosed within one year of HIV infection increased for those aged 13-24 years (EAPC = 3.52 [1.50, 5.59]) and decreased for those aged 25-34 years (EAPC = -2.32 [-4.01, -0.59]) and aged 35-44 years (EAPC = -2.26 [-4.44, 0.02]).
Conclusion: The percentage of diagnosis of HIV within one year of infection remained stable, leaving room for improvement. A lower probability of diagnosis in the first year of HIV infection can lead to more persons with undiagnosed infection, increasing the opportunity for HIV transmission. To promote early HIV diagnosis and treatment, HIV testing efforts should be intensified for those at risk.

849 INCIDENT STIs AMONG PLWH IN WASHINGTON, DC: MEASURING HIV TRANSMISSION RISK

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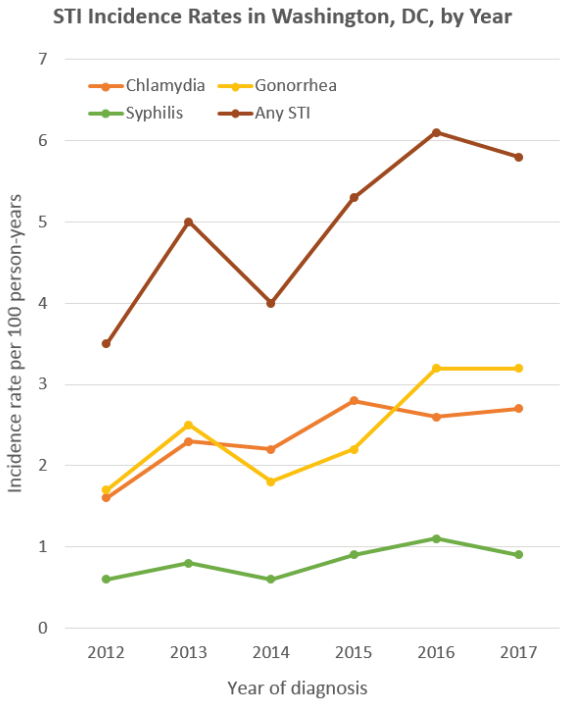
Background: Sexually transmitted infections (STI) are rising nationally and in Washington, DC, which has a generalized HIV epidemic. The DC Cohort study (a city-wide cohort of people living with HIV [PLWH]) previously identified a high proportion of PLWH with HIV viral load (VL) >1500 copies/mL near the time of STI diagnosis, marking potential for HIV transmission. However, the best measure to evaluate HIV transmission risk over time is uncertain. Therefore, we aimed to evaluate STI incidence trends, along with longitudinal and single-point estimates of HIV transmission risk.
Methods: We conducted an analysis of DC Cohort data, age ≥18 from 01/2011-03/2018. STI incidence rates were calculated per 100 person-years and stratified by patient demographics, as well as by STI (gonorrhea, chlamydia, and syphilis). HIV risk was represented by a single-point measure (VL >1500 copies/mL within one month of STI diagnosis) and longitudinal measures (viral load copy-years, and percent time under observation spent with VL >1500 copies/mL, "time >1500").
Results: During a median follow-up of 3.4 years, 786 (9.8%) of 8,021 participants were diagnosed with ≥1 STI episode; of these, 314 (39.9%) had ≥2 STI episodes. The overall STI incidence rate was 5.2 per 100 person-years (95% CI: 5.2, 5.5) and increased from 2012: 3.5 (2.9, 4.2) to 2017: 5.8 (5.1, 6.6) (Figure). The STI incidence rate was highest (p<0.001) in the following groups: age 18-34: 15 (14.0, 16.1), transgender women: 11.4 (9.0, 14.4), Hispanic ethnicity: 11.1 (9.5, 13.0), and men who have sex with men: 10.6 (10.0, 11.2). Among patients with ≥1 STI episode, 13.3% had VL >1500 within one month of STI diagnosis. Among sub-groups, this rate was: 18.7% with VL >1500 among those aged 18-34, 21.5% among cis-gender women, 16.2% among non-Hispanic Blacks, and 18.6% among heterosexuals. Among those with ≥1 STI episode, 33.8% spent some proportion of time with VL>1500 over the period of observation, and median cumulative HIV viral load copy-years was 1.62 (IQR: 0.75, 2.50).
Conclusion: An increase in STIs over time was observed among PLWH enrolled in the DC Cohort, consistent with national trends. Triangulation of measures of uncontrolled HIV virus over time, such as "time above 1500" and viral load copy-years, provide improved understanding of HIV transmission risks. Public health interventions should focus on reducing transmission risk and optimizing HIV outcomes in the groups at highest risk for STIs.



850 INFLUENCE OF HIV AND PrEP USE ON HIGH STI PREVALENCES IN MSM IN GERMANY, 2018

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Background: Men who have sex with men (MSM) are disproportionally affected by sexually transmitted infections (STI). Asymptomatic STI can delay diagnosis and treatment. HIV-positive (HIV+) MSM often show even higher STI prevalence. Approval of HIV pre-exposure prophylaxis (PrEP) in Germany in 2016 might have influenced sexual behavior and STI prevalence of HIV-negative (HIV-) MSM. Our aim was to estimate STI prevalence and risk factors amongst MSM in Germany and compare it systematically by HIV status to plan effective interventions.
Methods: We conducted a nationwide, cross-sectional study between 20th February and 2nd July 2018. Thirteen MSM-friendly STI-clinics systematically screened MSM for Chlamydia trachomatis (CT), Mycoplasma genitalium (MG), Neisseria gonorrhea (NG), and Trichomonas vaginalis (TV) using self-collected rectal and pharyngeal swabs, and urine samples. TMA-based APTIMA® STI-assays were used. We collected information on sociodemographics, HIV-status, clinical symptoms, sexual behavior of the last 6 months and PrEP-use. We combined HIV status and PrEP use for defining risk groups, and used multivariate logistic regression to identify risk factors for STI.
Results: 2,303 MSM were included: 50.5% were HIV+, median age was 39 years (range 18-71). Median number of male sex partners was 5 (range 0-820). 57.2% reported unprotected receptive anal intercourse (URAI), and 43.0% use of party drugs. 78.9% had a STI history, 32.1% of STI+ MSM reported STI related symptoms. 24.8% (283) of HIV- MSM reported PrEP use. Overall STI prevalence was 25.0% in HIV-/PrEP- MSM (CT: 7.2%; MG: 14.2%; NG: 7.4%; TV: 0%), 40.3% in HIV-/PrEP+ MSM (CT: 13.8%; MG: 19.4%; NG: 14.9%; TV: 0.4%), and 30.8% in HIV+ MSM (CT: 10.1%; MG: 18.4%; NG: 8.6%; TV: 0.1%). Independent risk factors were HIV/PrEP-status, having >5 sex partners, URAI, and use of party drugs (table 1).
Conclusion: We found a high STI prevalence in MSM in Germany, especially in PrEP users. A high proportion of STI+ MSM was asymptomatic. Higher STI prevalence in PrEP users than in HIV+ MSM could partly be explained by differences in risk behavior. As a relevant proportion of PrEP users will not use a condom while using PrEP, comprehensive and highly frequent STI screening is essential and should be available free of charge for PrEP users, which will be

introduced in Germany shortly. This will facilitate early treatment and thereby reduce further spread. Counselling of PrEP users should address condom use and risk factor party drugs.

Table 1
Multivariate logistic regression model for diagnosis of at least 1 STI (adjusted for: age, city of clinic, anamnestic STI)

	Odd's ratio	lower limit CI95%	upper limit CI95%
Risk group (ref: HIV-/PrEP-)	1		
HIV-/PrEP+	1.5	1.1	2.2
HIV+	1.6	1.2	2.2
Sex partner >5 (ref: no)	1.4	1.1	1.9
Unprotected receptive anal intercourse (URAI; ref: no)	1.6	1.3	2.1
Use of party drugs (ref: no)	1.7	1.4	2.2

851 WHY STIs ARE INCREASING IN AT-RISK BOSTON MEN: MORE SCREENING PLUS

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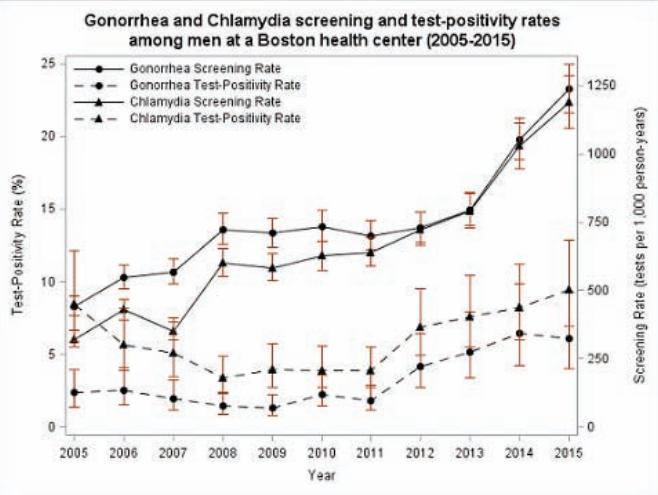
Background: Since the advent of HAART and PrEP, STI rates have increased in high risk men. However, it has not been clear if these increases were due to increased routine screening of HIV+ and PrEP patients, or due to increasing STI prevalence, or both.
Methods: Participants (Pts) were born male and were seen for ≥ 1 medical visit at a Boston health center specializing in HIV care between 2005 and 2015. Pts contributed person-time to any year in which a medical visit occurred. Gonorrhea (GC) or Chlamydia (CT) tests in different sites on the same day were considered 1 test in calculating the screening (S) and diagnoses (D) rates. We calculated the test-positivity rate (D/S; # positive tests / # tests), S rate (tests / 1,000 person-years) and diagnosis rate (positive tests / 1,000 person-years) adjusted for race, insurance status, sexual orientation, age, and year.
Results: Between 2005 and 2015, 19,232 men had at least 1 clinic visit. Most (72.4%) were white; 6.0% were black, and 6.1% were Latino. Almost half self-reported as gay (42.6%) or bisexual (3.2%). Most had private health insurance (61.7%); 5.4% had Medicare, 4.6% had Medicaid, and 8.4% reported no insurance. Between 2005 and 2015, the overall STI diagnosis rate increased more than 7-fold for GC and 4-fold for CT (see Figure). In 2005, there were 10 GC and 25 CT diagnoses per 1,000 person-years, compared to 73 and 106 in 2015, respectively. Among HIV- men, the GC diagnosis rate was 8 per 1,000 person-years in 2005, 14 in 2010, and 69 in 2015, and 19, 27, and 95 for HIV+ men during the same time, with comparable increases for CT. The adjusted GC screening rate per 1,000 person years went from 386 in 2005 to 702 in 2010 to 1244 in 2015 for HIV- pts, and from 646 to 861 to 1231 for HIV+ pts in the same years. CT screening also increased. GC test positivity rate increased significantly between 2005 and 2015, but the CT test positivity rate only increased between 2010 and 2015. In 2015, the GC D/S was 4.8% for HIV- pts who were not using PrEP, 6.8% for PrEP users, and 7.7% for HIV+ pts; the CT D/S was 7.3%, 10.8%, and 10.4% for the respective groups.
Conclusion: Over the decade since 2005, both GC screening rates and test positivity increased significantly in at risk Boston men with similar trends in CT since 2010, suggesting increasing community disease burden. Test positivity rates were highest among HIV+ and PrEP patients, underscoring the need for routine bacterial STI screening for at risk men .



852 THE BURDEN OF HIV AND OTHER STIs AMONG TRANSGENDER PERSONS IN NAIROBI, KENYA

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Background: Globally transgender persons (TP) are disproportionately affected by HIV and other STIs, as well as victimisation that may limit access to preventive and treatment resources. In Kenya, sexual and gender identities have been conflated in sexual health research into gay, bisexual and other men who have sex with men (GBMSM), hampering the articulation of sexual health needs and responses specific to TP.
Methods: The TRANSFORM study enrolled TP and GBMSM via respondent-driven sampling in Nairobi, 2017. Eligibility criteria: age 18+, male at birth/currently, Nairobi residence and consensual intercourse with a man in the last year. Participants completed a computer-assisted survey including sexual risk behaviour and HIV/STI testing & treatment history. Gender identity was elicited by a piloted two-step method recording natal sex and current identity. Participants tested for HIV, HIV viral load and anogenital gonorrhoea and chlamydia (Xpert® CTNG urine and rectal swab). Frequency measures, and multivariable logistic and ordinal regression analyses were weighted using the RDS-II method.
Results: Among 618 recruits, 522 (84.5%) identified as cisgender men, 86 (13.9%) trans-feminine & 4 (0.7%) trans-masculine (6 missing). Compared to cisgender GBMSM, trans-feminine and trans-masculine persons (TP) were similar in terms of age, education level, employment and country of birth. TP were more likely than cisgender GBMSM to be HIV positive (39.9 v 24.6%), have confirmed rectal gonorrhoea (23.6 v 11.8%) and report clinical symptoms of a rectal STI (18.6 v 7.0% aOR 3.6 (1.7-7.9) p=0.001). TP were more likely never to have tested for HIV (15.0 v 6.8% p=0.035). Among HIV negative participants, TP more often reported condomless receptive anal intercourse (46.6 v 20.6%, p=0.001) and exchange sex with men (53.0 v 39.0%, p=0.064) in the last 3 months than did cisgender GBMSM. Among HIV positive participants, 90-90-90 indicators were poorer for TG (63-81-82) than cisgender GBMSM (73-84-83; not statistically significant p=0.333)
Conclusion: TP persons in Nairobi have a higher burden of HIV and rectal gonorrhoea, report higher sexual risk behaviour yet have lower uptake of HIV testing than GBMSM in the same setting. Future research should assess wider sexual and reproductive health needs specific to TP in surveys directly addressing this population. Providers should reconsider the appropriateness of existing prevention and service models that may fail to distinguish between sexual and gender diversity of users.

	Transgender persons		Cisgender GBMSM		Adjusted association‡	
	n/N	% (95% CI)†	n/N	% (95% CI)†	aOR (95% CI)†	p
HIV [Determine®, First Response® & Xpert® HIV-Qual]						
Positive	35/90	39.9 (28.8- 52.1)	151/521	24.6 (20.7-29.0)	2.7 (1.5 – 4.8)	0.001
Rectal STI [Xpert® CTNG]						
Gonorrhoea	19/89	23.6 (14.7-35.6)	57/516	11.8 (8.9-15.6)	2.6 (1.3 - 5.3)	0.007
Chlamydia	9/89	8.1 (3.6-17.3)	44/516	8.2 (5.9-11.4)	0.8 (0.3 – 2.0)	0.580
Urethral STI [Xpert® CTNG]						
Gonorrhoea	4/89	3.7 (1.3-9.7)	23/519	4.6 (2.9-7.2)	0.8 (0.2 – 2.5)	0.676
Chlamydia	5/89	3.7 (1.3-9.6)	33/519	7.7 (5.3 – 11.0)	0.4 (0.1 – 1.3)	0.148
HIV testing history						
Never	10/89	15.0 (8.0-26.5)	34/522	6.9 (4.7-9.8)	2.3 (1.0 – 5.2)	0.043

†: RDS-II weighted & seeds excluded ‡adjusted for age, education level & international migration

853 NEISSERIA GONORRHEA INCIDENCE AND TESTING IN THE HIV OUTPATIENT STUDY, 2007-2017

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Background: Co-infection with Neisseria gonorrhea (GC) increases HIV transmission. Since 2013, incidence of GC has been increasing in the United States (US). We assessed temporal trends in incidence, testing rates, and associated risk factors among people living with HIV (PLWH). Among PLWH, men who have sex with men (MSM) are at high risk for GC; CDC recommends at least annual testing at 3—6-month intervals for MSM with persistent risk behaviors. We examined levels of up-to-date GC testing and anatomic testing sites among MSM.

Methods: We analyzed medical record data from HIV Outpatient Study (HOPS) participants who received care at nine US HIV clinics during 1/1/2007 to 9/30/2017. Incident GC cases were defined based on laboratory results, clinical diagnoses, and treatments. Up-to-date GC testing was defined as having ≥2 GC tests from 10/1/2016 to 09/30/2017. We calculated GC incidence and testing rates during 2007-2017, and assessed associations with sociodemographic and clinical factors using Cox proportional hazards and log-linear regression, respectively.

Results: Among 4,727 eligible PLWH, 327 had 852 GC infections during a median follow-up of 6.3 years, with an overall incidence of 2.85 per 100 person-years. GC incidence and testing rates increased by 4- and 3-fold, respectively from 2007-2017. In multivariable analysis, factors associated ($p<0.05$) with incident GC included younger age, non-Hispanic white race, being MSM, more recent HOPS enrollment, care at private clinics, higher CD4 cell count, and a history of sexually transmitted infections (STIs) (chlamydia, GC, or syphilis). Among MSM (N=1,159), only 583 (50.3%) had GC testing in the prior 12-months (2016-2017), with only 177 (30.4%) having up-to-date testing (Table). Multivariable factors associated with any GC testing among MSM included younger age, non-Hispanic black race, more recent HOPS entry, care at public clinics, being ART-naïve, and having prior STIs. The 583 MSM had 1,428 GC tests during 2016-2017: 68.3% of tests were urine-based only, and 23.5% were all-site (pharynx, rectum, and urethra) with positive rates of 1.6% and 13.4%, respectively (Table).

Conclusion: GC incidence and testing rates have increased among US patients in HIV care. However, only half of MSM were tested for GC during 2016-2017 and only one third had up-to-date testing. To promote sexual health and STI prevention among PWLH, including MSM, increases in GC testing across anatomic sites are needed.

Table. *Neisseria gonorrhea* testing among MSM, the HIV Outpatient Study, US, 2016 –2017.

Number of MSM with any GC test (n=583)*	n	Column %		
1 test	406	69.6		
2 tests	125	21.4		
3 tests or greater	52	8.9		
	Tested		Positive test	
Number of GC tests (n=1,428)	n	Column %	n	Row %
Pharynx only	6	0.4	0	
Rectum only	15	1.1	3	20.0
Urethra (urine) only	976	68.3	16	1.6
Any two sites	96	1.3	9	9.4
All three sites	335	23.5	45	13.4

* 576 patients had no GC test in the medical record

Abbreviations: GC, *Neisseria gonorrhea*; MSM, men who have sex with men.

854 ANTIBIOTIC USE AND VAGINAL DISCHARGE SYNDROME BY HIV STATUS IN PREGNANCY: BOTSWANA

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Background: High prevalence of vaginal discharge syndrome (VDS), a clinical diagnosis which may include both non-specific vaginal discharge and sexually transmitted infections (STIs), has been reported among pregnant women in Africa, including in Botswana. We set out to determine whether VDS prevalence or antibiotic treatment differed by maternal HIV status, CD4 cell count, and antiretroviral treatment (ART) use.

Methods: We abstracted pregnancy management data from obstetric records for all women who delivered at 8 large government hospitals in Botswana as part of the Tsepamo Birth Outcomes Surveillance Study. Data included all diagnoses made in pregnancy (including VDS and specific STIs when available), antibiotic treatment prescribed, and maternal HIV status. Comparisons were made using Chi-squared analysis on SAS.

Results: Between Aug 2014-May 2018, 91383 women delivered at the 8 surveillance sites and 91313 (99.9%) had information on maternal diagnoses in pregnancy. VDS was the most common diagnosis, occurring in 28296 (31.0%) of all pregnancies. Antibiotics were prescribed in 35258 (40.1%) of all pregnancies including in 25596 (90.5%) women diagnosed with VDS. Of 23265 women diagnosed with VDS as their only infection, 18509 (79.6%) were prescribed ceftriaxone, 11723 (50.4%) were prescribed metronidazole, 15317 (65.9%) were prescribed erythromycin/azithromycin, and 9518 (40.9%) were treated according to Botswana guidelines with ceftriaxone, metronidazole, and erythromycin/azithromycin together. There were small differences in the proportion of HIV-positive women and HIV-negative women with any antibiotic use (43.4% vs. 39.1%, p <.0001) and VDS diagnoses (31.7% vs. 31.0%, p=0.04). Among 5654 (25.0%) HIV-positive women with a CD4 cell count recorded in pregnancy, VDS was slightly more common among those with < 350 CD4 cells/mm3 vs. those with higher CD4 cell counts (37.4% vs. 34.2%, p=0.02). Among 20604 (91.2%) HIV-infected women with known timing of antiretroviral treatment (ART), women initiating ART prior to conception had significantly less VDS than those initiating ART during pregnancy (28.7% vs. 37.8%, p<.0001).

Conclusion: Vaginal discharge syndrome is the most common diagnosis among both HIV-positive and HIV-negative pregnant women in Botswana, and the most frequent reason for antibiotic use in pregnancy. Initial univariate analyses suggest that ART started prior to conception may reduce the prevalence of VDS among HIV-infected women.

855 A CASE-CONTROL STUDY OF OCULAR SYPHILIS IN BRITISH COLUMBIA, CANADA, 2010-2018

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Background: The incidence of syphilis has been increasing worldwide in the last 20 years, and has disproportionately impacted those living with HIV. Alongside this increase, several jurisdictions have reported increasing incidence of ocular syphilis (OS). If untreated or treatment is delayed, OS can lead to permanent blindness. We sought to characterize OS cases in British Columbia (BC), Canada, and identify associated factors.

Methods: This case-control study compared OS cases to syphilis controls (1:4 ratio) diagnosed in BC between 01/2010 – 03/2018. Cases and controls were matched on age, sex, and date of syphilis diagnosis. Data were extracted via chart review of the provincial STI surveillance database. Potential risk factors were entered into the logistic regression model, where the dependent variable was OS. Variables were included in the final multivariable logistic regression model if significant at the 0.05 level.

Results: 5681 syphilis cases were diagnosed in BC during the study period, where 61 (1.1%) had OS. Median age of OS cases was 47 years (interquartile range (IQR), 37-59). 88.5% of cases were male, among whom 55.7% identified as men who have sex with men. The most common ophthalmologic diagnoses in cases were panuveitis (44.3%), optic neuritis (19.1%), and retinitis (18.3%). Compared to controls, a greater proportion of cases had infectious syphilis (66.0% controls vs. 90.2% cases; P<0.001), and RPR titers >1:32 (26.2% controls vs. 88.5% cases; P<0.001). More than half of cases (50.8%) were HIV-positive at the time of syphilis diagnosis, compared to 25.8% of controls (P<0.001). Among HIV-positive individuals, 42.9% of cases had a suppressed viral load, compared to 79.7% of controls (P=<0.001). Cases also had higher HIV viral loads (P=0.011) and lower CD4 counts (P=0.014) than HIV-positive controls. The proportion of syphilis cases with ocular involvement increased significantly from 0.48% in 2010 to 2.99% in 2018 (P=0.04). Unadjusted and multivariable analysis findings are shown in Table 1. Infectious syphilis stages and HIV co-infection were statistically significantly associated with OS.

Conclusion: OS incidence increased over the study period, both in absolute numbers and as a proportion of all syphilis cases, a finding consistent with other jurisdictions. These findings highlight the importance of vigilance for OS, particularly in those in the early stages of syphilis and those living with HIV, to avoid diagnostic and treatment delays.

Table 1: Multivariable modeling of factors associated with ocular syphilis

	Unadjusted analysis			Multivariable analysis		
Variable	Odds ratio (OR)	95% CI	p-value	Adjusted odds ratio (aOR)	95% CI	p-value
Stage of Syphilis Infection			<0.001			
• Primary/Secondary	5.67	2.16- 14.9	<0.001	4.06	1.52-10.8	0.005
• Early latent	5.13	1.95-13.5	0.001	3.71	1.39-9.95	0.009
• Late latent	1	-	1	1	-	1
HIV Serostatus						
• HIV-positive	3.35	1.79-6.30	<0.001	2.49	1.27- 4.88	0.008
• HIV-negative						
HIV Viral Load (copies/ml)*				--	--	--
• Suppressed (<50)	7.51	1.59-35.51	0.011			
• Not Suppressed (50+)						
Syphilis reinfection						
• Yes	0.67	0.24-1.85	0.424	--	--	--
• No						
RPR Titre*			<0.001	--	--	--
• <1:8	1	-	1			
• 1:8-1:32	0.70	0.02-2.30	0.682			
• >1:32	24.3	7.92- 74.63	<0.001			

*Variables were not included in multivariable analysis due to interaction and multicollinearity.

856 INCIDENT INFECTION IN HIGH-PRIORITY HIV MOLECULAR TRANSMISSION CLUSTERS

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Background: CDC routinely analyzes HIV sequence data to identify priority clusters exhibiting recent and rapid transmission. Prevention efforts for clusters can include improving viral suppression among persons with diagnosed infection and finding undiagnosed infections; the relative importance of these two aims is unknown. We retrospectively identified priority clusters and determined the extent to which future, incident infections in these clusters were associated with presence of cases that, at the time of cluster prioritization, were diagnosed and viremic versus undiagnosed.

Methods: Using HIV-1 pol sequences reported to the U.S. National HIV Surveillance System for 6 states with ≥50% sequence data completeness for diagnoses during 2010–2017, we used HIV-TRACE to identify priority clusters among cases diagnosed in 2010–2012 (i.e., pairwise distance ≤0.005 substitutions/site; ≥3 cases diagnosed in 2012). We then identified cases diagnosed through 2017 that were genetically linked to these clusters, representing cluster growth in the 5 years after prioritization. We performed Bayesian molecular clock phylogenetic inference in BEAST on each cluster to estimate the number of 2013–2017 diagnoses that were incident infections (i.e., internal nodes after 2012) and prevalent, undiagnosed infections (i.e., internal nodes in or before 2012). For cases diagnosed in or before 2012, we determined viremia (i.e., viral load ≥200 copies/ml at last lab in or before 2012). These counts were treated as predictors in a cluster-level multivariate logistic regression analysis with incident infection as the outcome.

Results: Of 116 priority clusters (initial size: 3–33 persons), 76 gave rise to ≥1 incident infection after 2012 based on phylogenetic inference. Among priority clusters, both undiagnosed infections and diagnosed, viremic cases were independently and equally associated with incident cluster growth in the following 5 years: odds of cluster growth increased by 57% for each additional viremic person (adjusted odds ratio=1.57, p=0.010) and 51% for each person with undiagnosed infection (adjusted odds ratio=1.51, p=0.019).

Conclusion: These findings suggest that new infections in priority clusters originate equally from diagnosed, viremic cases and undiagnosed infections. These results highlight the importance of promoting retention in care and viral suppression as well as partner notification and other case-finding activities when investigating and intervening on priority molecular transmission clusters.

857 MOLECULAR SURVEILLANCE AS A MEANS TO EXPAND AN OUTBREAK INVESTIGATION: MA, 2015-2018

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Background: In mid-2016, the Massachusetts Department of Public Health (MDPH) identified increased HIV diagnoses among persons who inject drugs (PWID) in northeastern Massachusetts (NE MA). With CDC assistance, MDPH began an investigation in 2018 to characterize the outbreak and institute further control measures. We describe the contribution of molecular HIV surveillance to case finding and compare characteristics of cases initially determined to be linked through molecular surveillance with those already linked through traditional surveillance and partner services data.

Methods: HIV diagnoses occurring during 01/2015—05/2018 were considered epidemiologically linked to the investigation 1) through residence, homelessness, HIV diagnosis, or HIV care in the cities of Lawrence or Lowell or 2) as a named partner of an investigation case. In 11/2017, MDPH rapidly implemented molecular surveillance; HIV pol sequences for persons in MA with a drug resistance test conducted during 01/2016—05/2018 were reported to MDPH and analyzed with Secure HIV-TRACE to identify molecular clusters using a pairwise genetic distance threshold of ≤1.5%; cases that linked to ≥1 epidemiologically linked case in the investigation were considered molecularly linked. Characteristics of cases initially linked through molecular analysis and already epidemiologically linked cases were compared using Fisher's exact test.

Results: As of 07/11/2018, the investigation included 129 persons, of whom 93 were initially epidemiologically linked. Of 108 investigation cases with a sequence, 96 were molecularly linked to ≥1 other case, forming four clusters of ≥5 cases (range in size: 5–55). Molecular analysis identified 36 persons not previously epidemiologically linked to the investigation; epidemiologic links were later identified for 4 cases. Molecularly linked and epidemiologically linked cases were similar with respect to age (majority aged <40 years), sex at birth (majority male), race/ethnicity (majority white, non-Hispanic), and transmission risk (vast majority with injection drug-use related risk) (all p-values >0.05).

Conclusion: The presence of multiple molecular clusters among investigation cases suggests multiple introductions of HIV into the PWID community in NE MA, each with sustained transmission. The addition of molecular data expanded the number of persons linked to the investigation by 39%, improving prevention opportunities and highlighting the importance of molecular surveillance in HIV outbreak response.

858 WITHDRAWN / INTENTIONALLY UNASSIGNED

859 WITHDRAWN / INTENTIONALLY UNASSIGNED

860 USING NEAR REAL-TIME MOLECULAR SURVEILLANCE TO INFORM DATA-TO-CARE IN NEW YORK CITY

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Background: Molecular HIV surveillance has been proposed as a tool to augment traditional partner services and data to care (D2C) activities by adding persons with genetically proximate viruses to the pool of named partners and social network members receiving public health intervention after a new diagnosis of HIV.
Methods: The New York City Department of Health and Mental Hygiene conducted a pilot project to demonstrate whether early ascertainment of viral genetic proximity between newly diagnosed and prevalent cases was feasible and resulted in timely identification of and outreach to persons in transmission networks as defined by HIV-Trace, a genetic distance-based clustering tool. Persons newly diagnosed with HIV at the city's 8 sexual health clinics (SHC) were the Index cases; their partial pol sequences were analyzed for pairwise concordance to those of 71,189 prevalent cases using a 1.5% distance threshold. Clusters were mapped, and cluster members that were out of care for ≥13 months (OOC) or in care but viremic (>1500 copies/mm3) and their viruses immediately proximate to the Index virus were identified and prioritized for assistance with partner services and reengagement in optimal care.
Results: Between June 1, 2016, and June 25, 2018, whole blood specimens from 722 persons testing preliminary positive on point-of-care rapid HIV screening were submitted to the NYC Public Health Laboratory for confirmation and resistance testing, resulting in 526 interpretable genotypes. SHCs received resistance reports and sequences were posted a median of 10 days (IQR 8-15) after specimen draw date. Pairwise concordance analysis of the Index virus against the prevalence pool yielded a total of 225 clusters containing 2,778 unique members. Clusters ranged in size from 2-155 persons with diagnosis dates from 1981-2018, of whom 122 (4%) were deemed by surveillance to be currently OOC and 132 (5%) viremic; 91% of cluster members were MSM; clusters were homogeneous with respect to age at diagnosis (median 26) and race/ethnicity but not by neighborhood of residence.
Conclusion: Despite our optimized scenario (genotype ordered on day of diagnosis), cluster data were not available at the time of the Index partner services interview. However, analysis performed as soon as the sequence was posted allowed us to identify and prioritize for outreach previously diagnosed, genetically proximate OOC and viremic cluster members on a monthly basis, making it possible to achieve "near real-time" D2C for genetic partners.

861 MAPPING GROWTH OF LARGE TRANSMISSION NETWORKS USING DIFFERENT CLUSTERING ALGORITHMS

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Background: Phylogenetic surveillance of the HIV epidemic amongst Men having Sex with Men (MSM) has revealed that large transmission networks (20+ infections/ cluster) rose from 13% of new infections in 2004 to 49% of infections in 2016 in Quebec. Identifying and responding to these "active" transmission hubs in close to real-time will have the greatest impact in controlling the epidemic.
Methods: First genotypes were obtained from treatment-naïve MSM (n=4029) and heterosexual/intravenous drug user (IDU) (n=1072) groups having subtype B HIV-1 infections, as well as non-B subtype groups (n=1248). Unique non-nominative patient identifiers were assigned based on putative cluster group association, ascertained by Maximum likelihood (ML) methodology (high bootstrap support >97% and short genetic distance <0.015). Growth trajectories dynamics of 40 individual large transmission networks (20+ members/cluster) were compared with the San Diego-based HIV-TRACE (Transmission Cluster Engine) platform, and the Montreal-based Gap (distance-based) BD-SIR (cluster birth death), and the DM-PhyClus (Bayesian-based) methodologies.
Results: Heat maps indicated overlap between estimates produced by seven clustering algorithms, revealing the role of large transmission networks in the growth of the provincial epidemic in MSM. Cluster inferences with HIV-TRACE and DM-Phys were rapid, conducive to real-time monitoring of cluster dynamics. In general, putative cluster assignments by HIV-TRACE designated at <1.5% TN93 genetic distance measures paralleled ML-based assigned. Problematic issues arose in resolving and deducing transmission links of individual members within clusters using repeat patient sampling. HIV-TRACE could not resolve two K103N and WT waves for cluster 99 and several different non-B subtypes coalesced.
Conclusion: In this study, we compared the sensitivity and accuracy of different phylogenetic based methodologies in estimating transmission linkage and mapping epidemic growth in close to real-time. While several cluster-based algorithms can identify "actively" growing transmission hubs, resolving the linkage of individual members within clusters will require further optimization to maximize accuracy.

862 EPIDEMIOLOGIC CORRELATES OF HIV LINEAGE LEVEL DIVERSIFICATION RATE

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Background: Identifying risk factors and other epidemiological correlates of HIV transmission can inform the prioritization of health care services to specific groups. Typically transmission clusters are inferred based on genetic distance thresholds, then logistic regression is conducted to evaluate patient characteristics that are significantly associated with the probability of membership in an active transmission cluster. This method is limited in that all individuals within a cluster are treated as equally active transmitters, although in reality there is a range of transmission activity within a cluster. We introduce an alternative method to investigate risk factors associated with transmission in British Columbia (BC), Canada, based on the phylodynamically estimated viral diversification rate.
Methods: For 8,103 people living with HIV (PLHIV) in BC in March 2018, we recovered the oldest available HIV protease and RT sequences from the BC Centre for Excellence in HIV/AIDS database. Following alignment and removal of known drug resistance sites, we inferred 100 bootstrap approximate maximum likelihood phylogenetic trees in FastTree2.1 and then time-scaled the trees using Least Squares Dating. For each tip on each bootstrap tree, we calculated the lineage level phylogenetic diversification, which provides a proxy for transmission rates. The average diversification rate of all 100 trees for each tip was taken. We then built a generalized linear model (GLM) to evaluate patient attributes that were significantly associated with higher diversification rates.
Results: Having a high HIV diversification rate was positively associated with being younger, reporting injection drug use, having co-infection with hepatitis C virus, having a high most recent viral load, and residing within the Northern BC Health authority or the Vancouver Coastal Health authority (Table 1). Interestingly, having ever had AIDS and identifying as black were both significantly associated with lower diversification rates (Table 1).
Conclusion: By identifying risk factors associated with HIV transmission using the viral diversification rate among PLHIV in BC, we can confidently recommend prioritized provision of treatment and prevention services for these key groups. Relative to logistic regression of phylogenetic cluster membership, this method has the added benefit of resolving finer differences in transmission activity between individuals, resulting in a more accurate assessment of risk.

Table 1. A summary of the adjusted relative risk and significance for patient attributes associated with HIV lineage level diversification rate, as estimated using a multiple gamma regression with a log-linker equation.

Attribute	Category	Count	Adjusted Relative Risk (aRR)	aRR 95% CI	P-value
All	…	8103	…	…	…
Age group	61 and over	1742	…	…	…
	53-60	2245	1.11	1.00 - 1.22	0.050
	42-52	2358	1.36	1.23 - 1.51	<0.001
	41 and under	1627	2.12	1.89 - 2.38	<0.001
Men who have sex with men	No	2690	…	…	…
	Yes	3038	1.07	0.96 - 1.20	0.176
	Unreported	2120	1.02	0.89 - 1.16	0.817
Injection drug user	No	2139	…	…	…
	Yes	2431	1.39	1.21 - 1.58	<0.001
	Unreported	3278	1.24	1.13 - 1.36	<0.001
Hepatitis C virus infection	No	4592	…	…	…
	Yes	2586	1.17	1.05 - 1.31	0.003
	Unreported	380	0.80	0.68 - 0.95	0.010
Heterosexual activity	No	3822	…	…	…
	Yes	1906	0.97	0.87 - 1.09	0.606
	Unreported	2120	NA	NA	NA
Ethnicity: white	No	1521	…	…	…
	Yes	3310	1.03	0.90 - 1.18	0.642
	Unreported	3017	1.24	1.07 - 1.43	0.004
Ethnicity: first nations	No	837	…	…	…
	Yes	994	1.06	0.91 - 1.23	0.426
	Unreported	3017	NA	NA	NA
Ethnicity: black	No	4606	…	…	…
	Yes	225	0.58	0.46 - 0.74	<0.001
	Unreported	3017	NA	NA	NA
Health authority of residence at diagnosis	Unreported	832	…	…	…
	Fraser Health	1634	1.50	1.22 - 1.82	<0.001
	Interior Health	409	1.54	1.21 - 1.95	<0.001
	Northern Health	257	2.12	1.62 - 2.78	<0.001
	Vancouver Coastal Health	4224	1.65	1.36 - 1.97	<0.001
	Vancouver Island Health	730	1.41	1.13 - 1.74	0.002
Ever having AIDS	No	6683	…	…	…
	Yes	887	0.76	0.68 - 0.85	<0.001
Most recent log10(viral load)		…	1.12	1.09 - 1.16	<0.001

863 GEOSPATIAL DISPERSAL OF HIV-1 TRANSMISSION IN 6 MAJOR CITIES IN GERMANY

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Background: Geographic targeting of HIV prevention interventions to the highest risk individuals will increase the impact of these efforts. We combined molecular epidemiology and geospatial analyses to provide insights into the drivers of HIV-1 transmission in the German epidemic.

Methods: Sociodemographic, geographic and HIV-1 pol sequence data were collected from newly diagnosed individuals in six cities across Germany between 2001 and 2018. Genetic-distance based molecular network analyses were performed to infer putative transmission links. Similarity between genetically-linked individuals was assessed using the Assortativity Index (AI, i.e. shared attributes). Geospatial dispersal was determined by calculating the average distance between the residences of genetically linked individuals (centroids of 3-digit zip codes).

Results: We included data from 1,397 HIV-1 infected ART naïve individuals, of which 289/1,397 (20.7%) were putatively linked, forming 102 transmission clusters (size range: 2-12). The largest clusters (more than 10 individuals) consisted mainly of men having sex with men (MSM) from Cologne, Bonn and Frankfurt. Genetically linked individuals were significantly younger (<25 years of age, p= <0.001), more likely to reside in Bonn and Cologne (p<0.001 and p= 0.044, respectively), and more likely to report MSM as a risk factor (p=0.015). Genetically linked individuals were highly assortative by risk group (AI=0.08, p=0.006), age (AI= 0.06, p<0.001), and location (AI= 0.08, p<0.001) (Figure 1A), indicating that individuals tended to cluster with other persons of the same age, risk group, and from the same area. Geospatial analyses revealed that the median distance between residences of genetically linked individuals was 78 kilometers (km), significantly lower than the distance of the random sub-sampled population (median 269 km; p<0.001) (Figure 1B). This suggests that genetically linked individuals tended to be linked with partners within about an hour's travel time.

Conclusion: We found evidence that HIV-1 transmission in Germany is between younger MSM living in proximity to each other. This provides further support for real-time monitoring of HIV transmission using molecular epidemiology, which can be leveraged to target specific geographic areas where new transmissions are being observed. Furthermore, this work suggest that HIV prevention efforts targeted towards young MSM may provide the most impact on the German epidemic.

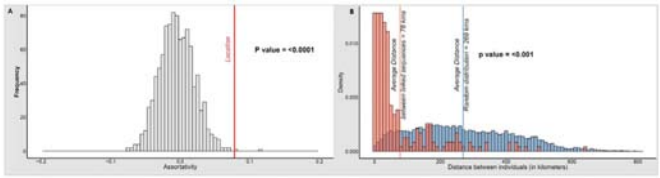

Figure 1: A) Geospatial mixing between HIV-1 genetically linked individuals using assortativity coefficients by cohort. B) Median distance between linked individuals and a random distribution. The distance between linked individuals (median 78 kilometers) was significantly lower than the random distribution (median 269 km, p<0.001). N= 1,397 (Bonn n= 152, Cologne n= 582, Frankfurt n= 215, Hamburg n= 48, Hannover n= 169, Munich n= 231).

864 PRETREATMENT HIV DRUG RESISTANCE SPREAD IN 6 GERMAN METROPOLITAN REGIONS

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Background: Transmitted HIV drug resistance impacts the choice and success of antiretroviral therapy (ART). In Germany, the reported prevalence of transmitted drug resistance mutations (DRM) differs between regions with a maximum of 12.4%. Here, we sought to understand the molecular epidemiology of DRM transmission in Germany, by analyzing data from six major cities with high rates of new HIV diagnoses (ranging from 5.6 to 17.3 per 100,000 habitants).

Methods: Phylogenetic and genetic network analyses were performed to infer putative transmission links and shared DRMs. Screening for DRM was performed according to the Stanford University Genotypic Resistance Interpretation. We defined a shared DRM as any DRM present in two or more genetically linked individuals (<1.5% genetic distance).

Results: We obtained 1,397 HIV pol sequences from HIV-1 ART naïve individuals. The prevalence of any DRM at time of diagnosis was 17.8% (248/1,397 individuals; 31.4% in Hannover, 18.9% in Cologne, 18.8% in Hamburg, 15.3% in Frankfurt, 14.5% in Bonn, 9.1% in Munich). The frequency of any DRM was comparable among risk groups but was highest among men having sex with men (MSM) (138/792, 17.4%). Genetic transmission network analyses showed comparable frequencies of DRM in clustering and not-clustering individuals (16.3% versus 18.1%; p= 0.46). Of the 47 sequences harboring DRM in the inferred transmission network, 30 (63.8%) were shared by HIV genetically linked partners, predominantly among residents of Cologne (19/30, 63.6%) and Bonn (7/30, 23.3%). Clustering individuals harboring shared DRMs were more likely than non-clustering individuals to be infected with HIV-1 subtype B (p<0.001), < 25 years of age (p<0.001), and living in Cologne (19/30, 63.3%) and Bonn (7/30, 23.3%) (p<0.001 each) (Figure 1A). The most frequently transmitted DRMs were E138A (11/30 in individuals sharing DRMs, 5 clusters) and K103N (9/30, 4 clusters) (Figure 1B).

Conclusion: We observed very high rates of DRMs in newly diagnosed individuals in Hannover, Cologne and Hamburg. Network analysis also revealed frequent cases of shared DRMs among genetically-linked individuals, especially K103N and E138A. Our findings highlight regional differences in transmitted drug resistance, and the necessity to focus prevention efforts on specific areas and risk groups to prevent onward transmission across Germany.

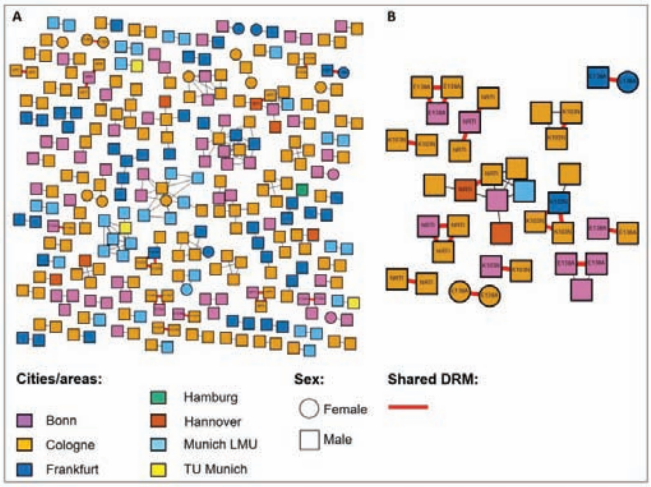

Figure 1. A) HIV-1 transmission cluster of pre-treatment drug resistance in individuals from six German cities (Bonn n= 152, Cologne n= 582, Frankfurt n= 215, Hamburg n= 48, Hannover n= 169, Munich n= 231). Transmission network analysis found a total of 289/1,397 (20.7%) genetically linked individuals forming 102 clusters ranging in size from 2 to 12, containing sequences from up to four different cities. The nodes are colored by cohorts, squares and circles indicating male and female. All edges represent a genetic distance of ≤1.5%. Lines in bold red indicate individuals who shared DRMs. B) Enlargement of clustering individuals harboring shared DRMs labeled with each nodes.

865 HIV DYNAMICS IN THE MOST AFFECTED AREA OF EUROPE: A TALE OF 2 COUNTRIES

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Background: In 2016, Latvia and Estonia continued to have the highest rate of new HIV diagnoses in Europe (1.85 and 1.74 per 10000, respectively). Both countries experienced an HIV outbreak among people who inject drugs (PWID) in the early 2000s.

Methods: Data from 2000-2016 for persons newly diagnosed with HIV in Latvia and persons newly appearing with HIV in health care registries in Estonia were used in a clinical-stage based back-calculation model to estimate: HIV incidence, time from infection to diagnosis and undiagnosed HIV prevalence. Population size estimates were calculated using national statistics and studies on sexual behavior and drug use. Statistical comparisons were carried out using Mann-Whitney test for incidence and undiagnosed prevalence rates, and using two-sided Kolmogorov-Smirnov test for the distribution of times between infection and diagnosis.

Results: In 2016, HIV incidence was twice as high in Latvia than in Estonia (3.5/10000 vs 1.9/10000, p<0.05). Between 2010-2016, HIV incidence decreased in Estonia but increased in Latvia (average annual change of -9.0% and +6.2%, respectively; Table). The incidence decreased for all exposure groups in Estonia and increased for most in Latvia, especially for women and men who have sex with men (MSM). Between 2012-2016, time to diagnosis took longer in Latvia than in Estonia (3.9 vs 3.4 years, p<0.05). In Latvia, getting diagnosed tended to take longer for heterosexual men and MSM than for PWID and heterosexual women (respectively 4.8 and 4.4 vs 3.4 and 3.7 years). A similar trend was observed in Estonia. Undiagnosed prevalence rate was higher in Latvia than in Estonia (13.7/10000 vs 10.3/10000, p<0.05). In 2016, PWID were the most affected population in terms of rates of new and undiagnosed infections in both countries, but the vast majority of new and undiagnosed number of infections occurred among heterosexuals and MSM. In Latvia, 61% of new infections and 65% of undiagnosed infections were among heterosexuals and MSM. In Estonia, they were 85% and 83%, respectively.

Conclusion: For the first time, we show stark differences in the HIV epidemic status in the neighboring countries most affected by HIV in Europe. Our results suggest that Estonia has started turning the tide of its epidemic while in Latvia it remains very active. Finding men and women who have acquired HIV sexually is one of the biggest challenges in ending HIV in these originally injection drug use driven epidemics.

Table. Estimates for Latvia (LV) and Estonia (EE), by sex and HIV exposure group.

Population in LV	HIV incidence in 2016 (95% CI)	Average annual change in incidence over 2010-2016	Median time (in years) from infection to diagnosis (IQR) 2012-2016	Number of undiagnosed HIV infections in 2016 (95% CI)	Population aged 18-69	HIV incidence rate per 10000 inhabitants in 2016 (95% CI)	Undiagnosed prevalence rate per 10000 in 2016 (95% CI)
Global[¶]	470 (341-632)	+6.2%*	3.9 (1.9-6.1)	1826 (1495-2249)	1337491	3.5 (2.6-4.8)	13.7 (11.2-18.8)
Male	274 (166-420)	+3%*	4.2 (2.1-6.3)	1196 (929-1609)	639056	4.3 (2.6-6.6)	18.7 (14.5-25.2)
Female	196 (121-285)	+13.5%*	3.5 (1.5-5.8)	630 (478-853)	698435	2.8 (1.7-4.1)	9.0 (6.8-12.2)
PWID	184 (110-278)	+3.4%*	3.4 (1.7-5.4)	631 (463-876)	12439	198.6 (118.7-300.0)	507.0 (372.2-704.3)
Male PWID	117 (62-186)	+0.8%*	3.5 (1.8-5.5)	459 (330-647)	8208	191.0 (101.4-304.2)	558.8 (400.9-788.2)
Female PWID	68 (26-132)	+13.0%*	3.1 (1.4-5.9?)	173 (87-313)	4229	261.3 (100.5-510.0)	406.9 (204.9-739.0)
Heterosexual men	84 (26-175)	-1.7%*	4.8 (2.8-6.9)	453 (284-734)	620304	1.4 (0.4-2.9)	7.3 (4.6-11.8)
Heterosexual women	126 (66-191)	+13.7%*	3.7 (1.6-6.2)	459 (338-637)	694206	1.9 (1.0-2.8)	6.6 (4.9-9.2)
MSM	73 (18-167)	+24.3%*	4.4 (2.3-8.7)	286 (163-501)	10544	72.6 (17.8-166.1)	270.8 (143.3-474.5)
Population in EE							
Global[¶]	171 (106-253)	-9.0%*	3.4 (1.2-6.1)	916 (765-1125)	887232	1.9 (1.2-2.9)	10.3 (8.6-12.7)
Male	98 (50-161)	-10.5%*	3.5 (1.1-6.5)	569 (455-729)	433497	2.3 (1.2-3.7)	13.1 (10.5-16.8)
Female	73 (32-125)	-6.3%*	3.2 (1.2-5.5)	347 (262-487)	453735	1.6 (0.7-2.8)	7.6 (5.8-10.7)
PWID	25 (8-57)	-14.6%*	2.8 (1.0-5.9)	155 (111-230)	7985	69.6 (22.3-158.6)	194.8 (139.0-288.1)
Male PWID	9 (3-21)	-17.7%*	2.3 (0.5-4.9)	103 (77-133)	3901	52.5 (17.1-119.6)	262.8 (196.5-339.6)
Female PWID	15 (2-44)	-0.2%	2.9 (1.2-4.9)	53 (22-120)	4084	84.2 (10.9-239.4)	129.7 (53.6-293.6)
Heterosexual men and MSM	88 (42-153)	-6.5%*	3.8 (1.3-6.8)	467 (353-630)	429596	2.1 (1.0-3.6)	10.9 (8.2-14.7)
Heterosexual women	58 (19-102)	-7.2%*	3.3 (1.2-5.8)	295 (221-403)	449651	1.3 (0.4-2.3)	6.6 (4.9-9.0)
MSM	x	x	x	x	8063	x	x

CI: confidence interval; IQR: Inter-quartile range; [¶] excluding vertical transmission; *p-values of the linear regression of incidence against time (years) less than 0.001; MSM: men who have sex with men; PWID: Persons Who Inject Drugs; x: There were not enough data to estimate the indicators for MSM in Estonia. Population sizes were estimated using national statistics on the size of adult populations aged 18-69 years by sex and surveys on drug use and sexual behavior. Population size of PWID were defined as 0.9% of the whole population aged 18-69 in Estonia (Uusküla et al. 2013) and as 0.93%of the whole population aged 18-69 in Latvia, distributed in 66% of men and 34% of women (Kivite et al. 2016). Population size of MSM were defined as 1.86% of men aged 18-69 in Estonia and 4.0% in Latvia (Marcus et al. 2013).

866 WITHDRAWN / INTENTIONALLY UNASSIGNED

867 CLUSTER SURVEILLANCE OF FRENCH PRIMARY INFECTIONS: TOWARD A MORE VIRULENT CRF02_AG?

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Background: Molecular epidemiology can be used to identify large recent transmission clusters (RTC) and describe core transmitters that fuel a large proportion of transmissions. We analyzed such RTC among primary infected patients (PHI) diagnosed in France in 2014-2016.

Methods: Protease and reverse transcriptase sequences were obtained from 1121 patients included between 2014 and 2016 from 46 centers. Phylogenetic trees were built by approximate maximum likelihood using FastTree to identify RTC (max genetic distance <4.5%, branch support value >95%).

Results: Most patients were men (90%), MSM (70%), born in France (70%) or Sub-Saharan Africa (6.6%), infected mostly by B (56%) or CRF02_AG (20%) clades. CRF02_AG tended to be increasingly represented across years (from 17 to 22%) and large (>3 patients) RTC (Table). Compared to patients infected by subtype B, patients infected by CRF02_AG presented a lower proportion of MSM (59 vs 78%, p<0.001), of individual born in France (67 vs 75%, p=0.02), higher viral loads (VL) (median at 5.83 log10 copies/mL [IQR: 4.96-6.60] vs 5.40 [4.66-6.26], p=0.004) and lower CD4 cell counts (463 cells/mm3 [25-903] vs 514 [1-1028], p=0.004). When analyzing patients born in France separately, CRF02_AG still presented higher VL than subtype B (5.79 vs 5.42 log10 copies/mL, p=0.012). Overall, 457 (41%) patients were included in RTC including 214 (47%) in 106 small (<4 patients) and 243 (53%) patients in 39 large RTC (from 4 to 14 patients). Paris area appeared as a hub for transmission with 31/39 large RTC including ≥1 patient from this area. RTC-patients were younger and more frequently MSM than non-RTC-patients (p<0.001). Most large RTC sustained active transmissions over the whole study period. Four large clusters were identified with transmitted drug resistance mutation(s) (T215S, L74M, K103N and L76V+L90M) but none achieved sustainable transmission of these mutations throughout their cluster.

Conclusion: This study highlights the important role of RTC achieving transmission throughout France with a large hub in Paris area. CRF02_AG is actively spreading among large RTC, participating to the epidemiological shift from B to CRF02_AG in France. CRF02_AG is also associated to higher VL among patients born in France, suggesting a higher virulence than subtype B. The increasing number of large RTC identified highlights the need for nationwide

surveillance and intervention programs to identify and fight these, sometimes massive, local outbreaks.

	Total (1121)	Non RTC (664)	Small RTC (214)	Large RTC (243)	p
Age (years) - *median [IQR]*	36 [28-45]	38 [30-47]	34 [26-45]	31 [26-39]	<0.001
Men - *n(%)*	1009 (90%)	568 (86)	200 (93)	241 (99)	<0.001
MSM route of transmission - *n(%)*	788 (70)	417 (63)	174 (81)	197 (81)	<0.001
Subtype – *n(%)*					<0.001
B	628 (56)	365 (55)	154 (72)	109 (45)	
CRF02_AG	222 (20)	122 (18)	30 (14)	70 (29)	
Other	271 (24)	177 (27)	30 (14)	64 (26)	

868 WITHDRAWN / INTENTIONALLY UNASSIGNED

869 NEW GENOMES FROM THE CONGO BASIN EXPAND HISTORY OF CRF01_AE ORIGIN AND DISSEMINATION

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Background: Although the first HIV circulating recombinant form (CRF01_AE) is a predominant strain in many Asian countries, it is uncommon in the Congo basin where it first originated. Therefore, we sequenced CRF01 genomes from Cameroon and the Democratic Republic of Congo (DRC) to characterize the molecular history of CRF01.

Methods: Near complete genomes were sequenced from N=13 specimens previously classified as CRF01 or CRF01-containing recombinants in the gag, pol, and/or env, regions through viral surveillance studies conducted in Cameroon and DRC between 2001-2006. Random primed libraries spiked with HIV specific primers were sequenced on an Illumina HiSeq and genomes were assembled using CLC Bio. Genome sequences were aligned to reference strains, including Asian and African CRF01 sequences, and evaluated by maximum likelihood phylogenetic inference (RaXML), REGA subtyping, jpHMM, Simplot, Sequence Signature Visual Analysis, and BLAST. The CRF01_AE evolutionary history was inferred with a Bayesian SkyRide coalescent tree prior under an uncorrelated lognormal relaxed clock assumption using BEAST v1.8.4.

Results: The spiked primer next generation sequencing method produced 8 HIV genomes (8800-9586 nucleotides (nt) long) with full coverage and 5 genomes with 95-98% coverage, which were completed with Sanger sequences. Phylogenetic and recombinant analyses identified 4 pure CRF01, 2 CRF02, 1 CRF27, and 6 unique recombinant form (URFs) genomes (01|A1|G, 01|02|F|U, F|G|01, A1|D|01, F|G|01, A1|G|01). All recombinants described in this study included at least 1000 nt long portions classified as CRF01. In Bayesian analysis of the pure CRF01 genomes, three reference CRF01 genomes isolated in the Congo Basin were basal to the Cameroon/DRC clade branch. Molecular dating indicates that the most recent common ancestor of this clade emerged around 1972 [95% Bayesian credible interval (BCI): 1970-1974] in the Congo basin. The Asian expansion of CRF01 started after 1976 (95% BCI: 1975-1978).

Conclusion: Full genome characterization is required to identify pure CRF01 strains since recombination was high amongst strains from the Congo basin. The complex patterns of recombination described here suggest that ancestral CRF01 sequences are circulating in the region within recombinant forms. Corroborating previous reports, phylogenetic analyses with the new pure CRF01 genomes indicated that CRF01 originated in the Congo Basin around 1972 and spread beyond Africa around 1976.

870 PERSISTENT OUTBREAK OF THE HIV-1 CRF19_CPX VARIANT IN TREATMENT-NAIVE MSM PATIENTS

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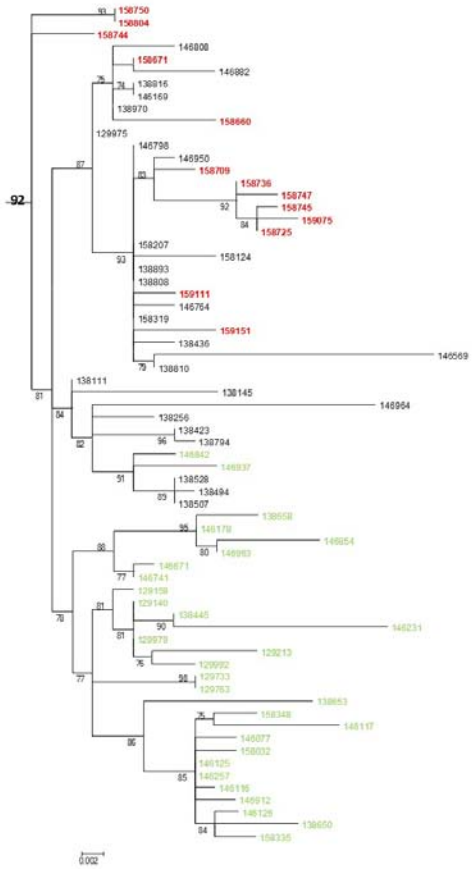
Background: During the period 2011-2016, the HIV-1 CRF19_cpx variant emerged as an outbreak in newly HIV diagnosed (NHIVD) in southern Spain. Our aim was to determine the current status of this outbreak, analyzing the new cases of this variant in our area and their epidemiological relationship with the previous ones.

Methods: We considered NHIVD at Virgen de la Victoria Hospital, reference center in southern Spain, from 01/17 to 06/18. Drug resistance mutations were determined with Viroseq HIV® system and the partial sequence of HIV-1 pol gene provided submitted to REGA v3.0 for subtyping. Sequences assigned as CRF19_cpx subtype were phylogenetically compared to the 254 reference sequences of the same variant retrieved from the LANL, as well as to the 55 ones comprising the already described CRF19_cpx variant outbreak. The alignment was done by Clustal X and the phylogenetic reconstruction inferred by maximum likelihood method (PhyML v3.0 program). The cluster reliability was supported on the value of SH-like aLRT test. The resistance mutations were predicted using Stanford algorithm v7.1.1.

Results: 523 resistance studies were performed in NHIVD; 13 (2.4%) had sequences consigned in REGA as subtype CRF19_cpx. All the new cases conformed a very well-defined transmission cluster (aLRT=92%) with the CRF19_cpx sequences from the previous outbreak, already comprising up to 67 patients. Eight of the new sequences were clustering within two subclusters previously defined: E and F, currently including 18 and 3 patients, respectively. We have not found the G190A mutation in any of the new sequences. The new cases of the CRF19_cpx were MSM, with an average age of 32.5 years (IQR: 27.1-43.6) and Spaniards, except one Italian patient. Half of them were seroconverters, mean seroconversion time of 17.0 months, (8.3-81.3).The initial CD4 count was 423 cells/μL (200-562) and viral load was 4.9 log copies/mL (4.6-5.2).

Conclusion: All the new cases of the CRF19_cpx variant emerged in our area during 2017 and half this year are phylogenetically clustered with the previous outbreak, pointing out its active status. The NHIVD infected with this variant possess similar epidemiological, clinical and immuno-virological characteristics to those already included in the outbreak. None of the new sequences of this subtype showed the G190A mutation. The active transmission of the CRF19_cpx variant in our area should warn us about the necessity of intense epidemiological surveillance programs.



871 PHYLOGENETIC ANALYSIS OF HIV FROM PWID IN EASTERN EUROPE AND ASIA: HPTN074

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Background: HPTN 074 is evaluating the efficacy and feasibility of using an integrated intervention (support for HIV treatment and substance use treatment) to reduce HIV transmission among people who inject drugs (PWID) in Indonesia, Vietnam, and Ukraine. We used phylogenetic methods to evaluate the relationship between HIV strains in the HPTN 074 study population.

Methods: HPTN 074 enrolled HIV-infected PWID (index participants) with up to five concurrent HIV-uninfected injection partners per index. Index-partner pairs were randomized 1:3 to the integrated intervention vs. standard of care study arms. HIV genotyping (pol region) was performed using the ViroSeq-1 HIV Genotyping System for 502 index participants and 7 partners who seroconverted during the study. Phylogenetic analysis was performed using RAxML v8.10.2. Individuals were considered to form a transmission cluster if the genetic distance of their sequences was ≤0.015 with ≥90% branch support. HIV strains from participants in pol transmission clusters were also analyzed using next-generation sequencing (NGS, env region). Participants were considered to have linked infections if their env sequences formed a distinct monophyletic cluster with ≥90% bootstrap support.

Results: Pol sequences were obtained for 452/509 HIV-infected participants (445 indexes, 7 seroconverters). Median pairwise genetic distances for sequences from each study site were 2.9%-3.3%; there was no evidence of large discrete subclades at any of the three sites. Linkage results from pol and NGS-env analyses were concordant for all 7 seroconverter cases. The index and partner were linked in 2/7 cases; in addition, two unrelated partners were linked. In addition, 15 index-index clusters were identified that included 36 indexes with 2-7 indexes per cluster (13 pairs, one triplet, one cluster of 7 indexes). Individuals in each cluster were from the same study site; the cluster of 7 indexes was from Vietnam. NGS-env data was available for 14/15 index-index clusters; this confirmed linkage for 11 (78.6%) of the 14 index-index clusters.

Conclusion: Analyses of HIV pol and NGS-env sequences revealed linked infections involving index-partner pairs, a partner-partner pair, and index-index groups that included 2-7 individuals. These findings suggest that there are complex patterns of HIV transmission among PWID in these communities, which should be considered when designing interventions for HIV prevention.

872 COMBINING OBSERVATIONAL AND PUBLIC HEALTH PHYLOGENETIC DATA TO IMPROVE HIV PREVENTION

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Background: Phylogenetic analyses can be used to highlight differences between the genetic sequences of persons infected with HIV. The findings from these analyses, however, are often limited in their interpretation and generalizability due to inherent limitations of collecting data in either clinical research or public health settings. The goal of this analysis was to combine these complementary data sources and explore how they may be used to inform HIV transmission network dynamics in Chicago.

Methods: Data came from the RADAR cohort study in Chicago as well as the Chicago Department of Public Health surveillance data. Participant plasma samples were collected and pairwise genetic distances of HIV pol sequences obtained from the protease and reverse transcriptase region. Viral genetic sequences ≤1.5% genetically distant defined putative molecular clusters comprising ≥2 persons. Information regarding demographic and HIV risk behavior data were included from each data source while detailed information regarding participant's sexual networks were obtained from the RADAR study.

Results: Among 2977 HIV viral sequences available, 72 clusters contained ≥2 sequences while 23 contained ≥5 sequences (Figure 1). Overall, 424 individuals were identified as members of molecular clusters with 717 total inferred ties between individuals. The race/ethnicity composition of partners differed significantly from that of RADAR participants in both the molecular clusters and sexual networks ($p<0.001$). In molecular networks, black and white participants' partners consisted primarily of other black (83%) and white partners (75%), respectively, while for Hispanics they were more heterogenous and consisted primarily of Hispanic (39%) and black (38%) partners. In network analyses, significant assortativity was observed with regards to both age ($r = -0.20$; p-value = 0.026) and year of HIV diagnosis ($r = -0.88$, p-value <0.001). Additionally, participants who always used condoms in the past six months, compared to those who had condomless sex at least once, had a significantly greater proportion of black partners (73% vs 67%) and a lower proportion of white partners (2% vs 12%).

Conclusion: These results highlight the utility of combining observational cohort and public health data in a multi-tiered approach towards HIV prevention. Further studies would strongly benefit from the combination of these data which have the potential to yield novel targets aimed at reducing HIV incidence.

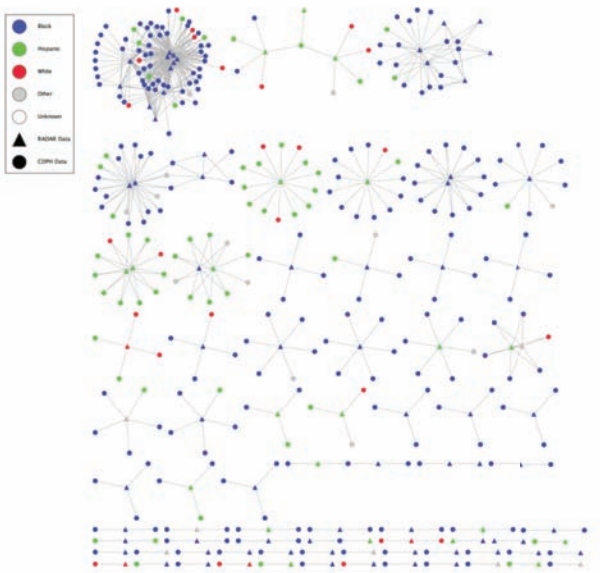

Figure 1. Inferred HIV molecular clusters among young men who have sex with men in the combined RADAR and CDPH datasets, limited to those individuals within one degree connection of a RADAR participant (n=424).

873 MOBILITY PATTERNS CREATE DYNAMIC WIDELY DISPERSED RISK NETWORKS IN NAMIBIA

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Background: Namibia has a severe HIV epidemic: prevalence is ~14%. In Namibia, as in other countries in sub-Saharan Africa, the population is highly mobile and the epidemic is generalized. Consequently, individuals may be at risk of acquiring HIV both in their home community (from other residents or from visitors from other communities) or in other communities (from residents of these communities). We use data from mobile phones and the 2013 Namibia Demographic and Health Survey (NDHS) to estimate the risks of HIV acquisition for individuals in their home community and when they travel.

Methods: The mobile phone data were collected between October 2010 and September 2011; the data set is based on 9 billion communications from 1.19 million unique SIM cards. These data were used to calculate a mobility network based on the average proportion of time residents spent in each of the 96 constituencies in Namibia that include cell towers. We coupled this network with demographic data from the 2011 census and HIV-testing data from 7,600 participants of the NDHS. We used the coupled epidemic-mobility network to calculate, for each constituency, the risk of acquiring HIV that was due to sexual contact with other residents (i.e., localized risk), with visitors, or when traveling.

Results: The calculated mobility network is shown in Figure 1. We find significant geographic variation in prevalence: 6%-40% for women, 0%-24%

for men. Our network analysis shows that individuals in communities where prevalence is high travel to areas where prevalence is low, and vice versa. We estimate that 60% of the overall risk of acquiring HIV in Namibia is localized, 17% is due to visitors, and 23% is due to travel; notably, 40% of the overall risk is related to mobility. Mobility is more important in some areas than others: it contributes to more than half of the overall risk for women in ~20% of constituencies, and for men in ~10%. Using our epidemic-mobility network and risk metrics, we identify which areas of the country are the most vulnerable to the importation of risk, and which are the most important in disseminating risk.
Conclusion: The HIV epidemic in Namibia is not simply driven by localized transmission; a high level of mobility has created a dynamic, widely dispersed risk network. Our results imply that it may be harder to eliminate HIV in Namibia than currently appears.

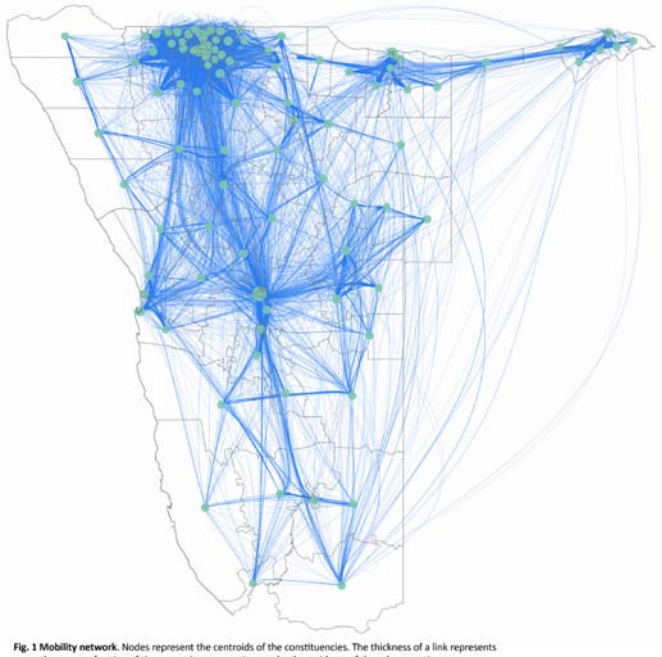

Fig. 1 Mobility network. Nodes represent the centroids of the constituencies. The thickness of a link represents the average fraction of time spent in one constituency by the residents of the other constituency.

874 SPATIAL ANALYSIS TO IDENTIFY EMERGING HOT SPOTS OF MTCT IN ZIMBABWE, 2012-2018

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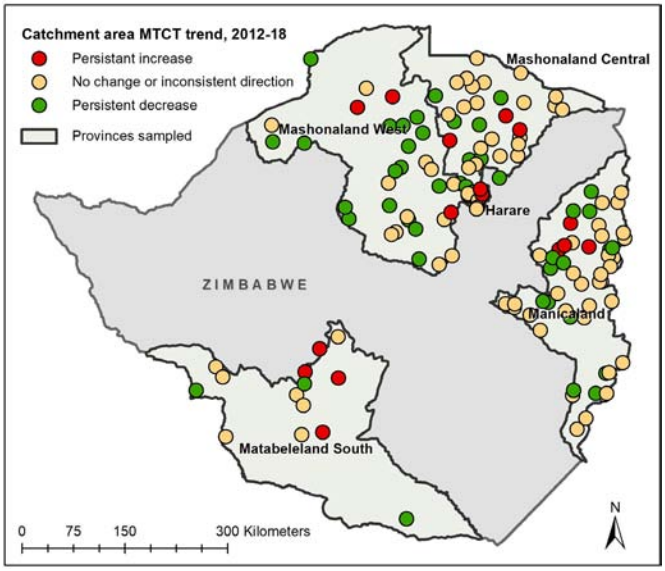
Background: To inform targeting of services for the elimination of mother-to-child HIV transmission (MTCT) in Zimbabwe, we examined spatio-temporal trends in MTCT from 2012 to 2018.
Methods: We conducted three serial cross-sectional serosurveys of infants (9-18 months old) and their mothers or caregivers (≥16 years old) to assess MTCT and related outcomes. Using a multi-stage sampling strategy, in five of ten provinces we randomly selected 157 of 699 health facilities offering prevention of MTCT (PMTCT) services. Within the catchment area (CA) of each facility, we enumerated infants born 9-18 months prior (alive or deceased) and selected a random sample. A total of 26,882 mother- or caregiver-infant pairs were interviewed and tested for HIV in 2012 (n=8,800), 2014 (n=10,404) and 2018 (n=7,678). Global Positioning System (GPS) coordinates were also collected for each facility. We calculated the MTCT rate for the 139 CAs which were included in all three waves and assessed overall temporal changes using a population-averaged model. We then classified changes in MTCT by CA as persistently decreasing (downward trend between each consecutive wave), persistently increasing, or no change/inconsistent direction and assessed spatial trends to identify emerging "hot spots" and diminishing "cold spots".
Results: Overall, catchment area MTCT declined from 9.7% (2012) to 5.1% in 2014 [-4.5 percentage points (pp); 95% CI: -7.2, -1.9] and to 3.6% in 2018 (-6.1 pp; 95 %CI: -8.8, -3.4). However, spatio-temporal analysis revealed heterogeneity in MTCT trends at various geographic levels. Within catchment areas, MTCT persistently decreased in 44 (31.7%) CAs, however 17 (12.2%) CAs had persistent increases in MTCT and 78 (56.1%) CAs had no change or inconsistent direction of change. By province, the proportion of CAs with increased MTCT was greatest in Harare (3/8, 37.5%) and lowest in Mashonaland Central (2/30, 6.7%) and Manicaland (4/52, 7.7%). Within-province variation was also apparent, for example with clusters of CAs with increasing MTCT evident within provinces such as Manicaland where proportionally few CAs had increasing MTCT (Figure).
Conclusion: While overall trends in MTCT show marked progress toward elimination in Zimbabwe, variability by health facility catchment area supports the need for differentiated strategies at the sub-national level. Spatial analysis provides a useful tool to identify high priority areas for targeted and efficient allocation of PMTCT services.



875 MAPPING OF HIV-1C TRANSMISSION NETWORKS IN BOTSWANA

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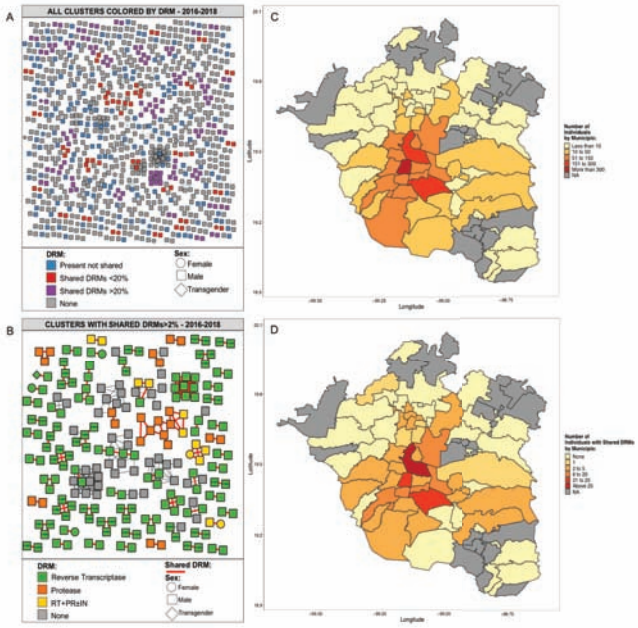
Background: Better understanding of HIV transmission networks and their dynamics could help to prevent new viral transmissions and ultimately curtail HIV spread. Phylogenetic mapping of HIV transmission networks is a promising approach in this process.
Methods: Using proviral DNA and/or viral RNA as a template for amplification, we obtained near full-length HIV-1C sequences from 5,182 HIV-infected individuals participating in four studies in Botswana from 1996–2018, including 4,473 (86%; 72% on ART) sequences from the Botswana Combination Prevention Project (BCPP) sampled 2013–2018. In addition, 444 non-Botswana sequences were included in analyses. Phylogenetic relationships among viral sequences were estimated by maximum likelihood using RAxML v.8 and the GTR+Γ4+I model. Genotyping density was defined as a proportion of genotyped cases among the estimated total number of HIV-infected community residents. We defined a cluster as a phylogenetically distinct viral lineage that gives rise to a monophyletic subtree of the overall phylogeny with bootstrap support of splits ≥0.80 and median pairwise distance <10th quantile of the overall distribution of pairwise distances in the analyzed set of near full-length genome sequences.
Results: We identified 781 phylogenetically distinct HIV-1C lineages circulating in Botswana by mid-2018, including 726 (93%) clusters with Botswana participants. The cluster size varied from 2 to 20 members per cluster. The

majority (63%) of identified HIV-1C clusters were dyads. In clusters spreading across BCPP communities (n=693), the median genotyping density was 13% (IQR 9–18%; range 3–47%). The median number of identified viral lineages was 38 (IQR 25–56) per community. Viral lineages spreading across multiple communities (median 32; IQR 22–47 per community) were identified more frequently than unique viral lineages seen in a single community (median 5; IQR 2–8 per community). Overall, 74% of HIV-1C lineages were spread across multiple BCPP communities, while only 26% were found in a single BCPP community. Men in clusters (median age 41 years old; IQR 34–47) were about 4 years older than women (median age 37 years old; IQR 31–44; p<0.001).
Conclusion: The study revealed a large number of phylogenetically distinct HIV-1C lineages circulating in Botswana by mid-2018. The vast majority of identified viral lineages were spread across multiple communities highlighting the complexity of HIV-1C transmission network.

876 HIV MOLECULAR SURVEILLANCE AND PRETREATMENT DRUG RESISTANCE IN MEXICO CITY

Antoine Chaillon[1], Margarita Matías-Florentino[2], **Santiago Avila-Rios**[2], Sanjay R. Mehta[1], Hector E. Paz-Juarez[2], Manuel A. Becerril-Rodríguez[2], Silvia del Arenal[2], Alicia Piñeirúa[3], Verónica Ruiz[3], Patricia Iracheta-Hernández[3], Israel Macías-González[3], Jehovani Tena-Sánchez[3], Florentino Badial Hernandez[3], Gustavo Reyes-Terán[2]
[1]University of California San Diego, La Jolla, CA, USA, [2]National Institute of Respiratory Diseases, Mexico City, Mexico, [3]Clinica Especializada Condesa, Mexico City, Mexico

Background: Non-nucleoside reverse transcriptase inhibitor (NNRTI) pre-treatment HIV drug resistance (HIVDR) has consistently increased in Mexico during the last decade, approaching 10%. Mexico City concentrates a fifth of all persons living with HIV in Mexico and is a main hub for viral dissemination within Mexico. Combining HIV molecular data and epidemiologic information might help to understand HIVDR transmission dynamics.
Methods: HIV pol sequences were obtained by next generation sequencing from 2,447 individuals initiating first-line antiretroviral therapy from 09/2016 to 06/2018 at Condesa Clinic, the largest HIV care provider in Mexico. Pre-treatment HIVDR was estimated using the Stanford Algorithm with a minimum threshold of 20% and 2% to define low-frequency variants. Genetic networks were inferred with HIV-TRACE, establishing putative transmission links with genetic distances <1.5%. Newman's assortativity coefficients for age and residence were estimated using igraph. Geospatial dispersal was determined by calculating the average distance between centroids of the municipalities of residence of linked individuals.
Results: At 20% threshold, pre-treatment HIVDR reached 14.8% overall and 9.6% to NNRTI. K103N/S was the most frequent surveillance drug resistance mutation (DRM) with 7.1% frequency (7.6% at 2% threshold). Putative links with at least one other sequence were found for 963/2,447 (39%) sequences, forming 99 clusters ranging in size from 2 to 20 individuals (Fig. 1A). Clustering individuals were younger (adjusted odds ratio, aOR=0.96, p<0.0001), included a higher proportion of males (aOR=2.3, p=0.001) and a lower proportion of persons residing outside of the central metropolitan area (aOR=0.11, p=0.003). Among clustering individuals, 175/963 (18%) shared drug resistance mutations at 2% threshold in 66 clusters, with 63/175 (36%) sharing K103N/S in 24 clusters (Fig. 1B). Eight municipalities (out of 75) harboured 65% of persons sharing DRMs (Fig. 1C & 1D). The inferred transmission network was assortative by age and municipality (p<0.001). The residence of genetically linked individuals was closer than expected in a random distribution (median distance: 13 km vs. 65 km, p<0.01).
Conclusion: DRMs (including low-frequency variants) are frequently transmitted in Mexico City metropolitan area, predominantly among recently diagnosed young men in a densely-sampled, geographically assortative network, warranting serious consideration of non NNRTI-based first-line regimens locally.



877 DETERMINANTS OF HIV DIFFUSION ACROSS MEXICO IDENTIFIED THROUGH SPATIAL EPIDEMIOLOGY

Santiago Avila-Rios[1], Simon Dellicour[2], Claudia García-Morales[1], Daniela Tapia-Trejo[1], Margarita Matías-Florentino[1], Hector E. Paz-Juarez[1], Sanjay R. Mehta[3], Davey M. Smith[3], Gustavo Reyes-Terán[1], Bram Vrancken[4], **Antoine Chaillon**[3], for the Mexican HIV ResNet Group
[1]National Institute of Respiratory Diseases, Mexico City, Mexico, [2]Rega Institute for Medical Research, Leuven, Germany, [3]University of California San Diego, La Jolla, CA, USA, [4]University of Leuven, Leuven, Germany

Background: The HIV epidemic in Mexico is highly complex. It is the result of multiple local but intermingled epidemics shaped by various factors including human migration. Here, we characterized the diffusion dynamics of HIV across Mexico.
Methods: Using a comprehensive data set of HIV-1 subtype B pol sequences sampled from across Mexico, we applied a multistep phylogenetic approach: (1) we first performed maximum likelihood phylogenetic inference to identify well-supported monophyletic clades within our dataset; (2) all clades of size ≥ 3 identified in step (1) were used to perform a discrete phylogeographic inference to evaluate the dispersal history across the Mexico states; (3) using a generalized linear model (GLM) to test the association of epidemiologic factors (i.e. population size, human emigration and immigration flows) and connectivity (i.e. geographic distances and the intensity of air traffic passenger flow among locations) with lineage dispersal frequencies among the states (Fig 1A).
Results: A total of 7,410 unique HIV subtype B partial pol sequences (HXB2 position 2253-3554) from participants originating from Mexico were collected between 2005-2018. After combining these with 2,629 publicly available HIV-1 B pol sequences with known sampling location, we identified 65 clades of size ≥ 3 that represent 798 sequences from 19 states. The discrete phylogeographic analysis based on these clades revealed high levels of virus exchange between Mexico state, Jalisco (including Guadalajara, the second largest city in Mexico) and the eastern touristic state of Quintana Roo (including Cancun), with the border state of Baja California (Fig. 1B). Furthermore, the GLM analysis also suggests that viral migration was strongly associated with the population density, and number of emigrants from the origin state (Bayes Factor, BF>105), the number of immigrants in the recipient state (BF>105), and the intensity of air passenger flows (BF=3.2). The distance between states was also negatively associated with viral movement (negative BF>105), Fig. 1C.
Conclusion: This comprehensive analysis of HIV dynamics within Mexico emphasizes the key role of human migration in the diffusion of the HIV epidemic. These results may help to more efficiently allocate prevention

resources and to evaluate the impact of changes in demographic trends and policies on the Mexico HIV epidemic.

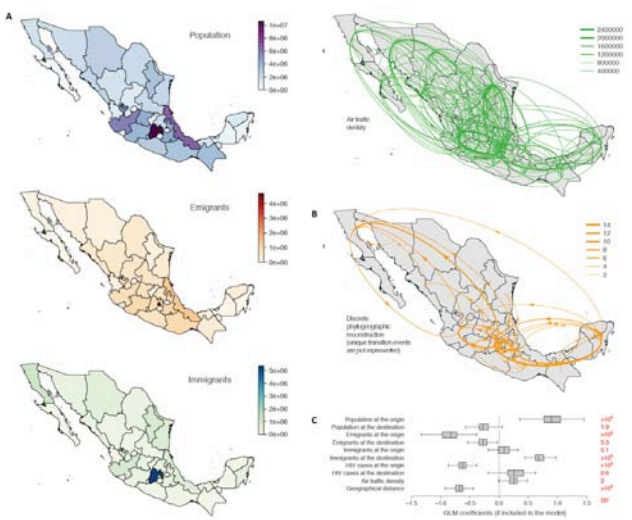


Figure 1. A. Predictors tested with the generalized linear model (GLM) analysis: Total population, total number of emigrants and immigrants (data from the National Institute of Statistics and Geography, INEGI, http://www.beta.inegi.org.mx/temas/migracion/) and air traffic passenger flux were included in the model. **B. Number of lineage dispersal events between Mexico states inferred by discrete phylogeographic analysis**. Only transition curves that represent ≥2 transition events are shown. **C. Summary of phylogenetic generalized linear model results.** Box plots of the GLM coefficients for all tested predictors. Bayes factors (BF) support for inclusion of each predictor in the model is indicated in red on the right.

878 WITHDRAWN / INTENTIONALLY UNASSIGNED

879 LOCAL HUMAN MOBILITY AND TRANSMISSION ROUTES OF HIV CRF01_AE ACROSS CHINA

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[1]Katholieke University Leuven, Leuven, Belgium, [2]China Medical University, Shenyang, China, [3]Shenzhen Center for Disease Control and Prevention, Shenzhen, China, [4]Shanghai Municipal Center for Disease Control and Prevention, Shanghai, China, [5]University of California San Diego, La Jolla, CA, USA

Background: China is witnessing a rapid growth of its HIV epidemic and now accounts for 3% of the global HIV incidence. This upsurge is driven by new HIV infections among men who have sex with men (MSM) often with CRF01_AE infection. Here, we characterized the dynamics and determinants of diffusion of HIV-1 CRF01_AE across China.
Methods: We applied a multistep phylogenetic approach on a large dataset of CRF01 AE pol sequences sampled across China. We first performed an overall maximum likelihood phylogenetic inference to identify well-supported monophyletic clades. All clades of size ≥ 3 identified were used to perform a discrete phylogeographic inference to evaluate the dispersal history across Chinese provinces. We then applied a generalized linear model (GLM) to test the association of epidemiologic factors and connectivity (i.e. geographic distances between each location and the intensity of air traffic passenger flow) with lineage dispersal frequencies among the provinces (Fig 1A).
Results: A total of 6,800 unique CRF01_AE HIV partial pol sequences from participants originating from China were collected between 2004-2017. After combining these with 6,423 publicly available HIV-1 CRF01_AE pol sequences with known sampling country, we identified 59 clades of size ≥ 3 that represent 458 sequences from 17 provinces. The discrete phylogeographic analysis based on these clades revealed varying levels of virus exchange between the sampled provinces (Fig. 1B). The GLM analysis also suggested that viral migration was strongly associated with the population density in both source and recipient provinces (Bayes Factor, BF>25.103 and 105.9 respectively), but not with the intensity of air passenger flows associated with a negative GLM coefficient (BF=59.5). Finally, the geographical distance between provinces was also negatively associated with viral movement (i.e. increased distance associated with less transition, negative BF>25.103), Fig. 1C. The negative correlations with both the air traffic and geographical distances underline the importance of local mobility (e.g. between adjacent provinces) in spreading the virus. Based on epidemiology, these observations could illustrate the role of migrant workers leaving their home towns for work.
Conclusion: This analysis of HIV CRF01_AE dynamics within China emphasizes the key roles of highly populated regions and human mobility in the dispersal of the HIV epidemic. Such information could be important in developing prevention strategies.

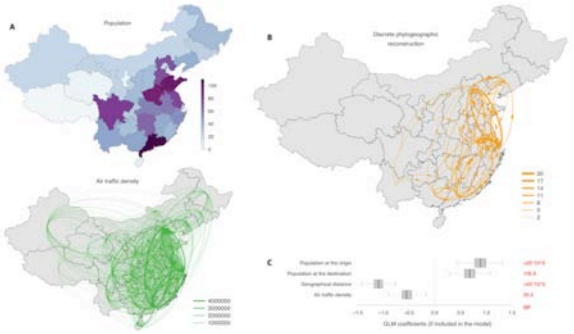

Figure 1. A. Predictors tested with the generalized linear model (GLM) analysis: Total population for each province and air traffic passenger flux were included in the model. **B. Number of lineage dispersal events between Province in China inferred by discrete phylogeographic analysis**. Only transition curves that represent ≥2 transition events are shown. **C. Summary of phylogenetic generalized linear model results.** Box plots of the GLM coefficients for all tested predictors. Bayes factors (BF) support for inclusion of each predictor in the model is indicated in red on the right.

880 SUBSTANCE USE DISORDERS ASSOCIATED WITH MORTALITY AMONG HIV+ IN WASHINGTON, DC

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Background: Substance use disorders (SUDs) are common among people living with HIV (PLWH) and may make achievement of optimal health outcomes challenging. We described the prevalence of alcohol, opioid and stimulant use disorders among PLWH in the DC Cohort and assessed the association of SUDs with viral suppression and death.
Methods: We analyzed diagnosis and treatment data for participants enrolled in the DC Cohort (2011-2017), a longitudinal study of PLWH receiving care at 14 clinical sites in Washington, DC, and reported on the prevalence of overall SUD, alcohol, opioid, stimulant, and polysubstance (all 3) use disorders at enrollment or during follow-up, and prevalence of hepatitis B (HBV) and hepatitis C (HCV) among the SUD groups. We used multivariable Cox proportional hazard models to evaluate the association of SUD with all-cause mortality, adjusting for demographics, CD4, and viremia copy-years. We calculated adjusted prevalence ratios (aPR) to assess the association of age at HIV diagnosis, gender, and race/ethnicity with SUDs, and association of SUDs with viral suppression (VS; <200 copies/ml at most recent measurement), adjusting for current age, gender, race/ethnicity, and mode of HIV transmission.
Results: Of 8,507 adults, 2,929 (34.4%) had history of any SUD. The most prevalent SUDs were: 73.6% only alcohol, 9.0% alcohol/stimulant, 7.0% only stimulants, 3.4% only opioids, 3.4% alcohol/opioids and 2.8% polysubstance use disorders. Chronic HCV was highest among those with alcohol/opioids (62%), polysubstance (60%), and opioid use disorders (49%). After adjustment, those with any SUD were older at HIV diagnosis (median 49.9 vs. 45.6 years), more likely to be Black (vs. White; aPR 1.37, 95% CI 1.23, 1.52) or Latino (aPR 1.29, 95% CI 1.10, 1.52), less likely to be female (aPR 0.75, 95% CI 0.69, 0.81), and more likely to have any mode of HIV transmission other than men who have sex with men (MSM; all p<.0001). Based upon 388 deaths, SUD was independently associated with all-cause mortality (aHR 1.49, 95% CI 1.18, 1.89). Overall VS was 87%, and SUD was not significantly associated with VS (aPR 0.99, 95% CI 0.97, 1.01).

Conclusion: Alcoholism was the most diagnosed single SUD in the DC Cohort. SUDs disproportionately affected Blacks, Latinos, men, and risk groups other than MSM. Chronic HCV was highly prevalent among PLWH with SUDs and warrants closer attention to ensure successful treatment. SUD was associated with mortality but not VS, suggesting substance-related causes of death.

881 ACCIDENTAL OVERDOSE DEATHS AMONG HIV+ INDIVIDUALS IN WASHINGTON, DC, 2013-2016

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Background: Drug overdose deaths in DC increased by 178% from 2014 to 2016 (DC Office of the Chief Medical Examiner), but the extent to which people living with HIV (PLWH) died of drug overdose is unknown. We compared the demographic profiles and markers of engagement in HIV care among PLWH in DC who died of accidental overdose (AOD) versus other causes of death (COD) from 2013 to 2016 using death certificate data.

Methods: Deaths reported to the DC Department of Health among PLWH from 2013 to 2016 were evaluated. AOD included ICD-10 codes X40, X41, X42, X43, X44, and Y12 in any death cause position. Individuals were classified as having either AOD or other COD. Univariate analyses (Cochran-Mantel-Haenszel and Student's t-test) and multivariate logistic regression were conducted to evaluate potential covariates, including age at HIV diagnosis, gender, race/ethnicity, mode of transmission, duration of HIV illness, and CD4 cell count, viral suppression (most recent viral load ≤ 200 copies per mL), and retention in care (at least 1 CD4 or VL) in the year prior to death.

Results: From 2013 to 2016, 1125 deaths among PLWH were reported; of these, 6% (n=68) were AOD. AOD among PLWH increased by 182% from 2013 (n=11) to 2016 (n=31), and PLWH who died from exposure to narcotics (X41) increased by 156% from 2013 (n=9) to 2016 (n=23). Among PLWH with AOD, 40% (n=27) had history of injection drug use (IDU) at the time of HIV diagnosis vs. 26% among PLWH with other COD (p=0.03). Among PLWH with AOD, mean age of HIV diagnosis was 38 years vs 42 years for other COD (p-value = 0.01). No statistical difference was found between the mean duration of HIV (AOD 13.7 years vs. other COD 12.5 years, p-value=0.21). In unadjusted analyses, retention in care, viral suppression, and rates of missing lab data were similar between AOD and other COD (Table 1). Based on multivariable analysis, those who died of AOD (vs. other COD) were more likely to have a history of IDU (aOR: 2.3, 95% CI 1.0,5.1) and CD4 count ≥ 500 (aOR: 3.6 95% CI 1.6,8.1).

Conclusion: AOD among PLWH in DC has increased substantially in recent years and was prominent among PLWH with history of IDU. CD4 was higher among PLWH with AOD, indicating HIV treatment success. Access to naloxone and opioid substitution therapy for PLWH should be enhanced, and provider awareness of IDU history and overdose potential should be increased, to address this rapidly increasing cause of mortality.

Table 1: Care Patterns with in the year prior to death

	Accidential Overdose n=68		Other Causes n=1068		Total n=1136		p-value
	n	%	n	%	n	%	
Retention in Care (yes)	53	78%	764	72%	817	72%	0.4519
Missing a viral load the year prior to death	23	34%	366	34%	389	34%	
Viral Load Supression LE 200 (Yes)	30	44%	416	39%	446	39%	0.326
Missing a CD4 count the year prior to death	23	34%	366	34%	389	34%	
CD4 count closest to death							0.0077
Stage 1 CD4 cell count ≥ 500 or CD4 % ≥ 29%	22	32%	204	19%	226	20%	
Stage 2 CD4 cell count ≥200 or CD4 % ≥19%	17	25%	268	25%	285	25%	
Stage 3 CD4 cell count < 200 or CD4 % < 14%	12	18%	290	27%	302	27%	

882 RELEASED TO DIE: ELEVATED MORTALITY IN PEOPLE WITH HIV AFTER INCARCERATION

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Background: People with HIV (PWH) released from the criminal justice (CJ) system experience poor HIV outcomes and high mortality. In a cohort of PWH incarcerated in Connecticut and returned to communities, we have shown that the risk of death is 8.47 (standardized mortality ratio [SMR]; 95% CI: 7.25-9.69) times that of the general Connecticut population and 6.97 (95% CI: 5.96-7.97) times that of the general US population. To guide future interventions, we aimed to identify demographic (age and race/ethnicity) disparities in comparative mortality.

Methods: We linked pharmacy, custodial, death, case management, and HIV surveillance data from Connecticut Departments of Correction and Public Health to create a retrospective cohort of all adult PWH released from jails and prisons in Connecticut (2007-2014). We compared mortality in this cohort with the general US and Connecticut populations and with a cohort of PWH from North America (NA-ACCORD) using SMRs. We assessed differences in cause of death and time-to-death within the cohort, stratified by race/ethnicity and age (<45, ≥45 years of age).

Results: Among 1,350 PWH released from CJ settings in Connecticut, median length of incarceration was 73 days (IQR=25-201). After stratifying by race/ethnicity and age, released PWH had significantly higher adjusted mortality than individuals within the general US, CT, and PWH populations (See Table). Assessment of within cohort differences found that among younger, formerly incarcerated PWH, Whites had a shorter time-to-death than Blacks (p<0.0001). In older, formerly incarcerated PWH, time-to-death was shorter among Hispanics compared to Whites (p=0.032). The most frequent causes of death were HIV/AIDS complications (46%), drug overdose (15%), and liver disease including hepatitis C (10%). Causes of death differed by race/ethnicity for younger (p=0.025), but not older PWH (p=0.526), with younger Hispanics dying most commonly from HIV/AIDS (50%) or liver disease (19%), younger Blacks dying most frequently from HIV/AIDS (23%) or accidental injury/suicide (23%), and younger Whites dying most frequently from HIV/AIDS (50%) or drug overdose (25%).

Conclusion: For PWH, release from the CJ is associated with markedly elevated risk for death relative to general and PWH populations in North America. To reduce mortality, linkage and retention in care post-release and expanded treatment provision for substance use disorders and other chronic conditions in prison are critically important.

Table 1. Standardized mortality ratios of formerly incarcerated people with HIV

Race/ Ethnicity	Comparison Populations: US General Population SMR (95% CI)	CT General Population SMR (95% CI)	NA-ACCORD Cohort SMR (95% CI)
Younger Age Group: <45 Years at initial release			
Black	**4.1 (1.8 – 6.3)**	**5.3 (2.4 – 8.2)**	1.0 (0.5 – 1.6)
Hispanic	**16.3 (10.5 – 22.1)**	**14.0 (9.0 – 19.0)**	**3.0 (1.9 – 4.1)**
White	**25.4 (15.5 – 35.4)**	**33.4 (20.3 – 46.4)**	**4.4 (2.7 – 6.1)**
Other	9.4 (0 – 22.6)	46.5 (0.0 – 110.9)	1.8 (0.0 – 4.3)
Older Age Group: ≥45 Years at initial release			
Black	**3.6 (2.6 – 4.6)**	**4.8 (3.4 – 6.1)**	**1.4 (1.0 – 1.9)**
Hispanic	**13.2 (9.4 – 17.0)**	**11.7 (8.4 – 15.0)**	**3.2 (2.3 – 4.1)**
White	**5.3 (2.7 – 7.9)**	**6.9 (3.5 – 10.4)**	1.6 (0.8 – 2.4)
Other	9.4 (0.2 – 18.6)	30.6 (0.6 – 60.6)	1.3 (0.0 – 2.7)

SMR=Standardized Mortality Ratio adjusted for race/ethnicity, age, and sex. Significant (p<0.05) SMRs in bold.

883 HIV AND OVERDOSE AMONG PEOPLE WHO INJECT DRUGS IN A COMMUNITY-BASED COHORT

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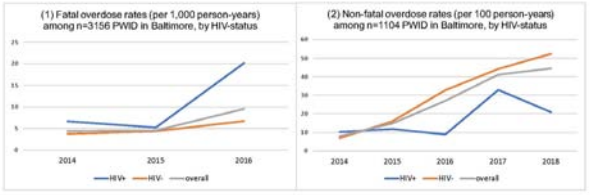
Background: Overdose mortality has been increasing in the United States for the past decade. People who inject drugs (PWID) with HIV infection may have heightened overdose risk due to a higher burden of age-related comorbidities. Moreover, the context of drug use has changed across the US. We characterize trends in fatal and non-fatal overdose and associations with HIV infection among a community-based cohort of PWID in a city with a long-standing opioid epidemic.

Methods: The AIDS Linked to the IntraVenous Experience (ALIVE) cohort has followed PWID in Baltimore since 1988. We characterize the incidence of fatal and non-fatal overdose from 2014-2018 among all PWID enrolled in ALIVE who were alive in 2014. Mortality through 2016 was ascertained via linkage to the National Death Index with death certificate confirmation. Deaths classified as overdose/drug-related were examined using survival methods with censoring (administrative, other causes of death). Non-fatal overdose was ascertained via self-report among PWID actively using drugs with >1 study follow-up visit on or after 2014. Poisson regression was used to evaluate time trends and covariate associations.

Results: Of 3,156 PWID enrolled in ALIVE who were living at the start of 2014, the median age was 54, 28% were female, 79% were African-American. 51 died of a drug-related cause between 2014-2016 (mortality rate: 6.2 per 1,000 person-years). PWID with HIV were at significantly higher risk of mortality from a drug-related cause (aHR = 2.40, 95% CI: 1.33-4.31) compared to HIV-negative PWID, adjusting for age, sex, and race. Overall, between 2014-2018 among 1104 in follow-up, 194 PWID experienced 530 non-fatal overdoses (rate: 28.5 per 100 person-years). Moreover, rates increased significantly between 2014 and 2018 (Figure) from 8.0 to 44.5 per 100 person-years (p-value for trend<0.0001). HIV-infection was associated with decreased risk of non-fatal overdose controlling for age, race and sex (adjusted incidence rate ratio (aIRR) =0.64, 95% CI: 0.42-0.98). There were no differences in non-fatal overdose by viral suppression for HIV-positive PWID.

Conclusion: While HIV-infected PWID in this cohort appear less likely to experience drug overdose, they may be at higher risk for drug-related mortality. Concurrently, overall rates of overdose are increasing among all PWID. Additional efforts are needed to mitigate the impact of non-fatal overdose among all PWID and fatal overdose among HIV-positive PWID.



884 ATTRIBUTABLE RISK OF METHAMPHETAMINE USE ON VIRAL SUPPRESSION AMONG MSM ON ART

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Background: Viral suppression improves clinical outcomes, while virologic failure (HIV RNA >200 copies/ml) increases risk of HIV morbidity/mortality. Substance use decreases the likelihood of achieving undetectable viremia; however, the comparative effects by substance have not been described. In this study, we examine the effect of different drugs on levels of viremia in a cohort of HIV+ men who have sex with men (MSM) on antiretroviral therapy (ART).

Methods: Participants (N=230) were selected from an ongoing cohort (The mSTUDY) of diverse young MSM enrolled from August 2014 to May 2018. Only participants who were HIV+ currently on ART as reported in review of concurrent medications and self-report were included. Plasma HIV RNA copies were measured at semi-annual visits and substance use over the preceding six months assessed by computer-assisted self-interview. Substance use and sociodemographic factors associated with viremia outcomes were assessed using ordinal regression analysis with generalized estimating equations. Viremia outcomes were grouped as undetectable (≤ 20 copies/ml), low level suppressed (21-200 copies/ml), or not suppressed (>200 copies/ml).

Results: The average age of included participants was 34 years with 38.5% African American and 37.2% Hispanic/Latino. The average years since HIV diagnosis was 8 years. The prevalence of substance use across 825 study visits was 73%, with methamphetamine (MA) use most prevalent (50%). After adjusting for unstable housing and ART adherence, MA use, either alone (adjusted OR=1.87; 95% CI 1.03-3.40) or with other substances (adjusted OR=1.82; 95% CI 1.12-2.95), was associated with higher odds of increasing viremia categories (low level suppressed 21-200 copies/ml; not suppressed >200 copies/ml) compared to non-substance users. Other substance use excluding MA did not show a similar association (adjusted OR=1.29; 95% CI 0.80-2.09). These findings suggest that among MA users, nearly half the instances of viremia would be reduced if MA was discontinued (attributable fraction=46%; 95% CI 3-71%).

Conclusion: MA use, either alone or in combination with other drugs, is associated with failure of viral suppression among HIV-positive MSM on ART independent of adherence and sociodemographic factors. This accounts for nearly half of the observed instances of unsuppressed viremia. In contrast, other substance use does not impose the same risk. This study underscores the importance of MA use on clinical outcomes among people living with HIV.

885 METHAMPHETAMINE DOSE, CLINICAL OUTCOMES, AND HIV STATUS LINKS AMONG DIVERSE MSM IN LA

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Background: Men who have sex with men (MSM) who use methamphetamine (meth) report patterns of use that accumulate to varying amounts of exposures each month. Reliable patterns are: users who dose daily, users for several days once or twice monthly ("weekend warriors") and users who rarely use over several months. Our hypothesis posits cumulative reported meth exposure over 6 month periods links significantly and in dose-dependent fashion with poorer physical and mental health outcomes and with confirmed HIV serostatus.

Methods: Data were baseline and follow-up visits (1,798 visits) from 529 mSTUDY participants (HIV+ 266; HIV- 263) in mSTUDY, a prospective cohort of diverse MSM in Los Angeles. Analyses tested links between pattern of self-reported past meth use (past 6 months) with other substance use and select physical and mental health status variables. Reported meth use data at each visit were: (none=1,116 visits; ≥ weekly=330 visits; ≤ monthly=352 visits).

Results: Univariate analyses supported our hypothesis of an ordered dose-response association over 6-month periods between outcomes of cumulative dose of meth use and other drug use, HIV-risk behaviors, HIV status, STIs and clinical conditions. By contrast, any reported meth use significantly correlated with HIV-seropositive status (see Table). In multvariable analyses, visits where MSM reported ≥ weekly meth use (compared to nonusers) showed significantly higher likelihood of clinical hepatic (AOR 2.4, 95%CI 2.2, 5.4), neurologic (AOR 2.1, 95%CI 1.2, 3.4), psychologic (AOR 1.6, 95% CI 1.2, 2.3) and renal abnormalities (AOR 2.2, 95% CI 1.1, 4.3). In visits where MSM reported ≤ monthly meth use, lower, but significantly higher odds than non-users were observed for all conditions, though less than visits where ≥ weekly meth use was reported (excepting renal conditions).

Conclusion: Findings show a robust and ordered signal between reported cumulative meth use and physical and mental health outcomes. By contrast, any reported meth use linked with HIV-positive serostatus. Findings also show a strong signal between level of reported meth use over 6 month periods and likelihood of hepatic, neurologic, psychologic and renal abnormalities, suggesting a dose-response link between cumulative dose of meth and negative health impacts in MSM in urban areas similar to Los Angeles.

	Amount of Methamphetamine use, past 6 months (n=1,798)						
	Weekly or more often (n=330 visits)		Monthly or less often (n=352 visits)		None (n=1,116)		P value~
	n	%	n	%	n	%	
Socio-demographic characteristics							
Age at study visit, mean (SD)	34.3 (6.8)		33.4 (6.8)		31.7 (6.9)		<.01
Unemployed	235	73.2	195	57.2	319	29.7	<.01
Unstable Housing, past 6 months*	163	49.4	125	35.5	209	18.7	<.01
Ever Incarcerated	204	61.8	157	44.6	318	28.5	<.01
Substance use behaviors							
Smoker, current (cigarettes)	158	51.5	133	40.4	225	23.6	<.01
Binge drinking, past 6 months	116	35.2	217	61.2	563	50.5	0.11
Other substances past 6 months							
Cocaine	77	23.3	94	26.7	174	15.6	0.02
Ecstasy	79	23.9	70	19.9	97	8.7	<.01
Heroin	31	9.4	16	4.6	9	0.8	<.01
Marijuana	191	57.9	217	61.6	526	47.1	0.01
Poppers	167	50.6	136	38.6	274	24.6	<.01
Sexual risk behaviors							
New Sex Partner, past 6 months	254	77.0	246	69.9	680	60.9	<.01
Transgender Anal Partner, 6 mos	49	14.9	26	7.4	53	4.8	<.01
IPV, past 12 months**	93	29.3	67	19.5	117	10.7	<.01
Concurrent Sexual Partnership,							
past 6 months	174	60.4	132	42.3	391	37.8	<.01
past 3 months	132	41.1	74	22.3	83	7.7	<.01
HIV-related factors							
HIV-serostatus							<.01
HIV-positive	227	68.8	233	66.2	457	41.0	
HIV-negative	103	31.2	119	33.8	659	59.0	
PrEP use, past 6-months ^	37	35.9	39	32.8	282	42.8	0.13
HIV-1 RNA ≤ 20 copies/mL^^	81	36.7	141	61.3	286	63.0	<.01
STI (laboratory testing)							
Infectious Syphilis)	85	26.2	67	19.4	167	15.1	<.01
Clinical Factors[#]							
Cardiovascular conditions	53	16.3	68	19.6	143	12.9	0.02
Endocrine abnormalities	23	7.1	26	7.5	70	6.3	0.52
Neurologic conditions	89	27.4	60	17.3	186	16.8	<.01
Psychologic conditions	131	40.3	125	36.0	323	29.2	<.01
Renal conditions	30	9.2	26	7.5	73	6.6	0.16

Abbreviations. IQR=Interquartile Range; PrEP=Pre-exposure Prophylaxis
~p value adjusts for the effect of the subject (i.e. multiple observations for the same participant)
*Defined as not having a regular place to stay in the past 6 months
**Defined as being hit, kicked, or slapped by a lover, boyfriend/girlfriend
^Among HIV-negative participants; ^^Among HIV-positive participants
#Clinical examination at each visit; Cardiovascular includes hypertension and hyperlipidemia
Endocrine includes diabetes/pre-diabetes,hypogonadism; neurologic includes neuropathy, headaches
Psychologic includes depression and anxiety; renal includes kidney stones, dysuria, and UTI

886 HIV DIAGNOSES AMONG PEOPLE WHO INJECT DRUGS BY URBAN-RURAL CLASSIFICATION, 2014-2016

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Background: Concurrent with the U.S. opioid epidemic, the decline in the number of HIV diagnoses among people who inject drugs (PWID) has slowed. Although HIV diagnoses among PWID have been concentrated in urban areas, a 2015 HIV outbreak among PWID in Indiana revealed the vulnerability of rural areas to HIV outbreaks. We assessed the number of HIV diagnoses among PWID and recent changes over time across the urban-rural continuum.

Methods: We used National HIV Surveillance System data reported through June 2018 for diagnoses occurring among persons aged ≥13 years during 2014 and 2016 (excluding the Indiana outbreak year) and preliminary data for 2017. We included persons with HIV attributed to injection drug use (IDU) only; those attributed to both IDU and male-to-male sexual contact were not included. Missing data on transmission category were imputed with standard methods. County of residence at diagnosis was categorized by the National Center for Health Statistics 2013 urban-rural classification scheme (Table) and the 220 counties identified by CDC as most vulnerable to HIV outbreaks.

Results: In 2016, of 2177 HIV diagnoses among PWID, 1982 (91%) occurred among residents of metropolitan counties; 971/2177 (45%) were from large central metro counties (Table). In the 220 most vulnerable counties, 45 diagnoses occurred. The number of diagnoses in 2016 was >5% lower than in 2014 for large central metro (-83 diagnoses; -8%) and small metro (-8; -6%) counties and >5% higher for large fringe metro (+22, 5%) and micropolitan (+10, 10%) counties and for the 220 most vulnerable counties (+22, 96%). Preliminary data suggest that HIV diagnoses among PWID in 2017 are higher in number than in 2016 and distributed similarly across urban-rural categories.

Conclusion: The vast majority of HIV diagnoses among PWID in the United States are among PWID who reside in metropolitan areas. Although diagnoses among residents of large central metro counties continued to decline through 2016, these counties still accounted for 45% of HIV diagnoses among PWID. Increases in diagnoses among PWID in 2016 compared with 2014 occurred outside of large, central metro areas, with the greatest absolute increase in large fringe metro counties, and the greatest relative increase in micropolitan counties. Recent increases in HIV diagnoses have occurred in non-metropolitan counties. Whether through outbreaks or slower trends of increased transmission, HIV diagnoses among PWID may increase in areas across the urban-rural continuum.

Table. HIV diagnoses among people who inject drugs, by urban-rural classification — United States, 2014 and 2016

NCHS Urban-Rural Classification*	2014 n (%)	2016 n (%)	Change from 2014 to 2016 n (%)
Total	**2224**	**2177**	**-47 (-2.1)**
Metropolitan	**2036 (91.5)**	**1982 (91.0)**	**-54 (-2.7)**
Large central metro	1,054 (47.4)	971 (44.6)	-83 (-7.9)
Large fringe metro	432 (19.4)	454 (20.9)	22 (5.1)
Medium metro	410 (18.4)	425 (19.5)	15 (3.7)
Small metro	140 (6.3)	132 (6.1)	-8 (-5.7)
Non-metropolitan	**170 (7.6)**	**179 (8.2)**	**9 (5.3)**
Micropolitan	97 (4.4)	107 (4.9)	10 (10.3)
Noncore	73 (3.3)	72 (3.3)	-1 (-1.4)
Unclassified county	*16 (0.7)*	*16 (0.7)*	*0*

Note. Data have been statistically adjusted to account for missing transmission category; therefore, values may not sum to the column total.
*2013 National Center for Health Statistics Urban-Rural Classification Scheme for Counties.

887 INJECTION AND SEXUAL BEHAVIORS AMONG PERSONS WITH DIAGNOSED HIV WHO INJECT DRUGS

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Background: Injection and sexual practices of HIV-positive persons who inject drugs (PWID) can affect HIV transmission risk, but have not been described using nationally representative data. We examined high-risk injection and sexual practices among HIV-positive PWID using nationally representative data from the Medical Monitoring Project (MMP).

Methods: During 6/2015–5/2016, interviews were conducted with adults with diagnosed HIV to assess sexual behaviors, injection drug use, and other behaviors during the past 12 months. Viral load results from the past 12 months were obtained through medical record abstraction. Among adults with diagnosed HIV who injected drugs in the past 12 months (n=113), we reported the percent who engaged in distributive sharing of syringes and other injection equipment (defined as giving used injection equipment to another person for use), injected drugs before or during sex, and needed and did not obtain alcohol or drug treatment. We estimated the percent of HIV-positive PWID who had condomless sex and were at high risk for sexual HIV transmission, defined as (1) having a detectable viral load (≥1 viral load ≥200 copies/mL), and (2) having condomless sex with an HIV-negative or HIV-unknown partner who was not known to be on PrEP, and compared estimates with HIV-positive adults who did not inject drugs (n=3,541) using Rao-Scott chi-square tests (P<.05). We reported weighted percentages to account for complex survey design.

Results: Overall, 3% of adults with diagnosed HIV injected drugs in the past 12 months, of whom 9% engaged in distributive syringe sharing and 11% in distributive sharing of other injection equipment; 65% reported injecting drugs before or during sex. Over half (56%) needed alcohol or drug treatment, of whom 32% did not obtain treatment. Seventy percent of all HIV-positive PWID, compared with 31% of HIV-positive non-PWID, had condomless sex; 25% of HIV-positive PWID, compared with 7% of HIV-positive non-PWID, engaged in behaviors associated with high risk of sexual HIV transmission.

Conclusion: Over 10% of HIV-positive PWID engaged in distributive injection equipment sharing, which is associated with HIV transmission. HIV-positive PWID were more likely to engage in behaviors associated with high risk of sexual HIV transmission. Additional resources to reduce HIV transmission risk among HIV-positive PWID, such as expanding access to sterile injection equipment, drug treatment options, and education on condom use, may be needed.

888 HIV PHYLODYNAMIC ANALYSIS CORRELATES WITH TRENDS IN ILLICIT OPIOID TRADE IN PAKISTAN

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Background: Pakistan is considered to have transitioned from a "low prevalence, high risk" epidemic to a "concentrated" HIV epidemic owing primarily to a rapid rise in infections among people who inject drugs (PWID). Prevalence among the country's nearly 105,000 PWID is estimated to be 37.8% but has been shown to be higher in several large urban centers. Here we evaluate the molecular characteristics of HIV sequences from PWID in several Pakistani cities to examine transmission dynamics and the association between rates of HIV transmission with regards to regional trends in opioid trafficking.
Methods: Tip-to-tip (patristic) distance based phylogenetic cluster inferences and BEAST2 Bayesian Markov Chain Monte Carlo phylodynamic analyses of time-stamped data were performed on HIV pol sequences generated from dried blood spots collected from 1,453 PWID as part of a cross-sectional survey conducted in Pakistan during 2014/2015.
Results: In total, we were able to amplify 290 pol sequences of the 367 HIV positive specimens. Overall, subtype A1 strains were dominant (75.2%) followed by CRF02_AG (14.1%), recombinants (7.2%), CRF35_AD (2.1%), G (1.0%) and C (0.3%). Nearly a quarter (n=72) of the PWID HIV sequences belonged to one of four distinct phylogenetic clusters. The largest cluster (n=53) mainly consisted of individuals who did not seek help injecting which was previously identified as a strong correlate of HIV infection. Spikes in estimated HIV population sizes coincided with increases in opium poppy cultivation in Afghanistan, Pakistan's western neighbor. Structured coalescent analysis was undertaken in order to investigate the spatial relationship of HIV transmission among the various cities under study. In general terms, our analysis placed the city of Larkana at the center of the PWID HIV epidemic in Pakistan which is consistent with previous epidemiological data.
Conclusion: The current epidemic among PWID is no longer dominated by transmission of a limited number of subtype A1 founder viruses as reported previously. The greater subtype diversity is consistent with sexual and/or drug injecting networks between PWID and other most at-risk populations. Although it is evident that unsafe injection behaviors played a significant role in driving the rise in HIV prevalence among PWID, local trends in opioid trafficking may have influenced injection behavior and facilitated HIV-1 transmission as a result.

889 IMPROVING CHRONIC OPIOID THERAPY AMONG PEOPLE LIVING WITH HIV: A CLINICAL RCT

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Background: Chronic pain is highly prevalent among people living with HIV (PLWH); managing pain with chronic opioid therapy (COT) is common. HIV physicians often diverge from opioid prescribing guidelines.
Methods: The Targeting Effective Analgesia in Clinics for HIV (TEACH) study was a 2-arm cluster randomized trial to assess whether a collaborative care intervention increased guideline-concordant care for COT compared to standard practice among PLWH. From 2015-2016 we recruited HIV care providers who prescribed COT and their patients from two safety-net hospital-based HIV clinics. We randomized 41 providers, in a 1:1 ratio, to receive either the TEACH intervention (an IT-enabled nurse care manager; education and academic detailing; and access to addiction specialists) or the control condition (educational brochure). We assessed: a) ≥2 urine drug tests (UDTs) (primary); b) any early COT refills (primary); c) having an opioid treatment agreement (OTA); d) virologic suppression (VS); and e) provider's routine use of prescription monitoring programs (PMP). An intention-to-treat analysis was conducted using generalized estimating equations (GEE) logistic regression models.
Results: The 41 providers and their 187 COT patients had the following baseline characteristics: providers - 34% male; age 46 years; 63% white; 78% MDs; 12% buprenorphine waivered; patients - 72% male; age 54 years; 28% white; 91% with undetectable HIV viral load; 15% with history of injection drug use. COT prescribers (n=21 with 87 patients) were randomized to the intervention arm. At 12-month follow up, the intervention arm had higher odds of ≥2 UDTs (70% vs. 18%, adjusted odds ratio [AOR]: 15.46, 95% confidence interval [CI]: 7.29-32.79; p<0.0001) and OTAs (75% vs. 11%, AOR: 128.21, 95% CI: 22.85-719.30, p<0.0001). We did not detect a difference in early refills (21% vs. 29%, AOR: 0.57, 95% CI: 0.26-1.24, p=0.15), routine use of PMP (55% vs. 25%, AOR: 3.65, 95% CI: 0.94-14.19, p=0.06), or HIV VS (88% vs. 84%, AOR: 1.14, 95% CI: 0.63-2.04, p=0.67) between the two arms.
Conclusion: Participants in the TEACH intervention had higher odds of following 2 important guidelines for COT: ≥2 urine drug tests and treatment agreements. We did not detect significant differences in early refills, use of prescription monitoring programs, or viral suppression. The TEACH intervention is a promising strategy to improve adherence to guidelines for COT and does not appear to compromise viral suppression.

Table 1. Effect of TEACH Intervention Compared to Standard Practice on Study Outcomes at 12-months

Study Outcomes	Intervention	Control	AOR (95% CI)	p-value
≥2 UDTs over 12 months*	70%	18%	15.46 (7.29, 32.79)	<.0001
≥1 early refills over 12 months*	21%	29%	0.57 (0.26, 1.24)	0.15
Opioid treatment agreement over 12 months	75%	11%	128.21 (22.85, 719.30)	<.0001
Provider routinely consulted PMP over 12 months	55%	25%	3.65 (0.94, 14.19)	0.06
Viral Suppression (<200 copies/mL)	88%	84%	1.14 (0.63, 2.04)	0.67

* primary study outcomes

890 HIV CARE OUTCOMES AMONG SUBSTANCE USERS IN PUERTO RICO FOLLOWING HURRICANE MARIA

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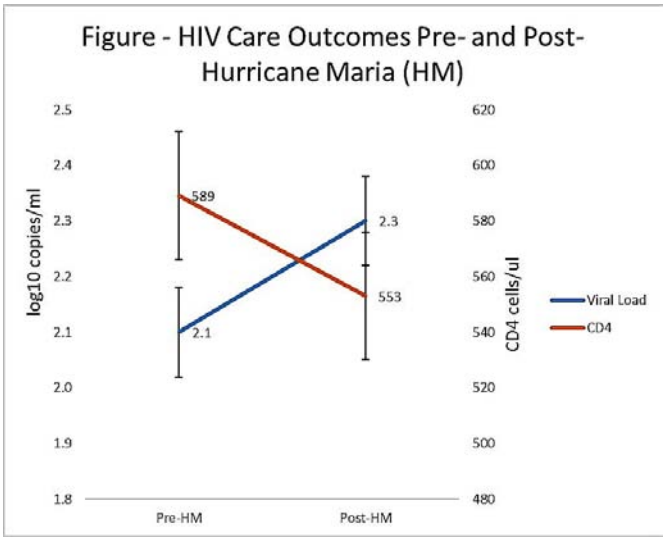
Background: In 2017, Hurricane Maria (HM) caused devastation to Puerto Rico and its residents. Based on an ongoing cohort study in San Juan, Puerto Rico (Proyecto PACTo), we examined the effects of HM on HIV care outcomes among people living with HIV (PLWH) and with a history of substance use.
Methods: We measured differences in HIV care outcomes - viral load, viral suppression, and CD4 counts - before and after HM using assessments conducted in 6-month intervals. Data are based on blood collected to measure CD4 and viral load and a social and behavioral assessment completed through a computer-assisted personal interview. Factors associated with HIV care outcomes were evaluated using generalized estimating equations to take into account repeated measures per individual.
Results: 219 participants completed a follow-up visit within the 9-month period before and after HM. The mean post-HM viral load was 2.3 log10 copies/ml (se=0.09), significantly higher compared to pre-HM (2.1 log10 copies/ml, se=0.08). CD4 counts also were lower post-HM (mean=553 cells/ul, se=23.2) compared to pre-HM (mean=589 cells/ul, se=24.7) (Figure). Viral suppression (<200 copies/ml) was 72% pre-HM compared to 65% post-HM. After controlling for age, gender, income, health insurance, incarceration history, homelessness, history of living in the mainland United States, severe drug use, and depression at baseline, there was a 9% reduction for viral suppression between pre- and post-HM time points (aIRR=0.91, 95% CI 0.84-0.98). Also, age (aIRR=1.01, 95% CI 1.00-1.02) and homelessness (aIRR=0.78, 95% CI 0.62-0.98) were independent predictors of viral suppression.
Conclusion: PLWH and with a history of substance use in San Juan, Puerto Rico demonstrated an increase in viral load and decrease in both viral suppression and CD4 counts following HM, critical factors in determining disease outcome and potential community transmission. Further post-HM research will focus on the barriers and facilitators related to accessing healthcare and resources and the effects of post-traumatic stress disorder, which may explain long-term HIV care outcomes.



891 AN OUTBREAK OF HIV IN HOMELESS HETEROSEXUALS WHO INJECT DRUGS IN NORTH SEATTLE, WA

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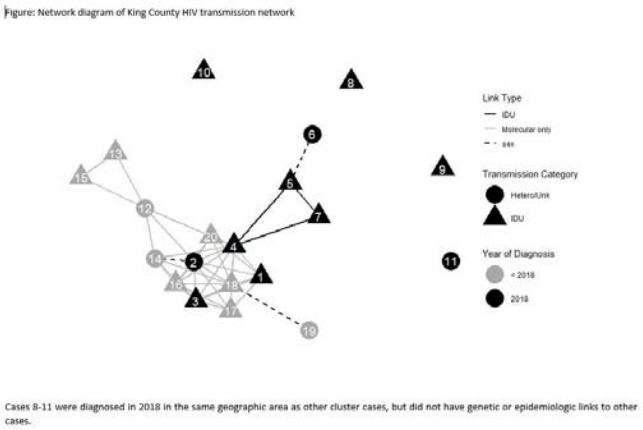
Background: King County, WA, was the first urban area in the US to achieve the WHO 90-90-90 objective and new HIV diagnoses in the county have declined almost 50% in the last decade. HIV infection among non-men who have sex with men (non-MSM) persons who inject drugs (PWID) has traditionally been rare, with an average of 9 diagnoses annually 2008-2017 and 7 diagnoses in 2017. However, the number of heroin overdoses in King County increased 264% 2007-2018, the number of persons living homeless (PLH) increased 129% 2010-2017, and >60% of PWID are PLH. The area has a growing, highly vulnerable PWID population.
Methods: We analyzed public health HIV surveillance, partner services (PS), and molecular HIV surveillance (MHS) data to characterize a cluster of HIV diagnoses among non-MSM PWID and their sex and injection partners. Cluster cases met ≥1 of the following criteria: 1) non-MSM diagnosed with HIV in 2018 with PS data indicating sex or injection drug equipment sharing with a cluster case; 2) HIV diagnosis in 2018 among non-MSM PLH in the outbreak area; 3) MHS showing HIV infection with a strain related to cases meeting criteria 1 or 2 (HIV-TRACE distance ≥1.5%). We excluded cases if MHS indicated infection unrelated to the cluster.
Results: From 1/1/18 to 9/15/18, 19 non-MSM PWID were diagnosed with HIV, a 171% increase compared to the 12 months of 2017. Eleven of the 19 cases, as well as 9 cases diagnosed 2008-2017, were part of a cluster. All 11 cluster cases diagnosed in 2018 were PLH in an area of approximately 3 square miles; 8 were cis-women, 2 of whom exchanged sex, and 8 were PWID, 7 of whom injected heroin. Public Health-Seattle & King County (PHSKC) initially identified the cluster through PS, with additional cases added using MHS data that were not available in real time. Ten cluster cases were diagnosed in the 20 months before disease investigators first identified links between cases. PHSKC has responded to the cluster by alerting medical and social service providers and the public; expanding outreach testing and condom distribution; promoting testing in emergency departments and jails; increasing syringe services; promoting PrEP in PWID; and working to build new clinical capacity in the area of the outbreak.
Conclusion: In the face of growing homelessness and heroin use, even areas with well-developed HIV care and prevention programs are vulnerable to outbreaks of HIV among the most disadvantaged persons. MHS procedures need to be improved to more quickly identify growing clusters.



892 ASSISTED PARTNER SERVICES AMONG PEOPLE WHO INJECT DRUGS IN NAIROBI, KENYA

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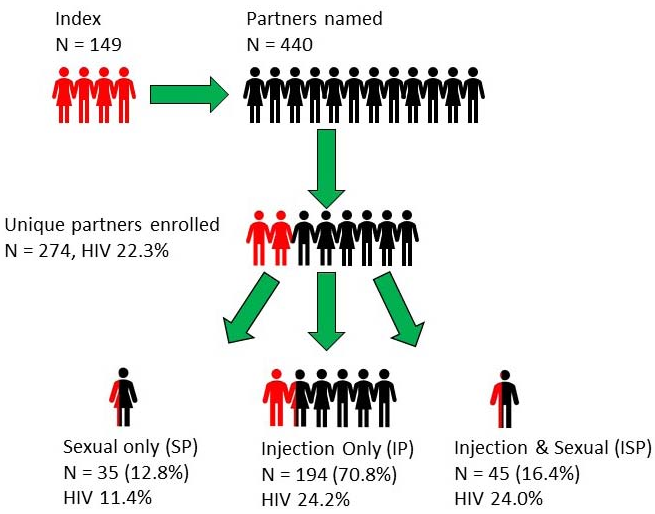
Background: Testing key populations (KPs) for HIV is essential to achieving the first of the UNAIDS 90-90-90 goals. Identifying and testing partners of HIV-infected individuals, or assisted partner services (aPS), is an efficient tool for case-finding. aPS has not been used among people who inject drugs (PWID), one of the highest risk KPs. We determined whether aPS could find, test, and link to care the injecting and sexual partners of HIV-infected PWID in Nairobi, Kenya.
Methods: Recruitment of index participants (indexes) occurs at 3 needle and syringe exchanges in Nairobi. Indexes provide contact information for injection and sexual partners in the past 3 years. Blinded to the index's identity, community-embedded peer educators (CEPEs) attempt to contact all named partners, first by phone, then community tracing. When partners are contacted, they are notified of their possible HIV exposure and are offered HIV counseling and testing. Participants also complete questionnaires and are offered rapid hepatitis C (HCV) testing. To examine aPS effectiveness, we determined the number of indexes needed to be interviewed (NNTI) to find a 1) first-time tester; 2) new HIV case; 3) known HIV-positive person not on treatment.
Results: To date, 149 indexes have enrolled who have named 440 partners (Figure 1). Of named partners 332 (76%) have been traced and enrolled. Because partners could enroll multiple times if named by multiple indexes, the 332 enrolled partners represented 274 unique individuals, of whom 194 (71%) were injection partners (IPs), 35 (13%) sexual partners (SPs), and 45 (16%) injection and sexual partners (ISPs). Among partners 63 (22%) were HIV-infected, of whom 7 (11%) were unaware of their status and 8 (13%) were aware but not on ART. HIV prevalence was highest among IPs and ISPs (24%) and lower among SPs (11%). NNTI was 19 per first-time tester, 21 per new HIV case, and 10 per HIV-infected person not on ART. HCV Ab was found in 50 (33%) indexes and 57 (20%) partners. Confirmatory RNA tests are pending. Almost all partners required in-person tracing, as they could not be reached by phone. No adverse events have been reported related to aPS.
Conclusion: aPS using CEPEs is an effective tool for finding and testing high-risk partners of PWID. Nearly one quarter of partners reached were HIV-infected. Among these, one quarter did not know his/her status or was not on ART. We conclude that aPS is a novel testing strategy that may reduce HIV transmission and promote engagement in care among PWID.



893 SUICIDE RATES AMONG US ADULTS LIVING WITH HIV, 2000-2015

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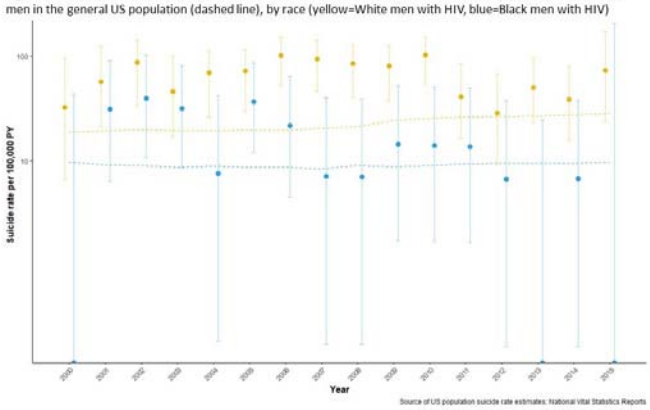
Background: It is unknown if the increasing suicide rate (particularly among White men) and the increased risk of suicide among those who use drugs in the US general population are mirrored among people with HIV (PWH). We estimated suicide rates in PWH in the US and Canada from 2000-2015.

Methods: Adults (aged 20-79) in the NA-ACCORD were followed from the later of enrollment into the cohort or 1/1/2000 to the first of death, loss to follow-up (2 years after last CD4 or HIV RNA), or 12/31/2015. Cause of death was ascertained by death certificate or electronic medical record notation. Suicide incidence rates (IR) and 95% confidence intervals (stratified by sex, Black/White race, history of injection drug use (IDU), and calendar year were calculated per 100,000 person years (pys). Adjusted incidence rate ratios (IRR) and 95% confidence intervals ([,]) were estimated using Poisson regression; Black/White race, IDU, diagnosed bipolar affective disorder, major depression, schizophrenia, HIV-associated dementia, efavirenz prescription, calendar year, and decade of age were in the final model.

Results: Among 81,123 adults contributing 547,278 pys (median follow-up of 5.6 years), 217 suicides were identified. Women were excluded from analyses due to limited outcomes (N=2 suicides, IR=4.17 [0.51,15.07]). Among men, 17% of White and 35% of Black men had a history of IDU. The suicide rate was 43.06 [37.30, 48.81]. This was higher in White vs. Black men from 2000-15 (Figure 1); overall there was a 4.4-fold greater suicide rate among White (66.55 [56.04, 77.06]) vs. Black (15.16 [9.73, 20.58]) men. Compared to Black non-IDUs, the suicide rate was greater among White IDU (IRR=9.87 [5.08, 19.17]), White non-IDU (IRR=5.52 [2.96, 10.29]), and Black IDU (IRR=2.21 [1.03, 4.72]) in the adjusted model. Under-ascertainment of suicide is possible (and may be differential by subgroups), which would underestimate suicide rates.

Conclusion: Suicide rates were much lower in women (vs. men) with HIV, corroborative of US general population findings. Among men with HIV, suicide rates were higher among White (vs Black) men. White men with a history of IDU had the highest rates of suicide, followed by White non-IDU, Black IDU, and Black non-IDU, suggesting the association between drug use and suicide in the general population may also be reflected in men with HIV. Men with HIV warrant targeted suicide prevention efforts, particularly White men with a history of IDU.

Figure: Suicide rates and 95% confidence intervals for adult men with HIV in the NA-ACCORD (circles) and rates for men in the general US population (dashed line), by race (yellow=White men with HIV, blue=Black men with HIV)



894 SUCCESSFUL cART NORMALIZES SURVIVAL FOR HIV-HTLV COINFECTED PATIENTS

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Federal University of Bahia, Salvador, Brazil

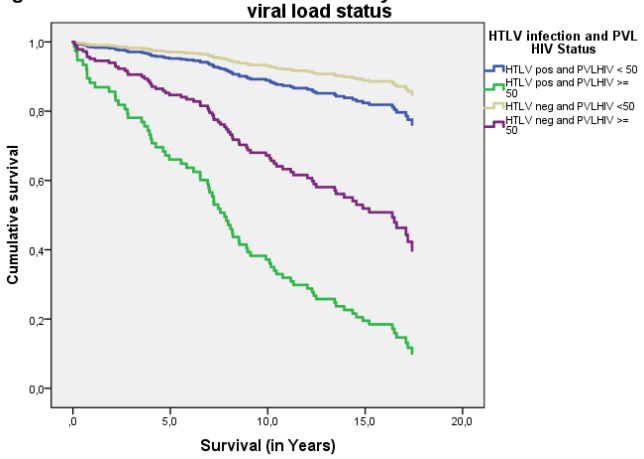
Background: coinfection by HTLV is associated with shorter survival for adults and children infected by HIV, but the reasons remain controversial. We aimed to evaluate the survival time and associated factors of co-infected and mono-infected patients treated with cART.

Methods: we reviewed medical records of 298 HIV-infected patients on cART, 149 (50%) of them co-infected by HTLV-1. Patients in each group were matched by age at HIV diagnosis and gender. Death rates, survival time, baseline and current CD4 count, last HIV-1 RNA plasma viral load (PVL) and causes of death were compared.

Results: Most patients were women (59.1%), mean age 39.0 ± 9.1 years. Survival time was 6,622 days for mono-infected, and 6,107 days for co-infected patients (p=<0.001). Survival persisted significantly different for those with PVL>50 (3,084 for co-infected, vs. 4,712 days for mono-infected subjects, p=0.02), or PVL>1,000 copies/ml (2,526, vs.3,329 days, for co-infected and mono-infected subjects, respectively, p=0.02). However, overall survival did not differ for patients with PVL<50 (mono-infected: 7,370 days; co-infected: 6,944 days, p=0.5) or <1,000 (7,218 vs. 6,929 days, for mono and co-infected patients, respectively, p=0.3) copies per ml (Figure 1). Baseline CD4 count for deceased patients was higher for co-infected (410±350 cells/ml) than for mono-infected (177±160 cells/ml, p=0.04) patients, but similar for survivors (417±299 vs. 396±336 cells/ml, p=0.7). Last CD4 count was similar for both groups, regardless of survival status. Causes of death were mainly (78%) AIDS-defining diseases and did not differ for groups.

Conclusion: In this large cohort, successful cART normalized survival time for HIV-HTLV co-infected subjects. The increased mortality for co-infected patients with uncontrolled HIV PVL, despite a higher baseline CD4 count, suggests HTLV co-infection boosts progression to AIDS in patients with active HIV replication.

Figure 1 - Survival of HIV infected cohort by HTLV infection and last HIV viral load status



895 RACIAL DISPARITIES IN BASELINE GENOTYPING IN THE ERA OF "ART FOR ALL"

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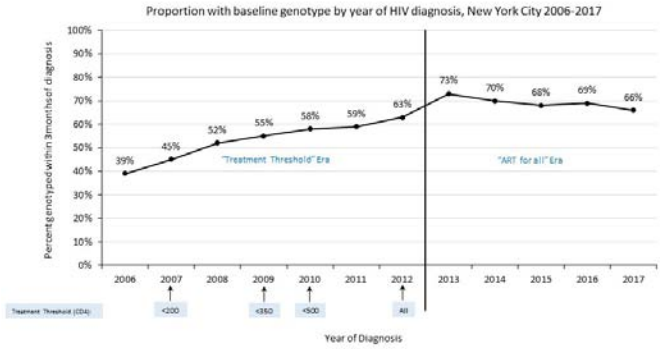
Background: Since 2007, federal guidelines for the care and treatment of persons with HIV have recommended genotyping at the initial care visit, both to establish a baseline and to guide antiretroviral therapy (ART). Previous studies indicated that patients were more likely to receive a baseline genotype if their CD4 at diagnosis reached the ART threshold in use at the time.

Methods: We used laboratory data routinely reported to HIV surveillance to measure compliance among New York City physicians in two time periods – the "treatment threshold" era (2006-2012) and the "ART for all" era (2013-2017). We examined differences in baseline genotyping by provider type, patient demographics, risk factor, and clinical characteristics. A baseline genotype was defined as a genotype performed within 3 months of initial HIV diagnosis.

Results: Baseline genotyping increased from 53% during the "treatment threshold" era to 63% during the "ART for all" era. The most important predictor of baseline genotyping between 2006 (39%) and 2012 (63%) was the CD4 count-genotyping was highest for people meeting the prevailing treatment threshold. In 2013, the year after guidelines recommended ART regardless of CD4, genotyping rose to 73%. After 2013, there was a steady decrease in percent genotyped overall, but relative increases in patients with CD4>500 and those receiving care at community-based organizations and free-standing clinics. Baseline genotyping in 2017, the last year for which data are complete, was 66%. Patients were more likely to receive a genotype if they were MSM, between the ages of 20-39 at diagnosis, white or Asian, acutely infected, CD4 <350, attended private providers or providers affiliated with hospitals and were diagnosed after 2012. Black race was independently associated with a 47.3% (95% CI 0.40, 0.69) lower likelihood of receiving a baseline genotype in the "treatment threshold" era, regardless of age, risk factor, neighborhood poverty level, clinical status, provider type, and year of diagnosis, and a non-significant 20.1% (95% CI 0.50, 1.26) lower likelihood of being genotyped in the era of "ART for all". Our analysis was not able to account for the temporal changes in cost, reimbursement, turnaround time, guidance on interpretation, or other issues that may have affected provider decision to test.

Conclusion: Five years into the era of "ART for all," substantial inequity in baseline genotyping remains. Strategies to increase testing of black people are needed to improve quality of care.



896 YIELD OF HIV TESTING AND RE-ENGAGEMENT OF KEY POPULATIONS IN UGANDA AND KENYA

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Background: The yield of key population outreach for HIV diagnosis and care re-engagement in settings that have surpassed the UNAIDS target of 90% of HIV+ persons aware of their status in sub-Saharan Africa is unknown.

Methods: The SEARCH trial (NCT01864683) achieved >95% adult resident HIV testing coverage by 3 years with a hybrid approach (study census, multi-disease campaigns and home testing of campaign non-attendees) in 32 rural communities in Kenya and Uganda. After 3 years, 16 communities implemented 2-week mobile outreach, that included multi-disease and HIV testing services, for resident key populations considered high-risk for HIV (Table), and in-migrants (newly living in community since year 3 of trial). Known HIV+ persons were not retested, but referred to clinic if out of care by self-report or clinic database. We assessed HIV testing coverage and compared yield of new diagnoses including seroconversions (documented prior HIV-) and yield of known HIV+ out-of-care residents, across key populations.

Results: HIV testing coverage of HIV-/unknown resident key populations was 16% (2,091/13,283) in Kenya, 14% (903/6,424) in West (W) Uganda, and 14% (1,830/13,555) in East (E) Uganda after the 2-week outreach. Yield of new HIV diagnoses among residents varied from 0% to 3.1% across key populations, and was highest among barmaids in Uganda (Table). Of 37 residents with newly-identified HIV, 29 (78%) were seroconversions. In-migrant testing yield was 19% (21/114) in Kenya, 17% (32/194) in W-Uganda, and 5% (13/287) in E-Uganda. Of 66 newly-identified HIV+ in-migrants, 40 (61%) reported prior HIV-/unknown status. The number needed to test to identify one newly-diagnosed HIV+ adult was 123 in Kenya, 69 in W-Uganda and 151 in E-Uganda among residents, compared to 12, 11 and 26 among in-migrants per region, respectively. Of HIV+ adult residents seen at mobile outreach, 28% (193/682) were out of care in Kenya, 21% (14/66) in W-Uganda, and 19% (10/53) in E-Uganda. Of all known HIV+, out-of-care residents within key population groups, 7% in Kenya and 3% in Uganda attended 2-week mobile outreach.

Conclusion: Mobile, multi-disease outreach to key populations in SEARCH communities in rural Uganda and Kenya where HIV testing coverage was already high continued to yield new HIV+ diagnoses among residents, most of whom were seroconversions, and in-migrants. Outreach facilitated re-engagement of known HIV+ persons who leave care but remain willing to access mobile services.

	Western Kenya (Baseline HIV Prevalence: 20%)			Uganda (Baseline HIV Prevalence: SW: 7% and E: 4%)		
Key Population	Key Pop Mobile Outreach Coverage (HIV Tested / HIV-Population by Study Census [%])	Yield new HIV+ diagnoses among tested	Yield of known HIV+ out-of-care residents (Known HIV+ out of care at mobile outreach / Total Known HIV+ out of care in Community)	Key Pop Mobile Outreach Coverage (HIV Tested / HIV-Population by Study Census [%])	Yield new HIV+ diagnoses among tested	Yield of known HIV+ out-of-care residents (Known HIV+ out of care at mobile outreach / Total Known HIV+ out of care in Community)
Transport Worker	95	0 / 95 (0%)	0 / 17	829	7 / 829 (0.8%)	7 / 34 (21%)
Bar worker	9	0 / 9 (0%)	0 / 24	226	7 / 226 (3.1%)	4 / 47 (9%)
Fishing	520	4 / 520 (0.8%)	27 / 285	138	0 / 138 (0%)	0 / 5 (0%)
Discordant couple	136	3 / 136 (2.2%)	24 / 305	68	0 / 68 (0%)	8 / 241 (3%)
Adolesc girls/young women	162	0 / 162 (0%)	3 / 258	57*	1 / 57 (1.8%)	0 / 57 (0%)
EtOH/Drug user	49	0 / 49 (0%)	1 / 62	62	0 / 62 (0%)	3 / 269 (1%)
Street Vendor	137	2 / 137 (1.5%)	18 / 347	60	0 / 60 (0%)	0 / 87 (0%)
Widow	197	0 / 197 (0%)	26 / 294	-	-	-
Widow Inheritor	47	1 / 47 (2.1%)	(3 / N/A)	-	-	-
Other	739	7 / 739 (1.0%)	N/A	1293	5 / 1293 (0.4%)	(2 / N/A)
Total (Residents)	2,091 / 13,283 (16%)	17 / 2,091 (0.8%)	99 / 1,392 (7%)	2,733 / 19,979 (14%)	20 / 2,733 (0.7%)	22 / 740 (3%)

* Adolescent girl/Young women testing in Uganda only performed in the East in Ugandа.

897 ED VISITS AND HOSPITALIZATIONS AS OPPORTUNITIES TO IMPROVE HIV CARE ENGAGEMENT

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Background: Many health departments around the United States use HIV surveillance data to identify poorly engaged persons living with HIV (PLWH) and direct HIV care relinkage activities. The effectiveness of these Data to Care (D2C) programs has been hindered by difficulty contacting individuals who appear to be out of HIV care. Identifying opportunities, such as emergency department (ED) and inpatient (IP) admissions, to interact with poorly engaged PLWH is crucial to improving their success. In this study, we describe the characteristics, ED/IP utilization, and viral load status of PLWH seen at a UW Medicine ED/IP.
Methods: We used UW Medicine's clinical data repository and Public Health Seattle and King County's HIV surveillance database to identify all PLWH residing in King County who had an ED/IP admission at a UW Medicine facility – one of the largest ED providers in King County– in 2017. Using HIV laboratory reporting data, we determined the HIV viral load status of patients at the beginning and end of 2017 and immediately prior to each ED/IP admissions. We compared the demographic characteristics and viral load status at the beginning and end of 2017 of patients who had at least one ED/IP admission while unsuppressed (i.e., viral load > 200) to those who had no ED/IP admissions while unsuppressed (i.e., viral load < 200).
Results: In 2017, 831 PLWH had 1841 ED/IP admissions at a UW Medicine facility. Of these, 189 (23%) had at least one ED/IP admission while virally unsuppressed. Of the 189 unsuppressed patients, 134 (71%) were unsuppressed at the beginning of 2017, and 114 (60%) were unsuppressed at the end of 2017. Of the 642 patients who were suppressed during their ED/IP admissions, 47 (7%) were unsuppressed at the beginning of 2017, and 23 (4%) were unsuppressed at the end of 2017. Unsuppressed patients were younger (mean age: 42 vs 47 years) and more likely to report injection drug use compared to suppressed patients (40% vs 28%; p<0.01). Unsuppressed patients were more likely to have 3 or more ED/IP admissions compared to suppressed patients (39% vs 18%; p<0.01).
Conclusion: In 2017, about 25% of PLWH who had an ED/IP admission had at least one visit while unsuppressed and 60% of unsuppressed patients remained unsuppressed at the end of 2017. ED/IP admissions provide an opportunity to interact with PLWH who experience sustained poor engagement in care. Interventions that leverage partnerships with emergency departments are needed to improve the HIV care outcomes of this population.

898 POVERTY STIGMA AND HIV TREATMENT OUTCOMES AMONG WOMEN LIVING WITH HIV IN THE US

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Background: Individuals with low income experience worse HIV treatment outcomes. Although such disparities may be due to financial barriers in accessing HIV care, stigma related to poverty may be another mechanism linking socioeconomic disadvantage to poor HIV-related health outcomes. We examined whether experienced poverty stigma was associated with worse HIV care and treatment outcomes and whether depression mediates these relationships.
Methods: We analyzed cross-sectional data from 436 women living with HIV enrolled in the Women's Adherence and Visit Engagement (WAVE) sub-study of the Women's Interagency HIV Study (WIHS), conducted in San Francisco, CA, Atlanta, GA, Birmingham, AL and Jackson, MS. The exposure was experienced poverty stigma, measured using 4 items from the Perceived Stigma of Poverty Scale. Outcomes were viral suppression, CD4 ≥ 350 cells/mm3, self-reported ≥ 95% adherence, and no missed HIV care visits in the past 6 months. The mediator was depression, measured by the 20-item Center for Epidemiological Studies Depression Scale. Multivariable logistic regression models were adjusted for income, age, race/ethnicity, education, non-prescribed drug use, and months taking ART. We tested whether the association of poverty stigma with the outcomes was mediated by depression scores, using indirect effects analysis with bootstrapping.
Results: Each unit increase in mean experienced poverty stigma score was associated with lower adjusted odds (aOR) of viral suppression (aOR:0.79, 95% CI:0.64, 0.98), having a CD4 count ≥ 350 cells/mm3 (aOR:0.69, 95% CI: 0.53, 0.89), ≥ 95% ART adherence (aOR 0.72, 95% CI: 0.55, 0.93), and no missed HIV care visits (aOR:0.71, 95% CI:0.53, 0.95). Depression significantly mediated the negative relationship between experienced poverty stigma and having a CD4 count ≥ 350 cells/mm3 (indirect effect: -0.09, 95% CI: -0.16, -0.04; direct effect: -0.27, 95% CI: -0.31, 0.05), as well as experienced poverty stigma and ≥ 95% ART adherence (indirect effect: -0.11, 95% CI: -0.18, -0.04; direct effect: -0.17, 95% CI: -0.26, 0.04).
Conclusion: Experienced poverty stigma was associated with worse HIV health outcomes, even after adjusting for income, and depression was a significant pathway for some of these relationships. Longitudinal research should assess these relationships over time. Findings support interventions and policies that seek to both reduce poverty stigma and address depression among people living with HIV.

Table 1. The adjusted associations between experienced poverty stigma and HIV care and treatment outcomes

Outcomes	Adjusted models [a]	Adjusted models + depression [b]
Viral suppression	0.79 (0.64, 0.98)*	0.82 (0.65, 1.03)
CD4 cell ≥ 350 cells/mm^3	0.69 (0.53, 0.89)**	0.77 (0.58, 1.02)
95% ART adherence	0.72 (0.55, 0.93)*	0.84 (0.64, 1.11)
Attending all HIV care visits in past 6 months	0.71 (0.53, 0.95)*	0.79 (0.57, 1.08)

*p<0.05; **p<0.01; ***p<0.001
[a]Adjusted for age, education, income, race/ethnicity, illicit drug use since last visit, and months on ART
[b]Adjusted for age, education, income, race/ethnicity, illicit drug use since last visit, months on ART, and depression score

899 RISK FACTORS FOR INCREASED HOSPITAL LENGTH OF STAY AMONG PWH, 2014-2015

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Background: Length of stay (LOS) is an important indicator of hospital efficiency and severity of illness but can vary by geographic region. The objective of this study was to evaluate inpatient LOS among PWH by diagnostic category and to identify factors associated with increased LOS.
Methods: Hospitalization data from 2014-2015 was obtained on all adults receiving longitudinal HIV care at 14 geographically diverse sites in the HIV Research Network. Modified clinical classification software from the AHRQ assigned primary ICD-9 codes into mutually exclusive diagnostic categories. Patient-specific mean LOS was used to calculate mean and median LOS per diagnostic category. Multivariate negative binomial regression analysis was used to evaluate factors associated with LOS.
Results: Of 20,608 patients followed, 3196 patients were hospitalized over 4704 person-years of active outpatient care. Study subjects had a median age of 50 (IQR 43 – 58), were predominately male (67.6%) and black (50.9%), had CD4 > 200 (72.8%), and were HIV-virally suppressed (65.8%). Health care coverage was Medicaid (46%), Medicare (11.9%), private insurance (9.4%), and uninsured (12.5%). Median LOS was 5 days (IQR 3-8); mean LOS was 6.8 days (SD 9.3). Mean LOS was longest for AIDS-defining illness (ADI) (9.3 days), non-AIDS defining infections (7.4 days), and pulmonary (7.3 days). In multivariate analysis, mean LOS for ADI was significantly longer than non-ADI (aIRR vs. non-ADI, 1.16 [1.02,

1.32]) (Table). Compared to CD4 > 350, CD4 51-200 (aIRR 1.13 [1.03, 1.23]) and CD4 ≤ 50 (aIRR 1.37 [1.22, 1.54]) were associated with increased LOS. Health care coverage with Medicaid and Medicare were each associated with increased LOS. Age ≥ 60 (aIRR vs. age 18-29, 1.17 [1.02, 1.34]) and Southern region (aIRR vs. Eastern region, 1.10 [1.01 1.20]) were associated with increased LOS, while Western region had lower LOS (0.87 [0.80,0.95]). Sex, race, and HIV risk were not associated with LOS.

Conclusion: Higher inpatient utilization in patients with ADI and low CD4 highlights the potential importance of early ART initiation to reduce LOS. The association of public health care coverage and geographic region suggests structural factors (poverty, inefficiencies in health care delivery, regulatory policies, etc.) that may be difficult to modify. Older age was generally associated with greater health care utilization, independent of diagnosis. Attention to preventive efforts to decrease the need for hospitalization is particularly important.

	aIRR (95% CI)
Diagnostic Category	
Non-AIDS related Infections	1.00 (Ref.)
AIDS-defining Illness	1.16 (1.02,1.32)
Oncology	0.97 (0.85,1.11)
Endocrine	0.86 (0.77,0.96)
Hematology	0.84 (0.73,0.97)
Psychiatry	0.92 (0.82,1.03)
Neurology	0.96 (0.78,1.17)
Cardiovascular	0.87 (0.77,0.99)
Pulmonary	0.98 (0.84,1.15)
Gastrointestinal	0.79 (0.71,0.87)
Renal	0.83 (0.73,0.95)
OB/Perinatal/Congenital	0.86 (0.67,1.10)
Dermatology	1.44 (0.91,2.29)
Orthopedics	0.76 (0.64,0.90)
Other/Missing	0.86 (0.78,0.95)
Age Category (years)	
18-29	1.00 (Ref.)
30-39	0.97 (0.85,1.11)
40-49	1.02 (0.90,1.15)
50-59	1.07 (0.94,1.20)
≥60	1.17 (1.02,1.34)
Health Care Coverage	
Private	1.00 (Ref.)
Medicaid	1.24 (1.11,1.39)
Medicare	1.16 (1.02,1.34)
Ryan White/Uninsured	1.05 (0.91,1.22)
Region	
Eastern	1.00 (Ref.)
Southern	1.10 (1.01,1.20)
Western	0.87 (0.80,0.95)

*Adjusted for sex, race, HIV risk, CD4 count, HIV-1 RNA

900 FIB-4 SCORE PREDICTS OVERALL MORTALITY IN HIV MONOINFECTED: A PROSPECTIVE STUDY

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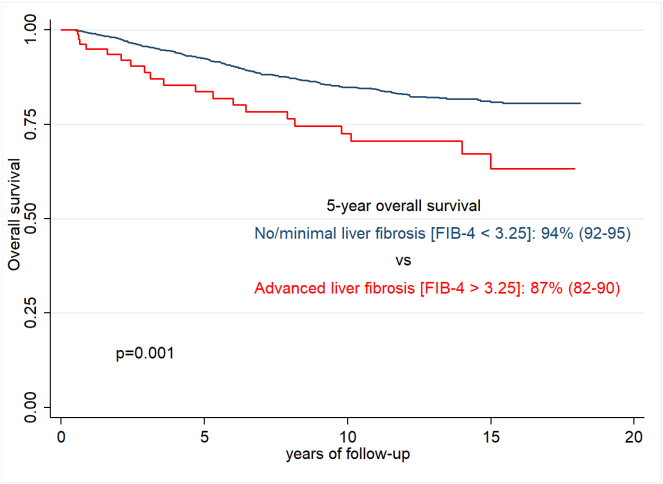
Background: The prognostic value of FIB-4 score, a serological biomarker for detection of advanced fibrosis, has been validated in HIV patients co-infected by viral hepatitis. We aimed to evaluate the prognostic value of FIB-4 score to predict overall mortality in HIV mono-infected patients.

Methods: A total of 3,989 HIV patients were prospectively followed from January 2000 to December 2016 at HIV-INI/FIOCRUZ cohort. The exclusion criteria were viral hepatitis co-infection (n=362); missing information of death (n=22); mortality up to 6 months after baseline (n=80) and absence of follow-up (n=21). Deaths were validated by two investigators. FIB-4 was calculated using parameters of the baseline visit by the following formula: FIB-4=(age [years]*AST [U/L])/(platelet [109/L] * sqr (ALT [U/L]). Published cut-off values were used to define low (FIB-4 < 1.45), intermediate (FIB-4=1.45-3.25), and high (FIB-4 > 3.25) probability of advanced fibrosis. Mortality rates were calculated, Kaplan-Meier curves were plotted and multivariate Cox models adjusted for age, gender and classic HIV factors were performed.

Results: 3,504 HIV mono-infected patients [66% male, age=39 (IQR 32-47) years, ALT=32 (23-45) U/L, 73% under combined antiretroviral therapy (c-ART), CD4=469 (249-703) cells/mm3 and 50% with detectable HIV viral load] were included. A total of 274 patients (7.8%) died during a mean follow-up of 5.3 (range, 0.2-18.1) years. The mortality rate (95%CI) was 14.7 (95%CI 13.1-16.5) per 1000 person-year. Patients with high FIB-4 score (> 3.25) had a significantly lower 5-year overall survival (95%CI) than those with intermediate/low score [87% (82-90) vs 94% (92-95), p=0.001] (Figure). In a multivariate Cox model the following factors [Hazard Ratio (95%CI)] were independently associated with mortality : age [per year; HR=1.02 (1.01-1.03), p=0.003], CD4 count [< 200 cells/mm3; HR=2.13 (1.66 2.75), p<0.001], detectable HIV viral load [> 40 copies/mm3; HR=1.66 (1.15-2.42), p=0.008], intermediate FIB-4 score [FIB-4=1.45-3.25; HR=1.36 (1.01-1.84), p=0.048] and high FIB-4 score [FIB-4>3.25; HR=1.72 (1.07-2.79), p=0.027].

Conclusion: Simple serological biomarker, such as FIB-4, can be used to predict overall mortality in HIV mono-infected patients. Intermediate to high FIB-4 score (>1.45) was associated with higher risk of mortality adjusted for age, sex and classic HIV risk factors.



901 LONG-TERM EFFECTIVENESS OF HIV TREATMENT IN ZAMBIA

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Background: Differences in mortality between HIV-infected patients on antiretroviral treatment (ART) and HIV-uninfected persons indicate the effectiveness of public health HIV treatment programs. We combine data from routine clinical care, intensive tracing of a sample of those lost to follow up from care, as well as external data from the Global Burden of Disease Project (GBD) to assess excess mortality up to 10 years after ART initiation in Zambia.

Methods: Between 1 August 2013 and 31 July 2015 we followed patients on ART – including both new initiators as well as those already on treatment in 64 clinics in Zambia supported by the CIDRZ program. Sociodemographic, clinical and visit information were obtained from the electronic medical record system. A probability sample of lost patients were intensively traced to ascertain vital status and inverse probability weights were used to incorporate these outcomes into estimates of mortality. We compared age-standardized mortality in HIV patients to age-standardized mortality among HIV-uninfected Zambians in 2015 provided by GBD estimates.

Results: Among 165,464 persons on ART followed for 217,849 person-years (pyrs), we observed an age-standardized death rate of 2.8 deaths/100 pyrs among all persons after ART initiation and a age-standardized mortality ratio 3.37 fold higher than HIV uninfected persons (95% CI:3.35-3.66). After excluding the first year of therapy, HIV patients experienced 2.28 deaths/100 pyrs, still 2.78 fold higher than the 0.82 deaths/100 pyrs in HIV-uninfected individuals with same age distribution (95%CI: 2.68-2.90). After one year of treatment, the

age-standardized mortality ratio was 2.74 (95%CI: 2.54-2.93) and among men and 3.15 (95%CI: 2.89-3.46) among women. During years 2-3, 4-5, 6-7 and 8-9 after ART start, age-standardized mortality ratio was 2.20 (95%CI: 2.02-2.39), 1.90 (95%CI: 1.72-2.10), 2.66 (95%CI: 2.42-2.92), and 4.52 (95%CI: 4.12-4.95).
Conclusion: Even after starting treatment, HIV-infected persons remain at elevated risk of death compared to a HIV-uninfected population of the same age in Zambia. Even though HIV infected men experience a higher rate of death than HIV infected women after starting ART, treated HIV women experience a greater risk of death compared to age-standardized uninfected Zambian women. Enhanced engagement and widespread use of TB prophylaxis are needed for HIV infected persons to reach mortality rates of HIV uninfected persons.

902 PREDICTORS OF LOSS OF VIRAL LOAD SUPPRESSION AMONG MSM IN ATLANTA

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Background: Inequalities in the HIV care continuum between Black and White MSM living with HIV, including maintenance of viral suppression with effective ART, contribute to disparities in morbidity, mortality, and HIV transmission rates between these groups. We conducted an interim analysis to assess predictors of incident loss of VL suppression among MSM in Atlanta, GA to gain a better understanding of individual factors that contribute to maintenance and loss of viral suppression and to inform effective interventions to reduce these disparities.
Methods: The EngageMENt study is an ongoing longitudinal cohort of HIV positive Black (n=207) and White (n=193) MSM in Atlanta, GA designed to examine racial disparities in the HIV care continuum. VL measurements were obtained at 0 and 12 months. Additional VL measures were available by self-report at 3 and 6 months. Among men who were virally suppressed at baseline, we compared the rate of loss of viral suppression (VL>40 copies/mL) between Black and White MSM. Potential predictors of incident loss of VL were measured at baseline and at each follow-up visit. Unadjusted and adjusted Cox proportional hazards models were used to assess predictors of incident loss of VL suppression.
Results: The rate of loss of viral suppression was 20.2/100 person-years (95%CI: 13.2, 29.6) among Black MSM and 11.9/100 PY (95%CI: 7.0, 18.9) among White MSM [unadjusted hazard ratio (HR) = 1.7, 95%CI: 0.9, 3.2]. Anxiety (HR = 2.3, 95%CI: 1.2, 4.3) and ARV non-adherence (HR = 2.4, 95%CI: 1.2, 4.9) were associated with incident loss of viral suppression in unadjusted models. Anxiety (HR = 2.0, 95%CI: 0.9, 4.5), ARV non-adherence (HR = 1.7, 95%CI: 0.8, 3.6), lack of health insurance (HR = 1.4, 95%CI: 0.7, 3.3), and not being in care (HR = 3.3, 95%CI: 0.9, 10.0) were associated with higher hazard of loss of viral suppression, though none was statistically significant in the adjusted model.
Conclusion: Approximately 1 in 5 Black MSM and 1 in 10 White MSM experienced incident loss of viral suppression per year in our cohort. Individual-level factors such as mental health issues and insurance status may be contributing to incident loss of viral suppression and need further exploration. Results of this interim analysis might change in terms of magnitude or statistical significance. This study will assist in the design of tailored interventions for Black and White MSM to prevent loss of and minimize differences in maintenance of HIV viral suppression.

903 IMPACT OF HIV TEST-AND-TREAT INITIATIVE IN MIAMI-DADE COUNTY, FLORIDA

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Background: Rapid access to antiretroviral therapy (ART) immediately following HIV testing is upheld as a prevention tool to reduce HIV transmission and improve outcomes along the HIV care continuum. In 2016, the Miami-Dade County Health Department launched a test and treat (T&T) initiative to offer same-day or next-day access to ART following initial HIV diagnosis. This study aims to evaluate HIV care outcomes, including viral load (VL) suppression (<200 copies/mL) and retention in HIV care (two or more HIV-related labs, medical visits or prescriptions at least three months apart), for persons whose HIV was diagnosed in Miami-Dade County in 2017.
Methods: Clinical and epidemiological data reported to the Florida Department of Health HIV/AIDS surveillance system were matched to lab, medical visit and prescription records in Ryan White Program databases, county health department electronic health records and Medicaid claims. HIV care outcomes among antiretroviral-naïve patients whose initial HIV diagnosis was in Miami-Dade County in 2017 and who engaged in HIV care (n=950), including patients in T&T (n=80), were evaluated to determine the impact of T&T.
Results: T&T did not significantly impact the rate of HIV care initiation within 30 days of diagnosis (85.0% vs. 81.5%). However, patients in T&T were more likely to achieve VL suppression within six months of diagnosis (87.5% vs. 66.1%, p<0.01) and be retained in care (91.3% vs. 81.6%, p=0.03). For patients with a suppressed VL within six months of diagnosis, the average number of days from diagnosis to VL suppression was lower for T&T (71 vs. 87, p<0.01). When evaluating patients retained in care, higher rates of VL suppression (90.4% vs. 76.1%, p<0.01) and more rapid VL suppression (72 vs. 89 days, p<0.01) persisted for T&T. Furthermore, patients in T&T were more likely to receive HIV resistance testing within three months of diagnosis (80.0% vs. 57.8%, p<0.01).
Conclusion: While T&T did not significantly impact the timing of HIV care initiation, patients in T&T were more likely to achieve VL suppression within six months of diagnosis and progress to VL suppression more rapidly. Patients in T&T were also more likely to receive a baseline HIV resistance test, indicating a complete initial HIV care assessment. Rapid access to ART following HIV diagnosis can help reduce HIV-related mortality, improve health outcomes of those living with HIV and reduce HIV transmission through VL suppression.

904 ANTIRETROVIRAL REGIMEN DURABILITY IS NOT DRIVEN BY VIRAL FAILURE IN AN AFRICAN COHORT

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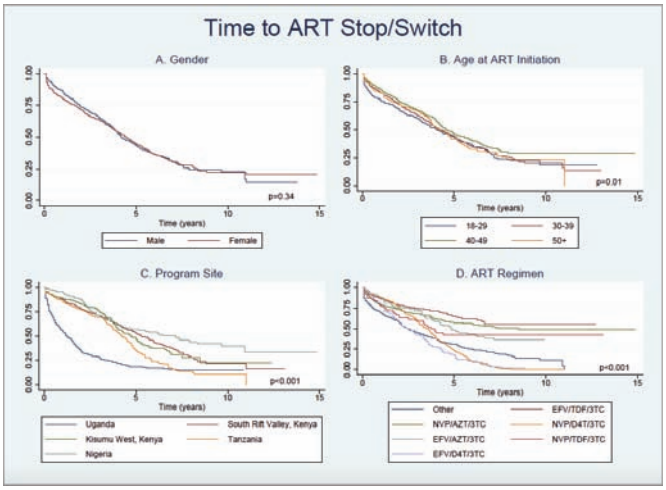
Background: Data on durability of first-line regimens in resource-limited settings are limited. We reviewed data from a large ongoing multinational African Cohort study (AFRICOS) to describe reasons and assess time to switching or stopping first-line antiretroviral therapy (ART).
Methods: AFRICOS prospectively enrolls HIV-infected and uninfected adults at 12 President's Emergency Plan for AIDS Relief (PEPFAR) supported facilities across 5 programs in Kenya (Kisumu and the South Rift Valley), Tanzania, Uganda, and Nigeria. ART regimen history is obtained at entry from available records and updated prospectively every 6 months. Reasons for switching or stopping ART are recorded by study physicians. For these analyses, we included HIV-infected participants who had documented ART start and stop dates, either prior to cohort entry or once enrolled. Time to switching or stopping a regimen was the primary endpoint used to assess durability. We generated Kaplan-Meier curves stratified by variables of interest and used the log-rank test to evaluate for significant differences.
Results: Between January 2013 and June 2018, we enrolled 2820 HIV-infected adults (58% female) with a median age of 36 (IQR 30-44) years. Of these, 2663 (94%) were ART experienced and have initial ART start dates available, including 1154 (43%) that began ART before the study initiation in 2013. The first regimen for the majority (1396; 52%) was efavirenz/lamivudine/tenofovir disoproxil fumarate. The median duration of this regimen was 2.25 (IQR 0.94-3.88) years. The initial regimen was switched or stopped for 1207 (45%) participants for reasons including change in country guidelines (344; 29%), toxicity (281; 23%), stock-out (262; 21%) and regimen failure (107; 9%). Regimen durability did not differ by gender (Figure, panel A), but was reduced in the youngest age group evaluated (18-29 years; panel B), varied substantially by site (panel C), and was reduced with initial regimens containing D4T (panel D).
Conclusion: In this large African cohort, the durability of first-line ART regimens was driven largely by factors other than viral failure. Specific regimens associated with high toxicity and abbreviated durability are no longer PEPFAR standard of care, but persistent programmatic factors that contribute to drug stock-outs and other barriers to ART maintenance require further investigation and intervention, especially as PEPFAR implements the program wide first-line transition to tenofovir/lamivudine/dolutegravir (TLD).



905 RESUPRESSION IN 1ST-LINE ART PATIENTS KENYA: DOES ART LONGEVITY AFFECT RESUPPRESSION?

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Background: As we enter the third decade of HIV/AIDS, more people living on lifelong ART (Antiretroviral therapy) are facing threats to HIV drug resistance (HIVDR) and subsequent treatment failure. World Health Organization 2016 recommended ART initiation for all HIV patients and use of viral load in monitoring treatment response. Kenya adopted these recommendations as part of the guidelines in the same year; which led to a rapid scale-up of ART uptake and viral load testing among HIV patients. Access to viral load testing presents opportunities for early detection of treatment failure and mitigating HIVDR, which is imperative in improving outcomes especially for treatment experienced patients who have been on ART longer. This study aims at determining if there are associations between the duration on ART and resuppression in HIV patients on first line regimen.

Methods: Data from 32 high volume facilities in western Kenya was extracted from the National EID/VL website, for patients with recorded high VL (>1000 Copies) in the period of October 2016 - 2017. Additional data was abstracted from patient records and high VL follow up register on the number of enhanced adherence counselling done, patients ART history, viral load, and patient's demographics. We used STATA version 13 for the statistical analysis, which included descriptive and bivariate analysis of years on ART and viral load suppression

Results: The sample had 1,636 patients who had been on ART for ≥ 6 years, 66% were females, 60% were adults aged between (20-49yrs), 21% were older patients aged (≥50 years), 18% were pediatrics and adolescents, Median age was 34 years (IQR: 24 - 43). Common ART regimen was TDF/3TC/EFV (39%) and AZT/3TC/NVP (28%). Ages between (15-19) years and (10-14) years had poorer resuppression rates 18.6% and 26% respectively. Overall resuppresion was 42% with males having 31% as compared to females who had 69%. There is an association between duration on ART and viral resuppression, and significance in the duration between (1-2) years (OR 0.70, 95% CI: 0.57 – 0.84), (4-6) years (OR 1.22, 95% CI: 1.05 – 1.43) and > 6 years (OR 1.35, 95% CI: 1.2 – 1.52)

Conclusion: Longevity on ART increases the risk of failing treatment, pediatrics, adolescents and men are at a higher risk of failing treatment. We need to optimize the use of newer highly efficacious regimens such as dolutegravir, and develop or customize the adherence counselling systems offered to patients who are maturing on ART to improve outcomes.

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. tabodds newvl newyrsonart

newyrso~t |      cases     controls       odds      [95% Conf. Interval]
----------+-------------------------------------------------------------
0 - 1 yrs |         58           44    1.31818        0.89084    1.95051
1 - 2 yrs |        180          257    0.70039        0.57891    0.84737
2 - 4 yrs |        365          325    1.12308        0.96714    1.30415
4 - 6 yrs |        359          292    1.22945        1.05350    1.43480
   6+ yrs |        666          492    1.35366        1.20478    1.52094
Missing~T |          5           11    0.45455        0.15793    1.30822
----------+-------------------------------------------------------------
Test of homogeneity (equal odds): chi2(5)  =    38.56
                                  Pr>chi2  =   0.0000

Score test for trend of odds:     chi2(1)  =     0.98
                                  Pr>chi2  =   0.3232
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906 SIX YEARS OF INTEGRASE INHIBITOR USE IN A METROPOLITAN CITY

B. Sharmila Mohanraj[1], Qingjiang Hou[2], Anne K. Monroe[3], Princy Kumar[1], Seble Kassaye[1], for the DC Cohort Executive Committee
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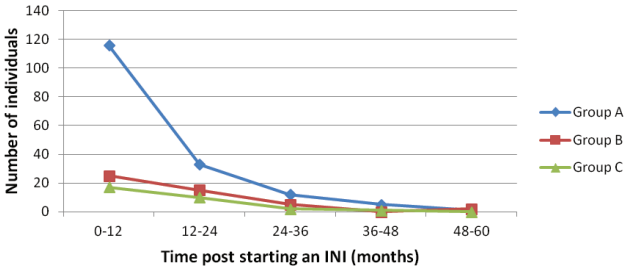
Background: Integrase strand-transfer inhibitors (INIs) have excellent efficacy, safety, tolerability and ease of dosing and are now part of first-line therapy in the U.S. We investigated trends in INI use in the District of Columbia (DC), an area with 1.9% HIV prevalence, to determine INI treatment effectiveness outside of clinical trials.

Methods: We conducted a retrospective analysis using data from the DC Cohort, a clinical cohort of HIV-infected persons receiving care at thirteen academic and community-based treatment sites in DC. We used descriptive statistics to determine the incidence of INI resistance and durability of viral suppression (two consecutive viral loads <200 c/mL). Drug resistance was defined using the International Antiviral Society-USA classification system. All analyses were conducted using SAS (v9.4.2).

Results: Among 6827 participants, 73% were male, 78% Black, and median age was 47 years (IQR:37.1-54.7). INI-based therapy increased from 23% (582/2490) in 2011 to 64% (3783/5898) in 2017, when 52% of total participants on INIs used dolutegravir. From 2011 to 2017 INI resistance was identified in only 1% (38/3783) of participants. Major mutations included Q148H/R (n=11), N155H (n=5), F121Y (n=4), Y143H/R (n=3), and G140S (n=3). Nine individuals had baseline INI resistance mutations. The mean time to suppression was 163 days among non-suppressed treatment-experienced persons starting their first INI regimen and 127 days for treatment-naive persons starting an INI regimen (p=0.003). Viral suppression at 6 months was similar between these groups, 70% among non-suppressed treatment-experienced individuals switching to INI regimen vs 76% among treatment naïve individuals initiating INI-based therapy (p=0.116). Rebound viremia after suppression was most frequent in the first year post INI initiation at 6.6% (158/2403) [Figure 1], and was least frequent for treatment-naïve persons.

Conclusion: The majority of participants in the DC Cohort are now on INI-based therapy. INI resistance remains rare. Long term viral suppression is evident among treatment naïve individuals starting INI-therapy, but remains a challenge for those with evidence of viremia on prior treatment regimens. Adherence likely plays a significant role, and increased attention to treatment outcomes and support measures should be in place during the first year of INI-based therapy as the risk for viremia appears to be greatest during this time period.

Figure 1: Annual frequency of individuals with loss of viral suppression (two consecutive VL >200 copies/mL). *Group A – Non-suppressed treatment-experienced persons starting their first INI regimen. Group B – Suppressed treatment-experienced persons starting their first INI regimen. Group C – Treatment-naive persons starting an INI regimen.*



907 ANTIRETROVIRAL ADHERENCE AND HIV-1 DRUG RESISTANCE IN THE US

Carmela Benson[1], Laura Mesana[2], **Keith J. Dunn**[1], Xiaotian Wu[3], Nicole Li[2], Johnny Lai[4], Eric Y. Wong[1], Kimberley Brown[1]
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Background: Adherence to antiretroviral therapy (ART) is critical to achieving viral suppression. However, social determinants of health (SDoH) can undermine patient adherence to ART, which can result in drug resistance that compromises future treatment options. We investigated SDoH factors and their impact on ART adherence, resistance and other HIV-related measures (prevalence, mortality, viral suppression).
Methods: Rates of HIV-related measures and SDoH (age, gender, education, poverty, employment) from publicly available databases during the period of 2014-2016 reported for each state in the US (N=50) were collected. ART adherence was measured by the average proportion of days covered (PDC) of all patients per state using the Symphony Health Solutions claims database (N=165K). Poor adherence was defined as PDC < 80%. Separately, isolates submitted to Monogram Biosciences for routine clinical testing from 2015-2017 (N=95,956) were used to determine rates of resistance, defined as proportion of isolates with a genotypic assessment for resistance to any commercially available NRTI, NNRTI, PI, and/or INI. Exploratory inferential analyses were performed to investigate associations between SDoH, HIV-related measures, adherence, and resistance, using correlation analysis.
Results: Rates of poor adherence ranged from 26% to 55% [median=44%] and resistance rates ranged from 20% to 54% [median=30%]. Adherence and resistance were both significantly correlated with gender and HIV prevalence ($p \leq 0.05$). States where poor adherence was more prevalent had a higher percentage of low education level, households living below poverty level, and unemployment rates; states with higher prevalence of poor adherence were also those with higher HIV prevalence and mortality rates and lower viral suppression rates (Table). States with higher resistance rates had higher HIV prevalence (Table).
Conclusion: Nationally, poor adherence and resistance rates exceeded 20%. State-level data showed gender, race, education level, poverty, and employment were associated with poor adherence to ART, and gender was associated with resistance to ART. Adherence was also correlated to HIV mortality and prevalence rates, whereas resistance was correlated to prevalence rates. Based on these results, patients could benefit from HIV treatment that is simple, convenient, and has a high genetic barrier to resistance.

Table 1. Associations between SDoH and poor adherence or resistance

Variable	Correlation	Education[1]	Poverty[2]	Employment[3]	Gender[4]	Race[5]	HIV mortality[6]	HIV prevalence[7]	HIV viral suppression[8]
Poor adherence[9]	*R*	0.42	0.29	0.39	–0.32	0.47	0.50	0.48	–0.23
	P-value	0.003	0.041	0.006	0.026	<0.001	<0.001	<0.001	0.175
Resistance[10]	*R*	–0.01	–0.13	0.02	–0.38	0.23	0.29	0.29	–0.04
	P-value	0.927	0.404	0.893	0.010	0.125	0.053	0.048	0.812

1 Education was defined as percentage of population 25 years and older without high school diploma per state, based on 2016 American Community Survey (ACS). 2 Poverty was defined as percentage of households living below the federal poverty level per state, based on 2016 ACS. 3 Employment was defined as unemployment rate for population 16 years and over per state, based on 2016 ACS. 4 Gender was defined as percentage of males per state, based on 2016 ACS. 5 Race was defined as percentage of non-Caucasian per state, based on 2016 ACS. 6 HIV mortality was defined as rate of HIV deaths per 100K population in 2015, reported by Centers for Disease Control and Prevention (CDC). 7 HIV prevalence was defined as rate of HIV prevalence per 100K population in 2015, reported by CDC. 8 HIV viral suppression was defined as percentage of HIV viral suppression among persons living with HIV infection in 2014, reported by CDC. 9 Poor adherence was defined as percentage of patients with PDC < 80%. 10 Resistance was defined as percentage of isolates submitted to Monogram Biosciences with a genotypic assessment for resistance to any commercially available NRTI, NNRTI, PI, and/or INI HIV drugs.

908 PROFILES OF HIV CARE DISRUPTIONS IN ZAMBIA: A LATENT CLASS ANALYSIS

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Background: Beyond observed traits (e.g., sex, age), there may also be unobserved (i.e., "latent") traits–each leading to distinct profiles of barriers to care–that influence retention in care. We used latent class analysis (LCA) of patient-reported reasons for HIV care disruptions in Zambia to identify these patient profiles and examine their associations with engagement in care.
Methods: We traced a probability sample of patients lost to follow-up (LTFU, >90 days late for last visit) as of July 31, 2015 from 64 clinics in Zambia. Among those found alive, we used a semi-structured instrument to identify patient-reported reasons for care disruptions. We performed LCA–incorporating sampling weights–to identify patient subgroups based on the number and types of patient-reported reasons for care disruptions. We characterized patient characteristics for each class and used logistic regression to assess the association between class membership and updated care status (disengaged vs. silent transfer to a new site).
Results: We successfully traced 642 patients LTFU (59.2% female; median age 35y [IQR 30-41]; median enrollment CD4 236 cells/µl [IQR 124-368]). We identified five classes of care disruptions (Table): 1) the "livelihood and mobility" class (29.9% of sample) reported work obligations and mobility/travel as reasons for their care disruptions; 2) the "mobility and family" class (27.5%) were likely to report mobility/travel, family obligations, and transport; 3) the "doubting need for HIV care" class (8.4%) reported care disruptions due to beliefs about their needs for HIV care; 4) the "clinic accessibility" class (25.1%) were likely to report transport-, clinic-, and disclosure-related care challenges; and 5) the "multidimensional barriers" class (9.2%) reported multiple reasons (mean 5.5) across categories. The "mobility and family" class was least likely to be disengaged (19.2% disengaged vs. 80.8% silent transfer), followed by the "livelihood and mobility" (44.1%), "clinic accessibility" (48.8%), and "multidimensional barriers" (57.2%) classes, with the "doubting need for HIV care" class most likely to be disengaged (100%).
Conclusion: There are distinct profiles for HIV care disruptions that are associated with whether a patient disengages or silently transfers their care. Strategies to target these unique patient profiles by concurrently addressing multiple barriers, rather than individual barriers, may be a more effective way to design and implement interventions to improve retention in care.

TABLE. PATIENT-REPORTED REASONS FOR HIV CARE DISRUPTIONS, PATIENT CHARACTERISTICS, AND CARE STATUS BY LATENT CLASS MEMBERSHIP

	"Livelihood and Mobility" (29.9%)	"Mobility and Family" (27.5%)	"Doubting need for HIV care" (8.4%)	"Clinic Accessibility" (25.1%)	"Multidimensional barriers to care" (9.2%)	Overall
Patient-Reported Reason, %						
Transport	18.1	28.8	5.2	23.3	18.6	21.3
Mobility/Travel	55.2	46.6	8.2	1.4	14.8	31.7
Work/School Obligations	91.0	3.8	0.2	1.3	26.7	31.0
Family Obligations	3.6	24.7	4.8	11.9	13.4	12.5
Personal Problems	6.4	0.0	5.7	12.8	22.8	7.7
Disrespectful staff	3.9	0.0	0.0	27.8	63.4	13.9
Quality of Care	0.0	0.0	0.0	22.1	48.1	9.9
Waiting Area Issues	0.0	0.0	0.0	0.0	62.0	5.7
Clinic Costs	2.7	0.0	4.2	8.0	17.9	4.8
Time Spent in Clinic	11.0	0.0	0.0	20.3	58.4	13.7
Clinic Administrative Issues	0.0	0.0	1.2	23.8	29.2	8.8
Poor facilitation of transfers	0.4	24.0	0.0	2.8	0.0	7.4
Fear of Disclosure	1.5	0.0	1.3	22.8	38.4	9.8
Beliefs about HIV Status	0.0	2.4	29.5	1.4	9.7	4.3
Beliefs about HIV care needs	7.1	0.0	98.8	0.0	26.7	12.8
Problems with Medications	0.0	0.0	13.0	1.4	7.4	2.1
Mean number of barriers reported	2.3	1.4	2.4	2.2	5.5	2.3
Female, % (95% CI)	46.6 (36.0-56.6)	68.2 (59.4-75.8)	56.5 (38.7-72.9)	66.0 (55.4-75.2)	52.4 (34.6-69.6)	59.2
Median Age, years (IQR)	36 (31, 41)	34 (28, 40)	36 (31, 42)	37 (30, 42)	35 (28, 39)	35 (30, 41)
Median enrollment CD4, cells/µl (IQR)	215 (128, 348)	263 (113, 472)	210 (137, 386)	239 (137, 330)	162 (113, 306)	236 (124, 369)
Median time to loss to follow-up, years (IQR)	1.9 (0.4, 4.1)	0.5 (0, 2.2)	0.1 (0, 1.5)	1.0 (0, 2.4)	2.1 (0.1, 3.9)	1.0 (0.1, 2.9)
Disengaged, % (95% CI)	44.1 (34.4, 54.2)	19.2 (12.9, 27.7)	100.0 (-)	48.8 (38.4-59.2	57.2 (39.2-73.5)	43.3

909 SURVIVAL OF PEOPLE LIVING WITH AIDS IN BRAZIL: BIAIDS-BRAZIL COHORT

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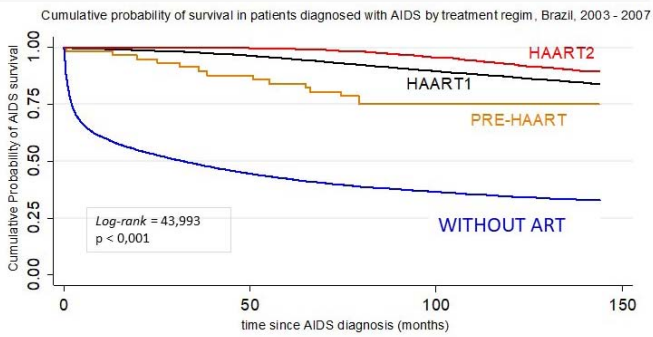
Background: Brazil was the first middle-income country to offer universal access to AIDS treatment. Monitoring the impact of this policy is relevant for continuous updating of intervention strategies. This study aimed to estimate the survival of people living with AIDS (PLWA) with > 13 years of age and to investigate predictors of death with a basic AIDS cause, in Brazil, among 2003-2007, followed up until 2014.

Methods: Retrospective cohort. Data from the Brazilian Integrated Base of AIDS Cohort (BIAIDS-BRASIL Cohort) was obtained from a probabilistic record linkage methodology applied to databases of the Ministry of Health: Information System of Notification Diseases, Control of Laboratory Tests, Logistic Control System of Medicines and Mortality Information System. Kaplan-Meier method, Cox model and estimates of the hazard ratios (HR), with 95% confidence intervals (CI = 95%) were used for survival analysis. The main variable was the antiretroviral therapy (ART). To identify factors associated with the outcomes of interest, sociodemographic characteristics, clinical, therapeutic and laboratory evolution were analyzed.

Results: During the 2003-2007 period, 104,806 PLWA were reported, with 27,147 deaths. The probability of surviving 144 months was 33% for those who did not use ART, 75% for those with Pre-HAART, 84% with HAART1 and 89% with HAART2. They were associated with AIDS death independent of other exposures: use of HAART1 (HR=2.1; 95%CI1.7-2.4); use of Pre-HAART (HR=4.8; 95%CI2.5-11.7); without ART (HR=5.3; 95%CI4.0-5.6); feminine gender (HR=0.8; 95%CI0.7-0.8), <8 years of study (HR=1.5; 95%CI1.4-1.6); without study (HR=1.8; 95%CI1.6-2.0); age of 30-49 years (HR=0.9; 95%CI0.9-1.0); > 50 years (HR=1.2; 95%CI1.1-1.3); heterosexual (HR=1.2; 95%CI1.1-1.3); injecting drug users (HR=2.1; 95%CI1.9-2.3); black (HR=1.3; 95%CI1.2-1.4); brown (HR=1.1; 95%CI1.0-1.1); indigenous (HR=1.7; 95%CI1.1-2.7); TCD4+ in the diagnosis among 350-499 cells/mm^3 (HR=1.2; 95%CI1.1-1.4); among 200-349 cells/mm^3 (HR=1.5; 95%CI1.3-1.6); <200 cells/mm^3 (HR=2.3; 95%CI2.1-2.5); and viral load >500 copies (HR=1.8; 95%CI1.7-2.0).

Conclusion: Survival was massively increased, from 33% to 89% in 144 months, due to the introduction of more potent therapeutic regimens adopted in the country. HAART, sex, schooling, ethnicity, exposure category, age, TCD4+, and viral load at the time of diagnosis were associated with survival time as an independent prognostic factor.



Note: PRE-HAART = Nucleosidic Reverse Transcriptase Inhibitors
HAART1 = Non-Nucleosidic Reverse Transcriptase Inhibitors / Protease Inhibitors
HAART2 = Schemes containing at least one THIRD LINE ART

910 HIGH HIV PREVALENCE AND LOW ART COVERAGE AMONG AGYW WHO SELL SEX: A POOLED ANALYSIS

Katherine Rucinski[1], Sheree Schwartz[1], Seni Koanda[2], Iliassou Mfochive[1], Ubald Tamoufe[3], Serge Billong[4], Douada Diouf[5], Fatou Drame[5], Vincent Pitche[6], Simplice Anato[7], Sindy Matse[8], John Nkonyana[9], Nancy Phaswana-Mafuya[10], Harry Hausler[11], Stefan Baral[1]

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Background: Adolescent girls and young women (AGYW) and female sex workers (FSW) are both at particularly high risk of acquiring HIV in sub-Saharan Africa. The extent to which AGYW who sell sex engage in HIV care and treatment is not fully understood. We assess age-specific HIV prevalence and antiretroviral therapy (ART) coverage among FSW in West and Southern Africa.

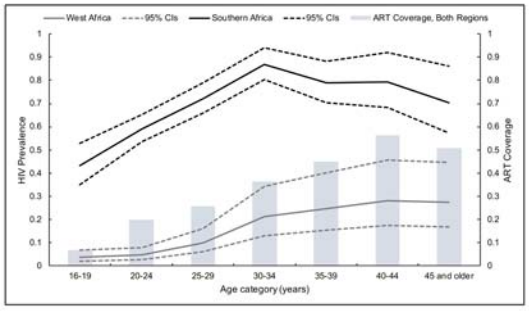
Methods: This pooled analysis includes respondent driven sampling (RDS) data from 2011-2016 in sub-Saharan Africa (West Africa: Burkina Faso (n=699), Cameroon (n=2255), Cote d'ivoire (n=466), The Gambia (n=251), Senegal (n=758), and Togo (n=684); Southern Africa: Lesotho (n=744), South Africa (n=410), and eSwatini (n=325)). Women were eligible to participate if they had engaged in sex work as their primary source of income in the past year. Interviewer-administered questionnaires used comparable data collection instruments across sites to assess demographics and prior history of HIV testing and ART use. All women received HIV testing and counseling. Generalized linear mixed effect models were used to calculate age-specific HIV prevalence estimates for West and Southern Africa. Differences in self-reported HIV testing and ART coverage were descriptively compared by age for both regions.

Results: A total of 6592 FSW were included in this analysis (median age: 27 years, IQR 22-33). Pooled HIV prevalence estimates increased with age and varied by region (Figure). In West Africa, estimated prevalence steadily increased from 4% (95% CI 2, 7) to 27% (95% CI 17, 45). Prevalence estimates for Southern Africa were greater by comparison, ranging from 43% (95% CI 35, 53) in very young FSW (≤19 yrs) to 87% (95% CI 80, 94) by ages 30-34. Among 1957 FSW living with HIV overall, 1140 (57%) had received a prior HIV diagnosis; 681 (35%) were on ART. Compared to older FSW living with HIV, young HIV-infected

FSW (≤24 yrs) were less likely to know their HIV status (47% (212/447) vs. 61% (928/1510), p<0.01) and less likely to be on ART (18% (81/447) vs. 40% (600/1510), p<0.01).

Conclusion: HIV prevalence among AGYW in Southern Africa was exceptionally high in this pooled analysis of women who sell sex. Limited knowledge of HIV status and low ART coverage in this age group suggests that even among key populations such as FSW, HIV risk may not be evenly distributed. HIV prevention interventions for AGYW that target those who engage in sex work and those who are vulnerable to early entry into sex work may be most effective in maximizing prevention impact.

Figure. Pooled HIV prevalence estimates (95% CIs) and ART coverage by age among female sex workers in West Africa (N=5113) and Southern Africa (N=1479)



911 TIME TO UNDETECTABLE VIRAL LOAD ACHIEVEMENT AFTER ART START AND RISK OF MORTALITY

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Background: No data on the association between the time to the first undetectable viral load (FUVL) after antiretroviral therapy (ART) initiation and mortality are available. In this study we evaluated whether time to FUVL after ART start is predictive of all-cause mortality in a large population of HIV-1-infected patients (pts).

Methods: We included HIV-1-infected treatment-naïve pts, from the ICONA Cohort, who started ART (≥3 drugs) >1998, with ≥1 viral load (VL) and CD4+ values before and after ART start, who achieved undetectable VL (defined by a single HIV-RNA <50 copies/mL) after ART start. Results described as median (IQR) or frequency (%). Cumulative risk of all-cause mortality was summarized using Kaplan-Meier method, with follow-up for these analyses from the date of FUVL achievement until patient's death, loss to-follow-up or last visit. Factors associated with all-cause mortality were identified using multivariate Cox proportional hazards regression models.

Results: Overall, 10,000 subjects achieved undetectable VL after ART start and were included in the analyses. At ART start, age was 38 (32-46) years, 7805 (78%) males, 1701 (17%) HCV-coinfected, 1028 (10.3%) had a previous AIDS diagnosis, CD4+ 319 (172-464) cells/µL, CD4+/CD8+ ratio was 0.35 (0.20-0.53), HIV-RNA 4.77 (4.20-5.26) log10cps/mL; calendar-year of ART start was 2012 (2007-2015), 153 (1.5%) started a NRTI-, 3540 (35.4%) a NNRTI- , 4074 (40.7%) a PI- and 1956 (19.6%) an INSTI-based ART, 277 (2.8%) started more complex regimens. After ART start, 3161 (31.6%), 3399 (34%) and 3440 (34.4%) achieved the FUVL ≤3 months (M), 3-6 M and >6 M, respectively. During a median follow-up of 4.0 years (2.0-7.0), 300 deaths for any-cause occurred. Kaplan-Meier cumulative mortality estimates at 1, 3 and 5 years were higher (log-rank test: p=0.001) in subjects who achieved FUVL >6M [0.8% (95% CI 0.5-1.2), 2.4% (1.9-3.0) and 4.0% (3.2-4.9)] as compared to those who achieved FUVL ≤6M [0.6% (95% CI 0.4-0.8), 1.6% (1.2-1.9) and 2.3% (1.9-2.8)]. The achievement of FUVL ≤6M as compared to >6M was associated with a lower risk of all-cause mortality in a single-factor analysis and remained predictive after adjusting for other factors (Table) with AHRs ranging from 0.69 to 0.77 depending on the considered model.

Conclusion: In a large cohort of naïve HIV-1 infected subjects, the achievement of undetectable viral load within 6 months from ART start was associated with a lower risk of all-cause mortality.

Multivariate Cox proportional hazard models on the risk of death from any cause in patients who achieved undetectable viral load after ART start

			Univariate analysis		Multivariate analysis: Model (1) on all subjects		Model (2) excluding subjects treated with NRTI-based regimens		Model (3) on all subjects		Model (4) excluding subjects treated with NRTI-based regimens	
		Number of deaths	HR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value
Months to FUVL after ART start												
	≤6M	176 (2.7%)	0.69 (0.55-0.87)	0.001	0.69 (0.54-0.88)	0.003	0.74 (0.57-0.96)	0.023	0.72 (0.56-0.92)	0.009	0.77 (0.60-0.99)	0.048
	>6M	124 (3.6%)	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
	≤3M	90 (2.8%)	0.74 (0.57-0.98)	0.032	0.74 (0.55-1.00)	0.050	0.81 (0.59-1.10)	0.176	0.78 (0.58-1.05)	0.103	0.85 (0.62-1.15)	0.288
	3-6M	86 (2.5%)	0.64 (0.48-0.84)	0.002	0.65 (0.48-0.86)	0.003	0.69 (0.51-0.93)	0.015	0.67 (0.50-0.89)	0.007	0.72 (0.53-0.97)	0.029
	>6M	124 (3.6%)	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-

Abbreviations: FUVL, first undetectable viral load; M, months; HR, hazard ratio; AHR, adjusted hazard ratio; 95%CI, 95% confidence interval.

Model 1 and 2 were adjusted for age, gender, HIV risk factor, HCV co-infection, pre-ART viral load, pre-ART CD4+, pre ART AIDS diagnosis, time to ART start, type of first-line regimen, CD4 at FUVL and CD4/CD8 ratio at FUVL.

Model 3 and 4 were adjusted for age, gender, HIV risk factor, HCV co-infection, pre-ART viral load, pre-ART CD4+, pre ART AIDS diagnosis, time to ART start, calendar year of ART start, CD4 at FUVL and CD4/CD8 ratio at FUVL.

912 CONTRIBUTION OF HIV DISEASE AND CARE STAGES TO HIV TRANSMISSION AMONG BALTIMORE MSM

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Background: HIV incidence remains high among men who have sex with men (MSM) in the United States. We estimated the contributions of MSM at different stages of HIV infection and the HIV care continuum to HIV transmission among MSM in Baltimore, MD, over the past 30 years.

Methods: A deterministic compartmental model of HIV transmission among MSM was parameterised using, and fitted to demographic, epidemiological and care continuum data for MSM in Baltimore, using multiple combinations of plausible parameter values. We estimated the fraction of new direct and secondary HIV infections transmitted by MSM in different disease or care continuum stages, using population attributable fractions (PAFs) estimated over 10-year periods between 1988 and 2017, obtained by comparing the estimated number of new HIV infections with the numbers that would have occurred if the population in that stage could not transmit HIV. Average per-capita HIV transmissions per 100 people living with HIV (PLHIV)/year were also estimated over these periods.

Results: We estimated that treated and untreated MSM transmitted a median 15% (95% uncertainty interval: 7-31%) and 89% (79-95%) of all new infections among MSM over 2008-2017 respectively. Untreated PLHIV in the acute stage were estimated to transmit 36 new HIV infections per 100py over 2007-2018, vs 25 and 8/100py for those with AIDS (CD4 <200 cells/µl) and those in the chronic non-AIDS stages (CD4 >200 cells/µl), respectively. The model PAF for undiagnosed MSM has declined over time, from 91% (68-98%) over 1988-1997 to 38% (30-49%) over 2008-2017, when undiagnosed MSM represented 87% and 22% of all HIV-positive MSM, respectively. PAFs for diagnosed MSM increased from 15% (5-44%) over 1988-1997 to 82% (67-87%) over 2008-2017. Most new infections attributable to diagnosed PLHIV were transmitted by untreated MSM (PAF for diagnosed untreated MSM: 67% (48-78%) over 2008-2017), who represented 41% of PLHIV (22-48%). Diagnosed MSM (including those treated) transmitted HIV to two-thirds as many individuals as undiagnosed PLHIV per capita over the last ten years (7 vs 11/100py), but around three times more than PLHIV on treatment (2/100py).

Conclusion: Increases in the relative contribution to transmission of diagnosed MSM reflect improvements in HIV testing, but the majority of these transmissions arise from those who remain untreated, showing gaps in treatment provision and retention. Future interventions will need to address the remaining diagnosis and treatment gaps.

913 CHANGING CONTEXTUAL FACTORS POST-HIV DIAGNOSIS PREDICT 5-YR MORTALITY IN SOUTH AFRICA

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Background: Changes in an individual's contextual factors following HIV diagnosis may influence long-term outcomes. We evaluated how changes to contextual factors between HIV diagnosis and 9-month follow-up predict 5-year mortality among HIV-infected individuals in Durban, South Africa.
Methods: We used baseline and 9-month survey data from the Sizanani Trial (NCT01188941) in which adults (≥18y) were enrolled prior to HIV testing in 4 outpatient sites between Aug 2010-Jan 2013. We assessed social support, mental health, and competing needs, meaning financial constraints that required deciding between meeting basic needs (food, clothing, or housing) or receiving healthcare. We used the South African National Population Register to ascertain vital status; median follow-up time was 5.8y (IQR 5.2-6.5). We used random survival forests to identify the most important 9-month variables predicting time to subsequent mortality. We incorporated these predictors into a Cox proportional hazards model that included age, sex, and starting ART by 9 months a priori; the full model included changes in social support, mental health, and competing needs between baseline and 9 months.
Results: Among 1,154 HIV-infected participants with valid South African ID numbers, 905 (78%) had baseline and 9-month data available. Mean age was 36 years, 49% were female, and 109 (12%) participants died after 9-month follow up. Time-independent parameters that increased mortality risk included male sex (HR 1.41, 95% CI 0.96-2.08) and not starting ART (HR 1.48, 95% 0.97-2.26). Less social support at 9 months compared to baseline significantly increased mortality risk (HR 1.17, 95% CI 1.03-1.33). Going without basic needs or healthcare at both baseline and 9 months more than doubled mortality risk compared to not going without these at either time point (HR 2.45, 95% CI 1.03-5.79). A change from not foregoing basic needs or healthcare to afford the other at baseline to needing to do so at 9-months increased mortality slightly more (HR 2.71, 95% CI 1.47-4.99) when also compared to not foregoing basic needs or healthcare at either time point.
Conclusion: Less social support and changes in competing needs between time of HIV diagnosis and 9-month follow-up significantly increase long-term mortality risk. Reassessing contextual factors during follow-up and targeting interventions to increase social support and affordability of seeking care may reduce long-term mortality for HIV-infected individuals in South Africa.

914 MORTALITY RATE AND ASSOCIATED RISK FACTORS AMONG HIV-INFECTED ADULTS ON ART IN KENYA

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Background: Since the early 2000s, Kenya has scaled up antiretroviral therapy (ART) for HIV-infected adults and children. However, significantly high HIV related deaths have been reported (approximately 36000 deaths per year as at 2016). We investigated mortality rate and associated risk factors among HIV-infected adults on ART in Kenya.
Methods: We conducted a retrospective national survey of HIV infected patients aged 15 years and above, who initiated ART from October 2003 to September 2013 at a representative sample of health facilities in Kenya. We abstracted data from patient medical records, including documented deaths during the study period. Patients were censored at the end of the study if they were still active in care. We used Chi-square statistics to compare patient characteristics by outcome status. We used Cox regression model to identify factors associated with mortality. Survey design parameters including weights, clustering and stratification were considered in all analyses.
Results: Of 2517 adult patients initiated on ART during the study period, 1850 (74%) had documented outcomes at the end of the study period. Sixty four percent (1178) were female, 1110 (60%) had been on ART for < 5 years, and 768 (60%) were enrolled with WHO stage 1–2 with median age at ART initiation of 35.1 years (inter-quartile range [IQR] 28.8–42.8). Median follow-up time was 4.1 person-years (PY) (IQR 2.1–6.6) and was significantly different among patients who died (0.6) versus those censored (4.4), p<.01. The total follow-up time was 8172 PY and resulted in 156 (8.4%) deaths and 1694 censored patients. The overall mortality rate was 1.9/100 PY. Patients who died were more likely to be male than female (12% versus 7%, p<.01), with WHO stage 3–4 (9%) compared to stage 1–2 (2%), p<.01, and had been of ART for < 5 years (13%) versus those with >= 5 years (2%), p<.01. The main factors associated with mortality were male sex (adjusted hazard ratio [aHR] 2.0; 95% confidence interval [CI] 1.1-3.5, p=0.01), WHO stage 3–4 vs 1–2 (aHR 6.9; 95% CI 3.3–13.7, p<.01) and been on ART for < 5 years (aHR 9.1; 95% CI 4.0–20.6, p<.01) (Table 1).
Conclusion: Despite accessibility of ART, HIV related deaths continue to be reported especially among men, adult patients initiating ART with advanced disease, and during early years of treatment. There is a need to improve strategies for HIV case identification and close monitoring of patients during early years of initiating ART. Male-targeted intervention are also needed.

Table 1: Summary of HIV related mortality and associated risk factors among HIV infected adult patients initiated on ART from Oct 2003 – Sept 2013 in Kenya

	Participant summary		Unadjusted hazard ratios			Adjusted hazard ratios		
Characteristic	Total N	Deaths, n (%)	HR (95% CI)	p-value	Global p-value	HR (95% CI)	p-value	Global p-value
Total	1850	156 (8.4)						
Age category								
15 - < 24 years	138	10 (7.2)	ref					
>= 24 years	1713	146 (8.5)	1.4 (0.7-2.9)	0.32	0.32	2.0 (0.4-9.3)	0.35	0.35
Sex								
Female	1178	76 (6.5)	ref					
Male	673	80 (11.9)	1.7 (1.0-2.8)	0.04	0.04	2.0 (1.1-3.4)	0.01	0.01
Marital status[1]								
Married	1060	82 (7.7)	ref					
Not married	655	57 (8.7)	1.1 (0.7-1.7)	0.72	0.72			
Employment status[2]								
Employed	645	54 (8.4)	ref					
Unemployed	276	26 (9.4)	1.4 (0.9-2.4)	0.15	0.15			
Facility tier								
Dispensaries/HC[3]	934	101 (10.8)	2.0 (1.1-3.6)	0.03	0.03	1.7 (0.9-3.1)	0.09	0.09
County/National	917	55 (6.0)	ref					
WHO stage[4]								
Stage 1 or 2	768	17 (2.2)	ref					
Stage 3 or 4	510	59 (11.6)	5.5 (2.6-11.7)	<.01	<.01	5.0 (2.5-9.9)	<.01	<.01
Initial ART regimen[5]								
AZT-based	566	52 (9.2)	1.4 (0.8-2.4)	0.21	0.31			
D4T-based	762	65 (8.5)	1.4 (0.9-2.1)	0.17				
TDF-based	517	39 (7.5)	ref					
Duration on ART								
< 5 years	1110	142 (12.8)	10.3 (5.2-20.2)	<.01	<.01	9.1 (4.0-20.6)	<.01	<.01
>= 5 years	740	13 (1.8)	ref					

[1] 136 excluded due to missing values
[2] 930 with missing values
[3] HC-Health Centre
[4] 864 with missing values
[5] 18 with missing values

915 MORTALITY RATES AND CAUSES OF DEATH ACCORDING TO INCLUSION PERIOD IN HIV/HCV PATIENTS

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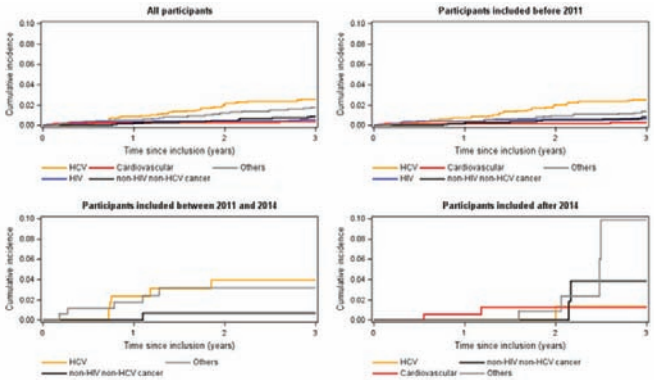
Background: Availability of direct acting antivirals (DAA) against HCV has potentially changed mortality rates and underlying causes of death in HIV/HCV co-infected patients. We aimed to compare the three-year mortality rates and underlying causes in a cohort of HIV/HCV co-infected patients, according to inclusion periods reflecting anti-HCV treatment periods.
Methods: The ANRS CO13 HEPAVIH cohort is a nationwide cohort of HIV/HCV co-infected patients with prospective data collection. We defined three inclusion periods: before 2011 (no DAA), between 2011 and 2014 (1st generation DAA), after 2014 (DAA period). Mortality rates were estimated overall and by cause (hepatic, HIV, cardiovascular, non-HIV non-HCV cancer, others (cerebral hemorrhage, overdose, septic shock, suicide, unknown cause…)) using Aalen-Johansen method accounting for competitive risks. Impact of inclusion period on all-cause and cause-specific mortality was evaluated using Cox proportional

or cause-specific Cox proportional hazard models, adjusted on age, sex, cirrhosis, CD4 and HIV viral load.
Results: Before 2011, 1175 patients were included, 212 between 2011 and 2014 and 323 after 2014. Median ages were of 44.9, 52.1 and 52.2 years, 70.3%, 78.3% and 77.9% were men, 17.4%, 42.2% and 20.7% were cirrhotic. Overall the three-year mortality rates were 57.1 [44.4-71.8], 77.8 [42.2-127.6] and 163.6 [66.5-298.4] for 1000 person-years (PY), respectively (p = 0.2203) (Figure 1). HCV was the first cause of mortality before 2011 (25.4 [17.3-35.9] for 1000 PY) and between 2011 and 2014 (39.1 [15.9-79.2] for 1000 PY) but was the third cause after 2014 (13.4 [1.1-64.7] for 1000 PY), p = 0.1796. Incidence rates of death from other causes significantly increased (13.6 [8.0-21.9], 31.9 [11.9-68.8] and 98.3 [24.9-232.9] for 1000 PY, p = 0.0331). Incidence of cardiovascular death tended to increase (2.7 [0.1-7.5] for 1000 PY before 2011 and 13.0 [2.5-43.1] for 1000 PY after 2014, p = 0.0667). All-cause mortality and cause-specific mortality were not significantly different between periods after adjustment.
Conclusion: In HIV/HCV co-infected patients, incidence of all-cause mortality did not differ significantly between the pre-DAA period and the post-DAA periods. However, a decrease of HIV related mortality, an increase in mortality from other causes and a trend for increased cardiovascular mortality was observed. These changes could be due to higher-risk profiles in patients included during the DAA period.



916 LOW RATE OF SEX-SPECIFIC ANALYSES IN CROI PRESENTATIONS IN 2018: ROOM TO IMPROVE

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Background: The National Institutes of Health, Food and Drug Administration, and journal editors require examination of sex as a biological variable in the design, analysis and reporting of studies, including clinical trials. As 52% of adults living with HIV worldwide are women, sex-specific analyses can provide insight into HIV prevention, pathogenesis, treatment, cure and HIV-associated conditions. CROI 2018 guidelines recommended reporting of sex-specific analyses. Members of the Women's Health Inter-Network Scientific Committee (WHISC) of the ACTG and IMPAACT networks reviewed adherence to these guidelines in oral presentations during CROI 2018.
Methods: Two independent reviewers from WHISC reviewed each original oral presentation's webcast to determine whether the abstract was relevant to both sexes and if it included human participants, animals, or specimens from humans or animals. If those criteria were met, reviewers assessed whether sex demographics were provided and whether sex-delineated outcomes or sex-stratified analyses were presented. If not, the reviewer determined whether an explanation was provided for excluding this information. Descriptive statistics summarized results.
Results: Of 83 original oral presentations, 16 (19%) were deemed relevant to one sex only and were excluded from the analysis. Of the remaining 67 relevant to both sexes, 35 (52%) presented the distribution of the study sample by sex; 7 (10%) presented sex distributions but mislabeled them as "gender"; and 25 (37%) did not. Basic science and animal studies were less likely to report sex distribution (1/13, 8%) compared to human observational studies and clinical trials (41/54, 76%). Only 16 (24%) of all oral presentations relevant to both sexes included sex-stratified analyses or sex-delineated outcomes. The remaining 51 (76%) did not, with only a subset (8, 12%) providing an explanation for why sex stratification was not presented. Of the 28 presentations from clinical trials, 25 (89%) included sex distribution, but only 6 (21%) presented results by sex.
Conclusion: Despite CROI 2018 providing guidelines for presentations consistent with US federal mandates on reporting by sex, more than a third of oral presentations failed to report sex demographics and only a quarter included sex-stratified analyses. Further education of researchers on guidelines requiring reporting of sex as a biological variable is essential to maximize knowledge about sex differences and similarities in HIV and its associated conditions.

917 DEPRESSION AND ANXIETY AS A BARRIER TO ART INITIATION IN KWAZULU-NATAL, SOUTH AFRICA

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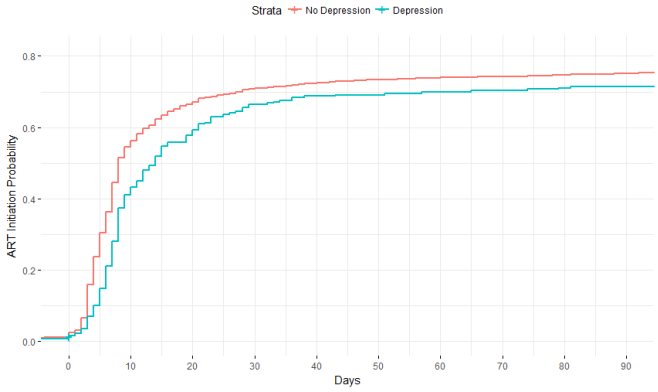
Background: The global burden for depression and anxiety remain high, and HIV-infected individuals are more vulnerable to experiencing these conditions. Our objective was to determine the association between depression and anxiety on initiation of antiretroviral therapy (ART) and the engagement in HIV care.
Methods: We conducted a prospective clinic-based cohort study of HIV-positive adults at HIV testing from the Umlazi township of KwaZulu-Natal, South Africa. We measured depression using the Patient Health Questionnaire (PHQ-9) and anxiety using the Generalized Anxiety Disorder (GAD-7) scale, both of which have been validated in sub-Saharan Africa, before HIV testing. We used cutoff scores of PHQ ≥10 to indicate depression and GAD ≥10 to indicate anxiety, as these are recommended cutoff scores for assessing depression and anxiety in clinical settings. We used univariate and multivariate logistic regression and Cox hazard analyses, adjusted for age and sex, to examine the associations between baseline depression and anxiety on ART initiation and engagement in HIV care over 12 months.
Results: Among 1,878 HIV-positive adults enrolled, the mean (SD) age was 33.1 (9.1) years and 1,110 (59.1%) were female. The prevalence of depression and anxiety was 15.3% and 11.1%, respectively. In adjusted models, HIV-infected adults with depression had a lower odds of initiating ART within 90 days of testing positive (odds ratio [OR]=0.72, p=0.03), and slower ART initiation throughout the one-year study period (hazard ratio [HR]=0.84, p=0.01). Among those who initiated ART, depression was associated with a lower likelihood of missing medication refills (OR=0.66, p=0.04) and missing clinic visits (OR=0.56, p<0.01). Among those who initiated ART, individuals who reported anxiety symptoms had a lower likelihood of missing clinic visits (OR=0.58, p<0.01).
Conclusion: Our finding in an urban township of South Africa suggest that depression and anxiety are significant barriers to ART initiation and engagement in HIV care. Thus, not only is it important to provide mental health screenings alongside HIV testing, but also more intensive follow-up may be required to ensure that HIV-positive adults initiate ART and remain engaged in HIV care. Integrated care models that offer mental health treatment alongside usual HIV care may improve HIV-related outcomes.



918 KNOWLEDGE OF HIV STATUS DECREASES DEPRESSIVE SYMPTOMS AMONG FEMALE SEX WORKERS

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Background: The causal effect of knowledge of HIV status on depression is not well understood. It is thus a major worry that knowledge of HIV-positive status may result in depression, which may be a barrier to scaling innovative HIV testing interventions that move testing outside the health system and away from the support of trained counselors (i.e., HIV self-testing).

Methods: To estimate the relationship between HIV status and depression, we employ a quasi-experimental approach, individual fixed effects analysis – which controls for all observed and unobserved individual level confounders that do not vary over time. We use longitudinal data from two female sex worker (FSW) cohorts, constructed from randomized controlled trials of HIV self-testing delivery models in urban Ugandan and Zambian transit towns. Participants were provided access to free standard of care HIV testing services and two HIV self-tests (intervention arms only) over the course of four months. Participants completed quantitative surveys at months 0, 1, and 3. At each survey, participants self-reported their knowledge of HIV status. We used the PHQ-9 depression scale (range 0-27 points) to measure the severity of participants' depressive symptoms (continuous scores) and prevalence of likely depression (scores ≥10 indicate clinical depression in this and other setting). To capture time-varying confounders shared by the participants, we controlled for calendar month and survey round.

Results: The majority of the 1,965 enrolled participants (960 Uganda; 965 Zambia) changed their knowledge of HIV status over four months (57% Uganda; 67% Zambia). Knowledge of HIV status significantly decreased the severity of depressive symptom among participants in both Uganda and Zambia and significantly decreased the prevalence of likely depression in Zambia (Figure 1). In Zambia, the prevalence of likely depression (45.7% at enrollment) decreased by 14.1% (95% CI -22.1% to -6.0%, p=0.001) with knowledge of HIV-negative status and decreased by 14.3% (95% CI -23.9% to -4.5%, p=0.002) with knowledge of HIV-positive status.

Conclusion: Knowledge of HIV status, be it positive or negative, significantly decreased depressive symptoms in two diverse populations of FSWs. This is finding is consistent with literature suggesting that certainty about a health condition is less stressful that uncertainty, even if the results are unwanted. Expansion of HIV testing programs could have mental health benefits for FSWs.

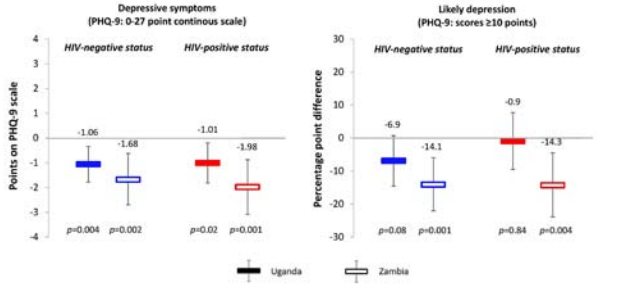

Figure 1. The effect of female sex workers' knowledge of HIV status on self-reported depressive symptoms and likely depression in Uganda and Zambia.

919 TREATED MENTAL DISORDERS IN PRIMARY AND TERTIARY HIV CARE PROGRAMS IN CAPE TOWN

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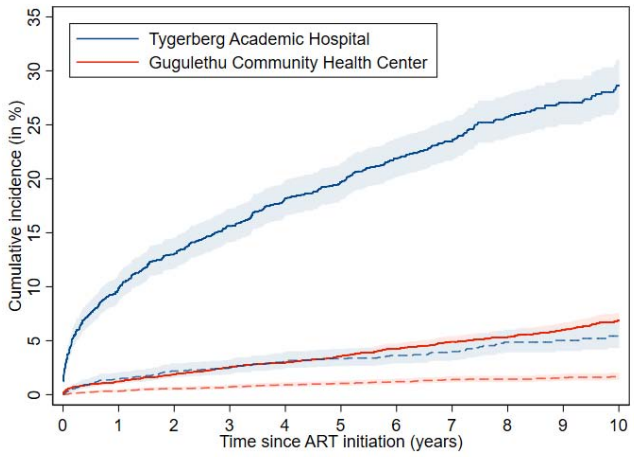
Background: The adult 12-month prevalence of common mental disorders in the Western Cape, South Africa is 20% and lifetime prevalence is 40% (South African Stress and Health study 2009). Untreated mental disorders may lead to suboptimal antiretroviral therapy (ART) outcomes. We describe the incidence of treated mental disorders among adults on ART in Cape Town.

Methods: Routinely collected data from two HIV care programs in Cape Town were linked to available province-wide pharmacy dispensing and hospital discharge data using national identifiers. We included adults who initiated ART between 2004 and 2017 at the Tygerberg Academic Hospital, a tertiary care facility and the Gugulethu Community Health Center, a primary care facility. We used the Kaplan-Meier method to estimate the cumulative incidence of pharmacological treatments with psychiatric medication and hospital admissions for mental disorders (i.e. admissions for a mental, behavioral or substance use disorder [ICD10 F00-F99] or admission to a psychiatric ward) after ART initiation.

Results: We included 4,051 patients from Tygerberg and 11,312 patients from Gugulethu. Out of a total of 15,363 patients, 939 (6.1%) received pharmacological treatments: 645 (4.3%) received antipsychotics, 568 (3.7%) antidepressants, and 297 (1.9%) anxiolytics. 197 patients (1.3%) had been admitted to a hospital for a mental disorder: 48 patients (0.3%) for a schizophrenic disorder (ICD10 F20-F29), 44 (0.3%) for a mood disorder (F30-F39), 34 (0.2%) for an organic mental disorder (F01-F09), 27 (0.2%) for a substance use disorder (F10-F19), 32 (0.2%) for other/unspecified mental disorders, and 84 patients (0.5%) had been admitted to psychiatric wards without a documented ICD10 diagnosis. Cumulative incidence of pharmacologic mental health treatment (solid lines) at 10 years after ART initiation was 28.6% (95%-CI 26.4-31) at Tygerberg and 6.9% (95%-CI 6.2-7.6) at Gugulethu (Figure). Cumulative incidence of hospital admissions for mental disorders (dashed lines) at 10 years was 5.4%(95%-CI 4.3-6.8) at Tygerberg and 1.7%(95%-CI 1.4-2.1) at Gugulethu (Figure).

Conclusion: While it is expected that not all mental health conditions would be diagnosed and treated, an appreciable burden of mental health disorders could be ascertained in these cohorts of patients on ART. The higher incidence of ascertained mental health disorders in the hospital settings likely reflects a combination of differences in underlying incidence, diagnosis and ascertainment of diagnoses.



920 DATING VIOLENCE AND HIV-ASSOCIATED OUTCOMES AMONG ADOLESCENT SEXUAL-MINORITY MALES

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Background: Adolescent sexual-minority males (ASMM) in the United States are disproportionally affected by HIV and dating violence (DV) compared to their heterosexual peers. While previous research has typically focused solely on one-sided DV, recent studies suggest bidirectional violence in relationships is associated with increased HIV risk and may affect healthcare service use. However, this association has not been examined among ASMM. We used data from CDC's National HIV Behavioral Surveillance to examine dating violence experiences of ASMM and estimate associations between DV profiles and behaviors known to increase HIV risk in 3 cities participating in the NHBS-Young Men who have Sex with Men pilot.

Methods: ASMM, defined as males aged 13-18 years who reported ever having sex with another male, gay/bisexual identity, or same-sex attraction, were asked about several past 12 month HIV-associated outcomes: condomless anal sex, ≥4 sexual partners, exchanged sex for money or drugs, sexually transmitted infection (STI) diagnosis, non-injection drug use, and HIV testing. DV experience in the past 12 months was divided into three profiles: DV perpetration only (DVP), DV victimization only (DVV), and DV perpetration and victimization (mutual DV). Using log-linked Poisson regression, we calculated separate adjusted prevalence ratios (aPR) for associations between DV profiles and HIV-associated outcomes. Models were adjusted for city and race/ethnicity.

Results: Of 548 ASMM, 6% reported DVP, 8% DVV, and 8% reported mutual DV. The majority of ASMM reporting any type of DV visited a healthcare provider in the last year (89%). Compared to those reporting no DV, ASMM reporting mutual DV were more likely to report condomless anal sex (aPR=2.47, 95% CI: 1.38–4.42). ASMM reporting DVP or mutual DV were more likely to report a STI diagnosis (aPR=2.71, CI: 1.09–6.68; aPR=2.71, CI: 1.30–5.62, respectively) drug use (aPR=2.33, CI: 1.12–4.85, aPR=2.45, CI: 1.26–4.94, respectively), and HIV testing (aPR=3.81, CI: 1.58–9.21, aPR=4.23, CI: 1.94–9.26, respectively).

Conclusion: Our findings suggest that DV is prevalent among ASMM. These results highlight that exposure to DV as a victim and perpetrator are associated with increased HIV-related behaviors. The majority of ASMM experiencing DV were engaged in healthcare suggesting an opportunity for provider-initiated screening for violence and additional integration of services to reduce HIV risk among this population.

Table 1. Associations between DV profiles and past 12 month HIV-associated outcomes

Past 12 month HIV-associated outcomes**	DVP only * aPR (95% CI)	DVV only* aPR (95% CI)	Mutual DV* aPR (95% CI)
Condomless anal sex	1.57 (0.8-3.1)	1.72 (0.9-3.2)	2.47 (1.4-4.4)
≥4 sexual partners	1.12 (0.50-2.50)	2.36 (0.99-4.50)	1.32 (0.68-2.56)
Exchange sex for money or drugs	1.96 (0.26-14.71)	1.67 (0.24-11.47)	1.93 (0.50-7.50)
Sexually transmitted infection diagnosis	2.71 (1.09-6.69)	0.36 (0.05-2.83)	2.71 (1.30-5.62)
Non-injection drug use	2.33 (1.12-4.85)	1.88 (0.99-3.53)	2.56 (1.44-4.54)
HIV testing	3.81 (1.58-9.21)	1.59(0.81-3.14)	4.23 (1.94-9.26)

Abbreviations: DV, Dating violence; DVP, dating violence perpetration only; DVV, dating violence victimization only; Mutual DV, mutual dating violence; aPR, adjusted prevalence ratio; CI, confidence interval
* Compared to those reporting no DV
** All models controlled for race/ethnicity, city, and recruitment method

921 MULTILEVEL PREDICTORS OF SUICIDALITY AMONG HIV+ SUBSTANCE USERS IN 11 US CITIES

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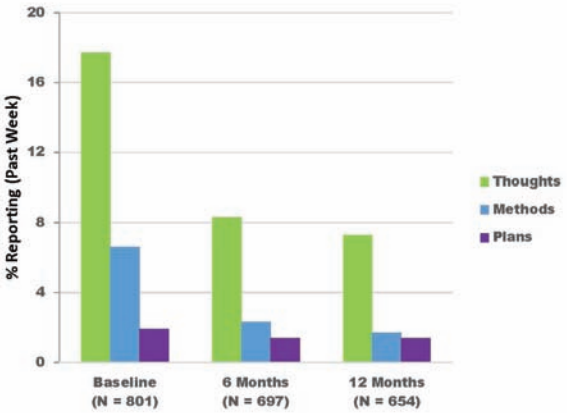
Background: People living with HIV/AIDS have an elevated risk for suicide. Although HIV+ substance users are at even greater risk, few studies have been conducted to inform comprehensive management of suicide risk in this population.

Methods: Project Hope (CTN0049) was a 3-arm randomized controlled trial that tested six months of patient navigation (with and without financial incentives) compared to treatment as usual in HIV+, substance-using hospitalized patients. Project Hope recruited 801 patients from 11 hospitals in the U.S. from 2012-2014. Predictors of two time-varying outcomes were examined over 12 months: 1) any suicidal thoughts (past week); and 2) a composite measure of suicidality measuring the frequency of suicidal thoughts, considering methods for suicide, and making plans for suicide in the past week. Medical, structural, and psychosocial predictors of these outcomes at baseline, six, and 12 months were examined using mixed linear and logistic regression models.

Results: The sample was predominantly Black (78%), middle-aged (Mean = 44.6; SD = 10.0), and male (67%) with a median CD4+ count of 109 cells/mm.^{3} Approximately 18% of participants reported any suicidal thoughts at baseline. The Figure summarizes the percentage of participants reporting any suicidal thoughts, methods, or plans over the 12-month follow-up. More severe substance (Adjusted Odds Ratio [AOR] = 1.29; 95% CI = 1.07 – 1.55) and alcohol (AOR = 1.26; 95% CI = 1.02 – 1.55) use disorder symptoms were independently associated with greater odds of reporting any suicidal thoughts over 12 months. Hispanic/Latino ethnicity, a CD4+ T-cell count < 200 cells/mm,^{3} injection drug use (IDU) during the past year, and more severe alcohol and tobacco use disorder symptoms significantly predicted higher suicidality composite scores over 12 months. In contrast, stable housing and greater social support were associated with significantly lower suicidality composite scores over 12 months. There were no intent-to-treat effects of patient navigation (with or without financial incentives) on any suicidal thoughts or suicidality.

Conclusion: Greater severity of alcohol, tobacco, and other substance use disorders as well as recent IDU are key risk factors for suicidality among HIV+ substance users. Findings also underscore the need for comprehensive approaches to address the medical, structural, and psychosocial factors that may modify suicide risk in this population.

Figure. Suicidality indicators in HIV+ substance users over 12 months



922 HIV-1/2 DIFFERENTIATION IN THE US HIV TESTING ALGORITHM: HIGH BURDEN, LOW YIELD

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CDC, Atlanta, GA, USA

Background: Since 2014, the national algorithm for laboratory-based HIV testing has recommended a supplemental HIV-1/2 differentiation test as the second test for confirmatory HIV diagnosis to resolve issues of HIV-2 antibody cross-reactivity with HIV-1 specific tests and to identify potential HIV-2 infections. HIV-1/2 differentiation testing requires laboratories to acquire specialized equipment or to send out specimens to commercial reference labs for additional testing, which may increase cost and delay confirmation of infection. We therefore sought to assess the burden and yield of HIV-2 testing in the United States under the current algorithm, particularly regarding the HIV-1/2 differentiation test.
Methods: We used results reported to the U.S. National HIV Surveillance System during 2012-2016. HIV-2 mono-infection was defined as confirmed HIV-2 infection (e.g., positive HIV-2 RNA or DNA) in the absence of HIV-1 infection. Dual infection was defined as confirmed infection with HIV-1 (e.g., positive HIV-1 RNA or DNA) and HIV-2. Infections were defined as not confirmed for HIV-2 if an HIV-2 antibody result was positive but there was no confirmatory lab test reported.
Results: Among 202,536 HIV diagnoses reported during 2012-2016, the annual number of persons tested with an HIV-1/2 differentiation assay increased from 9,785 (23.5%) in 2012 to 32,126 (80.6%) in 2016. The annual number of confirmed HIV-2 mono-infections ranged from two to five. Four total dual infections were identified. Possible HIV-2 infection could not be confirmed for 115 (0.06%) persons.
Conclusion: During 2012-2016, use of HIV-1/2 differentiation tests increased substantially, which is consistent with the implementation of the new guidelines for the U.S. HIV testing algorithm. Despite increased testing, the number of confirmed and possible (i.e., undetermined) HIV-2 diagnoses remained extremely low. In light of the substantial burden yet low yield of HIV-1/2 serological differentiation in the national testing algorithm, it's prioritization as the second step in confirmation of HIV infection merits reconsideration.

	Year of Diagnosis					
	2012 N=41,635	2013 N=40,026	2014 N=40,717	2015 N=40,288	2016 N=39,870	Total N=202,536
Persons tested with an HIV-1/2 differentiation test N (%)	9,785 (23.5)	13,874 (34.7)	26,027 (63.9)	31,466 (78.1)	32,126 (80.6)	113,278 (55.9)
HIV-1 diagnoses	41,610	40,016	40,683	40,258	39,833	202,400
Dual HIV-1/2 diagnoses	3	0	0	1	0	4
HIV-2 diagnoses, confirmed	5	3	4	3	2	17
HIV-2 diagnoses, not confirmed	17	7	30	26	35	115

923 HIV SEROLOGICALLY INDETERMINATE INDIVIDUALS: FUTURE HIV STATUS AND RISK FACTORS

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Background: Indeterminate HIV test results, where two EIA results contradict each other, are common, but little is known about longitudinal patterns in HIV testing results among those with indeterminate results or their sociodemographic and behavioral correlates. We assessed future HIV serological outcomes for people with indeterminate results and associated factors in Rakai, Uganda
Methods: 44,926 adults aged 15-49 years (total of 136,414 person-visits) from 1994 to 2011 in the Rakai Community Cohort Study were assessed. Modified Poisson regression models with generalized estimating equations were used to assess prevalence ratios (PRs) of subsequent HIV serological outcomes for participants with 2 or more visits (n=27,119) and factors associated with HIV serologically indeterminate results. Lorelograms were used to assess the within person correlation of indeterminate results over multiple study vi
Results: The overall prevalence of HIV serologically indeterminate results was 4.6%. Participants with an indeterminate HIV test result were more likely to have an indeterminate result at subsequent visits compared to those with negative results (PR 11.96, 95% CI 11.41,12.53). Subjects with an indeterminate result were twice as likely to have a subsequent HIV positive result compared to those with a negative result (PR 2.28, 95% CI 1.96, 2.65). The within-person correlation of indeterminate results was autoregressive with individuals being more likely to test indeterminate closer in time to a prior indeterminate result. In regression analyses, indeterminate results were less likely to occur in women than in men (adjPR 0.77, 95% CI 0.71,0.83), in unmarried participants than in married participants (AdjPR 0.92, 95% CI 0.85,1.00), and in individuals with an education relative to those with no education (primary education: adjPR 0.88, 95% CI 0.78,1.00; secondary education; adjPR 0.79, 95% CI 0.68,0.91; post-secondary education; adjPR 0.73, 95% CI 0.57,0.93). Occupation, number of sex partners, religion and malaria status, were not associated with indeterminate results.
Conclusion: Individuals with HIV indeterminate serological results were more likely to have future indeterminate and positive HIV results compared to those with negative results. Gender, marital status and education were independently associated with indeterminate serostatus. Individuals with indeterminate results should be targeted for follow-up testing as they are more likely to eventually test positive.

924 ROUTINE TESTING OF NONPATIENTS INCREASES HIV DIAGNOSIS IN WESTERN KENYA

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[1]US CDC Kisumu, Kisumu, Kenya, [2]Centre for Health Solutions, Nairob, Kenya, [3]Centre for Health Solutions, Siaya, Kenya, [4]Elizabeth Glaser Pediatric AIDS Foundation, Homa Bay, Kenya, [5]Kisumu County Department of Health, Kisumu, Kenya, [6]Homa Bay County Department of Health, Homa Bay, Kenya, [7]Siaya County Department of Health, Siaya, Kenya, [8]US CDC Nairobi, Nairobi, Kenya

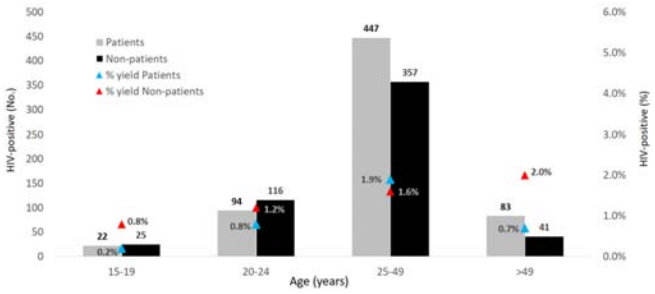
Background: An estimated 150,000 (36%) persons living with HIV (PLHIV) in Homa Bay, Siaya, and Kisumu counties in western Kenya do not know their HIV status. In 2016, health facilities in these 3 counties implemented universal access to provider-initiated HIV testing and counseling services for both patients and non-patients accompanying patients to the outpatient department (OPD). We assessed HIV testing outcomes among patient and non-patient clients at several health facilities.
Methods: We retrospectively analyzed routinely collected program data from 7 high-volume (>1,000 monthly OPD visits) health facilities in western Kenya. Data from patient and non-patient clients aged 15 years or older who received HIV testing services in OPDs (March–December 2017) were included. We conducted a descriptive analysis of client characteristics and HIV testing

outcomes. STATA v14.2 was used to calculate frequencies and proportions and to test for differences in characteristics and outcomes.

Results: During the 9-month period, of the 119,950 clients screened for HIV testing, 66% (79,021) were patients, and 34% (40,929) were non-patients. Overall, 73% (57,873) of patients and 90% (36,892) of non-patients were eligible for testing; testing uptake was >95% in both groups. Among 92,153 clients tested, the median age was 29 years, 57% (52,215) were women, and 40% (36,728) were non-patients. Although more non-patients were men (45% vs. 42%; p-value=<0.001), a greater proportion of patients were younger than 19 years (16% vs. 9%; p-value=<0.001) or older than 49 years (20% vs. 6%; p-value=<0.001). In total, 1.3% (1,185) of clients were HIV positive. Percent yield was higher among non-patients than among patients (1.5% vs. 1.2%; p-value=<0.001), overall and across age categories (Figure 1). Non-patients accounted for 45% (539) of all PLHIV identified, including 57% (117/205) of HIV-positive women aged 15–24 years, 46% (24/52) of HIV-positive men aged 15–24 years, 45% of HIV-positive men (169/377) and 44% of HIV-positive women (188/427) aged 25–49 years.

Conclusion: Nearly half of all HIV-positive individuals identified in the OPD were non-patients. Our findings suggest that in the setting of a generalized HIV epidemic, routine provider-initiated HIV testing and counseling of non-patients is a key strategy for timely diagnosis of PLHIV.

FIGURE 1. HIV-positive testing outcome by age category among patients and non-patients accessing outpatient departments in western Kenya



925 A NEW PREDICTION MODEL FOR CHLAMYDIA AND GONORRHEA SCREENING IN WOMEN WITH HIV

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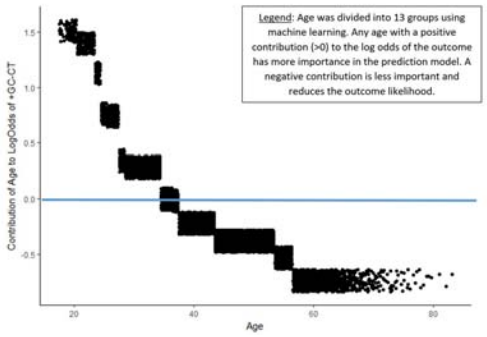
Background: CDC recommends universal, annual chlamydia (CT) and gonorrhea (GC) screening in sexually active adults with HIV, irrespective of age and gender. The yield of annual CT/GC screening in older women who are engaged in HIV care is low. We applied new epidemiologic techniques using machine learning to develop a more precise prediction model to guide cost-effective STI screening in HIV clinic.

Methods: We calculated annual CT/GC testing and positivity rates among US women in HIV care during 2007-2016 as part of the 8 site, CFAR Clinical Network of Integrated Clinical Systems (CNICS) cohort. Data was collected from the electronic medical record and validated surveys for risk behaviors were conducted every six months using patient reported outcomes (PRO). Traditional prediction models using multivariable logistic regression were compared to new prediction techniques for classification using machine learning, random forest algorithms and gradient boosted regression trees, which calculates the importance of each variable in predicting the CT/GC infection outcome and avoids model overfitting.

Results: We analyzed data from 5,084 women contributing 158,745 HIV visits from 2007 to 2016. During the most recent year in care, median age was 47 years (IQR 39-55), 62% were Black, 70% had CD4 count >350 and 74% had HIV viral load <500 copies/mL. In terms of risk during the most recent year in care, 61% were sexually active, 13% had alcohol abuse, and 12% had active drug use. Annual CT/GC positivity rates were stable across calendar years with estimates ranging from 1.9% to 3.4% (p=0.36). Prevalence was inversely associated with age: 2016 CT/GC positivity was 16%/3.9% in ages 18-24 compared to 1.1%/0.7% in age 50+. In every predictive model, despite including a variety of potential STI predictors (including race, region, recent STI, CD4/VL, sex partner characteristics, and substance use), age was the most important variable in predicting CT/GC positivity. In the full machine learning model with good performance (area under the curve [AUC] >0.85), women age <35 years were more likely to have CT/GC and older age (55+) was protective against STI. (see Fig)

Conclusion: In a nationally representative sample of US women living with HIV, younger age (<35 years) was the most important predictor of CT/GC infection in a complex machine-learning model. Age-based STI screening among women engaged in HIV care should be reasonable to adopt and simple to implement, although a precise age threshold is yet to be defined.

Figure 1: The importance of age in predicting chlamydia and gonorrhea in 5084 women with HIV (10,948 person-years)



926 SELF-TESTS FOR AT-HOME PARTNER TESTING ARE ACCEPTABLE & UTILIZED AMONG PREGNANT WOMEN

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Background: Increasing male partner and couples HIV testing among pregnant women in HIV high-burden settings remains a challenge. Secondary distribution of HIV self-tests within routine antenatal care (ANC) could provide an opportunity to close the gap on partner and couples testing.

Methods: In an ongoing cluster RCT (NCT03070600), we offered self-tests for at-home partner HIV self-testing (HIVST) to HIV-uninfected adult women seeking routine ANC services at 10 facilities in Siaya and Homa Bay, Kenya as part of the PrEP Implementation for Mothers in ANC (PrIMA) Study. Women were provided with instructions on how to use self-tests and received at least 2 oral-fluid-based rapid HIV tests (OraQuick Rapid HIV-1/2 Antibody Test, OraSure Technologies). Data on HIVST outcomes were ascertained in-person at one-month follow-up visits.

Results: Overall, 1239 pregnant HIV-uninfected women with male partners were offered self-tests for at-home partner HIVST. Median age was 23 years (IQR 20-28) and median gestational age was 24 weeks (IQR 20-28). Most women (75%) were in monogamous marriages; 11% were in polygamous marriages; 14% were unmarried. Overall, 43% reported having a partner of unknown HIV status; 52% had an HIV-uninfected partner and 5% HIV-infected. Among all women, 68% accepted self-tests. Self-test acceptance was 73%, 69%, and 20% among women whose partners' HIV status was unknown, HIV-uninfected, and HIV-infected, respectively. Among women with partners of unknown HIV status, the most frequently (48%) reported reason for declining self-tests was needing to consult their partner; 10% reported fear of intimate partner violence (IPV). HIVST outcomes were available for 391 (73%) women with partners of unknown HIV status. Among these women, 56% offered self-tests to their male partner; 20% had not seen their male partner since accepting self-tests and 13% feared their partner's reaction and/or IPV. Among women who offered self-tests to

their partner, 92% reported their partner used the self-test and 96% used a self-test with their partner; 6 (2%) male partners with previously unknown HIV status tested positive using self-tests.
Conclusion: Within routine ANC, acceptance of at-home male partner HIVST was high and frequently led to couples' HIV, enhancing mutual knowledge of HIV status. IPV was a barrier to acceptance and offering of self-tests. Given low male attendance at clinics, distributed HIVST is an attractive strategy to improve male partner HIV testing.

927 MALE PARTNER LINKAGE TO CLINIC STI-HIV SERVICES AFTER COUPLE EDUCATION & HIV TESTING

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Background: Home-based HIV testing and education has potential for increasing HIV testing and access to health information and services among men. However, the extent to which men follow-up to clinic based STI and HIV services is yet to be defined. We aim to understand how a home-based antenatal couple education and HIV testing intervention influences male partner follow-up to clinic-based HIV and STI services including STI treatment, HIV care and treatment, and medical male circumcision.
Methods: We conducted a randomized controlled trial of 601 unaccompanied pregnant women attending a first antenatal visit in Kenya from September 2013 to June 2014. Women and their male partners received either the intervention of home-based couple education and HIV-syphilis testing during pregnancy or an invitation letter for standard clinic-based couple HIV testing. Education included identification of STI symptoms and the importance of clinic treatment, in addition HIV treatment for PMTCT and circumcision for HIV-negative men. Male self-reported outcomes were compared between arms at 6 months postpartum.
Results: Among 525 women who completed the study to 6 months postpartum with their infants, we reached 487 men (93%), resulting in 247 and 240 men in the intervention and control arm, respectively. Men of the intervention arm were more likely to report seeking an STI consultation for symptoms [RR=1.59; 95%CI=1.33-1.89]. Syphilis testing at the intervention identified 4 couples requiring treatment and all 4 of these men reported later seeking treatment. Sixty-one men were HIV-infected at study exit, among whom 17 (42%) of 40 intervention men and 5 (24%) of 21 control men were newly diagnosed during the period of the study. Four of 17 men and 3 of 5 men with newly diagnosed HIV in the intervention and control arms, respectively, reported linking to HIV care services [RR=0.69; CI:0.50-0.96]. Few eligible men sought medical circumcision for HIV prevention (4 of 72 intervention and 2 of 88 control).
Conclusion: One-time home-based couple education encouraged male partners to seek clinic STI treatment, however, this was not the case for men with newly diagnosed HIV infection who would likely benefit from additional follow-up to link to care and treatment. Newly diagnosed men identified in home-based testing should be targeted to follow-up linkage to HIV care, which could result in equivalent or better access than clinic-based services alone.

Table 3. Male partner self-reported follow-up to clinic-based sexually transmitted infections services by 6 months after birth of child

	Intervention (n=247)		Control (n=240)		RR	95% CI
	n	(%)	n	(%)		
Self-reported Follow-up to Clinic-based services						
STI Services						
Sought any STI clinic services (non-HIV) [a,b]	47	(19)	16	(7)	**1.59**	**(1.33 - 1.89)**
Sought clinic if recommended for syphilis treatment	4 / 4	(100)	0 / 0	-	-	-
Voluntary Male Medical Circumcision						
Uncircumcised at baseline [b,c]	85	(34)	94	(39)	1.02	(0.86 - 1.24)
Recommended for circumcision as HIV prevention	72 / 85	(85)	88 / 94	(94)	-	-
Sought circumcision	3 / 72	(4)	2 / 88	(2)	**1.29**	**(0.62 –2.70)**
Linkage to HIV care and treatment services						
New HIV diagnosis during study, linked to care [a]	4 / 15	(27)	3 / 5	(60)	**0.66**	**(0.34 - 1.29)**
Diagnosis period unknown, linked during study [d]	2 / 3	(66)	2 / 3	(66)	**0.75**	**(0.21 - 2.65)**

RR = Relative Risk; CI = Confidence Interval
[a] Missing data= 1 intervention man missing data on STI clinic-services, 2 men of the intervention missing data on linkage to HIV care and treatment
[b] Prefer not to respond (included as % of respondents): 2 men of the intervention preferred not to respond regarding seeking STI clinic-services, 1 man of the intervention and 2 men of the control arm preferred not to respond to male circumcision status
[c] Does not know (included as % of respondents): 14 men of the intervention and 6 men of the control did not know about their male circumcision status
[d] Diagnosis period could not be differentiated to new diagnosis during the study, or known HIV positive before the study period

928 OUTCOME AND COST OF 3 METHODS FOR INCREASING MALE PARTNER TESTING IN SOUTH AFRICA

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Background: Despite high uptake of HIV testing among pregnant women, male partner testing within antenatal clinics (ANC) remains low. This study aimed to increase the proportion of men tested within ANC through promotion of facility and home-based HIV testing and distribution of HIV self-test kits.
Methods: This study was conducted at a large health center in the Bojanala District of South Africa from January 2017 – October 2017. All pregnant women, whose partner was HIV-negative or of unknown status, were offered three options for partner testing: (1) a partner invitation letter for facility testing; (2) home testing; or (3) up to 2 Ora-Quick self-test kits to take to their male partners. Instructions included with the self-test kit asked men to send a free "call me back" text to a counsellor after completing the test. Counsellors returned men's calls, collected their results, and provided post-test counseling over the phone. Men could receive up to two R25 (~US$2) airtime vouchers: one for receiving post-test counseling and one for returning the self-test kit via text or physically to the facility. Cost information was collected for all three testing options and is presented in 2017 US dollars.
Results: We enrolled 1,166 women (mean age: 28 years, 72% single, 37% primigravida). HIV prevalence was 21% (12% newly diagnosed, 9% documented known positive). Figure 1 illustrates the uptake of facility, home, and HIV self-testing during the study. Records indicated that 223 men tested at the facility (6% concordant positive, 3% sero-discordant), while 28 men tested in the home (7% concordant positive). HIV self-test kits were distributed to 668 men. Of the 313 (47%) test kits returned either physically or via text, no discrepancies were noted between men's interpretation of the test result and the result obtained by the counselor. The cost per partner tested was $77 for facility, $125 for home, and $83 for self-testing, while the cost per partner testing positive was $403, $1,483, and $2,742 respectively.
Conclusion: HIV self-testing was extremely popular among pregnant women as a method for partner testing, but even with incentives, only 60% of men received post-test counseling. The costs of HIV self-testing were similar to facility testing. Further operational research will be needed to ensure linkage to confirmatory testing and HIV treatment in the event of a positive HIV self-test, which will further reduce the cost per positive diagnosis associated with HIV self-testing.

Figure 1. Uptake of Home, Facility, and HIV Self-Testing as Options for Male Partner Testing among Pregnant Women in South Africa

929 INDEX CASE FINDING A STRATEGY FOR CLOSING THE GAP FOR HIV DIAGNOSIS IN TANZANIA

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Background: Tanzania adopted the 90-90-90 strategy as part of the National HIV Strategic Plan to end HIV by 2030. To achieve the first 90, the identification of PLHIV through HIV testing is key to the strategy's success, and the whole cascade. In Tanzania, only 52% of PLHIV ages 15 to 64 years know their HIV status of which 55.9% are females and 45.3% are HIV positive males. To increase

HIV case identification, the National AIDS Control Programme introduce new strategies including index case testing and partner notification services whereas a trained HTS provider ask people diagnosed with HIV about their sexual partners, drug injecting partners and biological children under 15 years from HIV positive mothers and offered them with HIV testing. These services are provided in both facility and community setting. The index client is the center and partners and contacts are either by the index or HIV testing providers

Methods: In 2017 reviewed its HIV strategic plans for 2018 to 2022, one among the new strategies the Ministry of health adopted is intensification of Index testing Services and Partner Notification services as one of the National strategy for Identification of the PLHIV .To prepare for facility and community index case testing, National guidelines, training package and HTS and Care treatment Monitoring tools were reviewed aiming to integrate index testing into existing health systems. Providers training and monitoring of services was important. Monthly data review meeting and identification of patient files which did not attempt to elicit index and took action . The Home Based Care teams facilitated contacts to come for testing. For convenience purposes, holidays and weekend are used for HIV testing services.

Results: From July 2017 to June 2018 total 12,455,037 people were tested among them 332,824 were HIV positive (2.7%). Through index tested 933,073 tested and Index positive 44,44796 (48%). Across the months, HIV positive yield increased with age and across the quarters, suggesting sexual partners testing. At the same time yield increase in lower age bands suggesting increased fidelity of index testing. Two third of the positive partners are from community index testing modality. The positive yield of sexual and needle sharing partners ranges from 10%-13%, while for children ranges from 1%-3%. These are the true index contacts that imply fidelity of the index testing.

Conclusion: Index case testing is a promising strategy for identification of New HIV case in Tanzania.

930 HIGH ACCEPTABILITY AND HIV YIELD AMONG PARTNERS OF KEY POPULATIONS IN CENTRAL AMERICA

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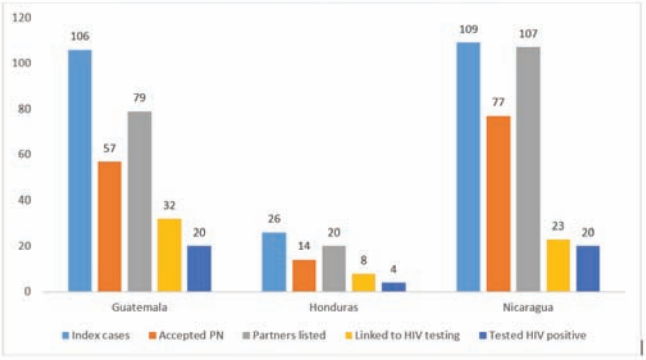
Background: Since December 2017, key population clinics, known as VICITS, have implemented assisted partner notification and partner testing in Guatemala, Honduras, and Nicaragua. We describe results of the first study utilizing four partner notification strategies to increase the uptake of HIV testing among partners of HIV positive key populations in these countries.

Methods: Individuals diagnosed with HIV between December 2017 and July 2018 at 9 participating VICITS clinics were included in the analysis. HIV diagnosis was performed on-site following national HIV testing guidelines. Newly diagnosed HIV individuals were offered partner notification/testing services and the rapid HIV recency assay (Sedia Biosciences) to determine recency of infection. Three assisted partner notification (dual, contract, provider) and one passive strategy (coupon) were offered to newly diagnosed cases. Non-identifiable demographic and behavioral data of index cases and their partners who returned to the clinic for HIV testing were captured using a smartphone based application on site and uploaded into a server daily. All analyses were conducted using STATA 13.0

Results: Of 241 index cases reported during the project period, 109 (45.2%) were from Nicaragua, 106 (44.0%) from Guatemala, and 26 (10.8%) from Honduras. Of these, 149 (61.8%) accepted partner notification and testing services, with higher acceptance seen in Nicaragua (105, 70.6%) followed by Honduras (86, 57.7%) and Guatemala (80, 53.8%) ($p<0.01$). Eighty (33.2%) index cases tested recent for HIV infection with 47 (58.8%) from Guatemala. A total of 206 sex partners were reported by index cases with 45 (21.8%) already linked to HIV testing services and 61 (29.6%) in care. Provider-assisted notification had the highest number of partners referred (39.3%) followed by contract (24.3%); however the highest proportion of partners returning to the clinic for HIV testing services was by contract (48.0%) followed by dual notification (46.9%). Of 63 partners tested for HIV, 44 (69.8%) tested positive and 8 (23.5%) tested recent for HIV. The highest HIV yield among partners was reported in Nicaragua (87.9%, $p<0.01$).

Conclusion: Partner testing at VICITS clinics was accepted and yielded high HIV positivity among partners in these three countries. Additional strategies are needed to increase notification and linkage of partners to HIV testing services among key populations.

Figure 1: Cascade of HIV index patients and partners through partner referral at VICITS in Guatemala, Honduras and Nicaragua. December 2017-July 2018



931 HIV SELF-TEST UPTAKE, YIELD, AND LINKAGE EXPERIENCES AMONG KEY POPULATIONS IN LESOTHO

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Background: Lesotho has one of the world's highest HIV prevalence of 25.6% with an annual incidence of 1.47%. While Lesotho seems to be on track in achieving the UNAIDS 90-90-90 targets, results from the recent 2017 LePHIA survey revealed that the 1st 90 was lagging behind at 77.2%, despite the increase and rapid scale-up of HTS in the country. Strategies to improve HIV testing uptake and yield are needed. We describe the HIVST uptake, yield and linkage to care among Men who have sex with men (MSM), Female Sex workers (FSW), and Partners of ART, ANC and PNC clients.

Methods: The 6-months HIVST project was undertaken in 19 facilities in 3 districts of Maseru, Mafeteng and Mohale's Hoek targeting key populations, MSM and FSW and their partners, adolescents, partners of ART, ANC and PNC clients, men, migrants and patients who decline conventional HTS. Trained peer educators and HTS counsellors distributed the HIVST kits to eligible clients. The kits were coded and tracked. Clients were encouraged to drop the used kits in a drop-box. Reactive kits were tracked and their users encouraged to come for confirmation and linkage to care.

Results: A total of 5394 HIVST kits were distributed over the project period between March 14, 2018 and September 14, 2018. 2244 kits were returned (42% return rate), 2164 returned with results, 80 returned unused, 98/2164 kits were reactive giving a 5% HIV reactivity rate. Females (67) had higher reactivity when compared to males (31). High reactivity was observed among ages 20-39 with the highest among age 25-29 (21). Reactive kits were mostly among decliners (13) followed by migrants (10) and key populations (9). 58/98 clients whose kits were reactive were linked to care (59% linkage rate).

Conclusion: HIVST is feasible and generally acceptable in the target population. It should be scaled up as one of the strategies to increase uptake of HIV testing services. Targeted HIVST identifies positives resulting in a high yield. Testing on site is a more effective linkage strategy

932 HIV TESTING RATES AMONG YOUTH AND ADOLESCENTS IN ZAMBIA: WILL HIV SELF-TESTING HELP?

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Background: Zambia's national HIV prevalence is 13.3 % among the reproductive age, and the 16-24 years constitute 33% of people living with HIV. Data from 2014 indicated low testing rates among the 15-24 age group with only 46% and 37% females and males respectively aware of their status. We describe EQUIP HIV testing uptake, knowledge and use of HIV-ST among 16-24 years age group in Ndola and Kabwe districts in Zambia.

Methods: This was a cluster randomized study with before and after population level cross sectional surveys in both intervention and control clusters administering structured questionnaires to randomly selected adolescents and youths. HIV testing kits were offered to all adolescents and youth who consented for testing. Proportions for HIVST uptake, positive rates and linkage were calculated.
Results: Out of 6552 screened for HIV ST, 5353 (82%) consented for testing, with 62% male and mean age (SD) of 19 (2.1). Out of the 5353 tested, 68 (1.3%) were positive with more females (47/68) compared to males (21/68). Out of those positive 9/68 knew their HIV status with more females. Of the 56 new positive cases, 33 (59%) (Male 11, and Female 22) were successfully linked. Linkage was more likely with assisted HIV ST and same day treatment.
Conclusion: While there a high uptake of testing HIVST among this age group, the yield and linkage was low low but high among female. Targeted testing among high risk adolescent and youth is recommended. Assisted HIVST and same day treatment has high probability of linkage to Care.

933 SUSTAINED INCREASES IN HIV TESTING IN MSM WITH HIVST: A RANDOMISED CONTROLLED TRIAL

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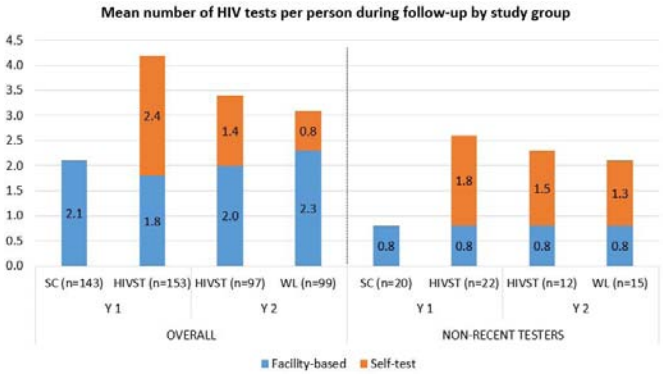
Background: HIV self-testing (HIVST) increases testing frequency in men who have sex with men (MSM). HIVST kits are not currently available in Australia. A randomised controlled trial (FORTH) in Australia showed access to free HIVST doubled the frequency of testing in high-risk MSM over 12 months, with 4-fold increase in non-recent testers (tested >2 yr ago or never tested). We report FORTH trial results from an additional year of follow-up to assess the effect of HIVST on testing frequency in the second year.
Methods: MSM who reported condomless anal intercourse or >5 male partners in the past 3 months were recruited at clinics and community sites between Dec 2013 and Feb 2015. Participants were randomly assigned (1:1) to the intervention (HIVST plus facility-based testing; n=182) or the standard care (SC; facility-based testing only; n=180) arms. After 12 months, all participants were offered HIVST for another year including SC arm (waiting-list [WL] arm in the second year). Participants completed a 3-monthly online survey to collect the number of HIV tests. The analysis population included MSM who completed the survey at 12 months, and of those who completed the end of study (24 month) survey. We calculated the mean number of tests per person and estimated the ratio of testing rates between groups using Poisson regression.
Results: 296 MSM were included in the first (153 HIVST, 160 person-years [PY]; 143 SC, 148 PY) and 196 in the second year (97 HIVST, 99 PY; 99 WL, 102 PY). Compared to SC arm (2.1), mean HIV tests per person in the second year was: 3.4 in HIVST arm (RR:1.66, 95%CI:1.42-1.94, p<0.001); and 3.1 in WL arm (RR:1.50, 95%CI:1.28-1.76, p<0.001). Testing frequency also increased among non-recent testers (RR:2.71 and 2.50, respectively). There was no statistical difference in testing frequency between HIVST and WL arms in the second year (3.4 vs 3.1, RR:1.10, 95%CI:0.94-1.29, p=0.211), but the frequency was lower in HIVST arm in the second compared to first year (3.4 vs 4.2, RR:0.83, 95%CI:0.73-0.95, p=0.008).
Conclusion: In this trial, compared to SC, HIV testing frequency was significantly higher in MSM who continued to access HIVST in the second year as well as those who accessed HIVST in the second year only. The increase in frequency was greater among non-recent testers. MSM, especially those who have not tested recently, continue to have an interest in HIVST. Thus, efforts are needed to make HIVST accessible.



934 EFFECTIVENESS OF DISTRIBUTING HIV SELF-TEST KITS THROUGH MSM PEER NETWORKS IN UGANDA

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Background: Men who have sex with men (MSM) continue to be disproportionately impacted globally by the HIV epidemic and are also highly stigmatized in Uganda. Peer-driven HIV testing strategies can be effective in identifying undiagnosed infections. We examined peer HIV oral fluid self-test kits (HIVST) network distribution effectiveness in identifying undiagnosed HIV infection among MSM in The AIDS Support Organization (TASO).
Methods: From June to August 2018, 15 MSM peers from TASO were identified and trained in HIVST and basic HIV counseling and asked to distribute 10 HIVST each through one wave to MSM who have never tested in the previous six months and link participants who test positive to care. We compared MSM peer HIVST distribution strategy to TASO MSM community and hotspot testing approaches in identifying undiagnosed HIV infection using Fisher exact test
Results: Peers distributed HIVST to 150 MSM participants,143/150 (95%) completed HIVST (72 Entebbe-urban) and 71 Masaka-semi-urban). A total of 8 participants were newly diagnosed with HIV infection; 8/72 (8.3%) from Entebbe and 2/71 (2.8%) Masaka. This is higher than 4/147 (2.7%) observed in the TASO program Jan-March 2018 (P=0.02). All participants newly diagnosed with HIV infection, disclosed their test results to their peers, were confirmed HIV positive, and initiated on ART. Compared to TASO MSM testing programs, 77% of the MSM reached through the peer HIVST distribution had never tested or tested in the last 12 months.
Conclusion: Our pilot findings suggest that distributing HIVST through MSM peer-network is effective and a promising strategy to increase uptake of HIV testing and reduce undiagnosed infections among MSM in Uganda

935 PREFERENCES FOR HIV SELF-TESTING IN SUBPOPULATIONS OF AUSTRALIAN GAY AND BISEXUAL MEN

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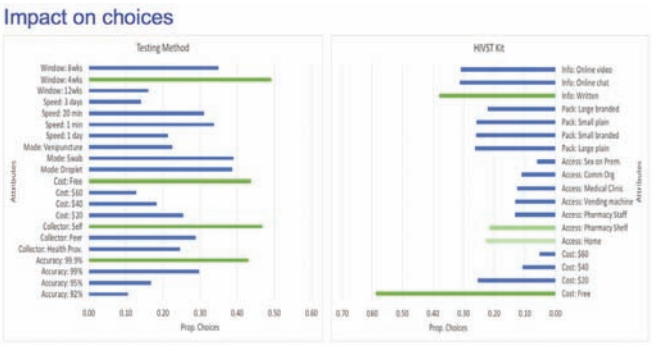
Background: In many high-income countries there are divergences in the HIV epidemic, with decreasing rates in locally born men who have sex with men but increasing or higher rates in recent migrants, ethnic populations and younger gay and bisexual men (GBM). Access to prevention services remains a challenge for these subpopulations, so innovative and discrete options for HIV testing are needed. We assessed the preferences among subpopulations of Australian GBM for HIV self-testing (HIVST) relative to other testing methods, and for how to access HIVST.
Methods: We conducted a discrete choice experiment (DCE) among HIV-negative GBM age ≥18 years in January 2018 through Grindr advertisements. Men were randomized to one of two DCEs which included a series of 16 choices, each with two alternatives for HIV testing: DCE1 for HIVST kit attributes (price, accuracy, test type, collection method and who collects the specimen) and DCE2

for HIVST access attributes (price, location, packaging and usage instructions). Latent class conditional logit regression explored variability in preferences among infrequent testers (tested >2 years ago or never tested), recent migrants (arriving in Australia <5 years), students, age and multiple partners in the last 6 months (i.e. more than one regular or casual partner). Random parameters logit model explored the most influential attributes on an individual's choice (Figure 1).

Results: Overall, 727 men participated in DCE1 and 275 men participated in DCE2. DCE1 contained four classes of men: 'recent migrants' (prefer fast results and cheaper tests, class size 23%); 'Australian-born men with multiple partners who were frequent testers' (prefer tests with shorter window periods and finger-prick HIVST, class size 33%). and 'students' (prefer fast results and oral HIVST, class size 28%). There were no significant differences in where to access HIVST according to age, number of partners in the last 6 months, recent migrant or student. There were three classes of men: 'price matters' (prefer purchasing kits online or off-the-shelf from pharmacies, class size 48%), 'infrequent testers' (prefer purchasing kits online and vending machines, class size 35%) and 'frequent testers' (disliked purchasing online and prefer purchasing off-the shelf from pharmacies or staff from medical clinics, class size 17%).

Conclusion: Quantifying preference heterogeneity in HIV testing among subpopulations of GBM may be useful for tailoring public health messages and informing HIVST distribution methods.



936 WILLINGNESS TO USE HIV SELF-TESTING AMONG MSM FROM BRAZIL, MEXICO, AND PERU

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Background: HIV self-testing (HIVST), an important tool within the combined HIV prevention package, is commercially available in Latin America since 2015. This study aims to describe factors associated with willingness to use HIVST among men who have sex with men (MSM) from Brazil, Mexico and Peru.

Methods: MSM were reached via advertisements on Facebook and GSN apps for sexual encounters (Grindr and Hornet) from March-May 2018. Participants were cisgender men, ≥18 years old and HIV negative. Willingness to use HIVST was defined as selecting the highest option on a five-point Likert scale. Factors associated with HIVST willingness were assessed using a logistic multivariable model.

Results: A total of 43,687 MSM started the questionnaire; 8,790(20%) were ineligible and 18,916(43%) completed and were included in this analysis. Median age was 28 years (IQR: 24-34). Most were from Brazil (59%), followed by Mexico (30%) and Peru (11%). The majority reported low (39%) or middle (43%) monthly income, and 32% ≤ secondary education. Recruitment was primarily (85%) via GSN apps; 46% of MSM reported daily use of these apps. Although 53% scored ≥10 points on the HIV Incidence Risk for MSM scale indicating high risk, 65% had low perceived risk of getting HIV in the next year. A total of 3,715(20%) had never tested for HIV, mostly due to fear of a positive result (28%), low self-perceived risk (21%) and shame (24%). HIVST awareness and willingness were reported by 6,578(35%) and 7,609(40%), respectively. In the multivariable model willingness to use HIVST was associated with: being from Brazil compared to Peru (AOR1.74[IC95%1.55-1.94]); being 18-24 (AOR1.19[IC95%1.08-1.31]) or 25-35 years of age (AOR1.26[IC95%1.17-1.37]) compared to ≥35; >secondary education (AOR1.33[IC95%1.24-1.44]) compared to ≤secondary education; middle (AOR1.42[IC95%1.32-1.52]) and higher income (AOR2.10[IC95%1.90-2.31]) compared to low; daily use of GSN apps (AOR1.11[IC95%1.32-1.52]); willingness to use PrEP (AOR1.44[IC95%1.35-1.54]); and recent sex under the influence of drugs (AOR1.08[IC95%1.01-1.16]). Testing-related variables (lifetime HIV testing, HIVST awareness and HIVST barriers) were also associated with HIVST in the same model (Table).

Conclusion: Willingness to use HIVST was low among MSM from Brazil, Mexico and Peru. Efforts to increase HIVST knowledge and resolve perceived barriers are warranted. HIVST delivery platforms could be incorporated to PrEP implementation programs in these countries.

Table. Factors associated with Willingness to use HIVST in Brazil, Mexico and Peru.

	aOR	95%CI	p-value
Lifetime HIV testing (at least once vs. never)	0.89	0.82-0.97	0.008
HIVST awareness (yes vs. no)	0.93	0.87-0.99	0.025
Barriers to HIVST:			
Afraid to use HIVST alone (no vs. yes)	1.12	1.03-1.20	0.002
Would know how to deal with positive result (no vs. yes)	0.70	0.65-0.74	<.0001
Would not trust in HIVST compared to conventional test (no vs. yes)	1.27	1.19-1.35	<.0001
Consider pre-test counseling essential (no vs. yes)	1.20	1.11-1.30	<.0001
Consider post-test counseling essential (no vs. yes)	0.73	0.65-0.80	<.0001
Logistic multivariable model adjusted by country, age, schooling, monthly income, daily use of GSN apps, recent sex under the influence of drugs			

937 SEXUAL RISK AND HIV TESTING DISCONNECT IN MSM RECRUITED TO AN HIV SELF-TESTING TRIAL

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Background: High levels of HIV testing in men who have sex with men (MSM) remain key to reducing HIV incidence. Current levels of testing remain sub-optimal; particularly the more frequent testing recommendations for men at higher risk of HIV through recent condomless anal intercourse (CAI). We report frequency of previous HIV testing at baseline in MSM who opted to enroll in a HIV self-testing (HIVST) RCT (SELPHI).

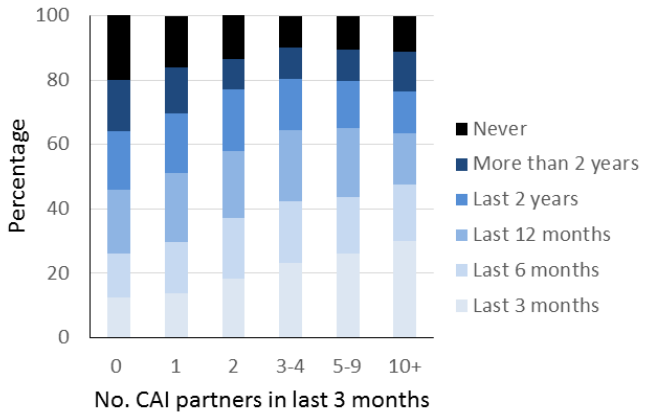
Methods: SELPHI is an internet based, open-label, randomised controlled trial, which aims to assess effectiveness of free HIVST kits on HIV diagnosis rates. Criteria for enrolment were aged ≥16 years old, male (including trans man) or trans women, ever had anal intercourse (AI) with a man, not known to be HIV positive and provided consent to link to national HIV surveillance databases. Participants were randomly allocated 3:2 at enrolment to a free HIVST versus no free HIV self-test. Data collected via an online survey included socio-demographics (gender, sexual identity, education, age, ethnicity, UK birth), sexual behaviour, HIV/STI testing history and PrEP and PEP use.

Results: 10,224 men were randomised; median age 33 years (IQR 26-44); 89% white; 20% born outside UK; <1% trans men; 47% degree educated; 8% ever used PrEP; 4% currently using PrEP. In the previous 3 months, 89% reported AI and 72% reported CAI with ≥1 male partner. Overall, 17%, 33%, 54%, and 72% had tested for HIV in the last 3 months, 6 months, 12 months, and 2 years respectively; 13% had tested more than 2 years ago and 15% had never tested. An association was observed between number of recent CAI partners and time since last HIV test (Figure 1). Among 3,972 men reporting ≥2 recent CAI partners, only 22% had tested in last 3 months and only 41% in last 6 months. In multivariate logistic regression analysis of selected sociodemographic factors, higher education level, being born outside UK and age between 20-40 years were independently associated with a higher likelihood of a recent HIV test. Only 9/388 men currently using PrEP had never tested for HIV.

Conclusion: MSM in SELPHI were not testing in line with current UK recommendations. Other SELPHI data suggest this is due to low perceived risk of HIV infection; structural barriers impacting testing opportunities (clinics difficult to access because of time constraints or capacity issues) and individual

psycho-social issues including perceived stigma. Online promotion of free HIVST may be key to addressing many of these barriers.

Figure 1. Number of condomless anal intercourse (CAI) partners in last 3 months and time since last HIV test



938 IMPACT OF EARLY ART INITIATION ON PERFORMANCE OF CROSS-SECTIONAL INCIDENCE ASSAYS

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Background: Antiretroviral treatment (ART) can impact results obtained with assays used for cross-sectional HIV incidence estimation, causing inaccurate HIV incidence estimates. We evaluated the relationship between the timing of ART initiation and the performance of two HIV incidence assays (the Sedia LAg-Avidity assay and the Johns Hopkins modified BioRad-Avidity assay).
Methods: We analyzed 302 samples from 55 individuals from, Thailand, Kenya, and Uganda (RV 217, Early Capture HIV Cohort Study). The average number of samples per participant was 5.5 (range 4-7); samples were collected 0.15 to 4.20 years after infection. Participants were assigned to one of three groups: never received ART (N=34); started ART 1-3 years after infection (N=12); started ART <1 year after infection (N=9). Samples were tested using the two assays. LAg-Avidity results from this cohort were compared to results from 17 participants in the Johns Hopkins HIV Cohort who started ART ~10 years after infection. All subjects on ART were virally suppressed.
Results: The rate of change for LAg- Avidity values in the first year after infection was 2.77 normalized optical density units (OD-n)/year for those who never started ART, and 2.65 OD-n/year for those who started ART 1-3 years after infection. Most participants (7/9) who started ART ≤1 year after infection, did not exhibit the usual increase in LAg-Avidity values early in infection. The mean decrease in LAg-Avidity values after ART initiation was 0.94 OD-n/year for those who started ART 1-3 years after infection, compared to 0.22 OD-n/year for those who started ART ~10 years after infection (p=0.003). There was no statistically significant difference in BioRad-Avidity values among those who did and did not receive ART (p=0.069).
Conclusion: Individuals who started ART 1-3 years after infection had a significantly faster decline in LAg-Avidity values than those who started ART ~10 years after infection. BioRad-Avidity values were not impacted by ART and use of this assay may provide more accurate incidence estimates in populations where ART use is unknown or inconsistent. Individuals who started ART <1 year after infection, (especially those that started ART ≤3 months after infection) had persistently low LAg-Avidity values; this could lead to overestimation of HIV incidence estimates.

939 POINT-OF-CARE RECENCY TEST TO MEASURE HIV TRANSMISSION IN KEY POPULATION IN GUATEMALA

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Background: Determining the recency of HIV infections, can help meet the UNAIDS target (90% of HIV-positive individuals knowing their status). We present preliminary results of the first point-of-care recency test in key population clinics (VICITS) in Latin America.
Methods: Men who have sex with men (MSM) and transgender women (TGW) 18 years and older who were seen at three VICITS (Colectivo-Amigos-Contra-El-Sida CAS, Fundación-Marco-Antonio FMA and Quetzaltenango health centers) in Guatemala, October 2017-July 2018, were invited to participate in the study. Rapid HIV testing was performed on site, followed by HIV-1 Asanté rapid recency test (SEDIA Biosciences) for HIV+ cases. Viral load ≥1,000 copies/mL confirmed recent infections. Reverse algorithm was used to diagnose syphilis. Sociodemographic data, risk behavior, and biological data were collected using routinely used sentinel surveillance forms and laboratory records. Data were analyzed using Stata 13.0.
Results: Of 4,264 MSM and 43 TGW reported during the project period, 3,888 (81%) were from CAS. Overall prevalence was 6.5% (95% CI 5.8-7.3 n=280) for HIV and 9.3% (95% CI 8.5-10.2 n=401) for syphilis. Of 232/280 participants who agreed to take the rapid recency test, 8 (3.4%) were not classifiable and 147 (63.4%) were long term infection. Of the 77 (33.2%) with recent infection, the majority (98%) reported a VL ≥1,000 copies/mL (median 86,400 copies/ml). Of those with recent infection, the median age was 26 years (interquartile range [IQR] 23-31), 99% were MSM, 61% self-identified as gay and 39% as bisexual, 1% reported sex work in the last 12 months, 8% reported drug use in the last 30 days, and 33% reported a syndromic STI. Highest proportion of recent infections were seen in age groups 40-49 years old (42%) compared to 20-24 years old (39%) (p=.6). Patients receiving control visits at VICITS were less likely to have recent infection compared to first time patients (Odds Ratio 0.39, 95% CI 0.27-0.57).
Conclusion: Our results show a high proportion of recent infections among MSM and TGW. This data can help improve prevention interventions targeting key populations in Guatemala and Central America. The use of a point-of-care recency test can help countries allocate resources, evaluate interventions, and adjust programs as needed.

940 FIRST USE OF POINT-OF-CARE HIV RECENCY TESTS AS A SURVEILLANCE TOOL IN NICARAGUA

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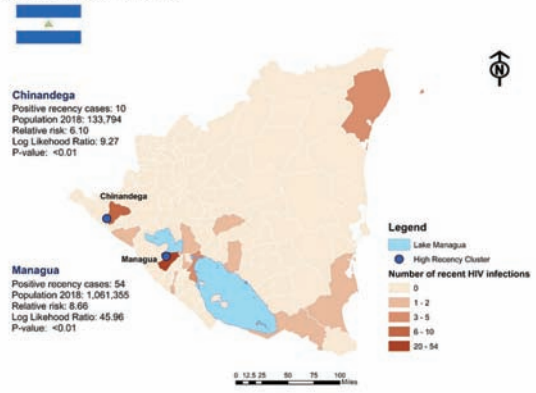
Background: Routine assessment of transmission dynamics facilitates the universal test-and-treat approach for persons living with HIV (PLHIV) and ensures that interventions target those with highest risk. Rapid recency tests can distinguish recent (on average, in the past 6 months) from non-recent infection, enabling healthcare workers to detect, monitor, and respond to recent infections. We describe the first use of point-of-care recency tests as a surveillance tool in Nicaragua.
Methods: From January to July 2018, all persons diagnosed with HIV per the national HIV testing algorithm at 205 public testing sites had blood samples sent to the National Center for Diagnostic and Reference (CNDR) for confirmation. The rapid recency assay for HIV-1 (SEDIA Biosciences) was performed onsite for PLHIV diagnosed at key population clinics and at the CNDR for all other samples. Viral load testing was performed using COBAS Amplicor/Ampliprep HIV 2.0 (Roche Diagnostics) on all samples testing recent to confirm recency of infection (≥1,000 copies/mL). Surveillance variables (age, sex, sexual orientation, and place of residence) were recorded in a database. We conducted univariate analysis to describe characteristics of PLHIV with recent infection (Stata 13.0) and identified areas with statistically significant recent HIV infection (p values

<0.05) by comparing observed versus expected number of recently infected individuals (SatScan).
Results: Of the 452 PLHIV with a new diagnosis and recency test performed during the assessment period, 84 (19%) tested recent; of these, 58 (69%) had a viral load ≥1,000 copies/mL. The median age (33 years; range, 14–64 years) among PLHIV with recent infections was significantly lower than the median age (49 years; range, 14–73) among PLHIV with long-term infections (p=0.03). Of those with a confirmed recent infection, 83% were men, 31% were men who have sex with men, and 59% lived in Managua. Of 17 clusters identified, 2 had high rates of HIV recency with 2.9–6.1 times more recent infections than expected, with Managua having the highest relative risk.
Conclusion: Most men and Managua PLHIV residents tested recent. A visual dashboard and maps identifying potential clusters of recent transmission were developed and are updated weekly to facilitate real-time analysis and response.

Figure 1. Municipalities in Nicaragua with high proportion of people recently infected with HIV (January–July 2018)



941 PERFORMANCE COMPARISON OF THE MAXIM AND SEDIA LIMITING ANTIGEN AVIDITY ASSAYS

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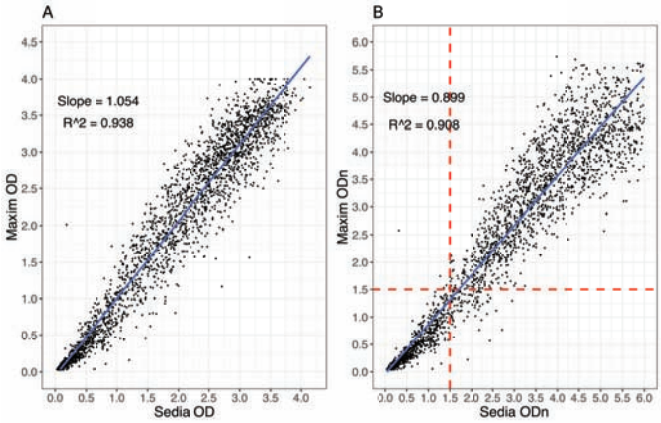
Background: The HIV-1 Limiting Antigen Avidity EIA (LAg assay) used for detecting 'recent' HIV infection is mainly from two manufacturers: Maxim Biomedical and Sedia Biosciences. We assessed and compared the performance, for incidence estimation, of the Maxim and Sedia LAg assays.
Methods: We ran both assays on a panel of 2,500 well-characterised HIV-1-infected specimens, most with estimable duration of HIV infection. We analysed concordance of assay results, assessed reproducibility using repeat testing, and estimated the critical performance characteristics of a test for recent infection – mean duration of recent infection (MDRI) and false-recent rate (FRR) – for a range of normalised optical density (ODn) recency discrimination thresholds, in combination with viral load thresholds. We further specified three surveillance scenarios defined by incidence, prevalence, treatment coverage, and subtype and infection-time distributions based on A) South African B) Kenyan, and C) concentrated MSM epidemics. Overall performance was measured as precision of incidence estimates.
Results: ODn measurements produced by the two assays on the same specimens were highly correlated (R^2=0.91). The Maxim assay produced systematically lower ODn values (mean ODn of 0.643 vs 0.749), largely as a result of higher calibrator readings. Correlation was greater for non-normalised OD readings (R^2=0.94) and the slope was closer to 1 (1.054 for OD vs 0.899 for ODn). Reproducibility of repeat testing (25 replicates of 3 blinded control specimens) was slightly greater for the Maxim assay (CoV 8.9% to 14.8% vs 13.2% to 15.0%). At the 'standard' recency discrimination threshold of ODn≤1.5, in combination with a viral load threshold (>1000), the Maxim assay had a longer MDRI of 201 days (95% CI: 180,223) vs 171 days (152,191) for Sedia, and a higher FRR in treatment-naive subjects (1.7% vs 1.1%). Under surveillance scenario A, the minimal relative standard errors achieved, in combination with viral load, were 22.8% (at ODn≤3.25 & VL>1000) for Maxim, and 23.4% (at ODn≤3.00 & VL>1000) for Sedia.
Conclusion: Maxim LAg ODn values can be approximately inferred from Sedia values with a conversion factor of 1.172, arising from differences in the reactivity of calibrators supplied in the assay kits. Performance for surveillance purposes was indistinguishable, although different thresholds were nominally optimal, and, crucially, different values of MDRI and FRR must be used in survey planning and incidence estimation.



942 IMPACT OF HIV-1 SUBTYPE AND SEX ON SEDIA LIMITING ANTIGEN AVIDITY ASSAY PERFORMANCE

Eduard Grebe[1], Gary Murphy[2], Sheila M. Keating[3], Dylan Hampton[3], Michael P. Busch[3], Shelley Facente[4], Kara Marson[4], Christopher D. Pilcher[4], Andrew Longosz[5], Susan H. Eshleman[5], Thomas C. Quinn[5], Alex Welte[1], Neil Parkin[6], Oliver Laeyendecker[5], for the Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA)
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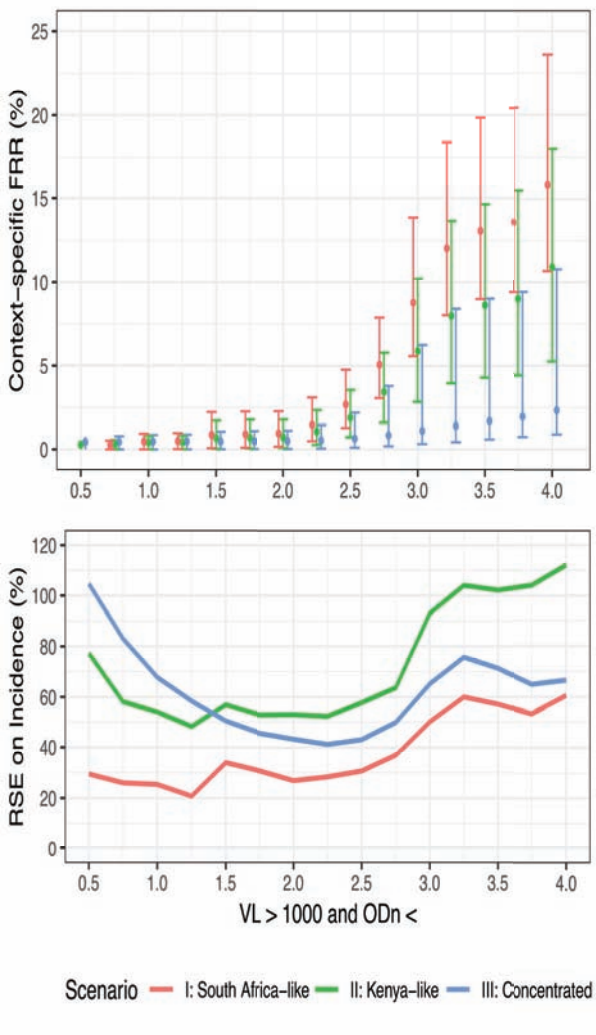
Background: We evaluated Sedia Limiting Antigen Avidity EIA (LAg)-based recent infection testing algorithms (RITAs) for incidence surveillance, using data from seroconverter cohorts, consisting of 10,322 specimens from 2,297 subjects.. We investigated the impact of HIV-1 subtype and sex on mean duration of recent infection (MDRI) and false-recent rate (FRR).
Methods: We estimated MDRI and FRR for a range of RITAs consisting of LAg ODn thresholds, alone, and in combination with viral load. To estimate MDRI, we harmonised time-since-infection estimates for all subjects based on diagnostic testing histories. We fitted regression models for the probability of exhibiting the recent biomarker as a function of time since infection, for each threshold combination and separately for each HIV-1 subtype, and integrated the function from zero to the time cut-off T (2 years) to obtain MDRI. To evaluate surveillance performance, we defined epidemiological scenarios (subtype distribution, incidence, prevalence, treatment coverage) based on (I) the South African, (II) the Kenyan, and (III) a concentrated MSM epidemic. We estimated context-adapted MDRI (weighted average of subtype-specific MDRIs, adjusted for screening test) and context-specific FRR (weighted according to density of the times-since-infection and treatment coverage in the population). Uncertainty in epidemiological parameters was incorporated. Performance was defined as precision of incidence estimates.
Results: Using all subtypes, MDRI for a RITA with ODn≤1.5 and VL>1000 was 143 days (95% CI:132,155) and FRR in untreated subjects 1.88% (1.26,2.68). Subtype MDRIs (in days) were as follows: A: 165 (128,210), B: 161 (136,190), C: 130 (116,143) and D: 184 (130,248). Differences between subtype-specific MDRIs were statistically significant for B&D (at 90% confidence level, p=0.071) and C&D (p<0.001). MDRIs and FRRs increased with ODn threshold. Women had a 47 day shorter MDRI than men (p<0001). No statistically significant difference was seen between pregnant and non-pregnant females (p=0.482). Context-

specific FRRs increased above 1% at ODn thresholds above 2.0, resulting in poorer precision, as shown in the figure. In scenarios I and II, precision was best at ODn≤1.25, and in III at ODn≤2.25.
Conclusion: MDRI and FRR vary by substantially HIV-1 subtype and sex. Optimal performance was achieved at ODn thresholds from 1.0-2.5. RITA properties depend strongly on population-level subtype and sex distributions.



943 ANTIBODY PROFILING IDENTIFIES NOVEL BIOMARKERS FOR DURATION OF HIV INFECTION

Oliver Laeyendecker[1], Kai Kammers[1], Athena Chen[2], Mariya V. Sivay[1], Brandon Sie[1], Tiezheng Yuan[1], Divya Mohan[1], Daniel Wansley[1], Tomasz Kula[3], Charles S. Morrison[4], Stephen Elledge[3], Ron Brookmeyer[5], Ingo Ruczinski[2], H. Benjamin Larman[1], Susan H. Eshleman[1]
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Background: Improved methods for cross-sectional HIV incidence estimation are needed for surveillance of the epidemic and for evaluating the impact of HIV prevention interventions. We used a massively-multiplexed system, VirScan, to identify novel biomarkers for estimating the duration of HIV infection. This system uses phage display immunoprecipitation sequencing to quantify antibody (Ab) binding to >3,300 peptides spanning the HIV genome.
Methods: We analyzed 403 samples from 57 African women with known duration of infection (14 days to 8.7 years). Ab binding to each peptide in the VirScan library was quantified, and peptides with the strongest association of Ab binding with duration of HIV infection were identified. We used generalized estimating equations to analyze the association of Ab binding with duration of HIV infection, accounting for repeat sampling from the same individuals. An independent sample set from the same cohort was used to validate results (72 samples from 32 women infected 84 days to 9.1 years).
Results: We identified 309 peptides that had a significant association between Ab binding and duration of infection ($p<0.05$ after adjusting for multiple comparisons); 266 peptides had increasing Ab binding over time and 43 peptides had decreasing Ab binding over time. Four peptides were selected for further analysis (two with increased binding: in gp120 and gp41; two with decreased binding: in gag and pol). The binding scores for these four peptides were combined in a simple, unweighted, linear model to estimate the duration of infection. This estimate was highly correlated with the observed (true) duration of infection ($p < 3 \times 10^{-36}$ in the independent sample set). The predictive value of the 4-peptide «serosignature» did not appear to be impacted by low viral load, low CD4 cell count, or HIV subtype. We also demonstrated that peptide engineering could be used to improve the association of Ab binding and duration of HIV infection.
Conclusion: Deep profiling of the antibody response to HIV infection identified novel peptide biomarkers for the duration of HIV infection. Peptides identified using this approach could be incorporated into simpler, high-throughput assays for cross-sectional HIV incidence estimation and other applications.

944 INCIDENCE OF HIV IN A NATIONAL COHORT RECEIVING PREEXPOSURE PROPHYLAXIS

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Background: Once daily tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) was FDA approved for pre-exposure prophylaxis (PrEP) for HIV prevention in July 2012. Veterans Health Administration (VHA) is the largest single provider of HIV care nationally thus offers a unique opportunity to examine PrEP in a large cohort. We aimed to determine the incidence of HIV infection in patients initiating PrEP and to describe relationships between HIV cases and patterns of PrEP use.
Methods: We conducted a retrospective cohort study among patients initiating PrEP in VHA between July 2012 and April 2016 using national VHA data and a previously described algorithm. We identified cases of HIV infection after PrEP initiation based on lab data (i.e. HIV serology and viral load results). We defined the date of PrEP initiation by date of first TDF/FTC fill. Adherence measure was calculated by determining the number of days with TDF/FTC in possession between the first day of the first TDF/FTC fill and the first day of the last fill in the year and dividing this by the number of days in this interval. We defined days without pills as numbers of days without TDF/FTC in possession prior to send date of first positive HIV test. To calculate HIV incidence, we considered the total patient time from first fill to the date of the last pill of the last fill available. We used chart review to determine patient-reported PrEP use around time of diagnosis.
Results: We identified 825 unique patients initiating PrEP with a median observed PrEP duration of 8 months and a cohort total of 736.6 years. Our cohort was composed of 97% men, 67% white patients, and with a mean age of 41 years. Two HIV infections occurred during active PrEP use for an incidence of 0.3 cases per 100 person years (Poisson exact 95% CI = (0.03, 0.98)). Both patients were infected with viruses containing the M184V mutation and had perfect adherence based on fill data. Four additional cases were observed in this cohort, diagnosed during periods without PrEP. Among these 4, days without pills ranged from 4 to 162 days.
Conclusion: HIV infection was rare in this nationwide cohort of PrEP users. Most HIV infections occurred off PrEP, emphasizing the need for interventions to improve PrEP persistence in persons with ongoing risk.

945 HIV-1 INCIDENCE AND RISK FACTORS FOR ACQUISITION AMONG KENYAN MSM WITH ACCESS TO PrEP

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Background: There are no data on reduction of HIV-1 incidence following programmatic pre-exposure prophylaxis (PrEP) uptake by men who have sex with men (MSM) in sub-Saharan Africa. We assessed HIV-1 incidence and predictors of HIV-1 acquisition in at-risk MSM with access to PrEP in coastal Kenya.

Methods: Since June 2017, at-risk MSM followed at monthly visits in an HIV-1 vaccine feasibility cohort study were offered PrEP with adherence and risk reduction counselling, monthly HIV-1 testing and X-pert RNA Qual testing if acute HIV-1 risk criteria were met. Participants who acquired HIV-1 and had documented seroconversion were offered immediate ART. MSM were categorized as taking PrEP if they received a PrEP refill at their previous visit and wanted to continue PrEP during their current visit. Those not receiving a PrEP refill in their previous visit or discontinuing, re-starting or starting PrEP during their current visit were categorized as not on PrEP. Participants who reported missing 6 or less days of PrEP since their last monthly refill were categorized as ≥80% adherent. We used population-averaged multivariable Poisson regression with robust variance estimation to identify predictors of HIV-1 acquisition, analyzing PrEP use defined as above, as well as based on ≥80% reported adherence.

Results: Of 178 MSM who were offered PrEP, 142 (79.8%) started, of whom 31 (17.4%) stopped during follow-up. 89.4% of PrEP users reported ≥80% adherence. During a median follow-up of 14.3 (interquartile range: 8.9–14.6) months, 7 MSM acquired HIV-1, for an incidence rate of 4.1 (95% confidence interval [CI] 2.0–8.7) per 100 person-years. Of the 7 MSM who acquired HIV-1, 4 were not taking PrEP and 3 were, including 2 who reported ≥80% adherence. In multivariable analysis, group sex (adjusted incidence rate ratio [aIRR] 9.9, 95% CI 1.4–68.2) and a recent gonorrhoea infection (aIRR 11.2, 95% CI 1.1–116.7) were independent predictors of HIV-1 acquisition, after adjustment for age, sexual orientation, and alcohol use. The aIRR for any PrEP use was 0.3 (95% CI 0.0–2.2). When ≥80% adherence was tested in the same model, the aIRR was 0.2 (95% CI 0.0–1.9).

Conclusion: HIV-1 incidence among at-risk MSM with access to programmatic PrEP was high, and did not differ by PrEP use or reported adherence. A substantial proportion of MSM stopped taking PrEP despite frequent risk reduction counselling. Further research on PrEP adherence and tenofovir drug levels in this cohort is necessary.

946 DOSE-DEPENDENT DECLINE IN BONE MINERAL DENSITY BY LONG-TERM TFV EXPOSURE IN IPREX-OLE

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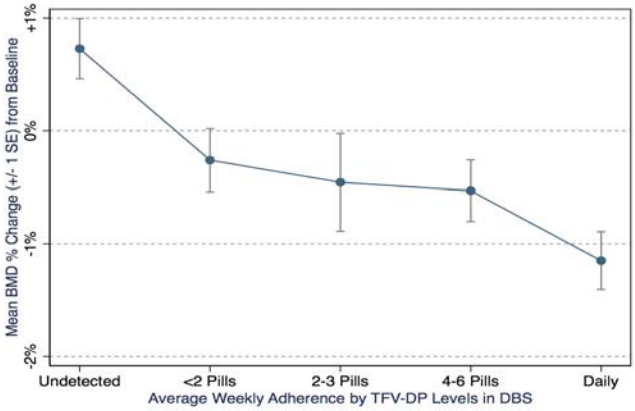
Background: Oral tenofovir (TFV)-containing PrEP is associated with modest declines in bone mineral density (BMD). TFV-DP in dried blood spots (DBS) is a long-term marker of TFV exposure well-suited for evaluating the relationship between exposure and toxicities. Characterization of BMD change by estimated weekly pill-taking can assist clinicians in counseling patients, and potentially support use of intermittent PrEP for those at high risk of toxicity. We evaluate the association of dosing frequency and BMD decline for the first time in a large PrEP demonstration project.

Methods: Men who have sex with men and transwomen in the optional dual-energy X-ray absorptiometry (DXA) substudy of iPrEx OLE underwent DXA scans and DBS collection at baseline and every 24 weeks. TFV-DP levels were measured in DBS; average weekly dosing adherence was estimated from validated cut-offs. The mean % change in BMD was estimated in each strata of average weekly adherence using a linear mixed effects model.

Results: DXA/DBS data were available for 254 individuals over a median of 24 weeks in iPrEx OLE from 6/11-12/13. Overall, the median age was 31 years and 9% identified as transwomen; 15% were Black, 38% Latino. At baseline, 9% had Z-scores <-2 at either spine or hip and 3% developed low Z-scores after starting PrEP. There was a dose-dependent % decline in spine BMD by strata of increasing average weekly adherence (p<0.001 trend); the p-value for trend using the hip BMD outcome was 0.07. When including age, race/ethnicity, gender, body mass index, smoking, stimulant use, and alcohol use in an adjusted model, only DBS levels predicted spine BMD decline (p<0.001). All who developed low Z scores had detectable TFV, and most (57%) had high adherence (≥700 fmol/punch). The average mean decline in spine BMD was -1.15% (95% CI: -1.65, -0.64) for estimated daily adherence vs. -0.53% (95% CI: -1.06; 0.00) for 4-6 doses per week vs. -0.46% (95% CI:-1.31, 0.39) for 2-3 doses/wk vs -0.26% (95% CI: -0.81, 0.29) for <2 doses/wk, compared to a 0.72% increase (95% CI: 0.20; 1.25) in those who were not taking PrEP (TFV-DP below limit of detection) (Figure).

Conclusion: We found approximately a 1% drop in BMD in highly adherent PrEP users over a median of 24 weeks, with a monotonic relationship between PrEP weekly pill-taking and degree of BMD loss. Future research should explore if dose-limiting strategies such as intermittent PrEP can decrease the risk of bone loss for individuals at higher risk.

Figure: Mean % Bone Mineral Density (BMD) Change from Baseline by Dried Blood Spot (DBS) Estimated Weekly Dosing Frequency in iPrEx OLE



947 LOW URINE TFV BY A NOVEL IMMUNOASSAY IS ASSOCIATED WITH HIV SEROCONVERSION ON PrEP

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Background: Pharmacologic adherence measures can be used to interpret and support PrEP adherence. Current methods to analyze tenofovir (TFV) levels use liquid chromatography-tandem mass spectrometry (LC-MS/MS), which limits clinical use given cost and run time. We developed a novel antibody-based assay (in development for point-of-care (POC) testing) to quantify TFV in urine. We then tested the association of urine TFV with HIV acquisition in iPrEx OLE, a PrEP demonstration trial that enrolled men and transwomen.

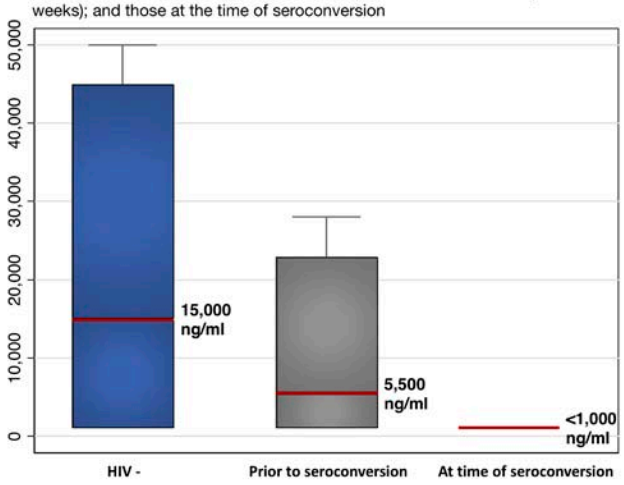
Methods: Spearman's correlations between urine TFV levels via the immunoassay and hair TFV/emtricitabine(FTC) and dried blood spot (DBS) TFV-DP/FTC-TP levels via LC-MS/MS in iPrEx OLE were calculated. We calculated the sensitivity/specificity of an undetectable urine TFV for very low DBS TFV-DP levels (estimated <2 doses/week). We then compared levels of urine TFV by the immunoassay at visits where seroconversion was diagnosed, prior to HIV seroconversion, and in those who remained HIV-negative using Kruskal-Wallis' test. We evaluated the association of an undetectable urine TFV with HIV seroconversion using generalized estimating equations.

Results: Among 125 participants, the median age was 33, 14% were Black, 44% Latino. Urine TFV levels correlated with hair TFV (P 0.4, p<0.001), hair FTC (P 0.5, p<0.001), DBS TFV-DP (P 0.5, p<0.001) and DBS FTC-TP levels (P 0.7, p<0.001). When comparing an undetectable urine TFV to very low adherence by DBS (estimated <2 tablets/week) it was 70% sensitive, but 94% specific (100% sensitive/81% specific compared to undetectable DBS levels). The median urinary TFV level by the immunoassay was 15,000 ng/ml (IQR: 1,000-45,000) in those who remained HIV-negative; 5,500 (IQR: 1,000-23-000) in 11 individuals who eventually seroconverted (median 36 wks prior); and undetectable (<1000 ng/ml) in all 9 individuals at the time of seroconversion (p<0.001) (Figure).

Undetectable urine TFV via the immunoassay was strongly associated with HIV seroconversion (OR 2.8; 95%CI: 1.5-5.4, p=0.002).

Conclusion: Urine TFV levels measured by a novel antibody-based assay were associated with protection from HIV acquisition among participants in a PrEP demonstration project. Urine TFV levels were correlated with other pharmacologic measures (hair/DBS), with high specificity in detecting sub-optimal dosing. Since immunoassays allow for POC testing, this novel assay could detect low PrEP adherence detected in real-time, allowing immedidate intervention to optimize PrEP outcomes.

Figure: Box plot showing ELISA-immunoassay urine TFV levels among iPrEx OLE participants who did not acquire HIV; those prior to seroconversion (median 36 weeks); and those at the time of seroconversion



*Red lines indicate median levels

948 NO EVIDENCE OF SEXUAL RISK COMPENSATION AMONG HIV SERODISCORDANT COUPLES ON PrEP

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Background: Recent studies suggest evidence of increased HIV risk-related sexual behaviors, such as condomless sex, following initiation of pre-exposure prophylaxis (PrEP) among men who have sex with men and female sex workers. We explored the effect of PrEP initiation on condomless sex among HIV serodiscordant heterosexual couples in Kenya and Uganda.

Methods: We used longitudinal data from HIV-uninfected participants enrolled in the Partners Demonstration Project, an open-label study of PrEP delivered to HIV-uninfected members of HIV serodiscordant heterosexual couples in Kenya and Uganda from 2012-2016. Participants were encouraged to use PrEP until their HIV-infected partner had used ART for ≥6 months (expected to be commensurate with viral suppression). At each quarterly visit, participants self-reported the frequency of sex and condom use with their study partner in the past month. We used linear regression models with individual-level fixed effects to measure the effect of PrEP initiation and time since PrEP initiation on reports of any condomless sex, controlling for the frequency of sex and self-reported pregnancy desires. We restricted our analysis to participants who reported any sex with their study partner in the past month during follow up time prior to the HIV-infected partner using ART for ≥6 months.

Results: Of the 1013 HIV-uninfected individuals enrolled in the study, 974 (96%) initiated PrEP and reported sex with their study partner in the past month. In the month following PrEP initiation, reporting any condomless sex decreased from 65% to 32%, a decline of 33% (95% CI -37% to -30%, p<0.001). The prevalence of condomless sex between study partners on PrEP then remained relatively constant over the next 20 months (median: 33%, IQR 30%-35%), Figure 1. The overall effect of time since PrEP initiation on condomless sex between study couples was a decline of 33% (95% CI -35% to -20%, p<0.001).

Conclusion: We found no evidence of sexual risk compensation following PrEP initiation in a cohort of Kenyan and Uganda HIV heterosexual serodiscordant couples followed for two years. Despite declines in condomless sex shortly after PrEP initiation, roughly a third of the HIV serodiscordant heterosexual couples in the study continued to engage in condomless sex, emphasizing the importance of continued PrEP use to sustain HIV protection.

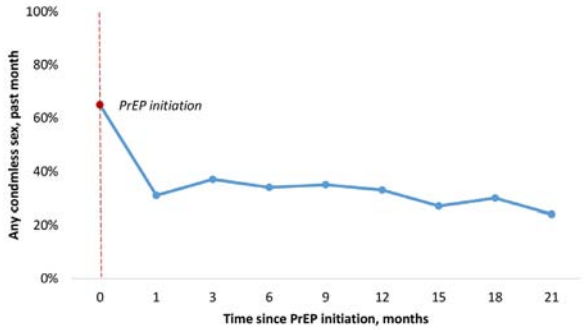

Figure 1. The prevalence of condomless sex between HIV serodiscodant heterosexual couples since PrEP initiation.

949 Y-CHROMOSOME DETECTION & CONDOMLESS SEX IN SEX WORKERS IN THE SENEGAL PrEP PROJECT

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Background: Oral Truvada (FTC/TDF)–based PrEP has the potential to reduce HIV acquisition in female sex workers (FSW). Condom use is still recommended with PrEP due to concerns about adherence, HIV and STI acquisition. If FSW think they are protected from HIV from PrEP there may be incentives to reduce condom use: costs, client preference and ability to charge more for condomless sex. Self-reported condom use measures have significant limitations and biases. Detection of male Y-chromosomes (Y-c) in FSW genital swabs is a potential biomarker for condomless sex.

Methods: During the Senegal PrEP Demonstration Project, vaginal swabs were collected from women at baseline (pre-initiation of PrEP) and quarterly from PrEP initiation for 1 year. Vaginal swabs were frozen and tested in bulk at UW-Seattle. A random sample of 165 swabs were chosen for Y-c testing throughout the study period. The Quantifiler® Duo DNA Quantification Kit was used for Y-c detection. We analyzed self–reported condom use, STI (N. gonorrhoeae and C. trachomatis by NAAT (GC/CT)) and Y-c detection.

Results: 165 vaginal swab samples from 132 FSW were tested for Y-c. 164 samples gave valid results. 35/164 (21.3%) samples from 32 (24.2%) FSW contained detectable Y-c. (Baseline: 7/42 (16.7%); M1-3: 11/39 (28.2%); M6: 6/21 (28.6%); M9: 4/25 (16.0%); M12: 7/37 (18.9%). Overall, there was no significant difference between baseline and PrEP use for detection of Y-c (P>0.05, Fisher Exact Test). In 32 FSW with serial Y-c sampling, 59.4% were always negative; 9.4% were always positive; 3.1% were initially negative and then positive; and 28.1% were initially positive and then negative. Eight FSW who were screened for Y-c presence had a positive NAAT for GC and/or CT on at least one visit, however only one FSW had concurrent tests positive for both Y-c, GC and CT. All FSW with available data (N=27), whom had detection of Y-c in vaginal swabs, also self–reported consistent condom use in the preceding 7 days with all clients. "Main partner" condomless sex did not account for the majority of Y-c detection.

Conclusion: A significant number (24.2%) of FSW had presence of Y-c on genital swabs suggesting lack of or inconsistent condom use. Y-c detection was consistent throughout the year–long study period, suggesting lack of risk compensation due to Truvada use. STI were infrequent. Condomless sex, as detected by Y-c in vaginal swabs, appears common in FSW who self-reported consistent condom use, casting doubt on this proxy for measuring their use.

950 RISK COMPENSATION FOLLOWING PrEP DISCONTINUATION AMONG HIV-SERODISCORDANT COUPLES

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Background: Time-limited PrEP use by HIV-negative members of HIV serodiscordant couples until the HIV-positive partner achieves and sustains viral suppression with antiretroviral treatment (ART) is a highly effective HIV prevention strategy. Whether transitioning from self-controlled PrEP protection by the uninfected partner to relying on effective ART use by the HIV-positive partner results in a reduction in condomless sex has not been assessed.

Methods: Data are from the Partners Demonstration Project, a prospective open-label PrEP demonstration study in Kenya and Uganda. HIV-negative partners in serodiscordant couples were provided with PrEP and encouraged to discontinue PrEP when their HIV-positive partner used ART for >6 months (unless there were additional partners, ART adherence concerns, or immediate fertility desires). We included all couples with an HIV-negative partner that discontinued PrEP due to the HIV-positive partner being on ART for ≥6 months. Self-reported numbers of sex acts and condomless sex acts in the past month were collected quarterly. We used segmented regression with zero-inflated negative binomial models to compare the levels and rates of change of sexual behaviors before and after the HIV-negative partner discontinued PrEP. Multivariable models adjusted for demographics, baseline sexual behavior, pregnancy and couple relationship status.

Results: We included 567 couples who were followed for 622 person-years while the HIV-negative partner was on PrEP and for 506 person-years after PrEP discontinuation. HIV-negative partners had a median age of 30 years and were female in 33% of couples. In multivariable analyses, there was a 40% decrease in condomless sex acts reported after PrEP discontinuation (rate ratio [RR]=0.60, 95% CI: 0.41-0.87) where the HIV-negative partner was female. There was no change among couples where the HIV-negative partner was male (RR=1.03, 95% CI: 0.84-1.28), ≤30 years of age (RR=1.06, 95% CI 0.83-1.38), or >30 years of age (RR=0.77, 95% CI: 0.58-1.02). We found no difference in the rate of change in sexual risk behaviors after PrEP discontinuation regardless of HIV-negative partner gender or age.

Conclusion: Discontinuation of PrEP by HIV-negative partners due to sustained ART use by their HIV-positive partners did not result in an increase in sexual frequency or condomless sex. However, couples with female HIV-negative partners engaged in fewer condomless sex acts immediately after PrEP discontinuation.

951 VOLUNTARY MEDICAL MALE CIRCUMCISION IN SWAZILAND: ACHIEVEMENTS AND GAPS

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Background: Medical male circumcision (MMC) lowers the risk of heterosexually acquired HIV infection in men by approximately 60%. In Swaziland, self-reported MMC prevalence among adult males (18+years) was 8% in the 2007 Demographic and Health Survey, and 17% in the 2011 Swaziland HIV Incidence Measurement Survey (SHIMS), SHIMS1. The global target for MMC coverage is 80% in high HIV prevalence countries, and the Swazi national target is 70% by 2018. We assessed self-reported MMC prevalence in the 2016/7 SHIMS (SHIMS2).

Methods: SHIMS2 was a nationally representative, two-stage cluster randomized, cross-sectional household survey. From August 2016 to March 2017, male participants 15+ years self-reported MMC status through an individual questionnaire. We calculated the MMC prevalence by sociodemographic characteristics and HIV status. The Rao-Scott chi-square test was used to test group differences. Multivariate logistic models evaluated the associations between MMC status and sociodemographic characteristics: age, education, wealth quintile, location, marital and HIV status. All analyses were adjusted for survey design, non-coverage, and non-response.

Results: Among the 4,815 men (median age 29.2 years, Interquartile range [IQR]: 19.9, 42.8), overall MMC prevalence was 27.1% (95% Confidence Interval [95% CI]: 25.3-29.0%) peaking in the age group 15-19 years 38.7% (95% CI: 35.1-42.3%) and lowest in the age group 65+ years 7.9% (95% CI: 4.8-11.1%), p<0.0001. In the multivariate analysis, the odds of self-reporting MMC were significantly lower among men aged 25+ (aOR=0.69, 95 CI%: 0.57-0.85) versus 15-24 yrs men; HIV positive men (aOR=0.55, 95% CI: (0.44-0.69); married men (aOR=0.72, 95%CI: 0.58-0.89) versus never married men; men with no education (aOR=0.52, 95%CI: 0.34-0.81) versus those with primary schooling. Compared to men in the middle wealth quintile, men in the highest quintile were more likely to self-report MMC (aOR=1.47, 95% CI: 1.09-1.97). Among males 18-49 years, MMC prevalence increased from 17% (95% CI: 16.2-18.4) in SHIMS1 to 28% (95% CI: 26.0-30.4) in SHIMS2.

Conclusion: Although a modest increase in MMC prevalence has been observed since 2011, the national and international targets will likely not be met. Innovative MMC approaches are needed to increase MMC prevalence, particularly among uneducated, low wealth and older men.

Table 1. The prevalence and risk factors of MMC among men 15 years and older in SHIMS2

	MMC%	(95% CI)	Unweighted number of circumcised men	Unweighted total number of men	Univariate model		multivariate model	
					Crude Odds Ratio	(95% CI)	Adjusted Odds Ratio	(95% CI)
Age*								
15-24	35.22	(31.87-38.57)	632	1764	1	Reference	1	Reference
25+	22.35	(20.63-24.06)	633	3051	**0.53**	**(0.45-0.62)**	**0.69**	**(0.57-0.85)**
Marital status*								
Never married	32.15	(29.39-34.92)	882	2735	1	reference	1	reference
Married	20.01	(17.6-22.41)	284	1558	**0.53**	**(0.44-0.63)**	**0.72**	**(0.58-0.89)**
Living together	21.17	(15.21-27.14)	45	223	**0.57**	**(0.38-0.85)**	0.77	(0.47-1.25)
Divorced/separated	22.66	(16.25-29.07)	39	178	**0.62**	**(0.42-0.90)**	0.99	(0.65-1.51)
Widowed	8.46	(1.65-15.26)	7	94	**0.2**	**(0.07-0.52)**	**0.32**	**(0.12-0.87)**
Education*								
No education	11.08	(6.83-15.33)	27	259	**0.4**	**(0.26-0.61)**	**0.52**	**(0.34-0.81)**
Primary	23.8	(21.46-26.13)	348	1466	1	reference	1	reference
Secondary	28.49	(25.38-31.61)	356	1279	**1.28**	**(1.05-1.55)**	1.09	(0.87-1.36)
High school	29.83	(26.38-33.27)	388	1356	**1.36**	**(1.12-1.65)**	1.1	(0.90-1.33)
Tertiary	32.24	(27.38-37.1)	146	449	**1.52**	**(1.20-1.94)**	**1.24**	**(0.96-1.59)**
Wealth quintile*								
Lowest	24.33	(21.26-27.4)	248	1060	0.97	(0.77-1.22)	1.03	(0.79-1.34)
Second	25.77	(22.63-28.9)	258	1025	1.05	(0.84-1.31)	1.04	(0.80-1.34)
Middle	24.9	(22.08-27.71)	276	1137	1	reference	1	reference
Fourth	27.17	(23.44-30.89)	215	786	1.13	(0.88-1.44)	1.15	(0.89-1.48)
Highest	34.42	(29.24-39.59)	268	806	**1.58**	**(1.17-2.13)**	**1.47**	**(1.09-1.97)**
HIV status*								
HIV positive	15.45	(12.64-18.26)	137	955	**0.42**	**(0.34-0.53)**	**0.55**	**(0.44-0.69)**
HIV negative	30.1	(28.02-32.19)	1025	3475	1	reference	1	reference

*p-value<0.05 for the group differences in MMC rate.

952 SHIKAMANA INTERVENTION SIGNIFICANTLY REDUCES HIV INCIDENCE AMONG FSW IN TANZANIA

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Background: Female sex workers (FSW) are at dramatically heightened risk for HIV compared to women overall, with 13.5 greater odds of being HIV-infected globally. In Tanzania, modeling has shown FSW and their clients represent 23% of incident HIV infections. A prior systematic review and meta-analysis found that community-driven combination prevention models have been found to reduce the risk for HIV infection by 32% among FSW in Latin America and South Asia, but no proven models exist for FSW in sub-Saharan Africa.

Methods: We conducted a two-community randomized controlled trial of a community-driven combination HIV prevention model among 496 FSW (203 HIV+ and 293 HIV-) enrolled in a longitudinal cohort in Iringa, Tanzania. The multi-level intervention model was developed based on extensive formative research and anchored on FSW needs and priorities. The intervention included: community drop-in-center and mobilization activities, peer education and navigation services, mobile HIV testing, clinical care provider and police sensitivity trainings, and SMS reminders to promote care engagement and ART adherence. At baseline and 18-month follow-up, study participants were surveyed and screened for HIV infection, the presence of ART in the blood, and viral load. Poisson robust regression and propensity score matching was utilized to compare HIV incidence and viral load at follow-up between the intervention and control communities.

Results: Participants in the intervention community were significantly (62%) less likely to become infected with HIV at follow-up (OR 0.38; p=0.047), with an HIV incidence of 5.0% in the intervention vs. 10.4% in the control arm. We also observed a significant difference in reductions in inconsistent condom use from baseline to follow-up between the intervention (72.0% to 43.6%) vs. control (68.8% to 54.0%) community (p=0.042). As shown in Table 1,

significant improvements were observed along the HIV care continuum among FSW participating in the intervention and control arms. A positive trend (RR 1.05), but non-significant difference across arms, was found in viral suppression among FSW in the intervention (40% to 50.6%) vs. control (35.9% to 47.4%) community.

Conclusion: Project Shikamana, a community-driven combination HIV prevention intervention developed by FSW in Iringa, Tanzania, was effective in significantly reducing HIV incidence. It is one of the first rigorously evaluated implementation models proven effective in reducing the heightened HIV risk among FSW in Africa.

	Intervention			Control			Compare @FU	
	BL N (%)	FU N (%)	P before -after	BL N (%)	FU N (%)	P before -after	RR	P
Prevention outcomes:	(N=211)			(N=176)				
Incident HIV infection	-	6/120 → 5.0%	-	-	10/96→ 10.4%	-	0.38*	0.047 *
Inconsistent condom use	152 (72.0)	92 (43.6)	<0.001	121 (68.8)	95 (54.0)	0.004	0.81	0.042
Treatment as prevention:	(N=91)			(N=80)				
Viral suppression (VL <400 copies)	36 (40.0)	46 (50.6)	NS	28 (35.9)	36 (47.4)	NS	1.05*	NS*
Ever linked to HIV care	26 (28.6)	72 (79.1)	<0.001	15 (18.8)	44 (55.0)	<0.001	1.44	0.002
In care, last 6m	19 (20.9)	70 (76.9)	<0.001	12 (15.0)	41 (51.2)	<0.001	1.50	0.001
ART ever	27 (28.0)	75 (82.4)	<0.001	15 (18.8)	54 (67.5)	<0.001	1.22	0.029
ART current	26 (28.6)	74 (81.3)	<0.001	14 (17.5)	51 (63.8)	<0.001	1.27	0.013
ART adherence, last 4 days	23 (25.3)	65 (71.4)	<0.001	9 (11.3)	37 (46.2)	<0.001	1.54	0.002

953 INTERDISCIPLINARY INTERVENTION FOR HOSPITALIZED PWID MAY INCREASE MAT USE

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Background: Medication assisted therapy (MAT) can prevent HIV in persons who inject drugs (PWID). For PWID, acute bacterial infections are one of the few conditions for which they seek medical care. The UAB Hospital Intravenous Antibiotics and Addiction Team (IVAT) uses a 9-item risk assessment to classify one's risk for continued IV drug use (i.e., low, moderate, or high) and inform discharge planning. We hypothesized that IVAT may improve MAT prescriptions on discharge, especially for "high" risk patients.

Methods: We compared outcomes of hospitalized PWID in the period before and after the IVAT. In the pre-IVAT period (January 2015-February 2016), we analyzed admissions in which IV antibiotics were received for ≥ 14 days by patients with a history of IVDU. In the post-IVAT period (October 2016-February 2018), all patients referred for IVAT consultation were included. MAT use on discharge included methadone, buprenorphine and naltrexone prescriptions. Specific substances used were defined by self-report and/or urine drug screen. Because the intervention included a risk assessment, we used logistic regression to determine if "high" risk participants were more likely to receive MAT on discharge in the post-IVAT era.

Results: A total of 37 and 98 patients met criteria in the pre and post-IVAT periods, respectively. 84% of pre-IVAT were opioid users compared to 80% post-IVAT. Most common bacterial infections in the pre and post-IVAT periods were endocarditis (57 and 34%, respectively) and vertebral osteomyelitis/ abscess (13 and 17%). In the pre- and post-IVAT periods, Hepatitis C was present in 68 and 80%, respectively, and HIV was present in 3 and 5%, respectively. Percentages with an ID consult (97% vs 94%) and Addiction Medicine (78% vs 84%) consult remained unchanged. Although MAT prescriptions increased, the percentage receiving MAT did not (32% pre and post IVAT). There was an increase for those deemed "high risk" for continued IVDU (55%). In univariate logistic regression models of those receiving IVAT, neither risk category, age, race, gender, length of stay, or insurance status was associated with MAT prescription.

Conclusion: An interdisciplinary hospital-based intervention may increase the number of MAT prescriptions for PWID, a critical step in the opioid cascade of care and an effective tool in HIV prevention. There is no evidence to suggest that MAT was preferentially prescribed to any group based on sociodemographic traits or results of 9-item risk assessment.

Table 1. Summary of hospitalized PWID receiving Medication-Assisted Treatment on discharge

Variable	No MAT N(%)	MAT N(%)	Total
Frequency	37	98	135
Age (years)			
Median (Q1,4)	37 (30,47)	36 (32,40)	37 (30,42)
Gender			
Female	30 (71)	12 (29)	42
Male	39 (70)	17 (30)	56
Race			
White	61 (68)	29 (32)	90
Other	8 (100)	0 (0)	8
9-item risk of continued injection drug use			
Mild	17 (77)	5 (23)	22
Moderate	33 (63)	19 (37)	52
High	4 (44)	5 (56)	9
Insurance			
Private	13 (76)	4 (24)	17
Public	25 (78)	7 (22)	32
Uninsured	31 (63)	18 (37)	49
Length of Stay (days)			
Median (Q1,4)	15 (8,33)	25 (14,44)	17 (8,37)

*Q1 is lower quartile, Q4 is upper quartile

954 LINKAGE TO CARE IN THE PARTNER SERVICES PRE-EXPOSURE PROPHYLAXIS (PS-PrEP) STUDY

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Background: Partner services is a public health intervention that contacts people who were exposed to sexually transmitted infection, including HIV. Black men who have sex with men (BMSM) have low uptake of pre-exposure prophylaxis. The Partner Services Pre-Exposure Prophylaxis (PS-PrEP) study tested the feasibility of integrating a tailored, in-person and mobile intervention into partner services to increase linkage to PrEP care for BMSM.

Methods: This single-blinded randomized control trial recruited HIV seronegative, PrEP-naïve BMSM aged 18-40 years old from partner services, network-based testing or health department STI testing sites. Inclusion criteria were being PrEP eligible, owning a cell phone, and living in metropolitan Chicago. The intervention consisted of an in-person session that used best linkage to care practices in tandem with cognitive-behavioral therapy and motivational interviewing techniques to develop a tailored Linkage Roadmap. This session was followed by 4 booster sessions for 12 weeks, with an optional in-person session for men reporting major barriers to PrEP care. The control group received a low threshold intervention through a phone-based PrEP linkage service that provided PrEP information and offered to schedule an initial PrEP visit. Men completed surveys and linkage to care was defined as having a PrEP care clinic visit within 3 months of enrollment. The difference between groups was determined by chi-squared test, p-value of 0.10, and effect size was determined using Cohen's h.

Results: The study population (n=143) had a mean age of 26 years (SD=4.5), most identified as gay (62%), were employed full- or part-time (65%) and had a high school education or more (91%). Overall, 85% of the intervention group (n =75) completed the booster sessions and none had an optional in-person session. Analyses comparing intervention to control showed that a greater proportion of the intervention group were linked to PrEP care compared to the control group (n = 68) (23% vs 12%; p = 0.08; cohen's h = 0.36).

Conclusion: This study demonstrated the feasibility of integrating a tailored PrEP linkage intervention into partner and network testing services. PS-PrEP increased linkage to PrEP care, and borderline statistical significance is likely due to a small study sample. Future studies that scale-up the PS-PrEP intervention with adequate power may be more likely to evaluate PS-PrEP's efficacy, and further improve linkage to PrEP care among BMSM at increased risk for HIV infection.

Table 1: Study population and linkage to PrEP care

	Control	Intervention	P value
Total	68 (100)	75 (100)	
Age in years (SD)	26 (4)	25 (5)	0.83[a]
Latino ethnicity	5 (7)	3 (4)	0.48[b]
Transgender or queergender identity	6 (9)	6 (8)	1[c]
Sexual orientation			0.08[b]
Straight	1 (1)	1 (1)	
Gay	47 (69)	42 (56)	
Bisexual	20 (29)	27 (36)	
Queer	0 (0)	5 (7)	
Employment			0.16[c]
Employed full-time	32 (47)	23 (31)	
Employed part-time	12 (21)	24 (32)	
Unemployed	18 (26)	20 (27)	
Other*	4 (6)	8 (11)	
Education			0.56[c]
Some high school	6 (9)	7 (9)	
High school	17 (25)	24 (32)	
Some college, associate's or technical school	35 (51)	38 (51)	
Bachleor's or post graduate studies	10 (15)	6 (8)	
Health insurance coverage	60 (88)	58 (77)	0.14[c]
Linked[d] to PrEP Care	7 (10)	17 (23)	0.08[c]

N (%) except where noted otherwise
PrEP = HIV Pre-Exposure Prophylaxis
a) T-test
b) Fisher's exact test
c) Chi-squared test
d) At least 1 PrEP care visit within 3 months of enrollment
* Full-time student, homemaker, unable to work due to illness, retired

955 PILOT TEST OF A PrEP TELEMEDICINE SYSTEM FOR YOUNG BLACK MSM IN THE RURAL US SOUTH

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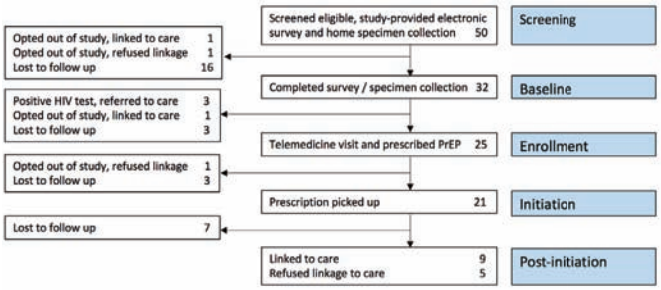
Background: HIV disproportionately impacts young and Black men who have sex with men (MSM), yet PrEP uptake is low among these groups. MSM living in rural areas face additional barriers to care, with an estimated 108,000 PrEP-eligible MSM living more than a one-hour roundtrip drive from their nearest PrEP provider. We sought to develop a culturally appropriate, smartphone-based PrEP telemedicine system to increase uptake by decreasing barriers to care.
Methods: We developed and piloted ePrEP, a smartphone telemedicine system with video consultations, lab testing using home specimen collection, and when possible home prescription delivery. The goal was to develop a low-touch system that removes barriers to PrEP care. Eligible participants were Black MSM, aged 18-24, and lived in small towns or rural areas in Georgia and Mississippi. We piloted using ePrEP to initiate patients into PrEP care, who were then linked to care to the nearest PrEP provider. Outcomes were feasibility (PrEP prescription filled) and acceptability ('acceptable' or 'very acceptable' on a 5-point Likert scale, and willingness to reuse).
Results: Of 50 screened-eligible participants contacted, 64% (n=32) completed a baseline survey, returned the self-collected specimen kit, and were enrolled in the study. 9% (3/32) tested positive for HIV. 86% (25/29) with a negative test for HIV had a telemedicine visit and were prescribed PrEP. A confirmed prescription fill was determined for 72% (21/29). A call referring participants to care after PrEP initiation through the study was only moderately successful, with 43% (9/21) linked to care, but 33% (7/21) lost to follow-up and 24% (5/21) refusing linkage to care. For those refusing linkage, the most commonly stated reason was the distance to in-person care. Among 15 participants completing a follow-up survey, the system was rated as acceptable by: video (93%), mailing specimens (93%), urine collection (93%), rectal swab collection (73%), and finger prick collection (53%). 93% (14/15) would choose the ePrEP system over standard PrEP care.
Conclusion: Among a group of young, Black MSM in the rural US South, the offer of telemedicine PrEP led many to initiate. ePrEP had high acceptability ratings, and most would choose it over standard care. Remote care interventions may be an important tool for increasing PrEP access and the ePrEP system holds substantial promise.



956 RAPID PrEP UPTAKE IN A PUBLICLY FUNDED POPULATION-BASED PROGRAM IN BRITISH COLUMBIA

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Background: In January 2018, a 100% publicly funded population-based HIV Pre-Exposure Prophylaxis (PrEP) program was launched in British Columbia (BC), Canada. Persons meeting BC PrEP eligibility criteria qualified for daily emtricitabine-tenofovir DF PrEP at no cost. Here we describe client and prescriber characteristics in the first 6 months of this province-wide program.
Methods: Clients enrolled from 1-Jan-2018 through 30-Jun-2018 were characterized by clinical and demographic characteristics. Prescribers were summarized by practice setting and HIV management experience. Comparisons between prescriber settings for PrEP enrolment, prescriber experience, and days from baseline HIV test to PrEP dispensing used Chi-Squared test for categorical and Wilcoxon rank sum test for continuous variables. Reported reasons for PrEP discontinuation and adverse drug reactions (ADR) were summarized.
Results: In the first 6 months, 1955 clients were approved for PrEP (see Table). Clients were 98.7% male, 0.9% transfemale, and <0.5% female, transmale, or other gender identity. Median (Q1-Q3) age was 35 (29-46) years. The majority (85%) of clients resided in the Greater Vancouver area. Most (73%) enrolees were PrEP-naïve, the remainder transferred from client-paid or private insurance coverage. There were 351 enrolling PrEP prescribers, of whom 46% had no previous HIV care and treatment experience. 67% of PrEP clients were seen at a Sexual Health or HIV Specialty clinic. The 21 prescribers at specialty clinics had median 32 (5-70) PrEP clients each vs. 1 (1-2) clients for the other 330 prescribers (p<0.001). Time from baseline HIV negative test to first PrEP dispensing was median 10 (7-13) days for specialty clinic clients vs. 10 (7-14) days for clients seen in general medical settings (p=0.028). PrEP discontinuation was reported for 25 clients (1.3%). Reasons for stopping included: 16 clients no longer at risk, 4 PrEP not tolerated, 1 drug interaction, 4 unspecified. Although BC guidelines recommend daily PrEP, intermittent use was noted for 17 clients. Overall, there were 7 reports of possible PrEP ADRs: 2 dermatologic; 2 gastrointestinal; 2 renal; 1 transient neutropenia.
Conclusion: Rapid uptake of PrEP was seen in the first 6 months of the publicly funded program in BC, with almost 2000 clients enrolled by over 350 prescribers. Early participation was largely represented by the at-risk MSM population in urban areas. To date, there have been few reports of PrEP discontinuation or adverse reactions.

Total applications for BC PrEP Program (1-Jan-2018 – 30-Jun-2018)	N=1989
Persons not meeting program eligibility criteria	**N=34**
	n (%)
Not at high risk for HIV acquisition per program criteria	12 (35%)
Not a resident of BC / no BC healthcare coverage	10 (29%)
Qualifying blood work not provided	10 (29%)
Compromised renal function: eGFR <60 mL/min	2 (6%)
Persons meeting program eligibility criteria	**N=1955**
Risk factor(s) for HIV acquisition:*	n (%)
Men who have sex with men, transgender women	
HIV Incidence Risk Index for MSM (HIRI-MSM) 10 - 24	1086 (55.6%)
≥ 25	541 (27.7%)
Infectious syphilis or rectal bacterial sexually transmitted infection	402 (20.6%)
HIV-positive sexual partner**	95 (4.9%)
Recurrent non-occupational post-exposure prophylaxis use	57 (2.9%)
Heterosexual men and women who have an HIV-positive sexual partner**	7 (<0.5%)
Persons who inject drugs who have an HIV-positive injecting partner**	<5 (<0.5%)
Public health referral following phylogenetic identification of a cluster	25 (1.3%)
Other risk factors	9 (0.5%)

*more than one risk factor per client may be reported
**partner not receiving stable antiretroviral therapy and/or viral load not < 200 copies/mL

957 RISK FACTORS ASSOCIATED WITH NONPRESCRIPTION USE OF HIV PREEXPOSURE PROPHYLAXIS

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Background: HIV pre-exposure prophylaxis (PrEP) and the required tests (e.g. for HIV, STIs) before and during PrEP use are currently not covered by health insurances in Germany. Generic PrEP can be purchased with private prescriptions through pharmacies since October 2017. Before, non-prescription PrEP use with drugs obtained through informal sources was common. The objective of this study is to estimate the extent of continued informal PrEP use in a sample of German PrEP users and to identify possible risk factors associated with non-prescription PrEP use.

Methods: From 24th July to 3rd September 2018 we recruited PrEP users on geolocation dating apps for MSM, community-based HIV testing sites, and a community website in Germany for an anonymous online survey. Prescription PrEP use was defined as use of PrEP drugs obtained through German pharmacies and clinical trials; other sources were classified as non-prescription drug use. Risk factors associated with non-prescription PrEP use were assessed with logistic regression models adjusting for age, country of origin, and annual gross income.

Results: We recruited 2,005 current PrEP users into our study, 78.7% of which completed the survey. The median age of the participants was 38 years (IQR: 31–45). 95.4% of the participants obtained medical tests before starting PrEP and 86.9% receive medical tests during PrEP use. 80.4% of the participants obtained PrEP through prescriptions, whereas 19.6% used non-prescription sources (Table 1). PrEP users with non-prescription drug use tended to have used PrEP longer than PrEP users with prescription drug use (median: 7-12 months vs 3-6 months, p<0.001) and were more likely to use PrEP intermittently or on demand (OR = 4.4, 95% CI 3.2, 5.9). PrEP users with non-prescription use were at higher risk of not obtaining medical tests before starting PrEP (OR = 8.1, 95% CI 4.5, 14.5) or during PrEP use (OR = 5.8, 95% CI 4.1, 8.3). We found that among daily PrEP users, non-prescription users were more likely to take PrEP fewer than 26 days per month on average than prescription PrEP users (OR =3.7, 95% CI 1.5, 8.7).

Conclusion: Non-prescription PrEP users were less likely to use PrEP according to current guidelines. This could increase the risk for undetected HIV and STI infections in this group. Our findings highlight the need for patients to access PrEP through healthcare systems in order to allow safe use.

Table 1: Sources of PrEP in Germany

Source	Participants [%]
Prescription use	80.4 %
Ordering online	9.9 %
Buying drugs in another country	3.2 %
Through friends	2.8 %
Using medication from post-exposure prophylaxis as PrEP	1.0 %
Buying from dealers	0.8 %
Sex Parties	0.8 %
Other sources	1.0 %

958 PREFERENCES FOR PrEP DELIVERY AMONG FSW IN MALAWI USING A DISCRETE CHOICE EXPERIMENT

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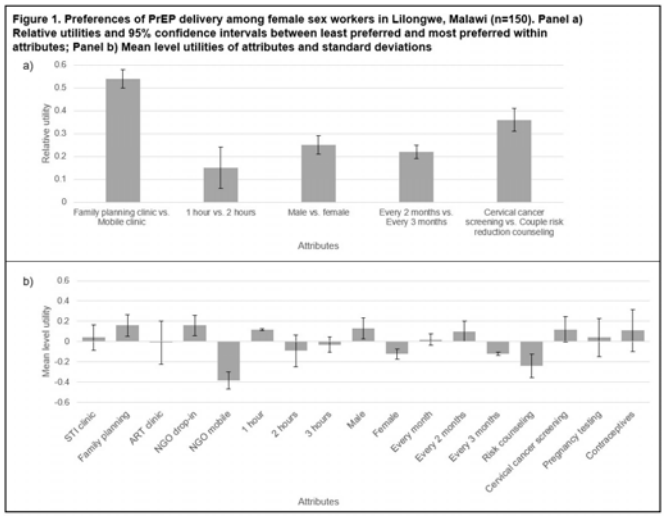
Background: Female sex workers (FSW) in Malawi have one of the highest HIV prevalence estimates worldwide. Daily oral PrEP is an effective HIV prevention method, yet implementation strategies for optimizing PrEP delivery among FSW are lacking in Malawi and other sub-Saharan African settings. Discrete-choice experiment (DCE) is a quantitative technique for eliciting preference by assessing how individuals value selected attributes of a program, product or service by asking them to state their choice over different hypothetical alternatives. This study used DCE to elicit preferences for PrEP delivery strategies among FSW in Lilongwe, Malawi.

Methods: After formative work involving focus group discussions, a literature review, and cognitive interviews, a DCE survey was developed with five PrEP attributes: dispensing location, clinic wait time, provider gender, frequency of pick-up, and provision of additional services. In June-August 2017, 150 FSW in Lilongwe were enrolled using venue-based sampling. Interviewer-assisted DCEs were administered along with a brief sociodemographic and behavioral survey. DCE data were analyzed within STATA using mixed logit regression to evaluate preferences for each PrEP delivery attribute. Mean level utilities and relative importance between least preferred and most preferred within attributes were also calculated across all respondents.

Results: Dispensing location was the most important factor (β or relative utility=0.54; 95%CI: 0.50, 0.58) for PrEP delivery, followed by the provision of additional services (β=0.36; 95%CI: 0.31, 0.41). Clinic wait time was the least important factor (β=0.22; 95%CI: 0.16, 0.26). Respondents preferred to receive PrEP at family planning clinics or at non-governmental organization (NGO) supported drop-in centers compared to STI clinics, ART clinics, or NGO supported mobile clinics. Male was the preferred provider gender. Respondents preferred picking up PrEP every 2 months to monthly or every 3 months. The preferred additional service was cervical cancer screening, followed by contraceptive provision, while pregnancy testing and partner risk reduction counseling were preferred less.

Conclusion: This was the first study to examine PrEP delivery preferences in Malawi using DCE-a powerful elicitation tool which can be applied within other FSW and key populations at risk for HIV. Dispensing location and the provision of additional services should be prioritized when designing and rolling out FSW tailored PrEP delivery strategies in Malawi.



959 PREEXPOSURE PROPHYLAXIS FOR KEY POPULATIONS IN UGANDA: EARLY SCALE-UP LESSONS

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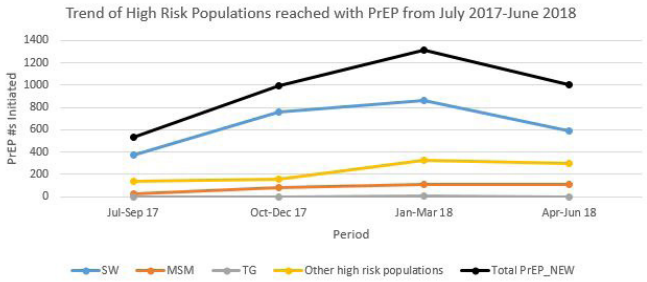
Background: In 2015, WHO recommended PrEP for persons at substantial risk of HIV. In 2016, UNAIDS set aspirational targets to enroll 3 million people on PrEP by 2020. HIV prevalence in Uganda is 6.2%, substantially higher among key populations (KP) including sex workers (SW, 33%) and men who have sex with men (MSM, 13.7%) yet the legal environment in Uganda undermines access to HIV services for KP. With support from the US Centers for Disease Control and Prevention (CDC) and in partnership with the Ministry of Health (MoH), Uganda implemented PrEP, reaching 3846 individuals between July 2017 and June 2018.
Methods: We reviewed PrEP data from PEPFAR Data for Transparency Impact Monitoring (DATIM) for July 2017 to June 2018. We compiled quarterly data from the 6 sites implementing PrEP for KP – including SW, MSM, Transgender (TG) persons and other high-risk groups (fisher folk [FF], discordant couples [DC], truckers, adolescent girls and young women [AGYW] and people who inject drugs). We also reviewed site-specific data from a rural fishing community in Southwestern Uganda, including 3- and 6-month retention within a 1.5 month window around timepoints.
Results: During the analyzed period, 3,846 individuals initiated PrEP; 2,568 (67.2%) SW, 327 (8.5%) MSM, 15 (0.4%) TG, and 918 (23.8%) other high-risk groups. PrEP initiations increased 112% from July–Sept. to Oct.–Dec. 2017 and 17% more Jan.–March 2018. From July-Dec. 2017 there was a 36% increase in an urban program providing PrEP at community-based MSM-friendly drop-in centers. In the rural fishing community, 58.1% (894/1538) of PrEP clients were SW, 25.4% (391/1538) FF, 7.4% (114/1538) DC and 0.5% (7/1538) MSM. Other high-risk groups included AGYW, migrant workers, truckers and uniformed forces among others. The majority (69.2%, 1064/1538) were reached through outreach models versus fixed public health facilities. Overall, only 33.8 % (404/1195) of clients returned for PrEP refills at or around 3 months (3m), and 24.2% (212/876) at or around 6 months (6m). Return rates were higher among DC (56.9%@3m, 46.8%@6m) and low among SW (37.5%@3m, 26.3%@6m) and FF (16.4%@3m, 14.2%@6m).
Conclusion: More SW than other KP and high-risk groups were reached with PrEP. Retention at 3 and 6 months was low for sex workers and fisherfolk, somewhat higher for discordant couples. Outreach approaches should be scaled up to reach more KP clients with PrEP. Retention strategies should be strengthened, especially for sex workers and fisherfolk, who may be highly mobile.



960 CHANGES IN KIDNEY FUNCTION AMONG MSM INITIATING ON-DEMAND TDF/FTC FOR HIV PrEP

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Background: Pre-exposure prophylaxis (PrEP) with TDF/FTC is recommended for HIV prevention. Daily PrEP with TDF/FTC is associated with a small but statistically significant decrease in estimated glomerular filtration rate (eGFR) similar to HIV-infected patients on TDF. We wished to assess whether on demand TDF/FTC based-PrEP could minimize the risk of eGFR reduction among MSM.
Methods: We used data from the randomized double-blind placebo-controlled ANRS-IPERGAY trial conducted among HIV-uninfected MSM with creatinine clearance >60mL/min. eGFR was assessed using CKD-EPI equation at enrolment, months 1, 2 and every 2 months thereafter. We evaluated the mean decline slope of eGFR change from baseline and the occurrence of eGFR <70mL/min/1.73m^2 in the placebo and on-demand TDF/FTC groups. We also determined risk factors for eGFR <70mL/min/1.73m^2 in all patients initiating TDF/FTC included in the blind or the open-label extension phases of the study.
Results: During the blind phase, 201 participants were randomized to placebo and 199 to on demand TDF-FTC. Participants on TDF/FTC took a median number of 15 pills/month (IQR 11 to 21). The mean eGFR at baseline was 106mL/min/1.73m^2. During a median follow up of 9.3 months, the mean decline slope of eGFR was -0.13 and -0.07 mL/min/1.73m^2 per month in the TDF/FTC and placebo group, respectively (P=0.27). The cumulative proportion of patients with an eGFR <70mL/min/1.73m^2 at 12 months was higher on TDF-FTC: 8% [95%CI 4-13%] than placebo: 3% [CI 0-6%], P=0.04. Compared to placebo, the risk of eGFR <70mL/min/1.73m^2 did not increase significantly in patients who took <15 pills/month: HR 1.75 [CI 0.65-4.7%] as compared to those using ≥15 pills/month: HR 2.54 [CI 1.07-6.04%]. Including both phases, 389 participants initiated on demand TDF/FTC with a median follow up of 19.1 months. Small but significant decline in eGFR occurred over time (mean slope: -0.09mL/min/1.73m^2 per month, P<0.01). Only 2 participants had persistent eGFR <60mL/min/1.73m^2 and 3 discontinued TDF/FTC for kidney function decline. The cumulative proportion of eGFR <70mL/min/1.73m^2 from baseline was 14% [9-18%] at 24 months. Factors associated with eGFR <70mL/min/1.73m^2 were high pill use (HR 1.9 [CI 1.03-3.49%], P=0.04), age > 40 years (P<0.01) and low eGFR at baseline (P<0.01).
Conclusion: On demand PrEP with TDF/FTC is associated with limited and non-clinically relevant eGFR decline, especially in young participants, those with low pill use and high baseline eGFR.

961 POINT-OF-CARE CREATININE TESTING WITHIN A PROGRAMMATIC PrEP DELIVERY SETTING

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Background: Creatinine (Cr) testing is recommended as part of PrEP delivery to identify pre-existing renal disease prior to PrEP initiation. Whether Cr testing is essential to assure safe use of PrEP is not yet known. We evaluated implementation of point-of-care (POC) Cr testing within a large-scale PrEP program in Western Kenya.

Methods: From June 2017 to August 2018, HIV-uninfected women seeking routine antenatal (ANC), postnatal (PNC), and family planning (FP) services were screened per national PrEP guidelines at 16 facilities in Kisumu, Kenya. Kenyan national PrEP guidelines currently recommend, but do not require, assessment of Cr clearance (CrCl) prior to PrEP initiation and annually thereafter when Cr testing is available. Prior to PrEP initiation, nurses measured height and weight, conducted Cr serum testing using validated Xpress StatSensor® POC machines (Nova Biomedical Cooperation, Waltham, MA, USA), and calculated CrCl by Cockcroft-Gault equation using a mobile application. If a single estimated CrCl measurement was below the normal range (<50mL/min according to Kenyan guidelines), the test was repeated before excluding that client from PrEP services. In a subset, we evaluated the cost and time required per test of the POC test compared to standard laboratory methods when a laboratory was present.

Results: In total, 4007 women were evaluated for PrEP eligibility and received POC Cr testing; 41% from ANC, 50% PNC, and 10% FP. The median age was 24 years (IQR 21-28) and 200 (5%) women were ≤18 years. The median CrCl was 113 mL/min (IQR 97-132) for ANC clients, 111 mL/min (IQR 93-130) for PNC, and 99 mL/min (IQR 82-120) for FP. Overall, 8/4007 (0.2%) women had estimated CrCL <50mL/min; 1 (0.06%) from ANC, 5 (0.2%) PNC, and 2 (0.5%) FP. POC Cr testing added a median of 3 minutes to PrEP eligibility assessments and cost USD 4.5 per test; in contrast, laboratory-based results took 3 hours and cost USD 5 per test.

Conclusion: It was feasible to implement POC Cr testing during PrEP delivery within MCH and FP settings and low CrCl was very rare among screened women. Given the rarity of medical ineligibility and safety of short-term PrEP, our data support the recommendation of not mandating Cr testing at PrEP initiation. PrEP programs could consider conducting Cr testing at one to three months post-initiation to reduce Cr testing-related time, costs and inconvenience.

962 IMMEDIATE PrEP INITIATION AT NEW YORK CITY SEXUAL HEALTH CLINICS

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Background: New York City (NYC) Sexual Health Clinics (SHC) patients are at increased risk of HIV acquisition. Immediate PrEP initiation (iPrEP) can increase PrEP uptake at walk-in settings where patient visits may be sporadic. At NYC SHC, tenofovir/emtricitabine is offered after a negative rapid HIV test but before results of other lab testing recommended for PrEP initiation are available. PrEP initiation is delayed (dPrEP) if patients report symptoms consistent with acute HIV (AHI), history of kidney disease (KD) and/or history of active hepatitis B virus infection (HBV). We determined the prevalence of PrEP-related medical contraindications among candidates evaluated for iPrEP at NYC SHC.

Methods: Using medical record data, we examined demographics and PrEP- related laboratory testing outcomes among patients evaluated for PrEP initiation. Patients were included in the analysis if they were cis-gender men or women, age>18 years, and had no prior HBV serology and serum creatinine testing at NYC SHC. Patients were considered to have PrEP medical contraindications if they had a positive HIV viral load test (absolute contraindication), glomerular filtration rate < 60 ml/min (absolute), and/or a positive Hepatitis B surface antigen (relative).

Results: From January 2017- June 2018, 1437 patients were evaluated for iPrEP; 1387 (97%) qualified and 50 (3%) were delayed. Median age was 28 years (IQR 25-33) and the majority (95%; 1361/1437) were men who have sex with men. Of all 1437 patients, 33% were non-Hispanic (NH) white, 30% Hispanic, and 23% NH Black. One third were foreign born (32%; 456/1437). Inconsistent condom use for vaginal/anal sex in the prior three months was reported by 76% (1059/1437) of patients. The prevalence of any PrEP contraindication was more common among dPrEP than iPrEP patients (14% vs 0.7%; p< 0.001) (see table). Patients ≥ 40 years were more likely to have any PrEP contraindication (3.0% vs 0.5%; p=0.01). PrEP was discontinued within 10 days among iPrEP patients with subsequently identified absolute contraindications (N=4). Among dPrEP patients without any contraindication, only 35% (15/43) initiated PrEP within 60 days. Per protocol, no dPrEP patients with contraindications (N=7) initiated PrEP.

Conclusion: Immediate PrEP initiation is a promising model for walk-in settings; PrEP was rarely discontinued (0.2%) among iPrEP patients due to absolute contraindications. There was a substantial loss to follow up among patients who delayed PrEP due to contraindications concerns.

Table: Prevalence of Medical Contraindications to PrEP among PrEP Initiation Candidates: Immediate vs. Delayed; January 2017-June 2018; New York City Sexual Health Clinics.

Contraindication Type	iPrEP (n=1387) n(%)	dPrEP (n=50) (n)(%)	*P* value
Acute HIV (+ HIV viral load)	2(0.1)	1 (2.0)	0.005
Chronic kidney disease (GFR < 60 ml/min)	2 (0.1)	4 (8.0)	<0.001
Active HBV Infection (+HBV SAg)	6 (0.4)	2 (4.0)	<0.001
Any of the above	10 (0.7)	7 (14.0)	<0.001

GFR: Glomerular filtration rate; HBV SAg: Hepatitis B Surface Antigen
iPrEP : immediate PrEP; dPrEP: delayed PrEP

963 PrEP PERSISTENCE AND DISCONTINUATIONS IN A COHORT OF YOUNG BLACK MSM IN ATLANTA, GA

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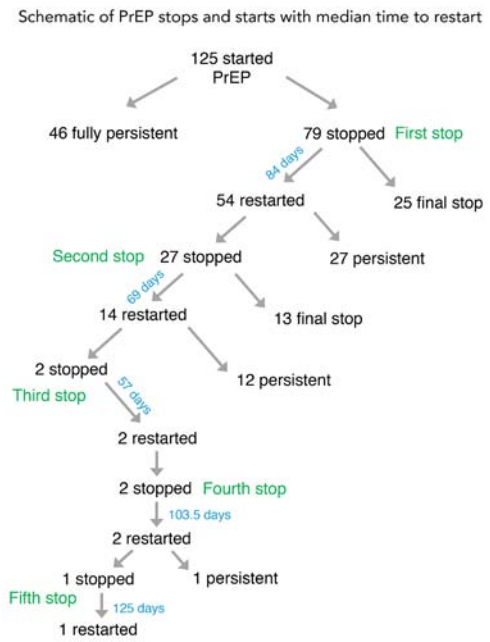
Background: HIV incidence is high among young black MSM (YBMSM) in the US, and effective implementation of pre-exposure prophylaxis (PrEP) has great potential to reduce new infections. Scale up of PrEP is ongoing in this key population; yet, we continue to observe high HIV incidence (interim estimate 6%/year) in our cohort of YBMSM with access to PrEP services. A better understanding of patterns of PrEP persistence and discontinuation among YBMSM is needed.

Methods: The EleMENt study is an observational cohort examining relationships between substance use and HIV risk behavior among HIV-negative YBMSM (n=299) aged 18-29 in Atlanta, GA. All participants were offered optional PrEP at each study visit over the 24-month follow-up. Clinical visits, labs, transportation, and navigation services for manufacturer assistance plans (MAP) to obtain no/low cost TDF/FTC were provided by the study. For initiators, we recorded time on and off PrEP based on frequent study surveys, prescription records, dates of MAP approvals, counseling notes, and other participant contacts. PrEP discontinuation events were defined as a ≥2 week lapse in PrEP use. Time to first PrEP discontinuation was assessed with the Kaplan-Meier method, with a Cox proportional hazard model used to identify factors associated with discontinuation.

Results: After 483 person-years of follow up, 42% (125/299) of YBMSM initiated PrEP through the EleMENt program. Overall, PrEP initiators were "on PrEP" for 69% of possible person-time after initiation. 63% (79/125) discontinued PrEP at least once during study follow-up, and 68% of discontinuers (54/79) subsequently restarted PrEP. 22% (27/125) discontinued two or more times. The median time to first PrEP discontinuation was 219 days (95% CI 181-280). In a multivariable model, marijuana use (adjusted hazard ratio [aHR] 2.07, 95% CI 1.24-3.47), age <22 years (aHR 3.63, 95% CI 1.95-6.74) and having fewer than 3 sex partners (aHR 2.16, 95% CI 1.30-3.58) were associated with PrEP discontinuation.

Conclusion: Persistent PrEP coverage in this cohort of YBMSM was suboptimal and discontinuations, including multiple discontinuations, were common despite additional support services available through the study. Interventions to support PrEP persistence, especially for younger and substance using YBMSM, will be necessary to achieve full effectiveness of PrEP. For the future, regimens that do not require adherence to a daily medication could help facilitate PrEP persistence in this key population.



964 LOW UPTAKE OF PREEXPOSURE PROPHYLAXIS AMONG KENYAN ADOLESCENT GIRLS AT RISK OF HIV

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Background: A fifth (21%) of new adult HIV infection in Kenya occur among adolescent girls and young women (AGYW) aged 15-24years. Asymptomatic screening of young women for sexually transmitted infections (STIs) is not the standard of care in Kenya. It has been proven that infection with most STIs make it easy to acquire HIV and even easier to transmit it. We examined whether availability of STI screening results would impact HIV Pre exposure prophylaxis (PrEP) acceptability and uptake in this population.

Methods: We recruited a prospective cohort of adolescent girls aged 16-20 years in Kenya. To be eligible, the girls were either sexually naïve or had reported one lifetime sexual partner. The girls were followed up every 3 months with regular STI testing, consisting of nucleic acid testing(NAAT) of vaginal swabs for Neisseria gonorrhea, Chlamydia trachomatis, and Trichomonas vaginalis, and vaginal gram stains for bacterial vaginosis (BV). ELISA assay for HIV and HSV-2 was also done. Starting in January 2018, girls were screened with an HIV risk assessment tool, including real-time STI testing and offered PrEP based on their score. We used descriptive analysis to characterize this cohort.

Results: We enrolled 400 girls, with a median age of 18.6 years (IQR 16-21); the cohort started prior to PrEP rollout in Kenya that was initiated in May 2017. After PrEP rollout, we identified 168 girls (42%) eligible for PrEP: 26 (15%) had a current STI, 133 (79%) reported inconsistent or no condom use with sex, 56 (33%) reported sex partner of unknown HIV status, and 6 reported (4%) other reasons. Median years of education for the eligible girls was 12 years. Ninety seven (57.3%) of these girls reported living in rural settlements. Only 9 (5.4%) of the girls who were offered PrEP, accepted it. The PrEP acceptance rate appeared higher in those with current STI (15%, or 4 of 26 accepted PrEP) than in those eligible for other reasons (4%, or 5 of 142 accepted PrEP). Girls who declined PrEP reported that they preferred condom use as a mode of HIV prevention.

Conclusion: In a cohort of young women with access to targeted PrEP services after testing positive for an STI, PrEP acceptance was low. Specific evidence of their own high HIV risk, coupled with low- barrier access to PrEP, did not translate into PrEP uptake among these girls. Specific and targeted research of PrEP uptake reluctance in young women is needed. HIV risk awareness and knowledge is not enough to result in high PrEP uptake in this cohort.

965 HIGH CURABLE STI PREVALENCE AND INCIDENCE AMONG YOUNG AFRICAN WOMEN IN HPTN 082

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Background: African women face overlapping HIV and STI risks. PrEP programs among men who have sex with men have seen high STI incidence, but few data from African women taking PrEP are available. Syndromic STI case management is the standard of care in Africa but is reliant on symptom recognition and has significant limitations in women.

Methods: HPTN 082 was conducted in Cape Town, Johannesburg (South Africa) and Harare (Zimbabwe) to evaluate the effect of drug level feedback on PrEP adherence. Sexually active HIV-negative women ages 16-25 were enrolled and enrollment vaginal swabs were tested for gonorrhea (GC) and chlamydia (CT) by nucleic acid amplification, and trichomonas (TV) by rapid test. Syphilis was assessed by serology. All women with positive test results received treatment. Repeat testing was conducted at 6 and 12 months.

Results: Of the 412 women who initiated PrEP at enrollment, the median age was 21 years and 84% reported a primary sex partner. Women reported a median of 4 vaginal sex acts (IQR 2,8) in the prior month and 35% reported that they never or rarely used condoms with vaginal sex. 22% reported anal sex in the past month and 27% never or rarely used condoms with anal sex; anal sex was more common among women with a partner ≥5 years older. At enrollment 29% of women had CT, 8% GC, 7% TV and 2% reactive syphilis serology. STI incidence was 29.5 per 100 person-years (p-yrs) for CT (95% CI 24.3, 35.4), 12.2 per 100 p-yrs for GC (95% CI 9, 16.2), and 6.9 per 100 p-yrs for TV (95% CI 4.6, 10.1). The majority of incident STIs were new infections: 74 of 113 CT infections, 40 of 47 GC infections, and 21 of 27 TV infections were diagnosed in women who did not have these infections diagnosed at enrollment.

Conclusion: The prevalence and incidence of treatable STIs were high among young women in a PrEP demonstration project in South Africa and Zimbabwe. Most incident STIs were new diagnoses, and unlikely to be reinfections or treatment failures. These data underscore the limitations of syndromic case management to control STIs in at-risk women, and the need for more sensitive diagnostic approaches. Innovative strategies that reduce STI acquisition and complications and their potential impact on future fertility need evaluation within the context of PrEP services.

966 HIGH PREVALENCE AND ANTIBIOTIC RESISTANCE OF M GENITALIUM INFECTIONS IN MSM ON PrEP

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Background: Mycoplasma genitalium (MG) is an emerging pathogen among MSM with raising rates of antibiotic resistance. We assessed the prevalence and incidence of MG infection in MSM enrolled in the open-label phase of the ANRS IPERGAY trial with on demand TDF/FTC for HIV prevention and the impact of doxycycline postexposure prophylaxis.

Methods: During the open-label phase of the ANRS IPERGAY trial, participants could also be enrolled in a prospective randomized (1:1) open-label sub-study of postexposure prophylaxis (PEP) with doxycycline. All subjects were tested at baseline and at 6 months by real-time PCR assays for MG detection in urine samples, oro-pharyngeal and anal swabs. Resistance to azithromycin (AZM) and to fluoroquinolones (FQ) were investigated by the detection of mutations in 23S rRNA (ResistancePlusTM MG test, SpeeDx) and in parC determining region, respectively.

Results: From July 2015 to January 2016, 210/232 (90.5%) participants randomized in the PEP study were tested. MG prevalence at baseline was 10.5% all sites combined (95% CI: 6.6-15.9), and was 6.3%, 4.3% and 0.5% for urine, anal and throat sites, respectively. Ten participants acquired M. genitalium infection at the 6-month visit, 6 participants in the PEP arm (6.7%) and 4 in the no PEP arm (4.9%, p= 0.75). These infections were detected in urine (n=5), anus (n=5) or throat (n=1, combined with anus). The overall rate of MG resistance (prevalent and incident cases) to AZM and FQ was 69.6% and 14.8%, respectively, with no difference between arms (p=1.00 for AZM, p=0.27 for FQ). The MG isolates were resistant by the presence of the substitutions A2058G/T or A2059G in the 23S rRNA and to FQ by the mutations S83I/B, D87Y and A88T in the QRDR of the topoisomerase ParC.
Conclusion: The prevalence of MG infection among MSM on PrEP with on demand TDF/FTC was high and its incidence was not decreased by doxycycline prophylaxis with a similar high rate of AZM- and FQ-resistance, raising challenging issues for the treatment of this STI.

967 ASSOCIATION OF PrEP USE AND PAST AND CURRENT STIs AMONG MSM IN WASHINGTON, DC, 2017

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Background: While daily, oral pre-exposure prophylaxis (PrEP) reduces HIV transmission risk, there is a growing concern of its potential association with elevated sexually transmitted infections (STIs). It is unclear whether increased STI diagnoses are a result of initial followed by regular STI testing among PrEP users or from an actual increase in risk while on PrEP. We examined the association between PrEP use and past year and current bacterial STIs among men who have sex with men (MSM) in the DC metro area.
Methods: We used data from the 2017 National HIV Behavioral Surveillance conducted in Washington, DC. MSM recruited via venue-based sampling completed a behavioral survey and HIV test and provided pharyngeal and rectal swab specimens. HIV-negative MSM who were PrEP eligible were included in the analysis (e.g., reporting condomless anal sex). Participants reported on past year PrEP use and physician diagnosis of either Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (GC) in the past year. Current STI (CT and/or GC) was assessed via lab testing of pharyngeal and rectal specimens. Multivariable logistic regression was used to assess the associations between past year PrEP use and past year STIs and also current STI status.
Results: Of 275 eligible participants, 41% used PrEP in the past year. PrEP users were more likely to be white and have ^{3}20 partners in the past year. Overall, 25% self-reported a STI diagnosis in the past year, and 13% were currently STI-positive via lab diagnosis. After adjusting for other confounding factors, past year PrEP users were three times as likely to self-report a STI diagnosis in the past year (aPOR= 3.0, 95% CI:1.43, 5.42) compared to non-PrEP users. However, in adjusted analyses, those using PrEP in the past year were not more likely to be currently infected with an oral or rectal STI compared to those not on PrEP (aPOR=1.70, 95% CI: 0.69, 4.3).
Conclusion: PrEP use was strongly associated with past year STIs but not with being currently infected, suggesting that being on PrEP may play a role in earlier, active clinical STI screening, diagnosis and treatment. PrEP users regularly interface with the medical system, leading to more opportunities for screening, diagnosis, and treatment, which may have resulted in the lower prevalence of active STIs diagnosed at the time of the survey. Future studies should examine the association of PrEP use with STI diagnosis in conjunction with treatment and use of health services.

Table: Unadjusted and adjusted odds ratios of past year PrEP use and current and past year bacterial STI diagnosis, National HIV Behavioral Surveillance for men who have sex with men in Washington, DC, 2017

	Unadjusted		Adjusted	
	uPOR 95% CI	ChiSq p-value	aPOR 95%CI	ChiSq p-value
Self-reported STI in past year (GC and/or CT)				
PrEP use in the past 12 months n=275	**3.81 (2.16-6.84)**	**<.0001**	**3.0 (1.43-5.42)**	**0.003**
Laboratory diagnosed rectal and/or oral STI (GC and/or CT)				
PrEP use in the past 12 months n=275	**2.11 (1.03-4.39)**	**0.04**	1.70 (0.69-4.3)	0.25

* Adjusted for age, race, education, income, health insurance, number of partners in past year

968 DETECTED EXTRAGENITAL STI AMONG US MSM BY PrEP STATUS

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Background: Men who have sex with men (MSM) using HIV pre-exposure prophylaxis (PrEP) may continue to be at high risk for bacterial STIs. We examined the positivity of extragenital gonorrhea and chlamydia among a multisite sample of non-HIV-positive MSM who report using and not using PrEP in the United States.
Methods: MSM aged ≥18 years were recruited via venue-based sampling to participate in the 2017 National HIV Behavioral Surveillance. In five cities (San Francisco, Washington DC, New York City, Miami, Houston), participants completed a questionnaire and were offered HIV testing as well as pharyngeal and rectal testing to detect gonorrhea and chlamydia. We estimated the positivity of pharyngeal and rectal gonorrhea and chlamydia among MSM who did and did not report PrEP use in the past year. We also examined PrEP use and STI testing in the past year and condomless anal sex with a male partner at last sex.
Results: In the five cities, 553 of 1922 (29%) self-reported non-HIV-positive MSM reported PrEP use in the past year. Compared to those not using PrEP, MSM using PrEP in the past year were more likely to test for STI in the past year (91% vs. 51%, p<0.01) and have condomless anal sex with a male partner at last sex (61% vs. 43%, p<0.01). MSM on PrEP in the past year were slightly more likely to have any gonorrhea or chlamydia detected at any anatomic site (15% vs. 12%, p=0.03), and have rectal chlamydia specifically (9% vs. 6%, p=0.04). MSM on PrEP and those not on PrEP had similar prevalences of pharyngeal chlamydia (1% vs. 1%, p=0.74), pharyngeal gonorrhea (5% vs. 4%, p=0.49), and rectal gonorrhea (3% vs. 4%, p=0.78).
Conclusion: The prevalence of extragenital STI was high for both MSM on PrEP and those not on PrEP in the past year. Our findings suggest that men on PrEP may engage in potentially higher risk behavior (condomless anal sex), yet may be screened more regularly for STI. PrEP use was not associated with either pharyngeal STI or rectal gonorrhea; however, men on PrEP were slightly more likely to have rectal chlamydia. Our findings support frequent and regular STI testing as recommended for MSM on PrEP to identify infections and initiate treatment.

969 STI COINFECTIONS DO NOT REDUCE THE PROPHYLACTIC EFFICACY OF CAB LA IN MACAQUES

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Background: Injectable long acting Cabotegravir (CAB-LA) allows for prolonged dosage intervals and is under evaluation for pre-exposure prophylaxis in women. We have previously shown that CAB-LA fully protected macaques from vaginal SHIV infection. Here, we assessed if CAB-LA efficacy is reduced by genital inflammation. We re-evaluated efficacy in a macaque model

of Chlamydia trachomatis (CT) and Trichomonas vaginalis (TV) co-infection that has been shown to increase susceptibility to SHIV.
Methods: Adult pig-tailed macaques were inoculated with CT and TV every 3 weeks to maintain infection. Their infection status was monitored with the APTIMA Combo 2 assay. The animals were untreated (n=5) or received CAB-LA intramuscular injections (n=6; 50mg/kg) 7 days prior to the start of biweekly SHIV intravaginal challenge series, and then every 4 weeks during virus exposures. Plasma viral RNA levels were measured by RT-PCR. Drug levels were measured using liquid chromatography coupled with tandem mass spectrometry with a lower quantification limit of 1 and 10 ng/mL for biopsies/swabs and plasma, respectively. The log-rank test was used to compare the survival distribution between untreated animals and those receiving CAB-LA.
Results: STI infections were maintained in all 11 animals during the entire study. The 6 drug-treated STI-infected animals remained protected after 14 SHIV exposures while all untreated animals became SHIV-infected ($p<0.0001$). Infection in the untreated animals (median=2 [range: 1-10] virus exposures) was seen earlier than in historical STI-naïve controls (median=4 [range: 2-8] virus exposures; $p=0.008$), demonstrating further that CT and TV infections increase the risk of SHIV acquisition. CAB-LA concentrations in plasma were maintained above 664ng/mL, four times the PA-IC90 (mean 2254ng/mL; range: 892-4280ng/mL).
Conclusion: Despite being a single drug agent, CAB-LA at a clinical dose maintained full and durable efficacy against vaginal SHIV acquisition in macaques continuously infected with CT and TV. The data from this model reflect robust protection that may not be sensitive to vaginal inflammation.

970 ANTI-A4B7 ANTIBODY REDUCES MACAQUE VIREMIA BUT NOT RISK OF RECTAL SHIV ACQUISITION

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Background: It has been shown that the simianized anti-α4β7 monoclonal antibody (mAb) partially protects against vaginal simian immunodeficiency virus (SIV) acquisition. We hypothesized that infusion of anti-α4β7 mAb in rhesus macaques prior to and during repeat low-dose rectal simian-human immunodeficiency virus (SHIV) exposures would offer significant protection against viral acquisition and suppress viremia in the gut-associated lymphoid tissues.
Methods: Adult rhesus macaques (n=6) received intravenous infusions of anti-α4β7 mAb (50mg/kg) 3 days prior to the first of the weekly SHIV162p3 challenges (50TCID50). The antibody dose and timing of first challenge were chosen to be identical to the prior study showing vaginal protection. Plasma viral RNA was measured by RT-PCR. Total SHIV DNA in PBMCs was quantitated using a double-stranded primer assay. Plasma and mucosal secretions were tested by ELISA for levels of anti-α4β7 mAb and rhesus anti-rhesus antibodies (RARA). CD4 levels were measured in PBMCs and rectal biopsies by flow cytometry.
Results: All anti-α4β7-treated animals became SHIV infected after a median of 2 challenges. Peak viral loads in anti-α4β7-treated animals were significantly lower (6.1 versus 7.8 log copies/ml; $p=0.0023$; unpaired 2-tailed t-test) than historical controls. In 4/6 anti-α4β7-treated animals, plasma viremia was rapidly controlled to <3000 copies/ml at 9 weeks; these four also had lower peak viremia compared to the other 2 (5.8 versus 7.1 log copies/ml; $p=0.113$; Mann-Whitney test). Average CD4 levels post-infection were significantly higher in the 4 animals that controlled versus the other two ($p=0.01$, rectum; $p<0.0001$, PBMCs). In all anti-α4β7-treated animals, total SHIV DNA levels in PBMCs began to decline 2 weeks post-peak viremia and were below the level of detection by week 4. RARA levels were close to baseline in all animals at time of challenge, and did not correlate with weeks to infection or viremia.
Conclusion: Infusion with anti-α4β7 mAb prior to SHIV exposures resulted in improved control of post-infection viremia in plasma and PBMCs. The antibody did not protect from rectal acquisition. Differences between rectal and vaginal compartments may influence anti-α4β7 antibody distribution and effects, and therefore differently modulate SIV/SHIV acquisition.

971 ESTIMATED PrEP ELIGIBILITY IN A NATIONAL SEXUAL NETWORK STUDY OF US MSM

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Background: A 2015 CDC analysis estimated that 24.7% of sexually active men who have sex with men (MSM) had indications for HIV preexposure prophylaxis (PrEP) based on 2014 US Public Health Service (USPHS) clinical practice guidelines. The USPHS revised those guidelines in 2017, with indications for MSM now targeting MSM based on four base indications: age (18+), HIV status (HIV-negative), recent sexual activity (within 6 months), sexual network configurations (not in a monogamous relationship with a HIV-negative partner); and recent behavioral risk (condomless anal intercourse (CAI) or bacterial STD diagnosis (BSTID) in last 6 months). Updated estimates of the fraction of MSM indicated for PrEP overall and stratified by demographic factors and geography are needed to optimally scale-up PrEP for MSM in the US.
Methods: We conducted a national web-based study of 2176 MSM (aged 15–65 who had ever had sex with another man) between July 2017 – February 2018. We estimated the proportion of MSM meeting USPHS-recommended indications for PrEP using the CDC analysis denominator: adult, HIV-negative MSM sexually active in the prior year.
Results: Of 1632 MSM (75%) comprising the CDC denominator, 46.1% (95% CI: 43.7, 48.6) met USPHS indications for PrEP, with percentages consistent across US census regions. Younger MSM (ages 15–24) were least likely to meet PrEP indications: 34.9%. PrEP eligibility varied by race/ethnicity (Black: 51.2%, White 46.3%, Hispanic: 47.1%, Other: 40.4%). Among individuals meeting USPHS PrEP indications, 80.5% were indicated due to recent CAI, 1.9% were indicated due to a recent BSTID, and 17.7% met both indications (CAI and BSTID).
Conclusion: Estimated percentages of MSM meeting indications for PrEP exceeded the previous CDC estimate across race/ethnicity, age, and census regions, with nearly one-half of adult, sexually active, HIV-negative MSM exhibiting indications for PrEP. These differences may reflect a combination of the 2017 changes to USPHS guidelines, increasing risky sexual behavior among US MSM, and rising incidence (and therefore diagnoses) of STIs across the US. This study suggests, given current guidelines for PrEP indications, that a lower fraction of eligible MSM may be receiving PrEP than previously estimated. Additional age- and race/ethnicity-based considerations for PrEP indications may be needed to address rising the higher prevalence of recent STI diagnoses observed among younger and minority MSM in this study and rising HIV case counts in these populations.

Estimated PrEP eligibility in a national sexual network study of US MSM

	Total Respondents (%)	CDC Analysis Denominator* (%)	Met Base Indications (CI)*	Base + Recent CAI (CI)*	Base + Recent STI (CI)*	**Base + Recent CAI or STI (CI)***
All	2176 (100.0)	1632 (75.0)	55.3 (52.9 - 57.7)	45.3 (42.9 - 47.7)	9.0 (7.6 - 10.4)	46.1 (43.7 - 48.6)
White	1549 (71.2)	1186 (76.6)	54.7 (51.9 - 57.6)	45.8 (42.9 - 48.6)	8.1 (6.5 - 9.6)	46.3 (43.5 - 49.1)
Black	135 (6.2)	82 (60.7)	57.3 (46.6 - 68.0)	47.6 (36.8 - 58.4)	15.9 (7.9 - 23.8)	51.2 (40.4 - 62.0)
Hispanic	297 (13.6)	223 (75.1)	56.5 (50.0 - 63.0)	45.3 (38.8 - 51.8)	10.8 (6.7 - 14.8)	47.1 (40.5 - 53.6)
Other	195 (9.0)	141 (72.3)	57.4 (49.3 - 65.6)	39.7 (31.6 - 47.8)	9.9 (5.0 - 14.9)	40.4 (32.3 - 48.5)
Northeast	439 (20.2)	335 (76.3)	56.7 (51.4 - 62.0)	45.7 (40.3 - 51.0)	10.1 (6.9 - 13.4)	46.9 (41.5 - 52.2)
Midwest	366 (16.8)	280 (76.5)	51.4 (45.6 - 57.3)	44.6 (38.8 - 50.5)	6.8 (3.8 - 9.7)	45.0 (39.2 - 50.8)
South	811 (37.3)	594 (73.2)	56.6 (52.6 - 60.6)	46.0 (42.0 - 50.0)	8.6 (6.3 - 10.8)	46.8 (42.8 - 50.8)
West	560 (25.7)	423 (75.5)	55.1 (50.3 - 59.8)	44.4 (39.7 - 49.2)	10.2 (7.3 - 13.0)	45.4 (40.6 - 50.1)
15-24	401 (18.4)	335 (83.5)	40.6 (35.3 - 45.9)	34.0 (29.0 - 39.1)	9.3 (6.2 - 12.4)	34.9 (29.8 - 40.0)
25-34	572 (26.3)	475 (83.0)	49.1 (44.6 - 53.5)	40.8 (36.4 - 45.3)	11.4 (8.5 - 14.2)	41.9 (37.5 - 46.3)
35-44	296 (13.6)	235 (79.4)	58.7 (52.4 - 65.0)	48.5 (42.1 - 54.9)	10.2 (6.3 - 14.1)	50.6 (44.2 - 57.0)
45-54	444 (20.4)	294 (66.2)	66.7 (61.3 - 72.1)	54.1 (48.4 - 59.8)	8.8 (5.6 - 12.1)	54.4 (48.7 - 60.1)
55-65	463 (21.3)	293 (63.3)	68.3 (62.9 - 73.6)	53.9 (48.2 - 59.6)	4.1 (1.8 - 6.4)	53.9 (48.2 - 59.6)

* CDC Analysis Denominator: 1) Age >= 18; 2) HIV-negative; 3) Sexually active in the prior 12 months
Base USPHS Indications: 1) Age >= 18; 2) HIV-negative 3) Sexually active in the prior 6 months; 4) Not in monogamous partnership with HIV-negative partner
Recent CAI: Condomless anal intercourse in the prior 6 months
Recent STI: Bacterial STI diagnosis in the past 12 months *(Note: USPHS guidelines specify 6 months)*
CI: 95% Confidence Interval

972 CHANGES IN HIV PrEP AWARENESS AND USE AMONG MEN WHO HAVE SEX WITH MEN, 2014 VS 2017

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Background: The US Food and Drug Administration (FDA) approved the first drug for daily HIV pre-exposure prophylaxis (PrEP) use in 2012. Subsequent to FDA approval, efforts have been made to raise awareness and use of HIV PrEP among men who have sex with men (MSM) and those who are at increased risk for acquiring HIV infection. We evaluated changes in PrEP awareness and use

among MSM in the US overall and by race between 2014 and 2017 using National HIV Behavioral Surveillance (NHBS) data from 20 U.S. cities.
Methods: Men were recruited at events frequented by MSM in each city using venue-based sampling. We used log-linked poisson regression models with generalized estimating equations clustered on event to estimate the prevalence ratios (PR) and 95% confidence intervals (CI) for PrEP awareness and use, adjusted for income and health insurance. Analyses were limited to HIV-negative men who reported substantial risk for HIV infection consistent with PrEP indications (had either a male sex partner who was not known to be HIV negative or >1 male sex partner in the past 12 months and had either a sexually transmitted infection or condomless anal sex with a male partner also in the 12-month period).
Results: We analyzed data from 3,978 MSM at substantial risk for HIV infection who were interviewed in 2014 and 4,182 who were interviewed in 2017. Between 2014 and 2017, PrEP awareness increased overall from 59% to 90% (adjusted PR (aPR) 1.14, CI: 1.13-1.16) and PrEP use increased from 5% to 34% (aPR 1.80, CI: 1.72-1.90). Both awareness and use increased in all racial and age groups. However, PrEP awareness was lower among black (85%; aPR 0.94, CI: 0.90-0.98) and Hispanic men (85%; aPR 0.92, CI: 0.89-0.96) than white men (94%). In 2017, PrEP use among men at substantial risk was lower among black (26%; aPR 0.71, CI: 0.60 – 0.84) and Hispanic men (29%; aPR 0.79, CI: 0.68 – 0.93) compared with white men (42%).
Conclusion: From 2014 to 2017 PrEP use increased over 500% among MSM who are at substantial risk for HIV infection. PrEP awareness also increased significantly. However, PrEP use remains low, especially among black and Hispanic men. Efforts to raise PrEP use among black and Hispanic men may help reduce HIV disparities in the US.

973 ASSESSING THE PrEP CONTINUUM IN THE SAN FRANCISCO BAY AREA: THE QUICKIE MOBILE SURVEY

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Background: Pre-exposure prophylaxis (PrEP) has great potential to curb the HIV epidemic. Population-level indicators of the PrEP continuum are lacking, yet are critical to monitor PrEP expansion and identify gaps. We report results of a mobile survey evaluating the PrEP continuum among MSM and transwomen (TW) in the San Francisco Bay Area (SFBA).
Methods: Participants (ppts) were recruited using social media/sexual networking sites, print ads and phone outreach. Eligible ppts were HIV-uninfected MSM or TW, age ≥18, sexually active with a man and/or trans partner in the past year, English/Spanish speaking, and SFBA residents. We used a Qualtrics mobile survey to assess metrics of the PrEP continuum including awareness, initiation, adherence, and persistence. We conducted multivariable logistic regression to identify factors associated with PrEP initiation and persistence.
Results: From June-September 2018, 460 ppts responded to the survey. Median age was 30; 46% were White, 22% Latinx, 15% Asian, 13% Black, 4% other; 86% were men, 14% TW/non-binary (NB). Over the past 6 months, the mean number of anal/vaginal sex partners was 7, and 74% reported condomless sex; 25% reported an STI in the past year. Overall, 96% had heard of PrEP, 47% had initiated PrEP, 33% were currently on PrEP, and 32% reported high adherence. Among 244 ppts never on PrEP, most (81%) expressed interest in taking it, but only 61% knew where to get PrEP, and few (36%) had talked with a provider about PrEP. In multivariable analyses, higher education, having a primary provider, and drug use were associated with PrEP initiation; younger age, other race, and TW/NB were associated with lower persistence; number of sex partners was associated with initiation and persistence (Table). Among 63 PrEP discontinuers, median duration of use was 7 months; the most common reasons for stopping PrEP included not feeling at risk for HIV (46%), insurance/access issues (36%), side effects/concerns (13%), and travel (10%). Among never/prior PrEP users, a substantial proportion would consider starting/restarting PrEP if offered on-demand PrEP (84%/73%), long-acting injectable PrEP (56%/68%), or a pericoital rectal formulation (douche/suppository) (32%/46%).
Conclusion: While PrEP initiations are relatively high in the SFBA, disparities in persistence exist, particularly in youth and TW/NB. Efforts to address cost/access barriers are critical to reversing disparities. Novel PrEP regimens and formulations could increase PrEP uptake and persistence.

Table: Multivariable Models for PrEP Initiation and Persistence among MSM and Transwomen in the San Francisco Bay Area (n=460)

	N	% never used PrEP (n=244)	% currently using PrEP (n=153)	% used PrEP in past (n=63)	AOR (95% CI) for PrEP initiation (Ever vs. never use)	P value	AOR (95% CI) for PrEP persistence (Current vs. former use)	P value
Mean Age/per 10 years	--	32.3	35.8	30.3	1.06 (0.88-1.27)	0.55	**2.08 (1.37-3.16)**	**0.001**
Race/ethnicity								
White	214	42%	55%	43%	(ref)		(ref)	
Black	58	12%	15%	8%	1.08 (0.56-2.05)	0.82	1.98 (0.58-6.73)	0.28
Latinx	100	24%	16%	27%	0.63 (0.36-1.09)	0.10	0.62 (0.25-1.55)	0.31
Asian	68	16%	14%	13%	0.85 (0.46-1.57)	0.61	1.73 (0.60-4.92)	0.31
Other	20	5%	1%	10%	0.54 (0.20-1.49)	0.24	**0.04 (0.00-0.58)**	**0.02**
Gender identity								
Man	396	85%	94%	71%	(ref)		(ref)	
TW/NB/GQ	64	15%	6%	29%	1.06 (0.59-1.88)	0.85	**0.18 (0.06-0.53)**	**0.002**
Education								
< College degree	160	42%	22%	40%	(ref)		(ref)	
≥ College degree	300	58%	78%	60%	**1.71 (1.11-2.66)**	**0.016**	1.70 (0.78-3.71)	0.18
Have a PCP/clinic								
No	80	22%	12%	14%	(ref)		(ref)	
Yes	380	78%	88%	86%	**2.38 (1.34-4.24)**	**0.003**	0.96 (0.33-2.82)	0.94
Mean number of anal/vaginal sex partners*	--	4.3	13.2	5.0	**1.08 (1.05-1.12)**	**<0.0005**	**1.13 (1.06-1.20)**	**<0.0005**
Recreational drug use*								
No	253	64%	44%	48%	(ref)		(ref)	
Yes	207	36%	56%	52%	**1.85 (1.22-2.78)**	**0.003**	0.65 (0.31-1.35)	0.24

*In the past 6 months; TW=transwoman; NB=non-binary; GQ=genderqueer woman

974 INFLUENCE OF PrEP4LOVE CAMPAIGN ON PrEP UPTAKE AMONG YMSM IN CHICAGO

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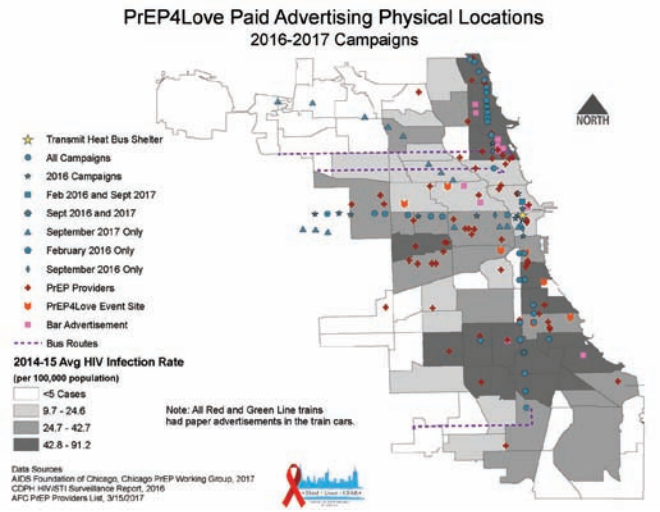
Background: While there have been significant increases in awareness of pre-exposure prophylaxis (PrEP) in recent years, uptake remains relatively low in populations most impacted by HIV – particularly young men who have sex with men (YMSM). This may partially be attributed to the lack of conversations between eligible individuals and their providers about PrEP and sexual health in general. Many major cities have launched campaigns aiming to address gap by using sex-positive messaging to empower individuals to be proactive in seeking out a PrEP prescription. In 2016, the citywide PrEP4Love campaign launched in Chicago. The campaign depicted racially diverse couples with catchy phrases ("Spread Tingle") in a variety of settings, including bus stops, fliers, and bar coasters. The campaign linked interested parties to additional information about starting PrEP, including a list of providers in Illinois.
Methods: RADAR is a longitudinal cohort study of YMSM to investigate multilevel factors associated with HIV infection in Chicago. At baseline, participants reported being assigned male at birth, aged 16-29 years, and either identified as LGBT or reported sex with another man. Between June 2017 and April 2018, additional questions were added to the core survey regarding awareness of the PrEP4Love campaign.
Results: 75.9% of the 700 people responding to PrEP4Love questions had seen the ads in at least one location. Most saw them online (57.8%), at pride events (50.7%), through friends (35.0%), or at a healthcare provider's office (32.0%). Participants who saw PrEP4Love ads were significantly more likely to have used PrEP in the prior 6 months (OR = 1.87; 95% CI: 1.15, 3.16). Further, those who saw PrEP4Love ads were nearly three times as likely to have spoken with a healthcare provider than those unaware of the campaign (OR = 2.77; 95% CI: 1.93, 4.00), and twice as likely to have initiated this conversation (OR = 2.07; 95% CI: 1.15, 3.85).
Conclusion: A multimedia PrEP campaign in Chicago was effective at reaching populations at greatest risk for HIV – YMSM. Seeing ads for PrEP4Love was associated with provider conversations as well as PrEP initiation, two major outcomes for the campaign. Although the impact of citywide campaigns can rarely be evaluated, we saw evidence for the success of PrEP4Love. To encourage PrEP uptake among at-risk populations, other jurisdictions need eye-catching and continuous campaigns similar to Chicago.



975 ASSOCIATION OF HIGHER RISK AND PrEP AWARENESS AMONG MSM IN BRAZIL, MEXICO, AND PERU

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Background: PrEP has been publicly available in Brazil since early 2018 and through demonstration projects in Mexico and Peru since mid-2018. We assessed the association between higher risk of HIV infection, indicative of PrEP eligibility, and PrEP awareness among men who have sex with men (MSM) from these countries.

Methods: MSM were recruited to complete an online survey via advertisements on Facebook, Grindr and Hornet from March-May 2018. Eligible individuals were cisgender MSM, ≥18 years old, HIV negative or of unknown status, lived in these countries and provided informed consent. Higher risk was defined using a CDC score indicating increased risk of HIV infection and the suggested cutpoint of 10. We used Poisson regression models to calculate adjusted prevalence ratios (aPR) testing the association between higher risk and PrEP awareness; socio-demographics and other risk variables were considered potential confounders. Analyses were conducted in STATA 14.

Results: After exclusion criteria were applied, 19,457 MSM were available for analysis of the 43,687 who began the questionnaire. Median age was 28 (IQR: 24-34), most respondents were Brazilian (58%), had post-secondary education (60%) and reported low to middle income (83%). PrEP awareness was 65%, 4% of respondents had ever used PrEP, and 53% were classified as higher risk. However, only 10% of respondents perceived their HIV risk as high. Among individuals classified as higher risk, 66.8% were aware of PrEP vs. 62.3% of lower risk respondents. The association between higher risk and awareness remained significant (aPR 1.03; 95% CI 1.00, 1.05) after adjustment. Additionally being 25+ years old (vs. 18-24 years), Brazilian, post-secondary education, high income and Gay Social Network (GSN) App use were associated with PrEP awareness. While being Peruvian, having less than secondary education and low income were negatively associated with PrEP awareness (all p-values<0.05).

Conclusion: Higher risk of HIV infection was associated with increased PrEP awareness. However, this association was weak indicating that MSM at higher risk, who would benefit from PrEP, are often not aware of this prevention strategy. As PrEP is introduced, awareness should increase, as seen in Brazil where PrEP has been available longer. Interventions to increase PrEP awareness are paramount, especially among MSM at higher risk, to increase PrEP uptake and prevent HIV infections. Gay Social Network apps and social media could play an important role to achieve this goal.

Table 1: Factors Associated with PrEP Awareness among MSM in Brazil, Peru, and Mexico in 2018

		% aware of PrEP	Crude PR	95% CI	aPR	95% CI
	Higher Risk of HIV infection	66.8	1.07	(1.04, 1.09)	1.03	(1.00, 1.05)
Country	Brazil	68.6	1.07	(1.05, 1.10)	1.18	(1.15, 1.21)
	Peru	46.5	0.73	(0.69, 0.76)	0.78	(0.75, 0.83)
	Mexico (ref)	64.0	1	--	1	--
Education	Post-secondary	68.0	1.24	(1.20, 1.28)	1.18	(1.14, 1.21)
	Completed Secondary School (ref)	54.7	1	--	1	--
	Less than Secondary School	39.6	0.73	(0.63, 0.84)	0.73	(0.63, 0.84)
Income	High	79.1	1.16	(1.14, 1.19)	1.15	(1.12, 1.17)
	Middle (ref)	67.9	1	--	1	--
	Low	56.4	0.83	(0.81, 0.85)	0.88	(0.86, 0.91)
	Use Gay Social Network Apps for Sex	66.0	1.27	(1.21, 1.33)	1.16	(1.10, 1.21)

976 PrEP-RELATED BARRIERS AMONG MEN WHO HAVE SEX WITH MEN IN BRAZIL, MEXICO, & PERU

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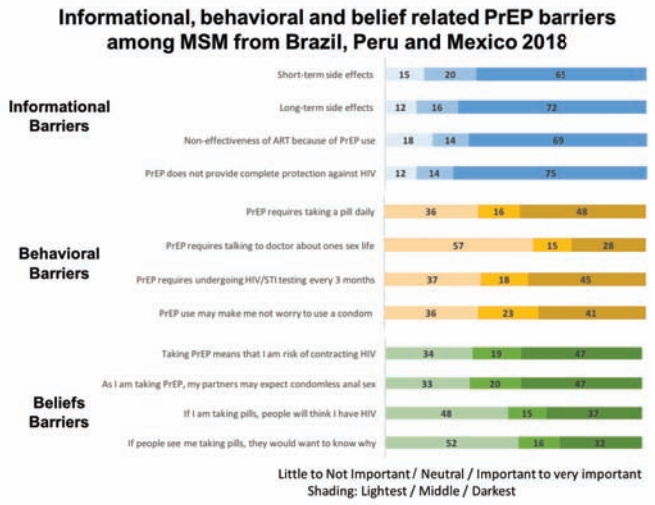
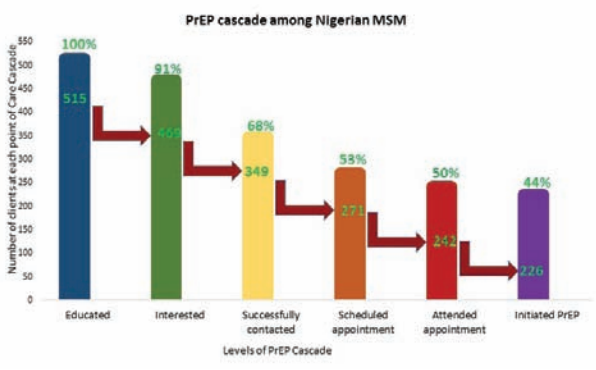
Background: Although PrEP has been publicly available in Brazil since early-2018 and through demonstration projects in Mexico and Peru since mid-2018, little is known about PrEP-related barriers. We examined factors associated with PrEP-related barriers among MSM in these countries.

Methods: MSM were recruited in 2018 to complete an online survey. Eligible individuals were cisgender MSM, ≥18 years old, HIV negative or of unknown status, lived in these countries and provided informed consent. The survey asked about 12 PrEP-related concerns on a 5-point Likert scale, which were then categorized into informational, behavioral and belief barriers. Responses by domain were summed to create three continuous outcomes; then, multiple linear regression was conducted for each outcome using Stata 14.

Results: Of the 43,687 participants who started the survey, 19,457 MSM remained for analysis after dropout and application of exclusion criteria. Most respondents were Brazilian (58%), had post-secondary education (60%), reported low to middle income (83%); and their median age was 28 (IQR: 24-34). Overall, concern regarding informational barriers was higher than behavioral or belief barriers (see graph). Respondents with lower informational barriers were: Brazilian(-1.7), aware of PrEP(-0.6), ever taken PrEP(-0.1) and at higher risk of contracting HIV(-0.4); while Peruvians(0.2) had higher informational barriers. Respondents with lower behavioral barriers were: Brazilian(-0.6), aware of PrEP(-1.1), 18-24 years old(-0.4), middle(-0.5) or high income(-1.2), used drugs(-0.7), had a stable male partner(-0.2) and ever tested for HIV(-0.7); whereas Peruvians(0.5) and those without secondary education(0.8) had higher behavioral barriers. Respondents with lower belief barriers were: Brazilian(-0.9), aware of PrEP(-1.5), 18-24 years old(-0.3), middle(-0.4) or higher income(-0.9), had a stable male partner(-0.3) and ever tested for HIV(-0.4). Peruvians(0.4) and those without secondary education(0.6) had higher belief barriers. All regression model coefficients had p-values<0.05.

Conclusion: Informational barriers were the highest of the 3 domains; simultaneously, those most informed (e.g., Brazilians and PrEP aware) had consistently lower barrier scores across all 3 domains. These findings indicate that PrEP barriers are likely amenable to interventions promoting PrEP awareness and education. Such interventions will be needed to reduce PrEP-related barriers, increase its uptake, and reduce HIV incidence in these countries.





977 DETERMINANTS OF PREEXPOSURE PROPHYLAXIS CASCADE AMONG NIGERIAN MSM

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Background: Pre-exposure prophylaxis (PrEP) is efficacious in preventing human immunodeficiency virus infection among men who have sex with men (MSM). Here we characterize engagement and correlates of the HIV PrEP cascade among Nigerian MSM

Methods: The TRUST/RV368 cohort employs respondent-driven-sampling to recruit MSM into HIV/STI prevention and treatment services in Abuja and Lagos, Nigeria. 515 HIV negative MSM at the Abuja site who completed a survey instrument on awareness and willingness to use PrEP were approached for PrEP initiation. To understand gaps at different levels of PrEP uptake, we categorized study participants (i) educated about PrEP (ii) showed interest (iii) successfully contacted (iv) scheduled appointment (v) attended scheduled appointment (vi) initiated PrEP. Multivariate logistic regression models were used to assess correlates of the HIV PrEP cascade.

Results: Of 515 participants, 469 (96.3%) showed interest taking PrEP every day and/or after a sexual act, 349 (67.8%) were successfully contacted and 271 (52.6%) scheduled an appointment, 242 (50.0%) attended scheduled appointment and 226 (43.9%) initiated PrEP (figure 1). Younger MSM, [≤19 years vs. ≥ 25 years (adjusted odds ratio (aOR) 0.6; 95% CI 0.4 to 0.9)] and religion, (Muslims vs. Christians, aOR 0.5; 95% CI 0.3 to 0.9) were associated with decreased odds of PrEP initiation. Having received information on HIV prevention in the past 12-months was associated with increased odds of PrEP initiation, (aOR 1.4; 95% CI 1.1 to 2.1). Furthermore, Muslims were significantly less likely to be successfully contacted and scheduled for an appointment ($p < 0.05$). Younger MSM had decreased odds of being successfully contacted (aOR 0.6; 95% CI 0.3 to 1.1) and attending an appointment (aOR 0.6; 95% CI 0.4 to 1.0) although associations were not statistically significant. Larger number of sex partners, > 5 vs. ≤ 5 was associated with increased odds of scheduling an appointment (aOR 1.8; 95% CI 1.1 to 3.0) and PrEP initiation (aOR 1.9; 95% CI 0.9 to 3.0). Of those successfully contacted and did not engage, 30% lost interest, 27% promised to engage and 18% perceived low HIV risk.

Conclusion: Engagement in PrEP in this population is relatively low with younger MSM less likely to engage in PrEP. Reinforcing HIV prevention education and facilitating young MSM to engage in PrEP is critical in order to prevent HIV transmission. Muslims lag behind Christians at different levels of PrEP uptake. Better support among Muslim gay men is needed.

978 WOMEN'S PrEP KNOWLEDGE, ATTITUDES, PREFERENCES AND EXPERIENCE IN CHICAGO

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Background: Black women in Chicago are disproportionately affected by HIV, but few are on PrEP. We report the results of a mixed methods study of knowledge, attitudes, experience, and preferences for PrEP among cis-gender women in Chicago.

Methods: We administered a survey to 370 HIV(-) women visiting either a public Sexually Transmitted Infection clinic or an Emergency department and conducted focus groups with 16 PrEP-naive women and in-depth interviews with 7 PrEP-using women. Survey data were analyzed using descriptive statistics and multivariate logistic regression as well as thematic analysis for qualitative data.

Results: Majority of women identified as black (83%) and had a regular source of healthcare (71%). In the last 6 months, 83% had vaginal or anal sex and 93% inconsistent condom. Women had low rates of perceived HIV risk (90% low/no). Only 30% (112) had heard of PrEP before the survey. The only factor associated hearing about PrEP was knowing someone on PrEP (OR 15.6 95%CI (3.0-80.3)). One third (29%(105)) considered starting PrEP in the next 6 months, with protecting health (77%) and reducing HIV worry (58%) most common reasons. Most (81%) had concerns about taking PrEP with side effects (68%)) and incomplete protection (25%) most common;72% would need some form of support. Most preferred source for information and PrEP was their primary care site, with cost (25%), clinic familiarity (23%) and confidentiality (24%) most important. Factors associated with starting PrEP included being Latina (OR 3.5 95%CI (1.2-10.0), recent STI (OR 2.6 95%CI (1.3, 5.0)), more worry about HIV (OR 1.2 95%CI (1.0-1.5)) and higher belief in PrEP effectiveness (OR 2.1 95%CI (1.4, 3.3)). Qualitative themes aligned with survey results including the lack of PrEP knowledge, viewing PrEP as beneficial, and importance of trusted health providers. FGs also found disconnection with current PrEP advertisements, need for community-level PrEP education and outreach, and differing understandings of HIV risk/vulnerability. PrEP-users offered insights into current pathways into PrEP and need for increased awareness and access.

Conclusion: Despite significant PrEP work in Chicago, only 29% of women in our study had heard of PrEP. However PrEP attitudes among these women were positive, and once made aware of PrEP, one third considered starting in the near future. Translating these results into interventions which reflect women's preferences and barriers are critical to increase PrEP uptake by cisgender women in Chicago.

979 HIV RISK AND CHARACTERISTICS OF WOMEN SEEKING PrEP IN A US DEMONSTRATION PROJECT

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Background: Little information is known about the risk profiles of women who initiate pre-exposure prophylaxis (PrEP) for HIV prevention in the US. We analyzed baseline risk factors of women in a PrEP demonstration project using TDF/FTC to assess correlates of PrEP uptake.

Methods: Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGiS) is a PrEP clinical trial in Southern California of 136 HIV-negative cisgender women ≥18 years old at risk for HIV who completed enrollment. At baseline, women were surveyed for sociodemographics and risk behaviors with testing for STIs. Women in three primary HIV risk groups according to main partner type ([1] serodiscordant partnerships (SD), [2] sex workers [SW], and [3] risk attributable to known and unknown partner behavior [UP]) were compared using Fisher's exact or Kruskal-Wallis tests to determine differences by risk group.

Results: Sixty-four women (47%) were grouped in the SD risk group, 21 (15%) in SW and 51 (38%) in UP. Despite SW reporting significantly more sex partners than SD or UP, overall baseline STI rate was low at 8% with no difference by risk group. SW were more likely to report problem drinking and drug use (p=0.002) and history of intimate partner violence in the last year (p<0.001) compared to SD and UP. HIV literacy was higher among SW vs. the other risk groups (p=0.023). Nearly all SW (95%) and most UP women (83%) wanted to take PrEP to protect themselves from HIV vs. only 33% of SD (p<0.001). There were no differences between groups in depression score or HIV risk perception. Of 103 women reporting a main partner, 80% were aware of partner's HIV status. Among the 51 women reporting an HIV+ partner, 96% thought their partner was on ART and 71% were suppressed. Black women were less likely to know if their partner was HIV+ compared to White and Latina women (p=0.032). Black and Latina women vs. White women (p=0.006), and SW and UP vs. SD (p<0.001) more frequently suspected partner infidelity.

Conclusion: Women enrolled in this PrEP demonstration project were predominantly in serodiscordant relationships but many had partners of uncertain risk and almost one in six were engaged in sex work. We found differences between individuals in the three HIV risk groups by race/ethnicity, employment, HIV knowledge and risk behaviors, PrEP motivations and main partner dynamics. Interventions to increase PrEP uptake among women may need to be customized based on the varying partnership types found among women at risk for HIV.

	Serodiscordant (n=64)	Sex Work (n=21)	Unknown Partner (n=51)	P-value
Mean Age (SD)	39 (10)	43 (11)	40 (12)	0.41
Race/Ethnicity				0.003
Non-Hispanic White	14 (22%)	7 (33%)	9 (18%)	
Non-Hispanic Black	16 (25%)	10 (48%)	26 (51%)	
Latina	13 (20%)	1 (5%)	12 (24%)	
Other	21 (33%)	3 (14%)	4 (8%)	
Education				0.95
≤ High School	29 (45%)	10 (48%)	22 (43%)	
≥ Some College	35 (55%	11 (52%)	29 (57%)	
Income				0.6
< 2000 per month	31 (63%)	13 (76%)	30 (70%)	
≥ 2000 per month	18 (37%)	4 (24%)	13 (30%)	
Employment				0.016
Full/Parttime/Retired	34 (56%)	4 (22%)	30 (61%)	
Unemployed/Unable to work	27 (44%)	14 (78%)	19 (39%	
Sex Partners last 3mo** (Median, IQR)	1, 1-1	10, 4-17	2, 1-3	<0.001
Main Partner	51 (80%)	10 (48%)	42 (82%)	0.01

*mean, SD = standard deviation; **median, IGR = interquartile range

980 CONCORDANCE OF HIV RISK PERCEPTION AND EMPIRIC RISK SCORE AMONG PREGNANT KENYAN WOMEN

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Background: Understanding pregnant women's risk perception and whether this correlates with their actual HIV risk is important to guide PrEP implementation in high HIV prevalence regions.

Methods: The PrEP Implementation for Mothers in Antenatal Care (PrIMA) study (NCT03070600) is a cluster-RCT in western Kenya that assesses strategies for delivering PrEP to pregnant women. At enrollment, HIV risk perception was assessed using two risk perception scales (Napper and Vargas). Intimate partner violence (IPV) was assessed using the Hurt, Insulted, Threatened with Harm and Screamed screening tool. HIV risk was assessed using a validated empiric risk score for predicting HIV acquisition designed for pregnant women which includes behavioral and partner characteristics: scores >6 indicate high-risk for HIV. Women self-reported their partner's HIV status. Women's perceived HIV risk was compared between women with a high (>6) and low (≤6) empiric risk scores.

Results: Of the 2,280 women enrolled, median age was 24 years (IQR 20-29), median gestational age was 25 weeks (IQR 20-30), and 84% were married. Overall, 33% reported having partners of unknown HIV status and 40% had empiric HIV risk scores >6; 7% believed they had a 'great chance' of acquiring HIV in the next year. Compared to women with lower risk scores, women with scores >6 were more likely to believe they had a 'great chance' of acquiring HIV in the next year (15% vs 2%). Mean perceived HIV risk was 21 (SD, 4.5) and 1.8 (SD, 1.9) using the Napper and Vargas scales, respectively, signifying moderate perceived risk. Women with high-risk scores (>6) reported greater perceived risk in both scales compared to women with low risk scores (Napper, Mean [M]: 23.2 vs 19.5 and Vargas, M, 2.69 vs 1.19). Women who experienced IPV had greater perceived risk in both scales (Napper, M: 24 vs 21) and (Vargas, M: 2.7 vs 1.7). Compared to women with HIV-uninfected partners, women with partners of unknown or known positive status had higher perceived risk (positive partners, Napper, M: 26 vs 19; Vargas, M: 3.8 vs 1.2) and (unknown partner status, Napper, M: 23 vs 19; Vargas, 2.6 vs 1.2). All P values <0.001.

Conclusion: Women with high empiric HIV risk scores were more likely to report a higher perceived risk of acquiring HIV. This suggests that women may accurately assess their own risk for HIV and providers may be able to universally counsel women on PrEP rather than conducting a risk assessment to target PrEP.

981 LOW PrEP AWARENESS AND WILLINGNESS AMONG TRANSGENDER WOMEN IN SOUTH AFRICA

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Background: Transgender women (TW) face elevated vulnerability to HIV. Recent studies indicate a pooled prevalence of 25% across 8 sub-Saharan African countries, with no data available for South Africa. In 2016, the South African National Department of Health implemented PrEP for high-risk populations at select sites. However, transgender people were only targeted as a subset of sex workers. Data are needed to guide strategies on how best to implement PrEP among TW in South Africa. This study aimed to identify predictors of PrEP knowledge, willingness, and uptake among South African TW to inform development of effective interventions.

Methods: Between May-September 2018, 210 TW were recruited in Cape Town, East London, and Johannesburg through community outreach. Each TW completed an interviewer-administered survey. Data were collected on psychosocial factors, HIV risk behaviors, self-reported HIV status, and PrEP awareness, willingness, and uptake. Bivariate and multivariable logistic regression modeling tested associations between HIV risk behaviors and perception, violence, and PrEP awareness and willingness. Multivariable models included random effects for city.

Results: Only 50% (105/210) of TW had heard of PrEP. Of those, 87% (91/105) knew where to get PrEP, and 19% (20/105) had ever taken it. The 67 (32%) TW who reported living with HIV had 2.6 times the odds (95% CI: 1.4-4.9; p=0.002) of PrEP awareness compared to HIV-negative TW. Among HIV-negative TW not on PrEP, 51% (54/106) were willing to take it. In multivariable modeling, violence victimization and history of substance abuse were significantly associated with PrEP awareness, while history of sexually transmitted infections

and violence victimization were significantly associated with PrEP willingness. In these models, history of sex work was not associated with PrEP awareness, and HIV risk perception was not significantly associated with willingness to take PrEP.

Conclusion: PrEP awareness, willingness, and uptake remain low among TW in South Africa. HIV-negative TW who perceived their risk for HIV acquisition to be high were not more willing to take PrEP than TW with low perceived risk. In adjusted analyses, TW sex workers were not more likely to be aware of PrEP or willing to take PrEP than TW who had not engaged in sex work. These findings suggest a need to raise awareness of PrEP in transgender communities and specifically include TW in strategies to increase engagement in PrEP services.

Table. Predictors of PrEP Awareness and Willingness among Self-reported HIV-negative Transgender Women in South Africa

Variable	Associations with PrEP Awareness OR (95% CI)		Associations with PrEP Willingness OR (95% CI)	
	Bivariate	Multivariable	Bivariate	Multivariable
HIV risk perception	0.52 (0.37, 0.75)*	0.42 (0.07, 2.54)	0.90 (.62, 1.32)	----
Lifetime history of sex work	3.29 (1.85, 5.82)*	0.38 (0.10. 1.45)	2.56 (1.09, 6.03)*	1.65 (0.59, 4. 62)
History of condomless receptive anal sex in prior 12 months	1.71 (0.96, 3.04)	----	0.77 (0.35, 1.68)	----
Lifetime history of sexually transmitted infections	2.31 (1.28, 4.18)*	0.85 (0.21, 3.32)	3.28, (0.98, 10.94)	4.72 (1.17, 19.1)*
Lifetime history of sexual violence victimization[†]	4.33 (2.41, 7.79)*	4.69 (1.49, 14.75)*	3.51 (1.60, 7.67)*	2.95 (1.19, 7.30)*
Lifetime history of substance use	2.11 (1.19, 3.73)*	3.62 (1.01, 13.00)*	2.08 (0.92, 4.73)	1.12 (0.42, 3.01)

*Significant at p<0.05. †Both physical and sexual violence were significant, only one was included in the model due to collinearity. Multivariable models include random intercept for city

982 POSTEXPOSURE PROPHYLAXIS AND HIV RISK IN RWANDA: POTENTIAL FOR PEP-TO-PrEP PROGRAMS

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Background: Rwanda and other African countries provide Postexposure Prophylaxis (PEP) at health facilities for HIV-negative persons with recent exposure to HIV, and are at early stages of implementing Pre-Exposure Prophylaxis (PrEP). PEP programs are an important, unappreciated opportunity to recognize and address HIV risk, both retrospectively relative to a suspected recent HIV exposure, and prospectively via PrEP. Women and girls may disproportionately seek PEP more often than men, often in response to gender-based violence and/or sexual assault. In addition, anecdotal evidence suggests some persons seek PEP repeatedly, and may be discouraged from doing so. We analyzed existing PEP data from a Rwanda national survey to determine whether PEP recipients (who were by definition HIV negative at the time of PEP services) had a higher burden of subsequent HIV, and might benefit from PrEP.

Methods: We performed secondary analysis of Rwanda's AIDS Indicator and HIV Incidence Survey 2013-2015. Logistic regression models were used to assess factors associated with HIV infection. All analyses accounted for the complex survey design and were done in STATA Version 13.

Results: A total of 101/13,893 respondents ages 15-56 reported receiving PEP in the prior 12 months, 40 males and 61 females. Recent PEP recipients had 6.5 times higher odds of being HIV positive (unadjusted Odds Ratio [uOR] 6.5; 95% CI 3.8-11.2). This effect was seen across age and sex disaggregation, and was exaggerated among youth, with persons under 25 years having >9 times higher odds of being HIV positive (uOR 9.1; 95% CI 2.1-39.4). Adolescent girls/young women 15-24 years old with recent PEP exposure had >10 times higher odds of being HIV positive (uOR 10.1; 95% CI 2.26-45.14).

Conclusion: Rwandan PEP recipients are at substantially increased risk of acquiring HIV, suggesting that existing prevention efforts are failing them. PEP programs should be re-emphasized and strengthened, and recipients should be provided effective ongoing prevention services including transition to PrEP for those with ongoing substantial HIV risk. Creation of PEP-to-PrEP transition programs would leverage the existence of PEP clients, who are already seeking HIV prevention services at health facilities because they recognize their own elevated HIV risk. Successful PrEP implementation will also require risk reduction and adherence support, and consideration of PrEP cessation when risk has reduced.

983 ARE ROUTINE RENAL AND LIVER LABS TESTING AMONG PEP PATIENTS ON TDF/FTC/DTV NECESSARY?

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Background: HIV post exposure prophylaxis (PEP) guidelines recommend routine glomerular filtration rate (GFR), aspartate aminotransferase (AST), and alanine transaminase (ALT) testing at PEP initiation and follow up visits. Once daily tenofovir (TDF)/emtricitabine (FTC)/ dolutegravir (DTV) is the first line PEP regimen in CDC guidelines and New York City (NYC) Sexual Health Clinics (SHC) due to its high safety profile. We assessed the prevalence of abnormal AST/ALT/ GFR at baseline (BL) and follow up (FU) testing among patients without self-reported kidney or liver disease who were provided 28 days of PEP at NYC SHC.

Methods: We extracted medical record data from PEP initiation visits during 9/2016-12/2017 with: TDF/FTC/DTV regimen, a baseline metabolic panel, and no HIV medication dispensed in the prior three months at NYC SHC. GFR/AST/ALT results were examined at BL and at the first FU testing 14-42 days. Normal renal function (RF) was defined as GFR ≥70 ml/min and normal liver function (LF) was defined as ALT and AST less < 50 U/L. Abnormal LF/RF tests were classified into grades based on the GFR and higher AST/ALT values (table). Chart review was done for visits ≥ grade 2 to determine whether PEP regimen was changed or discontinued.

Results: Overall 1115 PEP initial visits were identified of 1051 unique patients. Median age was 29 years (IQR 25-35); 92% were male. At baseline, 3% of visits had an abnormal RF (33/1115) and 9% had an abnormal LF (95/1115). The majority of BL abnormal labs were grade 1(RF: 31/32; LF: 77/95). Among 575 BL visits with FU labs, 9% had abnormal RF (50/575) and 11% had an abnormal LF (64/575). The majority of FU abnormal labs were grade 1(RF: 49/50; LF: 51/64) (table). Visits with and without FU labs were similar with regards to age, gender, race, and baseline RF. Visits with abnormal BL LF were more likely to have FU lab visits (aOR 1.7;95%CI 1.1-2.6). Only twice was a PEP regimen changed based on BL grade 2 RF or LF abnormality and no PEP regimens were changed based on FU lab abnormalities.

Conclusion: Baseline renal and liver testing among PEP visits on TDF/FTC/ DTV without known history of kidney and liver disease was normal in > 90 % and rarely resulted in changes in PEP regimen (0.2%). Follow up renal and liver testing did not result in any regimen change. As the safety profile of PEP regimens improves, routine renal and liver testing and monitoring for healthy patient population may not be necessary.

Table. Results of Renal and Liver Function Testing at Baseline PEP Initiation Visits and First Follow Up Visit within 14-42 Days; New York City Sexual Health Clinics; September, 2016- December, 2017. (N=575)

Baseline Laboratory Results	Follow up Laboratory Results			
	Normal	Grade 1	Grade 2	Grade 3
Renal Function	N (%)	N (%)	N (%)	N (%)
Normal RF (N= 561) (GFR>70 ml/min)	521 (93)	39 (7)	1(0.1)	0 (0)
Grade 1 RF (N=14) (GFR 50-69 ml/min)	4 (29)	10 (71)	0 (0)	0 (0)
Grade 2 RF (N=0) (GFR 30-49 ml/min)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 3 RF (N=0) (GFR<30 ml/min)	0 (0)	0 (0)	0 (0)	0 (0)
Liver Function	N (%)	N (%)	N (%)	N (%)
Normal LF (N=515) (AST and ALT< 50 U/L)	480 (93)	29 (6)	5 (1)	1(0.2)
Grade 1 LF (N=53) (AST/ALT 50-100 U/L)	30 (57)	20 (38)	3 (6)	0 (0)
Grade 2 LF (N=6) (AST/ALT 101-250 U/L)	1 (17)	2 (33)	2 (33)	1 (17)
Grade 3 LF (N=1) (AST/ALT >250 U/L)	0 (0)	0 (0)	0 (0)	1 (100)

RF= renal function; LF= liver function; FU= follow up

All Rows sum to 100%

984 POSTEXPOSURE PROPHYLAXIS NONCOMPLETION AND NONCONDOM USE IN FRANCE, 2004-2017

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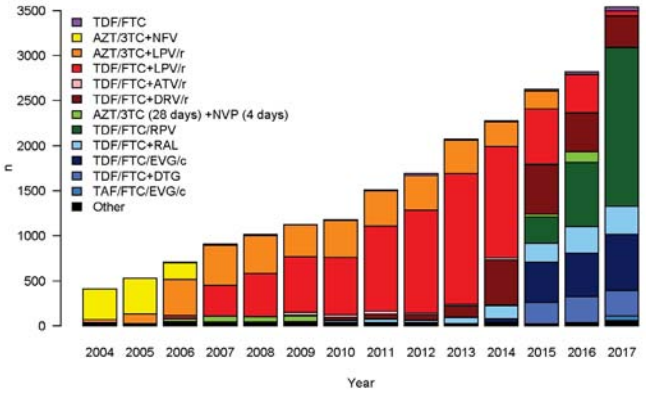
Background: The care of individuals exposed to HIV remains a challenge regarding postexposure prophylaxis (PEP) completion and is a unique occasion of sexual counseling. Identifying risks of not fulfilling PEP course and concomitant condom use among individuals demanding PEP may improve clinical practice.

Methods: Retrospective analysis from the French National Dat'AIDS cohort (NCT02898987) of individuals evaluated for PEP between 2004 and 2017. We assessed clinically relevant predictors (Odd-ratios [OR] and 95% Credibility Interval) and their probabilities (Pr) of both non-condom use and PEP premature interruption (< 20 days) by Bayesian modeling.

Results: Overall, 48947 potential exposures to HIV were evaluated for PEP, 19887 for occupational and 29060 for sexual risks. Participants were primarily male (54%) with a median age of 30 years (IQR, 24-39). The source had an unknown HIV serostatus in 38743 exposures. Among the 29060 sexual exposures (36% MSM versus 64% heterosexual), 48% reported non-condom use during the exposure. Non-condom use increased (Pr > 99%) with the year of exposure (OR per 10-years increment, 1.22 [1.14-1.29]), MSM (OR, 1.33 [1.16-1.53]) and rape (OR, 12.3 [10.6-14.3]). Non-condom use decreased (Pr > 99%) with age (OR per 10-years increment, 0.90 [0.88-0.93]), in the case of an intercourse with a sex worker (OR, 0.33 [0.29-0.36]), or a woman partner (OR, 0.83 [0.72-0.95]), and knowledge of the serological status of the partner, whether positive (OR, 0.79 [0.73-0.86]); or negative (OR, 0.84 [0.73-0.95]). Overall, 22 402 individuals (46%) effectively received PEP (14% occupational and 86% sexual exposures). PEP regimens varied among time (Figure). Overall, 20% of individuals discontinued their PEP regimen within 20 days. Age (OR, 0.87 per 10-years increment [0.83-0.92]), MSM (OR, 0.59 [0.47-0.73]), intercourse with a sex worker (OR, 0.41 [0.31-0.51]), rape (OR, 0.41 [0.32-0.53]), moderate depth of occupational accident (OR, 0.76 [0.58-0.98]) versus deep and superficial), and known HIV-infected source patient (OR, 0.50 [0.42-0.59]), were factors associated with reduced risks of PEP early discontinuation (Pr > 98%). Neither PEP regimen nor reported condom use were associated with a premature PEP stop.

Conclusion: Our study provides new insights for targeting groups of individuals with specific interventions, for improving both condom use and PEP completion. Especially Youth and MSM need more targeted interventions in risk behavior prevention and adherence.



985 E/C/F/TAF SINGLE TABLET REGIMEN FOR HIV POSTEXPOSURE PROPHYLAXIS

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Background: HIV Postexposure prophylaxis (PEP) completion rates are often low. Newer antiretroviral combinations, such as the recently approved elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide coformulation (E/C/F/TAF), may improve PEP adherence.

Methods: Prospective, open-label, single-arm trial conducted in 15 French centers (NCT02998320). Individuals with recent HIV exposure who met criteria for PEP initiation received once-daily E/C/F/TAF for 28 days. Follow-up visits were scheduled at days 14, 28, 60 and 120. The primary endpoint was PEP completion at day 28. Secondary endpoints were adherence, quality of life, adverse events and efficacy.

Results: Ninety-eight individuals exposed to HIV received at least one dose of E/C/F/TAF (8 occupational and 90 sexual exposures, of which 64% were MSM). Participants were primarily male (77%) with a median age of 33 years (IQR, 25-39). Seventy-eight individuals (80%) completed PEP course till day 28 visit. Completion failure (n=20, 20%) was due to lost to follow-up (n=16), sexual partner or source-patient tested HIV-negative (n=2), individual's own choice (n=1) and withdrawal of consent (n=1). No PEP interruption due to adverse events was documented. Fifteen additional participants (15%) were also lost to follow-up from day 28 to day 120. Self-reported adherence was 100%, between 90 and 99%, and <90% for 63 (76%), 18 (22%) and 2 (2%) individuals at day 14; and for 58 (75%), 13 (17%), 6 (8%) individuals at day 28, respectively. Median elvitegravir trough concentration at day 14 was 628 ng/mL (IQR, 471-934), therefore above 190 ng/mL for 96% of participants. Mean quality of life SF-12 measures of physical and mental health were of 50 and 47 on day 1, 52 and 48 on day 14, and 51 and 49 on day 28, respectively (p>0.05). Overall, 226 adverse events were reported in 58 (68%) and 43 (59%) participants, at day 14 and 28 respectively. At day 14; 93, 24 and 8 grade 1, 2 and 3 adverse events were observed, and 73, 21 and 7 on day 28, respectively. The most frequent reported adverse events were asthenia (19%), abdominal pain (16%), diarrhea (15%) and headache (14%). No renal or liver abnormalities occurred. Neither HIV seroconversion, nor acute hepatitis B infection were observed.

Conclusion: PEP E/C/F/TAF was well tolerated and demonstrated good completion rates. Self-reported and drug levels indicated good adherence, confirming that E/C/F/TAF could be a regimen of choice for PEP.

986 HIV INFECTION AND FTC/TDF IN DRIED BLOOD SPOT: A POOLED ANALYSIS OF GLOBAL STUDIES

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Background: Use of daily FTC/TDF for HIV pre-exposure prophylaxis (PrEP) substantially reduces HIV-1 acquisition for individuals at high sexual risk. Dried blood spot (DBS) analyses of tenofovir-diphosphate (TFV-DP) in red blood cells measure chronic TDF drug use and provide an objective evaluation of adherence for individuals who may develop HIV infection.

Methods: In 8 open-label HIV prevention studies, 3,058 participants were given FTC/TDF PrEP. Demographics, efficacy, and DBS measures of TFV-DP were collected at baseline and follow-up visits up to 3.4 years. We used logistic regression to estimate odds ratios (OR) for adherence, and Poisson regression to calculate incidence rates (IR) and incidence rate ratios (IRR) of new HIV cases.

Results: Of the 3,058 participants, 99% were men who have sex with men (MSM), 68% were in the USA, 29% in South America, 2% in Asia, and 1% in Africa; the median age at PrEP initiation was 30 years (interquartile range, IQR, 25–38). DBS analyses suggested 26%, 14%, 34%, and 27% individuals were taking ≤2 (below lower limit of quantitation–349 fmol/punch of TFV-DP), 2–3 (350–699 fmol/punch), 4–6 (700–1,249 fmol/punch), and ≥7 (≥1,250 fmol/punch) tablets of FTC/TDF PrEP per week, respectively. Forty-one of the 3,058 individuals tested HIV positive (IR=1.13/100 person-years exposure, 95% confidence interval, CI, 0.82–1.54), with 38 of the 41 cases (93%) had TFV-DP consistent with taking ≤3 FTC/TDF tablets/week. With a median PrEP exposure of 0.96 years (IQR, 0.90–1.39), the IR (95% CI) of HIV infection were 3.41 (2.37–4.90), 1.59 (0.76–3.33), and 0.14 (0.04–0.43) per 100 person-years for individuals who took ≤2, 2–3, and ≥4 tablets/week. Compared to individuals

taking ≥4 tablets/week, those who took ≤2 or 2–3 tablets had an IRR (95% CI) of 24.56 (7.48–80.63) or 11.44 (2.96–44.23), respectively. Individuals over 40 years old were more likely to be taking ≥4 tablets/week, the established protective dosage of FTC/TDF PrEP, as compared to those aged 30–39 years [OR (95% CI)=1.53 (1.18–2.00)]. Younger participants were less likely to remain adherent at ≥4 tablets/week [OR (95% CI)=0.73 (0.57–0.92)] for individuals age 25–29 and 0.30 (0.23–0.38) for those under 25 years.

Conclusion: In this multi-national pooled analysis of FTC/TDF PrEP use in a diverse geographical population of MSM, individuals taking ≥4 tablets/week were protected from HIV infection at a low incidence rate of 0.14/100 person-years. Age over 40 years was significantly associated with increased adherence.

987 PREDICTORS OF LONG-TERM HIV PrEP ADHERENCE AFTER TRIAL PARTICIPATION IN MSM

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Background: The efficacy of tenofovir disoproxil fumarate (TDF) / emtricitabine (FTC) for HIV pre-exposure prophylaxis (PrEP) in men who have sex with men (MSM) has been well documented in randomized controlled trials. Following trial completion, participants are challenged with establishing care, acquiring PrEP, and remaining adherent. This study aimed to identify predictors of PrEP adherence during a 12-month post trial period.

Methods: This study followed an existing PrEP demonstration project, the TAPIR randomized controlled multi-center trial of text messaging versus standard care for adherence to daily TDF/FTC PrEP in MSM, conducted in Southern California between 2014-2016 (NCT01761643). At the last TAPIR trial visit, study provided PrEP was discontinued and participants were provided with information about where to obtain PrEP in the community. During week 48 of the TAPIR trial and during prospective observational post-trial visits at months 6 and 12, adherence was estimated by dried blood spot (DBS) intracellular tenofovir diphosphate (TFV-DP) levels. Adequate adherence was defined as TFV-DP concentration of >719 fmol/punch reflecting four or more tablets per week. Binary logistic regression analysis was performed to assess predictors of completing post-trial visits and PrEP adherence among those who completed ≥ 1 visit.

Results: Of 395 TAPIR participants who were provided with free PrEP during TAPIR for a median of 585 days (range 3-757 days), 113 (29%) completed one or more post-trial visits. Multivariate predictors of completing post-trial visits included adequate adherence at the week 48 TAPIR visit, total days of TAPIR participation, and less problematic substance use (Table). Among 113 participants who completed ≥ 1 post-trial visit, 67 (59%) had adequate adherence at their last post-trial visit. Adequate adherence at the week 48 TAPIR trial visit was the only significant predictor of adequate adherence post trial (Table). Participants with adequate adherence at the week 48 TAPIR visit had also significantly higher DBS TFV-DP levels at last post-trial follow up (median 993 fmol/punch, IQR 0-1397 vs. median 636 fmol/punch, IQR 0-758; p=0.03).

Conclusion: PrEP users followed for up to 3 years had high rates of adequate adherence suggesting that PrEP can be used effectively by individuals for years. Longer term adequate adherence was best predicted by having adequate adherence at week 48 of the PrEP trial. Additional measures are needed for those that have persistent low PrEP adherence.

Table: Univariate and multivariate binary Logistic Regression Models for predicting ≥1 post PrEP trial study visit, and for predicting near perfect PrEP adherence 12 months post RCT.

Variables for Predicting Post-Trial Visit (n=395)	OR	95% CI	p value	OR	95% CI	p value
	Univariate Model			Multivariate Model*		
Intervention Arm (i.e. receiving individualized texting for adherence to daily TDF/FTC)	0.641	0·412 – 0.995	0·047			
Age (per year)	1.039	1.015-1.063	0·001			
Education category	1.169	0·975 – 1.402	0·092			
Income category	1.038	0.929 – 1.159	0.515			
Duration on PrEP trial (per day)	1.005	1.004 – 1.007	<0.001	1.006	1.003 – 1.008	<0.001
Adequate Adherence End of PrEP trial Study visit	3.693	1.756 – 7.765	0.001	2.724	1.245 – 5.961	0.012
DAST10 (per score point)	0.789	0.683 – 0.912	0.001	0.780	0.667 – 0.912	0.002
Stimulant Substance Use	0.665	0.408 – 1.085	0.102	Not included		
Non-stimulant Substance Use (alcohol, marijuana and poppers excluded)	0.722	0.464 – 1.123	0.148	Not included		
Popper use	0.663	0.426 – 1.031	0.068			
AUDIT (per score point)	1.003	0.954 – 1.054	0.910			
Variables for Predicting Adequate PrEP Adherence at the last post-trial visit (n=113)	OR	95% CI	p value			
Intervention Arm (i.e. receiving individualized texting for adherence to daily TDF/FTC)	1.117	0.519 – 2.402	0.777			
Age (per year)	1.006	0.968 – 1.044	0.772			
Education category	0.925	0.682 – 1.254	0.616			
Income category	1.062	0.855 – 1.321	0.585			
Duration on PrEP trial (per day)	1.002	0.999 – 1.006	0.110			
Adequate Adherence End of PrEP trial Study visit	4.741	1.183 – 19.001	0.028	4.741	1.183 – 19.001	0.028
DAST10 (per score point)	0.773	0.594 – 1.006	0.056			
Stimulant Substance Use	0.932	0.403 – 2.158	0.870			
Non-stimulant Substance Use (alcohol, marijuana and poppers excluded)	1.383	0.641 – 2.982	0.408			
Popper use	1.084	0.507 – 2.320	0.834			
AUDIT (per score point)	0.975	0.907 – 1.048	0.492			

* Chi square 5.704; p=0.680 Hosmer Lemeshow; Forward Wald Binary Logistic Regression

988 PrEP STIGMA PREDICTS PrEP UPTAKE AND ADHERENCE: RESULTS FROM THE RADAR COHORT STUDY

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Background: Increasing the uptake of pre-exposure prophylaxis (PrEP) to prevent HIV acquisition among at-risk populations, such as young men who have sex with men (YMSM), is of vital importance to slowing the HIV epidemic. Stigma and negative injunctive norms, such as the so called "Truvada Whore" phenomenon, hamper this effort. In our prior research we developed a measure of PrEP Stigma and Positive Attitudes (PSPA) and demonstrated that these injunctive norm beliefs differ by race/ethnicity and cluster geographically among YMSM in Chicago.

Methods: PSPA were measured in 622 participants in the RADAR longitudinal cohort study of YMSM and transgender women living in Chicago (YMSMT). Analyses were conducted on data from 105 YMSMT with PSPA measured at two time points 6 months apart (to assess measure stability), and 622 participants who reported on PSPA at one time point and reported on PrEP use and adherence 6 months later.

Results: There were no significant changes in either dimension of PSPA over 6 months. Participants with higher PrEP stigma were significantly less likely to report currently taking PrEP at the next visit 6 months later (OR=0.49, 95% CI: 0.29, 0.82) while controlling for age, race and gender identity. Of those participants taking PrEP at the next visit (n=24), participants who reported missing at least one dose in the past week had significantly higher PrEP stigma scores (t=-2.39, P < .05) compared to participants who did not miss a dose in the past week. Participants with higher positive attitudes towards PrEP were significantly more likely to have reported currently taking PrEP at the next visit (OR=5.07, 95% CI: 2.42, 10.61) while controlling for age, race and gender identity.

Conclusion: These results provide important information about PrEP attitudes and how PrEP stigma is related to PrEP uptake and adherence. In concert with previously published cross-sectional research on PrEP stigma, these prospective findings demonstrate the importance of addressing PrEP stigma in order to improve uptake and adherence among populations in greatest need of HIV prevention interventions.

989 LONGITUDINAL PREDICTORS OF PrEP DISCONTINUATION AMONG YMSM AND TRANSGENDER WOMEN

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Background: Pre-exposure prophylaxis (PrEP) is highly efficacious at preventing HIV but is dependent upon optimal adherence, including sustained use during high risk periods. PrEP uptake is escalating among young men who have sex with men (YMSM) and transgender women (TW), but evidence suggests that up to one-third of YMSM/TW PrEP users discontinued use in a 6-month period, which eliminates its protective benefit. The current analyses examined longitudinal predictors of PrEP discontinuation.

Methods: Data came from RADAR (N=1100+), an ongoing longitudinal cohort of YMSM/TW (aged 16-29) in Chicago. Using data from 7 visits at 6-month intervals (collected 2015-2018), mixed effects longitudinal regression models examined change in sexual behaviors and psychosocial factors as predictors of PrEP discontinuation (i.e., use at prior visit, no use at current visit). Predictors included change from the prior to current visit in condomless anal sex (CAS), number of sex partners, relationship status, substance use, and depression, as well as current insurance status. Models adjusted for demographic characteristics.

Results: PrEP use among HIV-negative YMSM/TW increased from 8.4% (visit 1) to 28% (visit 7). PrEP discontinuation similarly increased from 12.6% (visit 2) to 20% (visit 7). In a multivariate model, YMSM/TW who had increases in CAS across visits were less likely to discontinue PrEP (Odds Ratio [OR]=0.93, 95% Confidence Interval [CI]: 0.89-0.98), while those who entered a serious relationship were more likely to discontinue (OR=1.85, 95% CI: 1.08-3.19). Number of sex partners, substance use and depression were not associated with discontinuation. We observed no race or gender identity differences in PrEP discontinuation. In a separate model, we examined the association between current insurance status and discontinuation, adjusting for demographics. YMSM/TW who had insurance were significantly less likely to discontinue PrEP (OR=0.54, 95% CI: 0.32-0.92).

Conclusion: That YMSM/TW who increase CAS are less likely to discontinue PrEP is encouraging. Among those entering relationships, it remains unclear how and when YMSM/TW discontinue PrEP and whether or not transmission risk remains after discontinuation. Insurance status is a key structural determinant of the ability to sustain PrEP use and reduce transmission risk. These findings point to encouraging trends and opportunities for structural and behavioral intervention.

990 STOPPING HIV PREEXPOSURE PROPHYLAXIS: REASONS AND IMPLICATIONS

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Background: Use of HIV pre-exposure prophylaxis (PrEP) is increasing, but some users discontinue PrEP. We investigated former PrEP users in Germany and compared them to current PrEP users in order to elucidate reasons for stopping and implications for HIV prevention.

Methods: From 24th July to 3rd September 2018 we recruited current and former PrEP users on geolocation dating apps for MSM, community-based HIV testing sites, and a community website in Germany for an anonymous online survey. Risk factors were assessed with logistic regression models adjusting for age, country of origin, and annual gross income.

Results: We recruited 212 former PrEP users and 2,005 participants currently taking PrEP. 78.7% completed the survey. Most participants identified as male (99.1%, trans*: 0.4%, intersexual: 0.3%, non-binary: 0.2%) and indicated Germany as their country of origin (74.8%) with no significant differences between current and former PrEP users. The median age of former PrEP users (33 years, IQR: 27-41) was lower than of current PrEP users (38 years, IQR: 31-45). The reasons for discontinuing PrEP are shown in Table 1 (multiple responses allowed). Former PrEP users were much more likely to have used PrEP intermittently or on demand (OR = 2.8, 95% CI 2.0, 4.0). In addition, former PrEP users were more likely to be unhappy with their current sex life (OR = 4.1, 95% CI 2.6, 6.6). Most former PrEP users indicated that they always (35.8%) or often (27.9%) use condoms since stopping PrEP, whereas 35.8% indicated using condoms during half or less of their sexual acts. Compared to current PrEP users, former users were more likely to always or often use condoms (OR = 7.9, 95% CI 5.4, 11.6).

Conclusion: The analysis identifies important reasons for discontinuing PrEP, some of which could be overcome if PrEP were covered by health insurances. More than a third of former PrEP users reports inconsistent condom use indicating the need for developing HIV prevention strategies tailored to this population.

Table 1: Reasons for discontinuing PrEP (multiple responses allowed)

Reasons	Participants [%]
Issues related to taking the medication (taking a daily pill / chemical substance, side effects, fear of side effects)	45.3 %
Partner situation changed (fewer partners, no sex, trusted their partner/s)	32.1 %
Difficulties with obtaining PrEP (unaffordable or the former source unavailable)	28.3 %
Other prevention strategies are sufficient	25.0 %
Contracted too many sexually transmitted infections	8.5 %
Experiencing stigma	7.6 %
Positive HIV test	3.3 %

991 FACTORS ASSOCIATED WITH REFUSING OR STOPPING PrEP AMONG AT-RISK MSM IN KENYA

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Background: There are limited data on reasons for refusing or stopping programmatic pre-exposure prophylaxis (PrEP) among men who have sex with men (MSM) in Kenya, a country rolling out PrEP since May 2017. We assessed factors associated with refusing or stopping PrEP in this population, using a mixed methods approach.

Methods: Since June 2017, at-risk MSM followed at monthly visits in an HIV-1 vaccine feasibility cohort study in the coastal Kenya were offered PrEP with adherence and risk reduction counselling, monthly rapid HIV-1 antibody testing and X-pert RNA Qual testing if acute HIV-1 risk criteria were met. We assessed factors associated with refusing or stopping PrEP at the last available visit for those who refused PrEP and the date of PrEP discontinuation for those who stopped using generalized linear modeling with log-link Poisson regression and robust error variance. Variables associated with refusing or stopping PrEP at P<0.2 in the bivariable analysis were included in the multivariable model. We also conducted 2 focus groups discussion (FGDs) and 12 in-depth interviews among purposively sampled MSM who were eligible but did not start (N=6) or discontinued PrEP (N=6). Interviews and FGDs were recorded, transcribed and analyzed using a grounded theory framework.

Results: Of 178 MSM offered PrEP, 36 (20.2%) did not start and 142 (79.8%) started, of whom 31 (17.4%) stopped after a median of 4.3 (interquartile range: 1.7–8.9) months. In multivariable analysis, paying for sex (adjusted prevalence ratio [aPR] 1.6, 95% CI 1.0–2.5) was an independent predictor of refusing or stopping PrEP, after adjustment for religion and self-reported unprotected sex, anal sex position, and receipt of payment for sex. In qualitative analysis, participants who had refused or had stopped PrEP showed limited knowledge and misconceptions about PrEP, and often had low perception of HIV risk. Pill burden, side effects, stigma, and storage challenges were cited as reasons for stopping. There was a strong preference for long-acting oral or injectable PrEP as alternatives to daily oral PrEP.

Conclusion: Over one third of at-risk MSM followed up in the cohort study refused or stopped taking PrEP. MSM reporting paying for sex may have low perceived HIV-1 risk. Ongoing community engagement and education are needed to correct misconceptions, raise awareness, and decrease stigma in order to improve uptake and continuous use of PrEP among Kenyan MSM.

Table 1. Factors Associated with Refusing or Stopping PrEP Among 178 HIV-1 Negative MSM in Kilifi, Kenya, June 2017 - September 2018.

Characteristics	Refusing/Stopping PrEP n (%)		Bivariable Analysis PR (95% CI)	*P* value	Multivariable Analysis aPR (95% CI)	*P* value
Religion						
Christian	35	(38.0)	Reference		Reference	
Muslim	22	(50.0)	1.3 (0.9-2.0)	0.175	1.3 (0.9-2.0)	0.199
Other/none	10	(23.8)	0.6 (0.3-1.1)	0.127	0.6 (0.3-1.2)	0.143
Sexual exposure and protection with condoms in past week						
No activity	25	(43.9)	0.7 (0.5-1.1)	0.132	0.8 (0.5-1.2)	0.270
All protected	24	(31.2)	0.9 (0.6-1.5)	0.768	0.7 (0.4-1.3)	0.280
Any unprotected	18	(40.9)	Reference		Reference	
Anal sex position						
Insertive	14	(32.6)	Reference		Reference	
Receptive	26	(30.2)	0.9 (0.5-1.6)	0.787	0.9 (0.5-1.5)	0.787
Versatile	19	(51.4)	1.6 (0.9-2.7)	0.094	1.5 (0.9-2.7)	0.143
None	8	(66.7)	2.0 (1.1-3.7)	0.017	1.6 (0.8-3.0)	0.192
Received payment for sex with cash, living expenses, or goods in past 3 months						
No	37	(43.5)	Reference		Reference	
Yes	30	(32.3)	0.7 (0.5-1.1)	0.125	1.0 (0.7-1.6)	0.920
Paid for sex with cash, living expenses, or goods in past 3 months						
No	53	(34.2)	Reference		Reference	
Yes	14	(60.9)	1.8 (1.2-2.6)	0.004	1.6 (1.0-2.5)	0.061

PR, prevalence ratio; aPR, adjusted prevalence ratio

992 HIGH PrEP USE IN AFRICAN MEN AND WOMEN CONTINUING PrEP IN PUBLIC-HEALTH HIV CLINICS

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Background: Adherence is central to the protective effectiveness of pre-exposure prophylaxis (PrEP) against HIV infection. Limited data are available on adherence in persons initiating and continuing PrEP in real world PrEP programs in Africa.

Methods: The Partners Scale-Up Project is an ongoing cluster-randomized programmatic evaluation of national scale-up of PrEP delivery, primarily for HIV serodiscordant couples, integrated in 24 public health HIV care clinics in Kenya. Dried blood spots (DBS) were collected from individuals taking PrEP from randomly-selected clinics on a random subset of days each month. Intracellular tenofovir-diphosphate (TFV-DP) concentrations were quantified in DBS using validated liquid chromatography-tandem mass spectrometry.

Results: Between February 2017 and October 2018, 3761 initiated PrEP, median age was 31 years [IQR: 26-39], 3208 (85%) reported an HIV-positive partner, and 3487 (93%) reported recent condom use. A total of 2009 (53%) were women of whom 230 (11%) used PrEP while pregnant (130 were pregnant at PrEP initiation and 100 became pregnant while on PrEP). Among those who became pregnant while on PrEP, 47 (47%) reported intending to conceive, while 18 (18%) had not planned to get pregnant at baseline. Of all initiating PrEP, 2444 (65%) continued PrEP (≥1 refill in 3 months). Continuation was independently more likely for those >30 years (68% vs 61% for ≤30 years, p<0.01), those with an HIV+ partner (68% vs 45%, p<0.01), and for women (66% vs 63% for men; p=0.04) but did not differ by pregnancy status (68% pregnant vs. 66% not pregnant; p=0.63). A total of 71 DBS were testedat a median duration of PrEP use of 1 month (range 1 to 4). Evidence of PrEP use was high with TFV-DP detectable in 68 (96%) of DBS samples; the median TFV-DP concentration was 515 fmol/punch (IQR: 348 to 693) comparable to the estimate for ≥4 doses per week from a directly observed dosing study in the US. DBS TFV-DP concentrations were similar (p>0.05) by sex, age, and desire to conceive.

Conclusion: In a Kenyan PrEP program setting, PrEP uptake was high and was taken by men and women, including pregnant women. TFV-DP was detected in 96% of blood samples of persons continuing PrEP and levels suggested relatively consistent adherence; thresholds specific to African populations are needed. These data are encouraging that programmatic level adherence support may be sufficient to achieve PrEP uptake in motivated clients.

993 PERSISTENCE WITH PrEP USE IN AFRICAN ADOLESCENTS AND YOUNG WOMEN INITIATING PrEP

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Background: Young women in HIV high burden settings are a priority population for PrEP. Limited data are available on PrEP continuation in this population in real world settings.

Methods: Data are from the PrEP Implementation for Young Women and Adolescents (PrIYA) project, an implementation program of PrEP integrated in maternal child health (MCH) and family planning (FP) clinics. Between November 2017 and June 2018, women 15-45 years seeking antenatal (ANC), postnatal (PNC) and FP services in 16 health facilities in Kisumu, Kenya were universally screened and offered PrEP according to national guidelines. We assessed for PrEP use and continuation and used robust Poisson regression methods to identify correlates of continuation at 3 and 6 months adjusted for age, marital status, partner HIV status, PrEP delivery point, and facility clustering. Medication possession ratio, assumed to represent PrEP use, was computed as the ratio of the number of tablets dispensed divided by the number of days between initiation and return date, with ratios >1 imputed to 1.

Results: Of 2304 women initiated on PrEP [912 in ANC, 1114 in PNC, and 278 in FP], median age was 24 years (IQR 21-29), 58% had partner of unknown HIV status, and 96% reported recent history of condomless sex. Continuation at 1, 3, and 6 months was 38%, 21%, and 10% overall: 34%, 18%, and 8% for ANC; 39%, 24%, and 10% for PNC; and 41%, 25%, and 15% for FP. Of those continuing PrEP at Month 1 (n=866), median medication possession ratio was 1 (IQR: 0.86-1). Overall, continuation at 3 months was independently higher for women with HIV positive partners (positive 52%, unknown 19%, negative 18%; p<0.01) and in older women (<20 years 23%, 20-24 years 18%, 25-34 years 22%, and ≥35 years 37%; p=0.02). Only partner HIV status was independently associated with 6 month continuation (positive 30%, unknown 8%, negative 8%; p<0.01). Frequently reported reasons for discontinuing PrEP use were low perceived risk for HIV (23%), side effects (19%), pill burden (17%), and partner known to be HIV negative (17%).

Conclusion: Integration of universal screening and counseling for PrEP in routine MCH and FP clinics in Kenya was feasible. There was high drop-off in PrEP continuation, but subset of women persisted with PrEP use through at least 6 months. Greater efforts to support PrEP normalization and persistence for African women are needed.

994 HIGH ADHERENCE AMONG YOUNG WOMEN IN CAPE TOWN IN THE FIRST 3 MONTHS AFTER PrEP START

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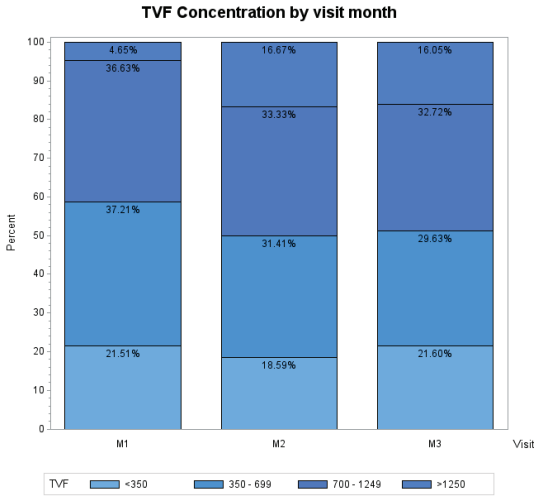
Background: In placebo-controlled PrEP trials, African adolescent girls and young women (AGYW) had low adherence; only 25-30% had any detectable tenofovir in blood samples. PrEP use may be higher when efficacy is known, as demonstrated among men who have sex with men (MSM) in open label studies. The 3P demonstration project was designed to evaluate PrEP demand creation, uptake, and adherence among AGYW in South Africa.

Methods: We enrolled 200 sexually active, HIV negative, PrEP-naïve AGYW ages 16-25 in Cape Town, South Africa from March 2017-2018, with visits at 0,1, 2, and 3 months. PrEP adherence was assessed by intracellular tenofovir diphosphate (TFV-DP) concentrations in dried blood spots, a measure of cumulative use in the prior month. All women received adherence counseling, including feedback about their drug levels at months 2 and 3. TFV-DP ≥700 fmol/punch was chosen as the threshold for high adherence, based on directly observed dosing (correlates with ≥4 doses/week and associated with high efficacy in MSM). Half of women were randomized to receive a 200 Rand ($13) incentive at 2 and 3 months if their TFV-DP was ≥700 at the prior visit.

Results: Women enrolled in 3P were young (median age 19) and at high risk for HIV; 30% had an STI (chlamydia, gonorrhea or trichomonas), 19% reported IPV, 13% weekly alcohol use and 71% who had a primary partner reported suspecting he had other partners . Retention was 89% at month 3. All but one sample had detectable TFV-DP, and median TFV-DP at months 1, 2, and 3 were 622, 707, and 694 fmol/punch, respectively. Half of AGYW had high (TFV-DP ≥700 fmol/punch) and ~80 % had medium (TFV-DP 350-699 fmol/punch) or greater adherence at months 2 and 3 (Figure). In univariate analyses, significant baseline correlates of TFV-DP ≥700 fmol/punch at month 3 included having an HIV positive partner or a partner of unknown serostatus (OR 2.0, 95% CI 1.1, 3.8), reporting no sex in the month before enrollment (OR 2.3, 95% CI 1.1, 4.9) and disclosure about their PrEP use (OR 3.5, 95% CI 1.0, 15.9).
Conclusion: PrEP adherence was higher in this demonstration project than previous placebo-controlled trials among African AGYW. Intracellular TFV-DP levels indicate that by 2 months half of AGYW were taking the majority of doses in the prior month. Having a partner of unknown or positive serostatus and disclosure about their PrEP use were associated with higher adherence; disclosure about PrEP should be supported among AGYW.



995 ADHERENCE 3 MONTHS AFTER PrEP INITIATION AMONG YOUNG AFRICAN WOMEN IN HPTN 082

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Background: Pre-exposure prophylaxis (PrEP) is highly effective when used consistently. Young women in sub-Saharan Africa are at high risk of HIV and could benefit from PrEP. We evaluated PrEP adherence in young women in the context of known efficacy and open label use.
Methods: HPTN 082 was conducted in Cape Town, Johannesburg (South Africa) and Harare (Zimbabwe) to evaluate the effect of drug level feedback on adherence. Sexually active HIV-negative women ages 16-25 were enrolled using the VOICE risk score and a PrEP readiness scale. Women starting PrEP were randomized to standard adherence support (counseling, 2-way SMS, and adherence clubs) or standard support plus drug level feedback at 2 and 3 months. Follow-up was 1, 2, 3, 6, 9 and 12 months. Adherence at 3 months was assessed by tenofovir-diphosphate (TFV-DP) in dried blood spots. High adherence is defined as TFV-DP >700 fmol/punch (>4 doses/week), which was associated with high protection in men, and medium adherence as 350-700 fmol/punch (2-3 doses/week). Baseline predictors of 3 month TFV-DP levels were assessed.
Results: Of 427 who started PrEP, median age was 21 and median VOICE risk score was 7 (≥5 associated with >6% HIV incidence in prior cohorts). Most (84%) reported a primary sex partner (74% HIV-, 21% unknown status, and 1% HIV+). 33% thought their partner had other partners and 47% did not know. 22% reported anal sex in the past month, 23% transactional sex in the past 3 months, 50% intimate partner violence in the past year, and 49% depression symptoms. Among the 381 with a 3 month visit, 69% had attended ³1 adherence club (median 2). Median TFV-DP at month 3 was 485 fmol/punch (IQR 166,775): 25% ³700, 23% 350-699, 36% detectable<349 and 16% undetectable. Significant predictors (p-value<0.05) of TFV-DP levels at 3 months in multivariate analysis were uncertainty if their partner had other partners (145 fmol/punch lower vs. those who reported their partner did not have other partners) and a higher score on the HIV prevention readiness scale (5 fmol/punch higher for each unit on 100 point scale).
Conclusion: Three months after starting PrEP, TFV-DP levels indicated that most young African women were taking PrEP in the prior month and 25% had high adherence, substantially higher than in the placebo-controlled trials which showed 25-30% had detectable tenofovir in plasma. Additional adherence support may be useful for young African women who are uncertain about their partner's behavior and are less sure about using PrEP.

996 SHORT-TERM RETENTION ON PREEXPOSURE PROPHYLAXIS IN DEMOCRATIC REPUBLIC OF THE CONGO

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Background: In the Democratic Republic of the Congo (DRC), HIV is concentrated in key populations (KP), primarily among female sex workers (SW) and men who have sex with men (MSM), with prevalence estimates of 7% and 18% respectively, compared to 1.2% in the general population. Pre-exposure prophylaxis (PrEP) to prevent HIV acquisition can impact the epidemic if made accessible to KP at trusted delivery points. In the absence of national PrEP guidelines, DRC's National AIDS Control Program, US Centers for Disease Control and Prevention, and ICAP at Columbia University collaborated to implement PrEP services for a limited number of clients at 7 HIV facilities providing regular services to KP in DRC. We examined PrEP initiation and retention at these facilities.
Methods: ICAP developed a PrEP training package to capacitate staff to deliver and monitor PrEP services at 4 facilities in Kinshasa and 3 in Lubumbashi. Active follow-up of PrEP patients included text message, phone, and face-to-face appointment reminders by both facility staff and peer outreach workers. PrEP initiation and follow-up visits were recorded by facility staff using ICAP-developed tools; data were summarized into aggregate reports by project staff. Retention on PrEP at 1 and 3 months was defined as a documented clinic visit within 14 days before or after the scheduled 1 month appointment date, and within 30 days before or after the 3 month appointment date. This analysis included data for patients initiating PrEP between February 20th to May 20th, 2018.
Results: During the enrollment period, 356 patients initiated PrEP; 57% (202) in Kinshasa and 43% (154) in Lubumbashi. PrEP patients were 80% (285) SW, 19% (68) MSM, and 1% (3) transgender (TG). Overall retention at 1 month following initiation was 78% (277), including 74% (212) among SW, 94% (64) among MSM, and 33% (1) among TG. Overall 3-month retention was 93% (331); including 92% (262) among SW, 99% (67) among MSM, and 67% (2) among TG.
Conclusion: Comprehensive training and clinic monitoring resulted in the successful introduction of PrEP in DRC. Although 22% of patients did not attend their 1 month appointment, increased outreach efforts led to improved 3 month retention for all clients. Focused efforts are needed to ensure high retention in PrEP services among these populations. Project findings will support the scale-up of PrEP in other impacted populations and facilities in DRC.

997 PREEXPOSURE PROPHYLAXIS: ACCEPTABILITY AND RETENTION IN SOUTH WESTERN UGANDA

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Background: Pre-Exposure prophylaxis (PrEP) has been recommended for key and priority populations most-at-risk of HIV. In 2017, one of the first larger attempts to scale up PrEP using tenofovir and lamivudine at population-level in Uganda, was initiated by the Rakai Health Sciences Program in HIV hyper-endemic trading centers and fishing communities on Lake Victoria with CDC-Uganda under PEPFAR support. We report on acceptability and retention of clients on the program at 9 months of follow-up.
Methods: Program data from implementing clinics were used for the evaluation. Acceptability of PrEP was defined as having been initiated on PrEP after satisfying the eligibility criteria of being at high HIV risk. Retention on PrEP was measured at months 1, 3, 6, and 9 following PrEP enrolment. Multivariable modified Poisson regression was used to estimate prevalence ratios and 95% confidence intervals for the association between covariates, acceptability and retention on PrEP.
Results: A total of 2637 individual were screened for PrEP of whom 2439 (93%) were eligible; 2285 (94%) of the eligible clients enrolled on PrEP. Enrolled clients included sex workers (54.0%), fisher folk (20.3%), truck drivers (11.2 %), Adolescent girls and young women (4.9%), HIV-negative individuals in discordant relationships (7.9 %) and others (1.7%). Acceptance of PrEP did not differ significantly by age, gender and risk categories, except for lower acceptance among fisher folk (PR=0.87, 95% CI=0.84,0.91) compared to individuals in discordant couples as well as a slightly higher uptake among those divorced/separated compared to married individuals (PR=1.03, 95% CI=1.0-1.06). Retention, as measured by returning to the clinic for refills, was 47.6% at month 1, 31.3% at month 3, 16.3 % at month 6 and 4.8 % at month 9. Retention was lowest among adolescent girls and young women who did not identify as sex workers (PR=0.38, 95% CI=0.23-0.64) and among fisher folk (PR=0.32, 95% CI=0.24-0.42) compared to individuals in discordant relationships. Retention was higher among individuals aged 25-34 (PR=1.21, 95% CI=1.04-1.42) and 35+ (PR=1.38, 95% CI=1.15-1.65) compared to ages 15-24. Retention did not differ by sex and marital status.
Conclusion: Acceptability of PrEP was high in this population; however, clients, especially younger women and fisher folk who are highly mobile, rapidly dropped out of the program. Research on reasons for discontinuation and interventions to optimize retention on PrEP are critical to program success.

998 IMPACT OF A CONTRACEPTIVE RING ON VAGINAL BACTERIA ASSOCIATED WITH HIV ACQUISITION

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Background: Specific vaginal bacteria have been associated with increased risk for HIV acquisition in sub-Saharan African women, including several linked to bacterial vaginosis (BV). Limited data support a favorable effect of a contraceptive vaginal ring (CVR) containing estrogen and progesterone (NuvaRing) on vaginal bacteria. Pregnancy is an independent risk for HIV acquisition and transmission; thus, contraception may comprise biomedical prevention for women with or at risk for HIV, and hormonal modulation of key vaginal bacteria, which are also impacted by menses, might also be advantageous. We randomized women treated for BV in Thika, Kenya to continuous (menstrual suppression) vs. cyclic (regular menses) use of NuvaRing, and assessed effects on key vaginal bacteria associated with HIV acquisition.
Methods: Women aged 18-40 years were enrolled and treated for BV with oral metronidazole. One month later, they were randomized and seen monthly for 7 months, when vaginal swabs were collected. Concentrations of bacterial taxa previously shown to be associated with increased HIV risk, and one associated with protection (L. crispatus), were measured using quantitative PCR. We used linear mixed models stratified by randomization arm and HIV status at enrollment to compare mean differences in log10 bacterial DNA concentrations at the visit prior to CVR initiation relative to 2-3 months post-initiation as an early marker of CVR impact.
Results: Between April 2016 to November 2017, 151 women (median age 27 y) were enrolled and 122 (81.9%) initiated CVR use, and 98 had qPCR data available (22 of whom were HIV-infected) at a total of 277 visits (98 pre-CVR and 179 post-CVR insertion). Women in the continuous use CVR group had significantly reduced concentrations of all high-risk bacteria measured at 2-3 months post-insertion (Table). Similarly significant results were seen in women with HIV, with the exception of no change in P. bivia.
Conclusion: Continuous CVR use with menstrual suppression over 2-3 months reduced quantities of bacteria previously associated with increased HIV acquisition risk in women. Vaginal rings are a promising strategy that should be evaluated for delivery of multipurpose prevention in Kenyan women.

Quantities of Vaginal Bacteria by CVR Use and HIV Status Pre- and Post (2-3 months) CVR Insertion (log10 copies per swab; p value)

Bacteria	All women N=98		Continuous CVR N=50		Cyclic CVR N=48		HIV-Infected N=22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Gardnerella vaginalis	5.9	5.36 (.047)	6.17	4.98 (<.01)	5.64	5.71 (.8)	6.02	5.37 (.26)
Lactobacillus crispatus	3.9	3.42 (.069)	3.61	3.32 (.42)	4.18	3.53 (.09)	2.59	3.07 (.15)
Gemella asaccharolytica	3.09	2.56 (.014)	3.25	2.26 (<.01)	2.94	2.84 (.76)	2.97	2.32 (.045)
Mycoplasma hominis	3.13	2.59 (<.01)	3.27	2.51 (<.01)	3.00	2.65 (.11)	3.94	3.24 (.04)
Leptotrichia/Sneathia	3.79	3.15 (<.01)	4.08	3.11 (<.01)	3.50	3.18 (.32)	4.54	3.72 (.015)
Prevotella bivia	4.13	3.74 (.096)	4.33	3.49 (<.01)	3.93	3.98 (.82)	4.08	4.03 (.92)
Eggerthella sp. type 1	3.21	2.6 (<.01)	3.52	2.6 (<.01)	2.91	2.61 (.33)	3.38	2.78 (.044)

999 DOES BV MODIFY THE EFFECT OF HORMONAL CONTRACEPTION ON HIV ACQUISITION?

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Background: Multiple studies have established an association between depot-medroxyprogesterone acetate (DMPA) and HIV acquisition in women. A recent study of serodiscordant couples in Zambia was the first to find that DMPA and oral contraceptive pills (OCPs) were associated with increased risk of HIV acquisition when BV was present, but not when BV was absent. The purpose of this study was to test the hypothesis that BV is an effect modifier of the association between hormonal contraception and HIV acquisition in the Mombasa Cohort, a long-term open cohort study of female sex workers in Kenya.
Methods: Visits contributed by HIV-negative women participating in the cohort between February 1993 and April 2017 were included. Women provided behavioral data (including contraceptive use) and underwent a physical examination and lab testing for HIV and sexually transmitted infections (STIs) at monthly visits. Cox proportional hazards models were used to assess the relationship between HIV seroconversion and use of DMPA, OCPs, or contraceptive implants (each evaluated separately), compared to no hormonal contraception. BV, defined as a Nugent score ≥7 was assessed for effect modification of the relationship between contraceptive use and HIV seroconversion.
Results: A total of 1,985 women contributed 7,107 person-years of follow-up, and 307 women seroconverted for antibodies to HIV (4.32/100 person-years). At baseline, 1178 (59.3%) women reported use of condoms only or no contraception, 410 (20.7%) reported using DMPA, 227 (11.4%) reported using oral contraceptives, 69 (3.5%) reported using implants, and 645 (32.5%) had BV. Both DMPA (aHR 1.72, 95% CI 1.34, 2.20; p<0.001) and OCPs (aHR 1.48, 95% CI 1.05, 2.09; p=0.02) were associated with increased risk of HIV acquisition in analyses adjusted for demographic factors, risk behaviors, and the presence of STIs. Contraceptive implants were not associated with HIV acquisition (aHR 0.99, 95% CI 0.40, 2.45; p=0.9). In this cohort, BV was not a significant modifier of the effects of DMPA (p=0.4), OCPs (p=0.9), or implants (p=0.5) on HIV acquisition.

Conclusion: A strong interaction between BV and hormonal contraceptives as mediators of women's HIV risk, if present, would be an important and potentially actionable finding. However, significant interaction was not observed in this cohort. Analyses of hormonal contraceptive and BV data from diverse HIV incidence cohorts will help to clarify this important question.

1000 CHANGES IN VAGINAL MICROBIOTA AMONG HIV-INFECTED AFRICAN WOMEN INITIATING DMPA

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Background: Depot-medroxyprogesterone acetate (DMPA) has been linked to HIV acquisition, and limited evidence also exists linking DMPA with higher risk of HIV transmission. The biological mechanism underlying these associations is not well understood. DMPA use has been documented to reduce bacterial vaginosis (BV), but there are few molecular studies assessing how DMPA alters vaginal microbiota. We hypothesized that a possible mechanism by which DMPA could increase HIV transmission would be to increase vaginal bacteria diversity.

Methods: We conducted a cohort study of postpartum, breastfeeding women in Kenya initiating DMPA or non-hormonal contraception (NHC). Women received their first DMPA injection or condoms at enrollment and were followed longitudinally. Vaginal Gram stains were assessed to calculate Nugent score. Vaginal swabs were analyzed with broad-range 16S rRNA gene PCR and sequencing to assess bacterial diversity using Shannon Diversity Index (SDI). Adjusted linear mixed-effects regression was used to estimate mean changes in Nugent score, SDI, and vaginal pH over time in women using DMPA compared to those using NHC.

Results: We enrolled 66 HIV-infected women, 50 initiating DMPA and 16 choosing NHC. At baseline, a greater proportion of DMPA users were married and had resumed sexual activity. Mean Nugent score, mean SDI, and mean vaginal pH were similar at baseline (Table). Over 3 months, Nugent score did not significantly change in DMPA users (Δ=-0.71; p=0.51), and this change was not significantly different from the change seen in NHC users (diff.=1.43; p=0.46). Mean SDI also did not change over time in DMPA users (Δ=-0.32, p=0.23), and again, this change was not significantly different from the change in NHC users (diff.=0.46, p=0.29). Lastly, vaginal pH decreased significantly over time in DMPA users (Δ=-0.64; p=0.01), however the change was not significantly different from the change in NHC users (diff.=-0.05; p=0.94).

Conclusion: In a cohort of African women, 3 months of DMPA use was not associated with acute, significant changes to vaginal bacterial diversity. Further, DMPA users did not have significantly different Nugent scores or greater vaginal bacterial diversity compared to NHC users. This finding suggests that change in vaginal bacterial diversity is not a main driver of increased risk of HIV transmission among DMPA users. Additional analyses of taxon-specific data will help determine if DMPA causes changes to specific vaginal microbiota which could explain this association.

Table. Baseline characteristics of women initiating contraception by contraceptive type

Characteristic		DMPA (n=50)	NHC (n=16)
Age (years)		26.6 (4.6)	26.7 (4.9)
Marital status	Single	4 (8.0)	2 (12.5)
	Married	45 (90.0)	12 (75.0)
	Separated/Divorced/Widowed	1 (2.0)	2 (12.5)
Plasma HIV RNA level ≥400 copies/ml		22 (44.0)	5 (31.3)
Resumed sexual intercourse since last delivery		23 (46.0)	5 (31.3)
Currently using condoms		1 (4.4)	1 (20.0)
Taken antibiotics in past month		0	3 (18.8)
Nugent score		4.6 (4.0)	4.6 (3.9)
Shannon Diversity Index (SDI)		1.2 (0.9)	1.2 (0.9)
Vaginal pH		5.5 (0.8)	5.4 (0.9)

Data presented at n (%) or mean (SD); SD=standard deviation

1001 MENOPAUSE IMPACTS THE VAGINAL MICROBIOME AND IMMUNE MEDIATORS IN WOMEN WITH HIV

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Background: Reproductive aging may affect the vaginal microbiome, mucosal immune environment and genital tract health in HIV-infected (HIV+) women.

Methods: A cross-sectional study of 102 HIV+ (51 premenopausal, 51 postmenopausal) and 39 HIV-uninfected (HIV-) (20 premenopausal, 19 postmenopausal) women was conducted in Bronx and Brooklyn, NY. Cervicovaginal lavage (CVL) was collected in 10 ml sterile water for quantification of innate antimicrobial activity against E. coli, HSV-2 and HIV and soluble immune mediators by Luminex and ELISA. Vaginal swabs were obtained for microbiome studies utilizing qPCR and 16S rRNA sequencing.

Results: HIV+ postmenopausal participants had significantly lower median E. coli inhibition, lower median gene copies of L. crispatus and L. iners, and lower mean log10 concentrations of human beta defensins (HBD-2, HBD-3) and secretory leukocyte protease inhibitor (SLPI) compared to HIV+ premenopausal women. In relation to premenopausal, HIV+ postmenopausal participants showed significantly higher proportions of Gardnerella and Atopobium vaginae and lower proportions of Lactobacillus sp. In contrast, HSV-2 inhibitory activity was higher in HIV+ postmenopausal women and correlated with the proinflammatory molecules interleukin (IL) 6, IL-8, human neutrophil peptide (HNP) 1-3, lactoferrin and fibronectin. The HIV inhibitory activity was variable, but higher in participants with suppressed plasma viral load, and inversely correlated with G. vaginalis and BVAB2. A significant proportion of HIV+ participants on antiretroviral therapy exhibited HIV enhancing activity. Similar trends were observed in HIV- postmenopausal compared to premenopausal participants.

Conclusion: HIV+ postmenopausal compared to premenopausal women have less CVL E. coli inhibitory activity, reflecting a lower proportion of lactobacilli species and a greater proportion of Gardnerella and A. vaginae, and more HSV-2 inhibitory activity, reflecting increased mucosal inflammation. The effect of menopause on mucosal immunity was greater in HIV+ than in HIV- participants, suggesting a synergistic impact. It is possible that promotion of a lactobacillus dominant vaginal microbiome and reduced mucosal inflammation in HIV+ menopausal women may improve vaginal health and reduce risk for shedding of HIV and potential for HIV transmission.

1002 PREVALENCE OF CHLAMYDIA AND GONORRHEA IN HIV-POSITIVE ADOLESCENTS IN ESWATINI

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Background: Sexually transmitted infections (STIs) are a key global health problem, contributing to infertility, cancer and HIV transmission. The WHO estimates 131 million cases of chlamydia (CT) and 78 million of gonorrhea (NG) among 15-49 year olds worldwide. There is no current prevalence data on STIs in adolescents living with or without HIV in Eswatini.

Methods: A cross-sectional study was done at Baylor Clinic in Mbabane, Eswatini. HIV positive participants, 15-24 years of age, were recruited serially. Participants completed a sexual health history and provided a urine sample. A subset of sexually active participants provided a pharyngeal swab and/or vaginal swab. Urinalysis (UA) was done on all urine samples. 299 samples were tested with the Xpert CT/NG test as per manufacturer guidelines. Statistical analysis included odds ratios and diagnostic performance tests.

Results: 300 participants were enrolled, 141 males and 159 females. The prevalence of CT and/or NG was highest in 20-24 year old females at 15.7% (Table 1). Of ever sexually active participants (ESAP), 12.4% (20/161) were positive for CT and/or NG vs. 0.7% (1/138) reporting no prior sexual activity. Urine sample results were 100% (38/38) concordant with vaginal swab results. STI type was 57.1% (12/21) NG, 28.6% (6/21) CT and 14.3% (3/21) CT and NG. Leukocyte esterase (LE) testing from UA in ESAP had a sensitivity of 85.0% (Male [M]: 100.0%, Female [F]: 80.0%), and specificity of 64.3% (M: 83.6%, F: 51.8%). Syndromic screening alone in ESAP had a sensitivity of 25.0% (M: 80.0%, F: 6.7%) and specificity of 88.7% (M: 88.8%. F: 84.9%). Risk factors associated with STIs in ESAP were sometimes to never using condoms (OR=3.1, 95%CI=1.1-9.2), sexually active in the past 6 months (7.2, 2.4-25.7), and most recent sexual partner 25 years or older (3.2, 1.1-9.5). Among ever sexually active women, the

number needed to test was 6.7 participants to diagnose one STI. In men, the addition of LE testing reduced this to 2.8 participants.

Conclusion: In our population of adolescents living with HIV, STIs were heterogeneously distributed, and highest in 20-24 year old females demonstrating significant gender based disparity. Syndromic screening alone demonstrated poor predictive utility for diagnosing CT and/or NG particularly in women; however, LE performed better, especially in men. Risk factor assessment and screening tests can guide targeted testing to reduce the number needed to screen to identify CT and NG among 15 to 24 year olds living with HIV.

Subset, (age)	Total	STI Positive	STI Rate	Age, Rate	Sex, Rate
Female, 15-19	89	4	4.5%	15-19:	All Females:
Male, 15-19	84	1	1.2%	2.9%	9.4%
Female, 20-24	70	11	15.7%	20-24:	All Males:
Male, 20-24	57	5	8.8%	12.6%	4.3%

Table 1: STI numbers and rates broken down into subsets: age (15-19 and 20-24) and sex (female and male).

1003 PREVALENCE AND DETERMINANTS OF STI IN HIV+ AND HIV- PREGNANT SOUTH AFRICAN WOMEN

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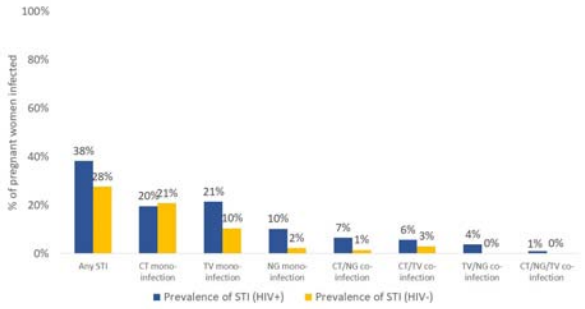
Background: Sexually transmitted infections (STI) increase HIV acquisition and transmission risk during pregnancy. Syndromic management is standard in many settings, but there are few data on the occurrence of STI in HIV-infected and uninfected pregnant women.

Methods: We conducted a cross-sectional study of pregnant women attending a public sector antenatal clinic (ANC) in Cape Town, South Africa. Separate from routine care, after first antenatal care (ANC) visit women ≥18 years were interviewed and self-collected vulvovaginal swabs that we tested for Chlamydia trachomatis (CT), Neisseria gonorrhoea (NG) and Trichomonas vaginalis (TV) using Xpert® assays (Cepheid, Sunnyvale, USA). We used multivariate logistic regression to identify factors associated with having a STI by HIV serostatus.

Results: In 241 women (median age 29 years [IQR=24-34], median gestation 19 weeks [IQR=14-24]) 44% were HIV-infected of whom 33% started ART at their first ANC visit. 47% of women were married/cohabiting. Almost all women reported vaginal sex during pregnancy (93%), 1% reported >1 partner in the past 12 months and 3% reported anal sex during pregnancy. Prevalence of any STI was 32%; 38% in HIV-infected women vs 28% in HIV-uninfected women (p=0.078); the prevalence of individual and co-infections was consistent by HIV status (Figure). STI-related symptoms in women diagnosed were reported infrequently (4% vaginal bleeding; 13% abnormal discharge; 6% dyspareunia). Of women with STI detected, 1% were diagnosed syndromically during routine ANC; this proportion did not vary by HIV status. In a multivariable model controlling for gestational age and relationship status, HIV+ status (adjusted odds ratio [aOR]=1.86; 95% CI=1.01-3.43), younger age (aOR=0.95/year; 95% CI=0.90-0.99) and suspecting partner of having other partners (aOR=1.68; 95%CI=1.00-3.10) were independently associated with STI detection. STI symptom(s) in pregnancy were not predictive of STI diagnosis (age-adjusted OR=0.58; 95% CI=0.28-1.21; p=0.15) and this did not vary by HIV status. In HIV-infected women, younger age was associated with increased odds of STI diagnosis (aOR=0.89/year; 95% CI=0.82-0.96).

Conclusion: We document a very high prevalence of treatable STIs in pregnancy in both HIV-infected and -uninfected women in this setting. Symptoms were not predictive of infection; novel approaches to improve STI diagnosis and management in pregnancy are urgently required.

Fig. 1: Prevalence of STI by type at first ANC in pregnant women in Cape Town, South Africa (n=241)



1004 INCIDENCE OF HSV-2 AND HIV IN A COHORT OF KENYAN ADOLESCENT GIRLS

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Background: Herpes simplex virus-2 (HSV-2) infection is a powerful cofactor for HIV acquisition in sub-Saharan Africa. Young women acquire HSV-2 and HIV earlier than men, but individual factors influencing HSV-2 incidence are not known. HSV-2 acquisition may be a modifiable risk factor for reducing HIV incidence.

Methods: Adolescent girls aged 16-21 were recruited at a suburban clinic in Thika, Kenya. Eligible participants were both HIV and HSV-2 seronegative and reported either sexual naiveté or having had one lifetime sexual partner. Girls under age 18 needed parental consent to participate. Quarterly testing was done for incident HIV-1 by ELISA and HSV-2 by the Focus ELISA test. HSV-2 PCR testing of genital swabs was also done quarterly to detect infection as early as possible. Incident HSV-2 infections were confirmed by Western blot. Girls were provided comprehensive reproductive health care including STI screening, contraception, condoms, and more recently, access to PrEP. We assessed potential associations of baseline characteristics with HSV-2 seroconversion using Fisher's exact test for dichotomous measures and Wilcoxon rank-sum test for continuous measures.

Results: We enrolled 400 participants with a median age of 18.6 years (IQR 16-21). The majority (322 girls, 80.5%) reported no history of sexual intercourse, while 78 (19.5%) reported sex with 1 lifetime partner. Over 4 years, with a median follow-up of 33 months per person, we detected 19 cases of HSV-2 and 2 cases of HIV. Incidence of HSV-2 was 21 cases per 1000 person/years (py); 45 per 1000 py among those with any STI at baseline and 16 per 1000 py among those without. For HIV, incidence was 2 cases per 1000 py. HSV-2 seroconversion was significantly associated with higher Nugent score at baseline (p=0.028), and there was a trend toward association for girls with baseline detection of STIs (p=0.058) and baseline diagnosis of bacterial vaginosis (p=0.072). Similar to other adolescent cohorts, some participants with STIs denied having sexual intercourse.

Conclusion: We present the first estimates of HSV-2 incidence in a cohort of sexually naïve young women followed over four years in Kenya. Higher Nugent scores and presence of other STIs were significantly correlated with incident HSV-2. Interventions to prevent STIs and promote healthy vaginal microbiota could influence HSV-2 acquisition in this age group.

Table 1. Correlates of HSV-2 incident infection in a cohort of Kenyan adolescent girls

Characteristic	Women without *incident HSV-2 (N=380)* Median (range) or N (%)	Women with *incident HSV-2 infection* (N=19) Median (range) or N (%)	p-value*
Age (years)	18 (16,21)	18 (16,20)	0.76
Education (years)	12 (0,14)	12 (8,13)	0.83
Employed	37% (142/380)	42% (8/19)	0.81
Age at first intercourse (years)	19 (14,24)	18 (16,21)	0.31
Household income (KSh)	0 (0, 13000)	0 (0, 6000)	0.66
Rural residence	62% (235/380)	53% (10/19)	0.47
Reported no intercourse at baseline	81% (308/380)	74% (14/19)	0.38
Reported no intercourse over follow-up	35% (133/380)	16% (3/19)	0.13
Nugent score at baseline	0 (0,10)	0 (0,8)	0.028
Presence of GC or CT at baseline	12% (41/354)	28% (5/18)	0.058
Gonorrhea at baseline	1% (4/354)	6% (1/18)	0.22
Chlamydia at baseline	10% (37/354)	22% (4/18)	0.12
Pregnancy prior to HSV-2	22% (82/380)	32% (6/19)	0.39
BV (Nugent ≥ 7) at baseline	5% (18/356)	17% (3/18)	0.072

1005 PARTNER NOTIFICATION: INCREASING EFFECTIVENESS WITH MODERN COMMUNICATION TECHNOLOGY

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Background: Prevalence of sexually transmitted infections (STIs) in STI contacts are high. Partner notification (PN) aims to inform and treat partners and reduce onward transmission. UK standards recommend 0.6 partners tested per index case (0.4 in large conurbations), however PN is time and labor intensive. Online platforms may reduce costs, expand coverage and increase efficiency although data remains limited. SXT is an electronic PN tool using interactive digital contact slips; this study aimed to assess effectiveness with number of contacts tested per index case compared to national data and examine factors associated with successful PN.
Methods: A retrospective analysis of PN initiated via SXT in the UK between 01/12/17-31/07/18 was performed using anonymized data on index case demographics, STIs and PN. Number of contacts screened per index case were compared to national data for chlamydia (CT), gonorrhea (GC) and syphilis (STS). Factors associated with testing at least one partner were examined using multivariable logistic regression. Analyses were performed using STATA 12.
Results: 6414 index cases initiated PN via SXT across 13 sexual health providers, median age 25 (IQR 21-32) years, 66% white ethnicity, 58% male and 26% men who have sex with men (MSM), with 6779 STIs; the majority CT (65%), GC (21%) and STS (5%). The number of verified tested partners per diagnosis via SXT vs. national data were higher for CT, GC and STS (Table 1). Based on known STI prevalence in partners, a predicted 133 GC, 77 CT and 12 STS additional diagnoses were made using SXT during the 7 month period. 23-34% of PN was self-verified online by partners. Compared to testing ≥1 partner, black vs. white ethnicity (adjusted OR [95% CI] black African 0.75 [0.58-0.96], black Caribbean 0.70 [0.56-0.89] and black other 0.77 [0.61-0.97]), MSM vs. heterosexual (0.74 [0.61-0.90]), living outside large conurbations (0.47 [0.37-0.59]) or testing online (0.30 [0.26-0.35]) vs. urban clinics and a diagnosis of trichomonas vaginalis (TV) vs. CT (0.57 [0.40-0.81]) were associated with fewer partners tested.
Conclusion: An electronic PN tool demonstrated increased PN compared to national data, exceeded national targets for CT, GC and STS, reduced workload, and was successful in large conurbations. Being MSM, of black ethnicity and a having a diagnosis of TV was associated with fewer partners tested, highlighting areas to target for future improvements.'

	CHLAMYDIA (CT)		GONORRHEA (GC)		SYPHILIS (STS)	
	PHE data* CT	SXT data CT	PHE data* GC	SXT data GC	PHE data* STS	SXT data STS
Diagnoses (a)	121536	4382	42442	1425	7014	355
PN contacts (b)	62766	2481	17276	1032	4127	318
PN ratio (b:a)	0.52	0.57	0.41	0.72	0.59	0.90
% partners positive*	35%		30%		11%	

PHE: Public Health England, UK, PN: partner notification
*Data is from 2017 national reported data based on coding of individuals who present as partners of infection

1006 INCIDENCE AND CORRELATES OF UNINTENDED PREGNANCY IN HIV-POSITIVE KENYAN SEX WORKERS

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Background: HIV-positive female sex workers (FSWs) often have high rates of unmet contraceptive need, but data on the incidence of planned, mistimed, and unwanted pregnancies are sparse. We examined incidence and correlates of pregnancy in HIV-positive Kenyan FSWs.
Methods: Non-pregnant FSWs enrolled in a cohort study in Mombasa, Kenya were eligible. Participants returned for monthly visits to ascertain sexual risk behavior, and were pregnancy tested quarterly. Pregnancies were considered planned, mistimed, or unwanted according to quarterly fertility desire and pregnancy intention questions. Cox proportional hazards models were used to estimate hazard ratios (HR) for the association between demographic, sexual, clinical, and behavioral characteristics and pregnancy. Correlates associated with pregnancy in univariate analysis at p<0.10 were included in the adjusted model.
Results: A total of 316 FSWs contributed 785.7 person-years of follow-up. Most women had a current/regular partner in the last 3 months (50.8%, 160/315), were not using modern non-barrier contraception (69.3%, 219/316), did not desire a child (69.9%, 221/316), and had CD4 counts >350 cells/mm3 (69.0%, 218/316). There were 46 first incident pregnancies, for a rate of 5.9/100 person-years (p-y; 95%CI 4.4-7.8). The incidences of planned (6.4/100 p-y, n=4), mistimed (10.1/100 p-y, n=12), and unwanted pregnancies (5.0/100 p-y, n=30) were similar (p=0.11), but 90% (n=42) of pregnancies were mistimed or unwanted. In univariate analysis, oral contraceptive pill (OCP) use (vs no contraception or condoms only), condomless sex, vaginal washing, transactional sex in the last year, having a regular partner in the last 3 months, and experiencing intimate partner violence in the last year were significantly associated with a higher pregnancy risk. Being ≥35 years old (vs <25) was associated with a lower pregnancy rate. In multivariable analysis, OCP use (aHR 2.92, 95%CI 1.09-7.80), reporting condomless sex (aHR 2.19, 95%CI 1.08, 4.46), and having a current/regular partner in the last 3 months (aHR 3.64, 95%CI 1.00-13.34) were associated with increased risk of incident pregnancy.
Conclusion: In this cohort of HIV-positive FSWs, 90% of pregnancies were unintended. As part of comprehensive HIV care for FSWs, identifying women's fertility desire and pregnancy intention could facilitate efforts to increase effective contraceptive use in women not trying to conceive and to implement safer conception strategies for women trying to have a child.

1007 DRIVERS OF UNPLANNED PREGNANCY AND UNMET NEED FOR CONTRACEPTION IN SOUTH AFRICA

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Background: Preventing unplanned pregnancies amongst HIV positive women is a pillar of the WHO prevention of mother to child transmission of HIV (PMTCT) strategy, yet 60% pregnancies in South Africa are unplanned. We sought to identify predictors of unplanned pregnancies and unmet contraceptive among postpartum women in South Africa.
Methods: This analysis involves data from a nationally representative, cross-sectional survey measuring PMTCT effectiveness, in 2012/13. A total of 9277 women with known HIV status were included. All data regarding pregnancy planning and contraceptive use were self-reported during interviews. Unmet need for contraception was defined as unintended pregnancy among women not using any contraceptive method. All analyses were weighted and accounted for the survey design. Multivariable logistic regression models were used to estimate factors associated with unplanned pregnancy and unmet need for contraception.
Results: The mean age of participants was 26.3 years (SD 6.35), with 31.7% (95%CI: 30.6-32.7) self-reported HIV prevalence. More than a third (35.5%) were unaware of their HIV-positive status before pregnancy. A total of 5524 (61.0%) reported that their pregnancies were unplanned; of these 3868 (70%) reported non-use of contraceptives before pregnancy. Women who were unaware of

their HIV-positive status prior to pregnancy were more likely to have unplanned pregnancy (67.9% vs. 62.7% p<0.05) and unmet need for contraception (71.4% vs 64.8% p<0.01) compared to those who knew their status. In multivariate analysis, factors associated with unplanned pregnancy were: being younger than 20 years (aOR=3.23; 95% CI: 1.83-5.67), being unmarried (aOR=2.99; CI: 2.42-3.68), primary or less education (aOR=2.40; CI: 1.03-5.61), unaware of partners HIV status (aOR=1.40; CI: 1.16-1.69) and nondisclosure of HIV status to partner (aOR=1.39; CI: 1.07-1.18). Factors associated with unmet need for contraception were: self-reported HIV-positive serostatus (aOR 2.37; CI: 1.33-4.41), being younger than 20 years (aOR=3.55; CI: 2.27-5.55), being single (aOR=2.15; CI: 1.73-2.67), unaware of partner's HIV status (aOR=1.33; CI: 1.11-1.60), and nondisclosure of HIV status to partner (aOR=1.53; CI: 1.22-1.93).
Conclusion: Interventions to reduce unplanned pregnancy and unmet need for contraception could include education of young women and programmes that increase sexual and reproductive health education and facilitate disclosure in young women and their partners.

1008 UPTAKE OF POSTPARTUM CONTRACEPTION IN BOTSWANA, A HIGH BURDEN HIV SETTING

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Background: In high burden HIV settings, well-functioning sexual and reproductive health programming prevents unplanned pregnancies and HIV transmission. In Botswana, where HIV incidence approaches 1% per 100 person-years and prevalence among adults age 15-49 is > 20%, we sought to quantify pregnancy intention and uptake of contraception among postpartum women living with HIV (WLHIV) and HIV-uninfected (HIV-U) women.
Methods: The Tshilo Dikotla study is prospectively enrolling pregnant WLHIV and HIV-U women ≥ 18 years old in Gaborone, Botswana, and following mother-infant pairs through 3 years postpartum. WLHIV are on dolutegravir (DTG)- or efavirenz (EFV)-based combination antiretroviral treatment (cART) regimens in pregnancy. Data on future pregnancy intention and contraception use are collected via questionnaire at 6 months postpartum. We compared the proportion of women without plans for pregnancy (ever or within 2 years), proportions of women reporting use of contraception, and adopted contraception methods by HIV status. In women reporting >1 type of contraception, the most efficacious method was used for analysis.
Results: Among 233 women attending the 6-month postpartum visit, 142 (61%) were WLHIV. WLHIV were older (28.5 vs 24.3 years; p<0.001) and had higher gravidity (3 vs 1; p<0.001) compared to HIV-U women. More WLHIV expressed a desire to prevent future pregnancies or defer pregnancy for ≥2 years compared to HIV-U women (87% vs 66%; p<0.001). Among women not planning pregnancy in ≤2 years, only 89 (49%) reported using contraception, with similar uptake by WLHIV and HIV-U women (50% vs 47% respectively; p=0.71). Of the 61 WLHIV using contraception, 57% were on DTG- and 43% on EFV-based cART, with none using hormonal implants. Only 14% of HIV-U women were using implants. (Table 1) Depot medroxyprogesterone acetate was the most commonly used method overall. Uptake of condom use was low as a primary or secondary method, yet a higher proportion of WLHIV reported condom use (39% vs 32%). Only 7 women were using more than one method.
Conclusion: Uptake of contraception at 6-months postpartum was universally poor among women desiring pregnancy prevention, regardless of HIV status. In addition, dual condom use with more efficacious methods was particularly low, a concerning finding in a high burden HIV setting. Understanding individual and programmatic impediments to contraception uptake is needed to better match contraception use to pregnancy desires in Botswana and prevent HIV transmission.

Table 1. Contraceptive Methods Used by HIV Status Among Postpartum Women Accessing Contraception

Contraceptive Type	Women Living with HIV (n=61)	HIV-uninfected Women (n=28)
Condom[1]	20 (32.8)	6 (21.4)
DMPA	26 (42.6)	11 (39.3)
Hormonal implant	0 (0.0)	4 (14.2)
Intrauterine device	2 (3.3)	1 (3.6)
Oral contraceptives	8 (13.1)	4 (14.3)
Tubal ligation	4 (6.6)	1 (3.6)
Other	1 (1.6)	1 (3.6)

[1]Condom use reflects the count of women reporting sole condom use. An additional 4 WLHIV and 3 HIV-U women reported condom use in addition to a more efficacious method.
Abbreviations: DMPA – Depot Medroxyprogesterone Acetate

1009 IMPACT OF INTEGRATION OF FAMILY PLANNING INTO HIV TREATMENT PROGRAMS IN CAMEROON

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Background: Uptake of family planning (FP) methods in Sub-Saharan Africa (SSA) is low among women living with HIV (WLHIV). Studies have shown increased use of modern contraceptive methods as a positive effect of integrating FP services into HIV treatment programs. This study evaluated changes in unmet need and modern contraceptive use after integration of FP services at HIV clinics.
Methods: A serial, cross-sectional study of sexually active WLHIV at two HIV Treatment Clinics in Southwest Cameroon at baseline, six-month and 12-month follow up visits was conducted. Data were collected through interviews and chart abstractions to evaluate the unmet need for FP and contraceptive prevalence rate (CPR).Demographic characteristics, FP practices, and selected clinical outcomes were described using frequencies and percentages. These were compared using Chi-square ($\chi 2$) tests, Fisher's exact tests, and independent samples t-tests. We compared baseline data with the 12-month follow-up data. Logistic regression was used to estimate the impact of the intervention adjusted to other covariates.
Results: A total of 852 eligible women were surveyed across two sites; 51.6% were married. Modern CPR increased from 33.7% to 43.8% (p=0.003) and unmet FP need decreased from 13.9% to 9.6% (p=0.02). However, unmarried participants showed no significant increase in modern CPR from 36.2% to 41.9% (p=0.235). Long-acting reversible contraceptive (LARC) use significantly increased from 15.4% to 38.4% (p<0.001) while use of short-acting methods decreased from 86.0% to 63.3% (<0.001). For specific LARC methods, use of implants increased from 8.8% to 36.2% (p<0.001), while intrauterine contraceptive device use significantly decreased (6.6% to 2.0%, p=0.034). For short-acting methods, condom use decreased (83.1% to 38.3%, p<0.001), while injectable use increased (2.9% to 6.3%, p<0.001). Adjusting for demographic and clinical characteristics, women with unmet FP need were significantly likely to be Catholics [odds ratio (aOR) =1.30, 95% confidence interval (CI): 1.02-1.65] compared to non-Catholics, and to be on HIV treatment for more than 5-years (aOR=1.06, 95% CI: 1.01-1.10) compared to one year HIV treatment.
Conclusion: Integration of FP services into HIV treatment programs in Cameroon resulted in a significant decrease in the unmet need for FP and a significant increase in CPR. Successes of this program, as well as lessons learned during the service integration process, will lay the groundwork for future related programming.

Table 1: Contraceptive prevalence rate and modern contraceptive method use among women currently using modern FP methods at baseline and 12 months by time point, Cameroon, 2015-2016[¥]

	Total		Married		Unmarried	
Characteristics	**Baseline**	**12-months**	**Baseline**	**12-months**	**Baseline**	**12-months**
Modern Contraceptive prevalence rate (CPR)	136 (33.7)	196(43.8) *	65 (31.3)	105 (45.5)*	71 (36.2)	91 (41.9)
Unmet need for family planning	56 (13.9)	43 (9.6)*	41 (19.7)	27 (11.7)*	15 (7.7)	15 (7.7)
Short acting methods [Ω√]	117 (86.0)	124 (63.3)*	55 (47)	69 (50.4)	62 (54.9)	55 (42.3)
Long acting reversible contraceptives[^√]	21(15.4)	75 (38.3)*	12 (10.3)	37 (27.7)*	9 (8)	38 (28.5)*
Any Implant use	12 (8.8)	71 (36.2)*	9 (7.7)	36 (26.3)*	3 (2.7)	35 (26.9)*
Any intrauterine contraceptive device Use	9 (6.6)	4 (2.0)*	3 (2.6)	2 (1.5)	6 (5.3)	2 (1.5)
Any Oral contraceptive pill use	5 (3.7)	15 (7.7)	2 (1.7)	10 (7.3)*	3 (2.7)	5 (3.9)
Any Injectable Contraceptive use	4 (2.9)	32 (16.3) *	3 (2.6)	23 (16.8)*	1 (0.9)	9 (6.9)*
Male Condom use	113 (83.1)	75 (38.3) *	53 (45.3)	35 (25.6)*	60 (53.1)	40 (30.8)*
Dual method use (modern method plus Condom)	9 (6.6)	10 (5.1)	5 (4.3)	7 (5.1)	4 (3.5)	3 (2.3)

¥Column totals for each characteristic may differ from total for all because of missing data

* p-value between baseline and 12-month follow up < 0.05

ΩShort-acting modern methods include Condoms (male and female), Injectables, Progestin Only Pills and Oral Contraceptive Pills.

^Long acting reversible contraceptives include implants and intrauterine contraceptive device.

√The total of appropriate individual method does not equal short-acting modern or LARC, respectively, because these methods include combinations of use (e.g., Female Condom + Female Condom & IUD + Female Condom Only + Female Condom & Implant, etc.).

1010 PHARMACOKINETIC AND PHARMACOGENETIC ASSESSMENT OF ART AND CONTRACEPTIVE IMPLANTS

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Background: Contraceptive implants containing the progestins levonorgestrel (LNG) or etonogestrel (ENG) are highly effective and are increasingly being used by HIV-positive women in Sub-Saharan Africa. However, concomitant use of efavirenz (EFV) reduces implant effectiveness due to induction of cytochrome P450 (CYP450) enzymes. We conducted an analysis among women using implants to evaluate whether EFV use results in lower serum progestin concentrations, and to test whether allele variants with possible links to antiretroviral or hormone metabolism modify any changes in progestin concentrations.

Methods: We included 60 HIV-positive implant users enrolled in the Partners PrEP Study in Kenya and Uganda. Blood samples were collected at 6-month intervals and antiretroviral therapy (ART) initiation was self-reported. We measured serum LNG and ENG concentrations using liquid chromatography-tandem mass spectrometry and genotyped 18 variants in CYP2B6, CYP2A6, CYP3A4, CYP3A5, NR1I2 and ABCB1. We used linear mixed models to calculate geometric mean ratios (GMRs) comparing post-ART to pre-ART progestin concentrations, and to assess for interactions between ART group and allele variants. Multivariable models adjusted for age, nationality, body mass index, closest HIV viral load, days from ART initiation, and implant type.

Results: EFV- and nevirapine (NVP)-containing regimens were initiated by 11 and 13 women during the study, respectively; 36 women did not initiate ART and therefore contributed only pre-ART initiation data. In multivariable models, geometric mean serum LNG and ENG concentrations were 61% and 49% lower with EFV use compared to pre-ART initiation, respectively (LNG GMR=0.39, 95% CI: 0.31-0.49; ENG GMR=0.51, 95% CI: 0.34-0.76). GMRs of EFV use vs. pre-ART initiation progestin concentrations were lower with CYP3A5 rs776746 (p=0.009), CYP3A5 rs41303343 (p=0.002), CYP2B6 rs28399499 (p=0.001), and ABCB1 rs1045642 (p<0.001) allele variants relative to the wildtype (Table 1). We found no significant differences in LNG or ENG concentrations, or interactions between ART group and allele variants, with NVP use.

Conclusion: Use of EFV but not NVP resulted in lower LNG and ENG concentrations among implant users, and polymorphisms in CYP450 enzyme (CYP3A5 and CYP2B6) and ATP-binding cassette transporter (ABCB1) genes resulted in greater decreases, suggesting a modulating role of genetics. Confirmation of these allele's roles in the interaction between EFV and implant progestins is needed.

Table 1. Interactions between ART group and allele variants

		Efavirenz			Nevirapine		
Allele variant		Samples n (%)	GMR post-ART: pre-ART (90% CI)	Interaction p-value	Samples n (%)	GMR post-ART: pre-ART (90% CI)	Interaction p-value
CYP3A5 rs776746	WT	16 (72.7)	0.49 (0.38, 0.62)	REF	26 (74.3)	0.95 (0.75, 1.20)	REF
	Variant	6 (27.3)	0.25 (0.18, 0.36)	0.009	9 (25.7)	1.33 (0.98, 1.81)	0.11
ABCB1 rs1045642	WT	18 (81.8)	0.49 (0.39, 0.61)	REF	31 (88.6)	1.00 (0.81, 1.24)	REF
	Variant	4 (18.2)	0.15 (0.09, 0.24)	<0.001	4 (11.4)	1.10 (0.71, 1.70)	0.73
CYP2B6 rs28399499	WT	19 (86.4)	0.45 (0.36, 0.56)	REF	35 (100)	1.03 (0.84, 1.26)	--
	Variant	3 (13.6)	0.14 (0.08, 0.25)	0.001	0 (0.0)	--	--
CYP3A5 rs41303343	WT	17 (77.3)	0.48 (0.38, 0.60)	REF	35 (100)	1.03 (0.84, 1.3)	--
	Variant	5 (22.7)	0.20 (0.13, 0.31)	0.002	0 (0.0)	--	--

GMR=progestin geometric mean ratio (ENG or LNG); WT=wildtype
All models adjusted for age, nationality, body mass index, HIV viral load at closest sample collection, days from ART initiation, and implant type

1011 EFFECTIVE TREATMENT OF LYMPHOGRANULOMA PROCTITIS WITH EXTENDED AZITHROMYCIN REGIMEN

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Background: Lymphogranuloma venereum (LGV) is an ulcerative and invasive sexually transmitted infection (STI) caused by Chlamydia trachomatis (CT) serovars L1, L2, and L3. In the last 15 years it has become hyperendemic among men who have sex with men (MSM) in Western Europe. Current guidelines suggest treatment with Doxycycline 100 mg twice daily for 21 days (DoxLGV). Azithromycin 1 g orally once weekly for 3 weeks (extended azithromycin regimen (EAzLGV)) may be an alternative treatment, and here we investigatedits effectiveness as a treatment for LGV proctitis.

Methods: A prospective study was conducted between 2010 and 2017 at the STD Unit of a tertiary referral hospital in Barcelona (Spain). Males over 18 years of age with clinical proctitis,a recent history of unprotected receptive anal intercourse and microbiological confirmation of the diagnosis of LGVwere eligible for inclusion. All patients received a single dose of 1 gr of intramuscular ceftriaxone and were randomly assigned to receive: (i) DoxLGV; or, (ii) EAzLGV. Following treatment, individuals were assessed weekly for clinical symptoms and microbiologically by real-time multiplex polymerase chain reaction (M-PCR) for CT-LGV. Clinical cure (CC) was defined as disappearance of symptoms for at least 12 weeks; and microbiological cure (MC) as a negative rectal PCR for CT-LGV at week 4-6.

Results: Of 152 individuals with LGV, 136 (89%) met inclusion criteria. All were MSM with a median age of 38 years (interquartile range 33;44), 46% foreigners and 95% HIV+. Median numbers of sexual partners were 3 [1-10] and 10 [4-37], 5] in the previous 3 and12 months, respectively. Average time between onset of the symptoms and diagnosis was 39 days (range: 1-180). Eleven patients with inclusion criteria were excluded because violation of assigned therapy. From the 136 individuals with proctitis, there were 125 patients left for final analysis, 82 received EAzLGV and 43 received DoxLGV. There were no treatment related adverse events or losses to follow up. CC was achieved in 81 of 82 (99%) vs 41 of 43 (95%) (p= 0,27) and MC in 97% vs 100% (p=1,00) in the EAzLGV and DoxLGV groups, respectively

Conclusion: Our findings show that an extended azithromycin regimen was as effective as standard doxicycline regimen and may be considered as an alternative treatment for LGV proctitis in an HIV-infected population of MSM

1012 ADHERENCE OF HEALTH CARE PROVIDERS TO CDC LUMBAR-PUNCTURE CRITERIA AMONG SYPHILIS/HIV

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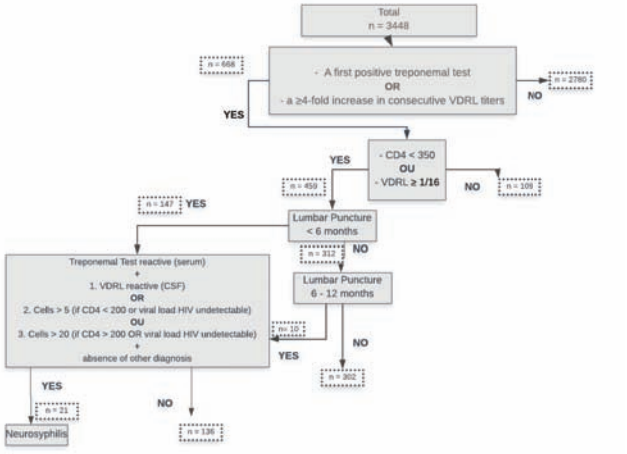
Background: Syphilis is a prevalent infection with increased morbidity and more frequent central nervous system invasion in HIV-infected persons. The CDC suggests laboratory criteria to guide cerebrospinal fluid (CSF) examination among asymptomatic HIV-infected patients. However, information about the degree of adherence to such criteria is scarce. In this study, we describe the proportion of adherence of Health Care Providers to CDC lumbar puncture (LP)

criteria in syphilis and HIV coinfected patients and report the frequency of neurosyphilis in these patients.
Methods: Retrospective cohort study carried out in all HIV-infected patients under outpatient follow-up in an academic center at São Paulo, Brazil, between 2000 and 2016. We identified all incident syphilis cases, defined as a first positive treponemal test or a ≥4-fold increase in consecutive VDRL titers. We considered lumbar puncture performed < 6 months after incident syphilis. We report the proportion of patients meeting CDC criteria for LP undergoing cerebrospinal fluid testing, and the frequency of confirmed (positive VDRL) or probable (abnormal leukocyte counts: >5 cells/ml among patients with T CD4+ counts <200 and suppressed viral loads; >20 cells/ml otherwise) neurosyphilis.
Results: The initial sample comprised 3448 persons living with HIV. Incident syphilis was detected in 669 patients. Of those, 459 met CDC criteria for CSF collection, and 147 (32%, 95%CI 28-37) were referred to LP. Confirmed or probable neurosyphilis was observed in 18 cases (12%, 95%CI 7-19). Of 312 patients not referred to LP despite CDC criteria, 10 (3%, 95%CI 2-6) collected CSF within 6 to 12 months and 3 (30%, 95%CI 7-65) had abnormal results compatible with neurosyphilis. Of those with abnormal results, 13 (72%) had a positive VDRL in the cerebrospinal fluid.
Conclusion: Adherence to CDC LP criteria for syphilis and HIV coinfected patients was low, despite follow-up in an academic center. In this subset of patients, the frequency of neurosyphilis was 12% for LP performed in the first 6 months and 30% among those submitted to LP within 6 to 12 months.



1013 HEARING LOSS IN UNSELECTED INDIVIDUALS WITH SYPHILIS

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Background: Little is known about the incidence and pathophysiology of otosyphilis.
Methods: Unselected individuals enrolled in a study of cerebrospinal spinal fluid (CSF) abnormalities in syphilis underwent screening audiometry, standardized medical history, lumbar puncture and venipuncture. Serum rapid plasma reagin titers (RPR) and detection of T. pallidum (Tp) in blood by PCR and CSF by RT-PCR were determined in a research laboratory. CSF white blood cell count, CSF-Venereal Disease Research Laboratory (VDRL) reactivity, CD4+ T-cells and plasma HIV RNA were determined in a clinical laboratory. Relationships between hearing loss (HL, unilateral or bilateral), defined as low-mid (500, 1000, 2000 Hz average) or high frequency (4000, 6000, 8000 Hz average) pure tone averages ≥26 dB, or either (any loss), and other variables were determined by logistic regression. For multivariate models, all variables significant at P≤0.10 were included. Those with P-values >0.05 in multivariate models were sequentially removed.
Results: 362 individuals without pre-existing HL were evaluated: 99% men, mean age 41 (SD 11), 82% HIV+ (70% on antiretrovirals [ARVs]), median serum RPR titer 1:64 (IQR, 1:16-1:128), 51% treated for uncomplicated syphilis before study visit. 186 (51%) had any HL; 83 (23%) low-mid and 168 (46%) high frequency HL. In univariate analysis, odds of any HL were higher in HIV+, those with reactive CSF-VDRL, CSF pleocytosis, detection of Tp in blood or CSF, injection drug use (IDU), older age and higher RPR titers (Table). In multivariate analysis, odds of any HL remained higher in those with CSF pleocytosis, Tp detection in blood, IDU and older age (Table). In multivariate analysis, odds of low-mid frequency HL were higher in those with Tp detection in CSF, IDU and older age, and odds of high frequency HL were higher in those with CSF pleocytosis, Tp detection in blood, and older age (Table). Syphilis stage, current ARV use, CD4+ T-cells and plasma HIV RNA were not associated with any category of hearing loss.
Conclusion: HL is common in individuals with syphilis and increases with age. While low-mid frequency HL is more likely in those with Tp detection in CSF, high frequency HL is more likely with CSF inflammation. Low-mid and high frequency HL due to otosyphilis may be due to different pathological mechanisms, and, as such, may respond differently to treatment.

Table

	Any HL		Low-mid frequency HL		High frequency HL	
	OR	aOR	OR	aOR	OR	aOR
HIV+	1.8*	NSa	NS		1.7	NSa
CSF-VDRL+	2.1*	NSa	NS		2.1*	NSa
CSF WBCs>10/ul	1.8*	2.2*	NS		2.1**	2.8**
CSF PCR+	2.6*	NSa	3.3**	3.2**	1.9	NSa
Blood PCR+	3.7***	3.3***	2.2*	NSa	3.3***	2.7**
Current IDU	1.7	2.6*	1.9	2.3*	NS	
Age per 10 y increase	2.4***	2.4***	1.7***	1.8***	2.8***	2.8***
RPR titer per 2 log increase	1.1**	NSa	NS		1.1*	NSa
Treated for uncomplicated syphilis before entry	0.7	NSa	NS		0.7*	NSa

HL, hearing loss; OR, odds ratio; aOR, adjusted odds ratio
NS, P>0.10; NSa, P>0.05
*P<0.05, **P<0.01, ***P<0.001
Shading indicates variables not included in multivariate models.

1014 COGNITIVE IMPAIRMENT IN INDIVIDUALS WITH SYPHILIS

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Background: Few studies have examined both cognitive function and cerebrospinal fluid (CSF) abnormalities in individuals with syphilis.
Methods: 186 individuals with syphilis underwent self-administered cognitive assessment with the Cogstate battery, and 132 (71%) underwent lumbar puncture. Cognitive function was categorized as unimpaired; mild, moderate or severely impaired; or unimpaired/mild or moderate/severe based on normative Cogstate data. Serum rapid plasma reagin (RPR) test titer, detection of *T. pallidum* in CSF by reverse transcriptase PCR and presence of recreational drugs in urine were determined in a research laboratory, and CSF white blood cell (WBC) enumeration and CSF Venereal Disease Research Laboratory (VDRL) reactivity were determined in a clinical laboratory. Neurosyphilis was defined as a reactive CSF-VDRL alone, or reactive CSF-VDRL or CSF WBCs>10/ul. Results are described as medians (interquartile range [IQR]) or percents, and differences determined by chi square or Fisher exact test.
Results: Participants were primarily men (98%), age 35 (28-46) with at least a high school education (91%); 62% were HIV infected with 90% on antiretrovirals. 82% had early syphilis, with RPR 1:64 (1:32-1:256). Urine toxicology was positive for stimulants in 19%, cannabinoids in 21% and both in 9%. Overall, 124 participants were cognitively impaired: 72 (39%) mild, 33 (18%) moderate, 19 (10%) severe. Among those with any cognitive impairment, the proportion of individuals with serum RPR titer ≥1:32 increased with increasing level of impairment (52/72 (72%) mild, 26/33 (79%) moderate, 19/19

(100%) severe, P=0.02). Individuals with asymptomatic syphilis (early latent or late latent) were more likely than those with primary or secondary disease to have moderate/severe impairment (33/97 (34%) vs. 19/89 (21%), P=0.05). There was no relationship between cognitive impairment and HIV status, a positive toxicology screen, either definition of neurosyphilis, or detection of *T. pallidum* in CSF.

Conclusion: Cognitive impairment was common in this cohort of individuals with syphilis, was not associated with HIV status or neurosyphilis, but was more common in those with high serum RPR titers, and those with latent syphilis. These results suggest that cognitive impairment in individuals with syphilis may be related to bacterial burden and may be seen in those without symptoms or signs of syphilis.

1015 RESPONSE TO SYPHILIS TREATMENT: CDC GUIDELINES IN HIV-INFECTED ADULTS ON cART

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Background: Guidelines define an adequate response to syphilis treatment as a four-fold decrease in serum RPR at 6-12 (primary, secondary syphilis) and 12-24 months (early latent, late latent, neurosyphilis). Previous studies reported that 15%–20% of HIV infected persons with primary and secondary syphilis will not achieve the fourfold decline at 1 year after treatment. We assessed if CDC guidelines capture the timeline of serologic response to syphilis treatment in HIV-positive adults in the era of modern ARVs.

Methods: We conducted a chart review of 532 HIV-positive adults with positive syphilis serology between 2000 and 2017. Inclusion criteria were: reactive pre-treatment RPR titer; documentation of date and type of syphilis therapy; reversion to a non-reactive RPR or at least 6 months or 1 year of follow-up for early syphilis and late syphilis/neurosyphilis, respectively. Only the first eligible episode was included. Time to four-fold decrease was calculated using Kaplan Meier estimates. Univariable proportional hazards models assessed associations between clinical covariates and time to four-fold decrease.

Results: 189 male patients (87% MSM) met inclusion criteria. At syphilis diagnosis, median age (IQR) was 42 (35, 48), median CD4 count (IQR) was 443 (273, 609). 56% had a suppressed viral load (VL). 75% were on ARVs. 12% were primary syphilis, 28% secondary, 12% early latent, 28% late latent, 19% neurosyphilis; stage was undefined for 1%. It was the first syphilis episode for 134 patients (71%), 55 (29.5%) had had previous syphilis. 72% received IM benzathine Penicillin G (27% 1 dose, 45% 2-3 doses), 21% IV Penicillin G, and 5% doxycycline. Median follow-up (IQR) was 2.55 (1.53, 6.14) years. In patients with suppressed VL 42 (97.7%) with primary or secondary syphilis experienced four-fold decrease by 12 months, 31 (91.2%) with early or late latent syphilis and 11 (84.6%) with neurosyphilis by 24 months compared to 21 (87.5%), 26 (89.7%), 18 (100%) in those without VL suppression. Overall, the cumulative incidence of achieving a four-fold decrease at 12 months was 0.94 (95% CI 0.83, 0.99) in patients with suppressed VL and 0.96 (95% CI 0.75, 1) in non-suppressed patients (p=0.56). Age, CD4 count, previous syphilis, current syphilis stage, and number of treatment courses were not associated with time to four-fold decrease.

Conclusion: We observed high rates of serologic response to syphilis treatment in HIV infected adults engaged in care that was not impacted by VL suppression with cART.

1016 "TREAT ALL" ADOPTION IMPROVES RAPID TREATMENT INITIATION IN 6 SUB-SAHARAN COUNTRIES

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Background: Most countries have formally adopted the World Health Organization's 2015 recommendation of universal HIV treatment (Treat All). Although effects of universal treatment eligibility interventions have been examined in large trials and using modeled data, there are few rigorous assessments of the real-world impact of Treat All on antiretroviral treatment (ART) uptake across different contexts.

Methods: We used longitudinal data for 814,603 patients enrolling in HIV care during 2004-2018 in six sub-Saharan African countries participating in the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium (Burundi, Kenya, Malawi, Rwanda, Uganda, and Zambia). Using a quasi-experimental regression discontinuity design, we assessed the change in the proportion of individuals initiating treatment within 30 days of enrollment in HIV care (rapid ART initiation) after country-level adoption of Treat All policies. A modified multivariable Poisson model was used to identify factors associated with failure to initiate ART rapidly among persons enrolling in HIV care under Treat All.

Results: In all countries, national adoption of Treat All was associated with large increases in rapid ART initiation. The greatest increase in rapid ART initiation immediately after Treat All policy adoption was observed in Rwanda, from 44.4% to 78.9% of patients (34.5 percentage points (pp); 95% CI: 27.2-41.7 pp), Kenya (25.7pp, 95% CI: 21.8 to 29.5pp), and Burundi (17.7pp, 95% CI: 6.5 to 28.9pp), while the rate of rapid ART initiation accelerated sharply following Treat All policy adoption in Malawi, Uganda, and Zambia. Under Treat All, younger patients (16-24 years) and men were at increased risk of not rapidly initiating ART (compared to older patients and women, respectively). However, rapid ART initiation following enrollment increased for all groups as more time elapsed since Treat All adoption.

Conclusion: Adoption of Treat All policies had a strong effect on increasing rates of rapid ART initiation and increases followed different trajectories across the six countries. Adoption and implementation of Treat All policies should be accelerated, with particular care to identify and address possible inequities in access to treatment by subgroups at higher risk of not rapidly initiating treatment following diagnosis and care enrollment.

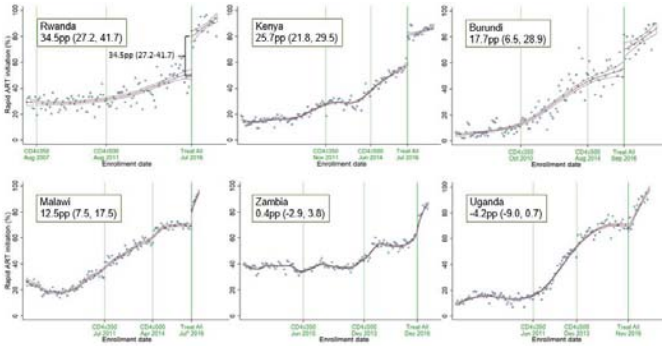

Figure. Rapid ART initiation by treatment eligibility period and country, 2007-2018. Text boxes include effect size (change in the proportion of patients rapidly initiating ART) from regression discontinuity analysis across the Treat All adoption date threshold.

1017 OUTCOMES OF "TEST AND START" AT SCALE WITHIN HAITI'S NATIONAL ART PROGRAM

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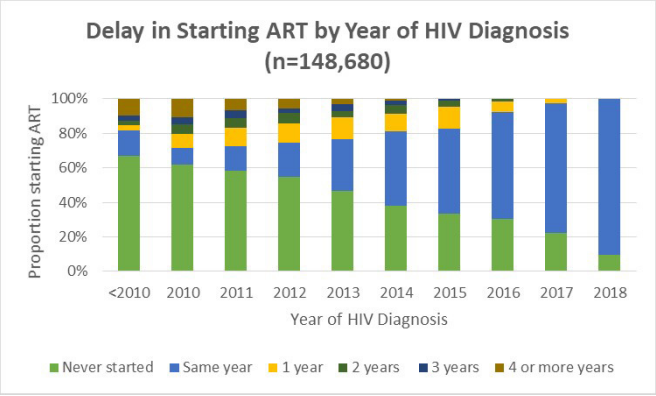
Background: In July 2016, Haiti's Ministry of Health endorsed the universal "test and start" (T&S) strategy, offering HIV antiretroviral therapy (ART) to all patients upon diagnosis with HIV, regardless of health status. The outcomes of Haiti's nationally scaled-up T&S initiative have not previously been described. This study's aims were to: 1) describe trends in timeliness of ART initiation before and after July 2016; and 2) explore the association between rapid initiation and retention on ART.

Methods: Our retrospective cohort study included data from 148,680 patients who received a first HIV diagnosis at one of 94 hospitals and clinics in Haiti from 2004 through March 2018. Data were drawn from a large electronic medical record system as well as Haiti's national HIV/AIDS case based surveillance data system. We studied trends in linkage to care and ART initiation using descriptive

and time-to-event analyses. Among those initiating ART, we calculated the proportion retained on ART at 12 months, and explored its association with timeliness of ART initiation using multivariable logistic regression, with adjustment for socio-demographic and clinical variables and clustering by site.
Results: Among the 148,680 patients diagnosed with HIV in our cohort, 61.7% were female, 66.5% were aged 25-54 years, and 83.5% were diagnosed within their home commune. The proportion of patients who never started ART dropped from 63.1% among those diagnosed with HIV before 2013 to only 9.4% for those diagnosed in the first calendar quarter of 2018. Among 8,429 patients who were first diagnosed with HIV after adoption of the T&S policy in July 2016, who started ART, and who had 12 months of time under observation in the cohort, 70.5% were retained on ART at 12 months. Retention was highest in patients with longer intervals between HIV diagnosis and ART start (64.3% retained for same day ART start, 66.9% for ART start within 2 weeks, and 75.7% retained for ART start after 2 weeks). In adjusted analysis, compared to the reference category of same day ART initiation, patients with longer intervals to ART start had likelihood of 12 month retention which was 1.24 – 2.01 times greater, a highly significant finding (p<0.001).
Conclusion: Haiti has rapidly expanded ART coverage; however, there is room for improvement in ART retention for patients rapidly initiating ART under T&S. Enhanced post-test counseling, patient education, and support may help patients who rapidly start ART to remain on treatment.



1018 SAME-DAY ART INITIATION IN THE SLATE TRIAL IN KENYA: PRELIMINARY RESULTS

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Background: WHO's and Kenya's HIV treatment guidelines recommend rapid initiation of ART (≤7 or ≤14 days of HIV diagnosis, respectively) and encourage same-day initiation. Identifying efficient procedures for determining same-day eligibility and readiness is a priority. The Simplified Algorithm for Treatment Eligibility (SLATE) trial is testing a clinical algorithm in Kenya and South Africa that allows clinicians to determine eligibility for immediate ARV dispensing at the patient's first visit. We report early results from Kenya.
Methods: SLATE is an individually randomized, pragmatic trial at 3 public hospital-based outpatient clinics in western Kenya. Ambulatory patients presenting for an HIV test or HIV care, but not yet on ART, were enrolled sequentially, consented, and randomized to intervention or standard care. Intervention arm patients were administered the SLATE algorithm, comprised of a symptom self-report, medical history questionnaire, brief physical examination, and readiness assessment, to identify patients eligible for immediate ART initiation ("screened in") or requiring further care, tests, or counseling before starting treatment ("screened out"). Patients who screened in were dispensed ARVs immediately; those who screened out were referred back to the clinic for further routine care. Follow up was by record review. We report ART initiation within 0 (same-day), 7, 14, and 28 days of study enrollment.
Results: From 12 July 2017 to 23 April 2018, we enrolled 477 adult, HIV+, non-pregnant patients. More patients initiated ART in the intervention arm than in the standard arm at 0 (70% vs 54%), ≤7 (86% vs 73%), ≤14 (90% vs 85%) and ≤28 days (94% vs 89%) (Table). In the intervention arm, 109 patients (45.4% of 240) screened out: 51 (47%) due to TB symptoms alone, 42 (39%) due to TB symptoms and ≥ 1 other reasons, and 16 for reasons other than TB. Among the 109 screened out and referred back to the clinic for further care, 36/109 initiated the same day and 64/109 initiated within 90 days; 9/109 patients did not start within 90 days.
Conclusion: Use of the SLATE algorithm increased uptake of ART within 7 days-the WHO's definition of "rapid" initiation-by 12.8%. Medical officers were able to implement it in routine care settings without additional equipment or clinical supervision. Current TB symptoms accounted for 3/4 of patients screened out. Early results suggest that a simple algorithm for treatment initiation procedures is feasible and can increase same-day and rapid ART uptake.

Table: Sample characteristics and primary outcomes, by arm

Value	Standard arm (n=237)	Intervention arm (n=240)	Crude risk difference (95%CI)*	Crude relative risk (95% CI)*
Sex (% female)	57%	59%		
Age in years (median, IQR)	34 (29-43)	35 (29-43)		
Baseline CD4 count in cells/m³ (median, IQR)	297 (94-577)	272 (124-522)		
Initiated within:				
0 days of enrolment	127 (53.6%)	167 (69.6%)	16.0% (7.4-24.6%)	1.30 (1.12-1.50)
=7 days of enrolment	173 (73.0%)	207 (86.3%)	13.3% (6.1-20.4%)	1.18 (1.08-1.30)
=14 days of enrolment	201 (84.8%)	217 (90.4%)	5.6% (-0.0-11.5%)	1.07 (1.00-1.14)
=28 days of enrolment	210 (88.6%)	226 (94.2%)	5.5% (0.0-10.6%)	1.06 (1.00-1.12)
=90 days of enrolment	222 (93.7%)	231 (96.3%)	2.6% (-1.3-6.5%)	1.03 (0.99-1.07)

* Reference group: standard arm

1019LB WITHDRAWN / INTENTIONALLY UNASSIGNED

1020 IMPLEMENTING UTT IN AFRICAN CORRECTIONAL FACILITIES: A PROSPECTIVE COHORT STUDY

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Background: Despite widespread HIV treatment and care scale up, corrections inmates continue to be left behind in the global HIV response. To provide inmates with the known benefits of universal test and treat (UTT) and to describe clinical outcomes for UTT delivery in southern African correctional facilities, we conducted an implementation research study enrolling a prospective cohort of HIV-positive inmates from Zambia and South Africa.
Methods: We offered immediate ART to inmates ≥18 years with newly diagnosed HIV or previously diagnosed HIV not yet on ART (regardless of CD4 or WHO stage) who were expected to be incarcerated ≥30 days at 3 high-volume correctional facilities in Lusaka, Zambia and Johannesburg and Cape Town, South Africa. To enable UTT delivery at each site, we strengthened public, on-site HIV care programming by supporting: HIV testing and anti-retroviral therapy (ART); viral load (VL) monitoring; and corrections officer, health worker, and peer educator training on UTT. We collected clinical and socio-demographic data at study baseline and follow-up visits. We calculated summary statistics for variables of interest, and conducted an exploratory risk factor analysis for unsuppressed VL using logistic regression modelling.
Results: From June 2016-March 2018, 1,562 HIV-positive inmates were identified across the study sites, of whom 1,022 (65%) met study eligibility criteria and 977 (96%) enrolled. Participants were mostly young men (n=824, 84%), with median age 32 years (interquartile range, IQR: 28–38) and 29% (n=287) having prior incarceration history. Of those enrolled, 835 (85%) started ART, and did so within 1 day (IQR: 0–17) of HIV diagnosis. Of 141 who did not start ART, most (n=113, 80%) were transferred or released prior to baseline evaluation. Among 384 (46%) participants with a documented 6-month post-ART VL, 74%, 89% and 91% achieved virologic suppression using thresholds of <50 copies(c)/mL, <400 c/mL, and <1,000 c/mL, respectively. Factors associated with VL ≥50 c/ml are reported in the table.

Conclusion: In the first prospective study of its kind from southern Africa, we demonstrate that it is feasible to implement UTT in correctional settings in Zambia and South Africa, and that such an intervention can achieve high early ART uptake and excellent viral suppression for HIV-positive inmates during incarceration. However, frequent facility transfer and release threatens to undermine UTT by limiting access to timely ART and fragmenting care for inmates living with HIV.

Table: Exploratory analysis of the association between factors of interest and unsuppressed viral load (VL) at a threshold of ≥50 copies/ml among 384 participants with a documented VL result 6 months after ART initiation.

Factor		% Having 6-month VL* ≥50 copies/ml (n/N)	OR** (95% CI)***
Sex	Male	26% (83/316)	1
	Female	22% (15/68)	0.79 (0.43-1.49)
Marital status	Married	21% (30/145)	1
	Cohabiting	53% (9/27)	4.31 (1.53-12.1)
	Widowed	33% (6/18)	1.91 (0.66-5.52)
	Divorced/separated	31% (12/39)	1.70 (0.77-3.75)
	Single	25% (41/165)	1.27 (0.74-2.16)
Age, years	<25	24% (12/50)	1
	25-29	22% (17/79)	0.87 (0.37-2.02)
	30-34	31% (30/96)	1.44 (0.66-3.13)
	35-39	22% (18/83)	0.88 (0.38-2.02)
	≥40	28% (21/76)	1.21 (0.53-2.75)
Correctional facility study site	Johannesburg	35% (43/124)	1
	Lusaka	21% (43/203)	0.51 (0.31-0.83)
	Cape Town	21% (12/57)	0.50 (0.24-1.05)
Timing of ART start after HIV diagnosis	Same day	24% (51/209)	1
	1-7 days after	21% (15/72)	0.82 (0.43-1.56)
	>7 days after	31% (32/103)	1.40 (0.83-2.36)

*VL: Viral load; **OR: odds ratio; ***CI: 95% confidence interval

1021 IMPROVEMENT IN TIME TO ART INITIATION REGARDLESS OF TB STATUS IN LATIN AMERICA

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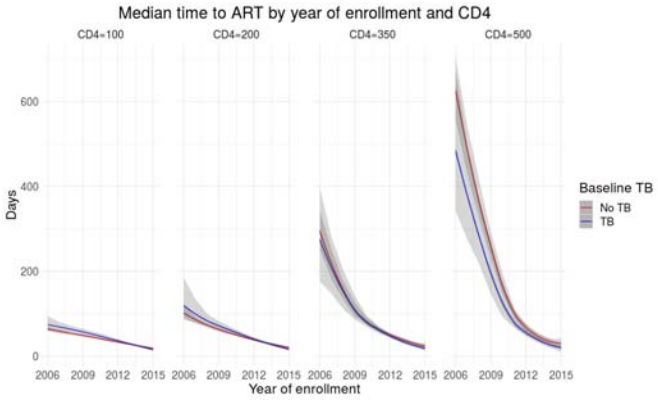
Background: In 2006, the World Health Organization recommended antiretroviral therapy (ART) for persons with CD4 count <200 cells/mm3 (<350 if co-infected with tuberculosis [TB]) or Stage 4 HIV disease. Subsequent guidelines recommended earlier ART initiation (2009: CD4 <350 cells/mm3 or Stage 3/4 disease [including TB]; 2013: CD4 <500cells/mm3; 2015: universal ART). The recommended timing of ART initiation relative to TB medications also changed during this period. We characterized temporal trends in the time to ART initiation and compared trends between HIV+ persons with and without TB.

Methods: The study included data from HIV clinical sites in Brazil, Chile, Haiti, Honduras, Mexico, and Peru participating in CCASAnet. We included all persons ≥18 years old who were ART-naïve at first clinic visit from 2006 to 2015. We estimated median time to ART initiation as a function of baseline TB status (within 30 days before or after enrollment), CD4 count, and year of enrollment from a multivariable Cox regression model that included these variables, two-way interactions between these variables, sex, education, and age, and stratified by study site. Continuous variables were fit with natural splines to relax linearity assumptions.

Results: Of 19,197 patients, 1306 (7%) were diagnosed with TB at enrollment. Patients with TB were more likely to be male, older, less educated, with lower CD4 counts, and living in Haiti or Peru. A total of 17,183 (93%) initiated ART during a median of 3.6 years of follow-up; 96% of those with TB compared to 93% without TB (p<0.001). The median time to ART initiation was 42 days for those without TB, and 43 days for those with TB (p=0.94). The Figure shows the estimated median adjusted time from enrollment to ART initiation as a function of TB status, calendar year, and CD4 count at enrollment. The association between CD4 count and time to ART initiation changed dramatically over time (p<0.0001). The association between TB status and time to ART initiation varied extensively based on CD4 count (p<0.0001) and to a lesser extent the date of enrollment (p=0.06). For a person enrolling with TB and a CD4 count of 500 cells/mm3, the estimated median time to ART initiation was approximately 500 days in 2006, compared to under 50 days in 2015.

Conclusion: In recent years in Latin America, there has been a dramatic shortening in the time from enrollment to ART initiation, for both those with and without TB, particularly among those with high CD4 counts.



1022 UPTAKE OF ANTIRETROVIRAL THERAPY IN THE "TREAT ALL" ERA IN RIO DE JANEIRO, BRAZIL

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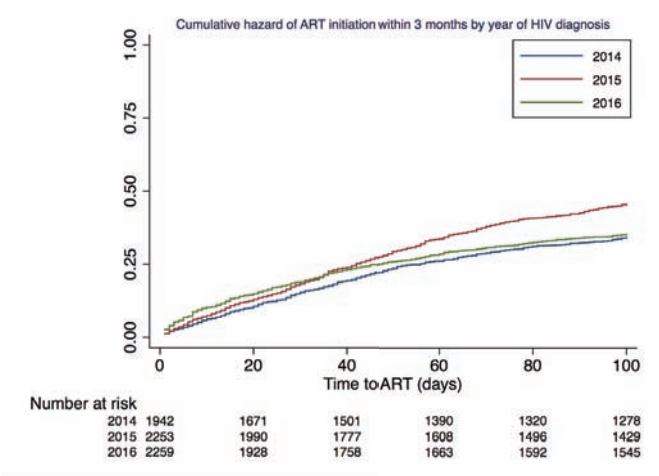
Background: Randomized controlled trials have proven the efficacy of early antiretroviral therapy (ART) for reducing HIV morbidity, mortality, and transmission. As a result, guidelines recommending treatment for all, regardless of CD4 count, are being scaled up worldwide. The Brazilian Ministry of Health has recommended treatment for all since 2013 and offers free antiretrovirals (ARVs) for all HIV-infected patients. We evaluated uptake of "treat all" guidelines in Rio de Janeiro, Brazil, from 2014-2017.

Methods: HIV has been a notifiable disease in Brazil since 2014. We included all patients diagnosed with HIV and reported to the Rio de Janeiro Health Secretariat from 2014-2016, with follow-up through 2017. HIV notifications and comorbidities were obtained from the national notifiable diseases information system; ARV prescriptions from the Rio de Janeiro pharmacy information system; and death notifications from the Rio de Janeiro mortality registry. We joined databases using a novel probabilistic linkage strategy. We assessed HIV notifications, prevalence of opportunistic infections (OIs), and median time to ART initiation over time. We used Nelson-Aalen cumulative hazard estimates to construct risk curves comparing 3-month ART initiation by diagnosis year and estimated the hazard of ART initiation by diagnosis year using Cox proportional hazards regression.

Results: From 2014-2016, 6,454 persons were diagnosed with HIV and notified to the Rio de Janeiro Health Secretariat. Of these, 2,009 (31%) were female and median age was 34 years (IQR 26-43). 1,725 (27%) had a documented OI, including 417 (6%) with pulmonary tuberculosis. Of 2,628 (41%) patients reported to have initiated ART, 2,028 (77%) did so within 3 months of HIV diagnosis; median time to ART initiation was 42 days (IQR 15-94) and decreased from 51 days [IQR 21-135] in 2014 to 46 days [IQR 20-92] in 2015 and 31 days [IQR 8-68] in 2016. Patients diagnosed in 2015 had an increased hazard of 3-month ART initiation compared to those diagnosed in 2014 (aHR 1.31, 95% CI 1.18-1.46). There was a non-significant increased hazard of 3-month ART initiation for those diagnosed in 2016 compared to 2014 (aHR 1.06, 95% CI 0.95-1.19).

Conclusion: The rate of ART initiation in Rio de Janeiro was low, despite the availability of free ARVs and guidelines recommending treatment for all. "Treat

all" guidelines should continue to be scaled-up to achieve 90-90-90 targets and reduce HIV morbidity and mortality.



1023 NARROWING THE GAP IN CD4 COUNT AT ENTRY INTO CARE AND AT ART INITIATION, 2005-2016

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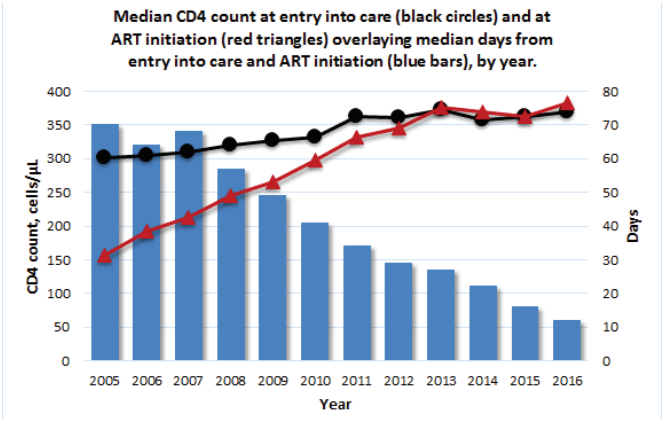
Background: In March 2012, the US Department of Health and Human Services updated HIV treatment guidelines to recommend antiretroviral therapy (ART) for everyone infected with HIV, regardless of CD4 count, to reduce morbidity and mortality among those infected and prevent transmission to others. Our objective was to describe observed trends in CD4 count, at entry into care and at ART initiation, among patients enrolled in US-based clinical cohorts of the NA-ACCORD between 2005 and 2016.

Methods: The study sample comprised treatment-naïve adults (aged ≥18 years) without a clinical AIDS diagnosis who presented for HIV care with a viral load >500 copies/mL (-180/+14 days) and a recorded CD4 count (-90/+30 days). A subset of the study sample initiated ART (defined as being prescribed a combination ART regimen) with a recorded CD4 count (-90/+30 days). For patients with >1 CD4 count collected during the 120-day window, we used the measurement obtained closest to the visit date of interest. We generated plots of median CD4 counts at entry into care and at ART initiation, by calendar year. We also calculated median number of days from entry into care to ART initiation, by calendar year.

Results: We identified 28862 patients who entered care; of those patients, 23521 initiated ART. Median CD4 count at entry into care was 302 (IQR: 115–481) cells/μL in 2005, 360 (IQR: 174–545) cells/μL in 2012, and 370 (IQR: 211–565) cells/μL in 2016. Median CD4 count at ART initiation was 157 (IQR: 51–287) cells/μL in 2005, 346 (IQR: 182–507) cells/μL in 2012, and 382 (IQR: 207–583) cells/μL in 2016. Median number of days from entry into care to ART initiation was 70 (IQR: 20–546) in 2005, 29 (IQR: 12–74) in 2012, and 12 (IQR: 0–25) in 2016. Of patients who initiated ART after entering care in 2016, 31% initiated ART on day of presentation and 4% initiated ART ≥60 days later.

Conclusion: Median CD4 counts at entry into care and at ART initiation have been trending towards convergence since 2005 and clinically equivalent since 2012, reflecting the reduction in time from entry into care to ART initiation and adoption of "treat all" in clinical practice in the US. Additionally, the increase in CD4 count at presentation over time indicates progress towards earlier HIV diagnosis and linkage to care, critical for reaching 90-90-90 targets. These trends suggest that CD4 counts at entry into care and at ART initiation will continue to jointly increase over time with expanded implementation of effective test-and-treat strategies.



1024 PATIENT-REPORTED REASONS FOR DECLINING IMMEDIATE ART INITIATION IN LUSAKA, ZAMBIA

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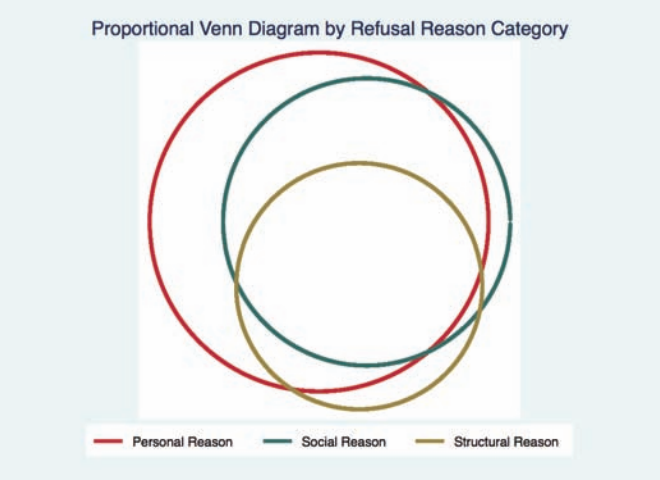
Background: Programs are focusing increased resources to meet the UNAIDS "second 90" treatment target. To help achieve this goal in Zambia, we developed a quality improvement tool to evaluate reasons people living with HIV (PLHIV) do not immediately link to care (LTC) and start ART. We designed the tool to be used in routine care settings to understand reasons for LTC and ART delays, and to improve individualized post-test counseling.

Methods: We created a simple 1-page screening tool with structured items to capture three broad categories for failed LTC and ART delay: social, personal, and structural. We implemented the tool in three facilities, two urban and one rural, in Lusaka District over a three-month period. We administered the tool to all individuals who refused LTC and immediate ART. Individuals were allowed to choose as many reasons as relevant. Failed linkage risk was modeled using mixed effects logistic regression controlling for age, sex and testing point, and allowing random effect for clinic.

Results: A total of 1,292 people with new HIV infection were identified across clinics, of whom 9.6% reported a refusal reason. Each respondent reported a median of three reasons (IQR:2-3). Of those who refused immediate LTC, 69.6% were female, with median age 30 years (IQR: 23-40 years). Females refusing LTC were younger on average at 28.5 years (IQR: 21-37 years) than their male counterparts at 34.5 years (IQR: 26-44 years). Of the 504 non-mutually exclusive responses, 87.3% were classified as personal, 62.7% as social, and 46.0% as structural. The two most commonly cited reasons for refusal were: "Clinics are too crowded" (12.3%), which was number one among females (13.8%), and "Friends and family will condemn me" (11.2%), which was most common among males (14.1%). Testing point was not significantly associated with LTC refusal (RR:1.15, 95% CI:0.03-51.51). Females were more likely to refuse (RR: 2.03, 95% CI: 1.69-2.45), as were PLHIV ages 20-24 years (RR: 5.18, 95% CI: 1.85-14.50). Structural, personal, and social reasons for refusal differed significantly (all $\chi 2$ $p<0.001$) across testing points.

Conclusion: The top refusal reason was associated with facility over-crowding, speaking to the importance of differentiated service delivery model scale-up to decompress busy clinics. Given the differences in refusal reasons observed across testing points, males and females, and different age bands, new, tailored LTC approaches warrant further study.



1025LB CASCADE TRIAL: 24 MONTH OUTCOMES AFTER SAME-DAY HOME-BASED ART INITIATION

Alain Amstutz[1], Isaac Ringera[2], Thabo I. Lejone[2], Josephine Muhairwe[2], Jennifer A. Brown[3], Thomas Klimkait[3], Tracy R. Glass[1], **Niklaus D. Labhardt**[1]
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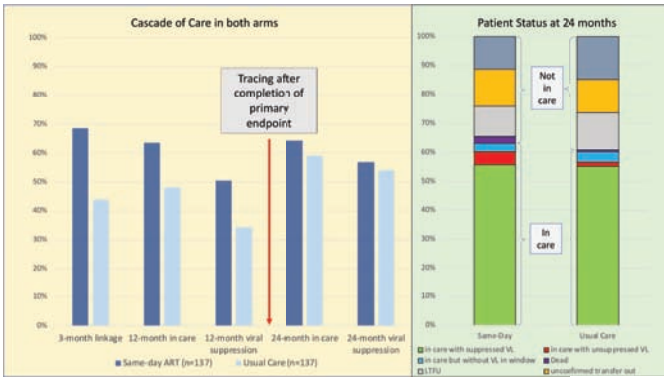
Background: The CASCADE trial, conducted in Lesotho, Southern Africa, has shown that offering same-day initiation of antiretroviral therapy (ART) to individuals found HIV positive during home-based testing resulted in significantly higher proportions engaged in care and virally suppressed 12 months after the testing campaign. At completion of the trial all patients not in care were traced and the protocol was amended to allow for a 24 months follow-up of study participants.
Methods: CASCADE was a randomized clinical trial that assigned individuals recruited during a home-based HIV testing campaign to either the offer of same-day ART start (SD) or referral to a nearby clinic for preparatory counseling and ART start after ≥2 pre-ART clinic visits (UC). Consenting ART-naïve, HIV-infected individuals, ≥18 years, were enrolled. Methods and 12 month results were published previously (Labhardt et al. JAMA. 2018;319(11):1103). At 12 months those not active in care were traced by health workers and encouraged to return to care. At 24 months (range 22-28 months), engagement in care, viral suppression (<100 copies/mL) and reasons for disengagement were assessed among all trial participants. Trial registration: NCT02692027
Results: The care cascade and the status of patients at 24 months are displayed in Figure 1. Of 274 individuals randomized (137 SD, 137 UC), 64% (87/137) in the SD and 48% (66/137) in the UC group were active in care 12 months after testing positive (p=0.011), and 50.4% (69/137) vs 34.3% (47/137) had documented viral suppression (p=0.007). At 24 months, 64% (88/137) in the SD versus 59% (81/137) in the UC arm were in care (p=0.38) and 57% (78/137) vs 54% (74/137) had documented viral suppression (p=0.28). Among those active in care at 12 months, 11% (10/87) and 9% (6/66) were no longer in care at 24 months (p=0.63). Among those not in care at 24 months, 31% (15/49) and 38% (21/56) had been found through tracing but refused care. Most cited reasons were disbelieving in diagnosis/ART (N=6), discomfort taking medication (5), rejection of any contact with health system (4) and perceived ill-treatment by health professionals (3).
Conclusion: After tracing of all participants not in care at 12 months, a significant difference was no longer observed between the SD and the UC arm regarding viral suppression and engagement in care at the 24-month follow-up. Both arms remained below the targeted 90% of people living with HIV receiving ART. One third of those not in care refused attending.



1026 ACCESS TO HIV CARE CORRELATES WITH DEPRESSION SEVERITY AND RATES OF VIRAL SUPPRESSION

Ann K. Avery[1], Mallika Lavakumar[1], Allison R. Webel[2], James Alsop[3], Doug Gunlzer[1], Diana Gurley[1], Steven Lewis[1]
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Background: Depression is among the most common, yet unaddressed, problems identified in people living with HIV (PLWH). Under-diagnosis and under-treatment of depression in PLWH contributes to negative health outcomes. The collaborative care model (CCM) has been shown to improve both depression outcomes and co-morbid medical outcomes in primary care but there is limited data on its use in HIV care settings. The CCM includes routine screening for depression with the PHQ-9, measurement-based care and care management for all patients scoring >=10. Using an implementation science framework, we rolled out the CCM in our HIV clinic from June 2015 -June 2016.
Methods: All patients with PHQ screening data were included. Patients with any score >= 10 entered the CCM. Data from June 2015 - Dec 2017 were analyzed to identify factors associated with greater severity of depressive symptoms at initial presentation. A multiple linear regression model was used to regress first PHQ-9 score for patients in CCM on a set of demographic, clinical, access-related characteristics to determine correlates of depression at baseline. A generalized estimating equations approach was used to evaluate if subjects in CCM compared to subjects not in CCM had higher HIV viral suppression over the subsequent 12 months after initial presentation.
Results: 1473 patients were screened for depression between 6/29/15 and 12/31/17; 594 reported moderate to severe symptoms at least once (PHQ-9 >= 10). Patients who did not have a viral load documented in the year prior to the initial PHQ-9 score reported more severe depressive symptoms than those who had a viral load collected in the year prior (p=.004). Additionally, compared to patients with Medicaid, patients who were uninsured had more severe symptoms (p=.0003), while Medicare recipients reported less severe symptoms (p=.0393). The GEE approach did not demonstrate differences in achieving viral suppression over time between groups. However, the CCM group were 34% less likely to be virally suppressed at first PHQ-9 (OR 0.66 CI 0.52, 0.84). Additionally, patients in CCM but did not follow up for re-measurement within 1 year (n=180) were 65% less likely to be virally suppressed at first PHQ-9 compared to patients who never reported depressive symptoms (OR 0.35 CI 0.19, 0.64).
Conclusion: Depressive symptoms were present in 1/3 of patients; interventions to engage PLWH reporting depressive symptoms should be given priority in efforts to improve HIV viral suppression rates.

1027 FACILITATED LINKAGE TO CARE FOLLOWING HOME-BASED HIV TESTING IN RURAL SOUTH AFRICA

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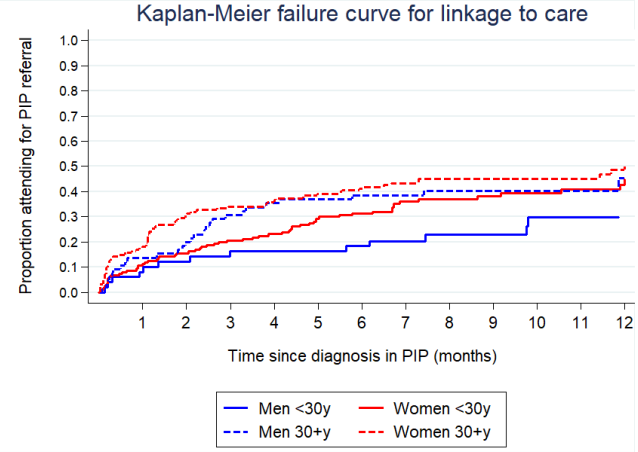
[1]London School of Hygiene & Tropical Medicine, London, UK, [2]Africa Health Research Institute, Mtubatuba, South Africa, [3]Heidelberg University, Heidelberg, Germany, [4]Brighton and Sussex Medical School, Brighton, UK, [5]University College London, London, UK

Background: South Africa has the largest HIV treatment programme globally, with 7 million people living with HIV and 4 million on antiretroviral therapy (ART). However, HIV incidence remains high, particularly among young women. In addition, persistent excess HIV-related mortality in men compared with women suggests that reaching men and young women with HIV testing and ART for those who test positive is a priority for HIV prevention. South Africa introduced universal test-and-treat (UTT) in 2016. We report on linkage to HIV care after the 2017 introduction of home-based HIV counselling and testing (HBHCT) and telephone-facilitated support for linkage in a demographic surveillance area in rural KwaZulu-Natal, where antenatal clinic HIV prevalence is around 40%.

Methods: All residents aged ≥15 years(y) were eligible for HBHCT. Those who tested positive and were not in care were referred for ART at one of the 11 public-sector clinics in the surveillance area. Individuals who did not attend the clinic within 2 weeks were sent an SMS reminder; those who had not attended after a further 2 weeks were contacted by telephone by a trained nurse counsellor, to discuss their concerns and encourage them to attend the clinic. Kaplan-Meier methods were used to estimate the proportion linking to care in the first 6 and 12 months(m), stratified by age group and sex.

Results: Among the 41,815 individuals who were contacted in 2017, 26% accepted HBHCT. Uptake was higher in women than men (29% vs 20%), but similar in people aged <30y and ≥30y (27% vs 25%). 1210 (11%) tested HIV positive, of whom 783 were in care (65%). The proportion in care was higher in women than men (68% vs 52%) and in ≥30y than <30y (73% vs 48%). Of the 427 not in care, only 18% and 31% of men and women <30y, respectively, had linked to care at 6 months(m), compared with 39% and 41% of those ≥30y (Figure 1). At 12m, 30% and 45% of men and women <30y had linked to care, vs. 45% and 50% of those ≥30y.

Conclusion: Our results suggest that both uptake of HBHCT and linkage to care, despite telephone follow-up and support, was low, particularly in young men and women in this hyper-endemic HIV setting. This shows that HBHCT and telephone-facilitated linkage to care may not be sufficient to obtain the desired effects of UTT on reducing HIV incidence in young women, or reducing HIV mortality in men.



1028 PROJECT CORECT: PRELIMINARY RESULTS OF DATA TO CARE WITH CT DPH AND HIV CLINICS

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Background: A significant portion of PLWH remain incompletely engaged in care resulting in poor individual health outcomes, as well as ongoing HIV transmission. The CDC sponsored Cooperative Re-Engagement Controlled Trial (CoRECT) tests a Data to Care strategy that aims to establish a collaborative approach between health departments and HIV clinics to identify, re-engage, retain and virally suppress PLWH recently out-of-care.

Methods: The CT DPH, Yale University School of Medicine and 23 HIV clinics conducted the study. Using the DPH eHARS surveillance database and individual clinic level data, "recently out of care patients" were further investigated by clinic personnel to assess eligibility for randomization to either clinic standard of care (SOC) vs DPH field workers(DIS) who were trained to locate, assess barriers to care, and facilitate re-linkage to care within 90 days of randomization. Clinic visit status was collected and compared between DIS and SOC. Additional data on linkage status and barriers to care were collected by DIS. We report this data on patients who completed 90 days post randomization.

Results: There were 655 patients randomized: DIS (N=333) vs. SOC (N=322), of which 588 were at 90 days post randomization. Demographics showed: Black (39.80%); Hispanic (38.10%); white (20.20%); male (62.41%); age <30 (16.84%); there was no difference between DIS and SOC arms. Comparison of successful attendance at scheduled clinic visits: DIS (42.6%) vs SOC (32.3%) (p<0.001). Clinic outcomes for patients randomized to DIS showed: returned to clinic by DIS (32.83%); unable to locate (22.80%); located but refused to return to clinic (14.89%). Demographic comparison showed that those who were unable to be located by DIS were not statistically different than those successfully returned to clinic. Last viral load recorded was significantly greater for those not returned to care vs those who did return to care (p<.0001); last CD4 was lower, (p<.0001). Among those randomized to DIS with successful linkage, the most common identified barriers to care were life issues (92.5%) and mental/physical health issues (38.3%).

Conclusion: 1)The DIS intervention was successful in returning recently OOC pts to care 2)Among OOC PLWH linked by DIS, the most common barriers were "life issues" and "mental/physical health issues" 3)Patients whom DIS were unable to locate were more likely to have higher viral loads and lower CD4 counts 4)This intervention can be used to improve the HIV Care Continuum

1029 DEVELOPMENT OF AN EMR-BASED ALGORITHM TO IDENTIFY PATIENTS LOST TO HIV CARE

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Background: Ending the HIV epidemic requires optimizing primary and secondary prevention. After diagnosis, many HIV positive patients drop out of the care cascade but continue to "touch" the hospital in a variety of settings. Identifying individuals out of care in real time allows for care coordination to engage in secondary prevention efforts, reaching out for re-linkage and restarting antiretroviral therapy. We used a novel EMR based algorithm to develop a dashboard that identifies all HIV positive patients who interact with our institution as well as their linkage and viral load status.

Methods: We identified all individuals with an International Statistical Classification of Diseases (ICD) code for HIV, positive HIV antibody, HIV RNA viral load, and the date of visit in any of our clinic locations that routinely provide HIV care. We developed an algorithm to highlight patients as a potential new diagnosis, unlinked to care, unsuppressed viral load, and most recent HIV visit in the past 6 months, 9 months, or longer. To evaluate accuracy, we created a reference standard to replicate a clinician's review of the chart and performed a review on a random 20% (128) of patients identified from 8/1/18 to 9/15/18.

Results: The algorithm correctly categorized 95% of HIV positives, 86% of patient's linkage to care status, and 91% of viral load status. Causes of errors were false positive HIV screening tests, perinatal HIV exposure, and individuals documented as receiving care at an outside hospital. In the validation cohort, 8/1/18 – 9/15/18, the algorithm identified 639 patients with a diagnosis of HIV, 78% who were linked to care in the past 9 months, and 66% who were virally suppressed. Of the 22% who were not linked to care 47% (66) were not virally suppressed. Over the prior year, 9/15/2017 – 9/15/2018. the algorithm identified 2851 patients with a diagnosis of HIV, 29% of who were categorized as out of care of the past 9 months

Conclusion: Population-level HIV care cascade tools can be developed that are accurate and efficient. Our algorithm has a high accuracy for identifying HIV positive individuals and individuals not linked to care. EMR based algorithms have the potential to provide an efficient method for care coordinators, reducing their workload but still allowing them to identify HIV patients requiring services. This algorithm is generalizable and has the potential to be

transported to other EMR systems allowing for the development of electronic care cascades and dashboards.

Figure 1: (Left) All patients with a history of a positive ICD code for HIV, positive HIV Antibody test, or positive RNA are identified and can be sorted by linkage status or viral load suppression. (Right) The "Never "Linked" filter shows patients with positive HIV test without evidence of a visit to our HIV clinic, patients can be potentially prioritized for linkage by their viral load status.

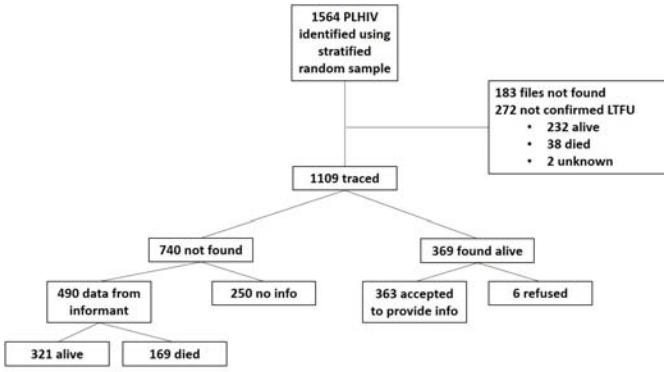

Figure 1: Flowchart indicating the outcome of people living with HIV meeting criteria for lost to follow-up and traced to find out their vital status

1030 ARE THEY REALLY LOST? MULTI-CENTER TRACING STUDY IN ART PROGRAMS IN SOUTHERN AFRICA

Benedikt Christ[1], Kathrin Zürcher[1], Frédérique Chammartin[1], Josephine Muhairwe[2], Laura Jefferys[3], Janneke van Dijk[4], Kombatende Sikombe[5], Monique van Lettow[6], Cleophas Chimbetete[7], Sam J. Phiri[8], Matthias Egger[1], Marie Ballif[1]
[1]Institute of Social and Preventive Medicine, Bern, Switzerland, [2]SolidarMed, Maseru, Lesotho, [3]SolidarMed, Pemba, Mozambique, [4]SolidarMed, Masvingo, Zimbabwe, [5]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, [6]Dignitas International, Zomba, Malawi, [7]Newlands Clinic, Harare, Zimbabwe, [8]Lighthouse Trust Clinic, Lilongwe, Malawi

Background: Low retention on antiretroviral therapy (ART) is a threat to the UNAIDS 90-90-90 targets. We studied outcomes of people living with HIV (PLHIV) on ART but lost to follow-up (LTFU) in Southern Africa.
Methods: We traced patients defined as LTFU (>90 days after a missed visit) using a common protocol in 6 ART programs of the International epidemiology Databases to Evaluate AIDS (IeDEA): Malawi (2 sites), Zimbabwe (2 sites), Lesotho and Mozambique. We randomly sampled PLHIV lost at each site, stratifying for age, sex and time on ART. Tracing consisted of text messages (one attempt), phone calls (max. 3 attempts) and/or home visits (max. 3 attempts). We used descriptive statistics and univariate logistic regressions to assess predictors for mortality.
Results: We included 1564 patients LTFU: 435 in Lesotho, 381 in Malawi, 408 in Mozambique and 340 in Zimbabwe. Median age at tracing was 35 years (interquartile range [IQR]: 26-46), 57% were female and 81% from rural clinics. Last median CD4 count was 392 cells/µl (IQR: 226-594, available for 741 [47%] PLHIV), median time on ART was 33 months (IQR: 21-47). Checking patients' files clarified vital status in 272 (17%) cases, without need for tracing. No file was found in 183 (12%) cases. Among 1109 patients traced, 369 (33%) were found after a mean of 1.4 attempts (range 1-5); 11% of patients were traced by phone calls, 71% by home visits and 17% by both. Text messages were only used for <1%. The remaining 67% were either not found (250; 34%) or their status was obtained from other informants (490; 66%; Fig. 1). Overall, 922 (59%) PLHIV were alive, 207 (13%) had died and in 435 (28%) cases, vital status remained unclear. Among those alive, 225 (24%) had never missed a visit or returned to care at the same clinic, 368 (40%) had transferred to another clinic (218 silently), 233 (25%) stopped taking ART and there are no details available for 97 (11%). Predictors for mortality were age ≤15 (odds ratio [OR] 1.9, 95% CI 1.2-3.1) and >50 (OR 3.4, 95% CI 2.2-5.1) compared to 26-50 years, LTFU for >1 year compared to ≤1 year (OR 2.7, 95% CI 1.3-5.7), WHO stages 3&4 compared to stages 1&2 (OR 3.4, 95% CI 2.2-5.1), and last CD4 count <200 compared to ≥200 cells/µL (OR 2.1, 95% CI 1.2-3.8).
Conclusion: Most PLHIV defined as LTFU were found alive and in care. Tracing remains necessary in most instances but needs improvement to locate all PLHIV lost. Better ways to inform health systems and novel approaches to follow up PLHIV are needed in the treat-all era.

1031 HEALTH DEPARTMENT RANDOMIZED TRIAL TO RE-ENGAGE OUT-OF-CARE HIV INFECTED PERSONS

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Background: Over a quarter of persons living with HIV in the United States do not receive care, and most transmissions of HIV come from persons known to be infected but not in care. We implemented a data-to-care model using health departments and local clinics to identify out-of-care (OOC) HIV-infected individuals with the objective of increasing the number of such persons re-engaged, retained in medical care, and achieving viral load suppression.
Methods: Criteria for inclusion were age ≥18, and in care at a trial clinic during a 12-month eligibility period followed by no evidence of care in ≥ 6 months (i.e., no visit or labs). OOC was determined by HIV surveillance and clinic data from three jurisdictions: Connecticut (CT), Massachusetts (MA) and Philadelphia (PHI). All patients deemed OOC were randomized to receive standard engagement in care (SOC) services from the trial clinic or an active public health field services intervention. Re-engagement in care was defined as linking to a trial clinic within 90 days of randomization, as determined by HIV surveillance data. Each jurisdiction was analyzed separately as interventions and services varied by health department. Chi-square tests were performed and a p-value <0.05 was considered statistically significant.
Results: Between 8/16/2016 and 7/31/2018, a total of 533 (CT), 591 (MA), and 609 (PHI) OOC HIV-infected persons were enrolled and had ≥ 90 days since date of randomization. Among all sites 64%-76% were born male, 38%-66% were non-Hispanic black, 55%-69% were aged ≥ 40 years, and 44%-62% were diagnosed with HIV ≥ 10 years. In CT, 222 (41.7%) re-engaged in care ≤ 90 days [118 (46.3%) in intervention vs 104 (37.4%) in SOC, P=0.038]; in MA, 285 (48.2%) re-engaged in care ≤ 90 days [153 (51.2%) in intervention vs 132 (44.9%) in SOC, P=0.108]; and in PHI 306 (50.2%) re-engaged in care ≤ 90 days [181 (58.6%) in intervention vs 125 (41.7%) in SOC, P<0.0001]. The median times to re-engagement in care for intervention vs SOC arms were: 37 and 48 days (p=0.011) in CT, 38 and 42 days (0.329) in MA and 29 and 45 days (p<0.001) in PHI, respectively.
Conclusion: This randomized controlled trial showed that a collaborative data-to-care model and field services intervention increased the proportion of persons re-engaged in care in two jurisdictions and decreased the time to re-engagement in all three. Health department interventions can improve re-engagement in care among HIV-infected persons who are out of care.

Table 1: Demographics and Proportion of out-of-care HIV-infected persons who re-engaged with HIV medical care within 90 days by randomization group— August 2016- July 2018

VARIABLE	INTERVENTION GROUP n (%)	CONTROL GROUP n (%)	TOTAL n (%)	*p* value†
DEMOGRAPHICS				
Connecticut (n=567)				
Male [a]	162 (63.5%)	165 (59.3%)	327 (61.3%)	0.3225
Non-Hispanic black	96 (37.6%)	123 (44.2%)	219 (41.1%)	0.3329
Age ≥ 40 years	177 (69.4%)	178 (64.0%)	355 (66.6%)	0.3997
HIV diagnosis ≥10 years	158 (62.0%)	162 (58.3%)	320 (60.0%)	0.8079
Massachusetts (n=591)				
Male	213 (71.7%)	219 (74.5%)	432 (73.1%)	0.4473
Non-Hispanic black	123 (41.4%)	107 (36.4%)	230 (38.9%)	0.6093
Age ≥ 40 years	192 (64.6%)	191 (65.4%)	383 (65.0%)	0.9732
HIV diagnosis ≥10 years	152 (51.2%)	159 (54.1%)	311 (52.6%)	0.3116
Philadelphia (n=609)				
Male	235 (76.1%)	215 (71.7%)	450 (73.9%)	0.2180
Non-Hispanic black	204 (66.0%)	196 (65.3%)	400 (65.3%)	0.7255
Age ≥ 40 years	171 (55.3%)	166 (55.3%)	337 (55.3%)	0.2493
HIV diagnosis ≥10 years	136 (44.0%)	151 (50.3%)	287 (47.1%)	0.3646
OUTCOME Link to HIV clinic ≤90 days				
Connecticut				
YES	118 (46.3%)	104 (37.4%)	222 (41.7%)	
NO	137 (53.7%)	174 (62.6%)	311 (58.3%)	0.038
Massachusetts				
YES	153 (51.5%)	132 (44.9%)	285 (48.2%)	
NO	144 (48.5%)	162 (55.1%)	306 (51.8%)	0.108
Philadelphia				
YES	181 (58.6%)	125 (41.7%)	306 (50.2%)	
NO	128 (41.4%)	175 (58.3%)	303 (49.8%)	<0.0001

†Chi-Square tests were conducted to assess differences of overall demographic variable by intervention group.

1032 PATTERNS AND PREDICTORS OF RETURN TO CARE AMONG DISENGAGED HIV PATIENTS IN ZAMBIA

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Background: Loss to follow-up from HIV treatment has been widely documented, but re-engagement in care – a critical dimension of long-term success – has not been examined closely. To inform interventions to reduce treatment interruptions, we sought to characterize re-engagement after peer-tracing and predictors of return.

Methods: We traced a stratified, random sample of patients from 64 Zambian health facilities who had at least one facility visit between 1st August 2013 – 31st July 2015 but were lost to follow-up, defined as an unknown care status and >90 days from last visit. Among patients reporting disengagement, tracers encouraged return to care and administered a survey recording potential return predictors: reasons for disengagement, internalized and anticipated stigma, household violence, alcohol use, past retention support, wealth, role in household, mobility, disclosure, marital status, education, proximity to facility, and requirements for return. Using electronic medical records (EMR) linked by patient identification number, we extracted visit dates subsequent to tracing to estimate the proportion with a return visit, demographic characteristics, and HIV and ART history. We used Kaplan-Meier methods to estimate cumulative incidence of return and Cox proportional hazards models to identify predictors of return. A combination of theory and univariate association significance was applied to determine the final model.

Results: Of the 2,769 'lost' patients traced, 603 reported disengagement, 571 had follow-up EMR visit data, and 38.0% (95%CI: 33.7-42.7) had a return visit by the end of the study. Median follow up time was 595 days (IQR: 214-667, max: 836). Proportions returning at 30, 180, and 365 days were: 11.2% (95%CI: 8.9-14.1); 24.5% (95%CI: 21.2-28.3); and 29.4% (95%CI: 25.9-33.4). Significant predictors of care included age >50 years (aHR: 1.89, 95%CI: 1.04-3.46, p=0.04) and reporting the most stigma (aHR: 1.73, 95%CI: 1.06-2.83, p=0.03) with residence in facility catchment suggestive of increased return (aHR:1.37, 95%CI: 1.00-1.89, p=0.05). Getting care at a hospital was associated with a reduced hazard of return (aHR: 0.55, 95%CI: 0.35-0.86, p=0.01) (Table 1).

Conclusion: Despite in-person peer educator tracing and encouragement to return, fewer than half of disengaged patients did so. Interventions which improve facility access and target young people may reduce treatment interruptions. New approaches to facilitate re-engagement and improve HIV program success should be explored.

Table 1. Predictors of re-engagement in HIV care or treatment among disengaged, traced patients living with HIV in Zambia

Characteristic		Adjusted^ Hazard Ratio	95% CI		p-value
Gender	Female	1.00			
	Male	1.07	0.79	1.44	0.66
Age	18-30 years	1.00			
	31-40 years	0.98	0.69	1.38	0.89
	41-50 years	1.33	0.86	2.04	0.20
	>50 years	1.89	1.04	3.46	0.04*
Time out of care	Time from last visit to tracer interaction (per month)	0.99	0.96	1.01	0.25
Residence in facility catchment	No	1.00			
	Yes	1.37	1.00	1.89	0.05
Spent >1 month away from usual residence in past year	No	1.00			
	Yes	0.89	0.66	1.20	0.43
Wealth quintile	Poorest	1.00			
	Poorer	1.04	0.67	1.60	0.88
	Middle	0.98	0.62	1.55	0.93
	Richer	0.79	0.49	1.28	0.34
	Richest	0.71	0.42	1.22	0.22
Facility type	rural	1.00			
	urban	0.81	0.57	1.16	0.26
	hospital	0.55	0.35	0.86	0.01*
Stigma	None	1.00			
	Some	1.48	0.94	2.34	0.09
	Most	1.73	1.06	2.83	0.03*
Something psychosocial needs to change for return	No	1.00			
	Yes	0.74	0.51	1.07	0.11

*signifiant at p<0.05

1033 LONG-TERM OUTCOME IN HIV-1 INFECTED ADULTS WITH ADVANCED IMMUNODEFICIENCY

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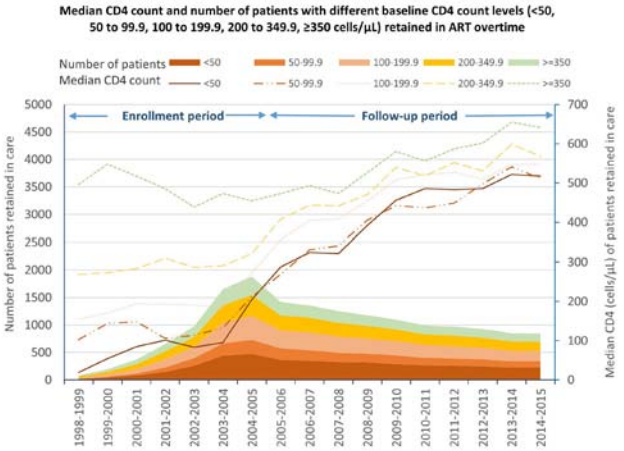
Background: Prior to the President's Emergency Plan for AIDS Relief (PEPFAR) Program, patients initiating antiretroviral treatment (ART) in resource-limited settings frequently had very advanced immunodeficiency. In this study, we examined CD4 cell count recovery and viral suppression among patients with very low baseline CD4 count in Côte d'Ivoire.

Methods: We identified 1,883 HIV-1-infected adults who initiated ART at clinics in Abidjan between August 1, 1998 and July 31, 2004 and had follow-up data between August 1, 2004 and July 31, 2015. Among them, 474 had CD4 cell count less than 50 cells/μL at ART initiation. We retrospectively analyzed baseline CD4 count, CD4 recovery, and viral suppression data collected from patient laboratory records (1998-2015) in the CDC Projet Rétrovirus Côte d'Ivoire (RETRO-CI) laboratory information system.

Results: After 10 years of follow-up, 231 of 474 patients (48.7%, 95% confidence interval [CI]: 44.3%-53.2%) with baseline CD4 count less than 50 cells/μL remained in care at the end of the study period, between August 2014 and July 2015. Their CD4 cell count increased from a median of 18.9 cells/μL at baseline to 517.5 cells/μL, with a sharp increase from 95.4 to 456.0 cells/μL occurring during the first six years of PEPFAR in the country (2004-2010). At their last visit, 50.6% of them had a CD4 count over 500 cells/μL, the proportion was comparable to that of patients with higher baseline CD4 counts of 50-99.9, 100-199.9, and 200-349.9 cells/μL, but was lower than that of patients with baseline CD4 count over 350 cells/μL (Bonferroni-adjusted P values <0.01). Logistic regression (adjusted for age and year of ART initiation) showed that females were more likely to achieve CD4 recovery (adjusted odds ratio is 2.56, 95% CI: 1.76-3.72). Among the 231 patients, 58.0% (n=134) had viral load (VL) results recorded between August 2014 and July 2015, and 87.3% (117/134) of them had

VL less than 1000 copies/mL. No significant difference in viral suppression at their last visit was detected between patients with baseline CD4 count less than 50 cells/μL and those with baseline CD4 counts of 50-99.9, 100-199.9, 200-349.9, or ≥350 cells/μL.

Conclusion: These findings showed that patients with very advanced immunodeficiency have equivalent capacity for immunologic recovery and viral suppression compared to those with higher baseline CD4 cell counts, if they are retained in care.



1034 PREVALENCE AND CORRELATES OF NONENROLLMENT IN HIV CARE, CHÓKWÈ DISTRICT, MOZAMBIQUE

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Background: HIV care and treatment is expanding in Mozambique and implementation of a national 'Test and Start' treatment program began in 2016. However, non-enrollment remains a barrier to epidemic control. To inform interventions to increase enrollment, we evaluated the prevalence and sociodemographic and behavioral correlates of non-enrollment in Chókwè District, Mozambique.

Methods: Data were sourced from a cross-sectional survey conducted annually in Chókwè District during 2014–2017, with participants aged 15–59 identified via a household demographic surveillance system (HDSS). We analyzed data from participants who reported ever having received a positive HIV test. If surveyed in multiple years, data from first survey were analyzed. The 2013 HDSS census estimates were used to weight by age, sex, and urban residence distributions. We calculated the prevalence of and reasons for non-enrollment. Logistic regression was used to calculate adjusted odds ratios (aOR) and 95% confidence intervals (CI) of the association between sociodemographic and behavioral variables and non-enrollment in HIV care, adjusting for intra-household sampling.

Results: Of 2,654 participants who reported ever having received a positive HIV test, 127 (5.3%) had not enrolled in HIV care. There was no difference in non-enrollment after district-wide implementation of Test and Start. Most frequently cited reasons for non-enrollment were did not need care due to good health status (33/126; 27.1%) and did not believe they had HIV (7/126; 7.6%). Participants who first tested positive since 2013 and those who received their first positive test <2 years had increased odds of non-enrollment (p=0.02 and p=0.002, respectively). Compared to testing at a district healthcare facility, testing positive at home had increased odds of non-enrollment (aOR: 3.92, 95% CI: 2.39, 6.45). HIV status nondisclosure was associated with non-enrollment (aOR: 6.15, 95% CI: 3.79, 10.00). Among participants who first tested positive ≤1 year , those who did not meet with someone to help them enroll in care had increased odds of non-enrollment (aOR: 4.60, 95% CI: 1.94, 10.93).

Conclusion: Obstacles to enrollment reflect the importance of accurate health messaging, strong social support, and prompt clinical linkage to care, regardless where HIV testing occurs. Enhanced patient advocacy and case management, particularly for newly-diagnosed cases, are needed to increase initiation of HIV care.

Table. Demographic and behavioral risk factors associated with non-enrollment in HIV care in Chókwè District, Mozambique, 2014–2017 (N=2,654).

Characteristic	Unadjusted OR	(95% CI)	p	Adjusted OR*	(95% CI)	p
Nondisclosure of HIV status	7.10	(4.56, 11.06)	<0.001	6.15	(3.79, 10.00)	<0.001
Last place tested for HIV†						
Health facility in Chókwè district	1.00	(Ref)		1.00	(Ref)	
Home in Chókwè district	5.47	(3.42, 8.74)	<0.001	3.92	(2.39, 6.45)	<0.001
Other location	1.33	(0.60, 2.93)	0.13	1.43	(0.53, 3.85)	0.50
Received first positive HIV test since 2013‡	7.32	(3.56, 15.07)	<0.001	2.85	(1.20, 6.79)	0.02
<2 years since first positive HIV test	5.24	(3.22, 8.54)	<0.001	2.38	(1.39, 4.09)	0.002

*All models are adjusted for number of sexual partners in the last 12 months (0, 1, or 2) and time since first tested positive (<2 years vs. ≥2 years).
†Model additionally adjusted for the year of the first positive test (before or since 2013).
‡Model additionally adjusted for the last place tested for HIV.

1035 HIV TREATMENT CASCADE AMONG MEN WHO HAVE SEX WITH MEN IN KIGALI, RWANDA

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Background: Men who have sex with men (MSM) have high HIV acquisition and transmission risk globally and are defined as a key population in the Rwanda national strategic plan. However, there are no published HIV epidemiological data among MSM in Rwanda. In this study, we characterize MSM engagement in HIV treatment cascade in Kigali, Rwanda.

Methods: MSM > 18 years were recruited in a cross-sectional behavioral and biological survey using respondent driven sampling (RDS) between March – July 2018 in Kigali, Rwanda. Data on socio-demographic characteristics, sexual behavior and engagement in HIV services were collected using an interviewer-administered structured questionnaire. HIV infection and viral load were biologically assessed. We used a cascade framework to characterize engagement in HIV care continuum.

Results: Overall, 736 eligible MSM were recruited in the study. The median age was 27 [range:18-68]. The HIV prevalence was 10.1% (74/736) [RDS adjusted prevalence: 9.2%; 95% CI: (6.4-12.1)]. Of the participants found to be living with HIV, only 61% (45/74) reported that they knew their HIV status before enrollment. Higher age (> 35 years) was significantly associated with both HIV positive status ($p < 0.01$) and knowing HIV diagnosis prior to enrollment ($p< 0.05$). Of MSM who knew their HIV positive status, 98% (44/45) reported to be on ART and 75% (33/44) were virally suppressed. Overall, we estimated that among the total population of MSM living with HIV in Kigali, 61% know their status, 59% are on ART and 59 % are virally suppressed. This represents gaps of 29%, 22% and 14% respectively to reach the 90-90-90 target in the MSM population in Kigali

Conclusion: Taken together, these data demonstrate high HIV prevalence with suboptimal engagement in HIV treatment services among particularly young MSM in Rwanda. A quarter of those reporting ART were viremic suggesting the need for improved retention and adherence programing in addition to screening for HIV-drug resistance. Given the challenges in addressing the needs of young MSM, interventions leveraging emerging technologies and social media in addressing engagement and retention may be particularly effective in Rwanda.

1036 LONGITUDINAL HIV CARE TRAJECTORIES IN THE CNICS COHORT: A RETROSPECTIVE COHORT STUDY

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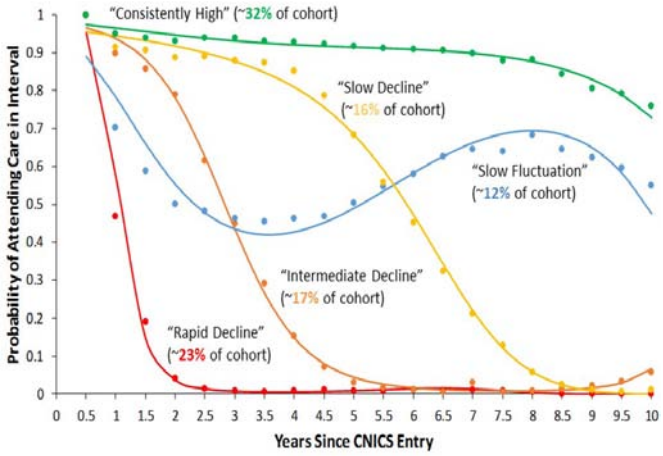
Background: Long-term HIV care engagement is required for optimal clinical and prevention outcomes, but longitudinal patterns of HIV care attendance are poorly understood. Identification of distinct longitudinal trajectories of

HIV care, along with predictors thereof, could inform the design of tailored interventions for improving HIV care engagement. We used visit data from the eight-site CFAR Network of Integrated Clinical Systems (CNICS) to examine patterns and predictors of HIV care attendance over a ten-year period.
Methods: We conducted a retrospective cohort study of all adults newly entering CNICS between January 1, 2005 and December 31, 2015 (N=18,160), following them longitudinally until death, ten years, or March 22, 2018. Our outcome was HIV primary care visit attendance (yes/no) in each six-month interval after CNICS entry. We used group-based trajectory modeling to: 1) identify a set of longitudinal HIV care patterns followed from the time of CNICS entry, and 2) examine associations between each pattern and race/ethnicity, age at entry, and transmission risk group. We tested models with 2-7 trajectory groups and selected the final model based on the Bayesian Information Criterion.
Results: We identified five distinct HIV care trajectories (Figure): ~32% of patients had consistently high care attendance over time (>75% probability of attendance in each interval); ~23% exhibited a rapid decline within two years to a sustained, low probability (<5%) of attendance; ~16% showed a very slow decline in attendance; ~17% had an intermediate rate of decline; and ~12% showed a slowly fluctuating pattern that started with a decrease but shifted to an increase starting ~three years after entry. Older age at entry was protective against all sub-optimal trajectories (with the "consistently high" pattern as referent): odds ratios per five-year age increase ranged from 0.79 (95% confidence interval: 0.77-0.81) for the "slow fluctuation" group to 0.86 (0.84-0.88) for the "intermediate decline" group. Race/ethnicity and transmission risk group had mixed associations with care patterns.
Conclusion: Most new CNICS entrants exhibited sub-optimal HIV care trajectories, but there was wide variation in the longitudinal pathways followed. By identifying heterogeneous care engagement patterns and predictors thereof, this analytical approach allows improved understanding of HIV care engagement over time for designing tailored interventions and refined models of the HIV care continuum.



1037 CALL FOR LIFE UGANDA TM: AN RCT USING INTERACTIVE VOICE RESPONSE FOR PLHIV ON ART

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Background: The WHO recommends use of mobile phone health technologies (mHealth) to support adherence in HIV. Studies on text messages show promise but with limited rigorous evaluations. The Call for Life UgandaTM (CfLU) study is a randomized controlled trial (RCT) using an interactive voice response (IVR) calls system designed to support PLHIV on ART. The primary study objective was to determine the effect of CfLU on quality of life (QOL) of people living with HIV (PLHIV) in Uganda.
Methods: MOTECH software-based Connect for LifeTM (Janssen, Johnson & Johnson) was adapted for Ugandan setting, with the Infectious Diseases Institute. The participants were randomized 1:1 to receive either CfLU or standard of care (SoC-clinic visits only). In English or 2 local languages, the CfLU arm received daily/weekly pill reminder calls or SMS messages, visit reminders, health information advice and symptom reporting. At 6, 12 and 24 months of follow up QOL assessments (HIV Medical Outcomes Survey, MOS-HIV including physical health score [PHS] and mental health score [MHS]) were done using Likert-type scale with difference in differences analysis and analysis of covariance (ANCOVA). Qualitative and tool use data also collected. Data from 6m are presented here.
Results: Between August 2016 and February 2018 across 2 sites, 1031 PLHIV accessing care were screened and 600 enrolled on the study (n=300/site). Sixty-nine percent were female and median age was 32 (IQR25-40). Eight four participants were ART naïve, remaining ART experienced. At baseline, 97% chose IVR over SMS. There was no difference in arms for education level, marital & employment status, previous TB or alcohol use. 277 in each arm attended at 6m. There is no statistical observed difference in mean percentage score of MOS-HIV, MHS and PHS at baseline and 6m between CfLU and SoC arms. In those starting first line ART or switching to second line, there was a significant improvement in PHS (ANCOVA 4.01, p=0.048). There was no significant difference between CfLU versus the SoC in the proportion of patients with viral load <50 copies at 6m (21% vs 18%: p-value=0.372).
Conclusion: This is the first RCT for PLHIV on ART incorporating options for IVR and SMS options; strong preference was shown for IVR over SMS. In this mixed group of patients, there was no statistical effect of CfLU observed on QOL at 6m. Within this study, a higher than expected baseline QOL and virological suppression was encountered for both sites which may have affected results.

Mean percentage scores of MOS-HIV, MHS and PHS by arm and site (Baseline to month 6 follow-up).

Outcome variable	BASE LINE			FOLLOW UP			DID		ANCOVA ANALYSIS	
	I (Mean)	S (Mean)	Diff (I-S)	I (Mean)	S (Mean)	Diff (I-S)	DID	P value**	F-value	p-value[$]
MOS-HIV										
Over all	85.5	85.6	-0.1	88.5	88.7	-0.2	-0.2	0.858	0.18	0.669
MHS	86.4	86.7	-0.3	90.1	89.8	0.3	0.6	0.568	0.48	0.488
PHS	86.7	86.8	-0.1	90.2	90.9	-0.7	-0.6	0.633	0.87	0.351

1038 HIV CARE CONTINUUM CHANGES AMONG PWID AND MSM IN INDIA: A TALE OF 2 KEY POPULATIONS

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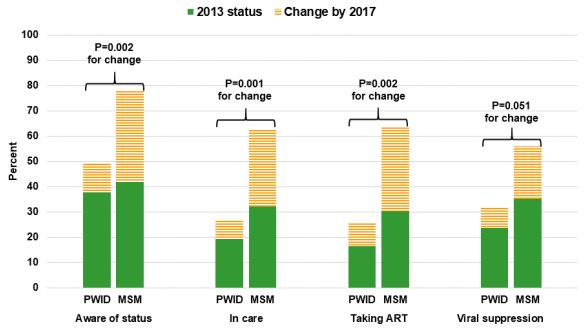
Background: Key populations account for the substantial majority of people living with HIV outside of sub-Saharan Africa. Advancing the HIV care continuum among key populations is necessary, particularly in low- and middle-income countries, to reach the UNAIDS HIV treatment goals. We present longitudinal changes in the HIV care continuum among PWID and MSM across multiple cities in India.
Methods: This is a secondary analysis of data collected in a cluster-randomized trial of an integrated care intervention to improve HIV outcomes among key populations in India. The study included 12 PWID sites and 10 MSM sites. We conducted baseline (2013) and follow-up (2017) respondent-driven sampling surveys of ~1000 participants in each of the 22 sites. We tested participants for HIV and measured HIV RNA and CD4 cell counts in HIV-positive participants. We used sampling-weighted estimates and linear regression to compare baseline and site-level changes in HIV continuum outcomes in PWID and MSM sites, controlling for outcome prevalence at baseline and study arm assignment.
Results: In the baseline survey, we recruited 11,993 PWID (2,544 HIV-positive) and 9,997 MSM (1,086 HIV-positive) participants. In the follow-up survey, approximately 4 years later, we recruited 11,721 PWID (2517 HIV-positive) and 10,005 MSM (1763 HIV-positive) participants. The intervention was not significantly associated with changes in care continuum outcomes. At baseline,

HIV-positive MSM were nominally (although not significantly) more likely than PWID to meet care continuum benchmarks, including awareness of status, HIV care received in prior 6 months, ART use, and suppressed viral load (HIV RNA <150 c/mL). Although care continuum outcomes increased over the next 4 years in both groups, the increases were markedly larger for MSM than PWID (Figure). For example, the increase in those reporting HIV care in the prior 6 months was 32 percentage points (95% CI: 16, 48) higher in MSM than PWID sites, and the increase in viral suppression was 15 percentage points (95% CI: 0, 31) higher in MSM than PWID sites.

Conclusion: In serial large population surveys across 22 sites in India, we found that HIV-positive MSM had substantially larger improvements in care continuum outcomes 4 years later compared with HIV-positive PWID. This highlights the value of high-quality HIV treatment surveillance data to target resources for key populations effectively.



1039 HIV OUTCOMES AMONG TRANSGENDER MEN IN HRSA'S RYAN WHITE HIV/AIDS PROGRAM, 2010-2016

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Background: Transgender men living with HIV have been underrepresented in HIV studies in the United States, yet many social, behavioral, and systemic determinants of health act as barriers to care and successful treatment of HIV. The Health Resources and Services Administration's (HRSA) Ryan White HIV/AIDS Program (RWHAP) supports direct medical and support services to uninsured and underserved people living with HIV (PLWH) and is uniquely situated to address these health determinants. This analysis examines sociodemographic and clinical information among transgender men receiving RWHAP services during 2010–2016. This study serves as the first focused analysis on transgender men using a national dataset of PLWH receiving care through the RWHAP in the United States.

Methods: Data from the RWHAP Services Report submitted to HRSA by RWHAP Parts A-D recipients were used to identify transgender men aged ≥13 years who received RWHAP services during 2010-2016. A 2-step method was used to calculate current gender, including sex assigned at birth and current gender identity. Sociodemographic characteristics, clinical information, HIV-related outcomes, and service utilization were examined during 2010-2016.

Results: The number of transgender men served by RWHAP increased from 161 in 2010 to 430 in 2016. In 2016, these clients accounted for 0.08% of all RWHAP clients and 6.0% of transgender clients. Among transgender men in 2016, 81.8% were racial/ethnic minorities, 59.7% were living at or below poverty, 10.2% had unstable housing, and 12.0% had no health care coverage. Clinical data for those receiving medical care in 2010-2016 (approximately two-thirds of total transgender men) showed viral suppression increased from 49.1% in 2010 to 84.1% in 2016. In addition in 2016, 91.4% were prescribed ART and 5.5% had a CD4 count <200 cells/μL at last test. Other services frequently accessed included medical case management (43.2%), mental health services (22.9%), and non-medical case management (14.3%).

Conclusion: Although they represent a small proportion of RWHAP clients, transgender men have unique healthcare needs. High proportions of these clients have unstable housing and access mental health services, both of which have been associated with poorer HIV-related health outcomes. Despite these challenges, transgender men are receiving ART and achieving viral suppression similar to the general RWHAP medical population.

1040 ENGAGEMENT IN CARE OF HIGH-RISK PATIENTS AT AN URBAN HIV PRIMARY CARE CENTER

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Background: Socioeconomic and behavioral factors are associated with poor engagement in HIV care (EIC) and lower rates of viral suppression (VLS) among persons with HIV. Our agency participated in a multidisciplinary care coordination intervention designed to address these disparities as part of New York City's Ryan White Part A HIV Care Coordination Program (CCP). In this study, we describe our experience with CCP in our hospital-based HIV center, which provides comprehensive HIV primary care with co-located mental health services to a predominantly poor, minority, and immigrant population.

Methods: Clients were eligible for CCP enrollment if they were newly diagnosed with HIV or met criteria for poor EIC. All were paired with a dedicated field navigator and received patient-centered care coordination, health promotion, and outreach services. This study includes all CCP participants enrolled between January 2013 and December 2016. Univariate and multivariate regression were used to evaluate the association between patient characteristics and CCP activities on VLS and EIC.

Results: 241 CCP clients were enrolled from 2013-2016. Factors significantly associated with VLS at 12 months include: EIC ($p < 0.05$), VLS at enrollment ($p = 0$), respiratory disease ($p < 0.01$), cardiovascular disease ($p < 0.06$), and mental illness ($p < 0.09$). In the multivariate model, EIC (OR 2.57, CI 0.29-0.81, p<0.01) and VLS at enrollment (OR 2.41, CI 0.32–1.04, p<.01) remained significant. Univariate analyses showed that new diagnosis ($p < 0.02$), engagement in psychiatric care ($p = 0$), VLS at 12 months ($p < 0.05$), malignancy ($p < 0.08$), serious mental illness (bipolar disorder and/or schizophrenia; $p = 0$), substance use ($p < 0.08$), and homelessness ($p = 0$) were associated with EIC. In a multivariate model, new diagnosis (OR 4.01, CI 1.26-1.24, p<0.02), VLS at 12 months (OR 2.32, CI 1.25-12.71, p<0.01), and mental illness (OR 2.59, CI 1.42-4.7, p<0.01) remained significant.

Conclusion: Despite intensive interventions, rates of VLS at 12 months and EIC among CCP clients remained below 90%. Disproportionately high rates of mental illness and substance abuse are likely playing in a role in this finding. However, mental illness was significantly positively associated with EIC which suggests that co-location of mental health services has had significant impact on key HIV outcomes. This suggests that additional embedded behavioral health resources are needed to address the complex psychosocial needs of people living with HIV.

Table 1: Multivariate models of Demographic and Clinical Characteristics of all CCP patients with respect to viral load suppression at 12 months (1a) and engagement in care (1b)

(1a)	Odds Ratio (95% CI)	p value
Engagement in Care[1]	2.57 (.29 - 0.81)	0.01
VLS at enrollment[2]	2.41 (1.30 - 4.54)	0
Respiratory disease[3]	0.58 (0.32 - 1.04)	0.06
Serious Mental Illness[4]	1.42 (0.79 - 2.58)	0.24

(1b)	Odds Ratio (95% CI)	p value
New Diagnosis[5]	4.01 (1.26 - 1.24)	0.02
VLS at 12 months[6]	2.32 (1.25 - 12.71)	0
Substance Use	0.67 (0.38 - 1.17)	0.43
Serious Mental Illness[4]	2.59 (1.42 - 4.7)	0

[1] Engagement in care (EIC) is defined as two medical primary care visits, one in the first six months prior to enrollment and one in the second six months post enrollment, with these visits being 90 days apart.
[2] Viral suppression (VLS) at enrollment was defined as the most recent VL at any time prior to enrollment being <200 c/mL.
[3] Respiratory disease defined as asthma and/or COPD
[4] Serious mental illness defined as bipolar disorder and/or schizophrenia; all mental illness included these and depression
[5] Newly diagnosed patients were diagnosed and enrolled during the study period.
[6] Viral suppression (VLS) at 12 months after enrollment was defined as the most recent VL in the time period 6 months to 12 months after enrollment being < 200 c/mL.

1041 PRAISE MESSAGES TO INCREASE ART ADHERENCE AND RETENTION IN CARE FOR FSW IN ETHIOPIA

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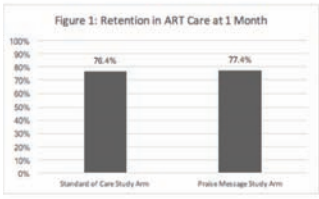
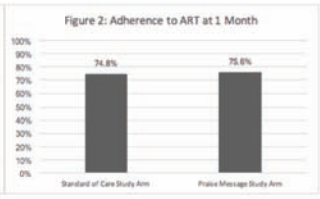
Background: Though female sex workers (FSW) in Ethiopia are disproportionally impacted by HIV, they face numerous barriers to accessing and remaining in HIV care services. PSI/Ethiopia provides HIV care services through a network of FSW-friendly drop-in-centers (DICs), and tested a "praise message" intervention to improve ART adherence and retention in care among FSW living with HIV.

Methods: FSW newly diagnosed with HIV were randomized to standard of care (SoC) or a "praise message" arm (PM). The PM arm received "praise messages" (short, positive calls from the DIC nurse thanking them for investing in their health) 24 hours and 2 weeks after each completed ART appointment. Praise messages were provided for those in the PM arm through 6 months on ART. Outcomes of interest included ART adherence and retention in care at 1, 3, and 6 months after enrollment. Data were collected using the project's routine monitoring and information system, and all study activities were carried out by existing DIC staff. Data were analyzed using OLS regression in STATA 15.0.

Results: We recruited 866 participants. Of these, 436 (50.3%) were randomized to the PM arm, and 430 (49.7%) were randomized to SoC. Participants were recruited from 25 DICs, with a median age range of 25-29 years old. Age did not vary significantly between the study arms (mean age SoC: 29.43; PM: 29.59, p-value=0.793). Of the 735 respondents with completed follow-up by September 3, 2018, overall one-month retention in care was 76.1% and ART adherence was 74.5%. Preliminary data analysis found that 1 month retention did not differ significantly by study arm (SoC: 76.4%; PM: 77.4%, p>0.05). Similarly ART adherence at 1 month did not differ significantly by study arm (SoC: 74.8%; PM: 75.6%, p>0.05).

Conclusion: The intervention did not improve retention in care or ART adherence among FSW living with HIV in our study, providing only a statistically insignificant 1.0 percentage point increase in retention and 0.8 percentage point increase in ART adherence at 1 month. While the intervention did not have an impact on the primary outcomes of interest, this study demonstrates the feasibility of conducting rigorous randomized evaluations of important health outcomes in the context of routine service delivery. With the continued scale-up of electronic, client-based record management systems, routine data should increasingly be leveraged to facilitate low-cost research under operational conditions.





1042 REPEAT NONADHERENCE TO CLINIC APPOINTMENTS AMONG HIV-INFECTED ADULTS ON ART IN KENYA

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Background: Since the early 2000s, Kenya has scaled-up antiretroviral therapy (ART) for HIV-infected persons. Patient adherence to medication is key to avoid drug resistance, treatment failure, and death among HIV-infected patients. Occurrences of non-adherence to clinic appointments could be an objective proxy for non-adherence to treatment. We investigated factors influencing repeat non-adherence among HIV-infected adults newly initiated on ART.

Methods: We conducted a retrospective, national survey of adult patients, aged 15 years and above, who initiated ART from October 2003-September 2013 in Kenya. Using clinic appointments data, patients were considered non-adherent if they missed a scheduled appointment by >90 days. We used Chi-square statistics to compare patient characteristics by non-adherence status. We used generalized estimating equations to investigate factors associated with repeated non-adherence. All analyses were weighted per study design.

Results: Of 2,517 adult patients initiated on ART during the study period, 1,622 (65%) were female, 1,203 (48%) from dispensaries/health centers (HC), 1,082 (44%) initiated D4T-based regimens. Median age at ART initiation was 35.1 years, (interquartile range [IQR]; 28.8–42.8), and median CD4 count at initiation was 174 cells m/L, (IQR; 78-258). Thirty-three percent of patients (839) were non-adherent at least once. Non-adherent patients were more likely to be from county referral (38.1%) or national hospitals (30.7%) versus dispensaries/HC (27%, p<.001); to have been initiated on TDF (32%) or D4T-based regimens (36%) compared to AZT-based regimen (28%, p=0.008). Factors associated with repeated non-adherence were being; males (Odds Ratio [OR] 1.4; 95% confidence interval [CI] 1.2-1.6, p|<0.004), from national facilities, OR 3.7: 95% CI 2.7-4.9, p<.001, from county referral facilities, OR 1.9; 95% CI 1.6-2.1, p<.001, and initiated on D4T-based regimen, OR 1.3; 95% CI 1.1-1.5, p<.001. Once categorized non-adherent, patients were more likely to have repeated instances of non-adherence, (OR 2.7, 95% CI 2.4-3.1, p<.001).

Conclusion: While patient retention is important to ensure adherence to treatment, substantially high rates of repeat non-adherence to clinic appointments continue to be observed. National and county referral hospitals had high non-adherence rates, possibly suggesting high patient load affecting the patient-caregiver relationship and reduced quality patient management. Males may need more targeted intervention to improve adherence.

Table 1: Factors associated with repeated non-adherence to clinic appointments among HIV infected adults patients on ART, in Kenya

	LTFU status	Unadjusted odds ratios			Adjusted odds ratios		
Characteristic	Frequency	OR (95% CI)	P-value	Global p-value	OR (95% CI)	P-value	Global p-value
Total	2517						
Age category							
15-24	251						
25-34	934	1.19 (0.86 - 1.66)	0.287	0.474	1.10 (0.75 - 1.63)	0.618	0.091
35-44	794	1.17 (0.84 - 1.64)	0.343		0.97 (0.65 - 1.46)	0.901	
45-54	386	1.04 (0.72 - 1.50)	0.828		0.85 (0.55 - 1.31)	0.459	
55 +	152	0.93 (0.60 - 1.45)	0.754		0.64 (0.37 - 1.11)	0.111	
Sex							
Female	1622						
Male	895	1.36 (1.23 - 1.68)	0.021	0.025	1.35 (1.15 - 1.62)	0.004	0.004
Facility tier							
Dispensary/HC	1203						
County referral	1158	1.94 (1.62 - 2.10)	.001	<.001	1.93 (1.57 - 2.06)	<.001	<.001
National referral	156	3.70 (2.83 - 5.12)	<.001		3.68 (2.65 - 4.89)	<.001	
CD4 category at enrolment[1]							
> 350	68						
200-350	626	1.07 (0.68 - 1.70)	0.764	0.044			
< 200	921	1.38 (0.88 - 2.16)	0.161				
Initial ART regimen							
AZT-based	717						
TDF -based	700	0.95 (0.77 - 1.28)	0.657	0.003	0.98 (0.78 - 1.24)	0.597	0.001
D4T -based	1082	1.33 (1.02 - 1.43)	0.007		1.33 (1.05 - 1.51)	<.001	
Total	2499						

[1] Excluded from multivariate analysis because of missing data

1043 ATTRITION ALONG THE CARE CASCADE IN SOUTH AFRICAN EMERGENCY DEPARTMENTS

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Background: The Eastern Cape region of South Africa is known for high prevalence of HIV worldwide. HIV service delivery in this region is challenged

by the rural landscape, lack of standardized training, and competing clinical care priorities. This study sought to characterize the HIV care cascade within the Eastern Cape, by conducting an assessment of emergency department (ED) patients.

Methods: We conducted a prospective observational study in three Hospitals in the Eastern Cape region of South Africa, from June 2017 to September 2018. All adult, non-critical patients presenting to the ED during this period, were systematically approached by trained HIV counselling and testing staff and offered a point-of-care test in accordance with South Africa's 2015 National HIV Testing guidelines. All HIV positive individuals were further tested for ARV presence and viral suppression. A pooled analysis is presented; no significant differences were observed across the three sites.

Results: Over the study period a total of 3,537 patients were approached in all sites, of which HIV status was determined in 2,901 patients. Of these, 794 (27.4%) were HIV positive, of which 216 had a new diagnosis. Of the 578 patients with a known positive diagnosis, blood samples were collected for 409 (70.8%) patients, of which 293 (75.9%) tested positive for the presence of ARVs. Of those in care with ARVs detected, 233 (80.6%) demonstrated viral suppression with a VL ≤1,000 (copies/ml). The majority of HIV positive ED patients were female (62.7%) and between the ages of 25-34 years (35.1%) and 34-44 years (29.3%). Males were significantly less likely to know their HIV status (60.5%) compared to females (80.1%). However, the remainder of the care cascade was similar in both groups with 51.4%-50.4% on ARVs and 80.4%-79.1% of those patients achieving viral suppression. In contrast attrition across the care cascade was greatest in younger patients (<25 years) compared to older patient populations (>45 years).

Conclusion: This study demonstrates a high prevalence of HIV (27.4%) among ED patients in the Eastern Cape. For those with known HIV infection and in care, viral suppression was high, but a significant proportion of patients were unaware of their HIV status emphasizing the need for innovative measures, particularly among young males, to improve access to HIV testing, the first critical step to meeting the 90-90-90 target.

	HIV Infected n=794 (%)	Known HIV + n=578 (% of HIV infected)	ARV Presence n=293 (% of Known HIV +)	Viral Suppression n=233 (% of ARV Presence)
Age				
<25	93 (11.7)	58 (62.4)	27 (46.5)	21 (77.7)
25-34	279 (35.1)	184 (65.9)	83 (45.1)	64 (77.1)
35-44	233 (29.3)	180 (77.3)	86 (47.7)	63 (73.3)
45-54	114 (14.4)	100 (87.7)	63 (63.0)	54 (85.7)
≥55	75 (9.4)	56 (74.7)	34 (60.7)	31 (91.2)
Gender				
Male	296 (37.3)	179 (60.5)	92 (51.4)	74 (80.4)
Female	498 (62.7)	399 (80.1)	201 (50.4)	159 (79.1)

1044 SMOKING AND UNHEALTHY DRINKING AND THE HIV CARE CONTINUUM

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Background: Smoking and unhealthy drinking can adversely impact HIV care continuum benchmarks (linkage to care, retention, and HIV viral control).

Methods: We examine associations between smoking and unhealthy drinking with linkage to care, retention and HIV RNA control among 9,397 people living with HIV (PWH) receiving care in the Kaiser Permanente Northern California (KPNC) integrated health care system, screened for unhealthy drinking (index date) and for smoking by providers between 07/01/2013 and 12/31/2017. Measures, derived from the electronic health record, included any self-reported unhealthy drinking in the prior 90 days (one or more days of 4+/5+ drinks per occasion and/or 7+/14+ drinks per week for women or men, respectively); smoking status closest to the drinking index date; linkage to care (≥1 visit within 90 days following a new HIV diagnosis); retention up to 12 months after alcohol screening (2 or more HIV care visits 60+ days apart); and HIV RNA control (<75 copies/mL) between 3 months prior and 12 months post alcohol screening. Unadjusted and adjusted odds ratios (OR) from logistic regression models (see Table for covariates in adjusted models).

Results: The overall sample had mean age 47.1 years and was 91.2% male; 53.3% white, 18.0% Latino, and 15.3% black; and 70.5% men who have sex with men. Sample size varied due to availability of lab data and because linkage analyses were restricted to those new to KPNC care: linkage to care (n=1,949), retention in care (n=9,397), HIV RNA control (n=8,758). In adjusted analyses, current smoking was associated with worse HIV RNA control (compared with not smoking at index date; OR=0.62 [95% CI 0.54-0.71], p<0.001), with some evidence of associations with worse retention (0.88 [0.77-1.01], p = 0.076) and worse linkage to care (0.6 [0.34-1.06], p=0.080). There was little evidence that unhealthy drinking at these thresholds was associated with linkage to care, retention in care or HIV RNA control.

Conclusion: Both unhealthy drinking and smoking were associated with worse retention in care and HIV RNA control among PWH, but only the effect of smoking on HIV RNA control remained in adjusted analyses. Future analyses will examine effects of higher levels of unhealthy drinking and changes in drinking, as well as unhealthy drinking in combination with smoking. Clinicians should make a particular effort to help PWH quit smoking.

Table: HIV Continuum of Care by Unhealthy Drinking and Current Smoking Status

HIV Outcome	HIV Outcome Category		Odds Ratio (Unadjusted)[1]		Odds Ratio (Adjusted)[1]	
LINKAGE TO CARE[2]	LINKED	NOT LINKED	OR (95% CI)	p	OR (95% CI)	p
Total (n=1,949)	**1,886 (96.8%)**	**63 (3.2%)**				
Unhealthy Drinking						
Yes	246 (13.0%)	11 (17.5%)	0.71 (0.36 - 1.38)	0.31	0.70 (0.35 - 1.43)	0.33
No	1,640 (87.0%)	52 (82.5%)	reference		reference	
Current Smoker						
Yes	430 (22.8%)	20 (31.8%)	0.63 (0.37 - 1.09)	0.10	0.60 (0.34 - 1.06)	0.080
No	1,456 (77.2%)	43 (68.3%)	reference		reference	
RETENTION IN CARE[3]	RETAINED	NOT RETAINED	OR (95% CI)	p	OR (95% CI)	p
Total (n=9,397)	**7,897 (84.0%)**	**1,500 (16.0%)**				
Unhealthy Drinking						
Yes	765 (9.7%)	184 (12.3%)	0.77 (0.65 - 0.91)	0.002	0.94 (0.79 - 1.12)	0.51
No	7,132 (90.3%)	1,316 (87.7%)	reference		reference	
Current Smoker						
Yes	1,392 (17.6%)	322 (21.5%)	0.78 (0.68 - 0.90)	<0.001	0.88 (0.77 - 1.01)	0.076
No	6,505 (82.4%)	1,178 (78.5%)	reference		reference	
HIV RNA CONTROL[4]	< 75 COPIES/ML	≥ 75 COPIES/ML	OR (95% CI)	p	OR (95% CI)	p
Total (n=8,758)	**7,112 (81.2%)**	**1,646 (18.8%)**				
Unhealthy Drinking						
Yes	677 (9.5%)	188 (11.4%)	0.82 (0.69 - 0.97)	0.020	1.07 (0.89 - 1.28)	0.48
No	6,435 (90.5%)	1,458 (88.6%)	reference		reference	
Current Smoker						
Yes	1,125 (15.8%)	435 (26.4%)	0.52 (0.46 - 0.59)	<0.001	0.62 (0.54 - 0.71)	<0.001
No	5,987 (84.2%)	1,211 (73.6%)	reference		reference	

1 Odds ratios (OR) and 95% confidence intervals (CI) from logistic regression models adjusted for drinking, smoking, race/ethnicity, HIV risk, gender, age, depression, and modified Charlson score (excludes AIDS).
2 Linkage defined as ≥1 visit within 90 days among those with a new HIV diagnosis
3 Retention in care defined as ≥2 visits 60+ days apart among all persons with HIV
4 HIV RNA CONTROL defined as <75 copies/mL among those with lab values

1045 VIRAL LOAD MONITORING AND FIRST-LINE FAILURE CASCADE OF CARE IN RURAL SOUTH AFRICA

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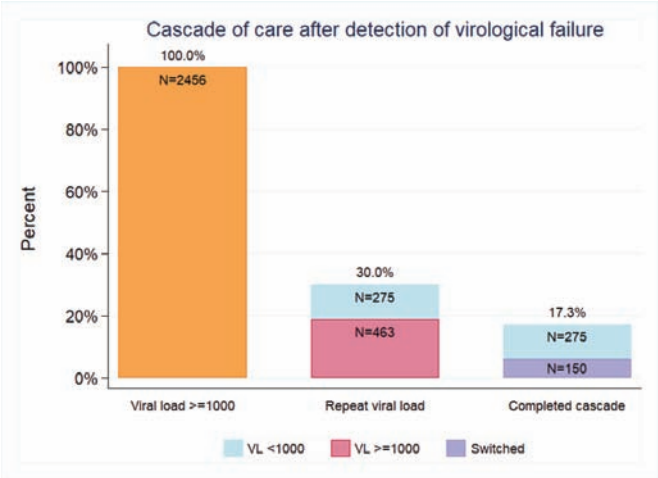
Background: Reports have demonstrated prolonged duration of virologic failure (VF) among patients in care across sub-Saharan Africa, and that drug resistance is more likely to develop in those without frequent monitoring. We investigated the patterns of viral load (VL) monitoring in the first 24 months on ART, and adherence to guidelines after detection of VF in public ART clinics in the Hlabisa sub-district of South Africa.

Methods: We analysed data from all patients initiating ART in 17 public sector clinics in the sub-district during 2010-2016, using the national HIV care electronic patient records system (TIER.Net). VL results are entered into TIER.Net manually. We first estimated the completion rate for VL monitoring at 6, 12, and 24 months. We then described the cascade of care for those with any VL measurement ≥1000 copies/mL after at least 20 weeks on ART, including the proportion with a repeat VL within 6 months, the proportion who re-suppressed, and the proportion who changed to a second-line regimen if a repeat VL remained ≥1,000 copies/mL.

Results: We analysed data from 31,493 individuals who initiated ART during the study period (69% female, median age 31 years (IQR 25-39). Of those in care at 6, 12, and 24 months, we found that 41% (10,518/25,690), 33% (7,553/22,730),

and 27% (4571/17,042) had a viral load test at each recommended time-point respectively. VL results were documented at all recommended time-points for 11.5% (2613/22,730) and 4.9% (838/17,042) of patients on ART for 12 and 24 months respectively. We documented 12% (2,456/ 20,405) individuals with at least one VL≥1000 copies/mL. Of these, 738 (30%) had a repeat VL within 6 months, and 425 (17%) achieved successful management of virologic failure with either re-suppression or appropriate change to second-line therapy (Figure). For the 150 individuals who switched to second-line, the median time to regimen change was 345 days (IQR 135-671) after their first elevated viral load measurement.

Conclusion: We found suboptimal VL monitoring, and delayed or absent responses to VF in public-sector ART clinics in rural South Arica. Such delays are likely to increase the likelihood of patient morbidity, and transmission of drug resistant HIV. We did not investigate how much of our finding could be explained by failure to capture VL results in Tier.Net. Future studies should investigate causes of suboptimal VL monitoring and consider what interventions are needed to improve attention to VF in the region.



1046 MACHINE LEARNING APPLIED TO ELECTRONIC ADHERENCE DATA TO INFORM VIRAL LOAD MONITORING

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Background: Approaches for tailoring ART monitoring are needed to optimize the impact and cost-effectiveness of differentiated care delivery systems. Real-time electronic adherence monitoring (EAM) could potentially inform ongoing risk assessment for virologic failure, and thus be used to modify viral load testing schedules. We evaluated the potential of EAM data to contribute to an individually differentiated viral load testing strategy by applying machine-learning approaches to real-time EAM data from Uganda.

Methods: We evaluated an observational cohort of persons living with HIV who were treated with ART and monitored with EAM (2005-2015). Super Learner, an ensemble machine-learning method, was used to build a risk score for virologic failure (>1000 copies/ml) based on clinical (CD4 count, pre-ART viral load, ART regimen) and demographic data, together with EAM-based adherence. Using sample-splitting (cross-validation), we evaluated the performance of this risk score to determine: 1) whether EAM improved prediction of failure beyond clinical and demographic data; 2) potential for real-time EAM data to selective defer viral load tests while minimizing delays in failure detection; and, 3) performance compared to WHO-recommended testing schedules.

Results: 485 individuals (242 of whom were initiating ART) contributed 2834 outcome viral loads over 930 person-years. Median CD4 at ART initiation was 200 cells/mm3 (IQR 111, 317); 45 patients (1.6%) experienced virologic failure. Super Learning applied to real-time EAM data achieved excellent prediction of virologic failure (cross-validated c-statistic=0.89; 95% CI:0.85, 0.94) and improved prediction of failure beyond demographic and clinical data alone (c-statistic=0.79; 95% CI: 0.72, 0.87; p=0.05). A hypothetical testing strategy using real-time EAM to decide when to order versus defer viral load testing would have reduced the number of viral load tests by 30%, while still detecting 87% of all virologic failures without additional delay. By comparison, the WHO-recommended testing schedule would have reduced the number of viral load tests by 69%, but resulted in delayed detection of virologic failure a mean of 74 days (SD = 41 days) for >80% of individuals with failure.

Conclusion: Our machine learning approach demonstrates potential for combining EAM data with other clinical measures to develop a selective testing rule that may reduce costs incurred by both researchers and patients, while still identifying those at highest risk for virologic failure

1047 PREDICTORS OF ART INITIATION AND VIRAL SUPPRESSION IN A LARGE COHORT IN UKRAINE

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Background: Rapid initiation of ART, treatment adherence support, proper management of virologic failure are important strategies for reaching the ambitious 90-90-90 goals in Ukraine and globally. Key national stakeholders and international donors have set ambitious fast track goals to increase the number of patients from 88,270 on 01/01/2018 to 140,000 by the end of 2018. This study was commenced to obtain reliable data on key treatment quality indicators, contributing factors and trends to inform program planning.

Methods: Data from medical charts of all patients who received care at HIV facilities in 2010-2016 in 18 out of 27 regions of Ukraine were entered into an electronic medical record system. After verification of data quality, depersonalized datasets linked by unique patient code were extracted at each facility and merged for analysis. This analysis focused on the effect of clinical variables (HIV mode of transmission, clinical stage, CD4, VL, TB, HCV, injecting drug use [IDU]) on time from diagnosis to ART initiation and to viral suppression (<200cp/ml). The entire dataset, excluding children younger than 15 at diagnosis, was analyzed using Cox proportional hazard models.

Results: The cohort included 37,690 patients with HIV infection, approximately 30% of all patients receiving care in Ukraine in 2016. Average age at diagnosis 46.4% were females. Median time from diagnosis to ART was 26 months (95%CI: 25.0-26.9) and 14 months (95%CI: 13.7-14.3) from ART to viral suppression. Multiple significant predictors were identified for both outcomes (see Table). Notably, the time to ART initiation was increasing with male gender (aHR=.91), negative TB status (aHR=.9), being at early clinical HIV stage (aHR=.53), IDU mode of transmission (aHR=.77). The chance of getting ART was increasing with lower CD4 (aHR=4.1 for CD4<200), reporting no recent IDU (aHR=1.11), having positive TB test (aHR=1.18), homosexual mode of transmission (aHR=1.18). Viral suppression was associated with younger age (aHR=.98), earlier clinical stage (aHR=1.08), having negative TB test (aHR=.86), IDU mode of transmission (aHR=.93). Overall, coverage of key clinical assessments was not universal, and completion was associated with both outcomes.

Conclusion: Quality of HIV care in Ukraine, characterized by coverage of key clinical tests, time to ART initiation and viral suppression indicators remains suboptimal. Patients with advanced disease had priority for ART, reflecting the delayed adoption of test-and-start strategy.

Table 1. Predictors of ART initiation and viral suppression among HIV patients in Ukraine

		% started ART	HR (95% CI)	aHR (95% CI)	% virally supressed	HR (95% CI)	aHR (95% CI)
Age			**0.995** (0.994-0.997)	**0.988** (0.987-0.990)		**0.98** (0.98-0.99)	**0.98** (0.98-0.99)
Sex	females	59.3%	ref		59.5%		
	males	54.0%	**0.90** (0.87-0.92)	**0.91** (0.89-0.94)	54.4%	**0.89** (0.86-0.91)	1.01 (0.98-1.05)
CD4	Untested	34.2%	ref		14.9%		
	<200	82.6%	**3.62** (3.48-3.76)	**4.07** (3.86-4.29)	51.8%	**6.88** (6.20-7.64)	**1.57** (1.40-1.75)
	200-349	77.1%	**2.76** (2.64-2.87)	**3.37** (3.20-3.56)	61.8%	**7.58** (6.83-8.42)	**1.37** (1.22-1.53)
	350-499	52.2%	**1.51** (1.44-1.59)	**1.90** (1.78-2.02)	66.4%	**7.82** (7.03-8.69)	**1.21** (1.08-1.36)
	500+	31.4%	**0.82** (0.77-0.87)	1.03 (0.96-1.11)	68.0%	**7.29** (6.56-8.11)	1.04 (0.92-1.16)
VL<200	Untested	51.0%	ref				
	No	67.4%	**1.32** (1.28-1.36)	1.01 (0.97-1.04)			
	Yes	50.3%	**0.80** (0.74-0.86)	**0.75** (0.70-0.82)			
Clinical stage	unverified	58.7%	ref		37.9%		
	stage I-II	42.5%	**0.55** (0.53-0.57)	**0.53** (0.51-0.56)	61.3%	**2.60** (2.45-2.75)	**1.08** (1.00-1.16)
	stage III-IV	67.5%	**1.15** (1.11-1.19)	**0.81** (0.77-0.86)	58.6%	**2.19** (2.08-2.32)	**0.88** (0.82-0.95)
IDU status	unverified	53.8%	ref		57.1%		
	no current idu	63.5%	**1.18** (1.15-1.22)	**1.11** (1.07-1.15)	56.7%	**1.10** (1.07-1.14)	**1.20** (1.16-1.24)
	current idu	54.1%	0.92 (0.84-1.00)	0.96 (0.87-1.05)	54.1%	1.03 (0.96-1.11)	**1.22** (1.13-1.33)
	on OAT	64.7%	0.98 (0.81-1.20)	0.91 (0.74-1.12)	60.3%	1.07 (0.93-1.23)	**1.24** (1.07-1.43)
HCV status	Untested	51.5%	ref		55.0%		
	Yes	65.6%	**1.28** (1.23-1.33)	**1.08** (1.04-1.13)	60.0%	**1.15** (1.11-1.19)	**1.03** (1.00-1.08)
	No	65.9%	**1.35** (1.30-1.39)	**1.14** (1.10-1.18)	57.3%	**1.20** (1.16-1.24)	**1.07** (1.03-1.12)
TB status	Untested	50.8%	ref		61.2%		
	No	61.1%	**1.17** (1.13-1.21)	**0.90** (0.87-0.94)	55.4%	**0.90** (0.88-0.93)	**0.86** (0.84-0.89)
	Yes	74.2%	**1.76** (1.69-1.82)	**1.18** (1.13-1.23)	49.3%	**0.91** (0.87-0.95)	1.04 (0.99-1.09)
Mode of transmission	heterosexual	58.3%			60.2%		
	injecting drug use	50.3%	**0.76** (0.74-0.79)	**0.77** (0.74-0.80)	59.0%	**0.91** (0.88-0.94)	**0.93** (0.89-0.96)
	homosexual	61.6%	1.12 (0.98-1.28)	**1.18** (1.03-1.36)	58.1%	1.06 (0.91-1.24)	1.06 (0.91-1.24)
	other	50.2%	0.94 (0.82-1.06)	0.93 (0.82-1.06)	54.9%	**0.85** (0.74-0.98)	1.03 (0.89-1.18)

1048 SOCIAL NETWORKS AND TIE STRENGTH PREDICT OUTCOMES OF HIV+ YOUTH IN SEARCH TRIAL

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Background: HIV+ youth in sub-Saharan Africa are at high risk of virologic failure on ART; peer support within their social networks may improve clinical outcomes. We used comprehensive social network and HIV testing data from the SEARCH test-and-treat trial (NCT01864603) to evaluate whether HIV+ youth with HIV+ social network contacts at baseline were more likely than those without this support to engage in care and virally suppress.

Methods: Adult (≥ 15 years) residents enumerated during a census in 32 communities in rural Kenya and Uganda named social contacts in five domains: health, money, emotional support, food, and free time. Named contacts were matched to enumerated residents to build social networks among 150,395 adult residents; 90% were tested for HIV. Among youth (15-24 years) who were ART-naive at baseline (2013-2014), we evaluated whether having ≥1 baseline network contact who was i) HIV+, or ii) HIV+ and virally suppressed (HIV RNA <400 copies/ml) predicted ART initiation and viral suppression 3 years later, and whether the association was greater for strong ties (network contacts named in >1 domain). We used logistic regression with robust standard errors to adjust for sex, study arm, new diagnosis, and region.

Results: Among 1,120 HIV+ youth who were ART-naive at baseline, 857 remained alive and resident in the community after 3 years of follow-up. At 3 years, 68% (579/857) had engaged in ART care and among 521 with viral loads, 400 (77%) were virally suppressed. Youth named an average of 2.7 contacts (SD 3.1); 275 (32%) named ≥1 HIV+ contact and 81 (9%) had ≥1 virally suppressed contact. 340 (42%) named ≥1 strong tie; 117 (15%) had HIV+ strong ties and 31 (4%) had virally suppressed strong ties. Youth with ≥1 HIV+ baseline contact were more likely to initiate ART (aOR 1.76; 1.26-2.46) and youth with ≥1 virally suppressed baseline contact were more likely to be suppressed themselves 3 years later (aOR 1.80; 1.11-2.89). The magnitude of these associations was (non-significantly) greater if ties were strong: ≥1 HIV+ strong tie was associated with ART initiation (aOR 2.07; 1.27-3.37) and ≥1 virally suppressed strong ties was associated with viral suppression (aOR 2.53; 1.18-5.42).

Conclusion: HIV+ peers, particularly those with viral suppression, in the local social networks of ART-naive HIV+ youth in rural East Africa may support engagement in care and viral suppression. Interventions that increase social connections to HIV-infected youth in HIV-care may improve clinical outcomes.

1049 ASSOCIATION BETWEEN HIV CLINIC CASELOADS AND VIRAL LOAD SUPPRESSION IN NEW YORK CITY

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Background: A goal of the New York State Ending the Epidemic (EtE) Initiative is to achieve viral load suppression (VLS <200 copies /μL) in 85% of all HIV-diagnosed persons by 2020. To accomplish this, factors associated with clinics already achieving VLS in ≥85% of their patients must be identified. We hypothesized that, compared to clinics with lower HIV caseloads, those with larger HIV caseloads are more likely to achieve ≥85% VLS.

Methods: Using purposive sampling, the New York City Department of Health and Mental Hygiene administered a survey assessing clinic capacity and practice to 154 HIV clinics in New York City; 110 (75%) responded. Clinics were classified as either ≥85% VLS (n=36) or <85% VLS (n=74). HIV caseload was defined by the total number of unique HIV patients receiving care at a clinic in 2016 and was categorized into quartiles. We used multiple logistic regression to examine the association between HIV caseload and clinics achieving ≥85% VLS, adjusting for age, sex, race, and ethnicity of clinic patient populations. Thereafter, chi-square/Fisher's exact/Mann–Whitney U tests identified clinic practice characteristics unique to caseload quartiles associated with ≥ 85% VLS.

Results: After adjusting for covariates, only quartile-2 (Q2) caseload of 61-200 HIV patients (n=31) was associated with significantly higher likelihood of achieving ≥ 85% VLS (OR = 6.6, 95% CI 1.2 – 37). Q2 clinics had significantly higher use of device based medication adherence reminders (p<0.01), Saturday hours (p=0.04), queried electronic medical records monthly for virally unsuppressed patients (p=0.02), utilized personal phone call reminders for patient appointments (p=0.03), and had more patients in Health Home medical case management (p = 0.04) compared to other quartiles combined. Q2 clinics also mandated more HIV-related continued medical education training (p=0.052); had lower rates of missed appointments (p=0.052); and reported hiring diverse, culturally competent staff based on patient population (p=0.10) than other quartiles combined. The majority of Q2 clinics (n=23) had HIV patients comprising fewer than 15% of total patient population and 16 reported >50% Black HIV patient population.

Conclusion: An HIV caseload of 61-200 patients may allow for best planning and execution of effective clinical practice particularly with demographics that may face more barriers in achieving VLS.

Table 1: Main Effects of HIV Caseload on Achievement of ≥85% VLS* in HIV Clinics (n=110)

	<85% VLS (n=74)	≥85% VLS (n=36)	Crude OR (95% CI)	P-Value / P-Trend	Adjusted† OR (95% CI)	P-Value / P-Trend
HIV Patient Caseload				0.04*		0.50
1-60	24 (32%)	8 (22%)	1 (Reference)	---	1 (Reference)	---
61-200	22 (30%)	9 (25%)	1.2 (0.40 - 3.7)	0.72	6.6 (1.2 - 37)*	0.032*
201-450	14 (19%)	6 (17%)	1.3 (0.37 - 4.5)	0.69	2.1 (0.35 - 12)	0.41
451-4200	14 (19%)	13 (36%)	2.8 (0.93 - 8.37)	0.068	2.0 (0.35 - 12)	0.43
Proportion of Patient Population > 50 years of age				0.002*		0.002*
0% - 24.9%	8 (11%)	1 (3%)	0.17 (0.021 - 1.5)		0.037 (0.0016 - 0.86)*	
25% - 49.9%	33 (45%)	8 (22%)	0.34 (0.13 - 0.88)*		0.20 (0.050 - 0.80)*	
50% - 74.9%	31 (42%)	22 (61%)	1 (Reference)		1 (Reference)	
75% - 100%	2 (3%)	5 (14%)	3.5 (0.63 - 19.8)		14 (0.89 - 230)	
Proportion of Patient Population Male				0.5		0.72
0% - 24.9%	2(3%)	1 (3%)	1.1 (0.097 - 13.0)		6.5 (0.35 - 118)	
25% - 49.9%	7 (9%)	3 (8%)	0.96 (0.22 - 4.05)		0.95 (0.12 - 7.6)	
50% - 74.9%	54 (73%)	24 (67%)	1 (Reference)		1 (Reference)	
75% - 100%	11 (15%)	8 (22%)	1.6 (0.58 - 4.6)		1.5 (0.35 - 6.4)	
Proportion of Patient Population Hispanic Ethnicity				0.8		0.10
0% - 24.9%	24 (32%)	8 (22%)	0.38 (0.4 - 1.04)		0.34 (0.083 - 1.4)	
25% - 49.9%	23 (31%)	20 (56%)	1 (Reference)		1 (Reference)	
50% - 100%	27 (37%)	8 (22%)	0.34 (0.13 - 0.92)*		0.031 (0.0044 - 0.22)*	
Proportion of Patient Population Black Race				0.02*		0.003*
0% - 24.9%	7 (9%)	7 (18%)	1.4 (0.42 - 4.8)		24 (2.3 - 240)*	
25% - 49.9%	24 (32%)	17 (47%)	1 (Reference)		1 (Reference)	
50% - 74.9%	26 (35%)	8 (22%)	0.43 (0.16 - 1.2)		0.20 (0.050 - 0.80)*	
75% - 100%	17 (23%)	4 (11%)	0.33 (0.095 - 1.16)		0.22 (0.035 - 1.3)	

† Adjusted OR is adjusted for all other covariates
* VLS = Viral Load Suppression.
* = Significant P-Value of less than 0.05

1050 VIRAL SUPPRESSION AMONG PEOPLE INITIATING HIV CARE: OUTCOMES FROM THE IENGAGE TRIAL

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Background: Optimizing engagement in HIV care represents the greatest opportunity to maximize the individual and population health benefits of sustained viral suppression (VS; <200 c/ml). Among people living with HIV (PLWH) initiating outpatient HIV care, early missed clinic visits and suboptimal

retention in care (RIC) result in failure to achieve and sustain VS, impacting personal health outcomes and onward HIV transmission.
Methods: The NIH-funded iENGAGE trial (NCT01900236) enrolled PLWH within 14 days of their initial outpatient HIV care visit at 4 CFAR-affiliated academic HIV clinics. Participants were randomized to an intervention or standard of care (SOC) control arm (1:1). The intervention integrated and adapted 2 evidence-based approaches with demonstrated efficacy for RIC and ART adherence; enhanced personal contact/reminders and a 4 session counseling program based on Motivational Interviewing and grounded in a situated information, motivation and behavioral skills (sIMB) framework. Participant baseline and 48-week computer assisted surveys were done using validated instruments. A sample size of 400, with 10% attrition, provided >80% power to detect a 15% difference in 48-week VS, with 60% VS estimated in the SOC arm based upon historical data.
Results: Between 12/13 and 06/16, 371 participants enrolled (62% black, 19% women, 24% uninsured, 60% MSM, 25% CD4<200). Baseline psychosocial co-morbidities included: 31% depression, 30% anxiety, 35% high-risk alcohol use, 18% active substance use. Roughly half the sample (49%) reported unmet need for supportive services (e.g. housing, employment, food and transportation). Overall, 86% of participants achieved 48-week VS; 86% intervention, 87% SOC; p=0.87. Median time to VS was 63 days (IQR 42-101) and did not differ between the two study arms (HR=0.94, 95%CI=0.75-1.19).
Conclusion: Among new to care iENGAGE participants with substantial co-morbid psychosocial illness and unmet need for supportive services, 86% achieved 48-week VS in a median time of 63 days with no differences between study arms. Similar findings by study arm and the higher than expected VS rate in the SOC group likely reflects a rapidly evolving HIV treatment landscape, which emphasizes the care continuum, rapid ART initiation and the emergence of integrase inhibitors as first-line therapies. Sustaining care engagement and VS among new to care PLWH beyond the first year is imperative to maximize the individual and population health benefits afforded by modern HIV treatment.

1051 INCREASES IN KNOWLEDGE OF HIV POSITIVE STATUS, ART, AND VIRAL SUPPRESSION IN BCPP

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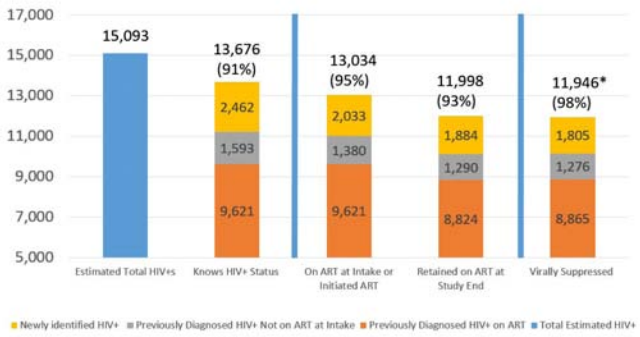
Background: Botswana approached the UNAIDS 90-90-90 targets at the onset of the Botswana Combination Prevention Project (BCPP). In this context, we examined the feasibility of further increasing HIV testing, ART coverage, and viral suppression through community-based HIV testing campaigns and universal ART.
Methods: BCPP is a community-randomized trial evaluating the impact of HIV testing and universal treatment on HIV incidence. The BCPP HIV testing campaigns included community-wide home, mobile and targeted outreach HIV testing. HIV testing was offered to all individuals who did not have documentation of positive HIV status. All HIV-positive community residents age 16-64 who were citizens were tracked to determine linkage to care, ART initiation, retention in treatment, and viral suppression. Electronic medical records were examined for clinical outcomes. We used household enumeration and community HIV prevalence data from BCPP in combination with 2011 census information to estimate the total number of adult residents living with HIV (PLHIV).
Results: A total of 15,093 estimated PLHIV resided in the 15 intervention communities. BCPP identified 13,676 (91% of estimated PLHIV) HIV-positive persons in these communities (Figure 1). Among these, 11,214 (82%) were known HIV-positive while 2,462 (18%) were newly-diagnosed through BCPP, a 22% increase in knowledge of positive status. Among the 11,214 who knew their HIV status, 9,621 (86%) were already on ART. Of those not on ART (newly and previously diagnosed; n = 4055), 3413 (84%) initiated ART, increasing the treatment coverage among all identified HIV-infected individuals from 70% (9621/13,676) at baseline to 95% (13,034/13,676) at study end. Among the 13,034 persons known to have taken/started ART, 191 (1.5%) people died and 11,998/12,843 (93%) were retained on ART at end of study. Viral load tests were available on 12,235/12,843 (95%) of persons on ART, and 11,946 (98%) of those had HIV-1 RNA <400 copies/mL.
Conclusion: Despite high levels of HIV testing, ART coverage and viral suppression at baseline, knowledge of HIV positive status, treatment uptake, and viral suppression increased substantially with enhanced testing, linkage interventions and universal ART.

Figure 1: HIV Care Cascade Among HIV-Infected Adults in 15 Intervention Communities



*Denominator (n=12,235) reflects people known to have started ART, are alive at end of study and have VL result

1052 SUCCESSFUL VIRAL OUTCOMES AFTER IMPLEMENTING "TREAT ALL" IN SOUTH AFRICAN CLINICS

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Background: There is little data to determine the impact of WHO 'Treat All' guidelines on retention in care and viral load (VL) suppression in low and middle income countries.
Methods: We analyzed routinely collected TIER.net and National Health Laboratory Service data from 8 public clinics in rural and urban KwaZulu-Natal, South Africa, where 'Treat All' was implemented in September 2016. Non-pregnant patients aged >15 years and initiating ART between September 2014-February 2017 were included in this analysis. We assessed the relationship between time period of ART initiation, initiation CD4 count and the outcomes of retention in care and VL suppression using logistic regression.
Results: Of 9526 patients, 57% (95% CI 56-58) were female, median age was 33 years (IQR 28-41) and median CD4 count was 288 cells/mm^3(IQR 151-429). At 12 months post ART initiation, 75% (95% CI 74-76%) were retained in care, 25% transferred care or were lost to follow up, and 0.5% were confirmed dead. In multivariable analysis, age >35 years (adjusted odds ratio [aOR] 1.54, p<0.001), female gender (aOR 1.42, p<0.001), not having TB at initiation (aOR 1.29, p=0.002) and initiation CD4 count >200 cells/mm^3 (p<0.001) were associated with retention in care at 12 months. Among the 7132 with VL and initiation CD4 results, 94% (95% CI 93-94) had VL suppression at <1000 copies/ml, at median 356 days (IQR 307-377) post ART initiation. In multivariable analysis, age >35 years (aOR 1.53, p<0.001), female gender (aOR 1.35, p=0.003) and not having TB at initiation (aOR 1.39, p=0.009) were associated with VL suppression. Patients with initiation CD4 count >500 cells/mm^3 had over 5 times higher odds of VL suppression compared to those with CD4 counts <200 cells/mm^3 (p<0.001). Retention in care (aOR 1.03, p=0.494) and VL suppression (aOR 1.03, p=0.811) did not differ between those initiated before and after ‹Treat All›, even among those with initiation CD4 >500 cells/mm^3 (p for interaction 0.654 and 0.465 respectively)
Conclusion: Implementing 'Treat All' in South African public clinics did not reduce retention in care or VL suppression. Furthermore, patients newly eligible for ART with CD4 counts >500 cells/mm^3 had the best viral outcomes. Overall retention in care was moderate, but amongst those retained with VL results, VL suppression was high. Efforts to implement ‹Treat All› and to improve retention in care should continue in order to acheive 90-90-90.

Table 1: Univariable & multivariable analysis of factors associated with viral load suppression (n=7132)

Characteristic		VL < 1000 copies/ml n/N (%)	Odds ratio* (95% CI)	P-value	Adjusted odds ratio*† (95% CI)	P-value
Age (years)	15-34	3703/3990 (92.8)	1	0.007	1	<0.001
	≥ 35	2966/3142 (94.4)	1.31 (1.08-1.59)		1.53 (1.25-1.86)	
Gender	Male	2732/2977 (91.8)	1	<0.001	1	0.003
	Female	3937/4155 (94.8)	1.62 (1.34-1.96)		1.35 (1.11-1.64)	
Previous TB	Yes	866/970 (89.3)	1	<0.001	1	0.009
	No	5803/6162 (94.2)	1.94 (1.54-2.44)		1.39 (1.09-1.76)	
Initiated during 'Treat All'	Yes	1976/2094 (94.4)	1	0.055	1	0.811
	No	4693/5038 (93.2)	0.81 (0.65-1.01)		1.03 (0.82-1.29)	
Initiation CD4 count (cells/mm^3)	<200	2002/2262 (88.5)	1	<0.001	1	<0.001
	200-349	1797/1910 (94.1)	2.07 (1.64-2.60)		1.99 (1.58-2.52)	
	350-499	1712/1776 (96.4)	3.47 (2.62-4.60)		3.24 (2.43-4.33)	
	≥500	1158/1184 (97.8)	5.78 (3.84-8.71)		5.31 (4.37-8.11)	

1053 REACHING TOWARD 90-90-90 AMONGST CORRECTIONAL FACILITY INMATES IN ZAMBIA

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Background: Achieving the 90-90-90 goals among key populations is believed to be critical for HIV control. We sought to implement a universal test and treat (UTT) program in correctional facilities in Zambia and South Africa and measure success with the 90-90-90 goals in mind. Here we describe outcomes from Lusaka Central Correctional Facility in Zambia.

Methods: We offered immediate ART to all inmates ≥18 years, with HIV regardless of CD4 or WHO stage who were expected to be incarcerated ≥30 days after ART initiation. We strengthened health services with personnel and training to make UTT feasible. We determined the corrections census on two days-a baseline day prior to UTT and an endline day 12 months after UTT initiation and 18 months after the baseline. We used the single day census to create virtual cross sections for HIV testing, ART initiation, and viral load suppression. The denominator for status was the prison census, the numerator included those in the census with HIV testing in the prior 12 months or known to be HIV-positive. The proportion on ART was assessed with a denominator of those known HIV-positive from the virtual cross-section and those HIV-positive and on ART as the numerator. Viral load suppression included the denominator of those known to be on ART and the numerator of those with a viral load <1000 c/mL.

Results: On the baseline cross-section day there were 1,467 inmates in the facility. Of these, 857 (58.4%) knew their HIV status and 277 were HIV-positive (18.9%). Of those with known HIV, 188 (67.9%) were on ART. Viral loads were not routinely obtained prior to UTT. On the endline day, 1,370 inmates were in the facility and 1,263 (92.2%) had been tested or were already known positive. Of those, 647 (47.2%) were HIV-positive of whom 438 (67.7%) were on ART (a 2.3 fold increase in inmates on ART). Of those on ART, 85 had a viral load result; 68 (91.8%) having a viral load <1000 c/mL. Expected release within 30 days of HIV testing was noted as an important reason for not initiating ART among some HIV-positives.

Conclusion: High levels of HIV testing and virologic suppression are feasible within correctional facilities. Although many more inmates were placed on ART, the second 90 goal was not reached possibly due to many inmates leaving the facility within 30 days of HIV testing. Justice involved populations should be included in efforts to achieve 90-90-90 goals and specific correctional facility programs are feasible.

1054 DIFFERENTIATED CARE PREFERENCES OF STABLE PATIENTS ON ART IN ZAMBIA

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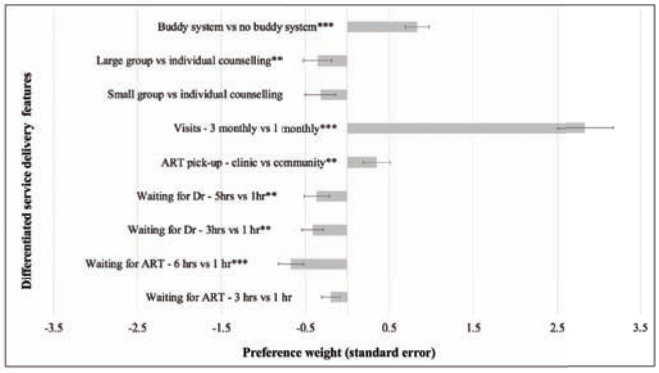
Background: Although differentiated service delivery (DSD) models offer a range of health systems innovations, their comparative desirability to patient populations, implementability and effectiveness remains unknown. We conducted a discrete choice experiment (DCE) to quantify model features most desired by patients to inform model prioritization during scale-up in Zambia.

Methods: We surveyed a random sample of HIV positive adults on ART at 12 clinics in Zambia and asked patients to choose between two hypothetical facilities which differed across six attributes: location of ART pick-up (clinic vs. community), frequency of ART pick-up (1 vs. 3 monthly), time spent waiting to pick up ART (1, 3 or 6 hrs), time spent waiting for a doctor (1, 2 or 5 hrs), type of adherence counselling (group vs. individual), and ability for a 'buddy' to collect ART. Each respondent answered one of two blocks of seven questions. We used mixed logit models to determine the degree of preference (i.e. preference weights - β) for each DSD feature, preference heterogeneity and willingness-to-trade.

Results: Of 486 respondents, 59% were female and 85% resided in urban locations. Patients strongly preferred infrequent clinic visits (3 vs. 1 month visits: β=2.84; p <0.001) (Figure). Milder preferences were observed for reduced waiting time for ART (1 vs. 6 hrs.: β=-0.67; p<0.001) and reduced waiting time to see a doctor (1 vs. 3 hrs., β=-0.41; p=0.002), and facilities accommodating 'buddy' ART collection (β=0.84; p <0.001). In order to obtain 3 instead of 1 monthly refills, patients were willing to wait 6 hrs. for ART (vs. 1), wait 3 hrs. for a doctor (vs. 1), pick-up ART in the community instead of clinic, attend large group counselling, and forego a buddy system (β difference: 0.23; p=0.487). When stratified by residence, urban patients had a strong preference for collecting ART in at the health facility (β=1.32, p<0.001) whereas rural patients preferred drug pick-up in the community (β=-0.74, p=0.049).

Conclusion: Patients in Zambia primarily want to attend health facilities infrequently, and this preference outweighs the desire for all other DSD features. Substantial preference heterogeneity was demonstrated by urban and rural participants, suggesting that Zambia should prioritize DSD models that remain facility-based but require infrequent contact, particularly in urban settings, with consideration of community based drug distribution for those more rural.



1055 DURABLE VIRAL SUPPRESSION AMONG PEOPLE WITH ACUTE AND NONACUTE HIV IN NORTH CAROLINA

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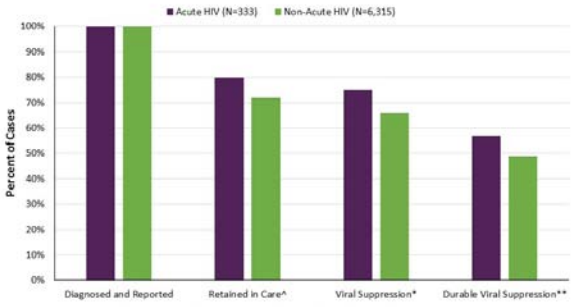
Background: North Carolina (NC) has had statewide screening for acute HIV infection (AHI) since 2002. The program involves a coordinated effort between NC Disease Intervention Specialists (DIS) who locate and interview people diagnosed with AHI within 72 hours of case notification and HIV providers who expedite their care appointments. Non-AHI cases take DIS approximately two weeks to locate and interview. We assessed whether prioritizing the linkage

to care of individuals with AHI improved the retention in care and durable viral suppression outcomes compared to those with non-AHI.
Methods: For all persons newly diagnosed with HIV during 2013-2017, we defined AHI as 1) a negative antibody test and either a positive HIV RNA or 4th gen HIV Ag/Ab test or negative HIV Ab test within 30 days, or 2) a positive HIV RNA and symptoms specific to AHI. Using the NC Engagement in Care Database for HIV Outreach (NC ECHO), laboratory, drug dispense, and claims data were assessed for AHI and non-AHI patients to determine time to initial viral suppression (VL<200 copies/ml), retention in care (at least one VL <200 copies/ml between January 2017 and June 2018 or two care visits at least 90 days apart between January 2017 and June 2018), and durable viral suppression (two most recent VLs <200 copies/ml between January 2017 and June 2018). Chi-square analyses were performed to determine if the proportions retained in care and durably virally suppressed differed by AHI vs non-AHI status. We conducted a Kaplan-Meier survival analysis to determine time to viral suppression (time between HIV diagnosis and first VL <200 copies/ml) for both AHI and non-AHI.
Results: Between 2013 and 2017, a total of 6,648 (333 AHI; 6,315 non-AHI) persons were diagnosed with HIV in NC. The median time to viral suppression for AHI was 112 days (95% CI: 100-136) compared to 157 days (95% CI: 153-162) for non-AHI (log-rank test p<0.0001). AHI patients were more commonly retained in care compared to non-AHI patients, (80% versus 72% respectively; p=0.002). Durable viral suppression was achieved by 57% of AHI and 49% non-AHI (p=0.01).
Conclusion: AHI prioritization as a public health emergency in NC and the subsequent coordinated response between health departments and HIV providers to expedite linkage to care among people with AHI was associated with better retention in care, time to initial viral suppression, and durable viral suppression outcomes.

Figure. HIV Continuum of Care in North Carolina for Acute and Non-Acute HIV Diagnosed from 2013 to 2017



^Retained in care is defined as at least one viral load <200 copies/ml between January 2017 and June 2018 or two care visits at least 90 days apart between January 2017 and June 2018.
*Viral Suppression is defined as the last viral load between January 2017 and June 2018 <200 copies/ml.
**Durable Viral Suppression is defined as the two most recent viral loads <200 copies/ml between January 2017 and June 2018.
Data Sources: enhanced HIV/AIDS Reporting System (eHARS) (data as of June 27, 2018), North Carolina Electronic Disease Surveillance System (NC EDSS) (data as of August 2018), and North Carolina Engagement in Care Database for HIV Outreach (NC ECHO) (data as of August 2018).

1056 IMPLEMENTING U=U IN THE HIV CLINIC: CAN WE PREDICT HIV NONSUPPRESSION?

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Background: Persons with an undetectable HIV viral load do not transmit HIV infection through condomless sex, hence the emergence of the "Undetectable equals Untransmissable (U=U)" HIV prevention strategy. We conducted a study to identify predictors of HIV non-suppression among clinic patients with one year of demonstrated HIV suppression to help inform the implementation of U=U.
Methods: We analyzed data from the Immunology Center in Providence, RI, first identifying all patients with HIV viral suppression [≥ 1 undetectable (<20 copies/ml) plasma viral load (PVL) and zero detectable (≥ 20 copies/ml) PVLs] in 2015. Among this baseline cohort, we determined the proportion of patients during follow-up years 2016-17 who maintained suppression, had non-suppression [≥ 1 detectable (≥ 20 copies/ml) PVLs], or did not have any PVL data. We conducted bivariate and multivariate logistic regression analyses to identify correlates of non-suppression.
Results: The baseline cohort included 1060 patients with viral suppression in 2015: 72% male, 28% female; 32% ages 18-44, 68% ≥ 45 years; 66% White, 31% Black, and 23% Hispanic. At clinic intake: 19% had unstable housing; 37% with psychiatric illness; 45% men who have sex with men; 19% injection drug use, 43% non-injection drug use; 35% foreign-born. Among the 1060 patients, 834 (79%) had viral suppression, 116 (11%) were non-suppressed, and 110 (10%) had no PVLs, in 2016. Among the 834 with viral suppression in 2016, 683 (82%) had viral suppression, 72 (9%) were non-suppressed, and 79 (9%) had no PVLs, in 2017. In sum, over the two years of follow-up, 683 (64%) maintained suppression, 188 (18%) became non-suppressed, and 189 (18%) had missing PVL data. In the bivariate analysis, younger age (p=0.001) and not being retained in care during 2015 (p=0.01), or during 2016-17 (p=0.02), were associated with non-suppression. In the multivariate analysis, increasing age was negatively associated with non-suppression (OR: 0.973, CI:0.958-0.988).
Conclusion: U=U represents a paradigm shift in HIV prevention but requires persistent HIV viral suppression. Among patients with one year of suppression in our clinic, approximately 10% per year became non-suppressed, and suppression couldn't be confirmed in another 10% per year due to lack of PVL testing. This has important implications for counseling, viral load monitoring, and assuring retention in care when implementing U=U, particularly for young patients who may be at higher risk for non-suppression.

1057 FACTORS ASSOCIATED WITH LACK OF VIRAL SUPPRESSION IN THE YEAR AFTER HIV DIAGNOSIS

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Background: Identifying factors associated with poor HIV care continuum outcomes in the first year after HIV diagnosis could guide care engagement efforts at time of HIV diagnosis. Our objective was to identify factors available in HIV surveillance and partner services (PS) interviews associated with failure to reach viral suppression within one year among newly diagnosed persons living with HIV (PLWH) in Seattle & King County, WA.
Methods: We analyzed data from a population-based cohort of individuals newly diagnosed with HIV who received a PS interview in King County, 1/1/2013-6/30/2016. The outcome measure was achievement of viral suppression in a year after HIV diagnosis, defined as ≥1 viral load (VL) <200 copies/mL reported to surveillance <12 months from diagnosis date. Predictor variables included patient demographics, HIV transmission category, and value of first VL from case and laboratory surveillance; housing status, foreign birth, primary language, drug use and engagement in exchange sex from PS interviews. We compared characteristics of persons who did and did not reach suppression using a t-test for continuous variables and Pearson's chi-squared for categorical variables. We used Poisson regression to calculate relative risks for variables associated with suppression failure and examined time to suppression with Kaplan-Meier survival curves.
Results: Of 549 persons diagnosed with HIV and received a PS interview, 69 (13%) did not reach viral suppression within a year. The two groups did not differ by gender, race/ethnicity, transmission category, foreign birth, primary language, drug use, exchange sex, or median VL at the time of first report post-diagnosis. Persons who reported having no plan for HIV care at the time of HIV PS interview (N=72; 13%) were less likely to achieve suppression than those with a plan [RR 1.2 (95% CI: 1.04-1.4], as were persons with unstable housing compared to stable housing (N=81; 15%) [RR 1.2 (95% CI: 1.1-1.4)]. However, the majority (74%) of persons who reported no plan for care or unstable housing reached suppression; 42% of non-suppressed persons had one of these risk factors. In the overall population, 42% were suppressed at 3 months, 73% at 6 months, 84% at 9 months, and 87% at 12 months.
Conclusion: PLWH with unstable housing or no plan for HIV care at the time of PS interview may benefit from early high-intensity intervention, but close monitoring of viral suppression and early identification of failure may be a more effective public health approach.

1058 THE IMPACT OF "CHURN" ON CUMULATIVE PLASMA HIV BURDEN WITHIN A POPULATION UNDER CARE

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Background: Background-The continuum of care (i.e. engagement, retention, treatment, viral suppression) is usually reported using cross-sectional data that often underestimates each stage, especially viral suppression rates. Recently, longitudinal approaches have been developed to address cumulative effects of HIV viral burden, however, these measures may further underestimate viral burden if 'churn' (the movements in/out of a population) are not taken into consideration. We examined the impact of churn on cumulative HIV viral burden over a 2 year period in a population under care.

Methods: Methods-All HIV+ patients followed at the Southern Alberta clinic in 2016/2017 with ≥1 clinic visit and >1 viral loads were included. Patients were grouped into 5 categories-i) continuously followed; ii) newly diagnosed entering care; iii) previously diagnosed patients moving into care; iv) patients who formally moved out of care; and v) patients followed then disengaged from care. We determined the number of days patients spend with a suppressed (≤200copies/ml); unsuppressed (>200), and transmittable (>1500) viral loads.

Results: Results-1498 (78%) of 1915 patients followed in 2016/2017 had suppressed VL for the entire 2 years; 22% had at least one unsuppressed VL, 19% had at least one transmittable VL. 88% of patients continuously followed had suppressed VL, 12% at least one unsuppressed VL and 10% ever transmittable. 90% of newly diagnosed patients entering the population had unsuppressed VL however most quickly became suppressed after initiating treatment (mean time – 62 days). 35% of patients entering from elsewhere presented with a transmittable VL. Of patients formally moving out of the population, 92% were suppressed prior to moving. Patients disengaging from care (n=106) had the highest rate of unsuppressed/transmittable VL of 54% and 49% respectively. Overall, of 1,168,782 total days followed, 92% were spent suppressed, 8.2% unsuppressed (105,011 days), and 6.6% (84,085 days) transmittable. Patients disengaging from care, although accounting for only 5.5% of all patients, accounted for 34% of days spent unsuppressed and 37% transmittable.

Conclusion: Conclusions-Churn adds complexity to reporting HIV viral burden but provides nuance as patients entering or leaving the population contribute disproportionally to overall viral suppression rates. Longitudinal approaches to HIV viral burden provide different perspectives on who may be driving the local HIV epidemic.

1059 RESUPPRESSION AFTER VIREMIA VERSUS VIROLOGIC FAILURE IN KHAYELITSHA, SOUTH AFRICA

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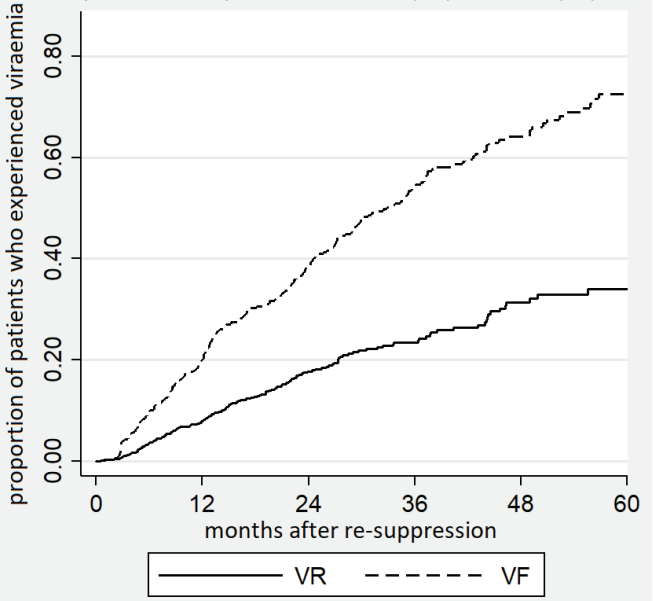
Background: Routine viral load (VL) testing is the recommended strategy for monitoring the effectiveness of antiretroviral therapy (ART) and identifying individuals on failing regimens. For patients with a VL >1000 copies/ml, a VL 3m later (preceded by enhanced adherence support) is recommended to confirm virological failure (VF) prior to switch to second-line. While one justification for this strategy is that suppression can be achieved without a change of regimen, Little information exists as to the durability of any re-suppression achieved, and some advocate for earlier switching based on a single elevated VL for both clinical and operational reasons as cost and safety of second-line regimens improve.

Methods: We included adults ≥15 years old initiating first-line ART between April 2010–March 2018 at 3 provincial primary healthcare clinics in Khayelitsha, South Africa. We estimated the probability and durability of re-suppression following initial viraemia (VR) and VF at different durations on ART in the subset of patients in continuous care.

Results: Of 4005 patients who experienced VR or VF, 2194 (54.8%) re-suppressed in median 29.4 (IQR 17.3-45.8) months after ART initiation. VF patients were less likely to re-suppress (HR 0.90; 95%CI 0.83-0.98) compared to VR patients. Among patients who re-suppressed and had at least one subsequent VL, 175 (12.1%) of 1 446 and 305 (24.8%) of 1228 patients who had VR and VF respectively experienced subsequent viraemia (aHR 2.40 for VF vs VR; 95%CI 1.85-3.10) adjusting for sex, baseline CD4, age, TB and pregnancy status. By 24 months after re-suppression 17.8% and 38.5% of VR and VF respectively patients had experienced viraemia (Figure).

Conclusion: A substantial and nearly comparable proportion of patients with VR or VF go on to re-suppress, despite programme expansion and variable adherence support after initial viraemia. The durability of re-suppression in those with VF was, however, appreciably lower than in those with VR. As regimen-sparing becomes less critical, in some settings the operational efficiency of early switching might outweigh the regimen-sparing which results from confirming failure.

Figure: Time to viraemia after re-suppression in patients with previous viraemia (VR) vs failure (VF)



1060 HIGH AWARENESS BUT UNCERTAIN BELIEF IN U=U AMONG PROVIDERS AND COUPLES IN KENYA

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Background: Sustained viral suppression resulting from antiretroviral therapy (ART) eliminates the risk of HIV transmission. Scientific and popular messaging has framed this elimination of risk in concepts such as treatment as prevention (TasP) and Undetectable = Untransmittable (U=U). We explored knowledge and acceptance of information around the elimination of HIV transmission risk with ART among health providers and HIV serodiscordant couples in Kenya.

Methods: The Partners Scale-up Project is evaluating PrEP delivery to HIV uninfected individuals in serodiscordant relationships in 24 public HIV clinics in Central and Western Kenya. We conducted semi-structured in-depth interviews with 69 health providers and 35 HIV uninfected people in serodiscordant relationships receiving PrEP services. Transcripts were coded using framework analysis.

Results: Health providers reported being aware of reduced risk of HIV transmission as a result of consistent ART use and used words such as 'very low', 'minimal', 'like zero' to describe HIV transmission risk after viral suppression: but did not use the words 'no risk.' Additionally, providers reportedly found viral load results helpful when counseling clients on the 'very low risk' of HIV transmission after viral suppression. Others believed that U=U works, but only in the context of consistent condom use but concerns were expressed that communicating this message to HIV infected persons would lead them to engaging in multiple sexual relationships. Other providers reported avoiding counseling on risk of HIV transmission even after viral suppression for fear in case a seroconversion occurred they would be blamed. Similarly, members of HIV serodiscordant couples reported being informed about U=U by the providers but they did not believe/trust the message. Even after the HIV infected partners reached viral suppression, most HIV uninfected members of couples reported unwillingness to stop PrEP while others reported that they would use condoms if they stopped PrEP.

Conclusion: Despite high awareness that ART eliminates HIV transmission risk, there is both a lack of in depth knowledge and conviction among health providers and PrEP users. New strategies to communicate U=U in a reliable and believable way are urgently needed.

1061 RESUPPRESSION AFTER POINT-OF-CARE VIRAL LOAD TESTING TO GUIDE ADHERENCE COUNSELING

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Background: Whilst implementation of virologic monitoring remains uneven across Africa, novel molecular platforms now facilitate adoption at point of care (POC). The OPTIMISE study explored POC viral load testing followed by immediate adherence counselling for its impact on rates of virologic resuppression in a programmatic care setting in Ghana. At the center, the second largest in Ghana, routine virologic monitoring is not yet available.
Methods: Consecutive patients who were established on ART and accessed outpatient care over a 2-week period in February 2018 (T1) were invited to complete an adherence questionnaire and to self-report adherence via a visual analogue scale (VAS). HIV-1 RNA was quantified with Cepheid Xpert over 90 min. Patients with viremia (>40 copies/ml) received immediate adherence counselling by trained nurses over 15-20 min, and were invited to reattend 8 weeks later (T2), when adherence was re-assessed and viral load testing repeated.
Results: At T1, 333 consecutive patients (74% females, median age 48 years, median CD4 count 626 cells/mm3) underwent POC viral load testing. Patients had received ART for a median of 9 years. Most (297/333, 89%) were on NNRTI-based ART (mainly efavirenz); 36/333 (11%) were on PI-based ART, mainly lopinavir/ritonavir. The NRTIs comprised mainly TDF/3TC (187/333; 56%) and ZDV/3TC (130/333, 39%). Overall, 164/333 (49%) subjects had viremia, with median levels of 423 copies/ml; 71/333 (21%) had levels >1000 copies/ml. By regression analysis, a self-reported history of ≥1 treatment interruption since first starting ART (usually due to unavailability of the dispensary) independently predicted viremia at T1 (adjusted OR 3.1; 95% CI 1.5-6.3; p<0.01). Of the 164 patients with T1 viremia, 150 (91%) attended at T2 and 32/150 (21%) showed resuppression. By multivariable analysis (Table 1), a T1 viral load >1000 copies/ml independently predicted lack of resuppression at T2.
Conclusion: In this programmatic HIV setting lacking access to routine virologic monitoring, half of the cohort had detectable viremia while on ART, and only a fifth achieved resuppression following adherence counselling. Patients established on long-term NNRTI-based ART who report a history of treatment interruption could benefit from viral load testing at POC regardless of current self-reported adherence. Those with a viral load >1000 copies/ml should be offered an immediate switch to alternative therapy.

Table. Univariable and multivariable logistic regression analysis of predictors of resuppression following point of care viral load testing and immediate counselling

Variable		Univariable analysis			Multivariable analysis		
		OR	95% CI	p	OR	95% CI	p
Gender	female vs male	1.05	0.45-2.42	0.92			
Age	per 5-years older	1.02	0.80-1.29	0.89			
In stable partnership	yes vs no	0.47	0.21-1.04	0.06	0.40	0.15-1.06	0.06
Children in the household	yes vs no	0.80	0.20-3.14	0.75			
Number of children	per number higher	0.97	0.78-1.19	0.74			
Duration of journey to clinic	>2 hrs vs <2hrs	0.71	0.28-1.81	0.48			
Education	≥ secondary vs <secondary	1.56	0.70-3.47	0.28			
Enough food for basic needs	Never vs at least sometimes	1.89	0.53-6.74	0.33			
Weekly alcohol consumption	yes vs no	0.39	0.05-3.20	0.38			
Use of traditional or herbal remedies	yes vs no	0.60	0.07-5.19	0.64			
On PI-based ART	yes vs no	1.58	0.56-4.48	0.39			
Time on ART	per year longer	0.99	0.89-1.09	0.83			
History of treatment interruptions	None vs ≥1	1.54	0.70-3.39	0.28			
T1 VAS	per 10% higher	1.09	0.75-1.59	0.64			
T1 doses missed in the previous week	≤1 vs ≥2	0.14	0.03-0.63	0.01	0.39	0.07-2.10	0.27
T1 doses missed in the previous month	≤1 vs ≥2	0.61	0.26-1.41	0.25			
Time since HIV diagnosis	per year longer	1.01	0.91-1.12	0.81			

1062 COMORBID CONDITIONS, VIRAL TRAJECTORIES, AND COORDINATED CARE IN LOS ANGELES COUNTY

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Background: In March of 2013, the Los Angeles County Division of HIV and STD Programs implemented a clinic-based Medical Care Coordination (MCC) Program for high-risk people living with HIV (PLWH) with comorbidities (e.g., substance use, homelessness, and mental health disorders) to improve viral suppression (VS) (<200 c/mL) through case management services. The present study aims to determine the odds of VS prior to and following MCC enrollment, and to compare trajectories by reported stimulant use, homelessness, and depressive symptom severity.
Methods: Data were 52,138 observations from 6,269 PLWH from 12 months (m) prior to MCC enrollment to 36 m post-enrollment. Piecewise mixed effects logistic regression estimated trajectories of VS (1) 12 m pre-MCC, (2) 0-6 m post-enrollment, and (3) 6-36 m post-enrollment--cut-points based on locally weighted scatterplot smoothing. We compared VS trajectories by reported stimulant use (methamphetamine, cocaine, and crack), homelessness, and depressive symptoms (PHQ-9 score), adjusting for sociodemographic and HIV-related covariates.
Results: At enrollment, 42.8% of the sample had VS. Reported stimulant use (OR=0.62, 95% CI [0.52, 0.74], p<.001) and pronounced depressive symptoms (OR=0.90, 95% CI [0.85, 0.96], p<.001) were associated with lower odds of VS, while homelessness was not. Odds of VS increased by a factor of 11 in the first 6 months in MCC (ΔOR=10.88, 95% CI [9.98, 11.87], p <.001), then did not significantly change 6-36 m post-enrollment (ΔOR=0.98, 95% CI [0.95, 1.00], p=.080). Post-enrollment changes in odds of VS did not differ by reported stimulant use. In the first 6 m in MCC, those reporting homelessness improved less in VS than those stably housed (ΔOR=0.42, 95% CI [0.34, 0.51], p<.001). In later months, those reporting homelessness improved more in VS than those stably housed (ΔOR=1.06, 95% CI [1.00, 1.13], p=0.035). Pronounced depressive symptoms were associated with greater improvement in VS 6-36 m post-enrollment (ΔOR=1.03, 95% CI [1.02, 1.04], p=0.001).
Conclusion: MCC patients significantly improved and sustained their VS, with the greatest increase occurring within the first 6 m, likely attributed to improved access and adherence to HIV care as well as support services. While there were significant differences in time to VS among patients with comorbidities, these results suggest potential for this patient-centered program to address these disparities.

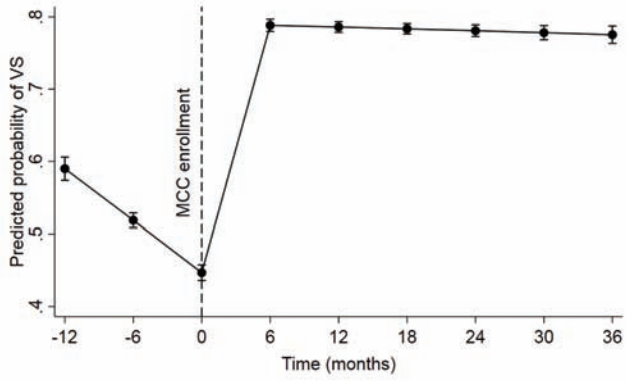

Figure. Predicted probabilities of VS across time from mixed logistic regression

1063 HIGH NCDs INCIDENCE AMONG PLHIV IN KENYA: LONGITUDINAL ANALYSIS OF TREATMENT OUTCOMES

Dunstan Achwoka[1], **Anthony Waruru**[1], Tai Ho Chen[1], Kenneth Masamaro[1], Evelyne Ngugi[1], Irene Mukui[2], Abraham Katana[1], Thomas Achia[1], Lucy Ng'ang'a[1], Kevin M. De Cock[1]
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Background: Over the last decade, the Kenyan national HIV treatment program has grown exponentially, with improved survival among people living with HIV (PLHIV). In the same period, noncommunicable diseases (NCDs) have become a leading contributor to disease burden in the country. There is limited data on the burden of NCDs among PLHIV in Kenya. We sought to characterize the burden of four major categories of NCDs (cardiovascular diseases, cancer, chronic respiratory diseases and diabetes mellitus) among adult PLHIV in Kenya.

Methods: We conducted a nationally representative retrospective medical chart review of HIV-infected adults aged ≥15 years enrolled in HIV care and treatment facilities in Kenya from October 1, 2003 through September 30, 2013. We estimated proportions of the four NCD categories among PLHIV at enrollment into HIV care, and occurrence and management during subsequent HIV care and treatment visits. We compared proportions and assessed distributions of co-morbidities using the Wald adjusted Pearson's χ-square test. We calculated NCD incidence rates and their jackknife confidence intervals in assessing cofactors for developing NCDs.
Results: We analyzed 3170 patient records; 2115 (66.3%) were from women. Slightly over half (51.1%) of patient records were from PLHIVs aged above 35 years. Close to two-thirds (63.9%) of PLHIVs were on ART. The proportion of any documented NCD among PLHIV was 11.5% (95% confidence interval [CI] 9.3, 14.1), with elevated blood pressure as the most common NCD (87.5%) among PLHIV with diagnosed NCD. Although serial elevated blood pressures were detected among 343 patients, only 17 had a documented diagnosis of hypertension in their medical record. The differences in overall NCD incidence rates for men and women were not statistically significant (42.3 per 1000 person years [95% CI 35.8, 50.1] and 31.6 [95% CI 27.7, 36.1], respectively). No differences in NCD incidence rates were seen by marital or employment status. At one year of follow up 43.8% of PLHIV not on ART had been diagnosed with an NCD compared to 3.7% of patients on ART; at five years the proportions with a diagnosed NCD were 88.8% and 39.2% (p<0.001), respectively.
Conclusion: PLHIV in Kenya have a high incidence of NCD diagnoses. In the absence of systematic screening, NCD incidence is likely underestimated in this population. In context of a rising national burden of NCDs and increased survival among PLHIV, Kenya should consider increasing investment in integrated HIV-NCD screening and care.

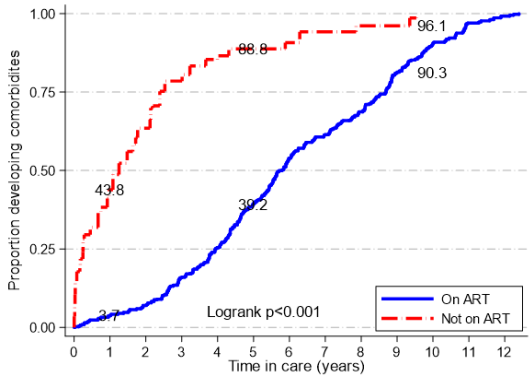

Figure 1: Proportion of patients developing comorbidities any time and during follow-up by ART status, Longitudinal Surveillance of Treatment in Kenya, 2016 (N=3170)

1064 NONCOMMUNICABLE DISEASES AS REASONS FOR ADMISSION AMONG HIV-INFECTED ADULTS IN ZAMBIA

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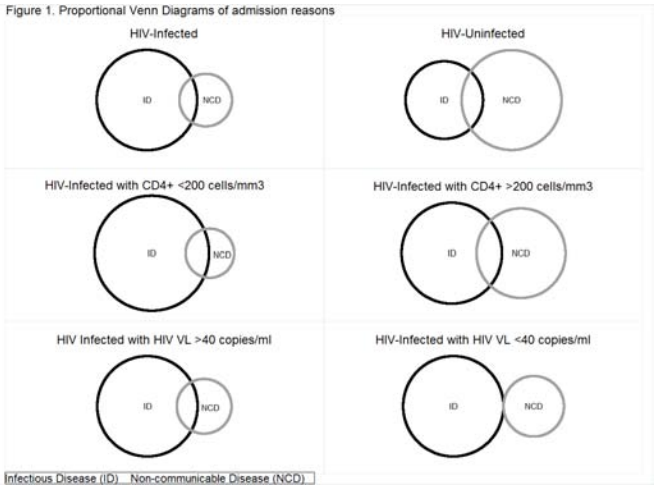
Background: Although rates of non-communicable diseases (NCDs) among HIV-infected individuals are anticipated to increase in sub-Saharan Africa (SSA); quantitative data characterizing the true burden of NCDs are scarce. We investigated the proportion of hospitalizations attributed to NCDs among adults with and without HIV at a hospital in Zambia
Methods: We extracted age, sex, HIV status, and reason for admission from a randomly-selected group of adults (18+ years) admitted to the internal medicine inpatient wards at University Teaching Hospital (UTH) in Lusaka. We defined HIV infection by self-reported positivity or a rapid test, and considered self-reported negative patients as unknown status. Among HIV-infected individuals, we also captured CD4+ and HIV viral load and defined viral suppression (VS) as <40 copies/ml. Reasons for admission (up to 2 per patient) were coded as infectious diseases (IDs), non-communicable diseases (NCDs), or unknown as well as by medical specialty (neurology, cardiovascular, renal, etc.). Two physicians coded each admission reason independently, with a third available to resolve disagreement. We displayed differences in the proportion with ID versus NCD admissions by HIV status and by CD4+ and viral load among HIV-infected individuals.
Results: From August 2017 to February 2018, we assessed 1,261 inpatients, 140 (11.1%) of whom were excluded for unknown HIV status. Among those included in analysis, median age was 38 years (interquartile range, 30-48), 564 (50.3%) were women, and 748 (66.7%) were HIV-infected. NCDs accounted for 29.2% of admissions overall and 17.8% among HIV-infected individuals. Among 143 patients with laboratory data (who had similar age and sex [P>0.05] to those without data), median CD4+ was 181 cells/mm^3 (interquartile range, 52-299), 42.9% had VS, and in those with CD4+ >200 cells/mm^3, NCDs were nearly as common as IDs (40.7% versus 51.2%; Figure 1). Among HIV-uninfected individuals, NCDs were slightly more common than IDs (53.6% versus 49.9%). Heart failure (9.5%), anemia (6.3%), stroke (4.3%), and diabetes (3.8%) were most common NCDs.
Conclusion: NCDs were a common cause of hospital admission among HIV-infected individuals and others in Zambia. These data inform recommendations to integrate NCD risk factor screening and care for HIV-infected individuals in SSA. Hospital surveillance data can provide useful information to HIV programs regarding emerging causes of non-HIV-related morbidity and mortality.



1065 PROJECTED GROWTH AND NEEDS OF AGING PLWH IN HRSA'S RYAN WHITE HIV/AIDS PROGRAM

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Background: With advances in science and antiretroviral therapy, HIV has become a manageable condition and people living with diagnosed HIV (PLWH) are living longer. In the United States (US), over 450,000 PLWH were aged ≥50 years in 2015, an increase of nearly 40% since 2011. This rapid growth of the aging population of PLWH highlights the need to identify and implement aging-appropriate HIV care and support services. The Ryan White HIV/AIDS Program (RWHAP) supports HIV care, treatment, and support services for more than 50% of PLWH in the US. This analysis examines sociodemographic characteristics, service utilization, and viral suppression (VS) among current RWHAP clients and projects the growth of the aging RWHAP population by 2030.
Methods: Client-level data from the RWHAP Services Report were used to calculate distributions among clients aged ≥50 (older) and <50 (younger), by race/ethnicity, gender, transmission risk, poverty level, health care coverage, and housing status, and trends in service utilization from 2010-2016. Among older clients, additional analyses examined differences by gender and race/ethnicity. VS was calculated among older clients receiving RWHAP outpatient

health services. Five-year age distribution trends were used to project the number of RWHAP clients aged ≥50 by 2030.
Results: In 2016, 44% of RWHAP clients were aged ≥50, an increase from 32% in 2010. A higher proportion of older than younger clients were White, lived above the poverty level, had stable housing, and accessed food-related services. Among older clients, women and transgender clients had higher housing instability and poverty compared to men. Variation was seen by race/ethnicity. In 2016, VS among older clients was 90% compared to 81% among younger clients. VS increased across all subpopulations of older clients from 2010 to 2016; however, clients with unstable or temporary housing had lower percentages compared to other key subpopulations. By 2030, a projected 66% of RWHAP clients will be aged ≥50 years.
Conclusion: Older PLWH receiving care and treatment through RWHAP have high percentages of VS. However, social and structural factors, such as housing stability, may impact HIV outcomes. In addition, aging PLWH may have unique needs, such as food insecurity, long-term HIV medication effects, behavioral health needs, and age-related comorbidities. As the population of older PLWH continues to grow, so too will the importance of further assessing and planning for the needs of this emerging population.

1066 CASCADES TO EVALUATE THE CERVICAL CANCER SCREENING PROGRAM IN A ZIMBABWEAN ART CLINIC

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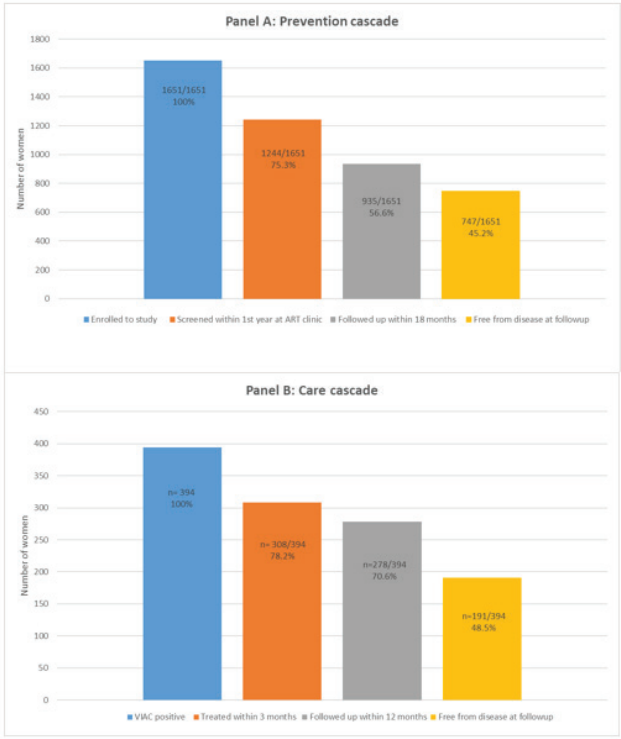
Background: The cascade approach, which is utilized for assessment of HIV care, might also be useful to strengthen cervical cancer (CC) screening programs for women living with HIV (WLHIV). We defined cascade indicators and piloted this approach in an antiretroviral therapy (ART) clinic in Harare, Zimbabwe.
Methods: We defined eligibility for inclusion into the study as women aged ≥ 18 years enrolled into the Newland's ART clinic between 06/2012 and 06/2017, and followed them up until 06/2018. We identified the number of women eligible for the study; screened and their screening results; receiving treatment; and the number of women receiving re-screening. We extracted data from routinely collected electronic data; some variables were extracted manually from electronic free text records into an EpiData database. The different steps of the Cascade were calculated, using the same denominator throughout the cascade.
Results: A total of 1,651 WLHIV were eligible for the study at enrolment into the ART clinic (median age 37 years (IQR 30 – 44)). At enrolment, 70.6% (1166) were HIV WHO stage 1 or 2, while 23.7% (391) were WHO stage 3 and 4, this data on the remaining 5.7% (94) was missing. Overall, 75.3% WLHIV (1244/1651) were screened within the first year of enrolment into the ART clinic. Of these, 935 (56.6%) were re-screened within 18 months and 747 (45.2%) were free from cervical disease at first follow-up (Figure Panel A). Most women (99.7%, 1241/1244) were screened using visual inspection with acetic acid and cervicography (VIAC), and 0.3% (3/1244) received a PAP smear. Of the 407 women who were not screened, 21.6% (88/407) reported that they were not yet sexually active and 9.3% (38/407) were pregnant at the time of enrolment into ART clinic. Of women who were screened within one year of enrolment, 29% (357/1244) were VIAC positive. Of these, 308 (78.2%) received treatment within 3 months, 278 (70.6%) were followed up within 12 months after treatment and 191 (48.5%) were free from cervical disease at follow-up (Figure Panel B).
Conclusion: In our pilot study, 75% of WLHIV were screened for CC within one year of enrolment into the ART clinic and about half of the women enrolled were known to be free from cervical disease at follow-up screening. The proposed cervical cancer prevention and care cascade allows monitoring patient flow through essential screening steps and identification of targets for interventions to further improve CC screening outcomes.

The cervical cancer prevention and care cascade



1067 EARLIER AGE OF ONSET AND HIGHER PREVALENCE OF COMORBIDITIES IN PEOPLE LIVING WITH HIV

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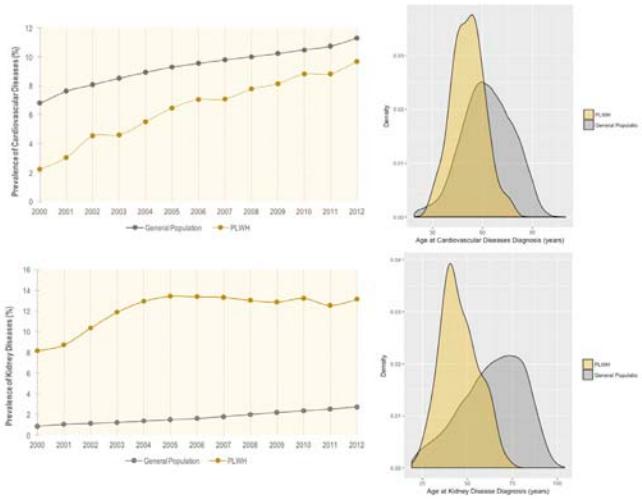
Background: As people living with HIV (PLWH) are living longer, premature morbidity and mortality from age-associated comorbidities are more common. Our objective was to compare prevalence trends and age of onset of comorbidities between PLWH and the general population in British Columbia (BC).
Methods: This retrospective cohort study used longitudinal data from the Comparative Outcomes and Service Utilization Trends study, a population-based cohort of PLWH and 10% random representative sample of BC population. Eligible participants were ≥19 years old and followed for ³1 year between 2000 and 2012. PLWH were antiretroviral therapy (ART) naïve. Age-related comorbidities were identified from hospital and physician billing provincial databases using the International Classification of Disease versions 9/10. Selected comorbidities included cardiovascular, kidney, lung, and liver diseases, non-AIDS-defining cancers, diabetes, osteoarthritis and hypertension. Generalized non-linear models (assuming a beta distribution and a logit link) modeled the prevalence trends, and the Mann-Whitney U test compared the distribution of age of onset of comorbidities between both populations.
Results: The study included 4,223 PLWH and 454,092 HIV-negative individuals (median age 37 vs. 39 years, 80% vs. 50% men, median follow-up 5 vs. 13 years, respectively). Yearly prevalence of diabetes, kidney, liver, and lung diseases were significantly higher among PLWH, while the remaining comorbidities were significantly higher among HIV-negative individuals. The gap in prevalence of kidney and liver diseases between the two populations is considerably wide, while for cardiovascular diseases and diabetes, it is rapidly narrowing. PLWH experienced all comorbidities at a significantly younger age than their counterparts, ranging between 8 years earlier for hypertension and 22 years for kidney diseases. See figure for an example of trends of prevalence and age of onset of two key comorbidities in these populations.

Conclusion: Our results showed that PLWH experience earlier onset of non-HIV related comorbidities that can contribute to accelerated aging. The gaps in the prevalence of comorbidities could be related to HIV related inflammation, life-style issues and toxicities related to older ART. These results further stress the need for early HIV diagnosis and ART initiation with maintenance of long-term virologic suppression, as well as optimized general clinical screening for comorbidities at earlier age among PLWH.



1068 POOR DIABETES CONTROL IN HIV+ AND HIV- WOMEN: OPPORTUNITIES FOR INTERVENTION

Karla I. Galaviz[1], Jonathan Colasanti[1], Cyra Christina Mehta[1], Phyllis Tien[2], Adaora Adimora[3], Maria L. Alcaide[4], Mardge H. Cohen[5], Deborah Gustafson[6], Roksana Karim[7], Deborah Konkle-Parker[8], Daniel Merenstein[9], Anjali Sharma[10], Michael F. Schneider[11], Gina Wingood[12], Igho Ofotokun[1]
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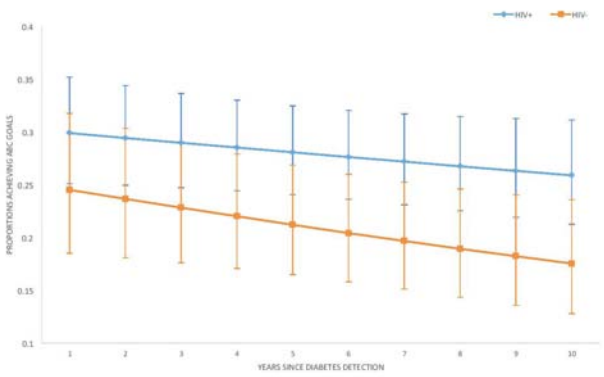
Background: Type 2 diabetes mellitus (DM) is an increasingly common comorbidity among HIV+ populations. It remains unknown whether there are longitudinal differences in achievement of DM care goals between HIV+ and HIV- adults. We examined DM care goal achievement between HIV+ and HIV- women within 10 years of DM detection.
Methods: We analyzed longitudinal data from the Women's Interagency HIV Study. We identified women with incident DM defined as the first visit when women self-reported DM medication use or had two fasting plasma glucose (FPG) measures ≥126 mg/dL, or Hemoglobin A1c (A1c) ≥6.5% plus a FPG ≥126 mg/dL. At 1, 3, 5, and 10 years after DM diagnosis, we estimated proportions of women who met the ABC DM treatment goals (glycated hemoglobin [A1c] <7.0%, blood pressure [BP] <140/90mmHg, LDL Cholesterol <100 mg/dL), by HIV status. Using generalized logistic mixed models, we estimated the probability of achieving ABC goals by HIV status controlling for age, race, body weight, DM, BP and Cholesterol medication use, time since DM diagnosis, and knowledge of DM diagnosis (i.e. self-reported DM diagnosis).
Results: There were 390 HIV+ (mean age 46.4 years, SD 8.5) and 169 HIV- women (mean age 45.2 years, SD 9.5) with incident DM and at least one follow-up A1c measure. At baseline, 80% of HIV+ and 86% of HIV- women did not know they had DM. Crude proportions of HIV+/HIV- women using DM, BP and Cholesterol medications were 7%/6% at 1 year, 9%/17% at 3 years, 12%/13% at 5 years, and 28%/25% at 10 years after DM diagnosis. Crude proportions of HIV+/HIV- women achieving ABC treatment goals were 33%/31% at 1 year, 19%/34% at 3 years, 28%/24% at 5 years, and 27%/17% 10 years after DM diagnosis. Adjusted analyses showed ABC goal achievement worsened over time to a similar extent in HIV+ women (from 30% [95%CI: 25%, 35%] at 1 year to 26% [95%CI: 21%, 31%] at 10 years after DM diagnosis) and HIV- women (from 25% [95%CI: 19%, 32%] at 1 year to 18% [95%CI: 13%, 24%] at 10 years after DM diagnosis; p=0.2902 for HIV status*time, see Figure).
Conclusion: We noted large and growing gaps in DM care goal achievement in both HIV+ and HIV- women. Opportunities to improve DM care are numerous; aggressive DM management interventions among HIV+ and HIV- women are needed.

Figure. Adjusted probability of achieving ABC goals by HIV status.



1069 TOTAL AND CENTRAL OBESITY PREDICT COGNITIVE DECLINE: MULTICENTER AIDS COHORT STUDY

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Background: Among adults with HIV infection, obesity may contribute to multisystem dysregulation including cognitive impairments. We examined body mass index (BMI) and central obesity (waist circumference, WC) in association with domain-specific cognitive function and 10-year cognitive decline in adult men living with HIV infection (HIV+) compared to at-risk men without HIV infection (HIV-).
Methods: The longitudinal Multicenter AIDS Cohort Study (MACS) of HIV infection among HIV+ men and at-risk controls (HIV-) provide data for these analyses. Inclusion criteria included: >40 years old at first neuropsychological testing; and for HIV+ men, ≥2 antiretroviral agents and HIV-1 RNA <400 copies/mL at >80% of visits. Outcomes included neuropsychological test scores measured every 2 years. Tests included: learning (RAVLT total learning, Rey immediate recall), memory (RAVLT delayed recall, Rey delayed recall), executive function (TMT-Part B, Stroop interference trial), processing speed (SDMT, Stroop color-naming trial), sustained attention and working memory (CALCAP mean simple and complex reaction time), and fine motor function (GPEG-dominant and non-dominant hand). Exposures included baseline BMI and WC. Linear mixed effects models included all available visits from 1996-2015, adjusted for baseline sociodemographic, behavioral, and clinical characteristics, stratified by HIV-serostatus.
Results: Among 972 (316 HIV+ and 656 HIV-) men at baseline, higher BMI (≥25 kg/m^2) was cross-sectionally associated with lower motor function in HIV+ and HIV-, and lower attention/working memory in HIV- men. Obese WC (≥102 cm, 40 inches) was associated with lower motor function in HIV+ and HIV- men. Longitudinal analyses (Fig 1) indicated that overweight (BMI 25.0-29.9 kg/m^2) or obese (BMI ≥30 kg/m^2) vs normal BMI (18.5 to 24.9 kg/m^2) was associated with less decline in motor function in HIV+ men, but greater decline in motor function, memory, and learning in HIV- men. WC showed similar patterns.
Conclusion: Higher BMI and central obesity are associated with lower cognitive performance cross-sectionally and greater cognitive decline, particularly in

HIV- men. Overweight and obesity may be important predictors of mid-life neuropsychological outcomes and later-life cognitive impairments, and should be considered in prevention and intervention planning.

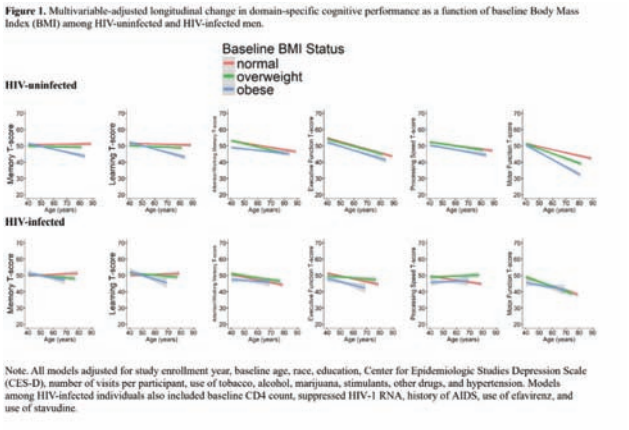

Figure 1. Multivariable-adjusted longitudinal change in domain-specific cognitive performance as a function of baseline Body Mass Index (BMI) among HIV-uninfected and HIV-infected men.

Note. All models adjusted for study enrollment year, baseline age, race, education, Center for Epidemiologic Studies Depression Scale (CES-D), number of visits per participant, use of tobacco, alcohol, marijuana, stimulants, other drugs, and hypertension. Models among HIV-infected individuals also included baseline CD4 count, suppressed HIV-1 RNA, history of AIDS, use of efavirenz, and use of stavudine.

1070 EFFECT OF OBSTRUCTIVE LUNG DISEASE ON MORTALITY AMONG HIV+ PERSONS WHO INJECT DRUGS

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Background: People living with HIV experience increased prevalence of obstructive lung disease (OLD), even after accounting for greater smoking prevalence in this population. Although excessive lung function decline has been shown to lead to increased mortality in HIV-negative individuals, the effect of OLD on mortality among people living with HIV has not been quantified. We investigated whether the effect of incident OLD on mortality differs by HIV status in a cohort of people with a history of injecting drugs.
Methods: The ALIVE study is a longitudinal, observational cohort of HIV-positive and negative people with a history of injecting drugs. This analysis included ALIVE participants who had at least one spirometry measure to assess OLD between 2007 and 2016, excluding those who reported never smoking (5%, n=62) or who had OLD at baseline (17%, n=269). Incident OLD was defined as a first measurement of pre-bronchodilator FEV1/FVC<0.70 during follow-up. The effect of incident OLD on mortality among HIV-positive and negative participants was estimated using an inverse-probability-of-treatment weighted marginal structural model controlling for confounders including baseline age, black race, sex, baseline calendar year, HIV, baseline smoking pack-years, time-varying smoking status, and calendar time.
Results: Among 1,216 participants, 272 (22.4%) experienced incident OLD and 157 (12.9%) deaths were observed over a median of 5 person-years (IQR=2-8) of follow-up. In the main analysis, OLD did not have a statistically significant effect on mortality (HR=1.22, 95% CI: 0.83-1.79). In the model that assessed effect measure modification by HIV, HIV-positive participants exposed to OLD experienced an increased risk of mortality (HR=1.72, 95% CI 1.06-2.81), while there was no effect of OLD on mortality among HIV-negative participants (HR=0.80, 95% CI: 0.45-1.42).
Conclusion: Although OLD did not have a statistically significant effect on mortality after properly accounting for baseline as well as time-varying confounders, there was an apparent effect of OLD among HIV-positive people with a history of injection drug use. These results highlight the need for greater screening and management of OLD among HIV-positive individuals. Further research is needed to determine if there are particular clinical characteristics of HIV-infection that mitigate the risk of death after the occurrence of OLD.

Estimates of the Effect of Incident OLD and HIV on Mortality in the ALIVE study (N=1,216)

	HR	95% CI
Main effects model[1]		
OLD	1.22	0.83-1.79
Assessment of effect measure modification by HIV[1]		
OLD and HIV-negative[2]	0.80	0.45-1.42
OLD and HIV-positive[3]	1.72	1.06-2.81

[1] Inverse-probability-of-treatment weights calculated using baseline age, black race, sex, baseline calendar year, HIV, baseline smoking pack-years, time-varying smoking status, and calendar time
[2] Reference group is HIV-negative individuals who did not experience OLD during follow up
[3] Reference group is HIV-positive individuals who did not experience OLD during follow up

1071 SYNDEMICS AND RETENTION IN CARE AMONG WOMEN LIVING WITH HIV IN RIO DE JANEIRO, BRAZIL

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Background: Syndemic psychosocial and reproductive factors impacting women's engagement in the HIV care cascade remain understudied worldwide. We hypothesized that syndemic conditions would limit retention in care among a cohort of women living with HIV in Rio de Janeiro, Brazil.
Methods: We analyzed baseline syndemic prevalence and correlates of non-retention in the INI-Fiocruz women's cohort from 2000-2015. A syndemic score was created for a lifetime history of: physical/sexual violence, illicit drug use, adolescent pregnancy (<20 years old), or induced abortion. Stepwise backward logistic regression models identified predictors of non-retention, defined as <2 HIV laboratory results within the first year of cohort enrollment. Two separate models analyzed syndemic contributions to non-retention: Model 1 incorporated individual syndemic variables; Model 2 used the syndemic score.
Results: Of 915 women, 18% met criteria for non-retention. Prevalence of syndemic factors was: physical/sexual violence 38.3%, illicit drug use 17.2%, adolescent pregnancy 53.2%, and induced abortion 27.3%. Nearly half (41.2%) experienced ≥2 syndemic conditions. Illicit drug use was associated with non-retention in unadjusted analysis (cOR 2.05, 95% CI: 1.37-3.05), but none of the syndemic variables reached statistical significance in adjusted models. In Model 1, <9 vs ≥9 years of education (aOR 1.59, 95% CI: 1.05-2.42), years with HIV (1.06, 1.01-1.11), and seroprevalent syphilis (1.85, 1.11-3.06) increased the odds of non-retention. ART initiation at ≤3 months (0.54, 0.31-0.93) and 4-24 months (0.57, 0.36-0.92) before enrollment (vs >24 months) and cohort enrollment from 2005-2009 (0.18, 0.12-0.32) and 2010-2015 (0.50, 0.31-0.81) vs 2000-2004 decreased the odds of non-retention. In Model 2, syndemic scores of 2 (1.94, 1.10-3.41) and 3 (2.16, 1.10-4.24) were associated with non-retention, and the effect of other covariates remained the same.
Conclusion: The syndemic of psychosocial and reproductive factors can limit retention in care for women living with HIV. Syphilis infection independently predicted non-retention, and could be explored as a syndemic factor in future studies. Interventions addressing sex-specific syndemics are needed to optimize HIV care in this vulnerable population.

Table 1. Unadjusted and adjusted associations with non-retention in HIV care among women living with HIV in Brazil, 2000-2015

	Non-retention (N=165)	Retention (N=750)	Unadjusted OR (95% CI)	Model 1[a] Adjusted OR (95% CI)	Model 2[b] Adjusted OR (95% CI)
Education <9 years (N=905)	100 (61)	375 (50.6)	1.52 (1.08-2.15)	1.59 (1.05-2.42)	1.58 (1.06-2.36)
Year of enrollment					
2000-2004	49 (29.7)	110 (14.7)	Ref	Ref	Ref
2005-2009	36 (21.8)	339 (45.2)	0.24 (0.15-0.39)	0.18 (0.12-0.32)	0.18 (0.11-0.30)
2010-2015	80 (48.5)	301 (40.1)	0.60 (0.39-0.91)	0.50 (0.31-0.81)	0.50 (0.31-0.80)
Time on ART					
0 (no ART)	74 (44.8)	304 (40.5)	Ref	Ref	Ref
≤3 months	26 (15.8)	164 (21.9)	0.65 (0.40-1.05)	0.54 (0.31-0.93)	0.53 (0.31-0.91)
4-24 months	49 (29.7)	235 (31.3)	0.86 (0.57-1.28)	0.57 (0.36-0.92)	0.59 (0.37-0.93)
>24 months	16 (9.7)	47 (6.3)	1.39 (0.75-2.60)	0.97 (0.45-2.10)	1.05 (0.49-2.21)
Median (IQR) years with HIV	1.9 (0.9,4.9)	1.1 (0.6,3.4)	1.04 (1.00-1.08)	1.06 (1.01-1.11)	1.05 (1.01-1.10)
Seroprevalent syphilis (N=884)	32 (20.8)	81 (11.1)	2.10 (1.34-3.30)	1.85 (1.11-3.06)	1.89 (1.15-3.11)
Lifetime physical or sexual violence (N=896)	72 (43.9)	271 (37)	1.33 (0.94-1.88)	1.13 (0.75-1.68)	
Lifetime illicit drug use (N=901)	44 (26.7)	111 (15.1)	2.05 (1.37-3.05)	1.50 (0.94-2.41)	
Adolescent pregnancy	98 (59.4)	389 (51.9)	1.36 (0.96-1.91)	1.36 (0.91-2.05)	
Lifetime history of induced abortion (N=907)	46 (28.6)	202 (27.1)	1.08 (0.74-1.57)	0.92 (0.59-1.42)	
Composite syndemic score					
0	28 (17)	191 (25.5)	Ref		Ref
1	53 (32.1)	266 (35.5)	1.36 (0.83-2.23)		1.51 (0.87-2.62)
2	51 (30.9)	189 (25.2)	1.84 (1.11-3.04)		1.94 (1.10-3.41)
3	27 (16.4)	87 (11.6)	2.12 (1.18-3.80)		2.16 (1.10-4.24)
4	6 (3.6)	17 (2.3)	2.41 (0.88-6.62)		1.34 (0.42-4.30)

[a]Model 1 includes individual syndemic factors; age and race were forced into the final model
[b]Model 2 includes the syndemic score; age and race were forced into the final model
Bolded text indicates p-value<0.05

1072 PROSTATE CANCER SCREENING AND INCIDENCE IN AGING VETERANS INFECTED WITH HIV

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Background: Non-AIDS defining cancers are increasingly important contributors to health outcomes for aging persons with HIV (PWH). Although prostate cancer is prevalent in aging men, the impact of HIV infection on prostate cancer risk remains unclear and may be obscured by less screening in PWH. Therefore, we aimed to study longitudinal prostate cancer screening, incidence, and disease characteristics in Veterans Aging Cohort Study (VACS), a national cohort of PWH and uninfected controls.

Methods: Using data from VACS (2000-2015) we identified a cohort of 119,336 (36,333 PWH, 83,003 controls) men ≥45 years of age. We ascertained PSA testing and prostate biopsy using relevant procedure codes, as well as incident prostate cancer diagnoses using linked cancer registry data. We calculated the incidence of PSA testing by HIV status and then fit multivariable Poisson models comparing the rates of PSA testing, prostate biopsy (among PSA tested persons) and prostate cancer incidence (in the whole cohort and restricting to only PSA tested persons) adjusting for age, race and smoking status. Among patients diagnosed with prostate cancer we compared Gleason grade and clinical stage.

Results: Mean age at enrollment was 50 years, and patients were followed for a median of 15 years. A majority received at least one screening PSA test in the study period, including PWH (30,837, 85% ever tested) and controls (75,929, 92%). Prostate cancer was diagnosed in 966 PWH and 2,778 controls. The adjusted incidence of PSA testing over the study period was lower among PWH (IRR 0.80, 95% CI 0.79-0.81). Among PSA tested persons, HIV infection was associated with similar incidence of subsequent prostate biopsy (IRR 0.97, 95% CI 0.93-1.00). The incidence of prostate cancer was lower in PWH (IRR 0.86, 95% CI 0.77-0.91), including upon restriction to only individuals who received PSA testing (IRR 0.90, 95% CI 0.82-0.98). Among patients diagnosed with prostate cancer, there was a trend towards higher Gleason grade (p=0.10) and distant disease (p=0.09) among PWH that did not reach predefined thresholds for statistical significance.

Conclusion: In longitudinal follow-up, there was a lower incidence of prostate cancer among PWH compared with matched controls but some suggestion of differences in grade and stage at diagnosis. Further study is warranted to understand the role of HIV status on prostate cancer treatment and outcome.

Table 1. PSA screening and prostate cancer incidence among PWH and Controls in VACS

	HIV+ (n=36,333)	Uninfected (n=83,003)	p-value
PSA ever	30,837 (85)	75,929 (92)	<0.001
ADJUSTED POISSON MODELS			
	Incidence Rate Ratio (95% CI)		
PSA Testing in HIV+ (2000-2015)	0.80 (0.79-0.81)		<0.001
Biopsy in PSA Tested HIV+	0.97 (0.93-1.00)		0.2
Prostate Cancer in HIV+	0.86 (0.77-0.91)		<0.001
Prostate Cancer in PSA Tested Only, HIV+	0.90 (0.82-0.98)		0.01
PROSTATE CANCER CASES	HIV+ (n=966)	Uninfected (n=2,778)	
Summary Stage			<0.001
Localized	809 (84)	2,395 (87)	
Regional	75 (8)	213 (8)	
Metastatic	52 (5)	103 (4)	
Missing	30 (3)	7 (<1)	
Gleason Grade (Sum)			0.1
6 or Less	314 (33)	1,011 (36)	
7	361 (37)	1021 (37)	
8 or Higher	156 (16)	401 (14)	
Missing	135 (14)	345 (12)	

Abbreviations: PSA=prostate-specific antigen; VACS=Veterans Aging Cohort Study; PWH=Persons with HIV

1073 SOCIOECONOMIC IMPACTS OF UNIVERSAL ANTIRETROVIRAL THERAPY IN THE SEARCH TRIAL

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Background: Improvements in community health due to multi-disease health services and universal antiretroviral treatment have the potential to improve various socio-economic indicators, thereby informing cost-benefit calculations for such investments in healthcare.

Methods: We conducted longitudinal socio-economic surveys over a 3-year period in households of approximately 100 HIV-infected and 100 HIV-uninfected adults sampled after baseline HIV testing in 30 pair-matched communities in the SEARCH trial (NCT01864603). Control communities received baseline multi-disease testing and antiretroviral therapy by national guidelines while intervention communities received annual testing and antiretroviral therapy irrespective of CD4 count via patient-centered care. Surveys assessed various outcomes including employment, consumption expenditures, asset holdings, survival expectations, and children's school enrollment. The primary outcome was employment hours in the past week for individuals aged 18-65 years. Regression models with individual fixed effects and time trends were used to determine causal effects of the SEARCH intervention. Effects were examined for subgroups of HIV-positive adults with CD4 cell counts ≥500 and <500 cells/mm3, their HIV-negative household members, and HIV-negative individuals in households without an HIV-positive adult.

Results: Longitudinal data were collected for 34,396 individuals from 5,283 households. Adults worked an average of 29.6 hours and the majority of employment occurred on households' own farms. Total employment hours among all adults did not change significantly due to the SEARCH intervention but among baseline HIV-positive adults, the intervention increased employment by 6.1 hours (p<0.001). Effects were largest among HIV-positive adults with baseline CD4≥500 (increase of 9.9 hours, p<0.01). Children in households with an HIV-positive adult were 5.3 percentage points more likely to complete

primary school due to the SEARCH intervention (p<0.001). Outcomes such as assets, non-food expenditures, and survival expectations improved significantly over time, but there were no significant differences between intervention and control communities.
Conclusion: Universal antiretroviral therapy provision led to significant economic benefits for HIV-positive adults, particularly those with high CD4 counts. Improvements in socio-economic outcomes and survival expectations were observed in all communities following multi-disease testing at baseline.

1074 CONDOM USE AND PRICES IN TRANSACTIONAL SEX ENCOUNTERS AMONG HIGH-RISK WOMEN IN KENYA

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Background: The exchange of money, goods, or services in sexual relationships is a key driving factor for HIV risk in areas where incidence is above elimination rates. We assessed factors that influence condom use and the monetary value of transactional sex encounters among high-risk women in a high prevalence setting in Kenya.
Methods: Baseline data were obtained for an ongoing cluster randomized trial of an HIV self-testing intervention among women in 66 community clusters in Siaya County, Kenya (NCT03135067). Clusters included fishing communities along Lake Victoria and market centers with hotspots for female sex workers. Eligibility criteria for for women in clusters included: age ≥18 years, HIV-negative status, and self-report of ≥2 sexual partners in the past month. Data were collected on participants' most recent transactional sex encounters, including sexual partner characteristics, condom use, and the "price" of each encounter as indicated by the total value of money, goods, and services received. Regression analyses with participant fixed effects were used to assess participant and partner factors that predicted condom use and the price of each encounter.
Results: Among 2,087 participants, 1,396 (67%) reported sex work as one of their income sources and 1,983 (95%) reported on 4,474 transactional sex encounters. Participants had an average age of 27.1 years (IQR 22-31) and for 62.2% the highest education level completed was primary or below. Condom use was reported in 51% of encounters and was significantly more likely with first-time male partners rather than with repeat partners (65% vs. 49%, p<0.001). The median price per encounter was $9.9 (interquartile range $5-$19.8). Prices were $1.8 higher with partners aged >30 years vs. ≤30 years (p<0.05). Higher prices were also reported partners who were wealthier ($5.4 higher, p<0.01) and rated as being handsome ($1.9 higher, p<0.01). Encounters in which either the participant or partner were intoxicated had significantly lower prices. Unprotected sex was associated with a 15% higher price among women with some secondary or higher education (p=0.05) but there was no significant difference among women with primary education or less.
Conclusion: Among high-risk women in Kenya, there is high prevalence of transactional sex and suboptimal condom use. The large monetary value of transactional sex encounters and lower condom use with repeat partners suggests a need for economic and behavioral interventions that facilitate reduced sexual risk-taking.

1075 SABES: A COST-EFFECTIVE TasP INTERVENTION TO IDENTIFY AND TREAT RECENT HIV INFECTIONS

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Background: *Sabes*, a treatment-as-prevention (TasP) intervention in Lima, Peru, was implemented to test the hypothesis that frequent HIV testing and initiation of ART during early (acute and recent [<3 months]) HIV infection will markedly reduce onward HIV transmission among men who have sex with men (MSM) and transgender women (TW). HIV-negative, high-risk individuals were identified, underwent monthly HIV testing, and were rapidly initiated on ART if they became HIV infected.
Methods: We evaluated the cost-effectiveness of the *Sabes* TasP intervention compared to the standard of care using a government health care perspective, 20-year time horizon, and 3% annual discounting. The epidemic model was adapted from a compartmental model of HIV transmission in Peru; cost estimates were based on those incurred during the implementation of the *Sabes* study, the Peru Ministry of Health HIV program, and the published literature. We estimated the cumulative number and fraction of HIV infections prevented, reduction in HIV incidence and prevalence, the incremental cost-effectiveness ratio (ICER), and net monetary benefit.
Results: Implementation of *Sabes* among MSM and TW in Lima, Peru, is projected to identify an additional 7,751 early HIV infections over 20 years, beyond the standard of care. By 2038, we estimate that the fraction of undiagnosed early HIV cases would decrease to less than half of what is expected with no intervention. We estimate that each additional diagnosis of early infection cost $6,412. *Sabes* improved health, resulting in greater total discounted QALYs per person than the standard of care (16.70 vs. 16.39) over the 20-year time horizon. *Sabes* had an ICER of $578 per QALY compared to the standard of care and was considered cost-effective using a threshold of the GDP per capita in Peru ($6,572 per QALY gained). Upfront costs to deliver the intervention were off-set by longer-term healthcare savings.
Conclusion: Our analysis suggests that the TasP intervention, *Sabes*, is a cost-effective approach to reducing the burden of HIV. Our study supports the implementation of such programs in vulnerable and high-risk MSM and TW in urban, epidemic hot-spots such as Lima, Peru. Given the public health crisis of the HIV epidemic, it is essential to capitalize on interventions with known efficacy, such as *Sabes*, for scale-up to reduce onward HIV transmission in a cost-effective manner.

Summary of results

Result	Reference	Sabes Intervention	Incremental
Acute Diagnoses over 20 years	0	7,751	7,751
Undiagnosed fraction of acute cases in 2038 (%)	1.904	0.720	1.185
Total QALYs	2,188,484	2,229,984	41,500
QALYs per person	16.39	16.70	0.311
Total Costs ($)	292,190,034	316,046,629	23,188.69
Cost per person ($)	2,188.71	2,367.41	178.71
Sabes program cost per acute diagnosis	-	6,382.74	6,382.74
ICER ($ per QALY gained)	-	-	578

NOTES: Costs are presented in common currency of 2016 US$. Costs and QALYs discounted 3% annually. Time horizon of 2018-2038.
Abbreviations: QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio

1076 COST-EFFECTIVENESS OF LONG-ACTING ART FOR ADOLESCENTS AND YOUNG ADULTS IN KENYA

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Background: Despite the high efficacy of oral antiretroviral therapy (ART), viral suppression among adolescents and young adults (AYA) living with HIV in sub-Saharan Africa (SSA) remains low. Without the need for daily adherence to oral ART, long-acting injectable ART (LA-ART) may simplify adherence and, consequently, decrease transmission, morbidity, and mortality in this priority population. However, LA-ART may cost more than oral ART and its threshold for cost-effectiveness has not been evaluated in SSA.
Methods: We adapted a mathematical model of HIV transmission and progression in Kenya to capture HIV acquisition and viral suppression among AYA (age 10-24). We projected the health and economic impact of LA-ART, assuming 75% of AYA on oral ART would switch to LA-ART with a two-month duration of viral suppression per injection. We evaluated two scenarios for LA ART adherence: the first similar to current oral adherence rates (75% viral suppression across AYA) and the second, higher adherence assuming 94% of AYA on LA-ART are virally suppressed (based on LATTE-2 Phase 2b trial results). In the first scenario, we assume AYA who are not adherent to oral ART receive only one two-month injection of LA-ART per year and are virally suppressed by LA-ART for 17% of the year, increasing overall (oral and long-acting) AYA viral suppression to 78%. The higher LA-ART adherence scenario increases overall AYA viral suppression to 89%. We assessed population-level effects of LA-ART over a 10-year time horizon. We calculated the maximum incremental cost of

LA-ART compared to oral ART under both scenarios that would be considered cost-effective, using $500/DALY averted as the cost-effectiveness threshold.
Results: Assuming adherence similar to oral ART, we project LA-ART would avert 10,439 HIV infections and 4,159 HIV-related deaths over 10 years compared to standard of care. With higher adherence (94%), LA-ART would prevent 52,971 infections and 18,433 deaths over 10 years. To have an incremental cost-effectiveness ratio (ICER) below the $500/DALY averted threshold, the annual per-person cost of LA-ART administration can be at most $191 and $266 USD higher than oral ART administration ($169 per year) for the similar and higher adherence scenarios, respectively.
Conclusion: Providing LA-ART to AYA could be cost-effective for reducing HIV burden in Kenya if it is low-cost. Increases in drug resistance due to non-adherence to LA-ART would decrease health benefits and should be evaluated in future analyses.

1077 COST-EFFECTIVENESS OF LONG-ACTING MULTIPURPOSE PREVENTION TECHNOLOGY IN SOUTH AFRICA

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Background: Although preexposure prophylaxis (PrEP) is an efficacious HIV prevention strategy, its preventive benefit has not yet been shown among young women in sub-Saharan Africa likely due to non-adherence. Adherence may be improved with the use of injectable long-acting PrEP methods currently being developed. We hypothesize that targeting long-acting PrEP to women already using injectable contraceptives, the most frequently used contraceptive method in sub-Saharan Africa, could improve adherence to PrEP, result in a reduction of new HIV infections, and be a relatively easy-to-reach-target population. In this modelling study we assessed the epidemiological impact and cost-effectiveness of targeting long-acting PrEP to injectable contraceptive users in Limpopo, South Africa.
Methods: We developed a deterministic mathematical model calibrated to the HIV epidemic in Limpopo. Long-acting PrEP was targeted to 50% of HIV negative injectable contraceptive users in 2018 and scaled-up over 2 years. We estimated the number of HIV infections that could be averted by 2030 and the drug price of long-acting PrEP for which this intervention would be cost-effective over a time horizon of 40 years, from a third-party payer perspective. In the base-case scenario we assumed long-acting PrEP is 75% effective in preventing HIV infections and that 85% of infected individuals are on antiretroviral drug therapy (ART). In sensitivity analyses we adjusted PrEP effectiveness and ART coverage. Costs between $519-$1119 per disability-adjusted life-year (DALY) averted were considered potentially cost-effective, and <$519 as cost-effective.
Results: Without long-acting PrEP, 220,000 (interquartile range 182,000–265,000) new infections will occur by 2030; use of long-acting PrEP could prevent 27,000 (21,000–32,000) or 11.9% (11.0%–13.0%) new HIV infections by 2030 (including 7000 (6000-8000) in men). Long-acting PrEP would prevent 40,000 (33,000-45,000) or 13,000 (9,000-18,000) at 75% and 95% ART coverage by 2030, respectively. To be considered potentially cost-effective the annual long-acting PrEP drug price should be <$28 and the ART coverage remains at most 85%. PrEP is not cost-effective at a ART coverage of 95%.
Conclusion: Targeting long-acting PrEP to injectable contraceptive users in Limpopo is only potentially cost-effective when long-acting PrEP drug prices are low and ART coverage below 95%. If low prices are not feasible, targeting long-acting PrEP only to women at high risk of HIV infection will become important.

1078 NONADHERENCE DUE TO PRESCRIPTION DRUG COSTS AMONG US ADULTS WITH HIV, 2015-2016

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Background: The United States spends more per capita on prescription drugs than other countries, and one-fifth of this cost is paid out-of-pocket by patients. Cost-saving strategies, including nonadherence to medications due to cost concerns, have been documented among U.S. adults, which can affect morbidity and, in the case of persons living with HIV, transmission. However, population-based data for persons with HIV are lacking.
Methods: The Medical Monitoring Project (MMP) is a surveillance system that collects interview and medical record data from a probability sample of adults with diagnosed HIV in the United States. Using weighted data collected 6/2015-5/2016 from 3560 persons taking prescription drugs, we examined the prevalence of 6 strategies used to reduce prescription drug costs, including 3 involving nonadherence (skipping doses, taking less medicine, delaying filling a prescription). Because nonadherence can affect health and transmission, we compared the prevalence of cost-saving related nonadherence by sociodemographic groups, and clinical outcomes among those who did and did not report cost-saving related nonadherence. We used prevalence ratios with predicted marginal means to evaluate significant (P<0.01) differences between groups.
Results: In all, 13% of persons reported using any cost-saving strategy and 8% reported any cost-saving related nonadherence; 8% asked a doctor for lower cost medicine, 1% bought drugs from another country, 2% used alternative medicine, 4% skipped doses, 4% took less medicine, and 6% delayed a prescription. Cost-saving related nonadherence was not associated with age, gender, race/ethnicity, poverty, or homelessness. Cost-saving related nonadherence was significantly higher among persons with a disability, private insurance, and unmet need for medications from the Ryan White AIDS Drug Assistance Program (ADAP), and lower among persons with Medicaid (Table). Persons reporting cost-saving related nonadherence were less likely to be virally suppressed and engaged in care, and more likely to have visited an emergency room or been hospitalized more than once.
Conclusion: Persons with diagnosed HIV in the United States used various strategies to reduce prescriptions drug costs. Cost-saving related nonadherence was relatively low, but was associated with poorer clinical outcomes. Increasing access to ADAP and Medicaid coverage may help to decrease nonadherence due to cost concerns among persons with diagnosed HIV.

Table. Cost saving-related nonadherence among persons with diagnosed HIV who are taking prescription medications by disability, insurance status, and clinical outcomes--Medical Monitoring Project, 2015-2016 (N=3,560)

	Prevalence of cost-saving related nonadherence			Clinical outcomes by cost-saving related nonadherence				
					No (n=3,308)		Yes (n=249)	
	n	Row % (95% CI)	Prevalence ratio (95% CI)		n	Column % (95% CI)	Column % (95% CI)	Prevalence ratio (95% CI)
No disability	104	5 (4-7)	Referent	Viral suppression at last test	2,552	74 (71-76)	165	61 (53-69)	0.83 (0.72-0.95)*
Had disability	144	10 (8-12)	1.91 (1.54-2.37)*	Viral suppression at all tests	2,255	66 (63-69)	142	54 (46-61)	0.81 (0.71-0.94)*
No private insurance	113	6 (5-7)	**Referent**	Engaged in HIV care	2,850	83 (81-86)	194	73 (65-81)	0.88 (0.79-0.98)*
Had private insurance	106	10 (8-12)	1.76 (1.35-2.29)*	No Hospitalizations	2,762	85 (83-86)	193	78 (72-83)	0.92 (0.85-0.99)*
No Medicaid	139	10 (8-12)	1.78 (1.37-2.32)*	1 hospitalization	318	9 (8-11)	20	9 (5-13)	0.96 (0.61-1.53)
Had Medicaid	84	5 (4-7)	Referent	2+ hospitalizations	220	6 (5-8)	36	13 (9-18)	2.15 (1.48-3.13)*
Received ADAP	113	7 (5-10)	1.12 (0.76-1.64)	No ER visits	2,135	65 (61-68)	132	52 (44-60)	0.80 (0.68-0.95)*
Unmet need for ADAP	24	26 (15-36)	3.88 (2.37-6.35)*	1 ER visit	583	17 (15-19)	49	23 (17-29)	1.33 (1.00-1.76)
No need for or receipt of ADAP	105	7 (5-8)	Referent	2+ER visits	580	18 (16-20)	68	25 (17-33)	1.39 (1.00-1.94)

CI, confidence interval; ADAP, AIDS Drug Assistance Program; ER, emergency room; all percentages are weighted; all variables measured by interview self-report except viral suppression and care engagement, which were abstracted from medical records; all variables measured in the past 12 months; cost-saving related nonadherence defined as skipping doses, taking less medicine, or delaying filling a prescription; disability defined as problems with hearing, vision, cognition, mobility, self-care, or independent living; viral suppression defined as viral load documented as undetectable or <=200 copies/mL; care engagement defined as receipt of at least two element of outpatient HIV care (i.e., encounter with an HIV care provider, viral load test result, CD4 test result, HIV resistance test or tropism assay, ART prescription, PCP prophylaxis, or MAC prophylaxis) at least 90 days apart; * *P*-values ≤0.01.

1079 HEALTH CARE UTILIZATION AND COSTS OF ACCESSING HEALTH CARE IN SOUTH AFRICA AND ZAMBIA

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Background: In much of Africa, accessing essential healthcare services is associated with costs to patients, even if there are no user fees. Patients need to pay for travel, and possibly accommodation, and they have a loss in earnings in travel time to and waiting at the facility. These costs can constitute substantial barriers to utilization of healthcare. User fees were abolished in public healthcare facilities in South Africa and Zambia to improving access, but patients may still incur costs. This study sought to determine costs of accessing care in the two countries and elicit factors affecting utilization of outpatient healthcare.
Methods: As part of the HPTN071(PopART) study, baseline data from a random sample of the general adult population aged 18-44 years in 21 communities (all Arms of the study) in South Africa and Zambia were collected between November 28, 2013 and March 31, 2015. Respondents were asked whether they had accessed outpatient healthcare within the past 3 months, and what costs they incurred at the facility, in form of fees for services and pharmaceuticals, costs for accommodation and travel, and how much time they took to travel

and wait at facilities. Multi variable logistic regression models were used to determine factors associated with accessing outpatient healthcare.
Results: 191 of 3,524(5.4%) and 482 of 3,900(12.4%) respondents in South Africa and Zambia, respectively, accessed general outpatient care within the past 3 months. The total monetary expenditures per healthcare visit were USD 6.57 for South Africa and USD 11.59 for Zambia. The costs of accessing care were higher for Zambia compared to South Africa (see Table 1). The majority of expenditure for Zambia (65%) were costs incurred at the facility while for South Africa (54%) the majority of the expenditure were travel costs. Regression results for Zambia show that being HIV positive and on ART significantly increased the odds of accessing primary healthcare while for South Africa having been diagnosed with TB in the past 12 months was associated with significantly increased odds of accessing healthcare (Table 1). Wealth, use of recreational drugs, and employment status were found not to affect the odds of accessing health care in both countries.
Conclusion: Patients incurred costs when accessing outpatient healthcare, despite the abolition of user fees.The odds of accessing healthcare were higher for people living with HIV & diagnosed with TB, suggesting financial burden for people with chronic diseases.

Table 1: Healthcare utilization and costs of accessing primary healthcare in Zambia and South Africa (2014 USD, per visit).

	South Africa				Zambia			
Proportion of respondents who accessed care in past 3 months	191/3524(5.4%)				482/3900(12.4%)			
Travel Costs	USD 3.52 (SD 7.73)	54%	Min 0	Max 47.59	USD 4.07 (SD 21.34)	35%	Min 0	Max 220
Costs at facility (services and pharmaceuticals)	USD 3.05 (SD 8.14)	46%	0	42.84	USD 7.52 (SD 35.42)	65%	0	508
Total Average cost	**USD 6.57**		0	76.15	**USD 11.59**		0	516

Factors associated with accessing outpatient healthcare in past 3 months

	Odds ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P value
HIV Status				
HIV Negative	1		1	
HIV-positive not ART	1.370 (0.87-2.15)		0.947 (0.69-1.30)	
HIV-positive on ART less than 3 yrs.	1.351 (0.67-2.72)	0.3534	1.784 (1.16-2.74)	0.0174**
HIV-positive on ART 3 or more yrs.	1.687 (0.79-3.61)		1.648 (1.02-2.67)	
TB Status				
Did not have TB in the last 12 months	1		1	
Diagnosed with TB in the last 12 months	4.131 (1.90-8.93)	0.000***	1.561 (0.66-3.67)	0.307
Number of Observations	3245[#]		3748[#]	

SD: standard deviation
Note: N- Sample comprises of fewer observations than total number of respondents due to missing values in reporting travel and waiting times.

Logistic regression models. Results presented as odds-ratios. Model adjusted for gender, age, education, wealth index, employment status, use of recreational drugs, having a disability and community fixed effects.
[#] This is the estimation sample which comprises of fewer observations than total number of respondents due to missing values in adjustment variables.

1080 COST AND IMPACT OF COMMUNITY-BASED, ASSISTED HIV SELF-TESTING AMONGST YOUTH IN ZAMBIA

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Background: Uptake of traditional facility-based HIV testing services among adolescents and youth is poor in many countries. HIV self-testing (HIVST) offers one strategy for increasing youth uptake. In order to assess scale-up feasibility, we conducted an economic evaluation of a pilot study that provided assisted, community-based HIVST for 16-24 year olds in Zambia.
Methods: 30 clusters were randomly allocated 1:1 to either intervention or facility-based standard of care (SOC) in Ndola and Kabwe districts. In the intervention clusters, community-based HIVST was implemented through the use of roving teams in 15 clusters over a 6-mo period. These teams conducted community sensitization, counseling and assisted self-testing to 16-24 year olds, and facilitated linkage to care for those testing positive through escort to the facility or referral slips. We estimated the cost (staff salaries, community sensitization, equipment, materials and HIVST kits) per new ART initiate if implemented under routine care and compared this with the cost/initiate for SOC. National census population data, provincial prevalence rates, and 2016 ZAMPHIA survey data were used to estimate national annual costs for scale-up and number of ART initiates.
Results: 5,353 youth accepted the offer of assisted HIVST. The yield of newly diagnosed positive per person tested was 1.0% (56/5,353) for community-based HIVST and 3.2% (214/6728) for facility-based SOC. Just over half of those who newly tested positive through HIVST initiated ART (33/56) within three months. The average cost per client tested was $7.96 for HIVST and $3.18 for facility-based SOC. The total testing cost per new positive diagnosis was $580 and $80 in the HIVST and SOC arms respectively. The cost per new ART initiate increases to $978 for HIVST due to low facility linkage. An estimated 1,114,000 youth tested through currently available testing modalities in 2018, leading to 31,663 ART initiations for an annual cost of $3.6m. National HIVST rollout would reach an additional 310,000 youth annually, increasing the proportion of youth diagnosed by 6%, at an additional cost of $2.5m. Of these, a maximum of 2,192 additional youth would initiate ART.
Conclusion: Community-based HIVST identifies youth who may not otherwise have tested for HIV, but is unlikely to be economically feasible at a national level. Other methods for improving youth HIV testing uptake, such as unassisted HIVST, index HIVST, or targeted community-based strategies should be evaluated and compared.

Table 1. Cost and impact of community HIVST scale-up and facility-based standard of care in Zambia

	Facility-based standard of care	*Community-based assisted HIVST added to facility-based standard of care*
Model parameters based on pilot project implementation		
Number tested	6,728	5,353
Number tested newly positive	214	56
Number initiated on ART	unknown	33
Cost per test provided	$2.54	$6.07
Cost per newly identified positive	$80	$580
Cost per new ART initiate	unknown	$978
National scale up estimates:		
Number of tests provided	1,114,000	310,000
Number of expected new ART-initiates	31,663	2,192
Total annual cost	$2,829,560	$1,881,700

1081 COST-EFFECTIVENESS AND NATIONAL IMPACT OF INDEX HIV SELF-TESTING IN MALAWI

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Background: Testing sexual partners of HIV-positive individuals (index testing) remains a high-yield testing strategy. The secondary distribution of HIV self-testing (HIVST) kits for index testing is highly acceptable in Malawi and promises to increase testing coverage. To assess the cost-effectiveness (CE) and feasibility of index HIVST, we modeled the cost per index partner tested positive and cost per newly confirmed positive (defined as a positive test at the health facility) for HIVST and for the current standard of care, partner referral slips (PRS), as well as the cost and impact of HIVST national scale-up.
Methods: A decision analytic model was parameterized using data collected as part of a randomized trial comparing uptake of HIVST to PRS among partners of antiretroviral therapy (ART) clients at 3 district hospitals in Malawi. Clients were randomized 1:2 to standard PRS or HIVST (Oraquick HIV Self-Test: demonstration and distribution). Baseline and follow-up surveys with ART clients were conducted. CE was measured as the cost per newly confirmed positive (index partner) and was calculated for HIVST (including cost of HIVST kit ($2), counselling, confirmatory testing) and PRS (cost of referral slip, counselling, and standard facility-based testing) divided by the total number of positives newly aware of their status and facility-confirmed positives. Model outputs were applied to national facility-level data on number of HIV tests from PRS to determine potential national increase in new diagnoses and related costs for index HIVST scale-up.
Results: The cost per index patient was $0.85 per PRS and $2.34 per HIVST provided and $3.08 and $3.17 per test completed, respectively. The cost per person newly aware of positive status was $19.27 for PRS and $16.14 for HIVST respectively. The cost per facility-confirmed positive was $84.53 for index HIVST due to low facility linkage. For national scale-up, 146,785 new positives were

identified in Malawi in 2017. 126,949 PRS were given to reach 6,023 new index positives, costing an annual $91,404. National scale-up of index HIVST in place of PRS would increase the number of people newly aware of their positive status by 8% per year nationally (17,545) at an annual cost of $401,795.
Conclusion: Index HIVST is less expensive per person newly aware of their positive HIV status than PRS but more expensive per facility-confirmed positive. Interventions to improve facility linkage should be investigated prior to national rollout.

Table 1. Cost and impact of HIVST for index testing compared to partner referral slips in Malawi

	Index testing modality	
	PRS	***HIVST***
Individual Level		
Cost per referral through index client	$0.85	$2.34
Cost per test completed	$3.08	$3.17
Cost per person newly aware of positive status	$19.27	$16.14
Cost per newly confirmed positive	$19.27	$84.53
National Scale-up		
Number of referrals through index clients	126,949	126,949
Number of HIV tests at the facility	34,419	3,509*
Number of people newly aware of HIV-positive status	6,023	17,545
Number of newly confirmed positive	6,023	3,508
Total annual cost	$91,404	$401,795

*These are confirmatory tests following a positive HIVST

1082 THE COST OF PrEP DELIVERY IN KENYAN ANTENATAL, POSTNATAL, AND FAMILY PLANNING CLINICS

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Background: Integrating PrEP provision through routine ante-/post-natal care (ANC/PNC) and family planning (FP) clinics is a potential strategy for efficient PrEP delivery to women in high HIV burden settings. The cost of delivering PrEP through ANC/PNC and FP clinics is unknown.
Methods: We estimated the incremental economic cost of PrEP delivery from the provider perspective within the PrEP Implementation for Young Women and Adolescents (PrIYA) program in western Kenya. We abstracted program data from November 2017 to June 2018 in 16 facilities and estimated annual numbers of PrEP screening and dispensation visits. We identified all within- and above-facility activities supporting PrEP delivery and measured clinical service time using time-and-motion studies. We obtained input costs from program budgets, expenditure records and staff interviews. We also projected costs under Ministry of Health (MOH) implementation assuming MOH salaries and PrEP supervision by county and sub-county health teams. Under this scenario, we explored the impact of task shifting PrEP screening to HIV counsellors, deferring creatinine (Cr) testing from initiation to first follow-up visit, and varying uptake (proportion of counseling encounters that result in PrEP initiation) and continuation (average number of follow-up visits among returning clients) on program costs. We report the cost per client-month of PrEP dispensed in 2017 USD.
Results: For an annual program output of 24,005 screenings, 4198 PrEP initiations, and 4427 follow-up visits, the average cost per client-month was $27. Personnel, drugs, and lab tests comprised 43%, 25%, and 14% of program costs, respectively. In the MOH scenario assuming no changes in outputs, the projected cost per client-month of PrEP dispensed reduced to $17, with drugs (41%), personnel (33%), and lab testing (15%) accounting for the majority of costs. Deferring Cr testing and task shifting PrEP counseling reduced projected costs by 5% and 8%, respectively. Halving both PrEP uptake and continuation increased the cost per client-month of PrEP to $25, while doubling uptake and continuation lowered the cost to $13.
Conclusion: The cost of PrEP delivery through ANC/PNC and FP was similar to costs reported for delivery to other key populations ($11-$44 per client-month). Streamlining service delivery and increasing volume may reduce unit costs. Empirical cost data on PrEP is essential for program planners to assess the cost-effectiveness and affordability of scaling up PrEP.

1083 COST-EFFECTIVENESS OF PREEXPOSURE PROPHYLAXIS AMONG ADOLESCENT SEXUAL MINORITY MALES

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Background: The U.S. Food and Drug Administration recently approved pre-exposure prophylaxis (PrEP) for adolescents at high risk of HIV infection, but it remains unknown whether this is a cost-effective intervention for adolescent sexual minority males (ASMM) generally or for certain highest-risk subgroups. Building on a recent network modeling study of PrEP among ASMM, we estimated the cost-effectiveness of PrEP use in black and white ASMM in higher prevalence US settings.
Methods: Based on the estimated number of infections averted and the number of ASMM on PrEP from the previous model and published estimates of PrEP costs, HIV treatment costs, and quality-adjusted life years (QALY) gained per infection averted, we estimated the cost-effectiveness of PrEP use in black and white ASMM over 10 years using a societal perspective and lifetime horizon. Effectiveness was measured as lifetime QALYs gained. Cost estimates included 10-year PrEP costs and lifetime HIV treatment costs saved. Cost-effectiveness was measured as cost per QALY gained. For our base-case analysis, we considered PrEP for 16-18-year-old ASMM, initiating PrEP 6 months after first anal intercourse, 40% coverage, adherence profiles from the ATN113 trial, and estimated baseline prevalence of 12.4% and 1.4% among black and white 18-year-old ASMM respectively. Multiple sensitivity analyses were performed to assess robustness of the results to uncertainty in the input parameter values and assumptions used.
Results: Under base-case assumptions, PrEP use would yield a cost-effectiveness ratio (CER) of $33,064/QALY in black ASMM and $427,788/QALY in white ASMM. In all PrEP scenarios considered (2 eligibility criteria, 5 coverage levels, 2 adherence profiles), the CER ranged from $10,461/QALY-$45,997/QALY in black ASMM, and $372,306/QALY-$603,887/QALY in white ASMM. In 95% of 10,000 simulation trials of the multivariate sensitivity analysis, the CER of the base-case PrEP scenario ranged from cost-saving to $69,404/QALY in black ASMM and ranged from $170,305/QALY-$538,881/QALY in white ASMM. PrEP use was cost-effective (<$100,000/QALY) in black ASMM but not cost-effective in white ASMM in all scenarios considered. This difference was mainly driven by the difference in the underlying prevalence.
Conclusion: PrEP use in higher risk ASMM can be a cost-effective HIV prevention intervention at current PrEP drug costs. Clinicians should consider black ASMM a priority group for PrEP access among adolescents.

1084 EPIDEMIC IMPACT OF SUSTAINED VIREMIA AMONG FEMALE SEX WORKERS IN SOUTHERN AFRICA

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Background: Key populations including cisgender female sex workers (FSW) face barriers that undermine broader programmatic efforts to achieve viral load suppression among people living with HIV. We estimated the potential onward transmissions that could stem from a failure to achieve viral load suppression among FSW living with HIV across subnational epidemics in Southern Africa
Methods: We used a deterministic mathematical model of heterosexual HIV transmission to reproduce the epidemiologic features of HIV epidemics in Southern Africa from 1990 to 2016. The model included 2 age-groups; 7 risk-groups (including two strata of FSW and their clients and intermediate and lower risk female and males); and turn-over in sex work and periods of higher risk behaviours. We synthesized subnational and subgroup data on HIV prevalence, sexual partnerships, condom-use, and HIV cascades across South Africa, Lesotho, and eSwatini to parameterize the model and generate 10,000 plausible epidemic trajectories across subgroups. We estimated the transmission population attributable fraction (tPAF), defined as the cumulative fraction of new HIV infections among current FSW and clients; and in the

wider population (excluding current FSW and clients) attributable to onward transmissions from sustained viremia among FSW living with HIV from 2016 onwards.

Results: Simulations reproduced the observed range of HIV prevalence and HIV cascade indicators over time, such that by 2016, overall HIV prevalence across epidemic realizations was 18-32% and FSW HIV prevalence was 43-76%. The model reproduced observed ART coverage: 49-90% among reproductive-age women compared with 20-40% among FSW living with HIV; and between 8-25% of FSW living with HIV were virally suppressed. From 2016 onwards, a failure to achieve viral load suppression among FSW could contribute to 7-12%, 26-34%, and 35-46% of cumulative HIV transmissions in the wider population over the subsequent 1, 10, and 20 years (Figure). After adjusting for current proportion of FSW who are virally suppressed, the tPAF was highest in settings with increasing HIV incidence among FSW; high turn-over in sex work; and larger number of non-paid partnerships among FSW.

Conclusion: Across the broadly generalized epidemics of Southern Africa, a failure to prevent HIV among FSW or to meet the treatment needs of FSW living with HIV could contribute to a large proportion of onward transmissions, and undermine existing efforts of achieving local epidemic control.

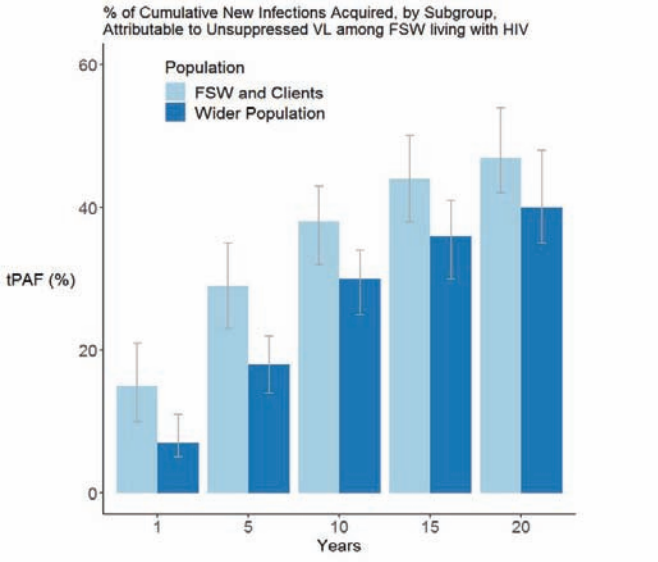

Figure. Transmission population attributable fraction (tPAF, % of cumulative new infections) attributable to unsuppressed viral load among FSW living with HIV, as measured among current FSW and clients; and in the wider population (excluding current FSW and current clients). The tPAF was estimated by 'turning off' (from 2016 onwards) all transmissions via all types of partnerships between FSW and their male partners, among FSW living with HIV.

1085 ESTIMATING HIV INCIDENCE AMONG YOUNG WOMEN IN HPTN 082 USING BASELINE HIV RISK SCORES

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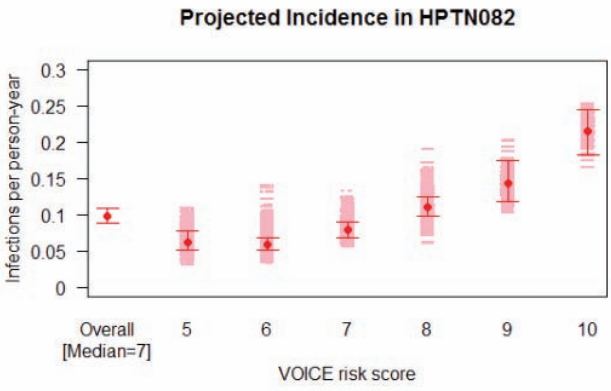
Background: Pre-exposure prophylaxis (PrEP) is highly efficacious for prevention of HIV acquisition, but adherence to PrEP remains a major barrier. HPTN 082 is testing strategies to support PrEP adherence in young African women. A mathematical modelling approach is used to predict HIV incidence in the absence of PrEP among HPTN 082 participants, using the previously validated VOICE risk score and baseline sexual activity data from HPTN 082. This predicted incidence will provide a counterfactual to estimate PrEP effectiveness in this population.

Methods: The VOICE risk score (5-10, with 10 the highest risk score) is calculated for each woman based on baseline factors including age, marital status, financial stability, STIs, and alcohol usage. Using these data and self-reported sexual behavior not included in the risk score, we developed a Markov chain model of partnership formation, sexual behavior, and HIV transmission and used it to predict HIV incidence in the absence of PrEP. The model is calibrated using reported sexual activity, incidence data from the VOICE trial, and epidemiological data from the 2012 South African National HIV survey.

Results: HPTN 082 enrolled 451 African women ages 16-25 with a median VOICE risk score of 7. 15% (68) reported anal sex in the last month, 30%(135) reported multiple partners in the last three months, and 49% (221) had a partner with unknown HIV status. Without PrEP, we predict an HIV incidence of 9.9% (95%CI 8.9-10.9), ranging from 6.3% (5.1-7.8) in women with a risk score of 5 to 21.5% (18.2-24.6) in women with a risk score of 10. Increased incidence at higher risk scores could be due to self-reported differences in sexual behavior. The remaining increase in incidence was attributed by the model to higher partner HIV prevalence. For example, women who did not live with their main partner were more likely to have multiple partners (OR=2.3, 95%CI 1.7-3.4) but also more likely to use a condom (OR=2.2, 95%CI 1.4-3.4). The model inferred a greatly increased HIV prevalence among their partners (OR=6.2, 95%CI 3.1-12.6).

Conclusion: HPTN 082 recruited a cohort of young African women who had multiple risk factors and would benefit from PrEP, given the predicted HIV incidence of 9.9%. These predictions will allow us to evaluate the effectiveness of PrEP stratified by VOICE risk score using an objective measure of adherence (tenofovir levels) from HPTN 082.



HIV incidence and 95% confidence intervals in the absence of PrEP by VOICE risk score. Each dot represents a single participant simulated with one of 100 calibrated parameter sets.

1086 A MATHEMATICAL MODELING ANALYSIS OF COMBINATION HIV PREVENTION IN ANTENATAL CLINICS

Kimberly A. Powers[1], Kate Orroth[1], Nora E. Rosenberg[1], Lauren A. Graybill[1], Andrew Kumwenda[2], Tiwonge Mtande[3], Katie Mollan[1], Oliver Mweemba[2], Wilbroad Mutale[2], Benjamin H. Chi[1]
[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [2]University of Zambia, Lusaka, Zambia, [3]University of North Carolina Project–Malawi, Lilongwe, Malawi

Background: Given high HIV acquisition risk and increased healthcare engagement during pregnancy, antenatal clinic (ANC) settings in sub-Saharan Africa present major opportunities for HIV prevention. Despite demonstrated success in reducing mother-to-child HIV transmission, few ANC-based programs have considered interventions to prevent horizontal HIV transmission and acquisition among pregnant women and their sexual partners. We hypothesized that combination HIV prevention strategies anchored in ANC settings could

substantially reduce HIV incidence among ANC patients, their partners, and their infants.

Methods: We constructed a mathematical model describing horizontal and vertical HIV transmission during pregnancy within patient-partner and patient-infant dyads, respectively. We based biological and behavioral inputs on literature estimates and ANC program data from Malawi and Zambia. We modeled three main HIV prevention strategies, alone and in combination, by varying: 1) male partner HIV testing from a base-case value of 15% to a target of 35%; 2) suppressive antiretroviral therapy (ART) for HIV-positive ANC patients and partners from a base-case of 70% to a target of 90%; and 3) adherent pre-exposure prophylaxis (PrEP) use for HIV-uninfected female ANC patients from a base-case of 0% to a target of 20%. Using the model, we estimated the percentage of horizontal and vertical HIV infections that could be averted with these strategies, relative to the current (base-case) scenario.

Results: Increasing male partner testing to 35% coverage was predicted to reduce horizontal and vertical transmissions by 16.7% and 15.1%, respectively (scenario 2, Table); corresponding reductions with 20% female PrEP use were 13.4% and 12.1% (scenario 4). Jointly increasing coverage of both interventions by 20 percentage points was predicted to reduce horizontal and vertical transmissions by ~one-quarter (scenario 7); this reduction increased to ~one-third with a combination of these two interventions plus increasing suppressive ART (scenario 8). Across scenarios, a 20-percentage-point increase in suppressive ART for HIV-positive patients and partners had only a modest incremental impact (scenarios 3 vs. 1, 5 vs. 2, 6 vs. 4, 8 vs. 7).

Conclusion: Our modeling suggests that combination HIV prevention in ANC settings – particularly approaches that increase male partner testing and female PrEP use – could substantially reduce HIV incidence among pregnant women, their partners, and their newborns in sub-Saharan Africa.

Table. Summary of Mathematical Modeling Scenarios and Results

Scenario	% ANC patients' male partners tested for HIV	% HIV+ ANC patients & partners on suppressive ART	% HIV- female ANC patients on PrEP	% horizontal transmissions* averted	% vertical transmissions averted
1	Current (15%)	Current (70%)	Current (0%)	--- (base case)	--- (base case)
2	↑ to 35%	Current (70%)	Current (0%)	16.7%	15.1%
3	Current (15%)	↑ to 90%	Current (0%)	1.1%	1.8%
4	Current (15%)	Current (70%)	↑ to 20%	13.4%	12.1%
5	↑ to 35%	↑ to 90%	Current (0%)	21.5%	19.9%
6	Current (15%)	↑ to 90%	↑ to 20%	16.3%	13.9%
7	↑ to 35%	Current (70%)	↑ to 20%	27.8%	25.1%
8	↑ to 35%	↑ to 90%	↑ to 20%	32.1%	29.2%

* both female-to-male and male-to-female

1087 SCALE-UP OF ART AND VMMC EXPLAIN A TWO-FOLD DECLINE IN HIV INCIDENCE IN WESTERN KENYA

Anna Bershteyn[1], Adam N. Akullian[1], Daniel J. Klein[1], Britta Jewell[2], Kennedy Mutai[3], Samuel M. Mwalili[4]

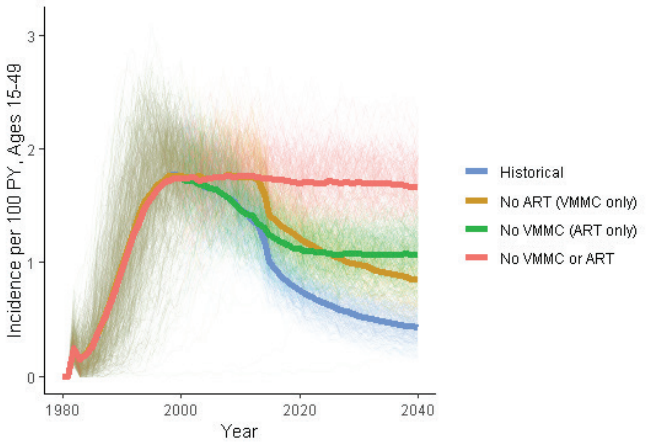
[1]Institute for Disease Modeling, Bellevue, WA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]National AIDS Control Council, Nairobi, Kenya, [4]CDC, Nairobi, Kenya

Background: Western Kenya has among the world's highest prevalence of HIV, with one in four adults infected in Siaya and Homa Bay Counties. Longitudinal surveillance of a community in Siaya found that incidence has fallen by two-fold between 2011 and 2016. We used mathematical modeling to estimate the relative contribution of antiretroviral therapy (ART) and voluntary male medical circumcision (VMMC) to the declines in HIV incidence in the Western Kenya region, including the county of Siaya.

Methods: EMOD-HIV, an individual-based HIV transmission and care continuum model, was used to simulate the HIV pandemic in Western Kenya. The model was calibrated to age-, sex-, and county-specific HIV prevalence estimates from four national surveys, as well as estimates of population size and structure, number on ART, number receiving VMMC, and national targets for VMMC coverage. Conservatively, we assumed a sustained ART coverage of approximately 60%. Calibration yielded 250 best-fitting model trajectories for each of six counties comprising the Nyanza region of Western Kenya. In Siaya County, EMOD-HIV recapitulated the halving of HIV incidence over 2011-2016 at the county level, despite the model fitting process not directly utilizing incidence estimates from the longitudinal surveillance site in this county. The baseline model trajectories were modified to simulate what would have happened in the absence of ART and/or VMMC.

Results: Estimated HIV incidence declined drastically in Siaya due to scale-up of ART and VMMC, without which incidence would have remained stable at 1.7 new infections per 100 person-years among adults age 15-49 (Figure 1). Incidence peaked in 2002, fell to half of its peak by 2018, and continued to decline to one-third of peak levels by 2028. ART is the predominant cause of incidence declines up until 2025, after which VMMC is expected to surpass ART as a driver of incidence decline, provided Siaya achieves and maintains a target of 80% VMMC coverage. Similar trends were found in other high-prevalence counties in Western Kenya.

Conclusion: Epidemiological modeling suggests that observed incidence declines in Siaya County, Western Kenya, can be fully attributed to scale-up of ART and VMMC, without which incidence would have remained stable. Incidence is expected to continue to decline due to these interventions, but enhanced efforts to prevent HIV infections will be required to accelerate declines and bring incidence to low levels.



1088 SIMULATED VACCINE EFFICACY TRIALS TO ESTIMATE HIV INCIDENCE IN KEY POPULATIONS

Andrew M. Abaasa[1], Stephen Nash[1], Yunia Mayanja[2], Matt A. Price[3], Patricia E. Fast[3], Pontiano Kaleebu[2], Anatoli Kamali[3], Jim Todd[1]

[1]London School of Hygiene & Tropical Medicine, London, UK, [2]MRC/UVRI and LSHTM Uganda Research Unit, Entebbe, Uganda, [3]International AIDS Vaccine Initiative, New York, NY, USA

Background: Fisherfolks (FF) on Lake Victoria shoreline and female sex workers (FSW) in Kampala, Uganda could be suitable key populations for HIV vaccine efficacy trials because of the high HIV incidence and good retention in observational cohorts. However, HIV incidence may vary from observational cohorts, once volunteers have enrolled into a trial. We used simulated vaccine efficacy trials (SiVET) nested within observational cohorts in these populations to evaluate this question.

Methods: SiVETs were nested in two observational cohorts, in FF (Jul 2012-Apr 2014) and FSW (Aug 2014-Apr 2017). When observational cohort participants presented for quarterly visits (3-18 months) they were consecutively screened for enrolment into SiVET. Eligibility was: age 18-49 years, HIV negative; at high risk of HIV infection; no history of severe allergic reaction to any substance. Those not enrolled continued participation in the observational cohort. In addition to procedures (HIV testing & risk assessment) in the observational cohorts, SiVET participants were given a licensed Hepatitis B vaccine following a standard schedule of 0, 1 and 6 months, mimicking a schedule of an HIV vaccine efficacy trial. HIV testing was carried out quarterly for one year.

Results: In total, 3989 participants were enrolled into the observational cohorts. Of these 3622 (90.8%) returned at least once and 1525 (42.1%) were eligible for SiVET screening: 672 (44.1%) were screened and 572 (282 FF and 290 FSW) enrolled. HIV incidence in the observational cohorts pre SIVET was 4.5/100 person years at risk (PYAR), 95%CI: 3.8-5.5 [FF=4.9 (3.9-6.2); FSW=4.0 (2.9-5.5)]. When a subset of participants was enrolled into SiVETs, the HIV incidence at 12 months was lower in SiVETs, 3.5/100 PYAR, 95%CI: 2.2-5.6 [FF=3.8 (2.7-7.1); FSW=3.2 (1.5-6.6)] compared to 5.9/100 PYAR, 95%CI: 4.3-8.1[FF=8.3 (5.6-12.4); FSW=4.1 (2.5-6.7)] in the observational cohorts' concurrent period, p=0.034. Compared to observational cohorts, SiVETs recruited more men, older

participants, long-term residents and non-users of illicit drugs, all previously associated with lower HIV risk.

Conclusion: HIV incidence was generally higher in these observational cohorts before and concurrent to SiVET than in the SiVET participants. This difference was greatest among FF. Researchers designing HIV efficacy trials using observational cohort data need to consider the potential for lower than expected HIV incidence following screening and enrollment.

1089 THE PROJECTED AGE DISTRIBUTION OF WHITE, BLACK, AND HISPANIC MSM ON ART, 2009-2030

Parastu Kasaie[1], Elizabeth Humes[2], Stephen J. Gange[1], Amy C. Justice[3], Kelly Gebo[4], Cynthia Boyd[2], Emily P. Hyle[5], Carolyn Williams[6], Jinbing Zhang[1], Raquel Cruz-Stratton[1], Robert S. Hogg[7], Mari Kitahata[8], Richard D. Moore[4], **Keri N. Althoff**[1], for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]Johns Hopkins University, Baltimore, MD, USA, [3]VA Connecticut Healthcare System, West Haven, CT, USA, [4]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [5]Massachusetts General Hospital, Boston, MA, USA, [6]National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, [7]Simon Fraser University, Burnaby, BC, Canada, [8]University of Washington, Seattle, WA, USA

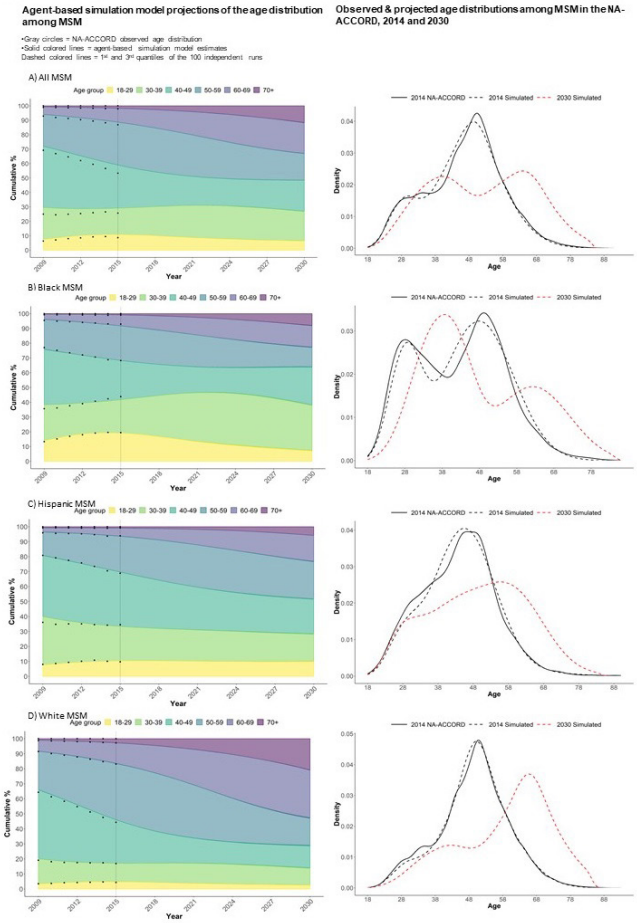
Background: There are unique age distributions for US Black, White, and Hispanic men who have sex with men (MSM) being treated for HIV infection. Underlying risk, prevention, testing and treatment factors may have created these differences in age distributions by race/ethnicity among MSM. This study aims to project the age distribution of these groups to the year 2030 to inform policy and planning.

Methods: The NA-ACCORD was the source for mapping age distributions of those receiving ART in 2009, estimating the annual trend in age distribution of those initiating ART from 2009 to 2015, and modeling mortality rates as a function of time, CD4 count, and age at ART initiation among White, Black, and Hispanic MSM. Annual number of new HIV diagnoses and proportion of ART initiators among the race/ethnicity subgroups of MSM were from the US Centers for Disease Control and Prevention. Assuming observed (2009-15) trends would be projected to 2030, these estimates informed an agent-based simulation modeling the dynamics of ART initiation, aging, and mortality among White, Black, and Hispanic MSM in the US. 100 independent runs allowed a precision level of <1% around the model's estimates.

Results: Observed age distributions for MSM subgroups in the NA-ACCORD from 2009-15 were a mixture of two distinct normally distributed age curves; this bimodal distribution was most distinct among Black MSM. Increased numbers of younger Black and Hispanic MSM on ART in the early Treat All era (2009-2015) impacted the projected age distribution to the year 2030, with younger age distributions among Black and Hispanic MSM and an older distribution among White MSM (Figure). As the number of White MSMs in the US is substantially greater than other racial groups, the overall age distribution of MSM with treated HIV shifted toward older ages through the year 2030.

Conclusion: The differences in age distribution by race/ethnicity indicate substantive differences continue in risk, testing, and treatment. The increase in younger Black and Hispanic MSM on ART is an encouraging indicator of effective test and treat interventions. This modeling indicates that a substantial proportion of MSM on ART will continue to be in high transmission risk age groups, particularly Hispanics, even in 2030. Among White MSM, the observed increases in the proportion of older men alive on ART indicates access to, and success of, treatment. We can expect increasing numbers of older treated MSM into 2030 and a corresponding increase in multimorbidity.

Figure: Observed and projected age distributions among a) all men who have sex with men (MSM) on ART, b) Black MSM, c) Hispanic MSM, d) White MSM, 2009-2030



1090 YOUTH-FOCUSED HIV TREATMENT-AS-PREVENTION YIELDS LARGE BENEFITS: A SIMULATION MODEL

John E. Mittler, James Murphy, Sarah E. Stansfield, Kathryn Peebles, Geoffrey S. Gottlieb, Neil Abernethy, Steven M. Goodreau, Joshua T. Herbeck

University of Washington, Seattle, WA, USA

Background: Despite increasing availability of Antiretroviral therapy (ART), heterosexual HIV-1 epidemics like those in sub-Saharan Africa continue to have high incidence in young people. ART for youth has the potential to protect their partners who also tend to be younger and at high risk. We hypothesized that focusing HIV interventions on youth could enhance the efficiency of treatment as prevention (TasP) campaigns in resource limited settings.

Methods: We used an agent-based network model that includes behavioral and clinical data from multiple sources to examine the effect of targeting different risk groups for linkage to HIV-related treatment services in a heterosexual population. The model accounts for age-based risk factors including the tendency for younger women to partner with older men. We used the model to identify strategies that reduce incidence to negligible levels 20-25 years after initiation of a targeted TasP campaign.

Results: Under random allocation or CD4-based targeting, our model predicts a TasP campaign would need to suppress viral replication in 70-80% of infected people to halt the epidemic. Under age-based strategies, by contrast, this percentage drops to 40% to 60% (for strategies targeting those <30 and <25 years old, respectively) (Figure 1). Age-based targeting also minimized both total and time-discounted AIDS deaths after 25 years. Age-based targeting did not need to be highly exclusive to yield benefits; e.g. in a model in which 50% of infected people were treated, the majority of those people receiving therapy during a campaign targeting those <30 fell outside the target group. Sensitivity analyses varying background incidence yielded qualitatively similar benefits. Age-based TasP is beneficial due to age-related risk factors (e.g. shorter

relationship durations) and age-specific herd immunity (ASHI) that protects adolescents entering the sexually active population. In sensitivity analyses, we found ASHI was the biggest driver of the success of age-based TasP. Over time, ASHI gives rise to an ever-expanding "AIDS-free generation" that drives HIV to extinction.

Conclusion: As testing rates increase in response to UNAIDS 90-90-90 goals, we suggest that efforts to link all young people to care and treatment could be an effective long-term strategy for ending the HIV epidemic. Youth focused treatment will be particularly important in low and middle income countries with demographic 'youth bulges' that are increasing the number of young people at risk for infection.

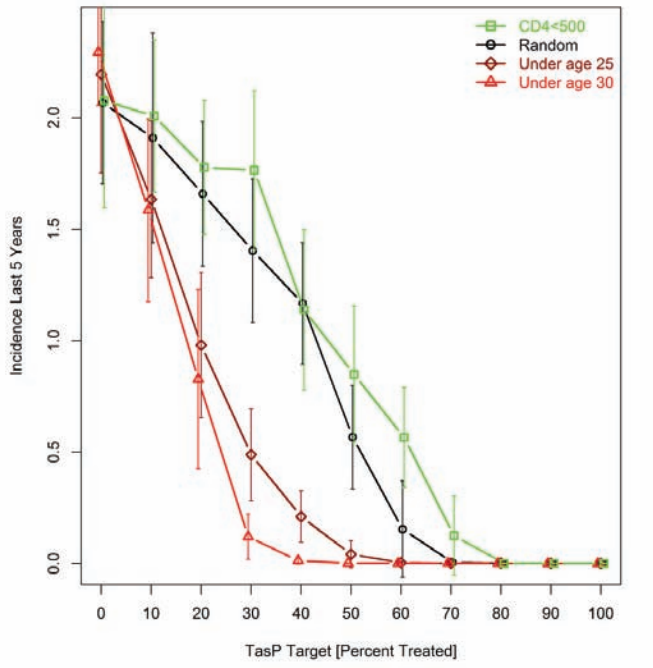


Figure 1. HIV-1 incidence 20-25 years after the start of a TasP Campaign as a function of the percent treated after the TasP campaign for different targeting strategies. Each point is the mean of 16 replicates. Error bars give standard deviations. The model allows for an additional 2% annual increase in the number treated after the TasP target has been hit.

1091 WHO IS LEFT IN 10-10-10? IMPORTANCE OF REACHING KEY POPULATIONS WITH THE HIV CASCADE

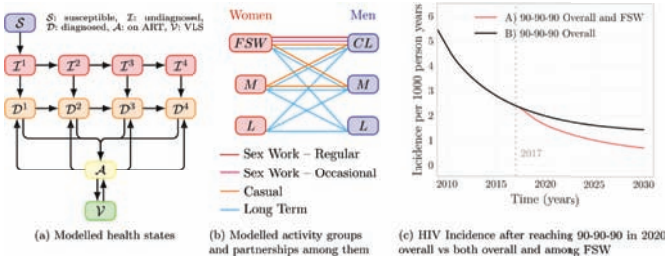
Jesse Knight[1], Huiting Ma[1], Stefan Baral[2], Sosthenes Ketende[2], Oluwasolape M. Olawore[2], Amrita Rao[2], Carly Comins[2], Sheree Schwartz[2], Harry Hausler[3], Katherine Young[3], Mfezi Mcingana[3], Vijayanand Guddera[3], Sindy Matse[4], Zandile Mnisi[4], Sharmistha Mishra[5]
[1]St. Michael's Hospital, Toronto, ON, Canada, [2]Johns Hopkins University, Baltimore, MD, USA, [3]TB/HIV Care Association, Cape Town, South Africa, [4]Ministry of Health, Mbabane, Swaziland, [5]University of Toronto, Toronto, ON, Canada

Background: Achievement of the UNAIDS 90-90-90 targets for HIV cascade of care (90% of infected are diagnosed, 90% of diagnosed are on treatment, 90% of those on treatment are virally suppressed) by 2020 is predicted to end the AIDS pandemic by 2030. We sought to determine the influence of heterogeneity across the remaining 10-10-10 on the epidemic features after the UNAIDS targets are achieved in a high-prevalence HIV epidemic in Southern Africa.

Methods: We built a deterministic mathematical model of heterosexual HIV transmission to simulate a high-prevalence epidemic in a Southern African context (using demographic health survey and female sex worker (FSW) survey data from eSwatini and South Africa). The model includes 6 different populations at risk for HIV, including FSW and clients; 4 sexual partnership types; and the HIV cascade (undiagnosed, diagnosed, on ART, and virally suppressed), Figure 1 (a-b). The model simulates observed HIV prevalence ratios by risk group, and trends in cascade of care to 2017. We then compared two scenarios where A) 90-90-90 is achieved in all populations, including FSW; B) 90-90-90 is achieved in the overall population, but not among FSW - and estimated the relative difference in cumulative HIV incidence between 2020 and 2030.

Results: By 2017, the modeled HIV prevalence was 17% overall (total population, including FSW), and 43% among FSW. Under Scenario A, HIV incidence declines to 0.59 per 1000 person-years by 2030. Scenario B (90-90-90 reached in the overall population) is actually achieved if the 2017 rates of testing and treatment are maintained; however the cascade among FSW only reaches 81-60-83 by 2020. As a result, incidence only declines to 1.22 per 1000 person-years by 2030, and the model projects a 60% increase in cumulative new infections in the total population between 2020 and 2030 versus Scenario A.

Conclusion: Heterogeneity in HIV transmission risks across the 10-10-10 could undermine the projected impact of achieving 90-90-90 across the Southern African region. Efforts to meet and surpass UNAIDS targets among key populations such as FSW and their clients should be prioritized to maximize incidence reductions and achieve pandemic control by 2030.



(a) Modelled health states (b) Modelled activity groups and partnerships among them (c) HIV Incidence after reaching 90-90-90 in 2020 overall vs both overall and among FSW

1092 TasP COVERAGE MAY INCREASE WITHOUT SELECTING FOR MORE VIRULENT HIV: A MODELING STUDY

Sarah E. Stansfield, Joshua T. Herbeck, Geoffrey S. Gottlieb, Neil Abernethy, James Murphy, John E. Mittler, Steven M. Goodreau
University of Washington, Seattle, WA, USA

Background: HIV-1 set point viral load (SPVL) influences both transmission potential and disease progression and is a proxy for HIV virulence. Multiple test-and-treat models have found that increasing the proportion of people who receive treatment selects for viruses with higher SPVL, i.e. higher virulence. Here we extend these modeling studies to evaluate the potential impact of different risk, treatment, and transmission scenarios on the evolution of HIV virulence.

Methods: We extend a stochastic, dynamic network model (EvoNetHIV) in which sexual network structure and behavioral parameters are derived from modeling studies of HIV among US men who have sex with men. Key agent attributes include SPVL and current viral load; SPVL was partially heritable so virulence could evolve over time. Our main input is treatment coverage and main output is mean population SPVL (MPSPVL). We vary the transmission model (increasing vs. plateauing transmission at very high viral loads), relationship patterns (relationships averaging 2.45 years and 1 sex act/day vs 100 days and 0.2 sex acts/day), and ART schemes (ART beginning at a fixed interval after infection vs. stochastic interval driven by testing) in isolation and in combination to determine those most integral to observed outcomes. In each case we explore mean times to ART initiation of 1-6 years.

Results: In scenarios most similar to those previously published, we confirmed that higher ART coverage led to higher MPSPVL. In contrast, in scenarios in which ART occurs immediately after individuals test positive, with shorter relationships and less frequent sex acts, and with the increasing transmission function, increasing levels of ART instead either led to no significant MPSPVL change or selected for viruses with lower MPSPVLs. Further analyses showed that changing any of these factors was enough to eliminate the relationship between high treatment levels and low MPSPVL and in some cases to reverse this pattern.

Conclusion: Under a set of realistic, data-derived modeling assumptions, we found that MPSPVL remains unchanged and/or decreases with higher ART coverage. These findings emphasize the impact of epidemiological conditions and model design on predicted evolutionary outcomes. Our results suggest that, under some realistic conditions, vigorous test-and-treat strategies may not need to face a previously-reported tradeoff in which increasing coverage fuels evolution of greater virulence.

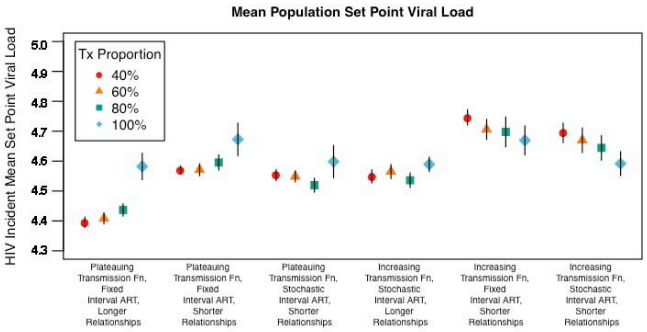


Figure: Mean population SPVL for each parameter set in scenarios with two year mean time to ART initiation. Each point is the mean of 16 simulations and lines show 95% confidence intervals.

2001 UPDATE ON HIV VIROLOGY

Paul Bieniasz, *The Rockefeller University, New York, NY, USA*

Dr Bieniasz will review aspects of the HIV-1 replication cycle. In particular he will discuss recent developments in the understanding of virus entry, capsid function and RNA turnover.

2002 UPDATE ON HIV IMMUNOLOGY

Penelope L. Moore, *University of the Witwatersrand, Johannesburg, South Africa*

Dr Moore will describe advances in eliciting protective antibodies by vaccination, highlight emerging insights at the interface between innate and adaptive immunity, and summarize key new immunological findings at CROI. Please see the session overview for the Program Committee Workshop for New Investigators and Trainees for a description of the session.

2003 UPDATE ON HIV PREVENTION

Sharon L. Hillier, *Magee–Womens Hospital of UPMC, Pittsburgh, PA, USA*

Dr Hillier will describe the current landscape of biomedical HIV prevention research including vaccines, broadly neutralizing antibodies, oral and injectable pre-exposure prophylaxis, vaginal and rectal microbicides, and combination approaches for prevention of HIV. Please see the session overview for the Program Committee Workshop for New Investigators and Trainees for a description of the session.

2004 UPDATE ON TUBERCULOSIS TREATMENT AND PREVENTION

Constance A. Benson, *University of California San Diego, San Diego, CA, USA*

Dr Benson will briefly summarize the current state-of-the-art for tuberculosis treatment and prevention, highlight recent new data in the field, including new information to be presented at CROI, and discuss research gaps in current knowledge that might generate new research in the field. Please see the session overview for the Program Committee Workshop for New Investigators and Trainees for a description of the session.

2005 UPDATE ON HIV CURE

Katharine J. Bar, *University of Pennsylvania, Philadelphia, PA, USA*

Dr Bar will review our current understanding of HIV persistence, highlight major obstacles to HIV cure strategies, and discuss pre-clinical and clinical developments in the pursuit of functional or eradicative HIV cure. Please see the session overview for the Program Committee Workshop for New Investigators and Trainees for a description of the session.

2006 HEPATITIS E: CLINICAL CHALLENGES

Sven Pischke, *University Hospital Hamburg–Eppendorf, Hamburg, Germany*

Dr Pischke will discuss the clinical challenges with the treatment of patients with hepatitis E. Please see the overview for the Interactive Case-Based Workshop on Hepatitis for a full description of the session.

2007 HEPATITIS D: CLINICAL CHALLENGES

Jeffrey Glenn, *Stanford University, Stanford, CA, USA*

Dr Glenn will discuss the clinical challenges in treating patients with hepatitis D. Please see the overview for the Interactive Case-Based Workshop on Hepatitis for a full description of the session.

2008 NASH IN HIV

Giada Sebastiani, *McGill University Health Centre Research Institute, Montreal, QC, Canada*

Nonalcoholic fatty liver disease has become the most frequent liver disease in the aging HIV-infected population, with a prevalence at 35%. Its severe form, nonalcoholic steatohepatitis (NASH), is found in 65% of HIV mono-infected patients with chronic elevation of transaminases, which is a frequent occurrence in the practice of HIV medicine. A complex multifactorial pathogenesis, including frequent metabolic comorbidities, lifelong use of antiretroviral therapy and HIV itself, is thought to drive this epidemic. Early diagnosis, preventive and therapeutic strategies may help reduce the burden of NASH in people living with HIV.

2009 RETREATMENT OF HCV IN ADVANCED LIVER DISEASE

John D. Scott, *University of Washington, Seattle, WA, USA*

Dr Scott will discuss the retreatment of HCV in patients with advanced liver disease. Please see the overview for the Interactive Case-Based Workshop on Hepatitis for a full description of the session.

DISCLOSURE OF FINANCIAL RELATIONSHIPS WITH COMMERCIAL CONCERNS

Disclosure information is presented generally as submitted by the corresponding presenting abstract author, invited speaker, session moderator, or member of the CROI Program Committee. The individuals 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 on their behalf (eg, for research where they are the principal investigator).

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Aberg, Judith
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To self, paid to my institution: Research grant/grant pending from Frontier Technologies, Gilead Sciences, GlaxoSmithKline, ViiV Healthcare, Inc.

Achenbach, Chad J.
Self: Consulting or advisor fees from and speaker's bureau for ViiV Healthcare, Inc.; research grant/grant pending from Gilead Sciences; membership in Abivax; board membership for Biotron

Achieng, Loice
Self: Speaker's bureau for Pfizer, MSD, GlaxoSmithKline, ViiV Healthcare, Inc., Gilead Sciences

Acosta, Rima K.
Self: Employment at and stock/stock options in Gilead Sciences

Adimora, Adaora
Self: Board membership for Merck & Co, Inc.; consulting or advisor fees and research grant/grant pending from Gilead Sciences; other from ViiV Healthcare, Inc.

Allavena, Clotilde
To self, paid to my institution: Board membership for Janssen Therapeutics, ViiV Healthcare, Inc., Merck & Co, Inc.

Alter, Galit
To self, paid to my institution: Research grant/grant pending from BioProtection Systems/New Link Genetics, Gilead Sciences, Merck & Co, Inc., Pfizer, Bristol-Myers Squibb; other from Sanofi, Curevac, Janssen Therapeutics, GlaxoSmithKline

Althoff, Keri, N.
Self: Consulting or advisor fees from Trio Health

Anderson, Peter, L.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Andreatta, Kristen
Self: Employment at Gilead Sciences

Anthony-Gonda, Kim
Self: Employment at Lentigen, a Miltenyi Biotec company

Averitt, Dawn
Self: Advisory board for Merck & Co, Inc.

Avery, Ann K.
Self: Consulting or advisor fees from and speaker's bureau for Gilead Sciences

Avihingsanon, Anchalee
Self: Speaker's bureau for Janssen Therapeutics

Back, David
To self, paid to my institution: Research grant/grant pending from AbbVie Inc., Merck & Co, Inc., Janssen Therapeutics, Gilead Sciences, ViiV Healthcare, Inc.
Self: Speaker's bureau for AbbVie Inc., Merck & Co, Inc., Gilead Sciences, ViiV Healthcare, Inc.

Bares, Sara H.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Baum, Marc
To self, paid to my institution: Patent holder

Beckwith, Curt G.
Self: Research grant/grant pending from Gilead Sciences

Bedimo, Roger
To self, paid to my institution: Research grant/grant pending from ViiV Healthcare, Inc., Merck & Co, Inc.
Self: Consulting or advisor fees from ViiV Healthcare, Inc., Merck & Co, Inc., Napo Pharmaceuticals

Behrens, Georg
Self: Consulting or advisor fees from ViiV Healthcare, Inc., Gilead Sciences, Janssen Therapeutics, MSD

Bekker, Linda-Gail
Self: Consulting or advisor fees from Merck & Co, Inc., Janssen Therapeutics, GlaxoSmithKline, ViiV Healthcare, Inc.; research grant/grant pending from Gilead Sciences; board membership for ViiV Healthcare, Inc.

Benson, Constance A.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences; consulting or advisor fees from GlaxoSmithKline, ViiV Healthcare, Inc.
Spouse or Partner: Stock/stock options in CytoDyn, Antiva Biosciences; consulting or advisor fees from VIR, Pfizer
Spouse or Partner, paid to institution: Consulting or advisor fees from Gilead Sciences, Monogram Biosciences

Betts, Michael R.
To self, paid to my institution: Research grant/grant pending from Merck & Co, Inc.

Bhattacharya, Debika
Self: Other from Regeneron, AbbVie Inc.

Bieniasz, Paul
Self: Stock/stock options in Gilead Sciences; speaker's bureau for ViiV Healthcare, Inc.

Blumenthal, Jill
Self: Consulting or advisor fees from Gilead Sciences

Boesecke, Christoph
Self: Consulting or advisor fees from AbbVie Inc., Gilead Sciences, Janssen Therapeutics, Merck & Co, Inc., ViiV Healthcare, Inc.

Bollen, Pauline
To self, paid to my institution: Research grant/grant pending from EC, DG Research, 6th Framework program, Bristol-Myers Squibb, Merck & Co, Inc., ViiV Healthcare, Inc., Janssen Therapeutics N.V., Gilead Sciences

Borges, Álvaro H.
To self, paid to my institution: Research grant/grant pending from Lundbeckfonden

Bradshaw, Daniel
To self, paid to my institution: Research grant/grant pending from ViiV Healthcare, Inc., Janssen Therapeutics

Brew, Bruce J.
Self: Consulting or advisor fees from AbbVie Inc., ViiV Healthcare, Inc., Biogen, Merck & Co, Inc.
To self, paid to my institution: Research grant/grant pending from Biogen

Brown, Dannae
Self: Employment at ViiV Healthcare, Inc.; stock/stock options in GlaxoSmithKline

Brumme, Zabrina
Self: Stock/stock options in Pfizer

Buchbinder, Susan P.
To self, paid to my institution: Provision of medicine or equipment from Gilead Sciences

Butt, Adeel, A.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Calcagno, Andrea
Self: Consulting or advisor fees from Janssen Therapeutics, Merck & Co, Inc., ViiV Healthcare, Inc.
To self, paid to my institution: Research grant/grant pending from ViiV Healthcare, Inc.

Cannon, Paula
Self: Expert Testimony for MilliporeSigma

Carlander, Christina
Self: Consulting or advisor fees from GlaxoSmithKline, ViiV Healthcare, Inc., Gilead Sciences

Castel, Amanda D.
Self: Stock/stock options in Gilead Sciences

Celum, Connie L.
Self: Board membership for Merck & Co, Inc.; provision of medicine or equipment from Gilead Sciences

Chaisson, Richard E.
Self: Speaker's bureau for Janssen Therapeutics
Spouse or Partner: Stock/stock options in Merck & Co, Inc.

Chappell, Catherine A.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences, Merck & Co, Inc.

Charpentier, Charlotte
Self: Board membership for Gilead Sciences, Merck & Co, Inc.
To self, paid to my institution: Research grant/grant pending from ViiV Healthcare, Inc.

Chéret, Antoine
Self: Research grant/grant pending from Merck & Co, Inc., Janssen Therapeutics, ViiV Healthcare, Inc.; consulting or advisor fees from Gilead Sciences, Janssen Therapeutics

Chew, Kara W.
To self, paid to my institution: Research grant/grant pending from Merck & Co, Inc.

Coffin, John M.
Self: Stock/stock options in Tocagen, Inc.; consulting or advisor fees from Tocagen, Inc.

Costagliola, Dominique
To self, paid to my institution: Research grant/grant pending from Janssen Therapeutics
Self: Speaker's bureau for Janssen Therapeutics, Gilead Sciences

Cox, Stephanie W.
Self: Employment at Gilead Sciences

Crane, Heidi M.
To self, paid to my institution: Consulting or advisor fees from ViiV Healthcare, Inc.

Currier, Judith S.
To self, paid to my institution: Research grant/grant pending from Theratechnologies Inc.

DeJesus, Edwin
Self: Consulting or advisor fees from Gilead Sciences, Janssen Therapeutics, Theratechnologies Inc.; speaker's bureau for Gilead Sciences, Theratechnologies Inc.

Delany-Moretlwe, Sinead
Self: Provision of medicine or equipment from Gilead Sciences

Dhody, Kush
Self: Employment at Amarex Clinical Research, LLC

Diaz, Ricardo S.
Self: Board membership for GlaxoSmithKline, ViiV Healthcare, Inc., Janssen Therapeutics, Merck & Co, Inc.

Dominguez Rodriguez, Sara
To self, paid to my institution: Other from ViiV Healthcare, Inc.

Dravid, Ameet N.
Self: Board membership for Mylan Pharmaceuticals; consulting or advisor fees from Cipla, Aurobindo Pharma; Emcure, Hetero Pharmaceuticals, Merck & Co, Inc.

Dryden-Peterson, Scott
Self: Royalties with UpToDate, Inc.

Dunn, Keith J.
Self: Employment at Janssen Scientific Affairs, LLC; stock/stock options in Johnson & Johnson

Eaton, Ellen F.
Self: Research grant/grant pending from Bristol-Myers Squibb, Gilead Sciences, ViiV Healthcare, Inc.

Eckard, Allison Ross
Self: Consulting or advisor fees from Gilead Sciences, Theratechnologies Inc.
To self, paid to my institution: Consulting or advisor fees from Gilead Sciences

Elias, Maria Jesus P.
To self, paid to my institution: Research grant/grant pending from ViiV Healthcare, Inc., Gilead Sciences, Janssen Therapeutics

Emerman, Michael
Self: Consulting or advisor fees from Qura Therapeutics

Emu, Brinda
Self: Consulting or advisor fees from Theratechnologies Inc.

Erlandson, Kristine M.
To self, paid to my institution: Consulting or advisor fees from ViiV Healthcare, Inc., Gilead Sciences

Eron, Joseph J.
Self: Consulting or advisor fees from Janssen Therapeutics, Gilead Sciences, ViiV Healthcare, Inc., Merck & Co, Inc.
To self, paid to my institution: Research grant/grant pending from Janssen Therapeutics, Gilead Sciences, ViiV Healthcare, Inc.

Felber, Barbara K.
Self: Patent holder

Fierer, Daniel S.
Self: Research grant/grant pending from and stock/stock options in Gilead Sciences

Firnhaber, Cindy
Self: Research grant/grant pending from Merck & Co, Inc.

Fishbein, Dawn
To self, paid to my institution: Research grant/grant pending from Gilead Sciences, Merck & Co, Inc.

Frange, Pierre
Self: Board membership for Merck & Co, Inc. France; other from ViiV Healthcare, Inc., Bristol-Myers Squibb, Janssen Therapeutics, Gilead Sciences

Gaisa, Michael
Self: Consulting or advisor fees from ViiV Healthcare, Inc.

Galloway, Denise
Self: Board membership for Merck & Co, Inc.'s Global Advisory Board for HPV
To self, paid to my institution: Research grant/grant pending from Merck & Co, Inc.

Gantner, Pierre
Self: Research grant/grant pending from Gilead Sciences

Garraffo, Rodolphe
Self: Speaker's bureau for ViiV Healthcare, Inc., Gilead Sciences, Merck & Co, Inc., Janssen Therapeutics; consulting or advisor fees from Mylan, Astellas, GlaxoSmithKline

Gaur, Aditya
Self: Research grant/grant pending from Gilead Sciences

Gill, Michael J.
Self: Board membership for ViiV Healthcare, Inc., Merck & Co, Inc., Gilead Sciences

Girardi, Enrico
Self: Speaker's bureau for Gilead Sciences; consulting or advisor fees from Mylan, ViiV Healthcare, Inc.; speaker's bureau for Angelini
To self, paid to my institution: Research grant/grant pending from Mylan, Gilead Sciences

Gisslén, Magnus
Self: Consulting or advisor fees from GlaxoSmithKline, ViiV Healthcare, Inc., Merck & Co, Inc., Gilead Sciences; speaker's bureau for Gilead Sciences, Janssen Therapeutics
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Glenn, Jeffrey S.
Self: Board membership for and stock/stock options in Eiger BioPharmaceuticals, Inc.

Goff, Stephen P.
Self: Consulting or advisor fees from Janssen Therapeutics, LabCorp/Monogram Biosciences

Golden, Matthew R.
Self: Research grant/grant pending from Hologic, GlaxoSmithKline

Gottlieb, Geoffrey S.
To self, paid to my institution: Royalties from Gilead Sciences, Alere Technologies, Merck & Co, Inc., Janssen Therapeutics, Cerus Corporation, ViiV Healthcare, Inc., Bristol-Myers Squibb, Abbott Molecular Di

Grebe, Eduard
To self, paid to my institution: Consulting or advisor fees from Sedia Biosciences Corporation

Grobler, Jay
Self: Employment at Merck & Co, Inc.; stock/stock options in Merck & Co, Inc.

Grulich, Andrew E.
Self: Speaker's bureau for Gilead Sciences, ViiV Healthcare, Inc.; consulting or advisor fees from Merck & Co, Inc.
To self, paid to my institution: Research grant/grant pending from Sequirus, Gilead Sciences

Güerri-Fernández, Robert C.
Self: Research grant/grant pending from Gilead Sciences

Gupta, Amita
Spouse or Partner: Consulting or advisor fees for Biogen, Roche, Genetech, Avexis, Ionis Pharmaceuticals, PTC Therapeutics, Cytokinetics, and Pfizer

Gupta, Ravindra K.
Self: Research grant/grant pending from Wellcome Trust; consulting or advisor fees from ViiV Healthcare, Inc.; speaker's bureau for Gilead Sciences

Gupta, Samir K.
Self: Consulting or advisor fees from Gilead Sciences. Bristol-Myers Squibb; travel support from Bristol-Myers Squibb, Gilead Sciences
To self, paid to my institution: Research grant/grant pending from Gilead Sciences, Merck & Co, Inc., Janssen Therapeutics

Hachiya, Atsuko
Self: Other relationship with ViiV Healthcare, Inc.

Havlir, Diane V.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Henrich, Timothy J.
Self: Consulting or advisor fees from Merck & Co, Inc.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences Biosciences

Hileman, Corrilynn O.
Self: Consulting or advisor fees from Gilead Sciences

Hillier, Sharon L.
Self: Consulting or advisor fees from Merck & Co, Inc., Lupin, Hennepin Life Sciences, Biofire Diagnostics, Pfizer, Hologic
Self, paid to my institution: Research grant/grant pending from Cepheid, Becton Dickinson

Ho, Ya-Chi
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Hoenigl, Martin
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Hoffmann, Christian
Self: Consulting or advisor fees from Gilead Sciences, Janssen Therapeutics, Theratechnologies Inc.; speaker's bureau for Gilead Sciences, HEXAL, Janssen Therapeutics, Merck & Co, Inc.; research grant/grant pending from Janssen Therapeutics

Hoy, Jennifer
To self, paid to my institution: Board membership for ViiV Healthcare, Inc., Gilead Sciences, Merck & Co, Inc.

Hu, Tony
Self: Stock/stock options in Naropin Technologies

Huhn, Gregory D.
Self: Consulting or advisor fees from Gilead Sciences, ViiV Healthcare, Inc., Janssen Therapeutics, Theratechnologies Inc.

Hunt, Peter W.
Self: Consulting or advisor fees from Janssen Therapeutics, ViiV Healthcare, Inc.; research grant/grant pending from Gilead Sciences

Iwuji, Collins C.
Self: Research grant/grant pending from Gilead Sciences

Jain, Mamta K.
Self: Research grant/grant pending from Gilead Sciences

Jani, Ilesh V.
Self: Provision of medicine or equipment from Roche, Abbott
To self, paid to my institution: Research grant/grant pending from Janssen Therapeutics

Jensen, Björn-Erik O.
Self: Consulting or advisor fees from Gilead Sciences, Janssen Therapeutics

Joseph, Davey D.
Self: Provision of medicine or equipment from Cepheid

Kashuba, Angela
Self: Consulting or advisor fees from Merck & Co, Inc.

Khalili, Kamel
Self: Board membership and consluting or advisor fees for Excision Biotherapeutics

Khoo, Saye
Self: Consulting or advisor fees from ViiV Healthcare, Inc.
To self, paid to my institution: Research grant/grant pending from ViiV Healthcare, Inc.

Koethe, John R.
Self: Consulting or advisor fees from Gilead Sciences

Kunisaki, Ken M.
Self: Consulting or advisor fees from GlaxoSmithKline

Lake, Jordan E.
Self: Consulting or advisor fees from Merck & Co, Inc., Gilead Sciences
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Landovitz, Raphael J.
Self: Consulting or advisor fees from Gilead Sciences, Merck & Co, Inc., Roche; provision of medicine or equipment from Gilead Sciences

Lederman, Michael M.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Lin, Jue
Self: Consulting or advisor fees from ViiV Healthcare, Inc., Telomere Diagnostics, Inc.

Liu, Albert Y.
To self, paid to my institution: Provision of medicine or equipment from Gilead Sciences

Lo, Janet
Self: Consulting or advisor fees from Gilead Sciences, ViiV Healthcare, Inc.

Luetkemeyer, Annie F.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences, AbbVie Inc., Merck & Co, Inc., Proteus

Ma, Qing
To self, paid to my institution: Research grant/grant pending from Gilead Sciences, Merck & Co, Inc.

Maartens, Gary
Self: Board membership for ViiV Healthcare, Inc.

Macías, Juan
Self: Consulting or advisor fees from Gilead Sciences, Merck & Co, Inc.; speaker's bureau for Gilead Sciences, Merck & Co, Inc., AbbVie Inc., Janssen Therapeutics
To self, paid to my institution: Research grant/grant pending from Merck & Co, Inc., Janssen Therapeutics

Mallon, Patrick W. G.
To self, paid to my institution: Research grant/grant pending from ViiV Healthcare, Inc., Gilead Sciences, Janssen Therapeutics
Self: Speaker's bureau for ViiV Healthcare, Inc., Gilead Sciences, Janssen Therapeutics, Bristol-Myers Squibb, Merck & Co, Inc.; board membership for ViiV Healthcare, Inc., Gilead Sciences, Janssen Therapeutics, Bristol-Myers Squibb, Merck & Co, Inc.

Marcelin, Anne-Geneviève
Self: Consulting or advisor fees from ViiV Healthcare, Inc., Gilead Sciences, Merck & Co, Inc., Janssen Therapeutics
To self, paid to my institution: Research grant/grant pending from ViiV Healthcare, Inc., Gilead Sciences, Merck & Co, Inc., Janssen Therapeutics

Marconi, Vincent C.
Self: Research grant/grant pending from Bayer, Gilead Sciences; speaker's bureau for Integritas Communications Group

Marcus, Julia L.
Self: Consulting or advisor fees from Kaiser Permanente Northern California, Research grant from Gilead Sciences

Marrazzo, Jeanne M.
To self, paid to my institution: Research grant/grant pending from Cepheid

Mauss, Stefan
Self: Board membership for AbbVie Inc., Janssen Therapeutics; speaker's bureau for AbbVie Inc., Gilead Sciences, Janssen Therapeutics, Merck & Co

Mayer, Kenneth H.
Self: Research grant/grant pending from Gilead Sciences, ViiV Healthcare, Inc.

McComsey, Grace A.
To self, paid to my institution: Research grant/grant pending from Merck & Co, Inc., Gilead Sciences, ViiV Healthcare, Inc.
Self: Consulting or advisor fees from Merck & Co, Inc., Gilead Sciences, ViiV Healthcare, Inc.

McDanal, Charlene
Self: Employment at ViiV Healthcare, Inc.

McFarland, Elizabeth J.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

McMahon, James
To self, paid to my institution: Research grant/grant pending from ViiV Healthcare, Inc., Gilead Sciences, Merck & Co, Inc., Amgen, Shire

Mellors, John W.
To self, paid to my institution: Research grant/grant pending from Janssen Therapeutics, Gilead Sciences
Self: Consulting or advisor fees from Gilead Sciences, Merck & Co, Inc., AccelevirDx, Yufan Biotechnologies; stock/stock options in Cocrystal Pharma, Inc.; patents with Cocrystal Pharma, Inc.

Merchante, Nicolás
Self: Consulting or advisor fees from Gliead Sciences; other from Bristol-Myers Squibb, Gilead Sciences, Merck & Co, Inc., Janssen Therapeutics, AbbVie Inc., ViiV Healthcare, Inc.

Mirochnick, Mark
To self, paid to my institution: Research grant/grant pending from Gilead Sciences, Merck & Co, Inc., ViiV Healthcare, Inc.
Spouse or Partner: paid to institution: Research grant/grant pending from Merck & Co, Inc., ViiV Healthcare, Inc.

Molina, Jean-Michel
Self: Board membership for Gilead Sciences, Merck & Co, Inc., ViiV Healthcare, Inc.; consulting or advisor fees from Merck & Co, Inc.

Moseholm, Ellen
To self, paid to my institution: Research grant/grant pending from Novo Nordisk

Muñoz-Moreno, Jose A.
Self: Board membership for AlbaJuna Therapeutics, SL

Myer, Landon
Self: Consulting or advisor fees from Pfizer

Newton, Alicia
Self: Employment at Monogram Biosciences

Nijhawan, Ank E.
Self: Research grant/grant pending from Gilead Sciences

Nussenzweig, Michel
Self: Board membership for Frontier Biotechnologies Inc, Celldex Therapeutics Inc.

Nwokolo, Nneka
Self: Speaker's bureau for ViiV Healthcare, Inc., Gilead Sciences, Janssen Therapeutics; consulting or advisor fees from GlaxoSmithKline, ViiV Healthcare, Inc.

O'Halloran, Jane A.
To self, paid to my institution: Research grant/grant pending from Merck & Co, Inc.

Okulicz, Jason
Self: Speaker's bureau for Gilead Sciences

Orkin, Chloe
Self: Consulting or advisor fees from AbbVie Inc., Bristol-Myers Squibb, Gilead Sciences, Janssen Therapeutics, Merck & Co, Inc., ViiV Healthcare, Inc.; research grant/grant pending from AbbVie Inc., Bristol-Myers Squibb, Gilead Sciences, Janssen Therapeutics, Merck & Co, Inc., ViiV Healthcare, Inc.; other from AbbVie Inc., Bristol-Myers Squibb, Gilead Sciences, Janssen Therapeutics, Merck & Co, Inc., ViiV Healthcare, Inc.

Overton, Edgar T.
Self: Consulting or advisor fees from Merck & Co, Inc., GlaxoSmithKline

Palella, Frank J.
Self: Speaker's bureau for Gilead Sciences, Janssen Therapeutics, Merck & Co, Inc.; consulting or advisor fees from ViiV Healthcare, Inc.

Parkes-Ratanshi, Rosalind M.
To self, paid to my institution: Research grant/grant pending from Janssen Therapeutics

Pavlakis, George N.
Self: Patent holder

Permar, Sallie
Self: Consulting or advisor fees from Merck & Co, Inc., Moderna, Pfizer, Sanofi
To self, paid to my institution: Research grant/grant pending from Merck & Co, Inc., Moderna

Persico, Marcello
Self: Other from AbbVie Inc., Gilead Sciences

Peters, Marion G.
Spouse or Partner: Employment at Roche

Phanuphak, Praphan
Self: Consulting or advisor fees from Merck & Co, Inc.

Poizot-Martin, Isabelle
Self: Board membership for Gilead Sciences

Pollock, Katrina
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Post, Frank
Self: Board membership for Gilead Sciences, ViiV Healthcare, Inc.; research grant/grant pending from Gilead Sciences, ViiV Healthcare, Inc.; speaker's bureau for Gilead Sciences, Janssen Therapeutics, Merck & Co, Inc.

Price, Jennifer
Self: Consulting or advisor fees from Surrizon
To self, paid to my institution: Research grant/grant pending from Gilead Sciences, Merck & Co, Inc.
Spouse or Partner: Stock/stock options in Bristol-Myers Squibb, Johnson & Johnson, Merck & Co, Inc., AbbVie Inc.

Rajasingham, Radha
Self: Research grant/grant pending from Gilead Sciences

Ram, Renee R.
Self: Employment at Gilead Sciences

Rauch, Andri
To self, paid to my institution: Consulting or advisor fees from Merck & Co, Inc., Gilead Sciences, AbbVie Inc., ViiV Healthcare, Inc.; research grant/grant pending from Gilead Sciences; travel grants from Gilead Sciences, Pfizer, AbbVie Inc.

Reiss, Peter
To self, paid to my institution: Consulting or advisor fees from ViiV Healthcare, Inc., Merck & Co, Janssen Therapeutics, Teva Pharmaceuticals; research grant/grant pending from Gilead Sciences, ViiV Healthcare, Inc., Janssen Therapeutics, Merck & Co, Inc.

Ribaudo, Heather
To self, paid to my institution: Research grant/grant pending from KOWA Pharmaceuticals

Riddler, Sharon
Self: Research grant/grant pending from GlaxoSmithKline, Gilead Sciences

Rockstroh, Jürgen K.
Self: Consulting or advisor fees from Abivax, Gilead Sciences, Janssen Therapeutics, Merck & Co, Inc., ViiV Healthcare, Inc.

Rodgers, Mary A.
Self: Employment at and stock/stock options in Abbott Laboratories

Rolle, Charlotte-Paige M.
Self: Speaker's bureau for Gilead Sciences, ViiV Healthcare, Inc.; consulting or advisor fees from Theratechnologies Inc., ViiV Healthcare, Inc.; research grant/grant pending from Gilead Sciences, ViiV Healthcare, Inc., Janssen Therapeutics

Ruel, Theodore
Self: Other from GlaxoSmithKline, ViiV Healthcare, Inc.

Sabin, Caroline
Self: Speaker's bureau for Gilead Sciences; consulting or advisor fees from ViiV Healthcare, Inc.

Sager, Jennifer E.
Self: Employment at and stock/stock options in Gilead Sciences

Sandberg, Johan K.
Self: Research grant/grant pending from Janssen Therapeutics

Santoro, Maria M.
Self: Research grant/grant pending from Gliead Sciences; consulting or advisor fees from ViiV Healthcare, Inc., Janssen Therapeutics

Schooley, Robert T.
Self: Stock/stock options in Antiva Biosciences; consulting or advisor fees from CytoDyn; board membership for Pfizer
To self, paid to my institution: Board membership for Gilead Sciences, LabCorp/Monogram Biosciences

Schuettfort, Gundolf
Self: Research grant/grant pending from Gilead Sciences

Scott, John D.
Self: Fees from for review activities Novartis

Sebastiani, Giada
Self: Consulting or advisor fees from Novartis, Merck & Co, Inc.; speaker's bureau for Gilead Sciences, Merck & Co, Inc., AbbVie Inc.
To self, paid to my institution: Research grant/grant pending from Merck & Co, Inc.

Serrano-Villar, Sergio
Self: Consulting or advisor fees from Merck & Co, Inc.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences; speaker's bureau for ViiV Healthcare, Inc., Gilead Sciences, Merck & Co, Inc.

Shah, Maunank
Self: Research grant/grant pending from Becton Dickinson

Shamsuddin, Hala H.
Self: Employment at Merck & Co, Inc.

Sharma, Anjali
Self: Research grant/grant pending from Gilead Sciences

Siegler, Aaron J.
To self, paid to my institution: Research grant/grant pending from Gilead

Simoncini, Gina M.
Self: Research grant/grant pending from Gilead Sciences

Snyder, Chelsea
Self: Employment at and stock/stock options in Gilead Sciences

Sohn, Annette H.
To self, paid to my institution: Research grant/grant pending and other from ViiV Healthcare, Inc.

Solomon, Sunil S.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences, Abbott Diagnostics

Spagnuolo, Vincenzo
Self: Consulting or advisor fees from ViiV Healthcare, Inc., Gilead Sciences
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Spudich, Serena S.
Self: Provision of medicine or equipment from ViiV Healthcare, Inc.

Stekler, Joanne
Self: Consulting or advisor fees from Gilead Sciences

Strickler, Howard D.
Self: Other from MTM Laboratories/Roche, Becton Dickinson, Alta Vista

Swindells, Susan
To self, paid to my institution: Research grant/grant pending from ViiV Healthcare, Inc., Merck & Co, Inc.

Tao, Li
Self: Employment at Gilead Sciences

Taskar, Kunal S.
Self: Employment at GlaxoSmithKline

Taylor, Kirk A.
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Tebas, Pablo
Self: Consulting or advisor fees from ViiV Healthcare, Inc., Gilead Sciences, Merck & Co, Inc.

Thio, Chloe
To self, paid to my institution: Research grant/grant pending from Sanofi

Thompson, Melanie
To self, paid to my institution: Research grant/grant pending from Bristol-Myers Squibb, CytoDyn, Inc., Frontier Biotechnology, Inc. Gilead Sciences. GlaxoSmithKline, Merck & Co, Inc., Roche, Taimed, Inc. ViiV Healthcare, Inc.

Thomsen, Nathan D.
Self: Employment at Gilead Sciences

Thornhill, John P.
Spouse or Partner: Employment at AbbVie Inc.

Tiraboschi, Juan M.
Self: Consulting or advisor fees from ViiV Healthcare, Inc., Gilead Sciences, Merck & Co, Inc., Janssen Therapeutics

Turrini, Filippo
To self, paid to my institution: Research grant/grant pending from Gilead Sciences

Uldrick, Thomas S.
To self, paid to my institution: Research grant/grant pending from Merck & Co, Inc., Celgene, Roche

Underwood, Mark
Self: Employment at ViiV Healthcare, Inc.

van de Vijver, D.
To self, paid to my institution: Consulting or advisor fees from ViiV Healthcare, Inc.; research grant/grant pending from Gilead Sciences, ViiV Healthcare, Inc., Merck & Co, Inc., Janssen Therapeutics

van Wyk, Jean
Self: Employment at ViiV Healthcare, Inc.

van Zyl, Gert U.
Self: Speaker's bureau for ViiV Healthcare, Inc.

Veltman, Jennifer
Self: Consulting or advisor fees from Gilead Sciences; speaker's bureau for Janssen Therapeutics

Vernazza, Pietro L.
Self: Fees for review activities from Teva Pharmaceutical Industries
To self, paid to my institution: Consulting or advisor fees from ViiV Healthcare, Inc., Sandoz

Verwijs, Rosanne
Self: Research grant/grant pending from Gilead Sciences

Walworth, Charles
Self: Employment at Monogram Biosciences

Wandeler, Gilles
To self, paid to my institution: Research grant/grant pending from Gilead Sciences; consulting or advisor fees from Gilead Sciences, AbbVie Inc., Merck & Co, Inc., ViiV Healthcare, Inc.

Waters, Laura
Self: Speaker's bureau for Gilead Sciences, Mylan, ViiV Healthcare, Inc., Janssen Therapeutics, Merck & Co, Inc.

Weinberger, Leor
Self: Board membership for Autonomous Therapeutics Inc.

Winston, Alan
Self: Consulting or advisor fees from ViiV Healthcare, Inc., Gilead Sciences, Merck & Co, Inc.; speaker's bureau for ViiV Healthcare, Inc., Gilead Sciences, Merck & Co, Inc.
To self, paid to my institution: Research grant/grant pending from ViiV Healthcare, Inc., Gilead Sciences, Merck & Co, Inc., Bristol-Myers Squibb

Yant, Stephen R.
Self: Employment at and stock/stock options in Gilead Sciences

Zoulim, Fabien
Self: Consulting or advisor fees from Arbutus, Gilead Sciences, MYR Pharma, Transgene, Vir Biotechnology
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