Infection par le VIH et vieillissement

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Conflits d’intérêts

- Contrats de recherche versés à UPMC-Sorbonne Université ou ANRS
  - ViiV Healthcare, MSD, Janssen
- Rémunération pour présentations académiques
  - ViiV Healthcare, Gilead, MSD, Janssen
- Participation à des boards scientifique
  - ViiV Healthcare, Gilead

- Espérance de vie des personnes vivant avec le VIH
- Prévalence augmentée des complications liées au vieillissement chez les PVVIH
- Physiopathologie du vieillissement : rôle de l'inflammation
- Inflammation chronique et activation immune chez les PVVIH et conséquences
- Que proposer ?

Les personnes vivant avec le VIH vieillissent

En France en 2017 : la moitié des hommes et le tiers des femmes vivant avec le VIH ont plus de 50 ans

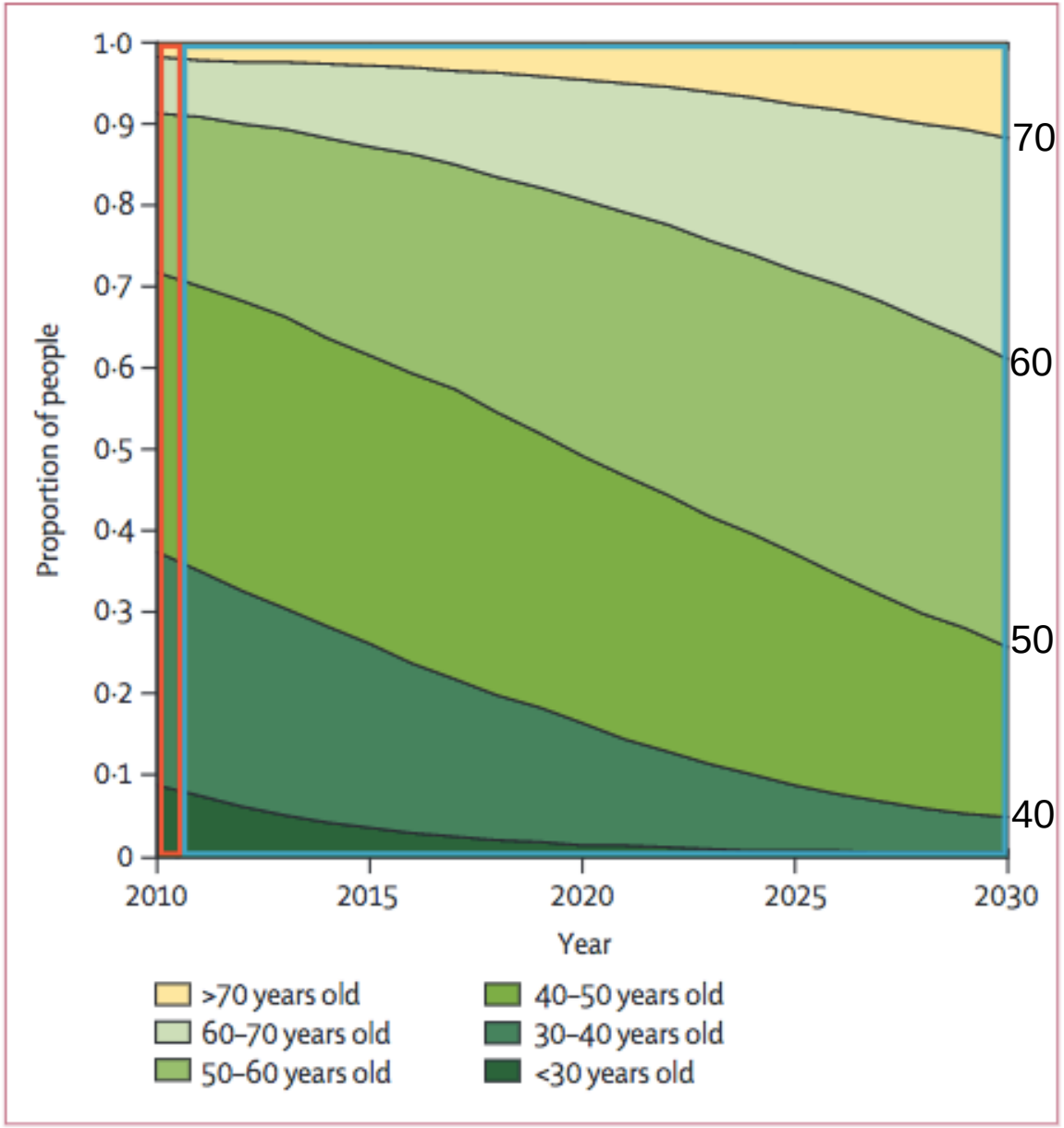


***Figure 2:* Projected age distribution of HIV-infected patients**
The red box shows the age distribution of patients on antiretroviral therapy in clinical care in the Netherlands in 2010, which matches the data exactly, and the blue box shows model output from 2011–30.

Smit Lancet Inf Dis 2015

Long-Term Mortality in HIV-Infected Individuals 50 Years or Older: A Nationwide, Population-Based Cohort Study

2440 HIV+
14 588 HIV-
Denmark

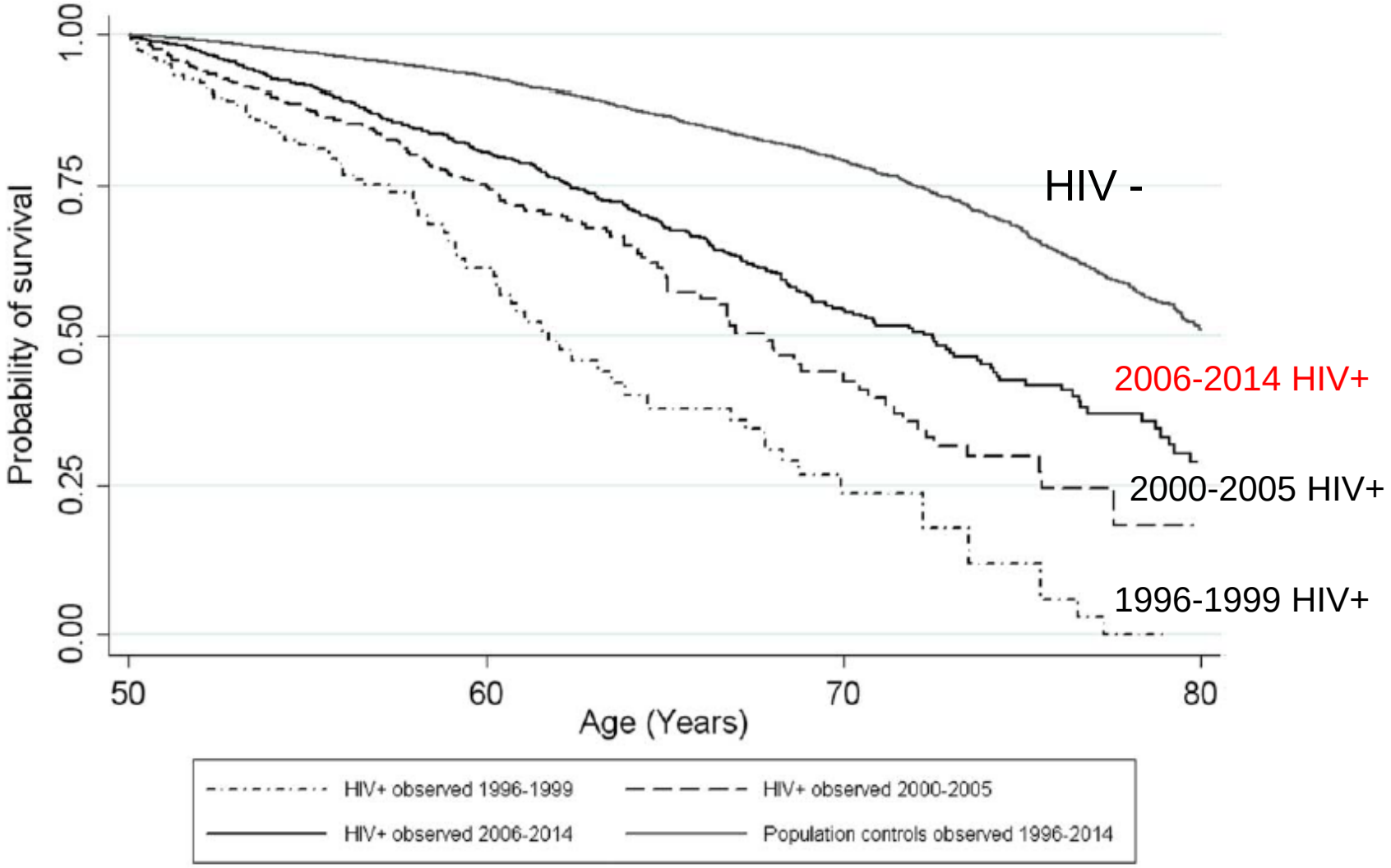
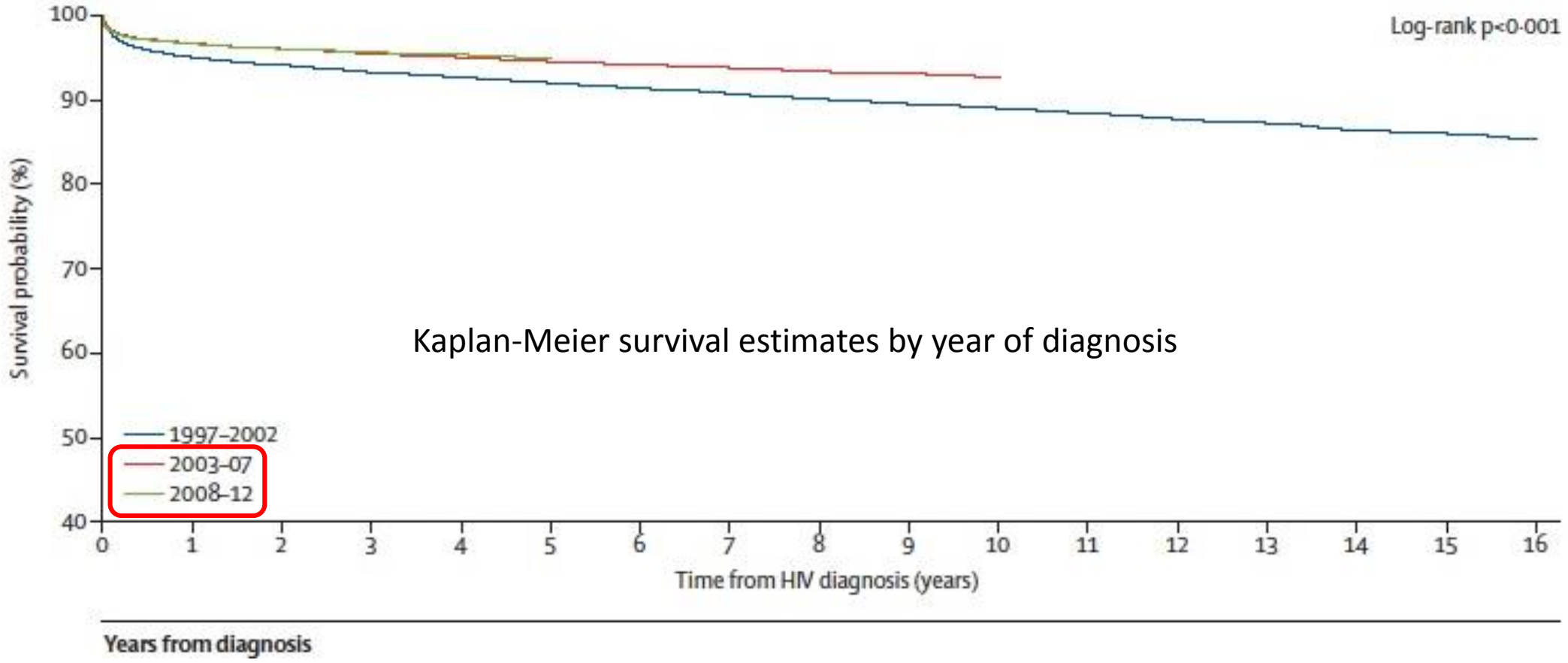


FIGURE 1. Kaplan–Meier curve showing survival from 50 years of age stratified by calendar period among HIV-infected individuals and population controls.

RA Legarth JAIDS 2016

Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort

In UK, 1997-2012: 88 994 diagnosed with HIV / 448839 PYFU
End of 2012: 5302 had died



Kaplan-Meier survival estimates by year of diagnosis

S Croxford Lancet Public Health 2017

MORTALITY IS HIGHER AMONG SUCCESSFULLY TREATED PLHIV COMPARED TO MATCHED CONTROLS

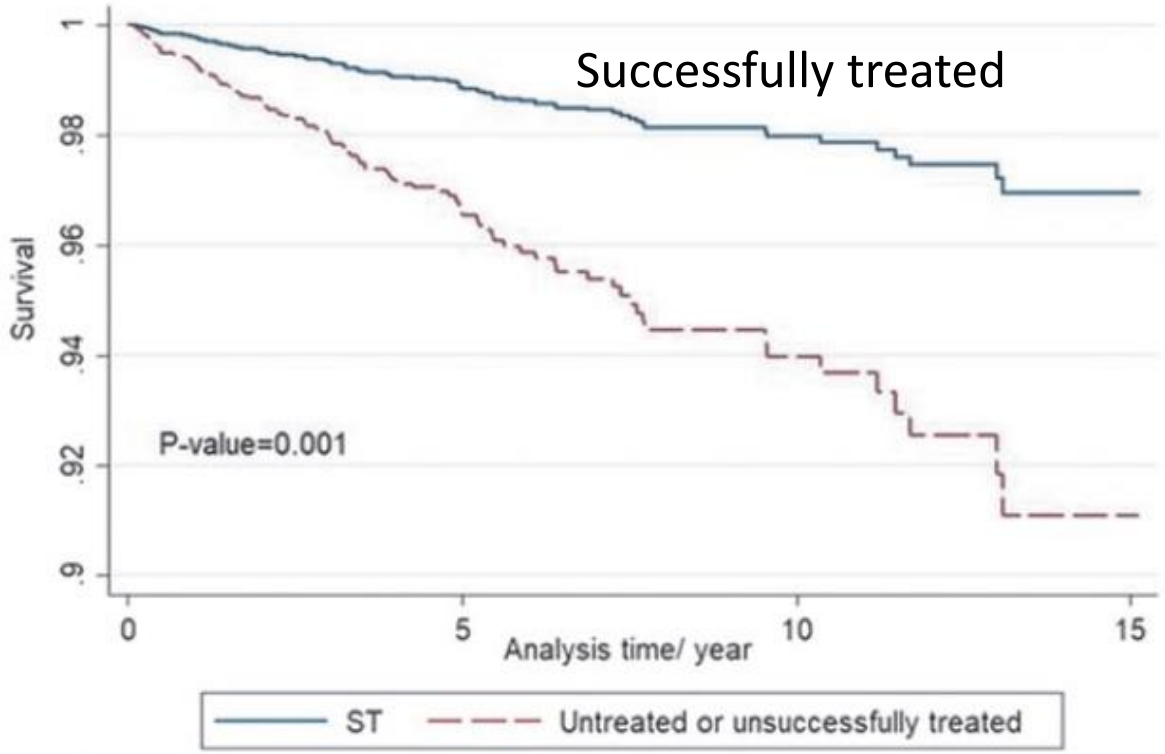
Zaake de Coninck[1], Laith Hussain-Alkhateeb[2], Göran Bratt[3] , Anna-Mia Ekstrom[1, 4] , Magnus Gisslén[5] , Max Petzold[6] , Veronica Svedhem[4, 7] .
[1]Centre for Global Health, Karolinska Institute, Stockholm, Sweden. [2] Occupational and Environmental Medicine, University of Gothenburg, Sweden, [3]Venhälsan, South General Hospital, Stockholm, Sweden. [4] Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden. [5]Department of Infectious Diseases, University of Gothenburg, Sweden, [6]Health Metrics at Sahlgrenska Academy, University of Gothenburg, Sweden, [7] Department of Infectious Diseases, Karolinska Institutet, Sweden

				Cude HR	
Follow – up period	Cohort	People at risk	Deceased	HR(95 % CI)	P-value
Entire period (15 yrs)	HIV – HIV+	4553 2297	47 58	Ref. 3.01 (2.05-4.44)	0.001
Ten years	HIV- HIV+	598 162	44 55	Ref 2.96 (1.99-4.41	0.001
Five years	HIV- HIV+	1,607 580	31 48	Ref. 3.45 (2.19-5.42	<0.001
Three years	HIV- HIV+	2,495 1,043	22 36	Ref. 3.48 (2.04-5.91	<0.001
One year	HIV- HIV+	3,845 1,836	6 18	Ref. 6.02 (2.39-15.2	<0.001

Successfully treated, PLHIV were 3 times more likely to die when compared to HIV-negative persons . The risk of mortality decreased from HR 6.02 after the first year of successful treatment.

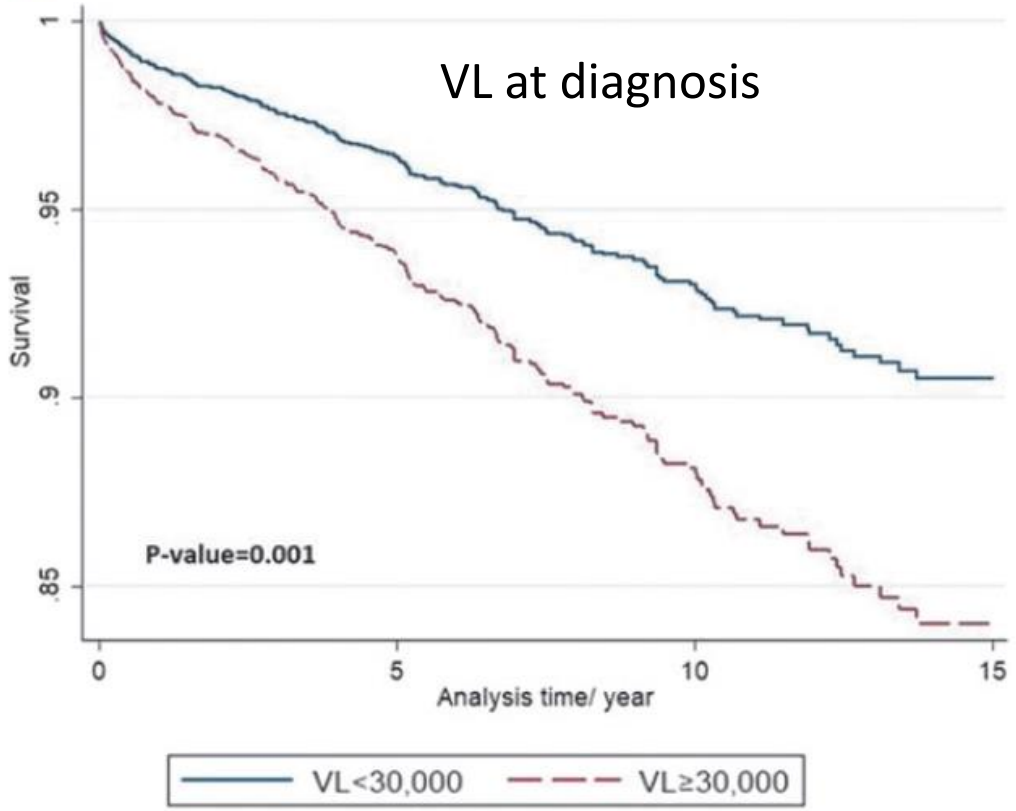
CROI 2018 poster 893

Non-AIDS Mortality Is Higher Among Successfully Treated People Living with HIV Compared with Matched HIV-Negative Control Persons: A 15-Year Follow-Up Cohort Study in Sweden



Number at risk

Untreated	1462	518	169	38
ST	2604	1549	627	92



Number at risk

VL >=30,000	1775	919	383	69
VL <30,000	2243	1126	398	59

Z de Coninck AIDS Patient Care and STDs 2018

Also: Role of CD4 count and VL, MT May AIDS 2014

Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort

	Mortality rate per 10 000 person-years (95% CI)	Observed deaths	Expected deaths*	Standardised mortality ratio (95% CI)
People diagnosed with HIV	375 874 person-years			
All-cause mortality	60·8 (58·4–63·4)	2288	816	2·8 (2·7–2·9)
Non-AIDS deaths	33·9 (32·1–35·8)	1275	803	1·6 (1·5–1·7)
Non-AIDS infections	5·3 (4·6–6·1)	198	29	6·8 (5·9–7·8)
Non-AIDS cancers	7·4 (6·6–8·3)	279	264	1·1 (0·94–1·2)
Cardiovascular disease and stroke	6·0 (5·3–6·8)	226	195	1·2 (1·0–1·3)
Liver disease	4·1 (3·5–4·8)	154	56	2·8 (2·3–3·2)
Accident	1·8 (1·4–2·3)	69	56	1·2 (0·96–1·6)
Suicide	1·5 (1·2–2·0)	58	40	1·5 (1·1–1·9)
Substance misuse	2·5 (2·0–3·0)	93	40	2·3 (1·9–2·8)
Other causes	5·3 (4·6–6·1)	198	123	1·6 (1·4–1·9)
Men	239 506 person-years			
All-cause mortality	70·5 (67·2–73·9)	1688	662	2·5 (2·4–2·7)
Non-AIDS deaths	41·1 (38·7–43·8)	986	651	1·5 (1·4–1·6)
Non-AIDS infections	5·6 (4·7–6·6)	134	23	5·8 (4·9–6·9)
Non-AIDS cancers	8·7 (7·6–10·0)	209	196	1·1 (0·93–1·2)
Cardiovascular disease and stroke	7·4 (6·4–8·6)	178	172	1·0 (0·89–1·2)
Liver disease	5·1 (4·3–6·1)	122	45	2·7 (2·3–3·2)
Accident	2·4 (1·8–3·1)	57	49	1·2 (0·88–1·5)
Suicide	2·3 (1·7–2·9)	54	36	1·5 (1·1–2·0)
Substance misuse	3·5 (2·9–4·4)	85	34	2·5 (2·0–3·1)
Other causes	6·1 (5·2–7·2)	147	96	1·5 (1·3–1·8)
Women	136 368 person-years			
All-cause mortality	44·0 (40·6–47·7)	600	155	3·9 (3·6–4·2)
Non-AIDS deaths	21·2 (18·9–23·8)	289	152	1·9 (1·7–2·1)
Non-AIDS infections	4·7 (3·7–6·0)	64	6	10·7 (8·2–13·6)
Non-AIDS cancers	5·1 (4·1–6·5)	70	67	1·0 (0·81–1·3)
Cardiovascular disease and stroke	3·5 (2·7–4·7)	48	23	2·1 (1·5–2·8)
Liver disease	2·3 (1·7–3·3)	32	10	3·2 (2·2–4·5)
Accident	0·88 (0·50–1·5)	12	8	1·5 (0·77–2·6)
Suicide	0·29 (0·11–0·78)	4	5	0·80 (0·21–2·0)
Substance misuse	0·59 (0·29–1·2)	8	6	1·3 (0·57–2·6)
Other causes	3·7 (2·8–4·9)	51	27	1·9 (1·4–2·5)

*Numbers might not add up because of rounding.

Table 8: Crude and age-standardised mortality in HIV-positive individuals by sex, cause of death, after the first year of diagnosis

S Croxford Lancet Public Health 2017

- Espérance de vie des personnes vivant avec le VIH
- Prévalence augmentée des complications liées au vieillissement chez les PVVIH
- Physiopathologie du vieillissement : rôle de l'inflammation
- Inflammation chronique et activation immune chez les PVVIH et conséquences
- Que proposer ?

Augmentation de la prévalence de comorbidités associées au vieillissement

- Maladies cardio-vasculaires et hypertension
- Cancers non-classants SIDA (HPV, HBV, HCV, EBV, tabac): foie, poumon, marge anale
- Ostéoporose
- Déficit neurocognitif
- Sarcopénie
- Fragilité
- Lipodystrophie
- Résistance à l'insuline, diabète et dyslipidémie,
- Stéatose et stéatohepatite (NAFLD et NASH)
- Plus dépression…

Patients à risque: >50 ans, infectés depuis longtemps, traités par des antirétroviraux de première génération, rapport CD4/CD8 bas, CD4 bas, CV détectable, lipodystrophie, mode de vie à risque, nadir CD4 bas, stade SIDA

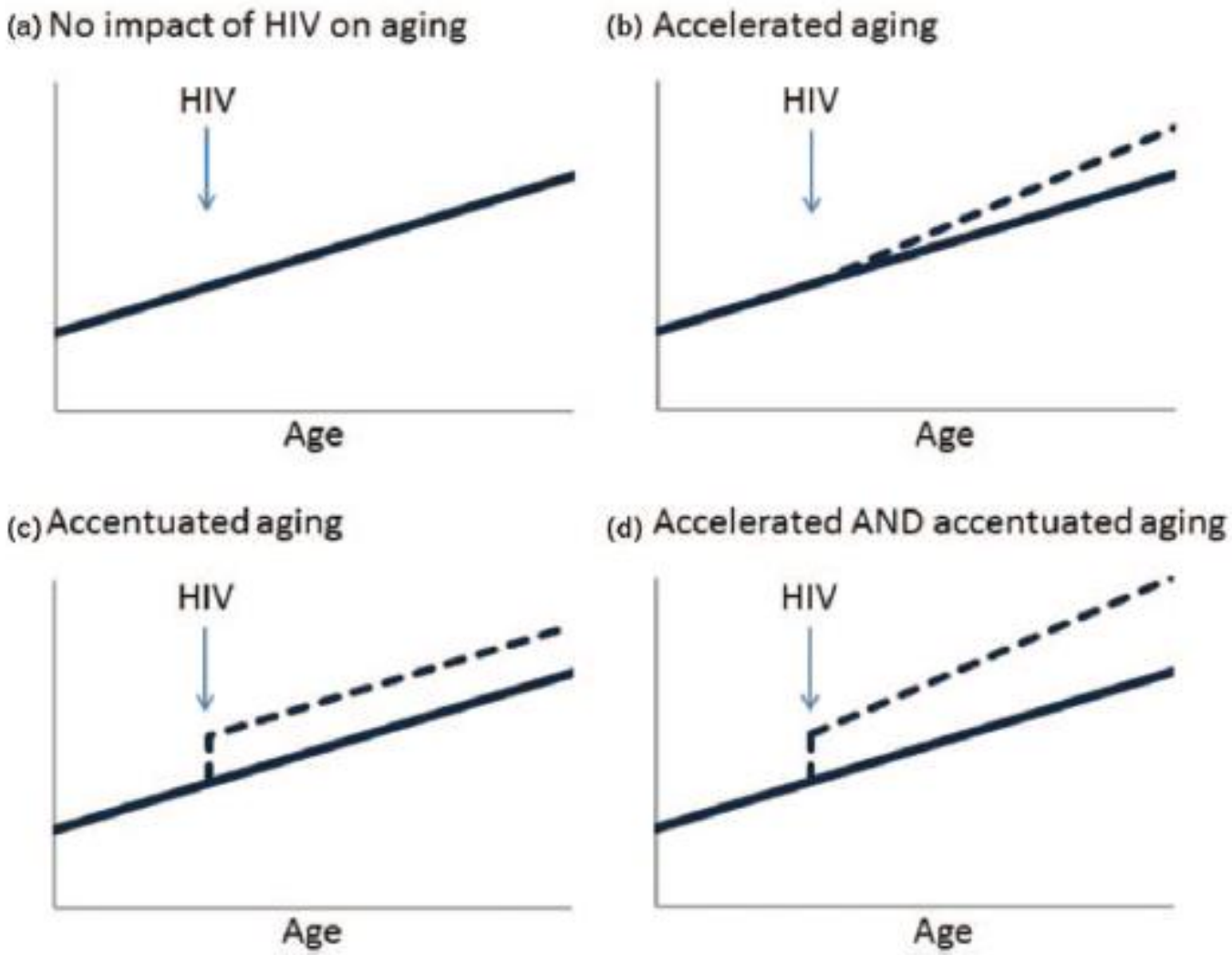
Burden of mental comorbidities

	Adults with HIV*	General pop in US
Major depressive disorder	20% – 40%	8% (NIMH)
Generalized anxiety disorder	10% – 25%	3% (NIMH)
Bipolar	3% – 9%	3% (NIMH)
Schizophrenia	4% – 15%	1% (NIMH)
PTSD Post-traumatic disorder	10% – 30%	8% (American Psychiatric Assoc.)
Heavy alcohol use	8% – 16%	6% (NIAAA)
Substance use disorders	12% – 40%	8% (SAMHSA)

**Not an exhaustive review. Bing EG, et al. Arch Gen Psychiatry 2001. O'Cleirigh C, et al, Psuchosomatics, 2015. Brand C et al, Clin Psychol Rev, 2017. Druss BG, et al, Arch Gen Psychiatry, 2007. Robins LN, et al, Arch Gen Psychiatry 1988. Israelski et al, AIDS Care 2007. de Sousa Gurgel, et al, AIDS Care 2013. Moore DJ et al, AIDS Behavior, 2012. Applebaum AJ, J Assoc Nurses AIDS Care, 2015. Blank MB et al, Psychiatric Services, 2002. Pence BW, et al, JAIDS, 2006. Galvan FH, Journal of Studies on Alcohol, 2002. Chander G, et al, HIV Med, 2008. Rabkin JG et al, AIDS 2004.*

K Althoff symposium S-6 CROI 2018

Vieillissement accéléré ou accentué?



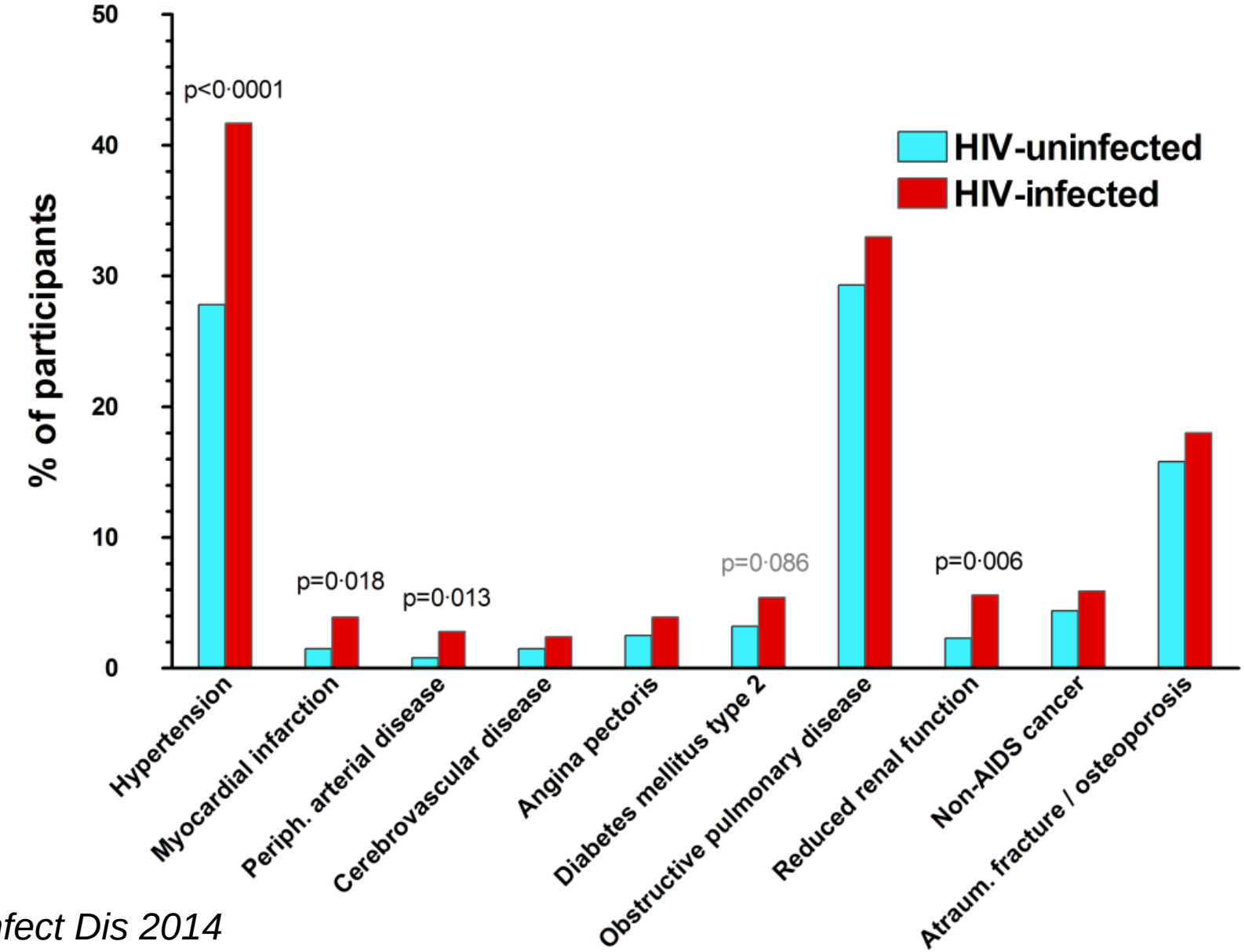
C Sabin AIDS 2017

Fig. 2. Schematic showing possible associations between increased age and the prevalence of an age-associated noncommunicable comorbidity in the situations where there is (a) no impact of HIV on aging, (b) accelerated aging by HIV, (c) accentuated aging by HIV, and (d) accelerated and accentuated aging by HIV.

Cardiovascular disease, hypertension, diabetes, reduced renal function are more prevalent in HIV-infected individuals

agehiv cohort study

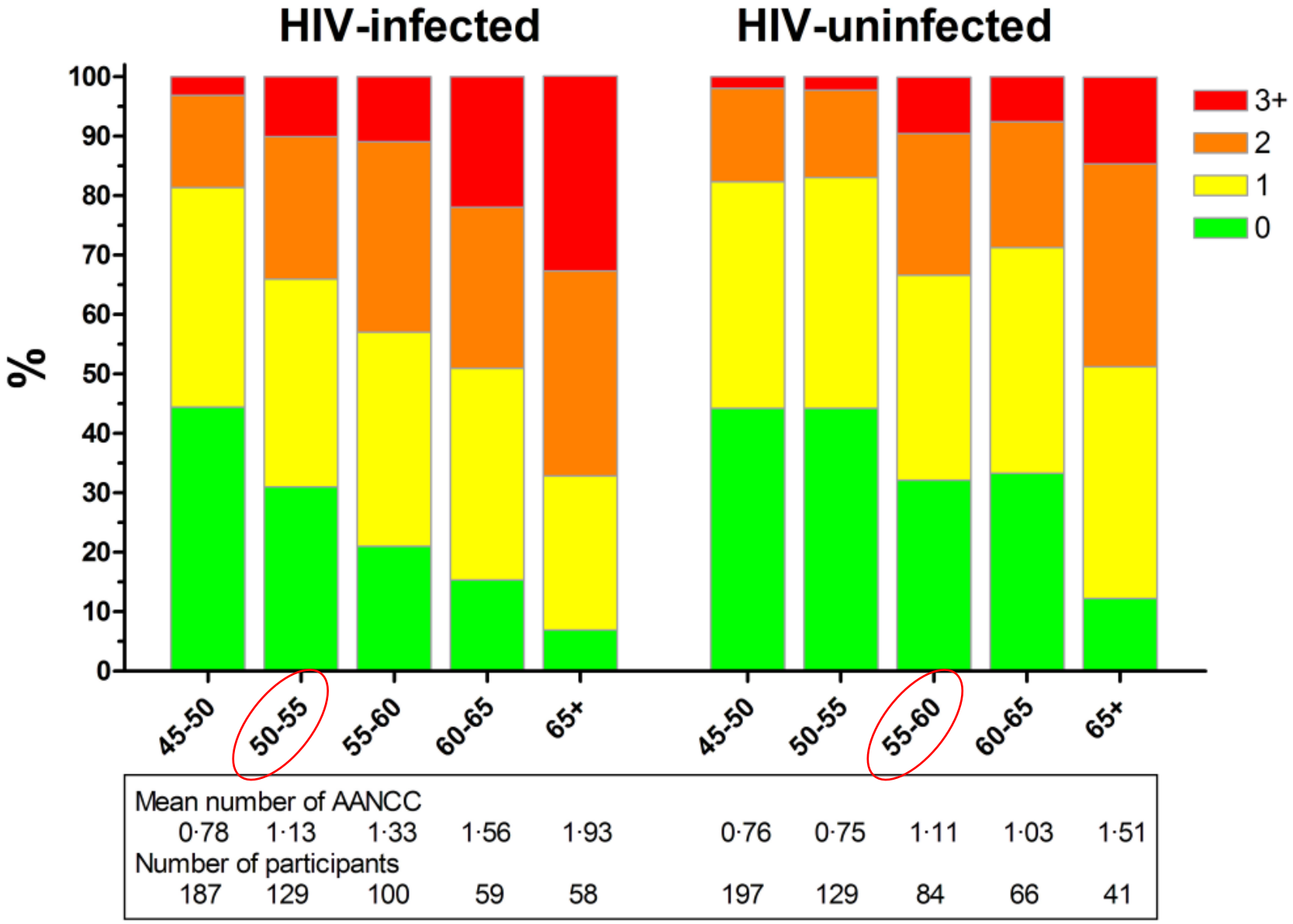
524 HIV-
540 HIV+



Schouten J et al. Clin Infect Dis 2014

The prevalence of multimorbidity is higher among HIV+ patients

agehiv cohort study



Schouten J et al. Clin Infect Dis 2014

Table 4. Risk Factors for Age-Associated Noncommunicable Comorbidities, Multivariably Analyzed Using the HIV-Infected and HIV-Uninfected Study Groups Jointly

	Univariable Analysis			Multivariable Analysis		
Risk Factor	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Age (per 5 years)	1.50	1.39–1.63	<.001	1.39	1.27–1.52	<.001
Smoking (per 5 pack-years)	1.10	1.07–1.13	<.001	1.08	1.05–1.12	<.001
Positive family history[a] (yes/no)	1.57	1.23–2.01	<.001	1.88	1.45–2.44	<.001
HIV infection (yes/no)	1.68	1.34–2.10	<.001	1.07	0.80–1.42	.661
Known cumulative duration of immunodeficiency (per year with a CD4 count <200 cells/μL)	1.33	1.20–1.48	<.001	1.23	1.10–1.38	<.001
Waist-to-hip ratio (per 0.1)	1.94	1.67–2.25	<.001	1.49	1.23–1.80	<.001
hs-CRP (per mg/mL)	1.06	1.03–1.09	<.001	1.03	0.99–1.06	.107
sCD14 (per 100 ng/mL)	1.02	1.01–1.04	.007	1.02	1.00–1.03	.074
Cumulative duration of ritonavir use in high dosages (≥400 mg/daily) (per year)	1.19	1.10–1.28	<.001	1.08	0.99–1.18	.083

The outcome variable is the number of age-associated noncommunicable comorbidities (AANCCs) per participant. Analyses were performed using ordinal logistic regression. This model was adjusted for sex, Dutch origin, sexual orientation, smoking, use of cocaine/ecstasy/cannabis, severe alcohol use, and hepatitis B/C coinfection (all of which were not significantly associated with risk for AANCC).

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; sCD14, soluble CD14.

[a] Positive family history: a first-degree family member suffering from myocardial infarction, hypertension, diabetes mellitus type 2, or hypercholesterolemia.

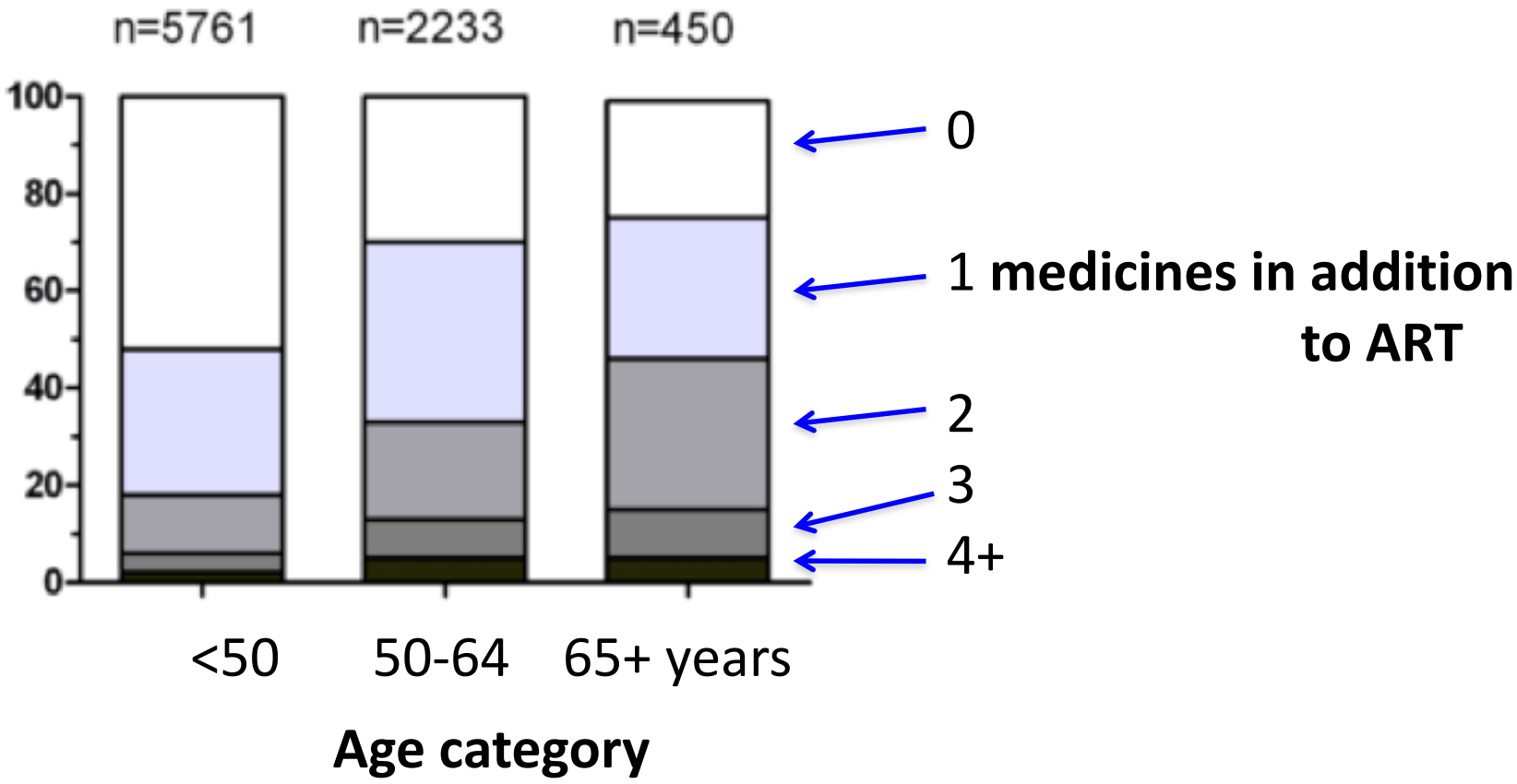
Facteurs personnels: âge, tabac, histoire familiale CVD ou diabète, RTH
Facteurs liés infection VIH : infection VIH, durée immunodéficience
Facteurs liés ART : RTV
Facteurs liés infection activation immune : CRP, sCD14

J Schouten
CID 2014

With successful ART …. HIV+ persons are aging … and are experiencing more comorbidities and more co-medications

against what? Hypertension, Dyslipidemia, Diabetes, Depression ….

Concept de polypharmacie



P Tarr HIV and Aging meeting Baltimore October 2013

Hasse CID 2011

- Espérance de vie des personnes vivant avec le VIH
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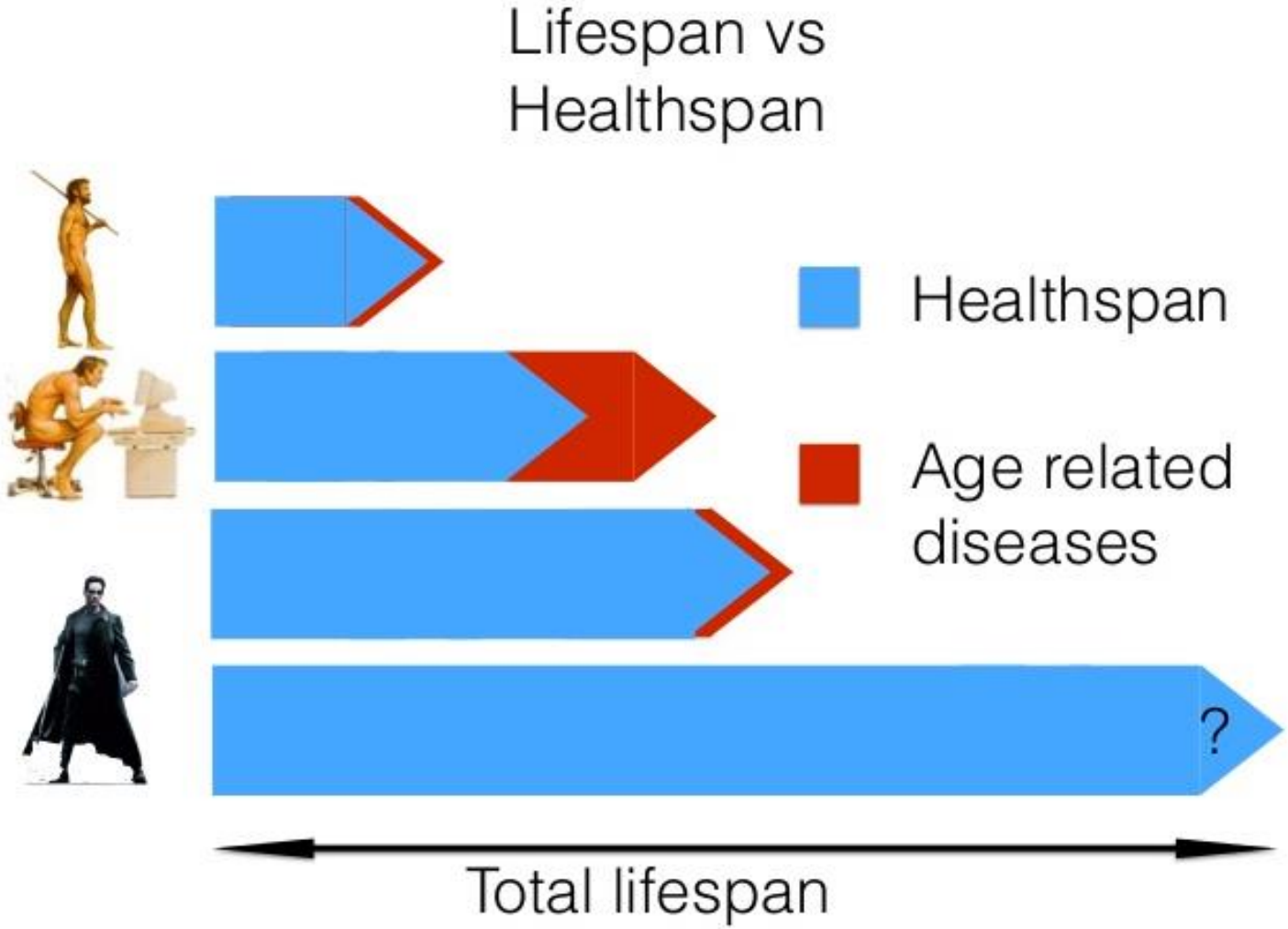
Vieillissement

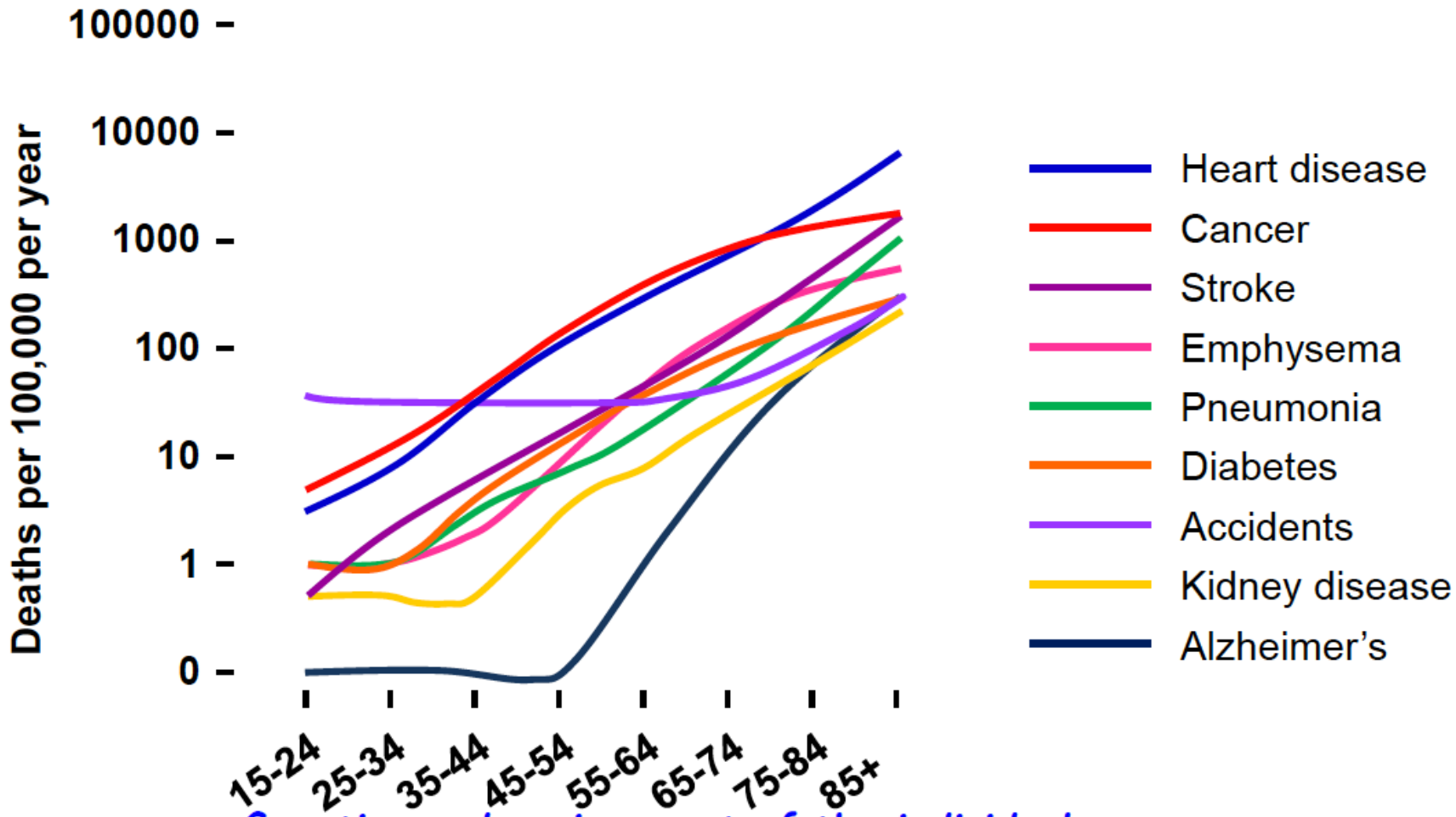
- ✓ Perte progressive de l'intégrité physiologique
- ✓ Conduisant à des atteintes fonctionnelles hétérogènes selon les organes
- ✓ Et à une augmentation de la vulnérabilité (frailty) et de l'incapacité (disability)
- ✓ Associée à une augmentation de la prévalence des maladies associées au vieillissement
- ✓ Avec comme conséquence ultime et naturelle le décès
- ✓ Notion de « lifespan » et de « healthspan »

Durée de vie en bonne santé



Le vieillissement est le facteur de risque majeur des comorbidités associées au vieillissement

(The Milbank Quarterly, Vol. 80, No. 1, 2002 from 1997 U.S. Vital Statistics)



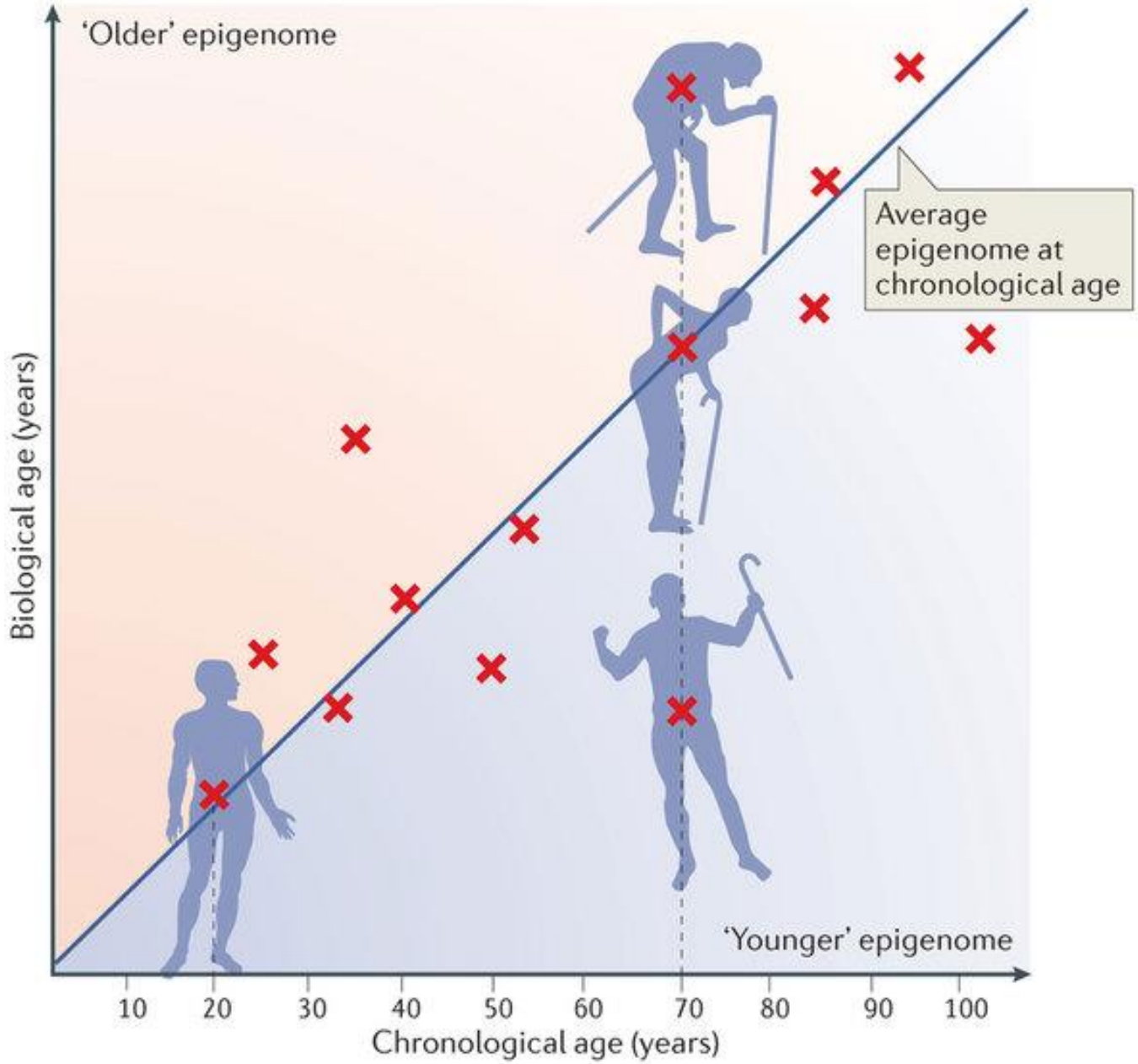
Genetics and environment of the individual determine which disease occurs first

Hallmarks of aging

C Lopes-Otin Cell 2013

Epigenetic modifications as biomarkers of aging: epigenetic clock

Age biologique
Vs
Age chronologique



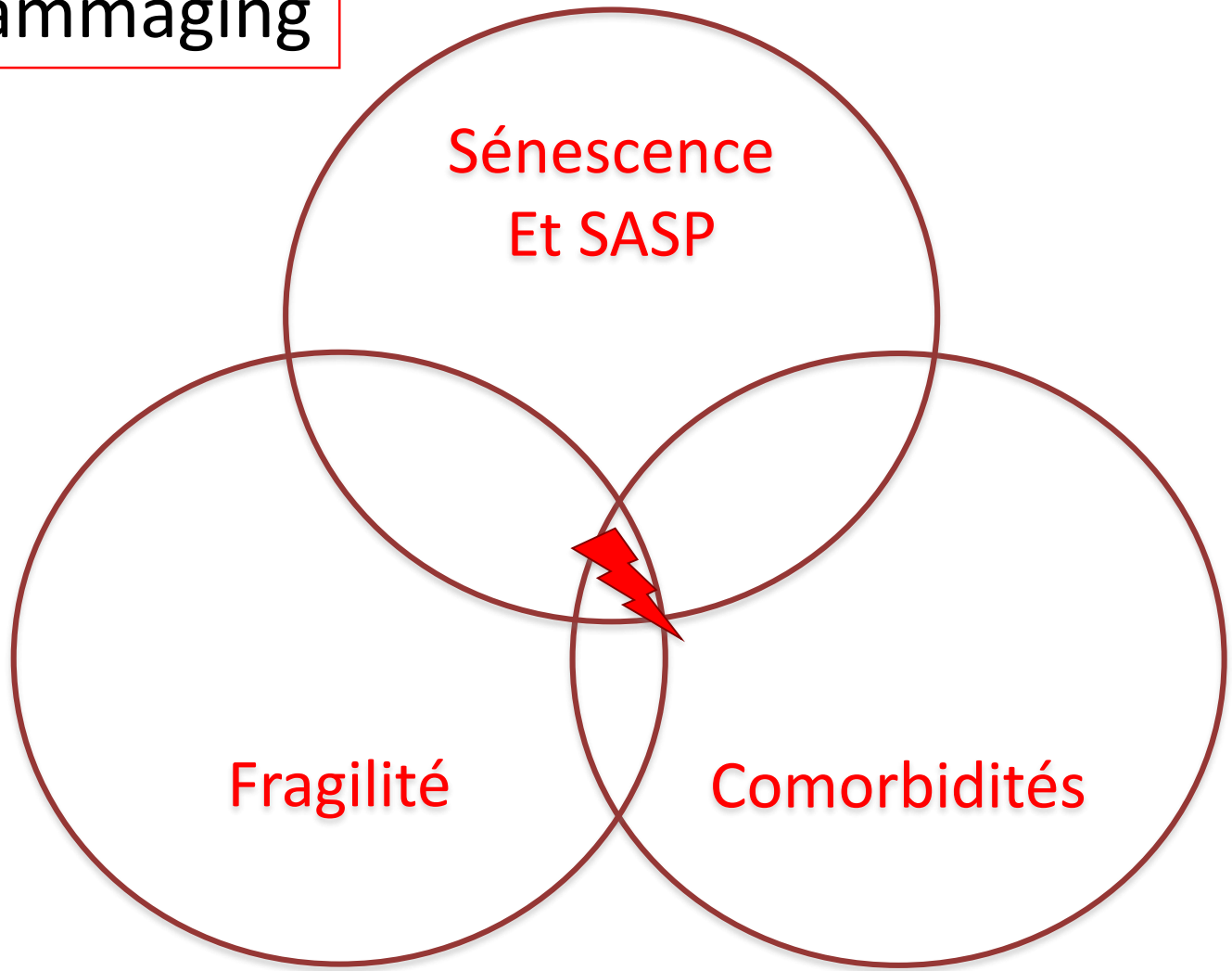
BA Benayoun Nat Rev Mol Cel Biol 2015

Nature Reviews | Molecular Cell Biology

L’inflammation joue un rôle central dans les processus de sénescence, de fragilité et les comorbidités au cours du vieillissement

Mais mécanismes et marqueurs différents

Concept d’inflammaging



Simple Biologically Informed Inflammatory Index of Two Serum Cytokines Predicts 10 Year All-Cause Mortality in Older Adults

Table 2. Mortality Risk of Inflammatory Phenotype in 1-, 2-, and 10-Year Cardiovascular Health Study (CHS) Cohort

	10-Year CHS			1-Year CHS			2-Year CHS		
Variables	HR	95% CI		HR	95% CI		HR	95% CI	
Log(IL-6)	1.42	1.36	1.49	1.87	1.56	2.24	1.72	1.52	1.95
Log(sTNFR1)	1.46	1.39	1.53	1.98	1.69	2.32	1.72	1.52	1.94
Log(CRP)	1.25	1.19	1.31	1.63	1.33	1.98	1.59	1.39	1.82
Log(IL-18)	1.10	1.05	1.15	1.26	1.02	1.56	1.25	1.08	1.44
Log(IL-1RA)	1.21	1.15	1.26	1.44	1.19	1.73	1.29	1.13	1.48
Age	1.80	1.72	1.87	1.53	1.27	1.83	1.62	1.43	1.83
WSS	1.47	1.41	1.54	2.14	1.77	2.58	1.88	1.65	2.15
PCS	1.44	1.37	1.50	2.04	1.69	2.47	1.85	1.62	2.11
IIS	1.62	1.54	1.70	2.45	2.02	2.96	2.06	1.80	2.36
IIS*	1.88	1.77	2.00	3.21	2.50	4.11	2.58	2.16	3.08

Inflammation:
- hsCRP
- hsIL-6
- D-Dimer
- sTNFR1
- sTNFR2

Immune activation:
- sCD14
- sCD163

All analyses were adjusted for age, CVD, gender, education, smoke, and body mass index (BMI; except for age-only model), and the IIS* model was only adjusted for age, education, smoking, and BMI.

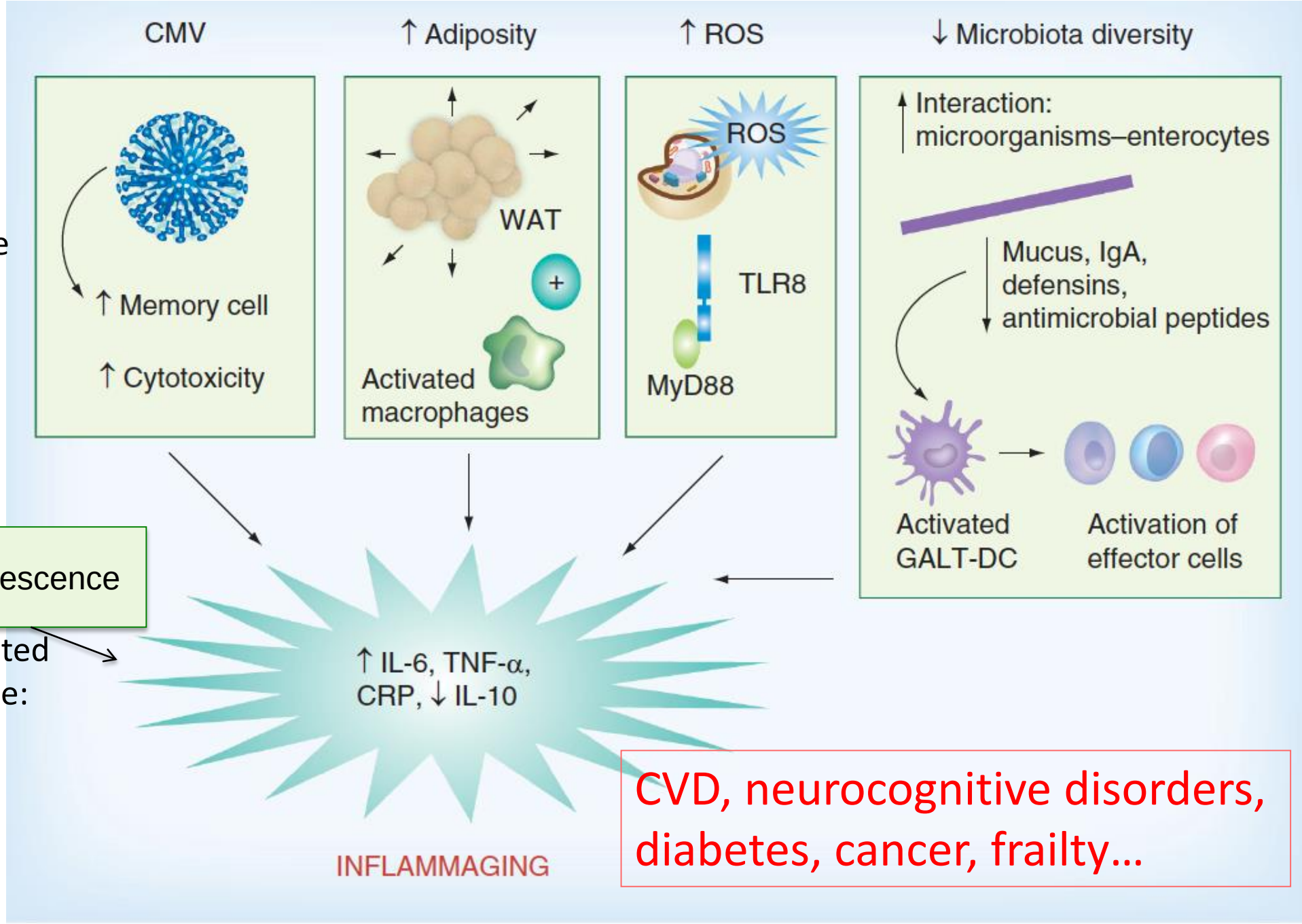
IIS and IIS* was calculated as follows:

IIS = 1/3 log(IL-6) + 2/3 log(sTNFR1), for all individuals.

IIS* = 1/3 log(IL-6) + 2/3 log(sTNFR1), if female and non-CVD.
2/5 log(IL-6) + 3/5 log(sTNFR1), if male and non-CVD,
1/4 log(IL-6) + 3/4 log(sTNFR1), if female and CVD,
1/3 log(IL-6) + 2/3 log(sTNFR1), if male and CVD.

R Varadhan J Gerontol 2013

Immune senescence



Senescence-associated secretory phenotype: Endothelium, lung, adipose tissue…

CVD, neurocognitive disorders, diabetes, cancer, frailty…

AL de Araujo Future Medicine 2013

Figure 2. The main factors contributing to inflammaging. Chronic viral infections, such as CMV,

Vieillissement chez les PVVIH

Methylome-wide Analysis of Chronic HIV Infection Reveals Five-Year Increase in Biological Age and Epigenetic Targeting of HLA

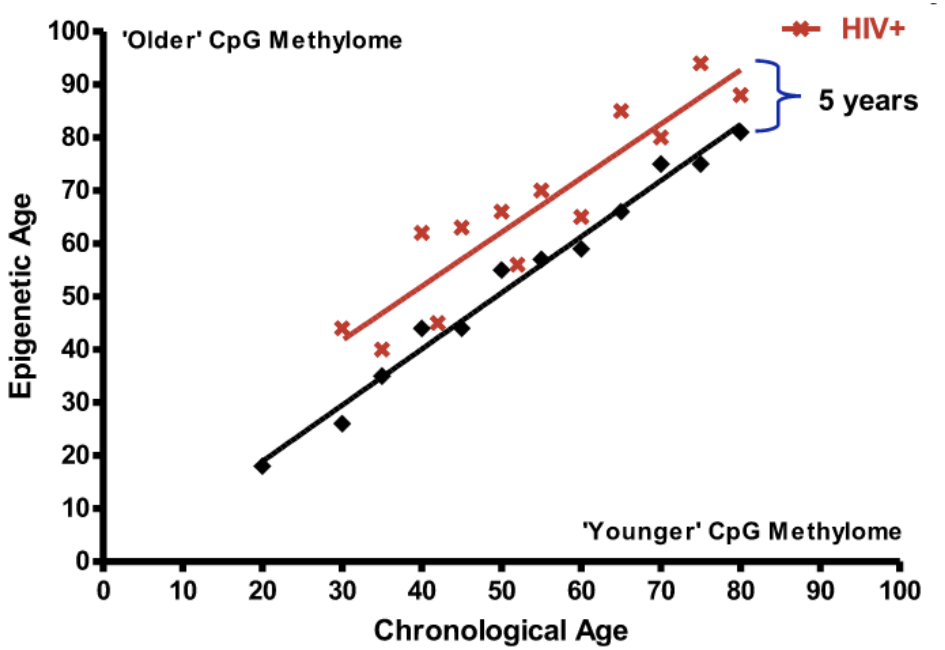
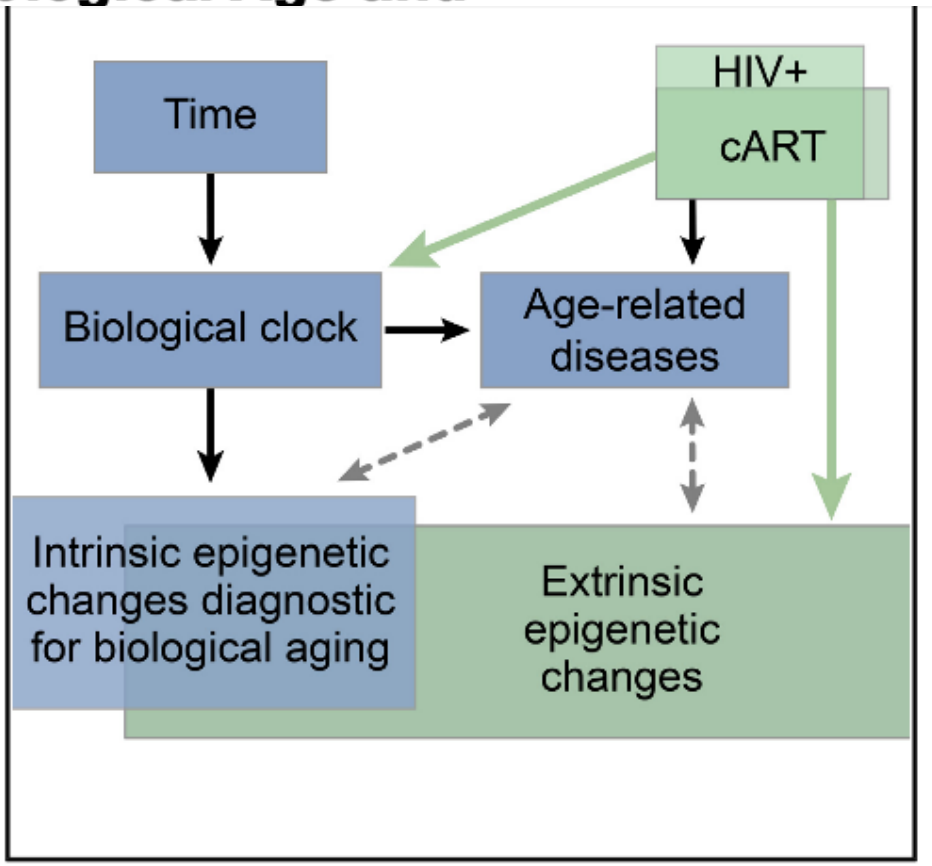


Figure 1. Treated HIV-Infected Individuals' Display Accelerated Aging as Assessed by 5mC Patterns

5-methyl cytosine DNA methylation levels across the genome are used to create an epigenetic clock to assess individuals' age. Blood DNA methylomes of HIV-infected HAART-treated individuals reveals a ~5 year acceleration of aging.



Highlights

- Methylome-wide analysis of HIV chronically infected, cART treated individuals
- HIV+ individuals have an epigenetic age 4.9 years older than healthy controls
- HLA locus is hypomethylated in HIV+ individuals
- HIV methylation aging signature is validated in purified cells

K Boulias Molecular Cell 2016

AM Gross Molecular cell 2016

COBRA
CO-MORBIDITY IN RELATION TO AIDS

- **134 PLWH** aged ≥45, on cART and with a plasma HIV viral load <50 copies/mL for ≥12 months prior to enrolment were recruited at HIV outpatient clinics. Median (IQR) duration of HIV was 15 (9-21) years and nadir CD4⁺ was 180 (90-250).
- **79 similarly aged HIV-negative controls** with comparable socio-demographic and lifestyle characteristics, were recruited from sexual health centres.
- **35 age-matched healthy BD** were recruited from the Dutch national blood bank.

Median (IQR) or n (%)		PLWH	HIV-ve	BD
Age [years]		56 (51, 62)	57 (52, 65)	59 (52, 65)
Male		125 (93%)	73 (92%)	18 (51%)
Black-African		16 (12%)	2 (3%)	N/A
MSM		104 (78%)	59 (75%)	N/A
Self-reported smoking:	*Current smoker*	40 (30%)	20 (25%)	N/A
	Ex-smoker	58 (43%)	29 (37%)	N/A
Self-reported Alcohol:	*Current drinker*	104 (78%)	71 (90%)	N/A
	Previous drinker	18 (13%)	3 (4%)	N/A
Recreational drug use (self-reported)		44 (33%)	18 (23%)	N/A
Chronic HBV		7 (3%)	0 (0%)	0 (0%)
Chronic HCV		5 (2%)	0 (0%)	0 (0%)
CMV infection		129 (98%)	63 (80%)	8 (23%)
CD4⁺ count [cells/µL]		618 (472-806)	900 (692-1174)	N/A
CD8⁺ count [cells/µL]		770 (611-947)	422 (313-614)	N/A

De Francesco CROI 2017 #672, IAS 2017

COBRA
CO-MORBIDITY IN RELATION TO AIDS

Age advancement

The biological age of each individual was derived using a set of 10 biomarkers (see box) identified through the EU FP7 MARK-AGE project (www.markage.eu) and measured in blood cells (B), plasma (P) or serum (S).

They were selected as best predictors of chronological age among approximately 400 candidate biomarkers and combined using a set of weights.

- cumulative level of cytosine methylation at gene positions (B):
  - ELOVL Fatty Acid Elongase 2 CpG 15,16,17
  - ELOVL Fatty Acid Elongase 2 CpG 11,12,13,14
  - FHL 2 CpG 11,12
  - FHL 2 CpG 13,14,15
  - FHL 2 CpG 16,17
- Dehydroepiandrosterone sulphate (P)
- N-glycan peak 6 (S)

only male subjects:

- Alpha-2 macroglubulin (S)
- Lycopene (P)
- Prostate specific antigen (S)

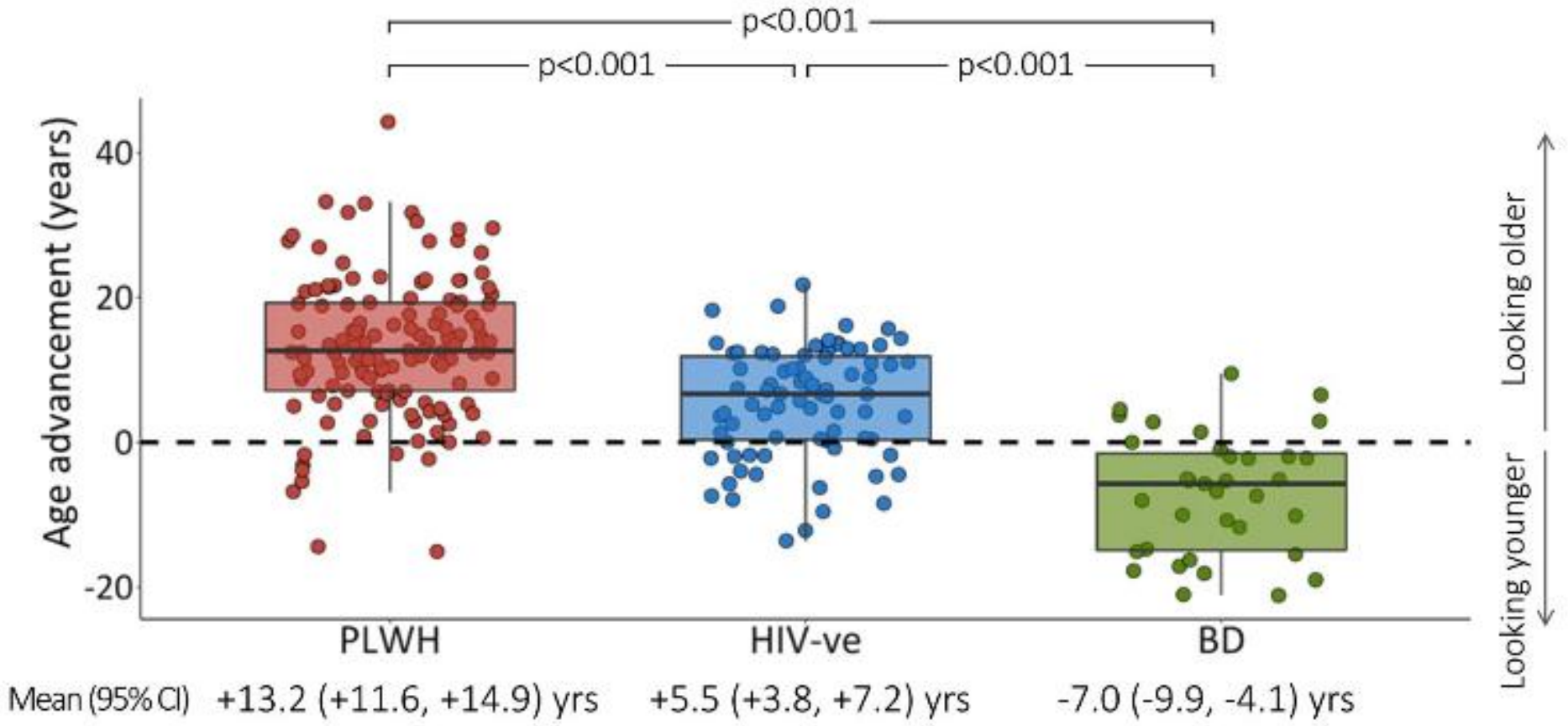
only female subjects:

- Ferritin (S)
- N-glycan $\log_{10}$(peak 1/peak 6) (S)
- a-Tocopherol (S)

Age advancement for each individual was defined as the difference between biological and chronological age.

De Francesco CROI 2017 #672, IAS 2017

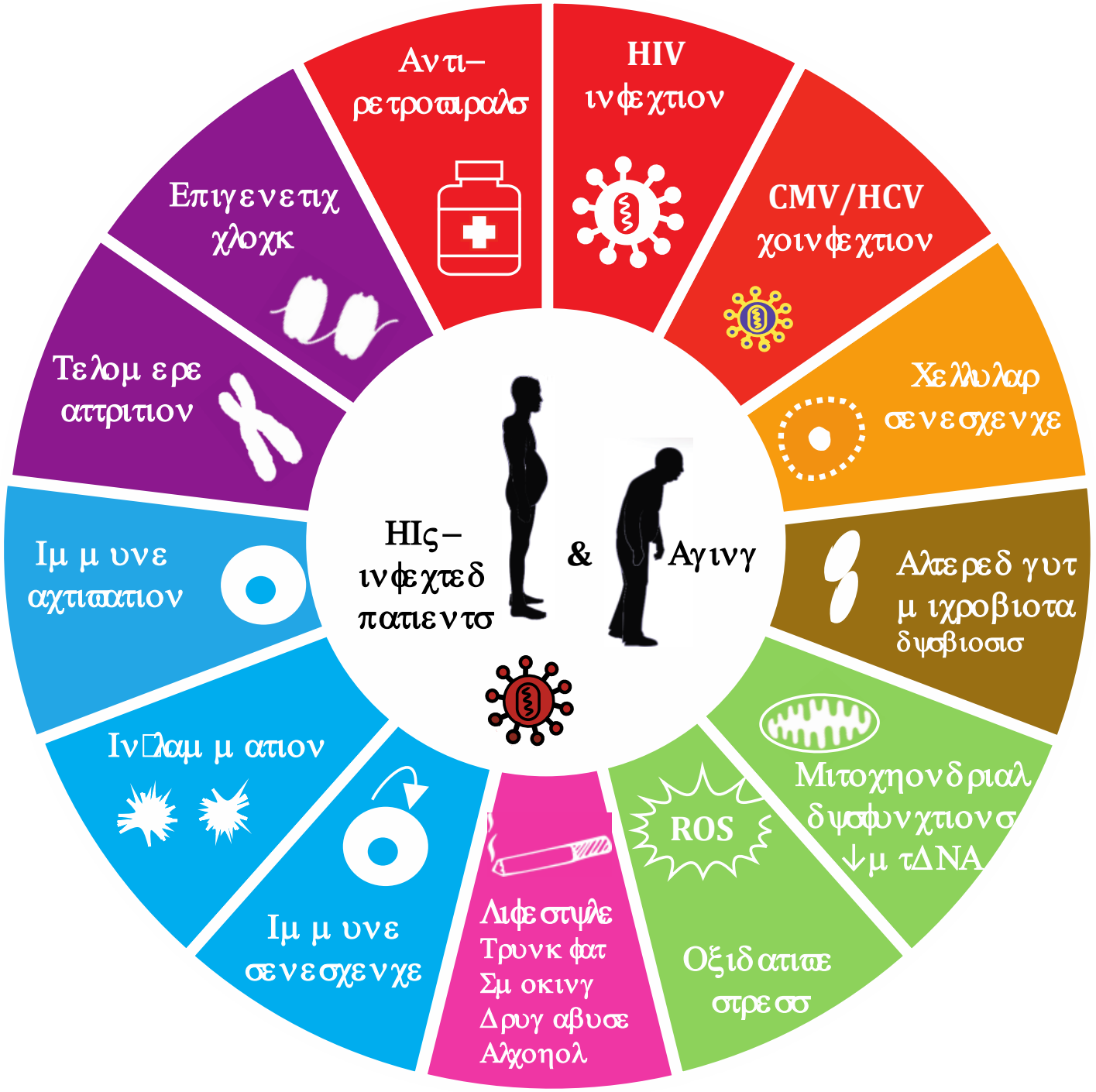
Age-advancement was more pronounced among HIV+ patients



Risk factors: Chronic HBV infection, total anti-CMV IgG, CD8 count, nadir CD4, Treatment with Saquinavir

De Francesco IAS 2017

HIV-specific mechanisms of aging



Modified from C Lagathu AIDS 2017

- Espérance de vie des personnes vivant avec le VIH
- Prévalence augmentée des complications liées au vieillissement chez les PVVIH
- Physiopathologie du vieillissement : rôle de l'inflammation
- Inflammation chronique et activation immune chez les PVVIH et conséquences
- Que proposer ?

Increased level of systemic biomarkers of inflammation and immune activation in HIV-infected individuals compared to the general population

Table 1. Characteristics and levels of immune activation and inflammatory markers in HIV-infected patients and controls

	HIV-infected patients, $n=352$	Controls, $n=59$	P^a
Demographic data			
age (years), current	49 (45–56)	41 (37–48)	0.001
age (years) at PI initiation	38 (34–44)		
male sex	81.5% (287)	85% (50)	NS
BMI (kg/m^2), current	23.0 (21.1–25.4)	23.8 (22–25.6)	NS
WHR, current	0.95 (0.90–1.00)	NA	
smoker ($n=342$), current status			<0.001
never	32.7% (112)	96.6% (57)	
current	40.4% (138)	0% (0)	
former	26.9% (92)	3.4% (2)	
HCV coinfection ($n=333$), current status	18.9% (63)	0% (0)	<0.001
hsCRP (mg/L)	2.1 (0.9–4.5)	0.8 (0.4–2.15)	<0.001
hsIL-6 (pg/mL)	1.3 (0.7–2.6)	0.85 (0.6–1.0)	<0.001
D-dimer (ng/mL)	252 (177–374)	158 (116–212)	<0.001
sCD14 (ng/mL)	1356 (1027–1818)	1199 (1106–1366)	0.02
B2M (mg/L)	2.4 (2.0–3.1)	1.4 (1.2–1.7)	<0.001
cystatin-C (mg/L)	0.93 (0.82–1.10)	0.77 (0.71–0.82)	<0.001

JP Bastard J Antimicrobiol Chem 2015

HIV-infected individuals present an enhanced level of several inflammatory and immune activation biomarkers as compared to matched HIV-negative controls

Table 3. Values of Several Markers of Systemic Inflammation, Compared Between the 2 Study Groups

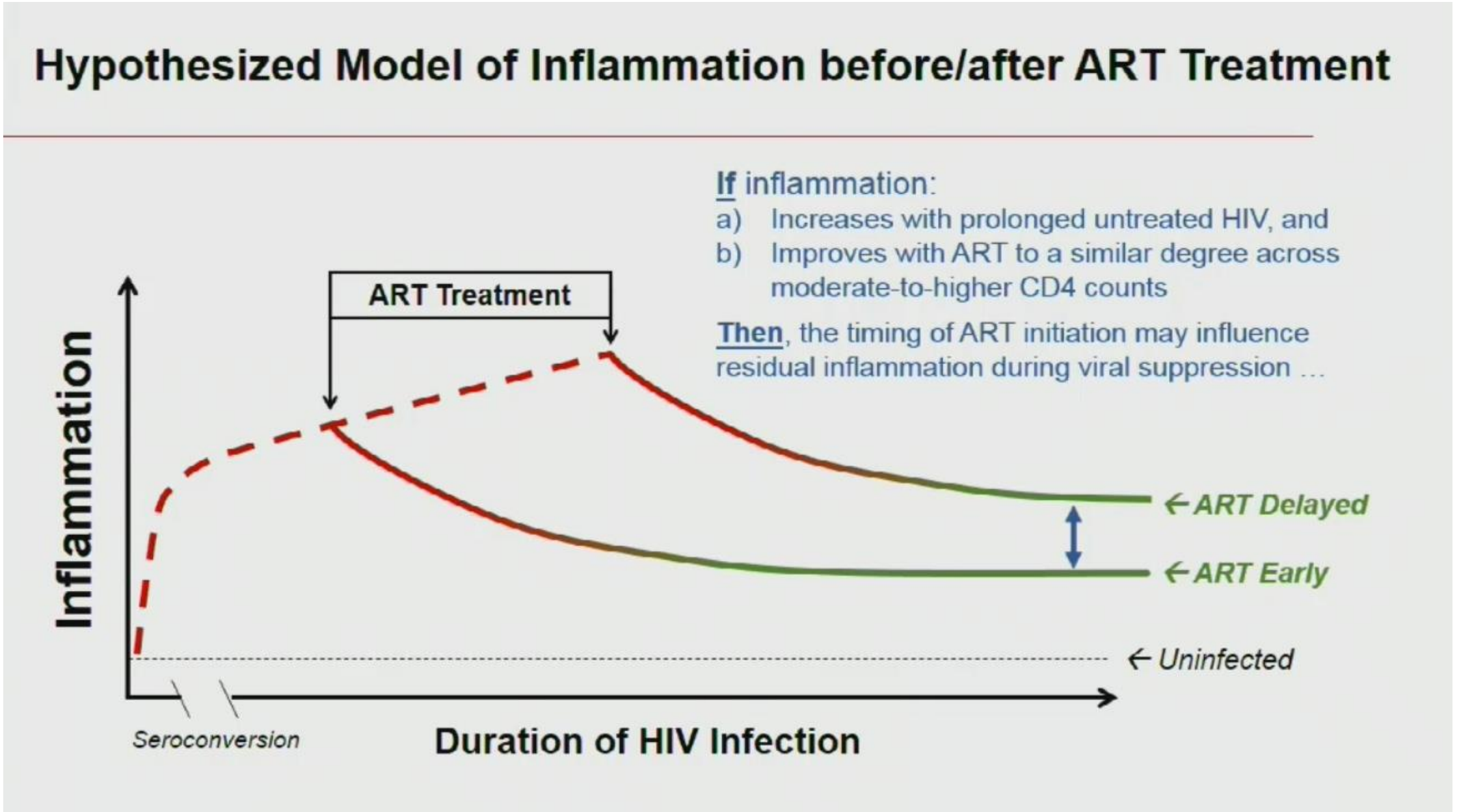
Marker	HIV-Uninfected Participants (n = 524)	HIV-Infected Participants (n = 540)	*P* Value
hs-CRP, mg/L	1.0 (0.6–1.9)	1.5 (0.7–3.5)	<.001*
hs-CRP >10 mg/L	1.6%	6.7%	<.001**
D-dimer, mg/L	0.24 (0.20–0.38)	0.23 (0.20–0.36)	.078*
D-dimer >0.5 mg/L	14.1%	13.2%	.659**
sCD14, ng/mL	1356 (1080–1738)	1576 (1305–2011)	<.001*
sCD163, ng/mL	252 (182–342)	289 (207–419)	<.001*

Data are presented as median (interquartile range) or percentage.

Abbreviations: HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; sCD14, soluble CD14; sCD163, soluble CD163.

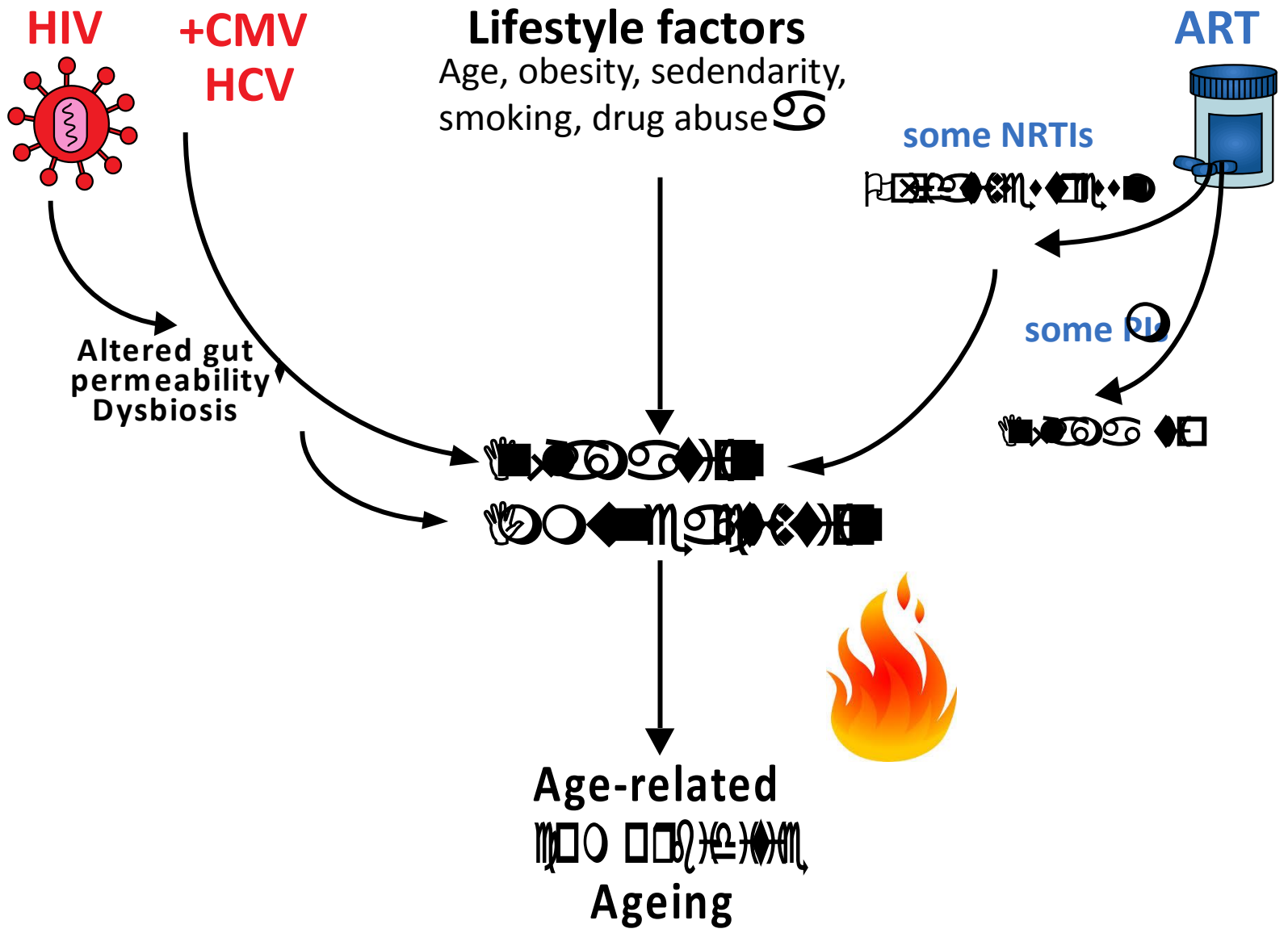
J Schouten CID 2014

Hypothesized Model of Inflammation before/after ART Treatment



J Baker symposium S-6 CROI 2018

In ART-controlled HIV+ patients, chronic inflammation/immune activation results from multiple mechanims and is involved in non-AIDS-related comorbidities



Modifed from C Lagathu AIDS 2017

Role of HIV

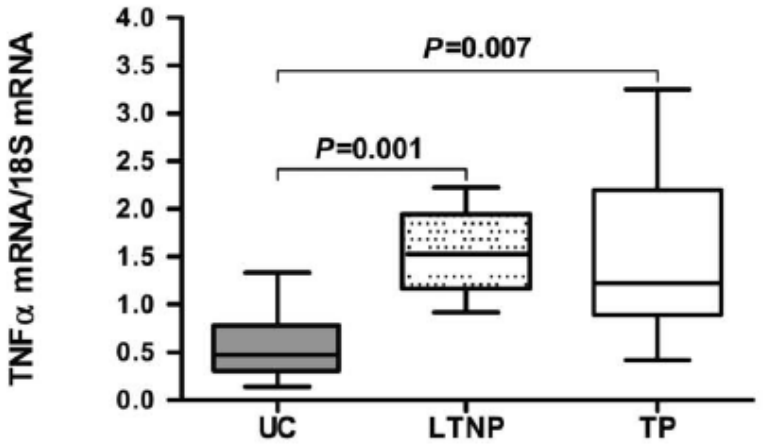
Adipose Tissue Is a Neglected Viral Reservoir and an Inflammatory Site during Chronic HIV and SIV Infection

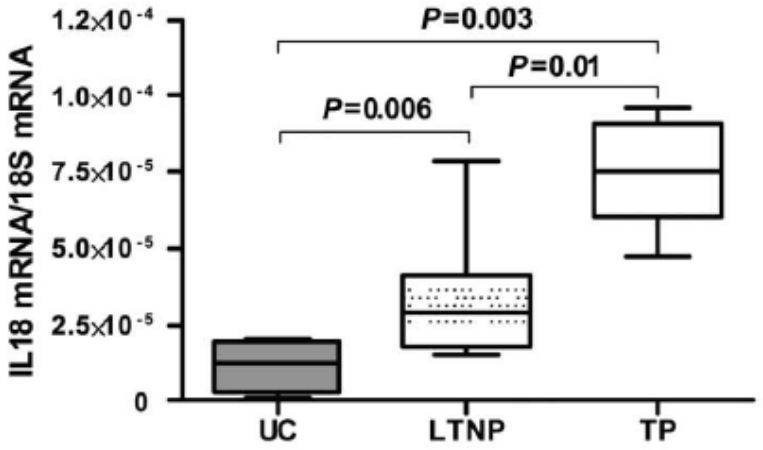
A Damouche PLOS Pathogens 2015

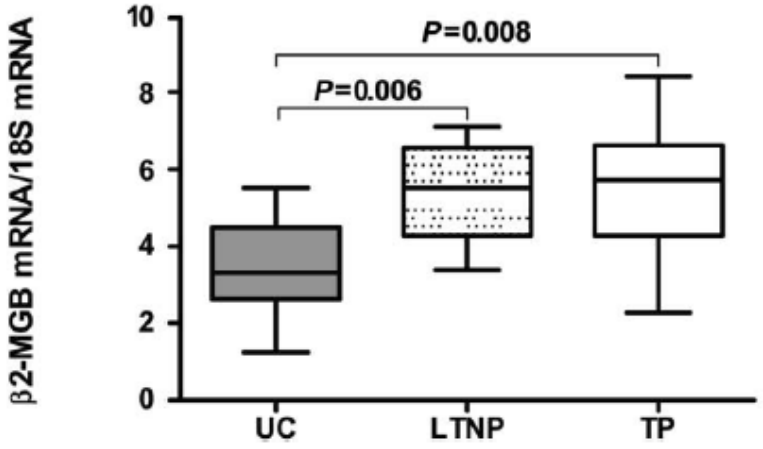
Decreased adipocyte differentiation and increased inflammation in adipose tissue from long-term non-progressors

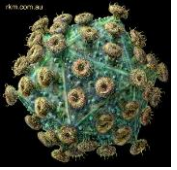
UC: uninfected controls
LTNP: long-term non progressors
TP: typical progressors ART-naive patients

F Vidal JAIDS 2012









Do Biomarkers of Inflammation, Monocyte Activation, and Altered Coagulation Explain Excess Mortality Between HIV Infected and Uninfected People?

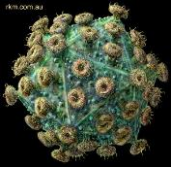
TABLE 2. Association Between HIV Infection and IL-6, sCD14, and D-dimer Adjusted for (a) Age and Race-Ethnicity and (b) All Covariates

		Proportional Odds Ratio (95% CI)*			
	Outcomes	HIV Uninfected	HIV+ HIV-1 RNA <500 Copies/mL	HIV+ HIV-1 RNA 500–9999 Copies/mL	HIV+ HIV-1 RNA ≥10,000 Copies/mL
(a) Model (age, race-ethnicity adjusted)					
1	IL-6 quartiles	1 (Ref)	1.14 (0.96 to 1.35)	1.32 (1.01 to 1.73)	2.99 (2.32 to 3.84)
2	sCD14 quartiles	1 (Ref)	0.93 (0.78 to 1.10)	0.85 (0.65 to 1.12)	2.05 (1.61 to 2.62)
3	D-dimer quartiles	1 (Ref)	0.50 (0.42 to 0.59)	0.88 (0.67 to 1.16)	1.91 (1.49 to 2.45)
(b) Model (fully adjusted)					
1	IL-6 quartiles	1 (Ref)	1.35 (1.11 to 1.64)	1.46 (1.10 to 1.95)	2.78 (2.11 to 3.65)
2	sCD14 quartiles	1 (Ref)	0.77 (0.64 to 0.93)	0.71 (0.54 to 0.95)	1.49 (1.14 to 1.94)
3	D-dimer quartiles	1 (Ref)	0.51 (0.43 to 0.62)	0.95 (0.71 to 1.26)	1.73 (1.32 to 2.26)

Fully adjusted model adjusted for age, race-ethnicity, prevalent cardiovascular disease, cancer, diabetes, chronic obstructive pulmonary disease, hypertension, smoking, hepatitis C, obesity, total cholesterol, and cholesterol lowering medication, alcohol use, cocaine use, hemoglobin, FIB-4, estimated glomerular filtration rate. IL-6, sCD14, and D-dimer quartile thresholds were defined using quartile levels (25th, 50th, and 75th percentiles) among those who died. For, IL-6 these thresholds were 1.727, 2.91, and 5.043 pg/mL. For sCD14: 1592.84, 1883.51, and 2334.18 μg/mL. For D-dimer: 0.23, 0.39, and 0.86 μg/mL.

*The proportional odds model estimates the proportional odds of being above the Nth quartile of the biomarker distribution versus being in the Nth quartile or lower.

KA So-Armah JAIDS 2016



Incomplete ART adherence is associated with higher interleukin-6 in individuals with HIV who achieved virologic suppression in the immediate arm of the Strategic Timing of Antiretroviral Treatment (START) study

Adjusted[a] fold difference in plasma concentrations of biomarkers of inflammation and coagulopathy in participants who achieved viral suppression (<50 copies/mL) and reported incomplete ART adherence after 8 months of therapy in the immediate arm of START.

Biomarker	Number of participants	Fold higher level vs. 100% adherence[b]	95% CI	P-value
IL-6 (pg/mL)	1,627	1.14	(1.01 - 1.28)	***0.03***
D-dimer (µg/mL)	1,622	0.97	(0.88 - 1.07)	0.55
CRP (mg/L)	1,627	1.25	(1.00 - 1.57)	0.05

[a]Models were adjusted for age, race, level of education, region, HIV risk group, hepatitis B or C co-infection and baseline levels of biomarkers.[b]100% adherence was defined as reporting taking "all of my pills" for all ART medication doses in the preceding 7-day period.

J Castillo-Mancilla AIDS 2018 abstract # THPEB090

Role of coinfection: CMV

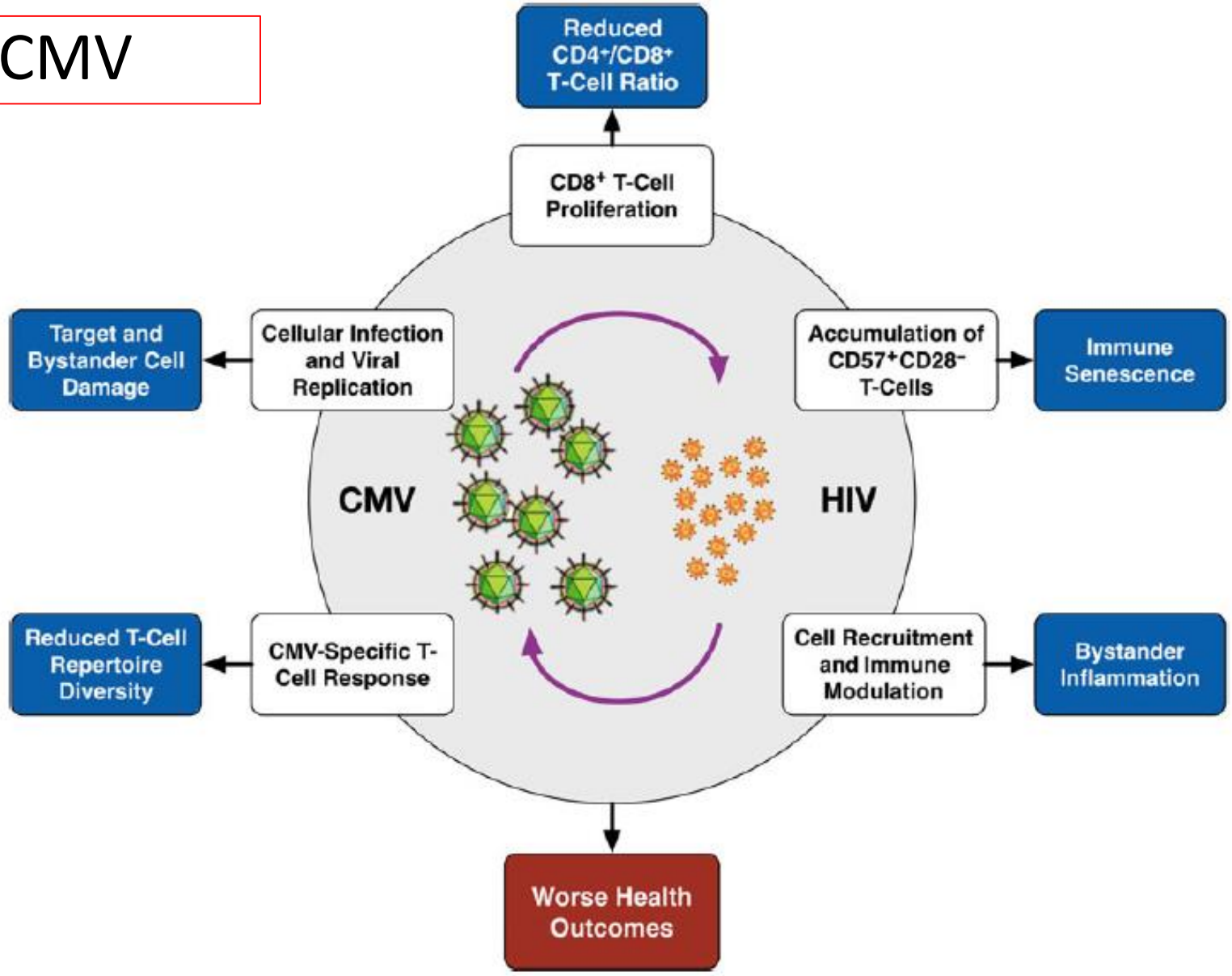
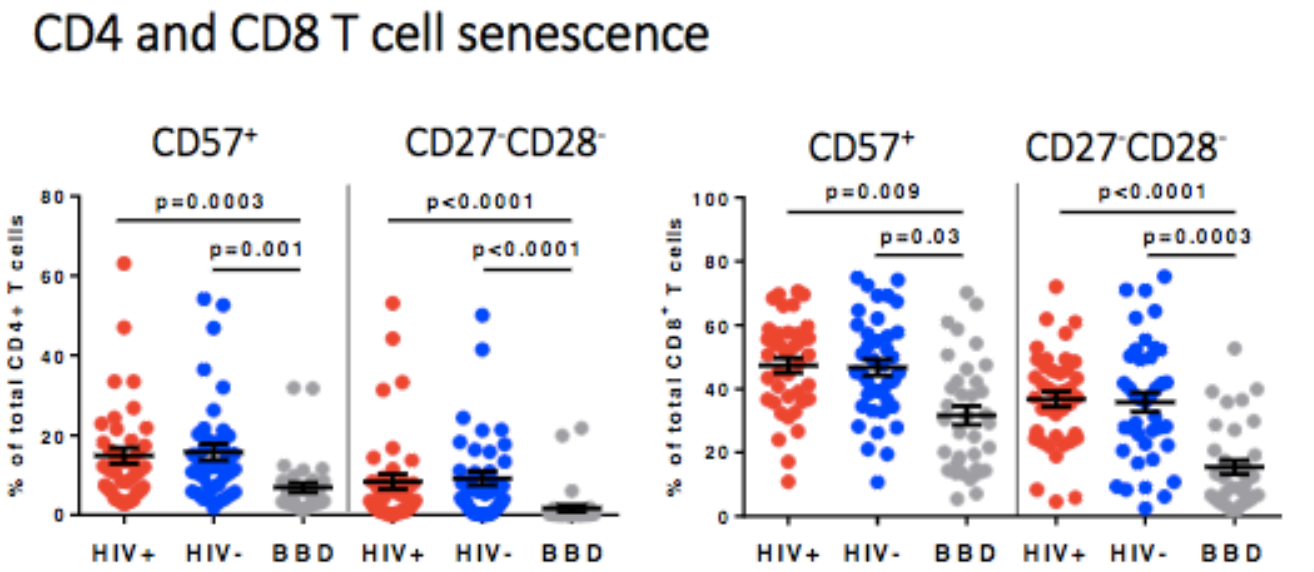


Figure 1. Proposed model connecting cytomegalovirus (CMV), human immunodeficiency virus (HIV), immune dysfunction and worse disease outcome. HIV infection induces $CD4^+$ T cell loss and dysfunction, thereby failing to provide help to $CD8^+$ T cells and permitting more CMV replication. Both viral infections contribute to inflammation, immune senescence and promote the expansion of $CD8^+$ T cells. Such $CD8^+$ T cell expansion, coupled with a loss of $CD4^+$ T cells (leading to a lower CD4/CD8 T cell ratio) are linked to morbid outcomes of CMV and HIV infections. Additionally, CMV might cause direct cellular damage to endothelial cells and other cell types further contributing to end organ damage.

Gianella JID 2016

L'immunosénescence des CD4 et CD8 associée au statut CMV chez les HIV+ et HIV-



	HIV+	HIV-	BBD
Age (yrs), median (IQR)	58 (53-63)	59 (53-64)	58 (52-65)
Male sex, %	90	92.5	51.4
CMV+ve, %	95.0	77.5	22.9

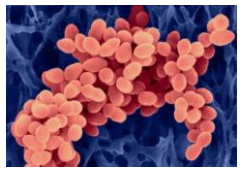
Clear differences observed between PLHIV+ vs. age-matched blood-bank donors

No evidence for increased immune senescence in PLHIV+ vs. matched COBRA HIV- controls

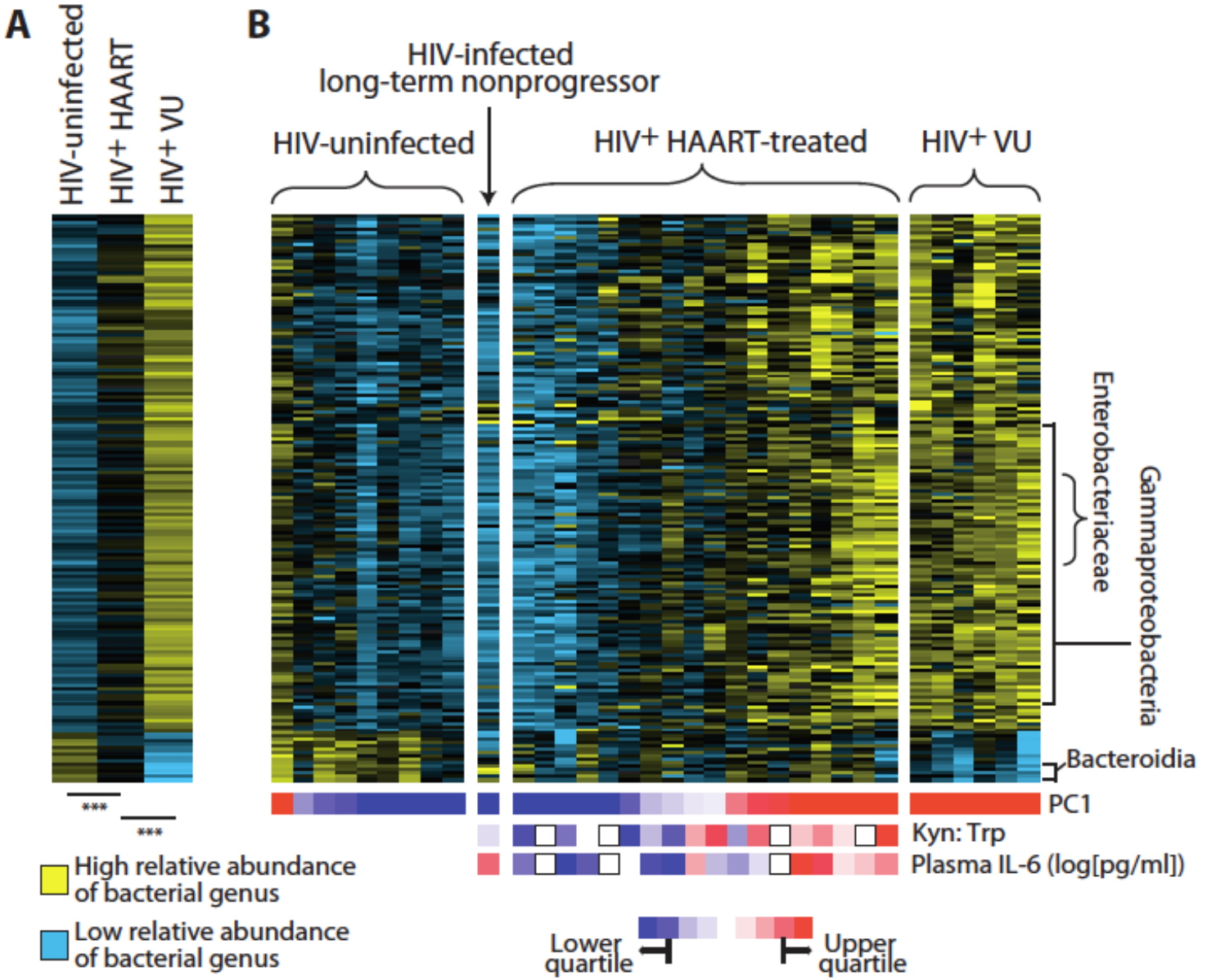
T Booiman PLOS One 2017

COBRA
CO-MORBIDITY IN RELATION TO AIDS

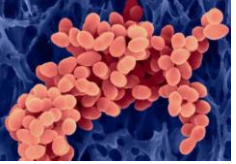
Role of gut dysbiosis



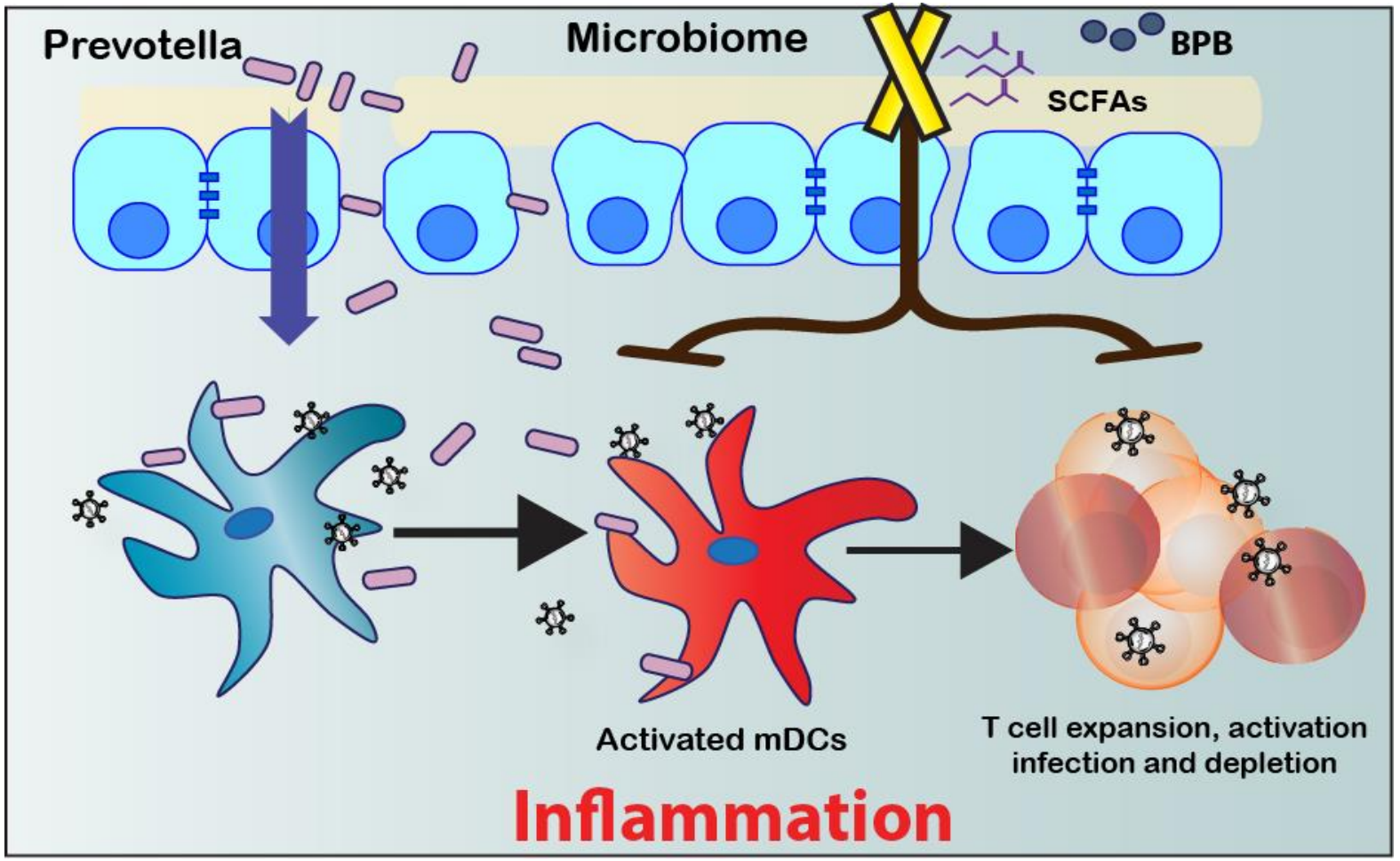
Dysbiosis of the Gut Microbiota Is Associated with HIV Disease Progression and Tryptophan Catabolism



I Vujkovic-Cvijin Science Translational Medicine 2013



“Dual-hit Hypothesis” for Dysbiosis-induced Pathogenesis

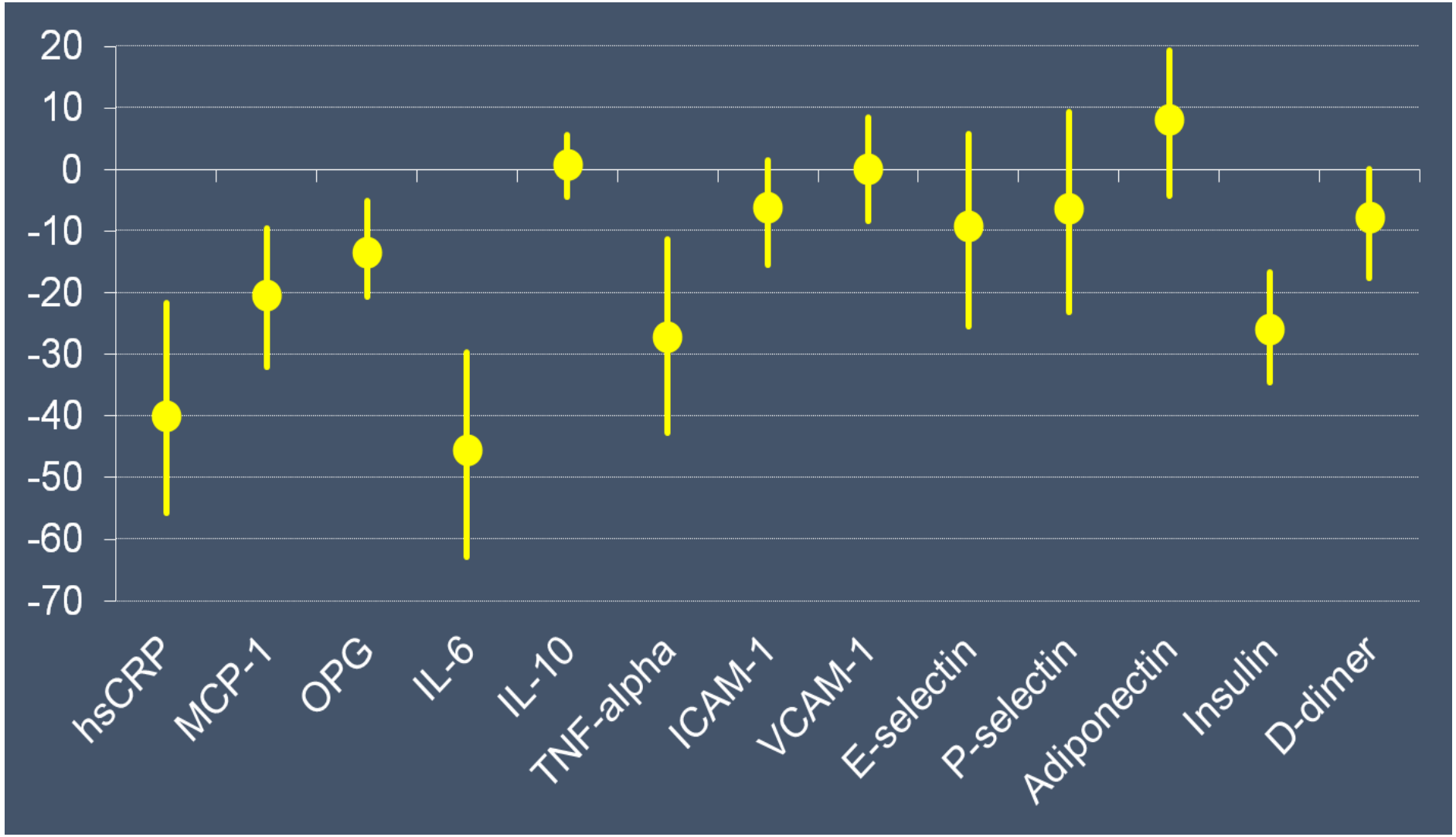


HIV-associated intestinal inflammation is a result of both increased exposure to bacteria with “pro-inflammatory” properties and a loss of immuno-regulation due to lower abundance of intestinal BPB (and lower tissue butyrate levels)

C Wilson HIV and Aging 2015

Role of ART

Modifications of inflammatory and metabolic biomarkers after switching an IP/r regimen to raltegravir : The SPIRAL study

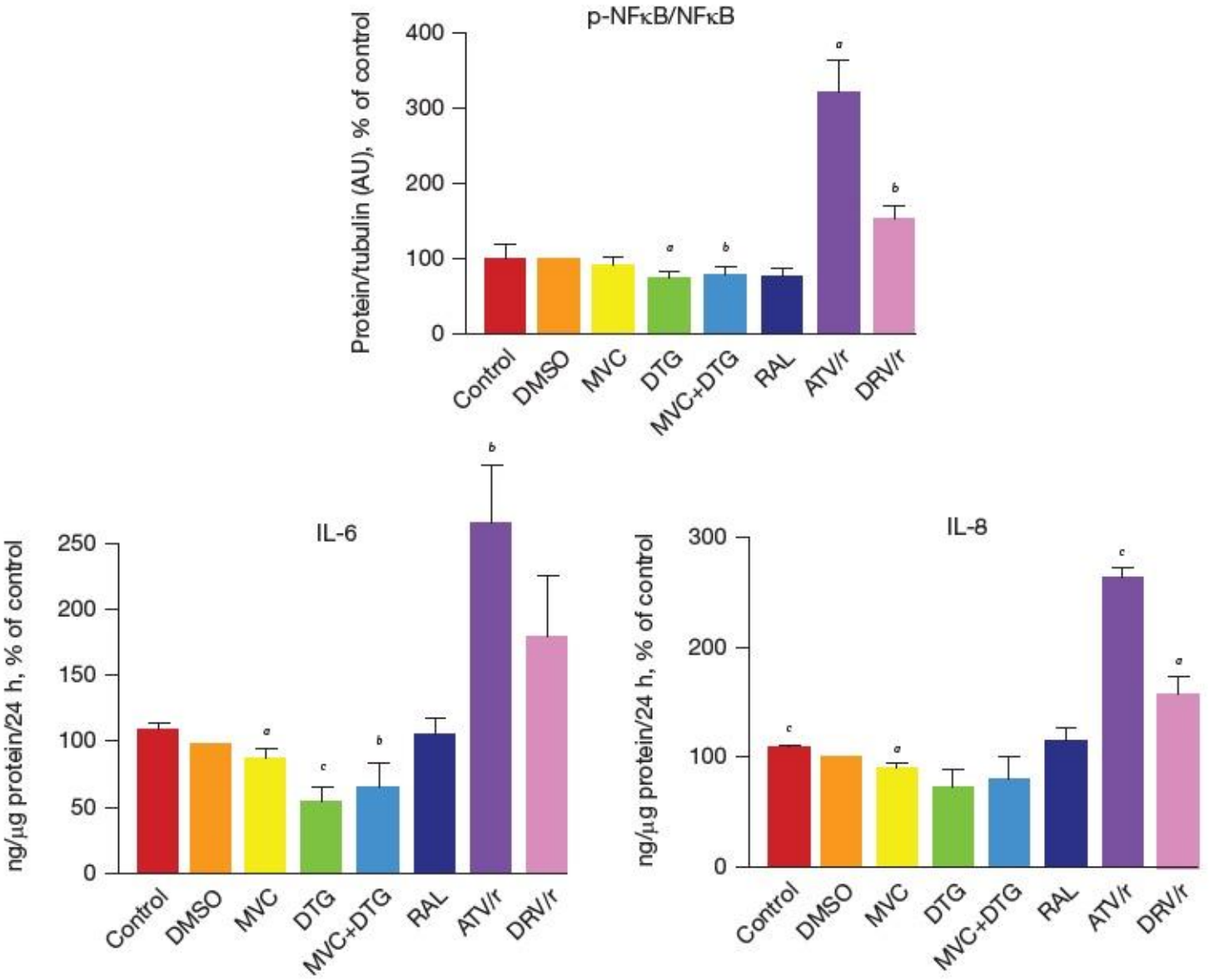


E Martinez CROI 2012 #834

Curran AIDS 2012

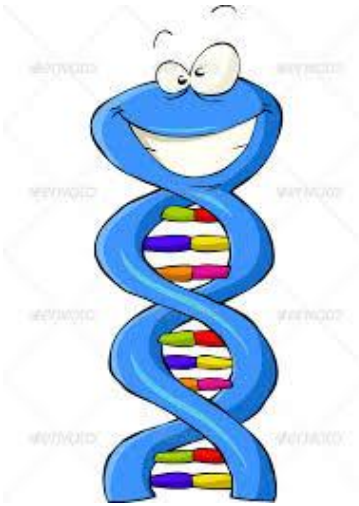
Ability of Integrase inhibitors and protease inhibitors to modify inflammation in cultured endothelial cells

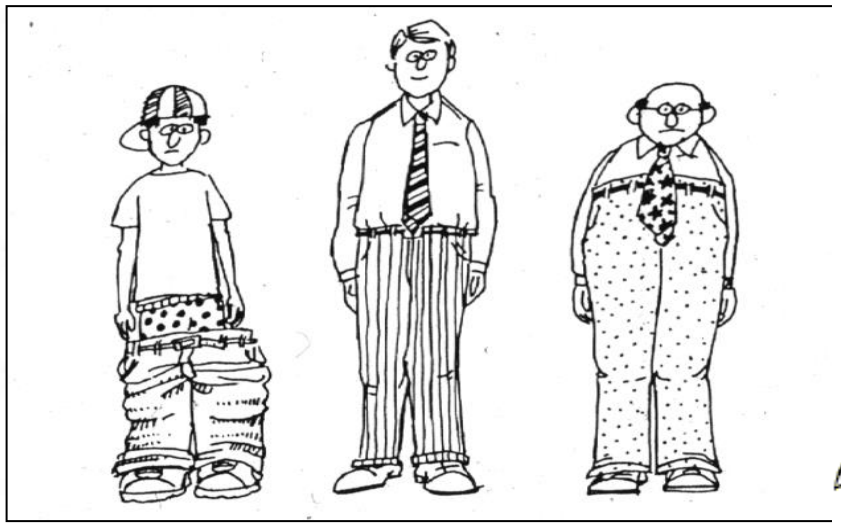
Figure 2. Effect of antiretrovirals on inflammation in adult donors' cells

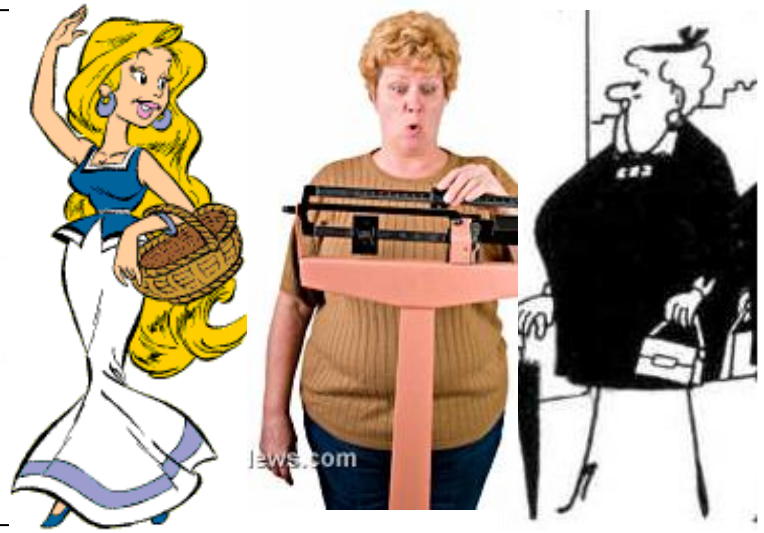


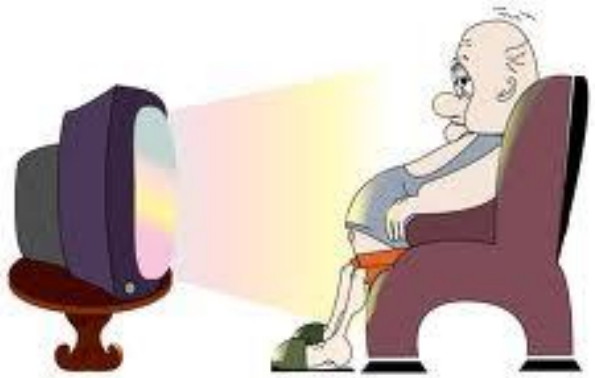
P Afonso Antiviral Ther 2017

Role of personal and environment-related factors: age, genetics and sex are non-modifiable. Sedentarity, diet, smoking can be modified









Increased systemic immune activation and inflammatory profile of long-term HIV-infected ART-controlled patients is related to personal factors, but not to markers of HIV infection severity

Table 3. Associations between personal factors and factors related to the severity of HIV infection and the level of immune activation and inflammatory markers in HIV-infected patients ($n=352$)

	CRP	IL-6	D-dimer	sCD14	B2M	Cystatin-C
Age	—	—	0.32, $P<0.0001$	—	0.24, $P<0.0001$	0.25, $P<0.0001$
HCV coinfection	—	—	—	—	—	yes: 1.10 mg/L, no: 0.81 mg/L, $P<0.005$
Smoking	—	never: 1.5; current: 2.4; past: 1.4; $P<0.01$	—	—	—	never: 0.74 mg/L; current: 1.07 mg/L; past: 0.83 mg/L; $P<0.0001$
BMI	0.24; $P<0.0001$	—	—	—	—	—
WHR	0.25; $P<0.0001$	—	—	—	—	—
CD4, current	—	—	—	—	—	—
CD4 <500 versus >500 cells/mm^3	—	—	—	—	—	—
CD4 at PI initiation	—	—	—	—	0.14; $P<0.01$	—
CD8	—	—	—	—	—	—
CD4 nadir	—	—	—	—	—	—
CD4/CD8	—	—	—	—	—	—
VL ≤50 versus >50 copies/mL	—	—	—	—	—	—
AIDS at PI initiation	—	—	—	—	—	—
Duration of ART	—	—	—	—	—	—

JP Bastard J Antimicrobiol Chem 2015

Elevated Soluble CD14 and Lower D-Dimer Are Associated With Cigarette Smoking and Heavy Episodic Alcohol Use in Persons Living With HIV

689 participants to the SUN study (Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy), Aged 41 years, 77% on ART, 90% CD4>200 cells/mm3, 43% current smoker, 65% ever smoked

Smoking was significantly associated with elevated sCD14, independant of age, CD4 and HIV-VL

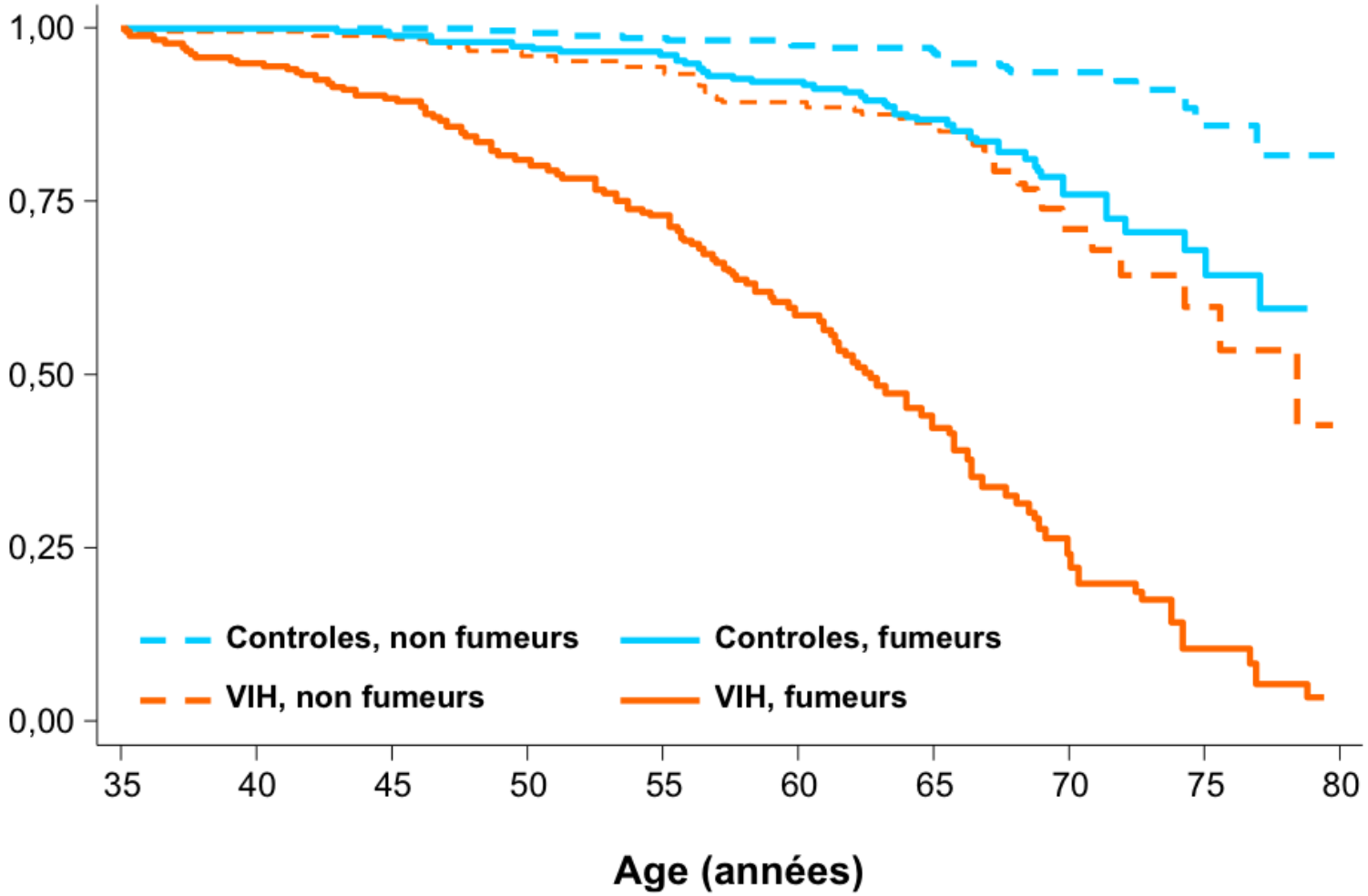
TABLE 2. Regression Models of Factors Associated With sCD14 and D-Dimer Levels Among 689 Participants in the SUN Study Recruited From 2004 to 2006

	sCD14			D-Dimer		
	Estimate	*P*	95% CI	Estimate	*P*	95% CI
Current smoking	135.57	<0.001	84.95 to 186.1	0.023	0.25	−0.016 to 0.064
$CD4^+$ T-cell count	−0.25	<0.001	−0.34 to −0.15	0.00	0.95	0.00 to 0.00
Undetectable VL	−36.84	0.26	−100.45 to 26.78	−0.11	<0.001	−0.16 to −0.07
Heavy month*	−6.11	0.83	−61.23 to 49.01	−0.06	0.007	−0.10 to −0.02
Race	−10.81	0.52	−43.71 to 22.08	0.00	0.68	0.00 to 0.00
Age	4.33	0.003	1.49 to 7.18	0.001	0.58	−0.002 to 0.003

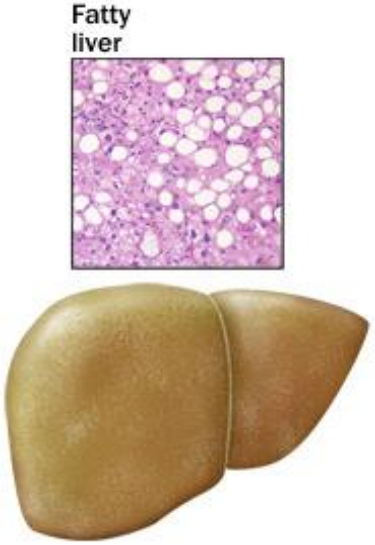
PA Cioe JAIDS 2015

La mortalité attribuable au tabagisme chez les sujets infectés par le VIH

2921 HIV+ et 10642 HIV- suivis pendant 14281 et 45122 PYFU.
L'augmentation du risque de mortalité du au tabac était de 4,8 pour les HIV- et de 5,3 pour les HIV+. Chez les fumeurs actuels vs les non-fumeurs, l'excès de risque était de 4,8 pour les HIV- et de 17,6 pour les HIV+



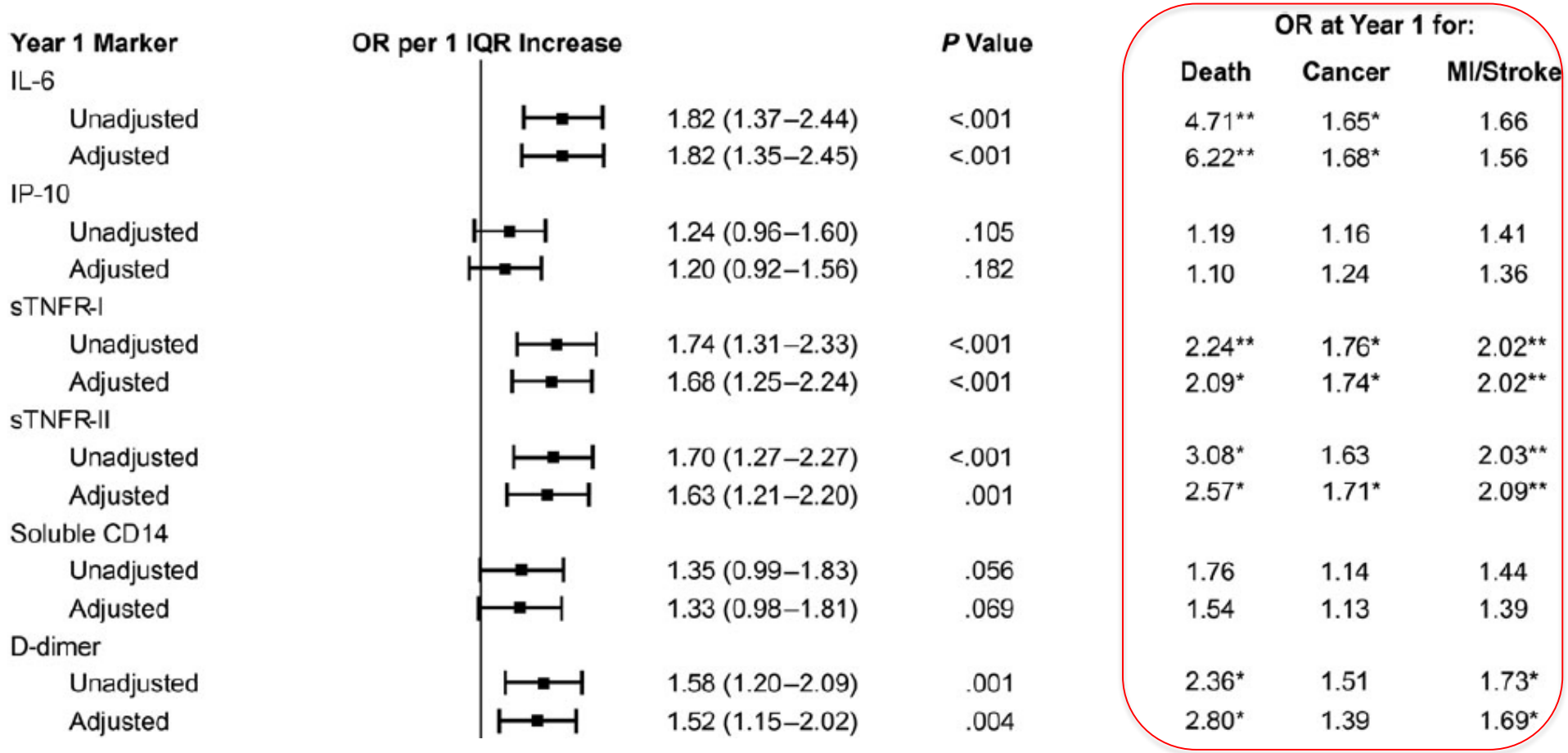
M Helleberg CID 2013



Immune activation and inflammation are involved in mortality and several comorbidities in HIV-infected patients

Some systemic biomarkers of inflammation and immune activation are predictive of morbidity and mortality in HIV-infected individuals

Soluble Markers of Inflammation and Coagulation but Not T-Cell Activation Predict Non–AIDS-Defining Morbid Events During Suppressive Antiretroviral Treatment



Year 1 Marker	OR per 1 IQR Increase	*P* Value	OR at Year 1 for: Death	Cancer	MI/Stroke
IL-6					
Unadjusted	1.82 (1.37–2.44)	<.001	4.71**	1.65*	1.66
Adjusted	1.82 (1.35–2.45)	<.001	6.22**	1.68*	1.56
IP-10					
Unadjusted	1.24 (0.96–1.60)	.105	1.19	1.16	1.41
Adjusted	1.20 (0.92–1.56)	.182	1.10	1.24	1.36
sTNFR-I					
Unadjusted	1.74 (1.31–2.33)	<.001	2.24**	1.76*	2.02**
Adjusted	1.68 (1.25–2.24)	<.001	2.09*	1.74*	2.02**
sTNFR-II					
Unadjusted	1.70 (1.27–2.27)	<.001	3.08*	1.63	2.03**
Adjusted	1.63 (1.21–2.20)	.001	2.57*	1.71*	2.09**
Soluble CD14					
Unadjusted	1.35 (0.99–1.83)	.056	1.76	1.14	1.44
Adjusted	1.33 (0.98–1.81)	.069	1.54	1.13	1.39
D-dimer					
Unadjusted	1.58 (1.20–2.09)	.001	2.36*	1.51	1.73*
Adjusted	1.52 (1.15–2.02)	.004	2.80*	1.39	1.69*

Figure 4. Biomarker levels in specimens obtained at the visit approximately 1 year after ART initiation (year 1) and odds ratios (ORs) of having a non–AIDS-defining event. Adjusted analyses controlled for concurrent $CD4^+$ T-cell count. *P = .01 to <.05; **P<.01. Abbreviations: IL-6, interleukin 6; IP-10,

AR Tenorio JID 2014

Studies Linking Inflammation to Mortality Among HIV+

2008-2017

Systemic Inflammation
- **IL-6**[1-7], hsCRP[1,5,8], sTNFR-1[4,5], sTNFR-2[4]

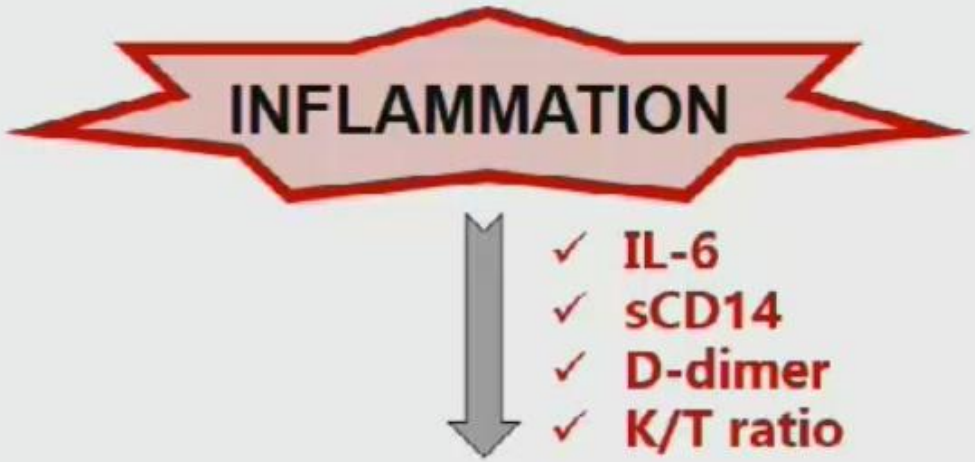
Coagulation
- **D-dimer**[1,2,5,-7], Fibrinogen[8]

Innate Immunity (Monocyte/Macrophage)
- **sCD14**[3-7,9]

Adaptive Immune response
- CD8+ T-cells: CD38+/HLA-DR+ [5]
- sIL-2Rα (T-cells)[3]
- CXCL13 (B-cells)[3]

Kynurenine Metabolic Pathway (IDO)
- **K/T ratio** [5-7]

Mucosal Integrity
- Zonulin,[5] IFABP[5]



Mortality
- **Non-AIDS death**
- **AIDS death**

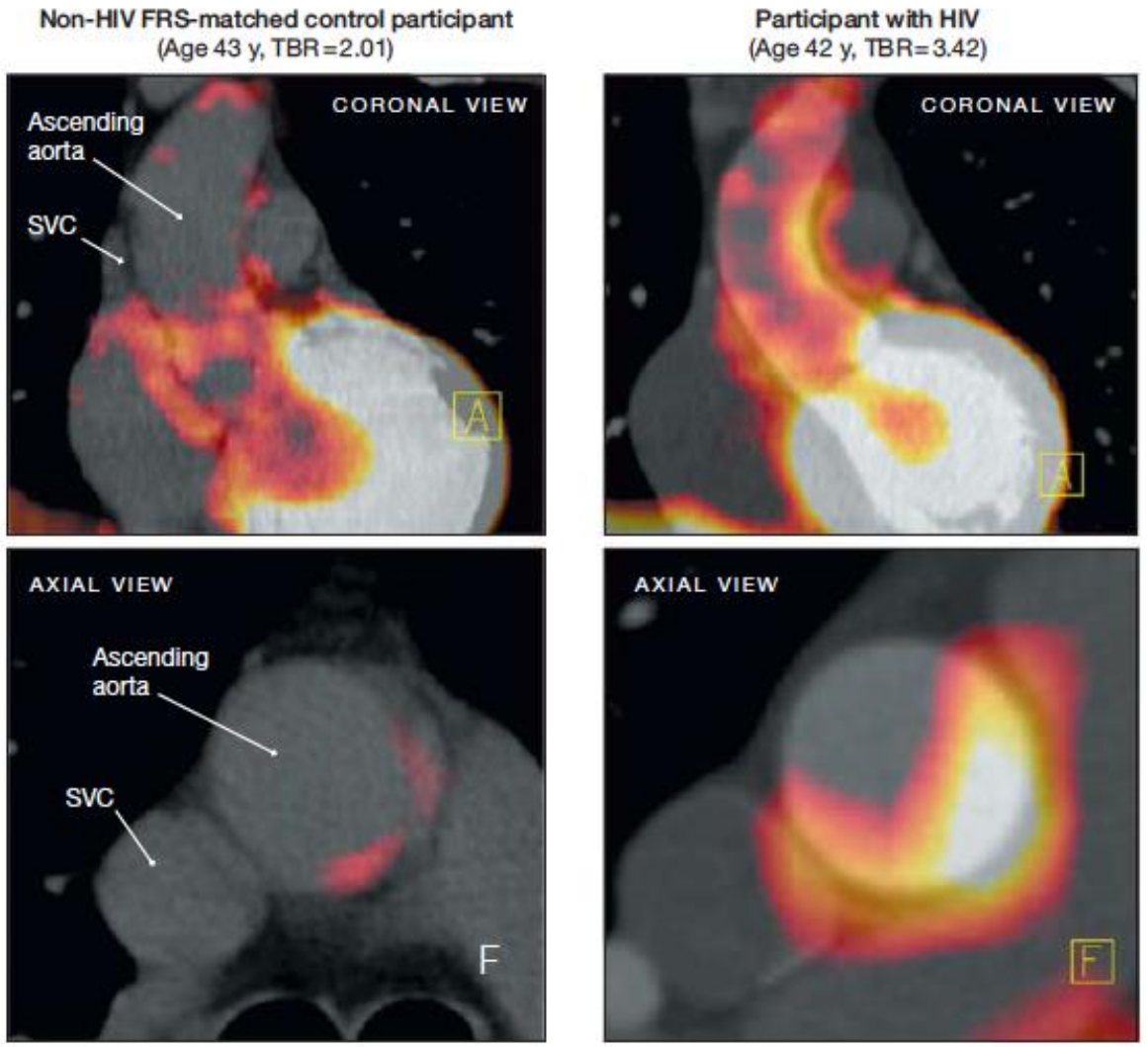
REFERENCES:
1. Kuller et. al. PLoS Med 2008,5:e203
2. Ledwaba et. al. PLoS One 2012;7:e24243
3. Wada et. al. CID 2016; 63:984
4. Tenorio et. al. JID 2014;210:1248
5. Hunt et. al. JID 2014;210;1228
6. Byakwaga et. al. JID 2014;210:383
7. Lee et. al. JID 2017;215:1270
8. Tien et. al. JAIDS 2010;55:316
9. Sandler et. al. JID 2011,203.780

J Baker symposium S-6 CROI 2018

Arterial inflammation in HIV-infected individuals

Arterial inflammation as measured by PET-scan is increased in HIV-infected patients as compared to VIH-subjects with the same FRS

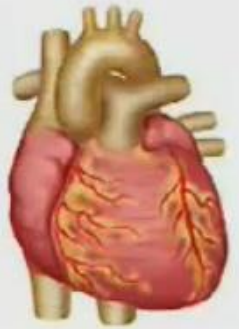
Figure 2. Representative ^{18}F-FDG-PET/CT Imaging of the Aorta



^{18}F-FDG-PET indicates ^{18}fluorine-2-deoxy-D-glucose positron emission tomography; CT, computed tomography; FRS, Framingham risk score; HIV, human immunodeficiency virus; SVC, superior vena cava; TBR, target-to-background ratio. There is increased aortic PET-FDG uptake (red coloration) in a participant infected with HIV compared with a non-HIV FRS-matched control participant. Neither participant had known heart disease. For each participant, the FRS was low with a score of 2 and calcium was not present on the cardiac CT scan. Neither participant was receiving a statin. A indicates anterior-posterior orientation and F, foot-head orientation.

Subramanian S, JAMA 2012

Studies Linking Inflammation to CVD among HIV+



Innate Immunity (Monocytes/Macrophages)
- sCD163[1-5], sCD14[4,5], CCL2[5], CD14varCD16+[6]

Systemic Inflammation
- IL-6[7], hsCRP[7,8], sTNFR-1[9], sTNFR-2[9]

Coagulation
- D-dimer[7,10]

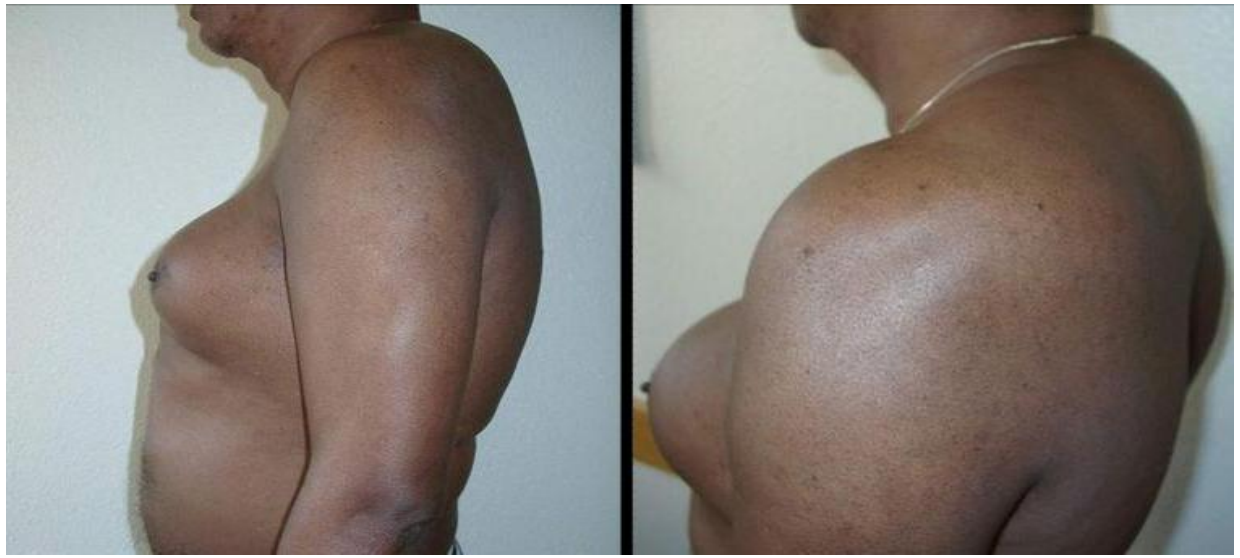
INFLAMMATION

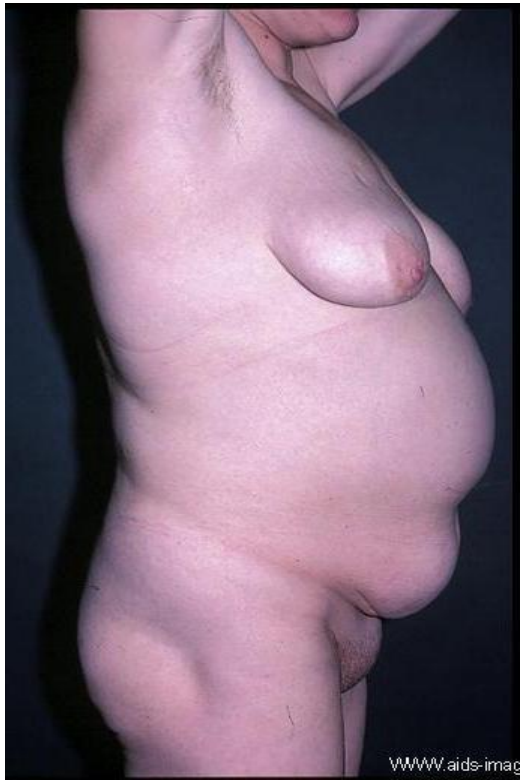
Cardiovascular Disease
- Carotid IMT
- Coronary calcium (CAC)
- Aortic artery Inflammation
- Myocardial infarction
- CVD event composite (MACE)

REFERENCES:
1. *Subramanian et. al.* JAMA 2012;308:379
2. *Burdo et. al.* JID 2011;204:1227
3. *Fitch et. al.* JID 2013;208:1737
4. *Hanna et. al.* JID 2017;215:1352
5. *McKibben et. al.* JID 2015;211:1219
6. *Baker et. al.* AIDS 2014;28:831
7. *Duprez et. al.* PLoS One 2012;7:e44454
8. *Triant et. al.* JAIDS 2009;51:268
9. *Tenorio et. al.* JID 2014;210:1248
10. *Ford et. al.* AIDS 2010;24:1509

J Baker symposium S-6 CROI 2018

« Second generation lipodystrophy »





Lipodystrophy worsen inflammatory state and metabolic disorders

Long-term body composition changes in antiretroviral-treated HIV-infected individuals

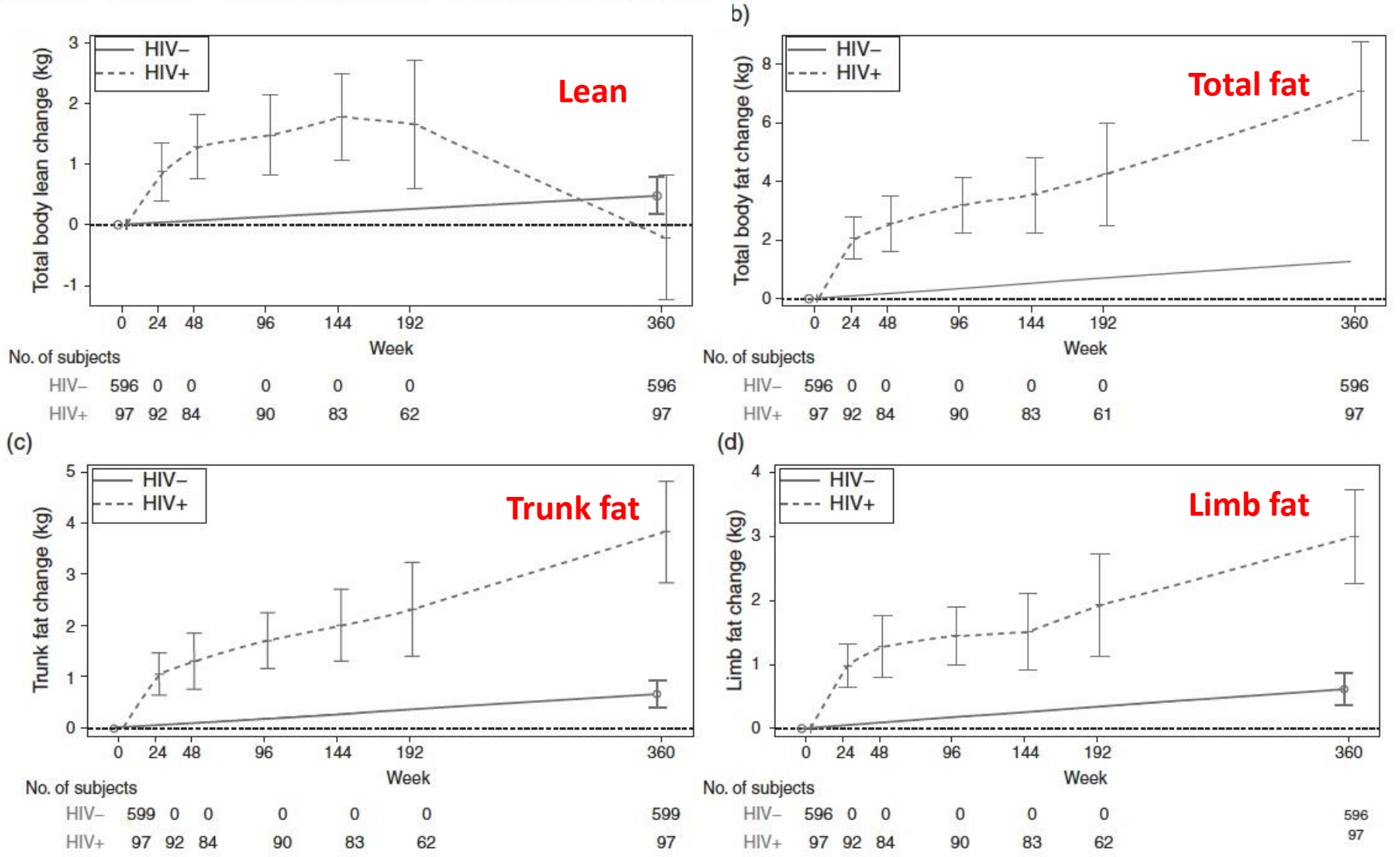
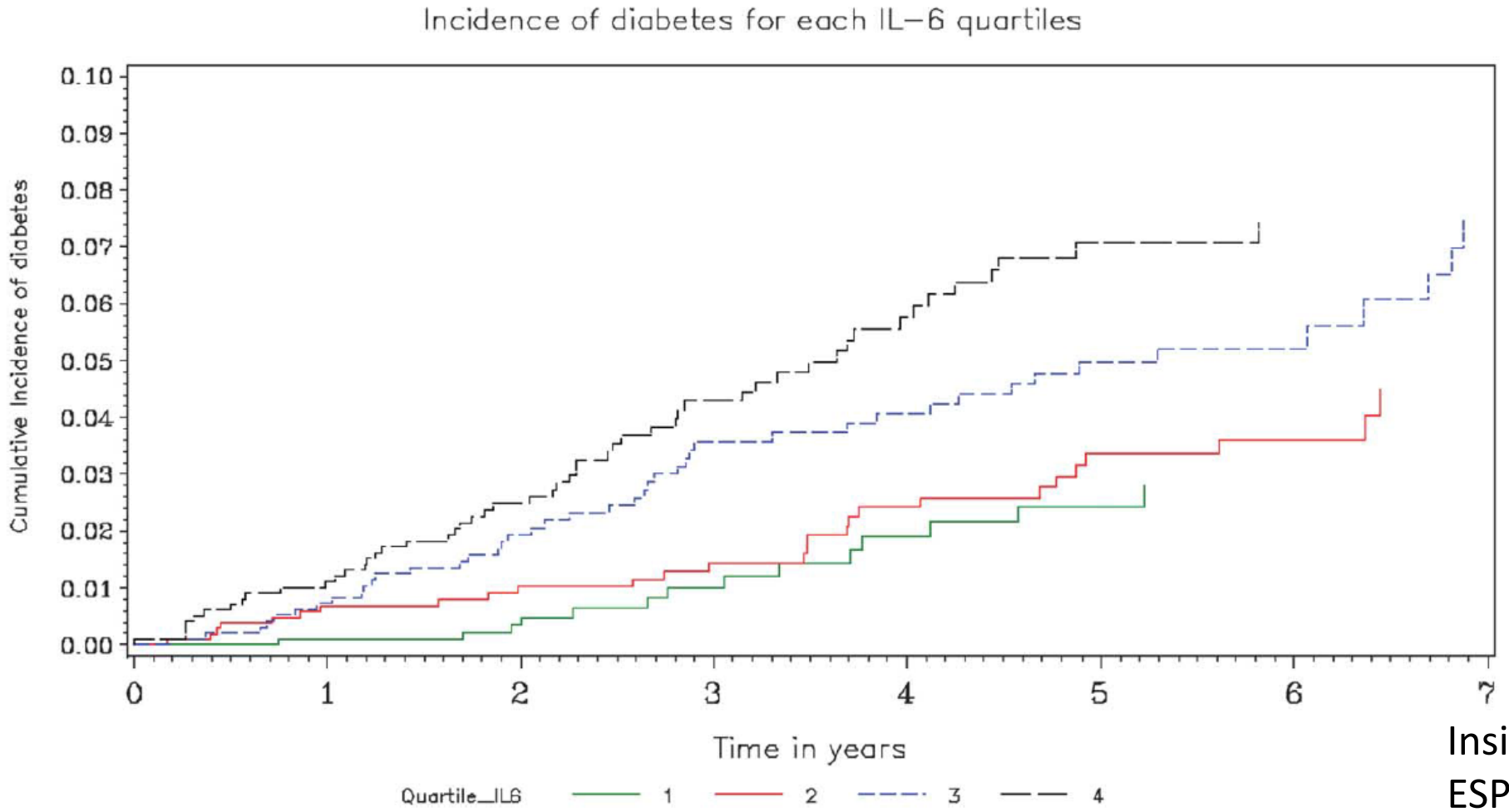


Fig. 1. (a) Change in lean mass by serostatus (in kg), (b) change in total fat by serostatus (in kg), (c) change in trunk fat by serostatus (in kg), and (d) change in limb fat by serostatus (in kg).

PM Grant AIDS 2016

Diabetes and metabolic syndrome

Interleukin-6, High Sensitivity C-Reactive Protein, and the Development of Type 2 Diabetes Among HIV-Positive Patients Taking Antiretroviral Therapy



Insight SMART ESPRIT study group

A cohort of 3695 participants without diabetes, taking antiretroviral therapy and with an average $CD4^+$ count of 523 cells/mm^3, were followed for an average of 4.6 years.

C Béténé A Dooko JAIDS 2014

Role of inflammation in the risk of cancer

Predicting risk of cancer during HIV infection: the role of inflammatory and coagulation biomarkers

5023 patients all receiving ART, 24,000 PYFU, 172 cancers (70 infection-related and 102 non-infection related), median follow-up 59 months

AH Borges AIDS 2013

Table 2. Baseline characteristics ESPRIT, SILCAAT and SMART control patients.

	Developed cancer		
	Yes	No	*P**
Age in years (median, IQR)	48 (41, 56)	42 (36, 49)	<0.001
Female sex (%)	12.2	22.7	0.005
Race (%)			0.05
Black	16.3	19.6	
White	76.7	67.2	
Other	7.0	13.1	
BMI (median, IQR)	24 (22, 26)	24 (22, 27)	0.67
AIDS (%)	25.0	26.1	0.67
Hepatitis B/C coinfection (%)[a]	27.9	18.6	0.04
Diabetes[a]	8.6	4.9	0.02
Smoking[b]	60.3	40.5	0.003
$CD4^+$ cell count (cells/μl) (median, IQR)	421 (305, 585)	488 (370, 672)	0.27
$CD4^+$ nadir (cells/μl)(median, IQR)	143 (44, 262)	200 (87, 319)	0.01
HIV RNA ≤500 copies/ml (%)	72.7	76.7	0.15
CRP (μg/ml) (median, IQR)	2.51 (1.25, 5.24)	1.54 (0.67, 3.54)	<0.001
D-dimer (μg/ml) (median, IQR)	0.28 (0.22, 0.47)	0.24 (0.15, 0.38)	<0.001
IL-6 (pg/ml) (median, IQR)	2.40 (1.80, 3.58)	1.80 (1.17, 2.80)	<0.001
Study			0.03
ESPRIT participant	40.7	35.2	
SILCAAT participant	25.6	13.6	
SMART participant	33.7	51.2	
No. of patients	172	4851	

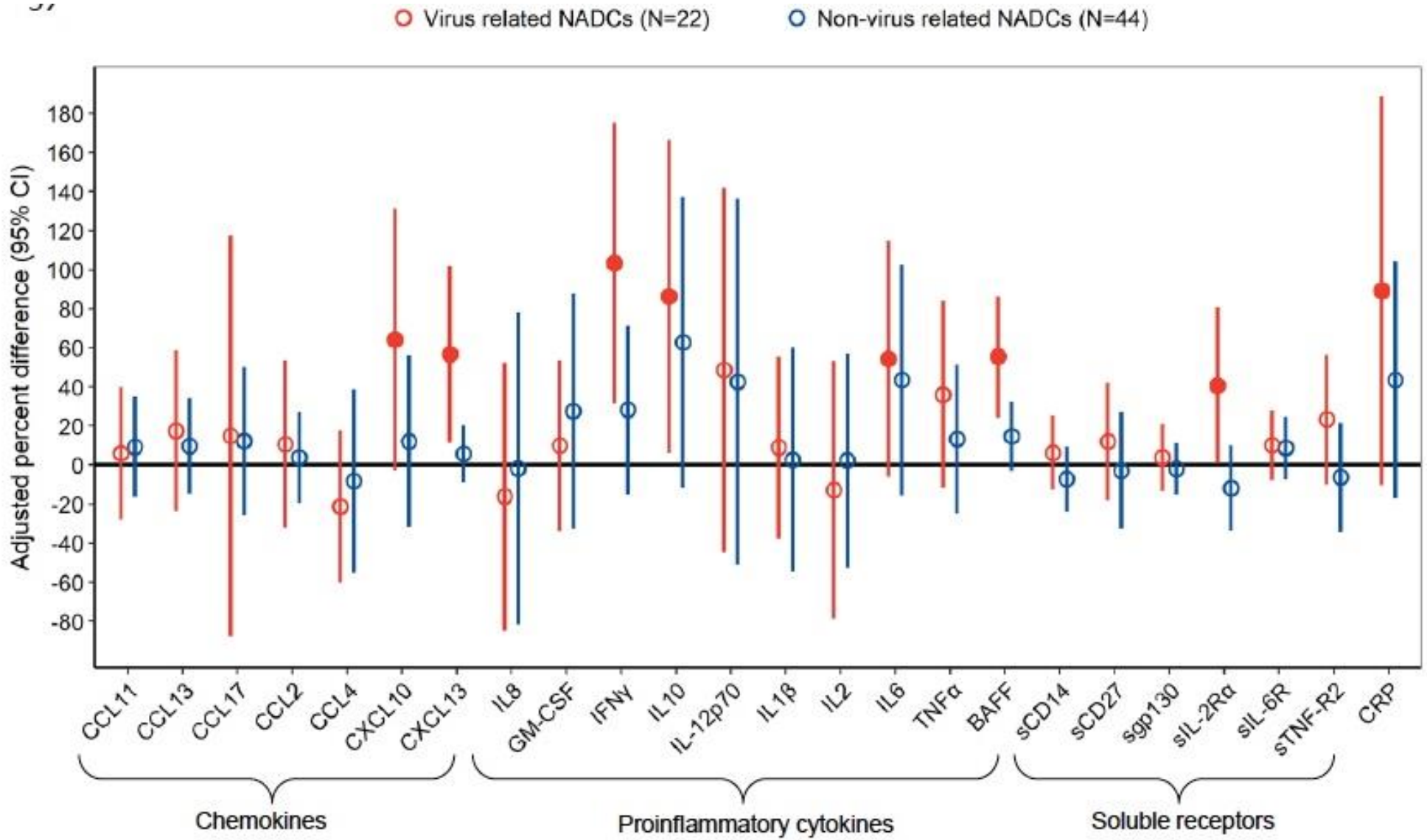
Table 5. Sensitivity analysis – adjustment for BMI, diabetes and smoking hazard ratios for one $\log_2$ (i.e. doubling) increment in biomarkers ESPRIT, SMART and SILCAAT.

	CRP		D-dimer		IL-6	
	HR[b]	*P*	HR[b]	*P*	HR[b]	*P*
Any cancer						
Full adjustment[a]	1.16	0.001	1.17	0.03	1.38	<0.001
No. of patients (events)	5022 (172)		5006 (171)		4994 (171)	
Full adjustment + BMI	1.16	<0.001	1.16	0.04	1.37	<0.001
No. of patients (events)	4948 (170)		4932 (169)		4920 (169)	
Full adjustment + smoking (SMART)	1.10	0.20	1.12	0.28	1.37	0.006
No. of patients (events)	2541 (58)		2526 (57)		2514 (57)	
Full adjustment + diabetes (SMART and ESPRIT)	1.15	0.008	1.14	0.10	1.42	<0.001
No. of patients (events)	4307 (128)		4291 (127)		4279 (127)	
Infection-related cancer						
Full adjustment[a]	1.18	0.02	1.19	0.13	1.42	0.002
No. of patients (events)	5022 (70)		5006 (70)		4994 (70)	
Full adjustment + BMI	1.18	0.02	1.19	0.15	1.40	0.004
No. of patients (events)	4948 (69)		4932 (69)		4920 (69)	
Full adjustment + smoking (SMART)	1.15	0.30	1.25	0.22	1.45	0.07
No. of patients (events)	2541 (18)		2526 (18)		2514 (18)	
Full adjustment + diabetes (SMART & ESPRIT)	1.20	0.03	1.25	0.08	1.56	<0.001
No. of patients (events)	4307 (51)		4291 (51)		4279 (51)	
Infection-unrelated cancer						
Full adjustment[a]	1.15	0.02	1.15	0.12	1.35	0.002
No. of patients (events)	5022 (102)		5006 (101)		4994 (101)	
Full adjustment + BMI	1.15	0.02	1.15	0.13	1.35	0.002
No. of patients (events)	4948 (101)		4932 (100)		4920 (100)	
Full adjustment + smoking (SMART)	10.08	0.39	1.06	0.65	1.35	0.04
No. of patients (events)	2541 (40)		2526 (39)		2514 (39)	
Full adjustment + diabetes (SMART & ESPRIT)	1.12	0.10	1.08	0.45	1.32	0.02
No. of patients (events)	4307 (77)		4291 (76)		4279 (76)	

AH Borges AIDS 2013

Inflammation and Immune Activation Markers Associated with Non-AIDS Defining Cancers in HIV

Muhaimen Siddiqui[1], Elizabeth C. Breen[2], Jay Bream[1], Yue Chen[3], Dana H. Gabuzda[4], and Eric C. Seaberg[1]



Solid circles indicate statistically significant (α=0.05) marker elevations based on Benjamini-Hochberg procedure with a 25% false discovery rate.

CROI 2018 poster 764

Frailty = Fragilité = Vulnérabilité

Patient gériatrique
(vieux biologiquement)

versus

Patient âgé
(vieux chronologiquement)

M Cesari

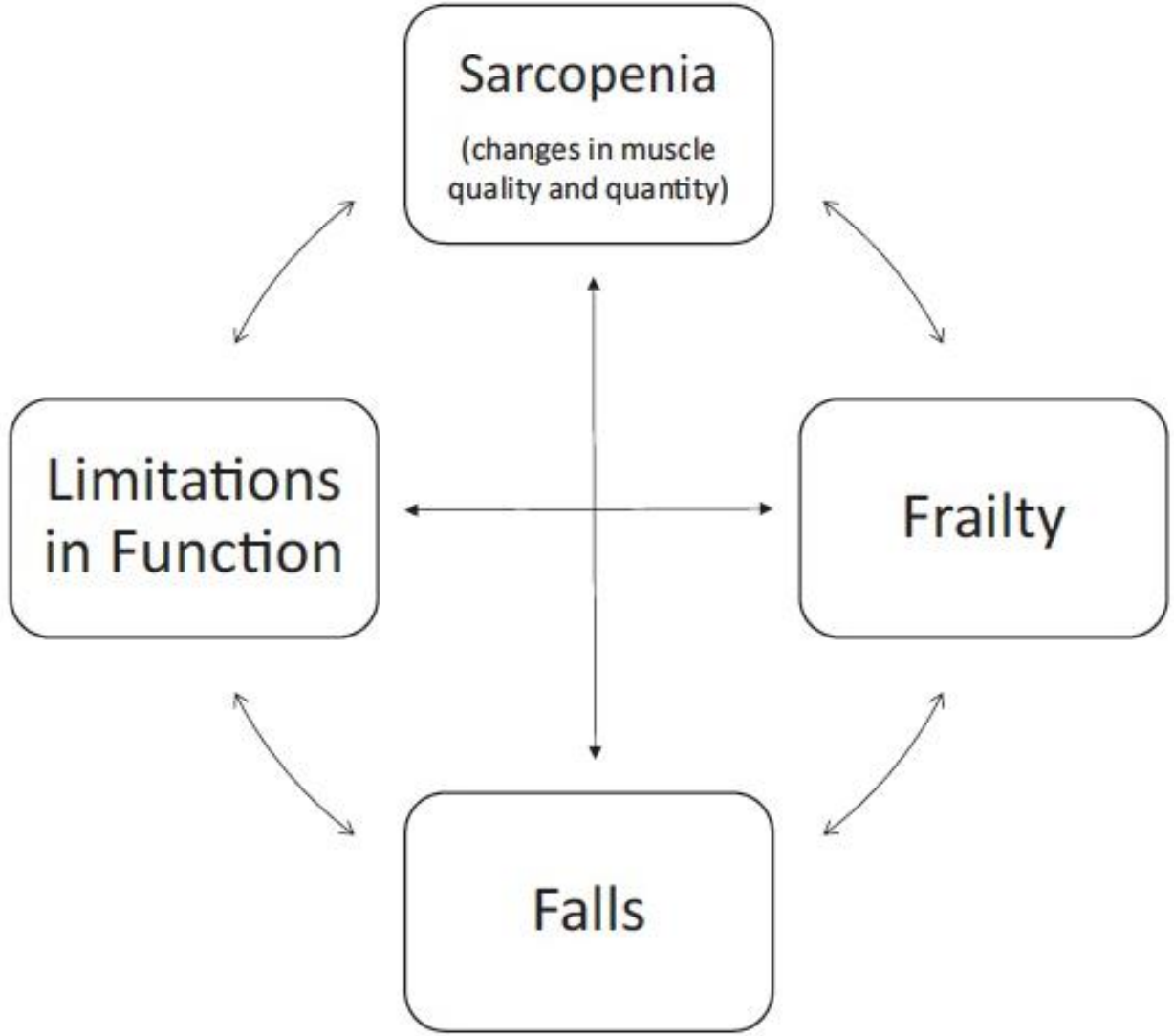


Fig. 1. Relationship of sarcopenia, frailty, falls, and functional limitation. The interconnectedness of sarcopenia, frailty, falls, and physical function is demonstrated in this figure. Each syndrome contributes to the cause and consequence of the others.

KL Hawkins AIDS 2017

La fragilité chez les PVVIH

Katherine Kooij, Peter Reiss

Phénotype de fragilité à l'inclusion :

- Perte de poids non-intentionnelle
- Peu d'endurance à l'effort, fatigue
- Faible activité physique
- Faible force physique
- Lenteur à la marche

0 critère présent →Robuste

1-2 critère(s) présent(s)→Pré-fragile

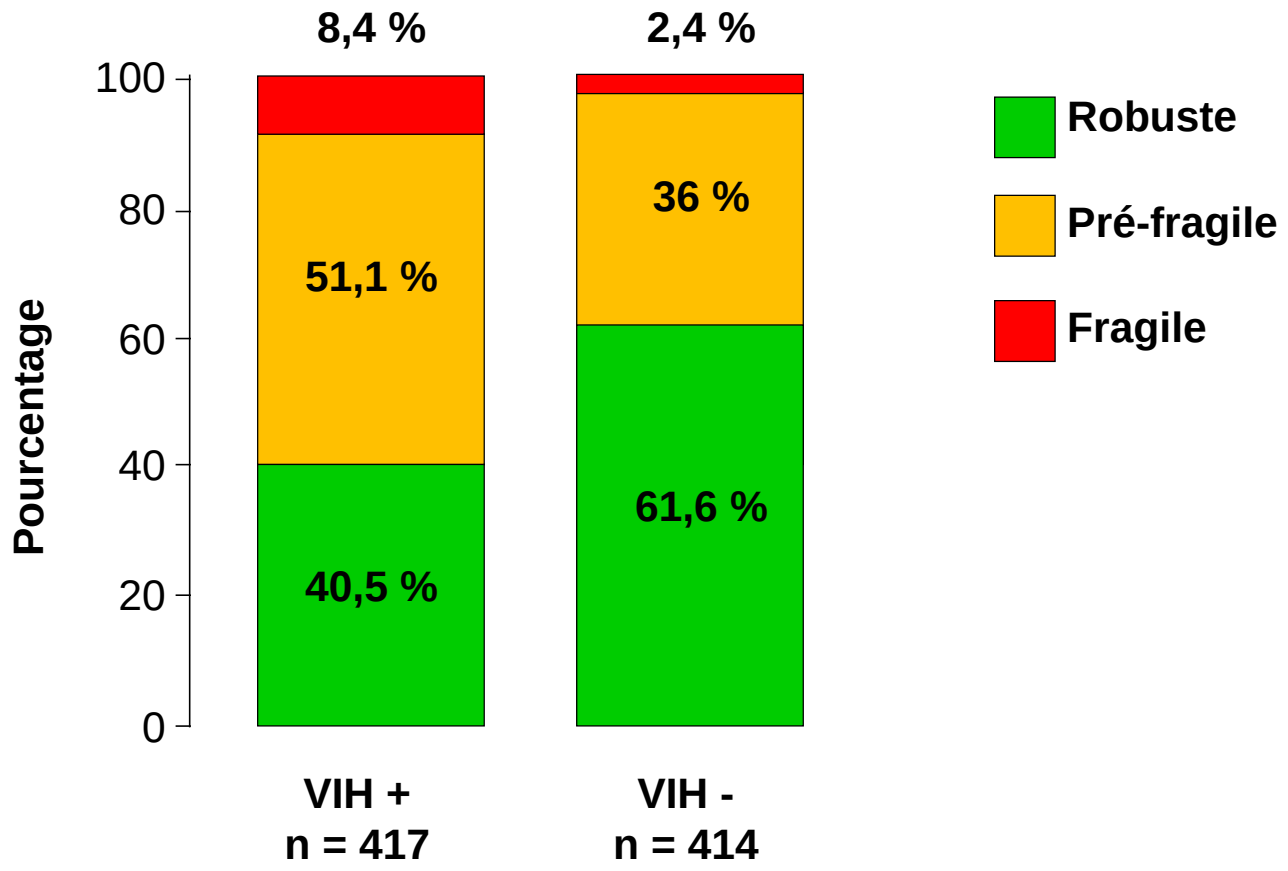
≥3 critères présents →Fragile

Mortalité toute cause

Statut vital tous les deux ans

Evaluation aussi à la visite de suivi après deux ans

Prévalence de la fragilité et risques



La diagnostic de fragilité prédit la survenue de chutes, d'hospitalisations et de mortalité toute cause mais pas de fractures chez des sujets d'âge médian infectés ou non par le VIH

Abdominal obesity, sarcopenia, and osteoporosis are associated with frailty in men living with and without HIV

199 HIV+ and 200 HIV- from the MACS, aged 50-69 years

Frailty prevalence : 16% in HIV+ vs 8% in HIV-

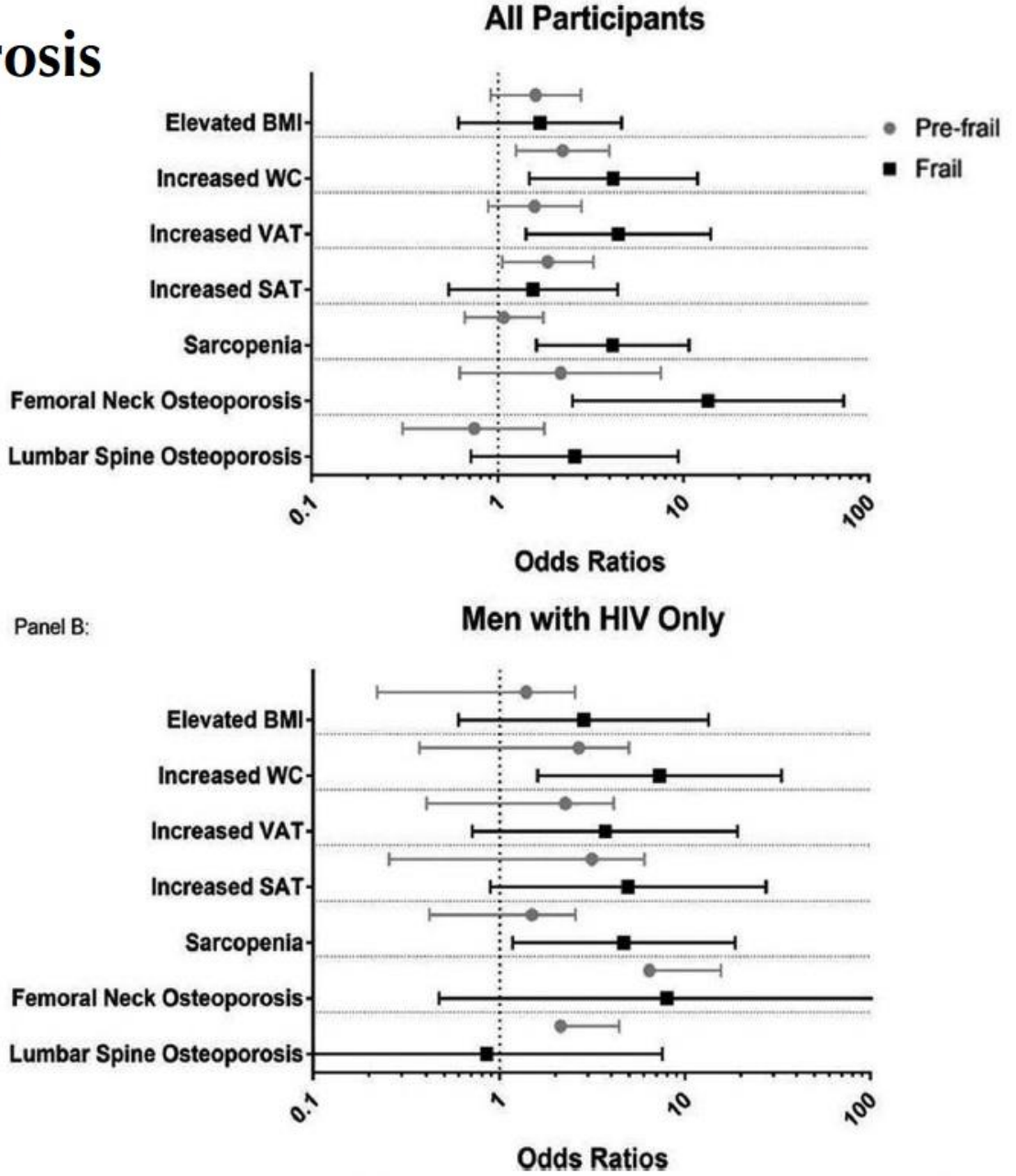
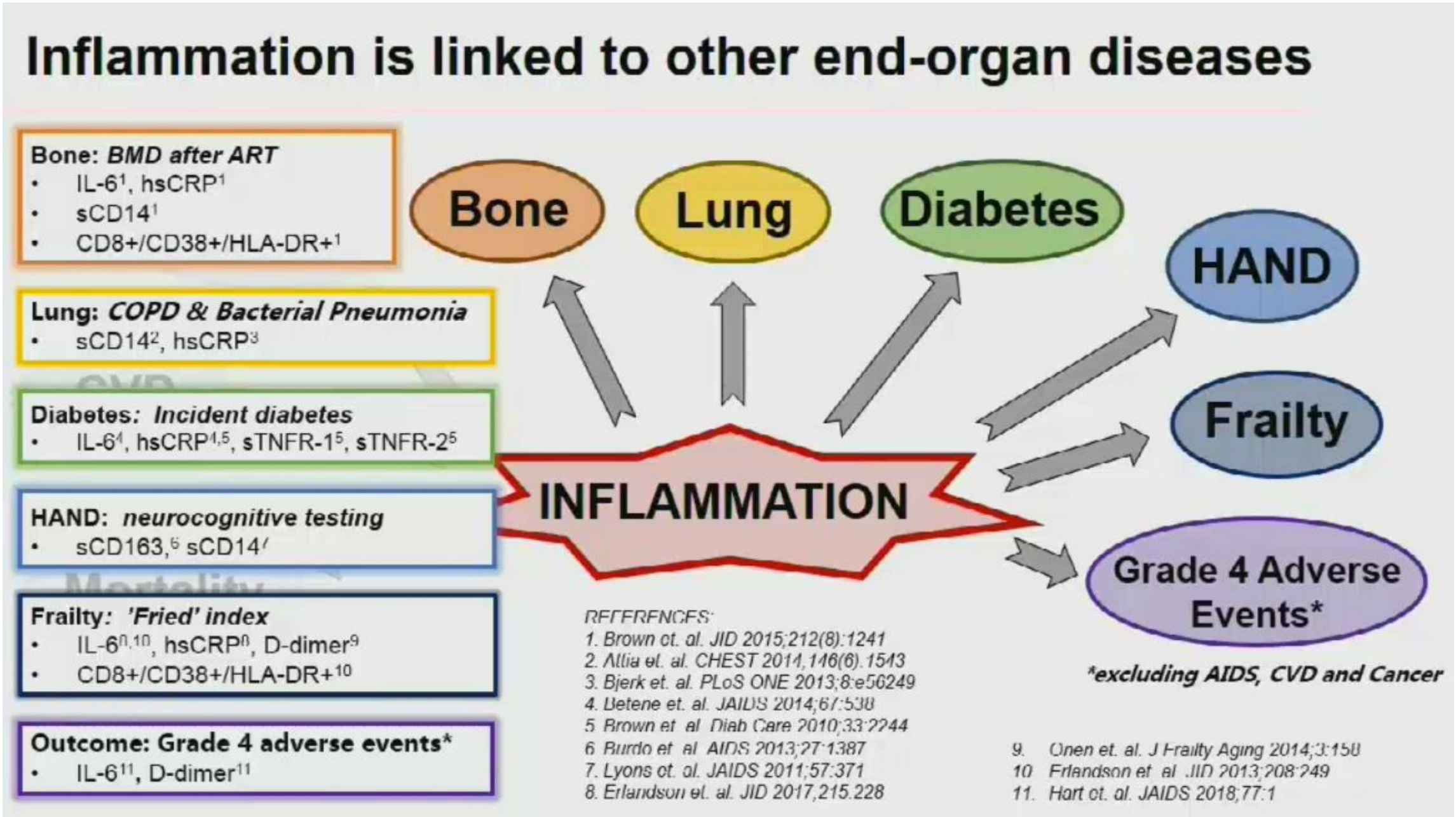


Fig. 2. Odds ratio (with confidence intervals) of frail vs. non-frail and pre-frail vs. non-frail for different body composition measures. (a) Overall cohort adjusted for HIV serostatus and (b) men with HIV only, additionally adjusted for HIV-specific variables. All models were adjusted for age, cohort, race/ethnicity, education, physical activity level, smoking, alcohol and other substance use, depression, viral hepatitis (HBV/HCV), diabetes, kidney disease, and hypertension. The HIV-specific model also included $CD4^+$, $CD4^+$ nadir, cumulative exposure to ART, PI, D4T, ZDV, and/or TDF. *BMI, WC, VAT and SAT are reported as

KL Hawkins AIDS 2018

Inflammation is linked to other end-organ diseases



J Baker symposium S-6 CROI 2018

- Espérance de vie des personnes vivant avec le VIH
- Prévalence augmentée des complications liées au vieillissement chez les PVVIH
- Physiopathologie du vieillissement : rôle de l'inflammation
- Inflammation chronique et activation immune chez les PVVIH et conséquences
- Que proposer ?

Diagnostiquer et traiter tôt, prévenir

- Biomarqueurs, pourquoi pas mais intérêt non prouvé à l'échelle individuelle : CRPus, D-Dimers peuvent être demandés en routine, IL-6, sCD14, sCD163..?
- Scores : FRS?, FRAX?, VACS?
- Albumine?
- Prévenir : dépister et traiter tôt, ART de faible toxicité, traitement personnalisé, facilité de prise et compliance
- Modifier l'environnement: tabac, alimentation, exercice, alcool
- Dépister les patients à risque chez les patients de plus de 50 ans : en fonction nadir CD4, taux bas de CD4, rapport CD4/CD8, CV détectable, stade SIDA, longue durée infection et de traitement
- Rechercher fragilité, invalidité,

Serum Albumin as a Prognostic Marker for Serious Non-AIDS Endpoints in the Strategic Timing of Antiretroviral Treatment (START) Study

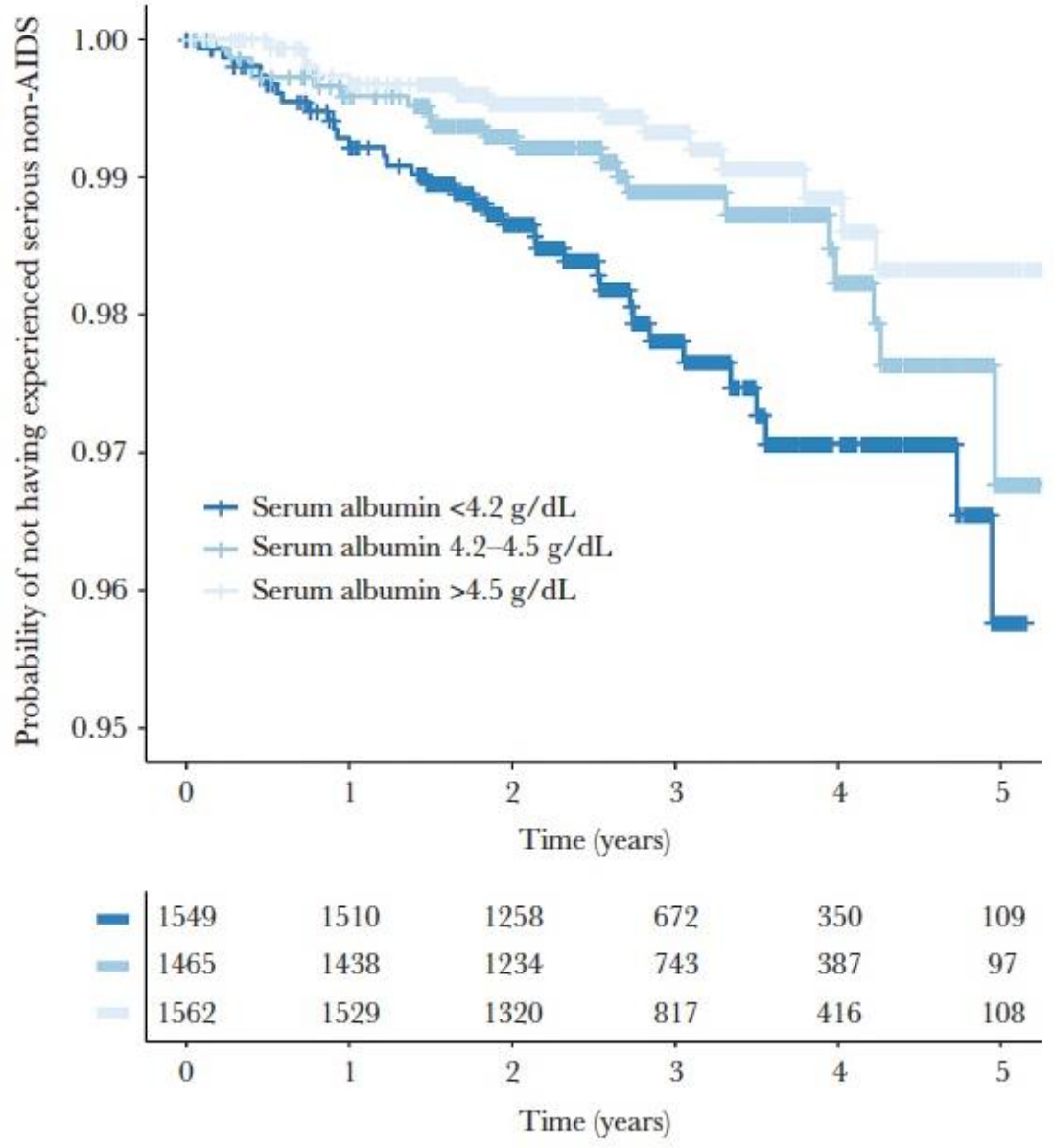


Figure 1. Kaplan–Meier survival curves for serious non-AIDS events according to baseline serum albumin levels. Kaplan–Meier survival curves with risk table for serious non-AIDS events (n = 71) stratified by serum albumin tertiles at baseline. Log-rank test of equality of strata ($P = .001$).

A Ronit JID 2018

Does an Index Composed of Clinical Data Reflect Effects of Inflammation, Coagulation, and Monocyte Activation on Mortality Among Those Aging With HIV?

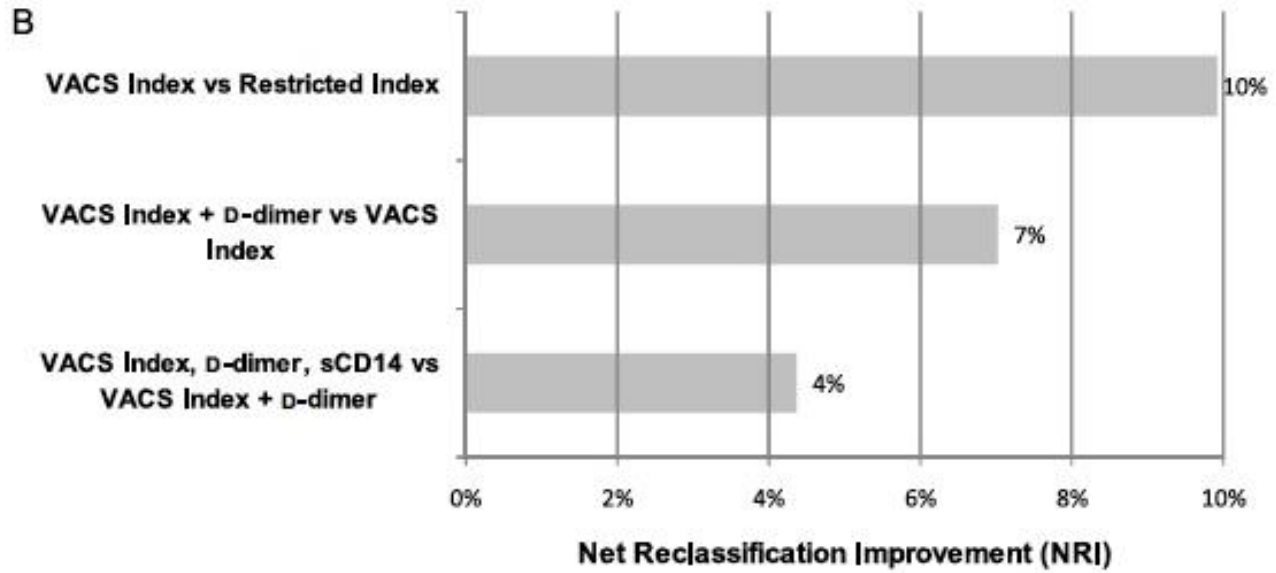


Figure 3. Net reclassification improvement shown in detail for adding D-dimer to the Veterans Aging Cohort Study (VACS) Index (*A*) and final result only (*B*) for adding VACS Index components to the Restricted Index, adding D-dimer to the VACS Index, and further addition of soluble CD14. Abbreviations: NRI, net reclassification improvement; sCD14, soluble CD14; VACS, Veterans Aging Cohort Study.

Table 1. Point Values for Restricted Index (Age, CD4, and HIV-1 RNA) and Veterans Aging Cohort Study Index, Derived in 4932 Male Veterans After 1 Year of Antretroviral Therapy

		Points	
		Restricted Index	VACS Index
Age (years)	<50	0	0
	50–64	23	12
	≥65	44	27
CD4 (cells/mm^3)	≥500	0	0
	350–499	10	6
	200–349	10	6
	100–199	19	10
	50–99	40	28
	<50	46	29
HIV-1 RNA (copies/mL)	<500	0	0
	500–1 × 10^5	11	7
	≥1 × 10^5	25	14
Hemoglobin (g/dL)	≥14		0
	12–13.9		10
	10–11.9		22
	<10		38
FIB-4	<1.45		0
	1.45–3.25		6
	>3.25		25
eGFR (mL/min)	≥60		0
	45–59.9		6
	30–44.9		8
	<30		26
HCV infection			5

FIB-4 was calculated as (years of age × AST)/(platelets in 109/L × square root of ALT); eGFR was calculated as 186.3 × (serum creatinine$^{-1.154}$) × (age$^{-0.203}$) × (0.742 for women) × (1.21 if black); HCV infection was defined as diagnosis with a positive antibody test or detectable virus.

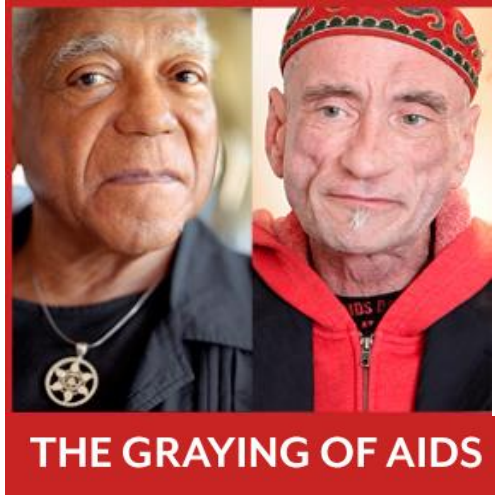
Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FIB, fibrosis index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; VACS, Veterans Aging Cohort Study.

A Justice CID 2012

Diagnostiquer et traiter tôt, prévenir

- Biomarqueurs, pourquoi pas mais intérêt non prouvé à l'échelle individuelle : CRPus, D-Dimers peuvent être demandés en routine, IL-6, sCD14, sCD163..?
- Scores : FRS?, FRAX?, VACS?
- Albumine?
- Prévenir : dépister et traiter tôt, ART de faible toxicité, traitement personnalisé, facilité de prise et compliance
- Modifier l'environnement: tabac, alimentation, exercice, alcool
- Dépister les patients à risque chez les patients de plus de 50 ans : en fonction nadir CD4, **taux bas de CD4, rapport CD4/CD8, CV détectable**, stade SIDA, **longue durée infection et de traitement**
- Rechercher fragilité, invalidité,

Suivi des patients âgés



- Suivi régulier, bilan annuel
- Evaluation de l'efficacité et de la toxicité des ART
- Biomarqueurs :
  - Paramètres lipidiques et glucidiques
  - Marqueurs nutritionnels (albumine, préalbumine)
  - statut vitaminique D
  - Fonction rénale
  - Ferritine, folates, vitamine B12
- Tests cliniques
  - tests simple pour rechercher un déficit cognitif
  - fonctions motrices, fragilité
- Ostéodensitométrie si traités depuis longtemps ou facteurs de risque
- Mammographie et examen gynécologiques chez la femme
- Examen proctologique chez les sujets à risque

recommandations de F Rollot et S Moulias, ANRS

Specific treatment of inflammation:

can we identify a central pathway at the trunk level to reverse inflammation and pathology or do we need to cut several branches targeting different pathways?

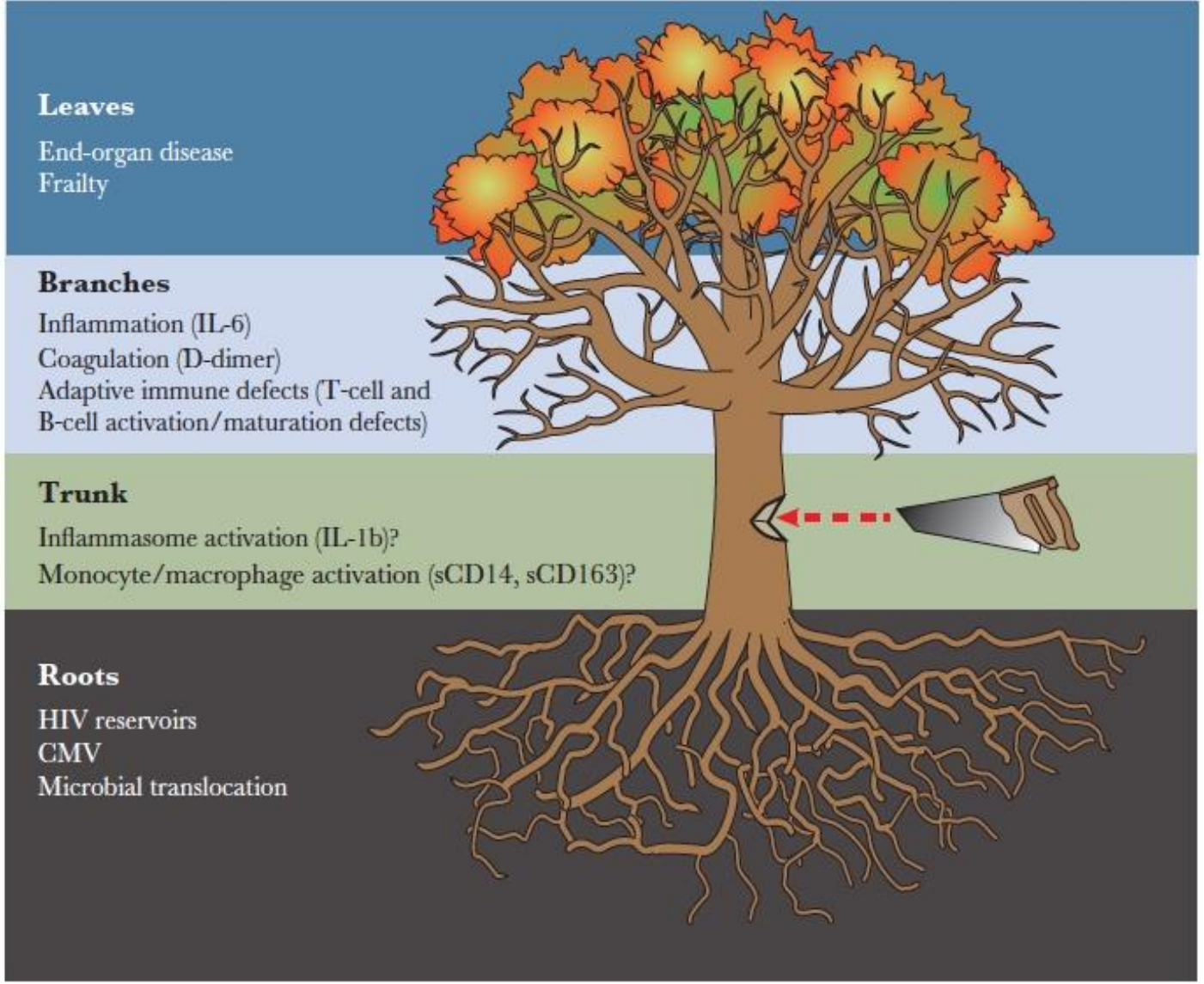


Figure 1. Can we find the tree trunk? One might liken the optimal process for identifying therapeutic targets to cutting down a tree. One could attempt to identify targets in a piecemeal fashion by cutting off each individual "root" driver of the inflammatory state (eg, human immunodeficiency virus [HIV]–associated microbial translocation) or by cutting off each "branch" (eg, hypercoagulability). However, piecemeal approaches may fail to reverse pathology if all important "root" causes are not blunted and/or downstream pathways reversed. Identifying the "trunk"—a central pathway activated by all major drivers and giving rise to all parallel pathways—would be optimal. Applying systems biology and assessing multiple parallel inflammatory pathways in the context of trials of immune-based interventions may help identify promising central pathways. CMV, cytomegalovirus; IL-1β, interleukin 1β; IL-6, interleukin 6; sCD14, soluble CD14; sCD163, soluble CD163.

AC Justice JID 2018

Recent Data from RCT on Anti-inflammatory Strategies*

*List is not intended to be comprehensive

	Intervention Strategy	Sample	Treatment Effect	REFERENCE	
	Traditional Risk Factor Target				
+	Rosuvastatin ('SATURN-HIV')	N=147	Reduction in sCD14 & $CD14_{dim}$CD16+TF+	*CID 2014;58:588*	
	Aspirin	N=121	Null effect on inflammatory markers	*OFID 2017:ofw278*	
	GI/Microbiome				
	Rifaximin	N=35	Possible/transient reduction in LPS	*JID 2015;211:780*	
→	Rifaximin	N=42	**Presented at this meeting**	***CROI 2018 (#313)***	negative
→	Isotretinoin (pro-PMN)	N=81	**Presented at this meeting**	***CROI 2018 (#219)***	negative
→	Visbiome	N=93	**Presented at this meeting**	***CROI 2018 (#275)***	negative
→	Synbiotics	N=77	**Presented at this meeting**	***CROI 2018 (#276)***	negative
	Anti-inflammatory				
	Hydroxychloroquine (dec. TLR)	N=83†	Increased viral load and CD4 decline	*JAMA 2012;308:353*	
→	LD Methotrexate (T/B-cell inh.)	N=176	**Presented at this meeting**	***CROI 2018 (#79)***	negative

†Target population was HIV+ not on ART

J Baker symposium S-6 CROI 2018

Recent data from AIDS 2018 Amsterdam

- Dipyridamole which inhibits cellular adenosine uptake: no decrease in inflammation/immune activation markers after 12 weeks *(BJ Macatangay THPEB095)*
- CC-11050, a phosphodiesterase 4 inhibitor, anti-inflammatory medication (PDE4i used in psoriasis and COPD): no decrease in inflammation/immune activation markers after 12 weeks *(A Boulougoura LBPEB021)*

Upcoming Data from RCT on Anti-inflammatory Strategies*

**List is not intended to be comprehensive*

	Intervention Strategy	Sample	Anticipated Results	ClinicalTrials.gov
	Traditional Risk Factor Intervention			
+	Pitavastatin ('REPRIEVE')	N=6500	2020-2021	NCT02344290
	Losartan	N=108	2018	NCT02049307
	Metformin	N=88	2020-2021	NCT03129113
	Exercise	N=72 N=250	2018 2020-2021	NCT02404792 NCT02711878
	Anti-inflammatory/Anti-coagulation			
→	Canakinumab (IL-1β inhibitor)	N=110	2019	NCT02272946
	Ruxolitinib (JAK inhibitor)	N=60	2018-2019	NCT02475655
	CC-11050 (PDE-4 inhibitor)	N=36	2018	NCT02652546
→	Edoxaban (FXa inhibitor)	N=44	2018	NCT02339415
→	Vorapaxar (PAR-1 inhibitor)	N=60	2018	NCT02394730

Résultats négatifs vont être présentés au « 20th International Workshop on Comorbidities and Adverse Drug Reactions in HIV » October 2018

J Baker symposium S-6 CROI 2018

Conclusion

- Les PVVIH vieillissent et présentent une prévalence augmentée de certaines comorbidités associées au vieillissement
- Les sujets à surveiller en priorité sont ceux de +50 ans, infectés et traités depuis longtemps. Les principaux facteurs de risque sont des CD4 bas, un rapport CD4/CD8 bas (<0.5), une CV détectable
- Leur prise en charge relève de compétences multidisciplinaires y compris gériatriques avec la prise en charge des problèmes posés par la multimorbidité et la polypharmacie
- Une inflammation bas grade et une activation immune contribuent à leur morbi-mortalité.
- Les traitements anti-inflammatoires n'ont pas été validés dans ce cadre sauf statine chez les patients à risque cardio-vasculaire et aspirine en prévention secondaire
- Les modifications de mode de vie sont essentielles dans leur prise en charge: régime, exercice physique, arrêt du tabac, contrôle de la prise de drogues.

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