



Overview of our HIV Aging Populations: Closing remarks

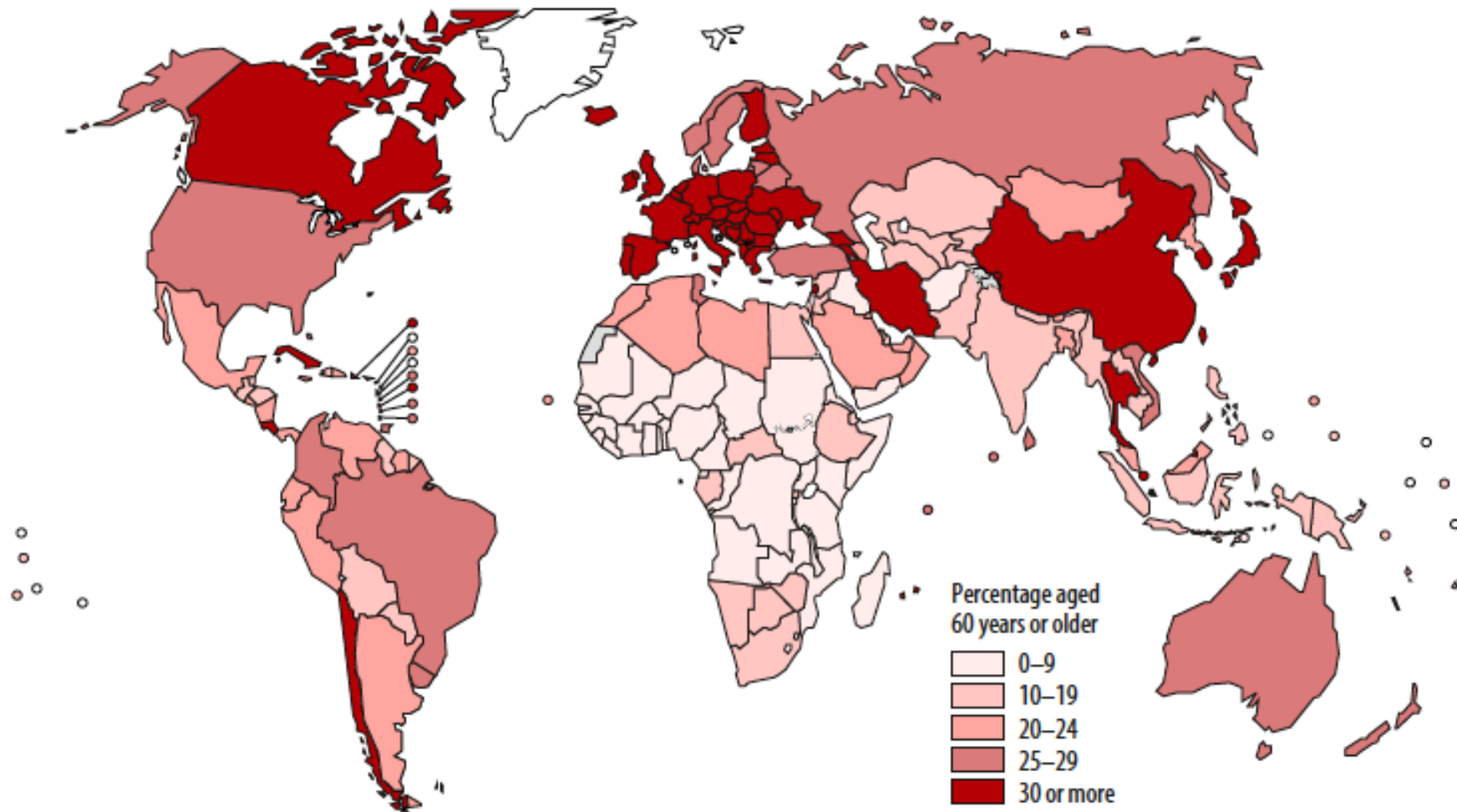
Pedro Cahn
Fundación Huesped
Buenos Aires, Argentina



OUTLINE

- Prevalence and forecasts
- Aging in Latinamerica
- The impossible task: To summarize 2 days in 40 minutes
- Some final remarks

Fig. 3.2. Proportion of population aged 60 years or older, by country, 2050 projections

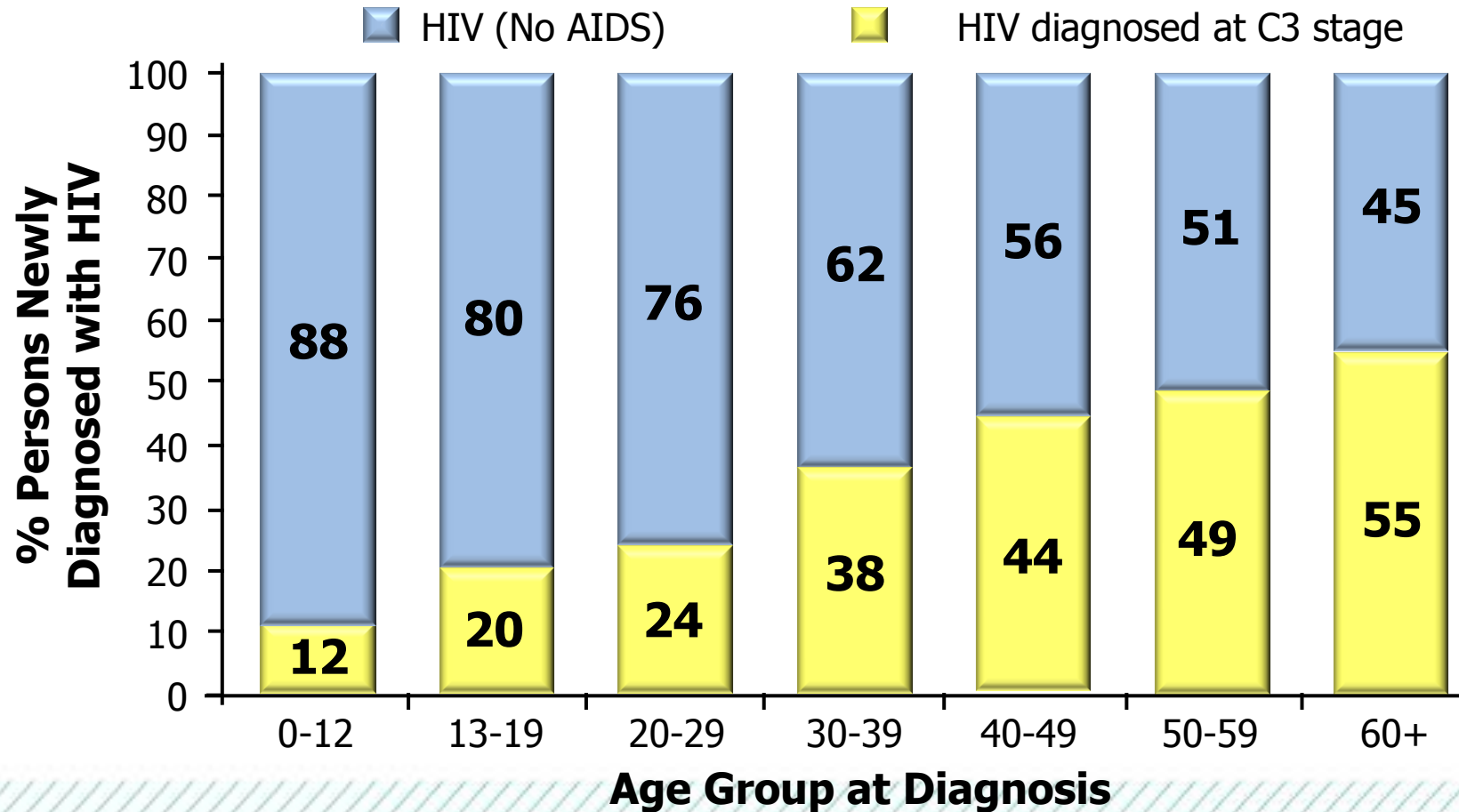


WHO, World report on ageing, 2015

(http://apps.who.int/iris/bitstream/10665/186463/1/9789240694811_eng.pdf)

Elderly patients are frequently late presenters

Concurrent HIV/AIDS Among Persons Diagnosed with HIV in US in 2006, by Age Group



Comparison of the Late Presenter Profile Across Europe

Country	UK ¹⁻³			France ^{4,5}	
Nomenclature	Late presenters	Late diagnosis CD4+ count <200 cells/mm ³	Late presenters CD4+ count <200 cells/mm ³	Late diagnosis CD4+ count <200 cells/mm ³ or AIDS at diagnosis	Delayed access to care
Frequency	15.3%	33%	33.7%	33%	35.7%
Risk factors/ More likely to be:	<ul style="list-style-type: none"> •Female •Heterosexual •Black-African ethnicity 	<ul style="list-style-type: none"> •Non Caucasian •Non-MSM •Older age 	<ul style="list-style-type: none"> •Female •Heterosexual •Black-African ethnicity 	<ul style="list-style-type: none"> •Older age •Male sex •Immigrant 	<ul style="list-style-type: none"> •Migrant women •Migrant and non-migrant men

1. Sabin CA, et al. AIDS 2004;18:2145-2151.

2. Sullivan AK, et al. BMJ 2005;330:1301-1302.

3. Waters L, et al. HIV Med 2010 [Epub ahead of print].

4. Delpierre C, et al. Int J STD AIDS 2007;18:312-317.

5. Lanoy E, et al. Antivir Ther 2007;12:89-96.

Comparison of the Late Presenter Profile Across Europe

Country	Spain ^{6,7}		Italy ⁸	Sweden ⁹
Nomenclature	Delayed HIV diagnosis	Late diagnosis CD4+ count <200 cells/mm ³ or AIDS at diagnosis	Late diagnosis CD4+ count <200 cells/mm ³ or AIDS within 1 month	AIDS within 3 months of diagnosis
Frequency	35.6%	43.8%	29%	45%
Risk factors/ More likely to be:	<ul style="list-style-type: none"> •Lower education level •Heterosexual •IDUs •Uncommon HIV transmission mechanisms compared to gay men •More common in men and older people 	<ul style="list-style-type: none"> •Older age •Male 	<ul style="list-style-type: none"> •Older age 	<ul style="list-style-type: none"> •Heterosexual •Older age •Foreign origin

6. Sobrino-Vegas P, et al. Curr HIV Res 2009;7:224-230.

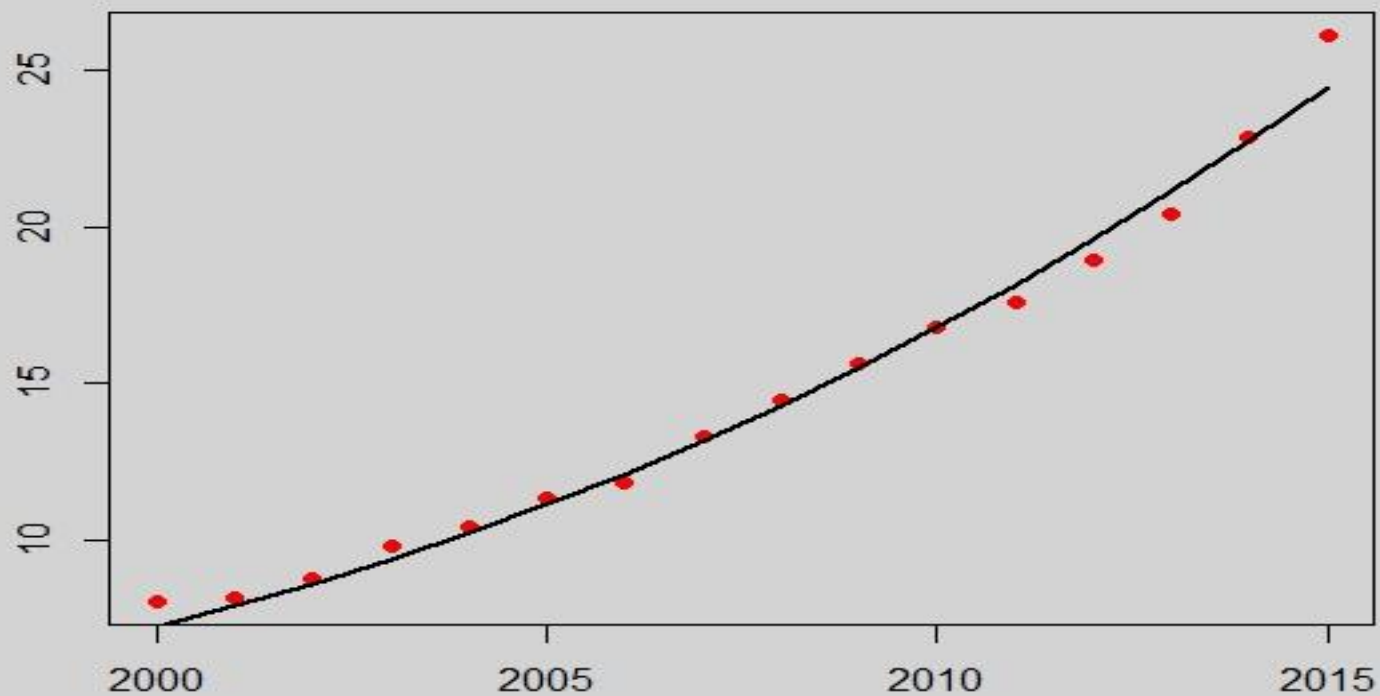
7. Castilla J, et al. Gac Sanit 2006;20:442-448.

8. Girardi E, et al. J Acquir Immune Defic Syndr 2004;16:951-959.

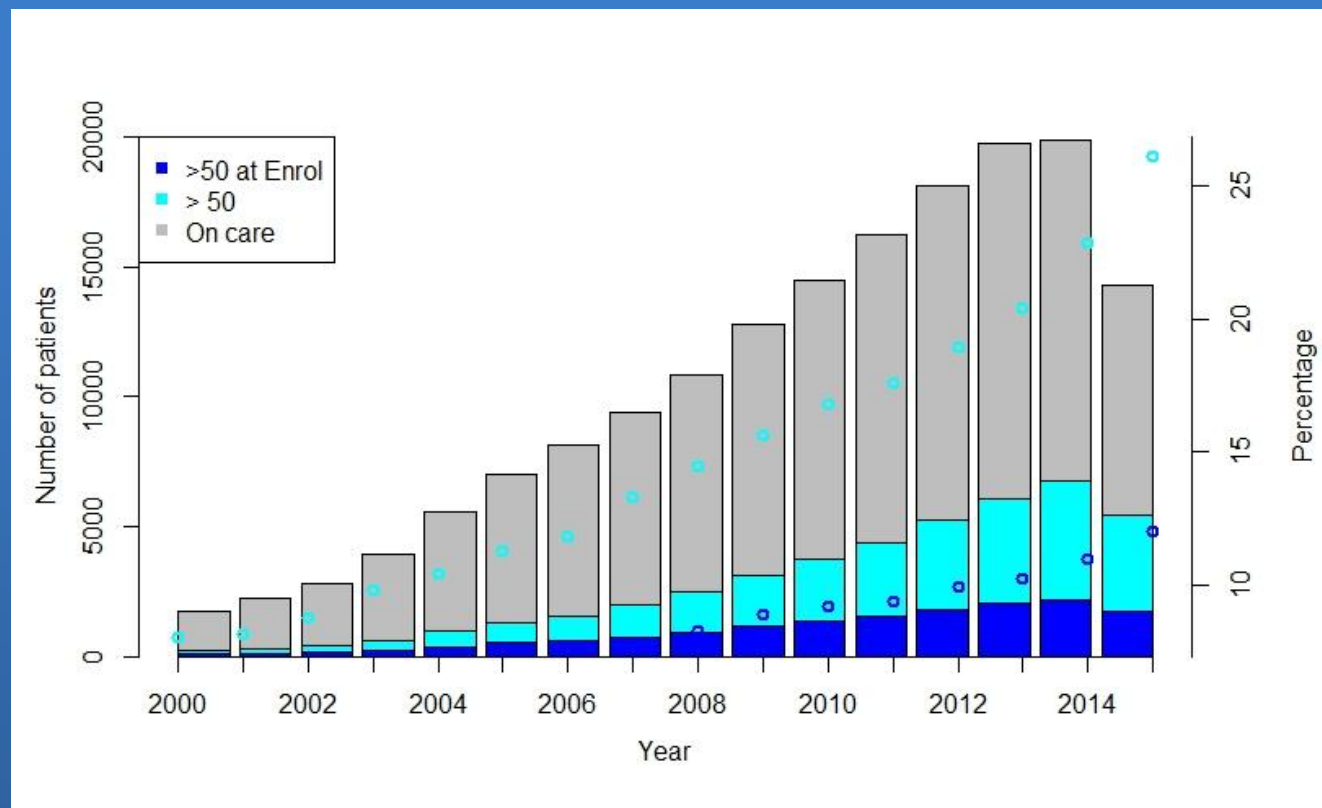
9. Brännström J, et al. Int J STD AIDS 2005;16:702-706.

Proportion of patients > 50 years in CCASANet*

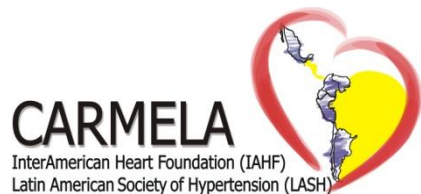
* Network of 7 cohorts
Involving > 15,000 patients
In 7 countries



Proportion of patients > 50 years in CCASANet

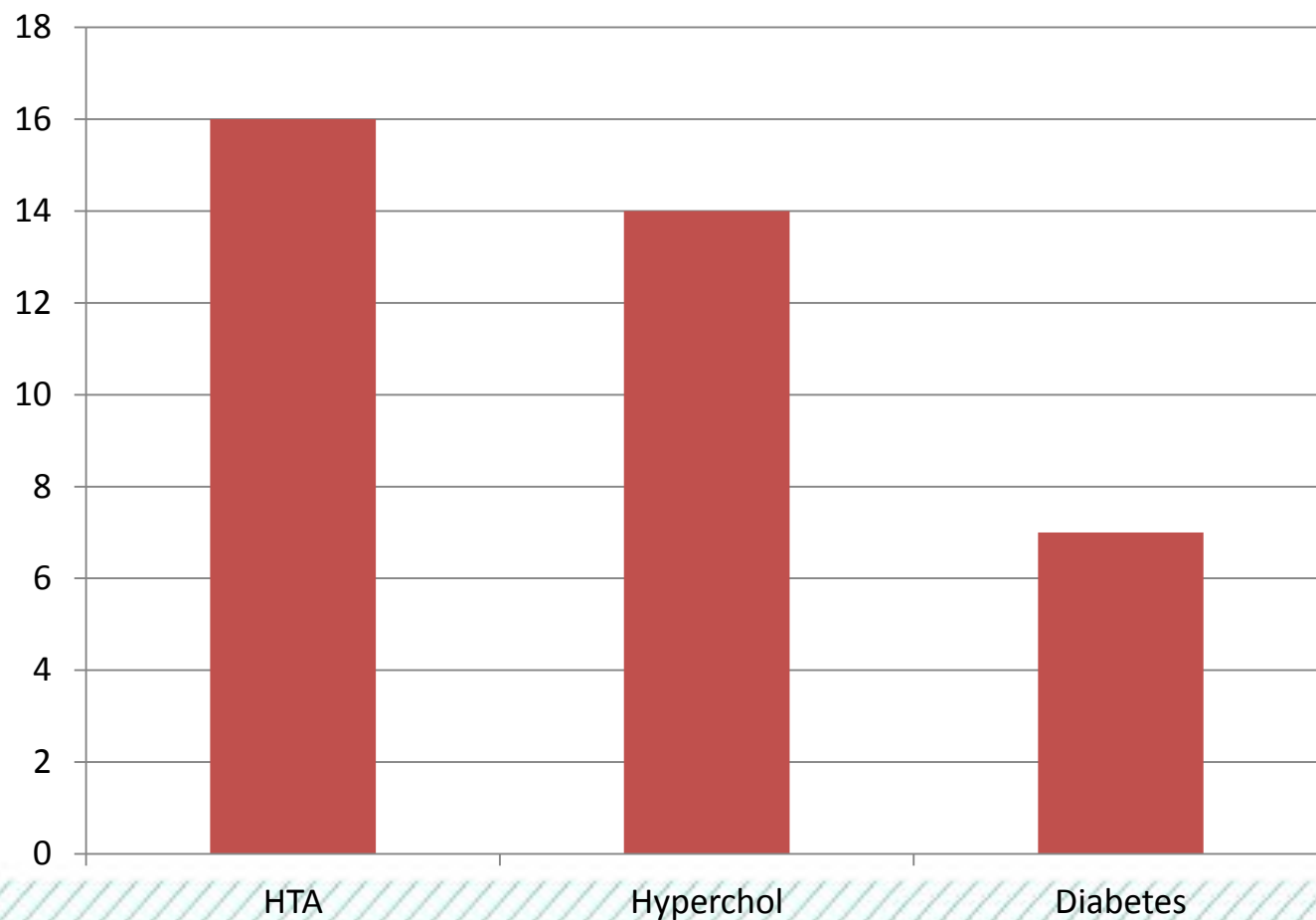


Risk factors in 7 sites in Latin America



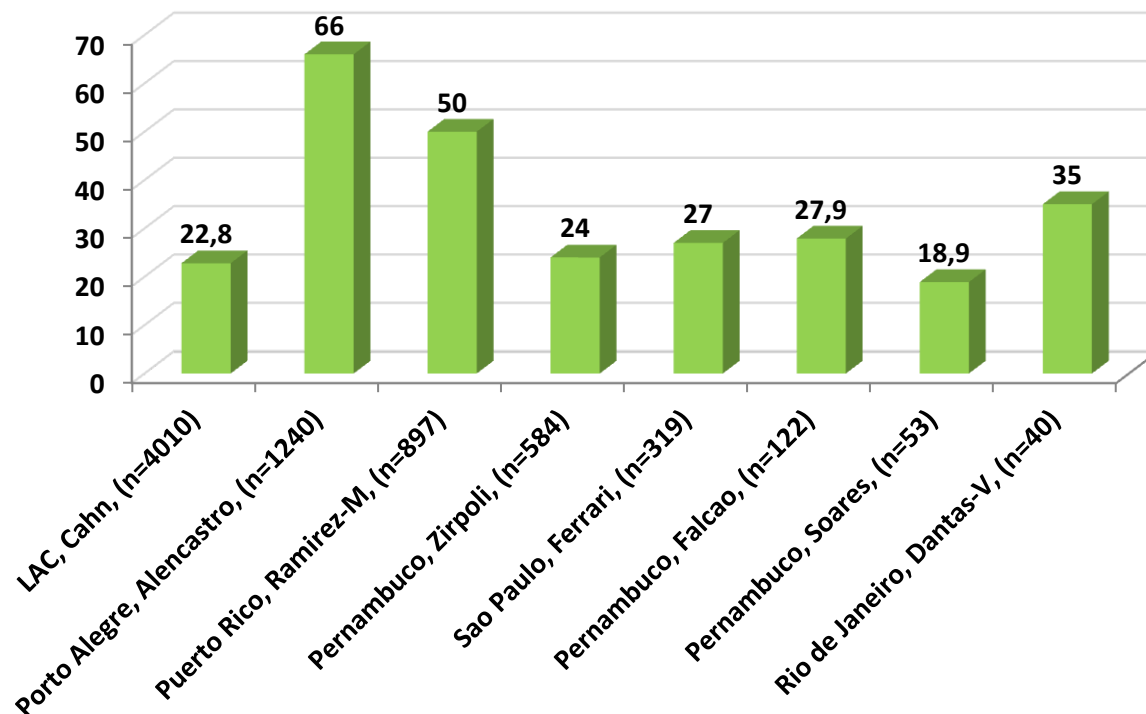
N: 11550

Prevalence %



1) Carmela Study, AJM, 2008,

Risk factors in LAC patients: Smoking



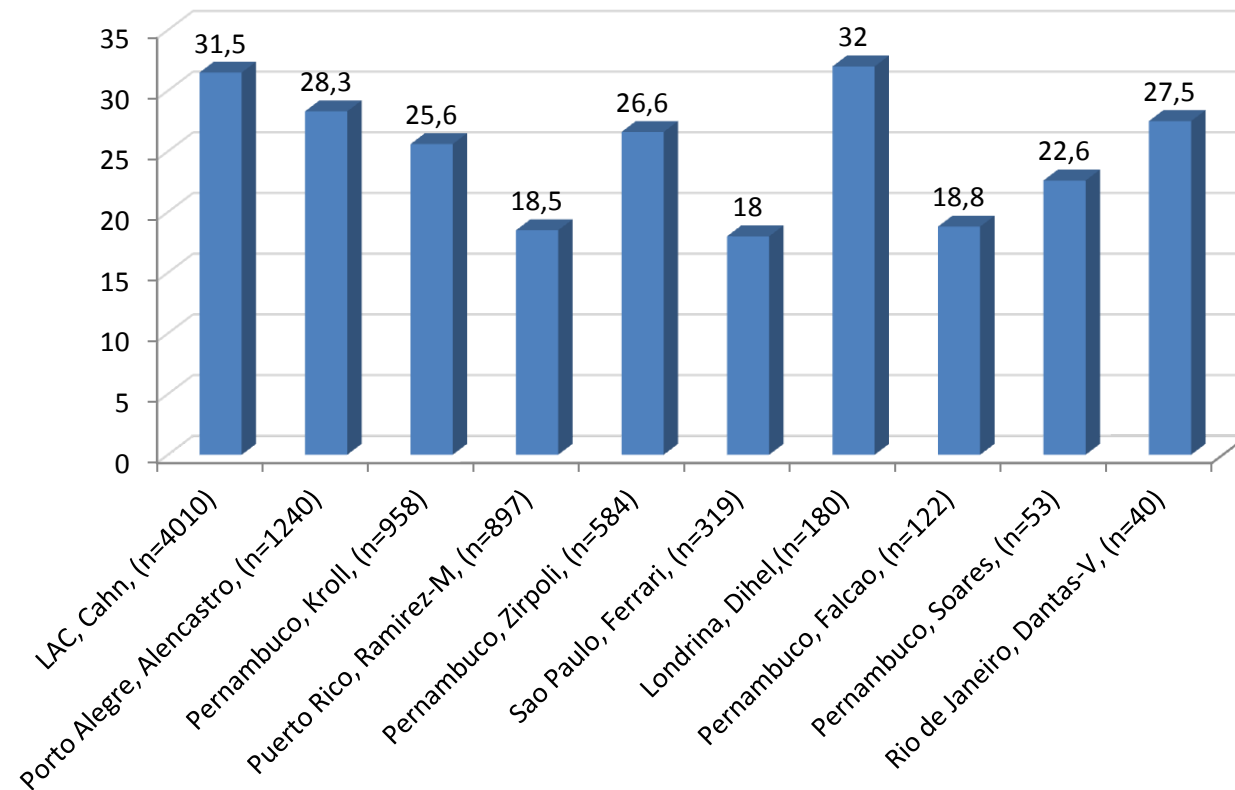
19-66% of LAC patients regularly smoke

Slightly higher than HIV negative: 30% (22-45%)¹

“Smoking is the most important modifiable cardiovascular risk factor among HIV patients”²

Double contribution to Acute MI in HIV vs in HIV negative (54% vs 30%)

Risk factors in LAC patients: HTA



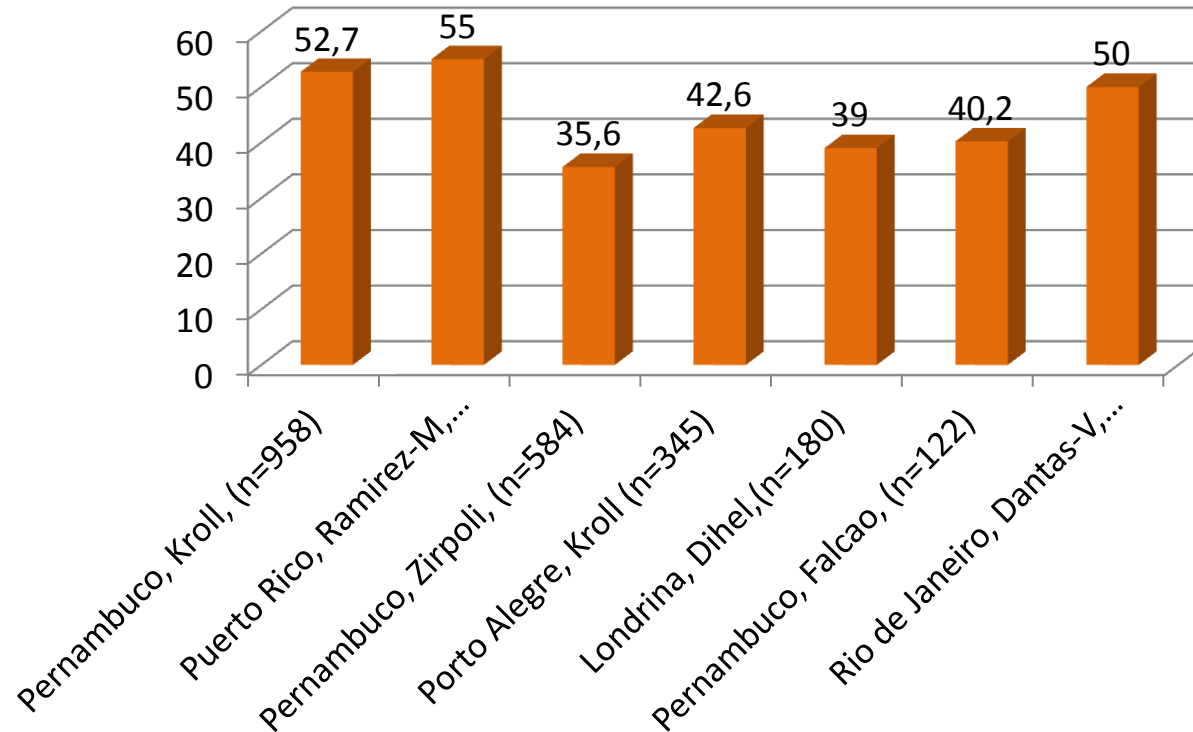
19-32% of HIV LAC patients have HTA

Higher than HIV neg:
18% (9-29%)¹

“No clear evidence as to how HIV or antiretroviral therapy plays a role under these conditions”²

- Low CD4 nadir predicts HTA development (aOR 2.31 for CD4 <50 cells/uL)³
- Hypertension associated with bacterial translocation and inflammation, as demonstrated by high levels of sCD14 and LPS⁴

Risk factors in LAC patients: Obesity



36%-55% of LAC patients have BMI >25
8% have BMI >30.

Higher than HIV negative :
23% (18%-27%)¹

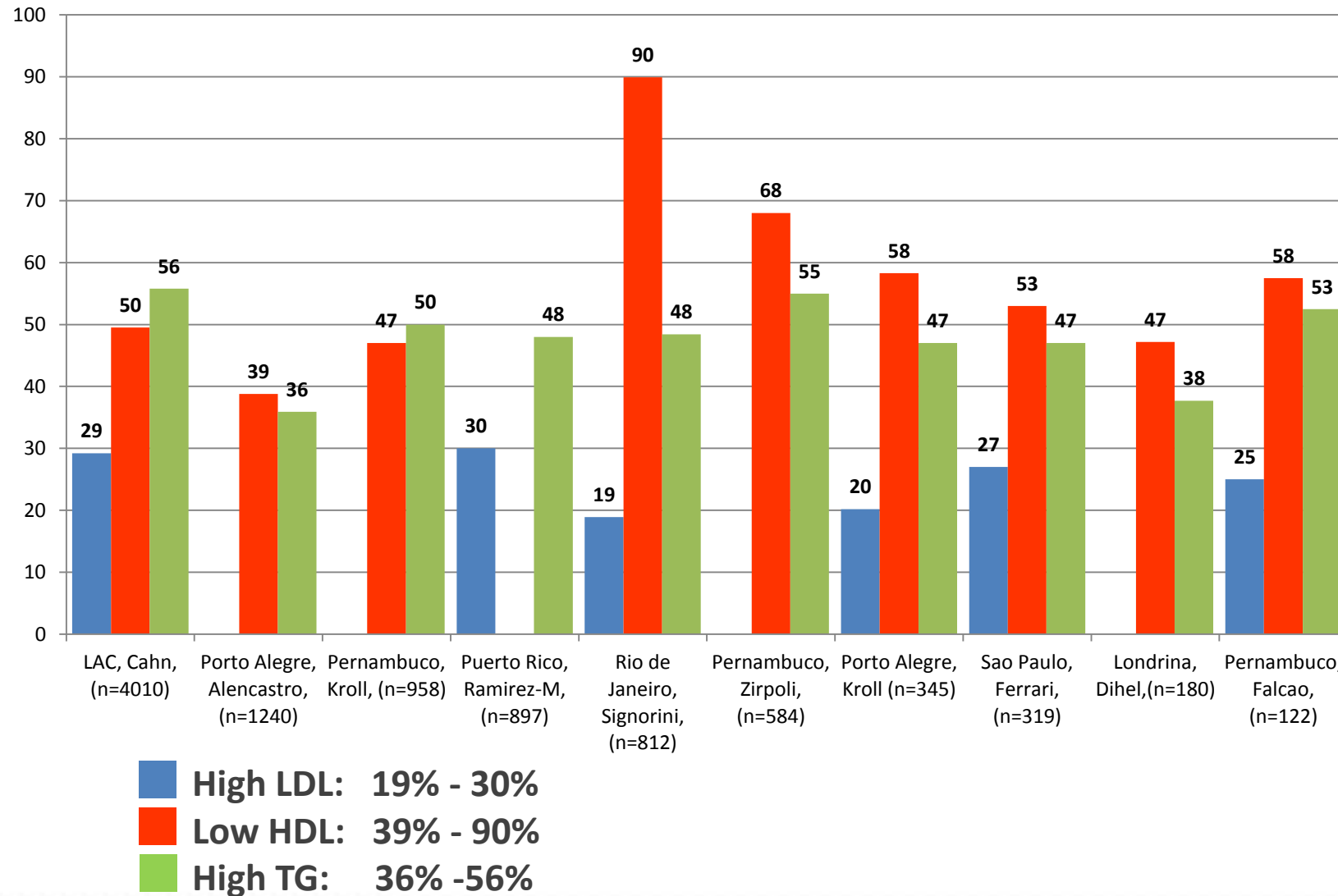
“Women with <200 CD4 starting a PI based HAART at higher risk to become obese”²

- Associated to higher frequency of HAND³
- 19% incidence in patients starting HAART⁴

1) Carmela Study, AJM, 2008, 2) Lakey, Aids Res, 2013,

3) Charter study, 4) Maia Leite, Nutrition Hosp 2010.

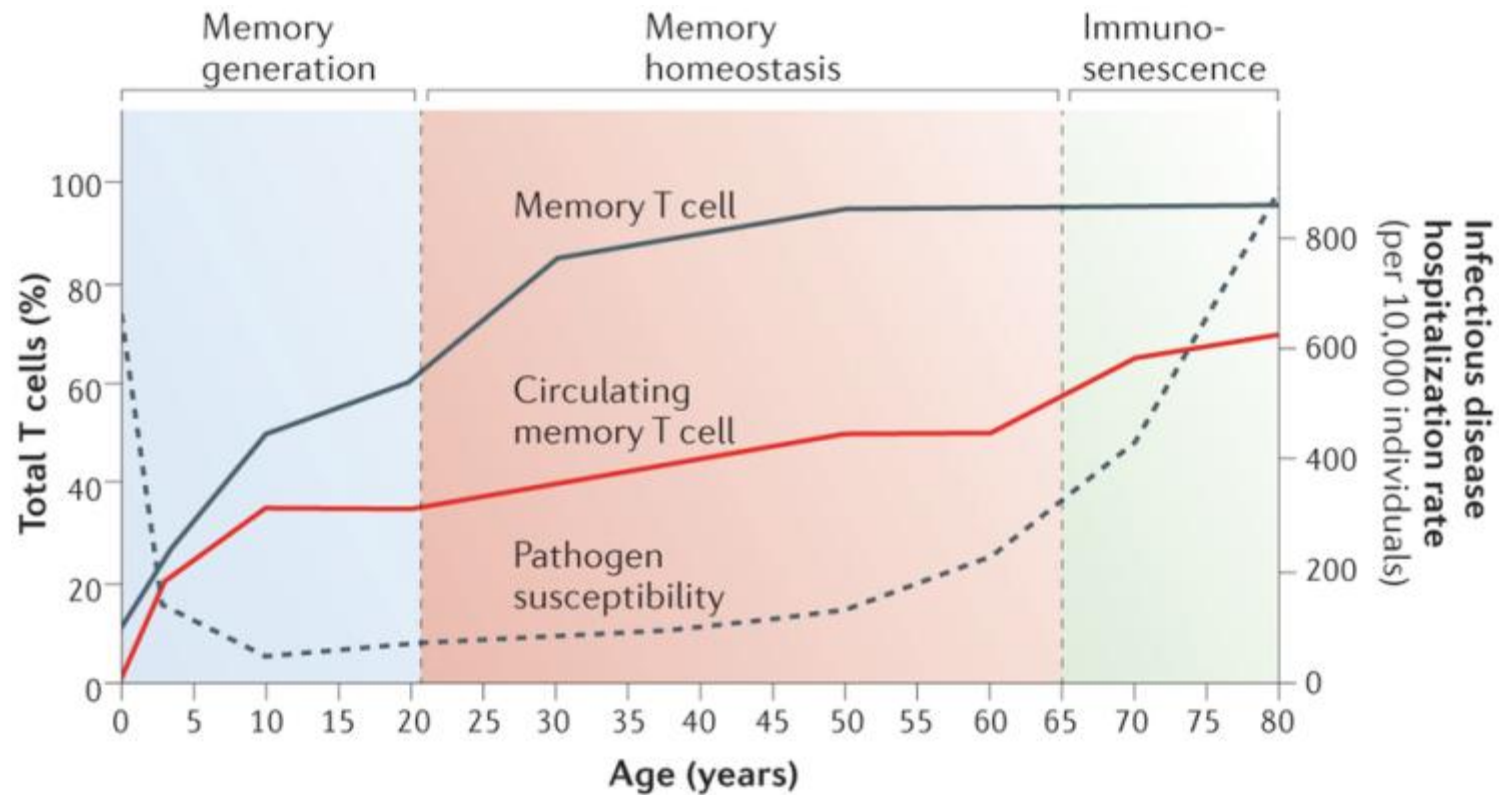
Risk Factors: Dyslipidemia



Pathogenesis of HIV and aging share similarities, common link may be inflammation



Immunosenescence. A natural process

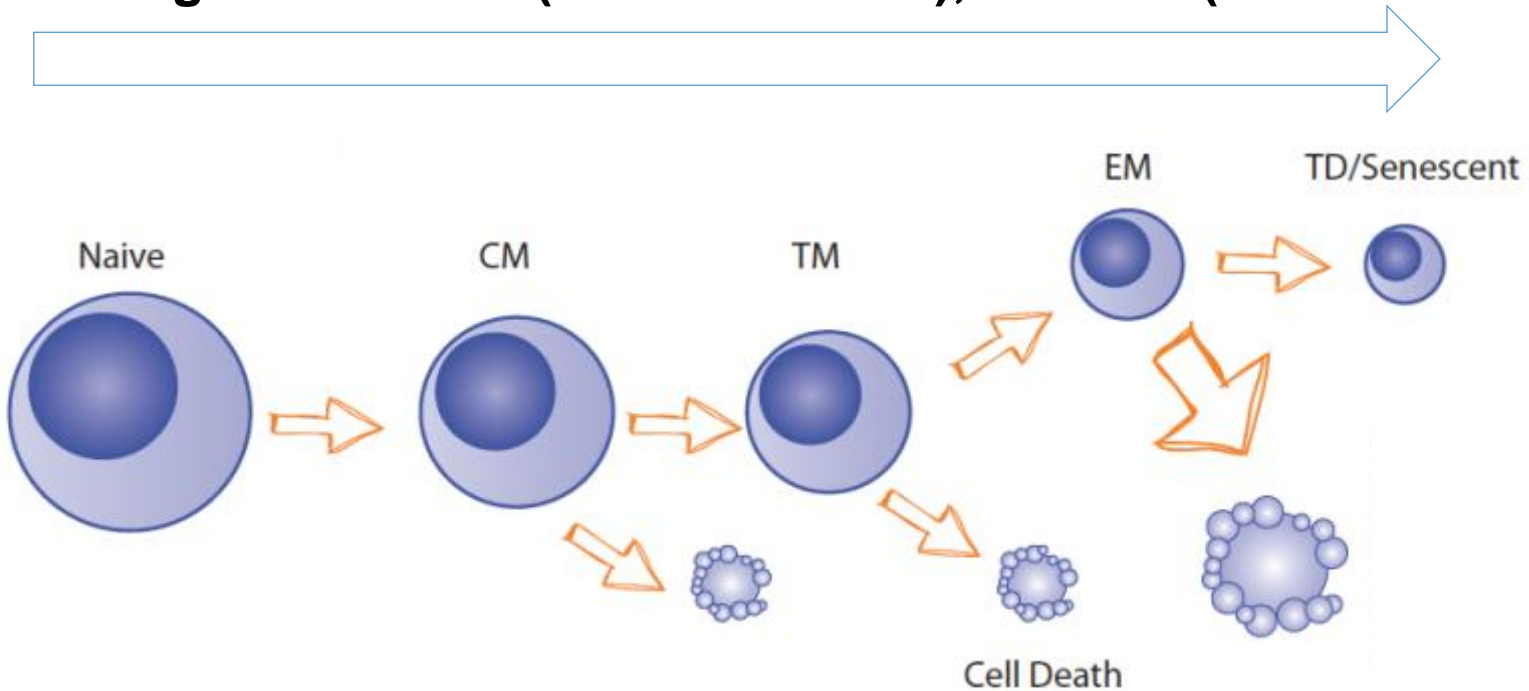


Nature Reviews | Immunology

The life and death of a T cell

Inflammation (inflam-aging)

Pathogens: Viruses (CHRONIC CMV), bacteria (MICROBIOTA?)



Immunosenescence. A natural process

Cells undergo a limited number of divisions. This number is controlled by the quality of the chromosome ends (TELOMERS)

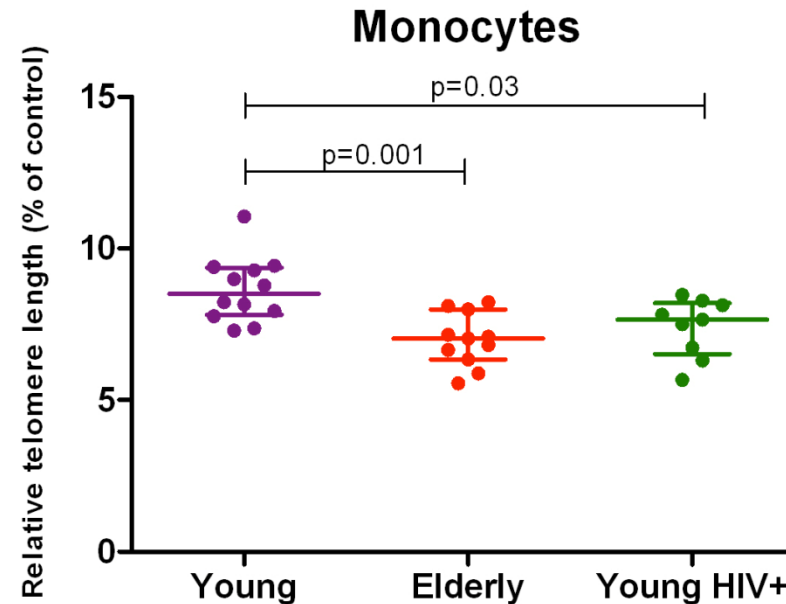


Cells with damaged (short) telomers undergo apoptosis or become refractory to division signals (senescence)

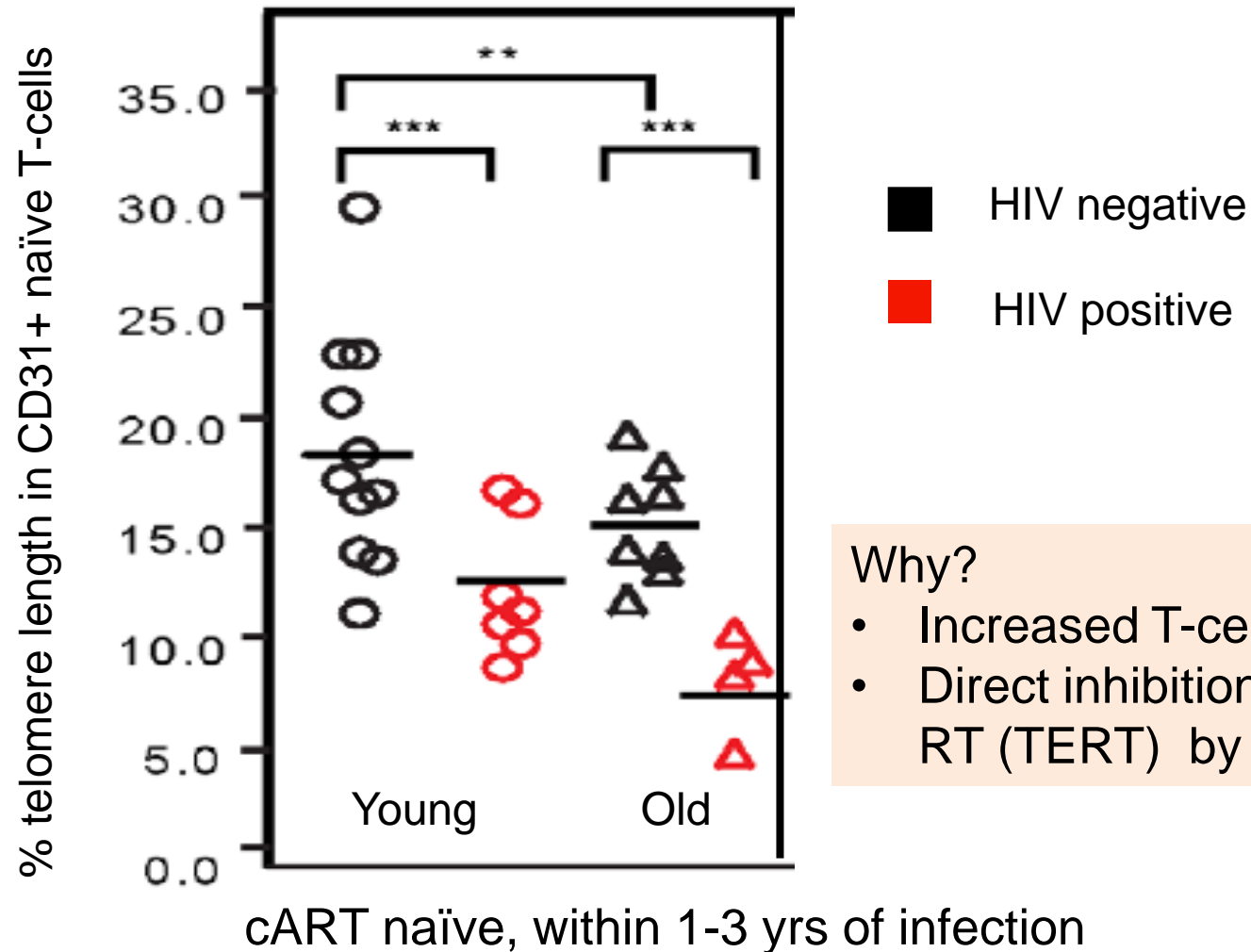
Shortened telomeres in young HIV+ and in healthy elderly

- Short hexonucleotide repeats at ends of chromosomes
- Protect the DNA
- Telomeres are shortened during each cell division
- If telomeres shorten, cells age
- Classical marker of immune ageing

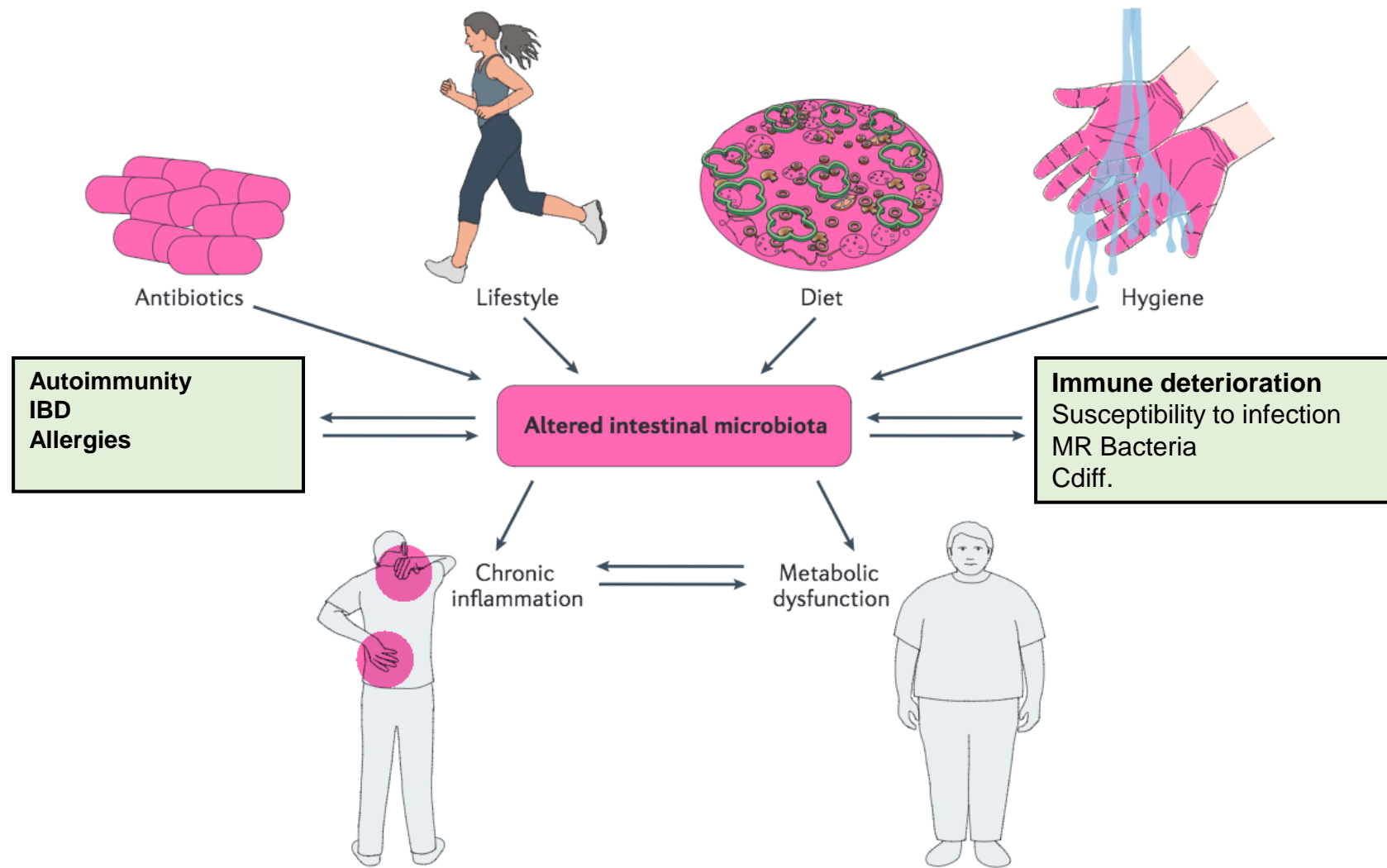
Telomere length is shorter in healthy elderly and young HIV+



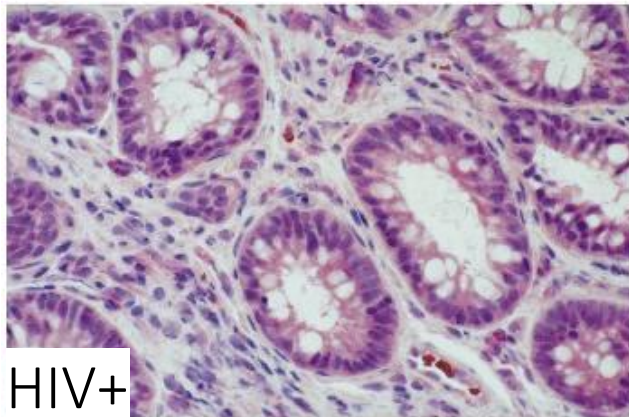
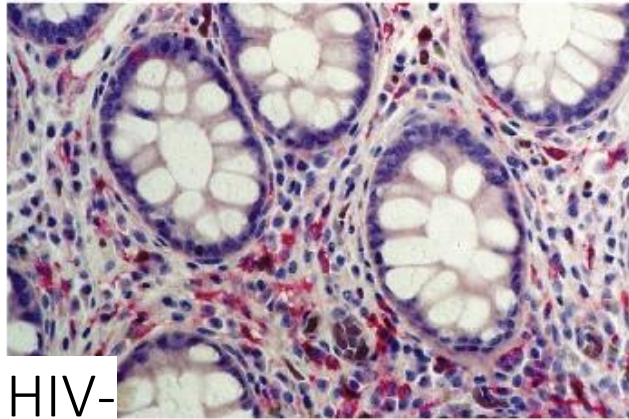
Telomere length is significantly reduced in cART naïve HIV+ individuals



- ❑ DESPITE FULL RECOVERY OF CD4 T CELL NUMBERS, IMMUNOCONCORDANT TREATED HIV INFECTED INDIVIDUALS MAINTAIN IMMUNOLOGICAL ALTERATIONS IN ALL CD4 AND CD8 T CELL COMPARTMENTS.
- ❑ SENESENCE ACCUMULATED DURING UNTREATED INFECTION LEAVES A IRREVERSIBLE? IMPRINT IN THE IMMUNE SYSTEM

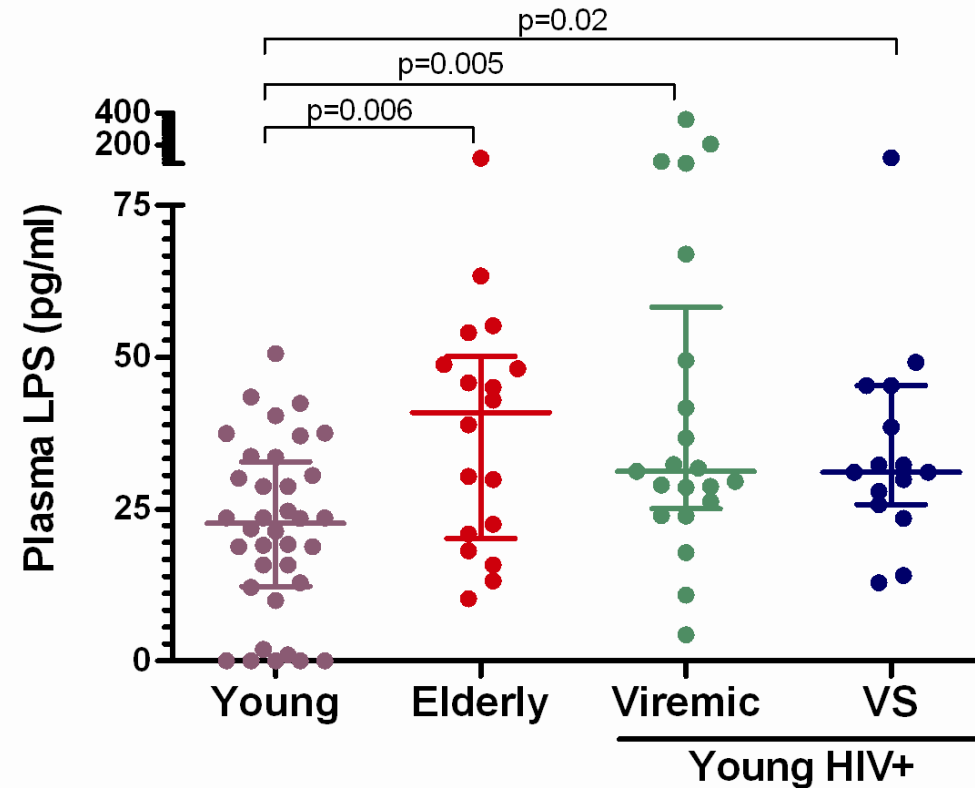


Damaged gut lymphoid tissue in HIV+ patients promotes microbial translocation

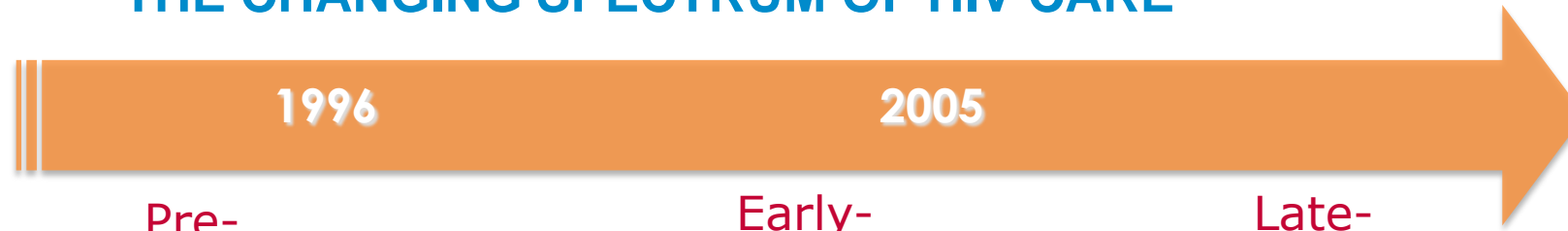


HIV-
HIV+
Colon lamina propria, acute/early HIV
Red=CD4+ T cells

Chronic endotoxemia in elderly and HIV+, not reversed by cART



THE CHANGING SPECTRUM OF HIV CARE



Pre-
HAART



Opportunistic infections
AIDS cancers

Early-
HAART



Lipodystrophy
Co-morbidities

Late-
HAART

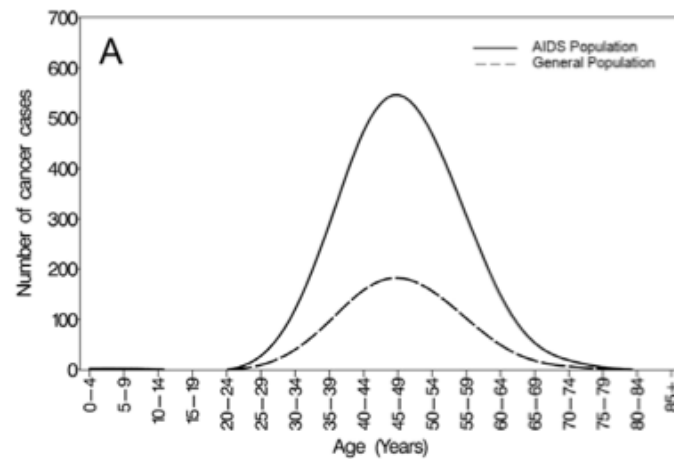


Multimorbidity
Frailty & Disability

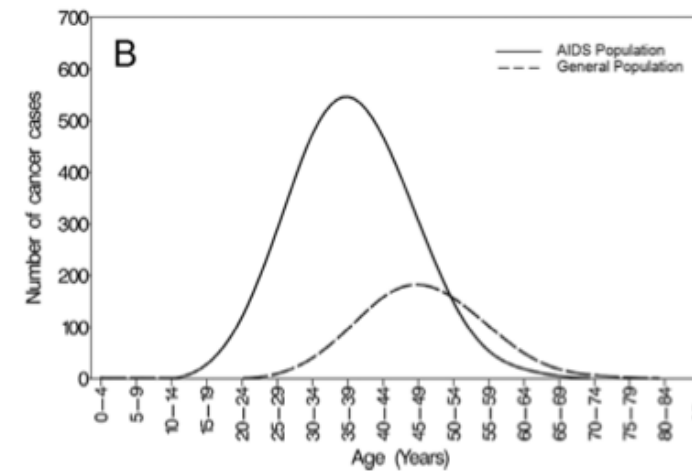
Review Article

Is HIV a Model of Accelerated or Accentuated Aging?

Sophia Pathai,^{1,*} Hendren Bajillan,^{2,*} Alan L. Landay,^{3,4} and Kevin P. High⁵



Accentuated Aging: cancer (and **geriatric syndroms**) occurs at the same ages but more often among HIV-infected participants than among HIV-uninfected comparators. This configure a **Premature aging process**.



Accelerated Aging and accentuated aging: cancer (and **geriatric syndroms**) occurs earlier among HIV-infected participants compared with HIV-uninfected comparators and there are more cancer events.

Potential covariates and Confounders

Demographics

Age, gender, ethnicity, yrs education, socio-economic, un/employment, etc.

NeuroPsych

HAND, dementia, depression, disposition/mood, substance ab/use, etc

Medical-Physion

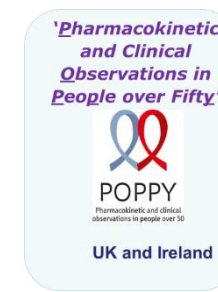
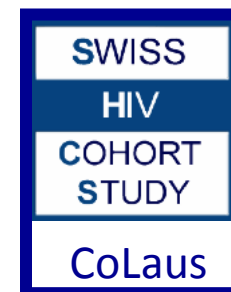
Other meds, cardiometabolic risk, hepatorenal status, cancer BMD, lat/lean, endocrine and inflammatory markers, lifestyle, tobacco, rec. drugs, diet, physical inactivity, ADL, IADL, etc

HIV Related

Yrs HIV, AIDS dx, HIV med compliance-complication, CD4, plasma and CSF viremia, immune activation, co-infections, chronic inflammation, etc

Social Vulnerability aspects

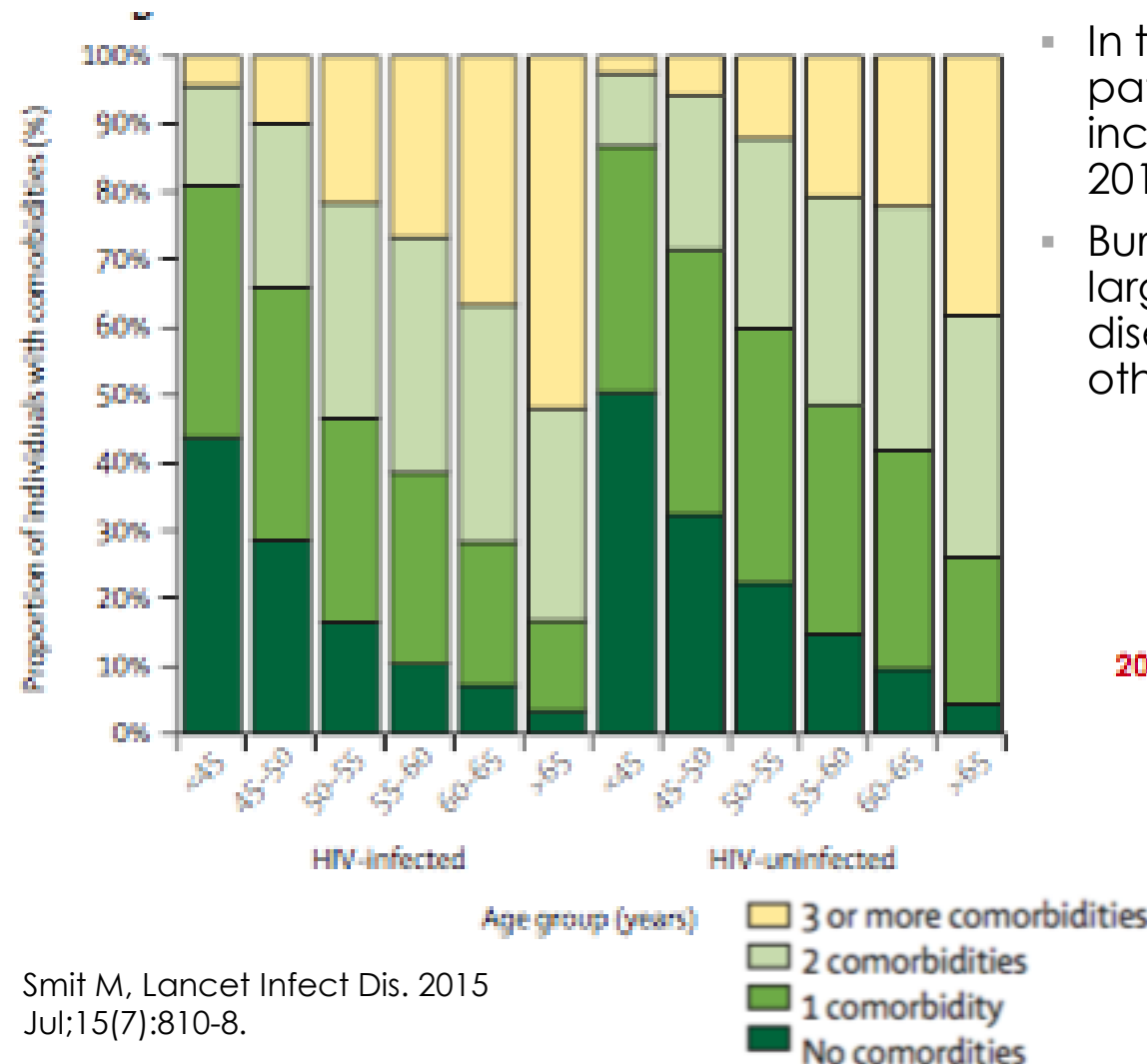
Poverty, food security, Access to care, social justice, etc.



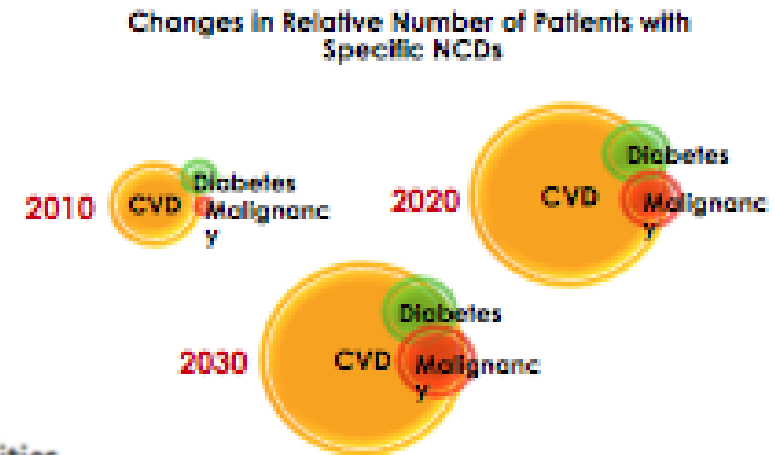
Future challenges for clinical care of an ageing population infected with HIV: a modelling study



Mikaela Smit, Kees Brinkman, Suzanne Geerlings, Colette Smit, Kalyani Thyagarajan, Ard van Sighem, Frank de Wolf, Timothy B Hallett, on behalf of the ATHENA observational cohort

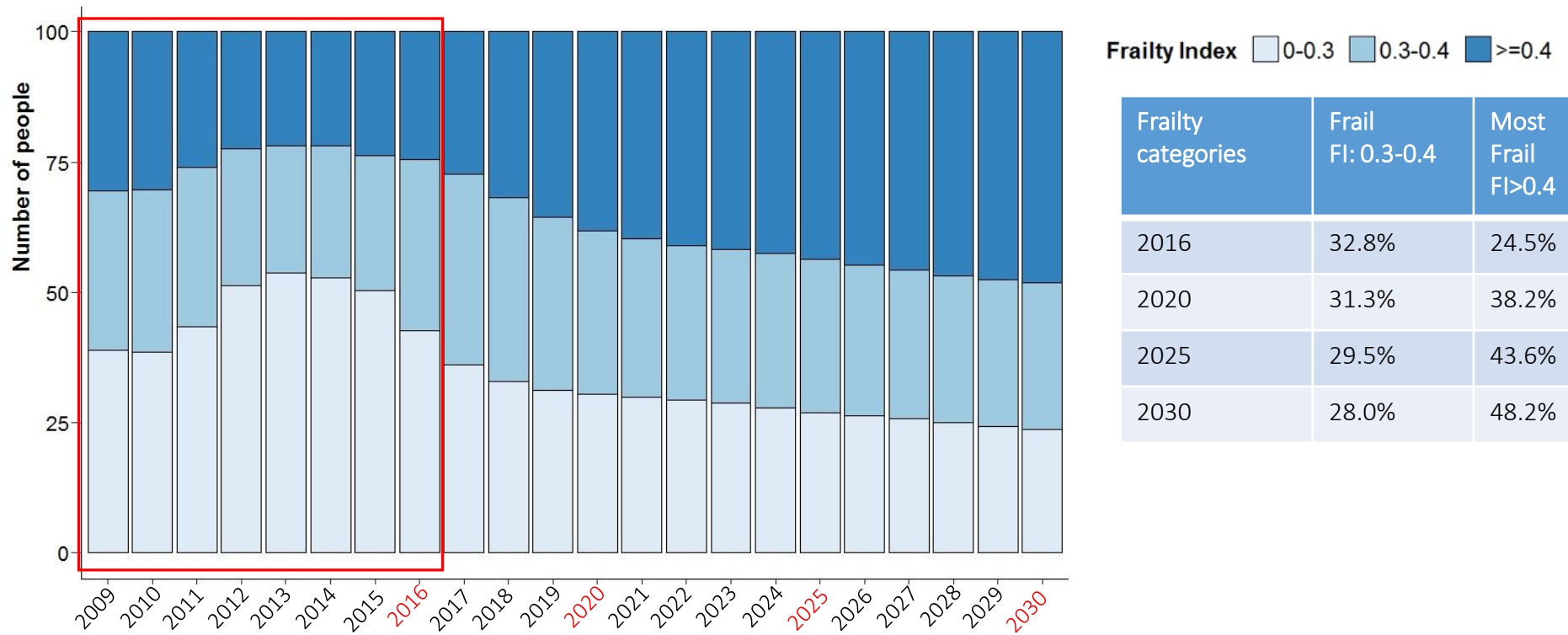


- In the ATHENA cohort, proportion of patients on ART aged ≥ 50 years old will increase from 28% to 73% between 2010 and 2030
- Burden of NCDs mostly driven by larger increases in cardiovascular disease compared with increases in other comorbidities



Smit M, Lancet Infect Dis. 2015 Jul;15(7):810-8.

Observed (red area) and predicted burden of Frailty in HIV-infected patients between 2009 and 2030 as simulated by the model



In 15 years time the most frail HIV population will increase from 24% to 48%

Multiple Mechanisms of Brain Injury

- **Comorbidities**

- Vascular disease
- Metabolic syndrome
- Frailty and sarcopenia
- Anemia and iron metabolism
- Other neurodegenerative diseases

- **Cellular senescence**

- Immune senescence
- Telomere length

- **Neuronal vulnerability**

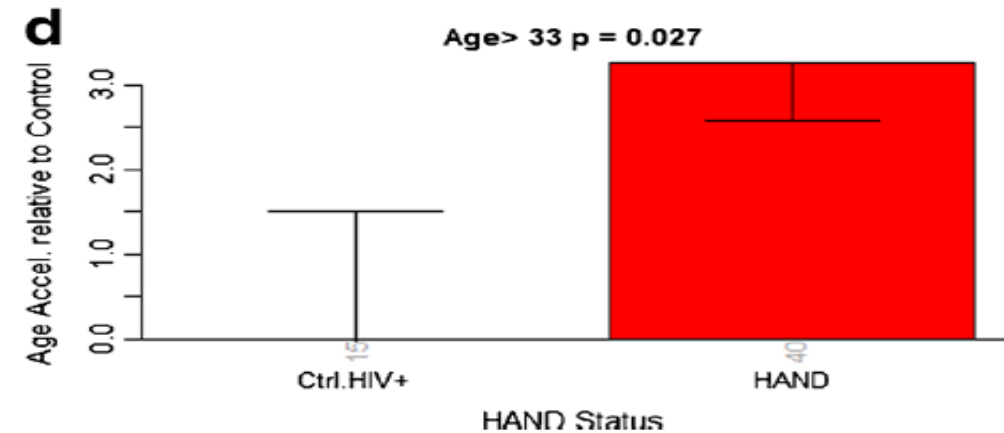
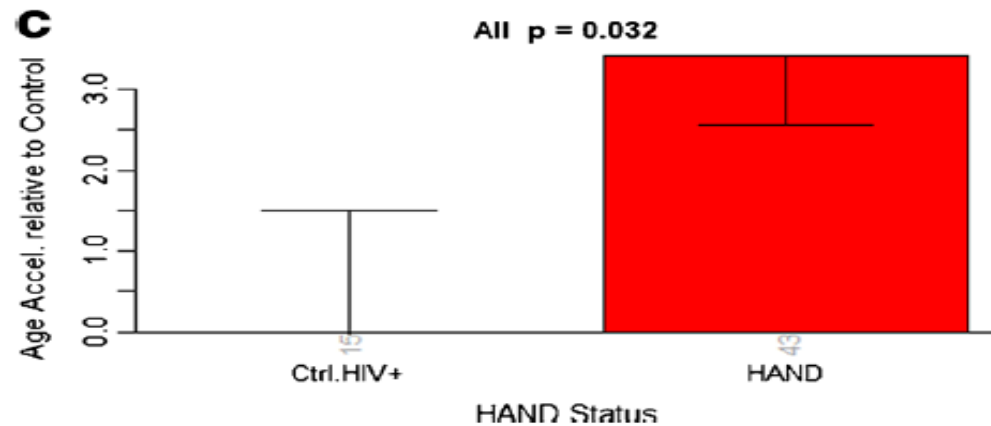
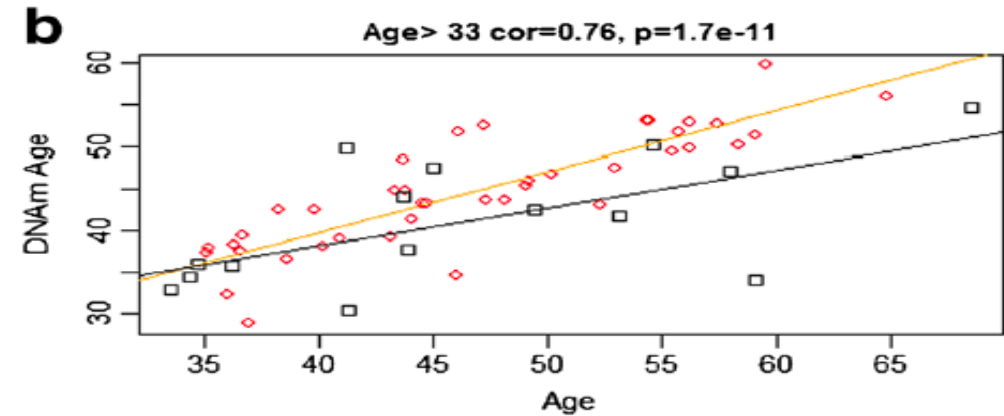
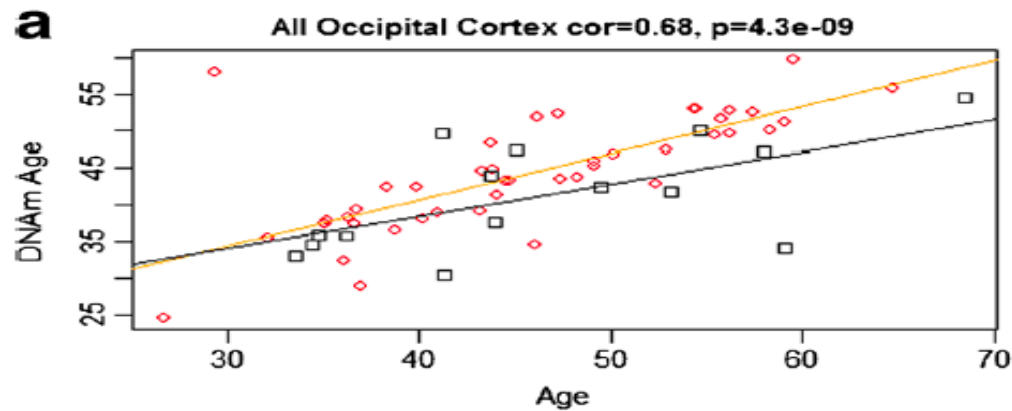
- Mitochondria and oxidative stress

- **Polypharmacy and Drug interactions**

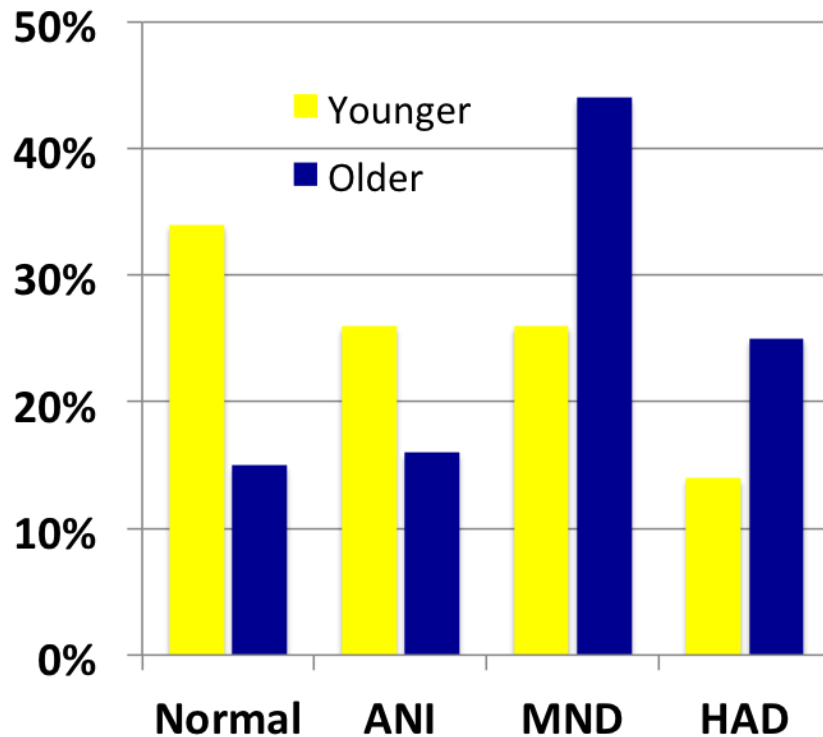
- **Drug metabolism and distribution**

- Reduced elimination
- Reduced drug binding proteins
- Altered blood-brain barrier permeability and molecular drug transporter functioning

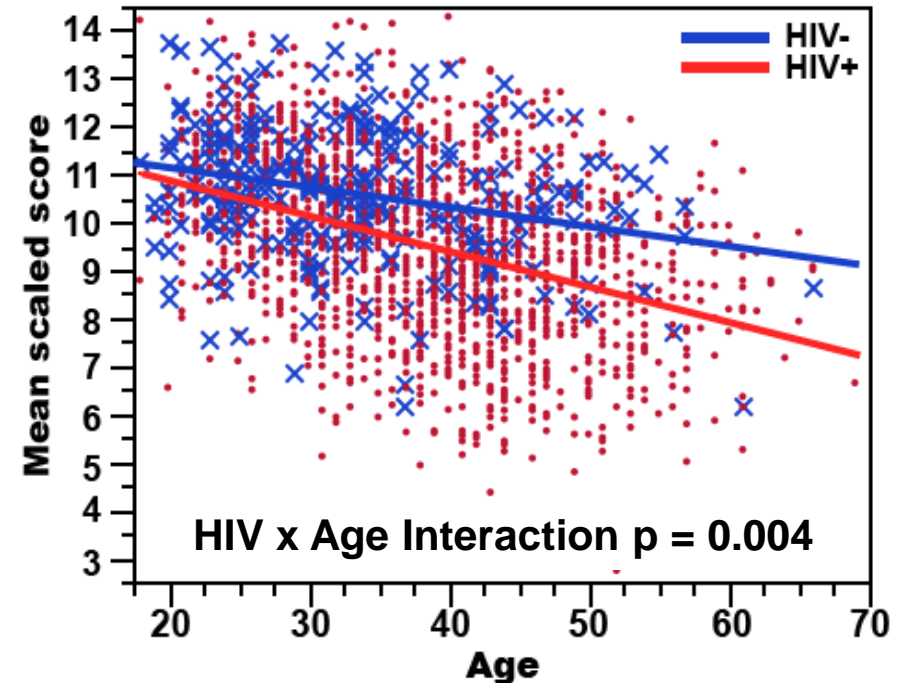
HIV may Accelerate Aging to a Greater Extent in the Brain



HIV May Cause Premature Neurocognitive Decline



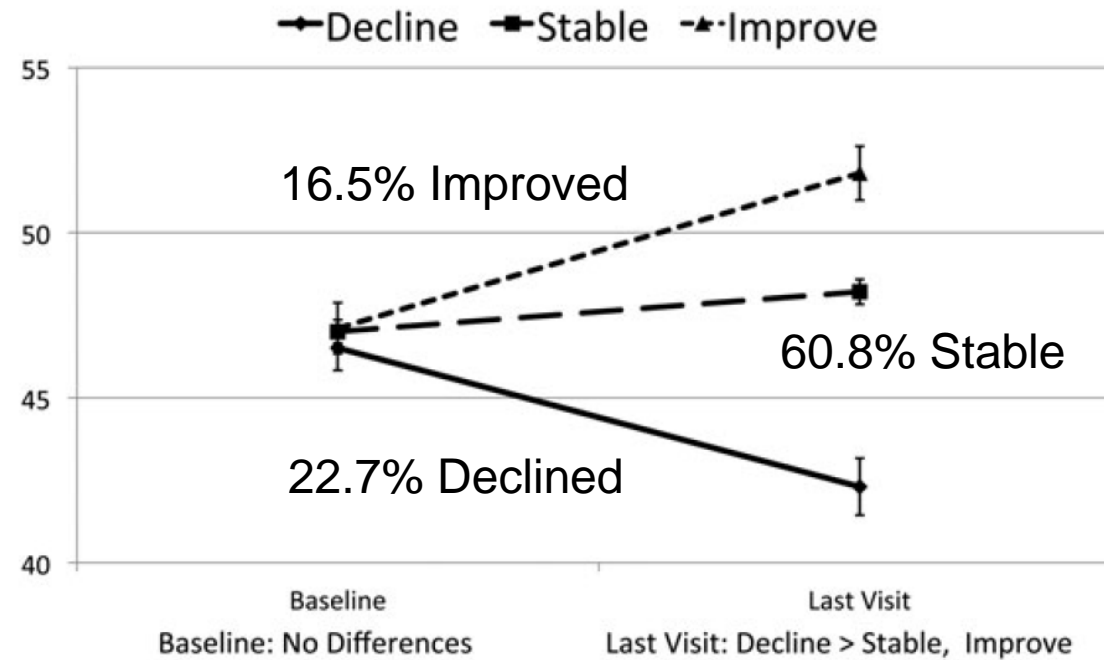
*Modified from Valcour et al,
Neurology 2004;63:822–827*



*Heaton et al, J Neurovirology,
2012, 18(Suppl 1): S46*

Neurocognitive Change in the Era of HIV Combination Antiretroviral Therapy: The Longitudinal CHARTER Study

- Analyzed incidence and predictors of neurocognitive change over mean 35 months in 436 HIV+ adults who were assessed every 6 months



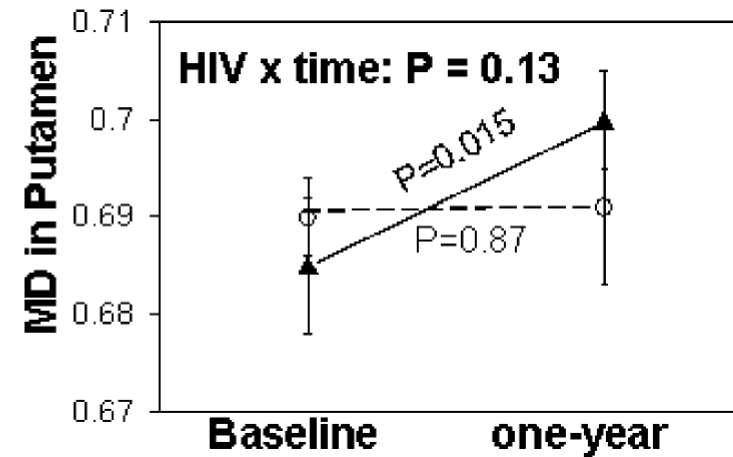
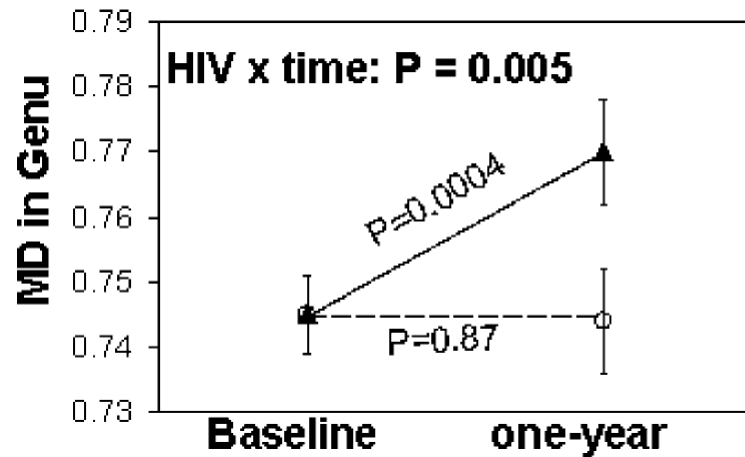
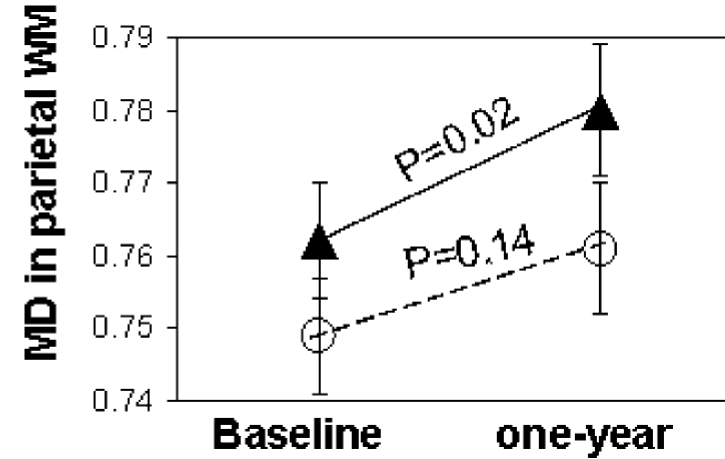
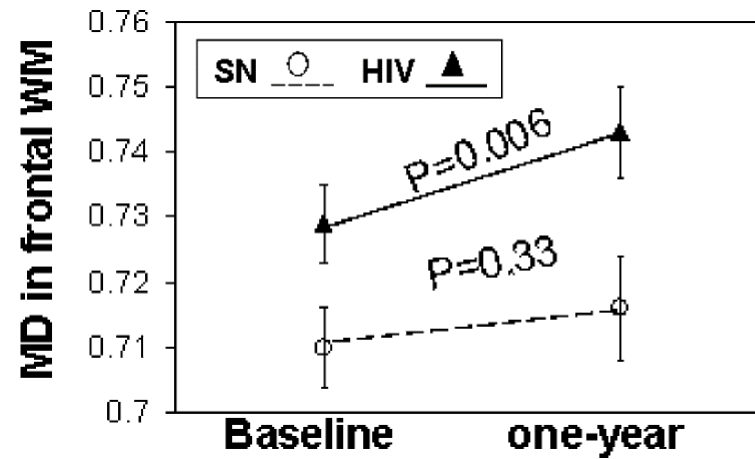
	Decline			Improvement	
	Risk	RR		Risk	RR
Sex	Female	1.76*	Sex	-	-
Ethnicity¹	Hispanic	2.35**	Education	Higher [†]	1.10
ART Use¹	Off ART	1.91**	Est. IQ Before HIV¹	Higher [†]	1.02*
Current CD4 Count	Lower [†]	1.14**	HIV RNA in CSF	Lower [†]	1.47*
HIV RNA in Plasma	Higher [†]	1.26**	HIV RNA in Plasma	Lower [†]	1.27*
Serum Albumin¹	Lower [†]	2.36***	Serum Total Protein¹	Lower [†]	1.96***
Hematocrit¹	Lower [†]	1.10***	Hematocrit	Higher [†]	1.06*
Neuropsychiatric Comorbidities¹	Severe	2.47**	Serum Hepatic AST¹	Lower [†]	1.01*
Lifetime Methamphetamine Diagnosis¹	Present	1.81*	Lifetime Substance Use Diagnosis	Absent	1.63
Beck Depression Inventory¹	Higher [†]	1.03	Lifetime Major Depression Disorder¹	Absent	1.63*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$

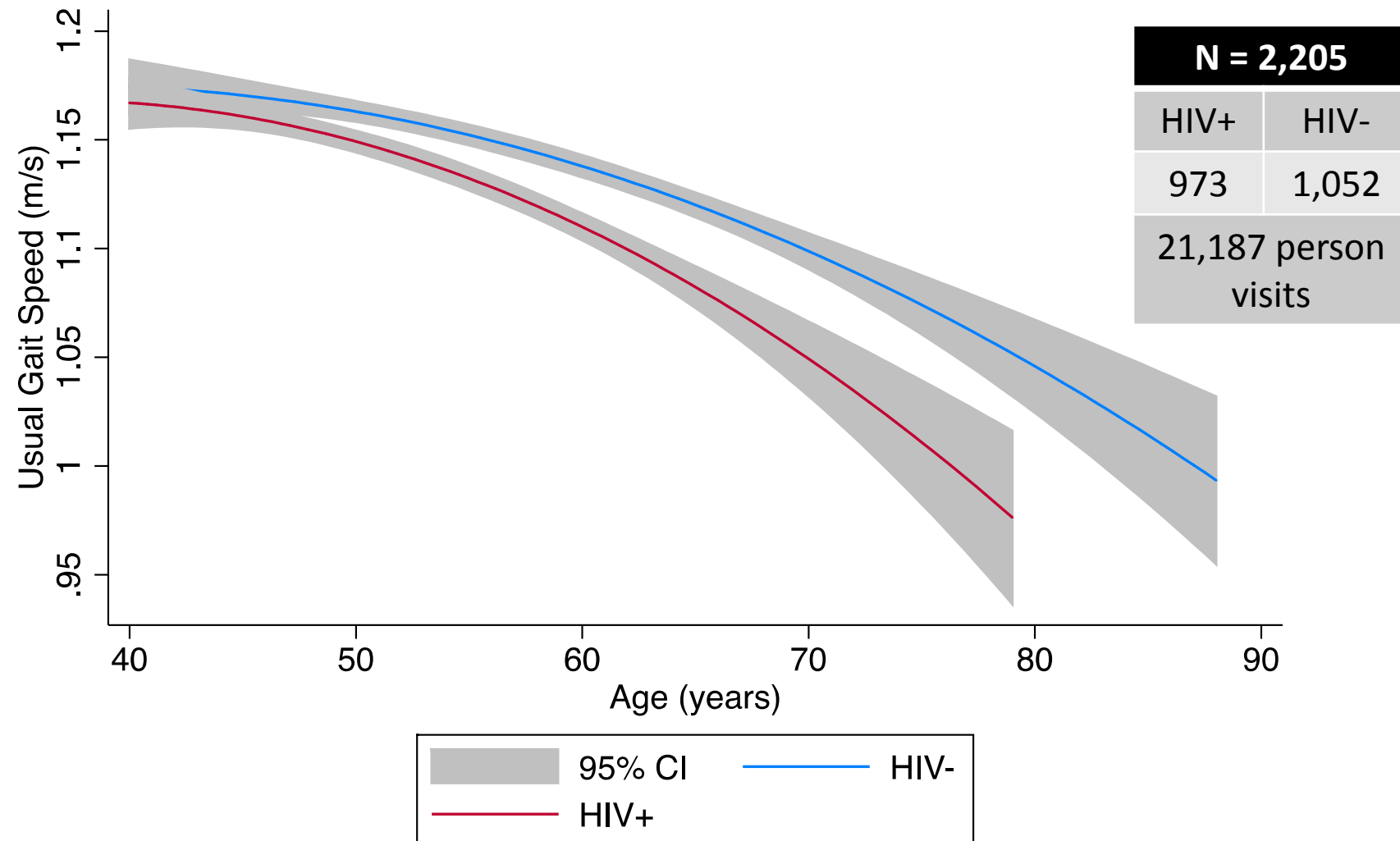
[†]CD4: per 100 cells; HIV RNA: per 1 \log_{10} c/mL; Albumin, Hematocrit, Total Protein, AST: Per 1 "unit"; Beck Depression: Per 1 unit; IQ: Per 1 unit; Education: Per year; Hepatic AST: Per 1 mg/dL; Total Protein: Per 1 g/dL

¹Included in the final multivariable model (in red)

HIV May Accelerate White Matter Injury in the Brain



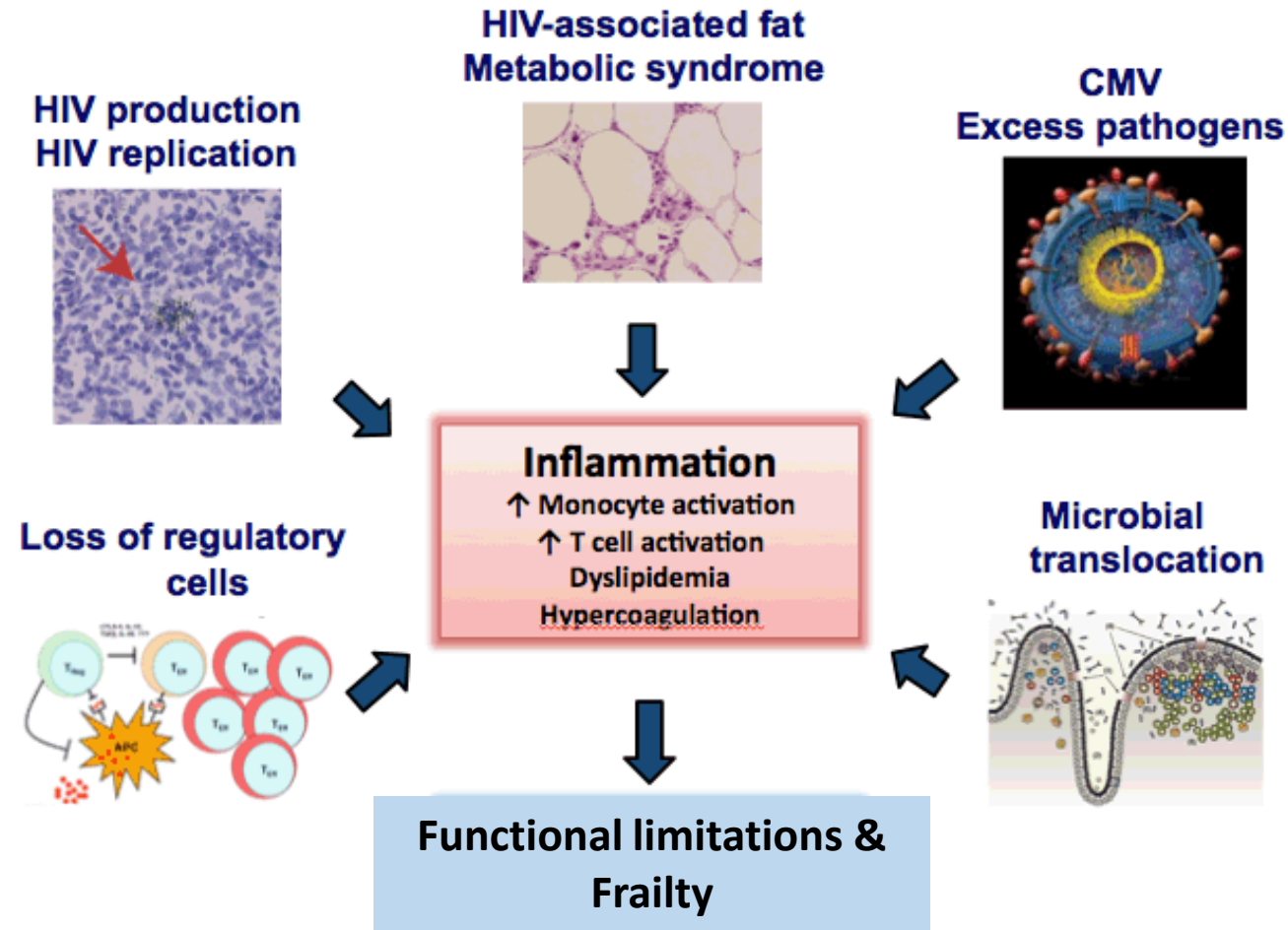
Gait speed declines faster in HIV men



C. Jankowski

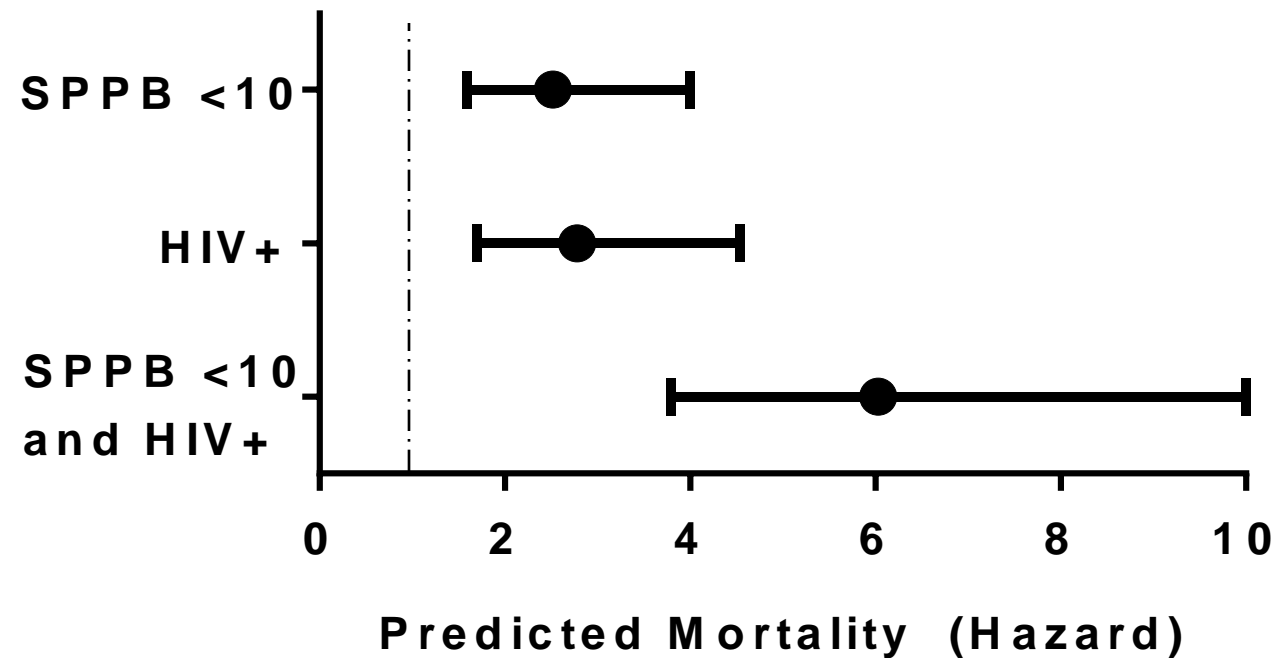
Schrack J, et al. *JAIDS* 2015.

What Contributes to Frailty or Physical Performance Limitations?



HIV and Physical Function Impairment Have Synergistic Effects on Mortality

- 12,270 person-visits (N=1627) ALIVE participants (30% with HIV)



Age-adjusted Odds of Frailty in Women

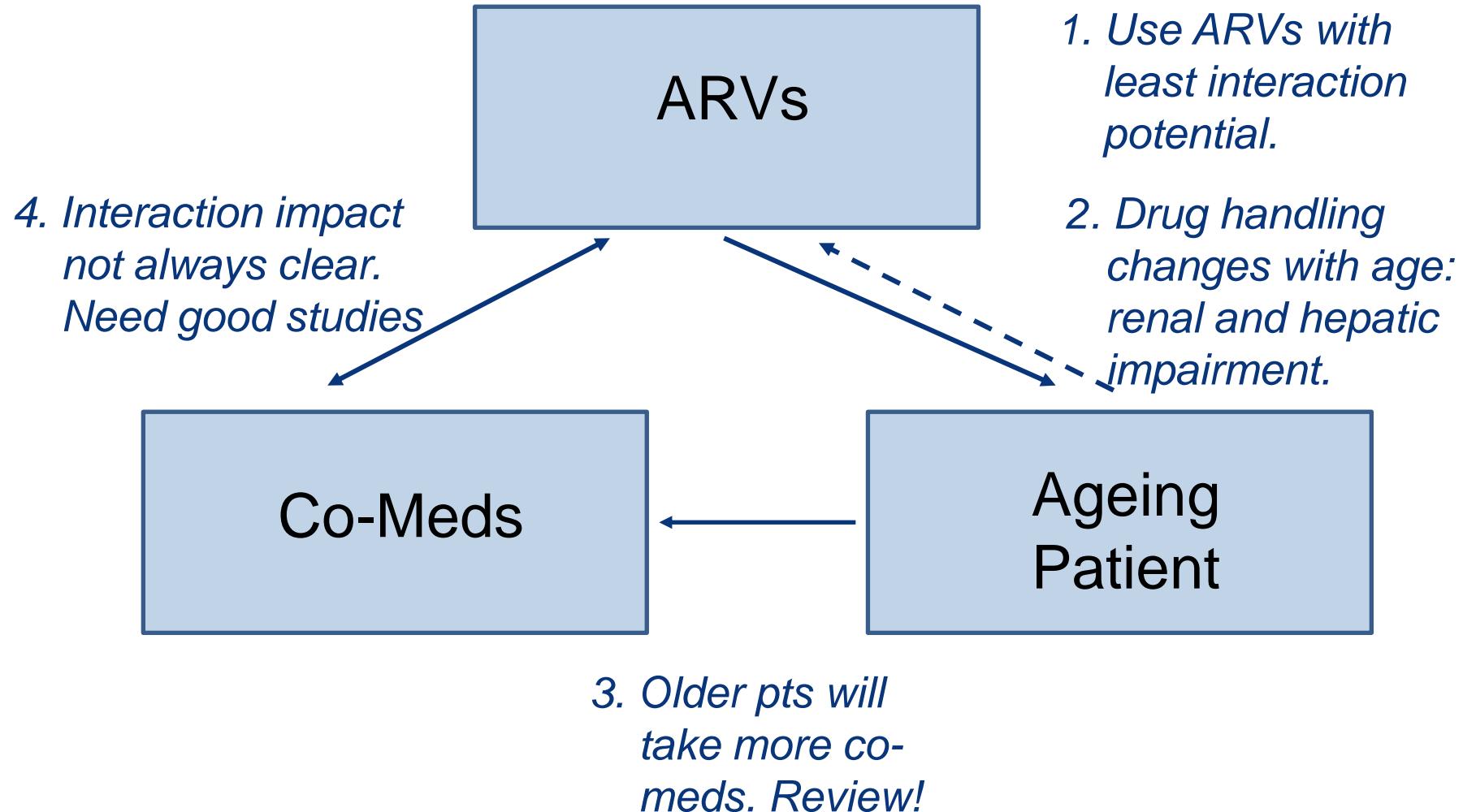
Variable	OR [95% CI]
HIV status, cells/mm ³	
Negative	Reference
Positive, CD4 ≥ 500	1.14 [0.79, 1.64]
Positive, CD4 200-499	1.64 [1.16, 2.32]
Positive, CD4 < 200	2.63 [1.74, 3.99]
Smoking, current/former	1.78 [1.29, 2.45]
Income < USD\$12,000	1.92 [1.48, 2.49]
IV drug use	1.63 [1.23, 2.16]
BMI (kg/m ²)	0.91 [0.70, 1.18]

1. HIV+ women more likely to be frail, independent of age
2. Association between frailty and degree of immunosuppression

Multivariate Logistic Regression Models: Frailty ≥ 3

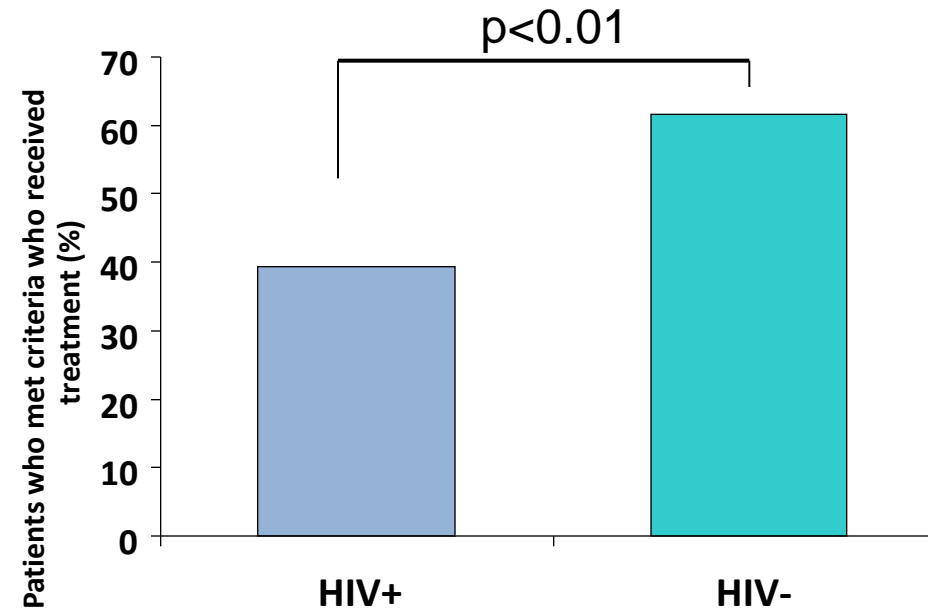
Variable	HIV, Age	+ Demographics	+ Chronic Disease	Combined
HIV & CD4 count				
Negative	Reference			
Positive, CD4 ≥ 500	1.14 [0.79, 1.64]			
Positive, CD4 200-499	1.64 [1.16, 2.32]			
Positive, CD4 < 200	2.63 [1.74, 3.99]	2.56 [1.67, 3.94]	2.08 [1.33, 3.28]	2.07 [1.29, 3.31]
Age				
< 30	Reference			
30-39	2.48 [1.21, 5.09]	2.32 [1.12, 4.79]	2.23 [1.08, 4.60]	2.13 [1.02, 4.43]
40-49	4.53 [2.25, 9.11]	3.54 [1.74, 7.18]	3.53 [1.74, 7.18]	2.86 [1.39, 5.88]
50+	8.72 [4.29, 17.73]	6.38 [3.10, 13.10]	4.84 [2.29, 10.21]	3.71 [1.74, 7.92]
Hypertension			1.61 [1.22, 2.13]	1.67 [1.25, 2.23]
FIB4 > 3.25			2.49 [1.55, 4.00]	2.27 [1.39, 3.69]
eGFR 30-44.9 ml/min			3.70 [1.42, 9.61]	3.74 [1.37, 10.22]

ARVs, Ageing Patients and Co-meds



Are HIV Specialists treating Co-Morbidities?

- US study explored use of lipid-lowering therapy in HIV+ or HIV- veterans:
 - HIV+, n=926; HIV-, n=651
 - NCEP/ATP III factor criteria guidelines used to assess need for lipid-lowering therapy



- Receipt of therapy lower in HIV+ vs. HIV- patients (39% vs. 61%)

Multimorbidity, Polypharmacy, and ART Use in HIV+ Pts 75 Yrs of Age or Older

- GEPPPO: prospective cohort study of geriatric HIV+ pts older than 65 yrs of age with matched group of HIV- pts
- Current cross-sectional analysis assessed polypharmacy, multimorbidity, and ART use by HIV status in pts 75 yrs of age or older (N = 492; HIV+: n = 292; HIV-: n = 200)
 - HIV+ pts stratified by duration of HIV infection
 - < 10 yrs, 10-20 yrs, > 20 yrs
 - Multimorbidity: ≥ 3 comorbidities (not due to infection)
 - Polypharmacy: ≥ 5 medications (excluding ART)

HIV+ > 20 Yrs Major Driver of Multimorbidity and Polypharmacy

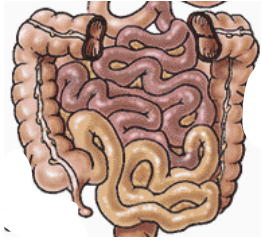
- 35.3% of HIV+ pts on low-drug ART regimens
 - Dual therapy: 28.7%
 - Monotherapy: 6.6%
- 56.4% of HIV+ pts on NRTI-sparing regimens; 59.3% on booster-free regimens
- Statins prescribed more often in HIV+ vs HIV- pts (47.6% vs 22.3%), benzodiazepines prescribed less often (3.5% vs 18.4%)

Significant Predictors of Outcomes*	OR (95% CI)	P Value
Multimorbidity:		
▪ Male vs female	2.06 (1.12-3.793)	.02
▪ HIV+ > 20 yrs	2.31 (1.05-5.435)	.044
Polypharmacy:		
▪ HIV+ < 10 yrs	1.99 (0.989-4.011)	.05
▪ HIV+ > 20 yrs	2.36 (1.224-4.612)	.01
Dual/Mono ART Regimen:		
▪ Polypharmacy	3.09 (1.328-7.502)	.01

*Multivariate logistic regression.

Should we be concerned about age and drug pharmacokinetics?

Absorption



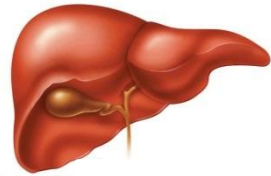
Increased gastric pH and decreased small bowel surface area may lead to a ***higher inter individual variability in drug exposure.***
[1]

Distribution



Increase in body fat with older age increases V_d of some drugs and may increase the $t_{1/2}$. ***Greater drug accumulation and increased risk of toxicity*** are possible.

Metabolism



Reduced liver volume and blood flow with reduced enzyme activity can give ***decreased drug clearance.*** Also altered transporters.
Hepatic Impairment.

Renal elimination



GFR may decrease as much as 50% with increasing age, which can affect renal elimination of some drugs. Clinical consequence (***toxicity***) depends on the extent of renal elimination.

Interaction Potential of ARVs

Higher potential	Moderate Potential	Lower Potential
Boosted PIs <u>Perpetrators</u> – enzyme and transporter Inhibition <u>Victim</u> - absorption (ATV); induction	Rilpivirine <u>Victim</u> of enzyme inhibition and induction. Also absorption.	Raltegravir <u>Victim</u> of few induction and absorption interactions
EVG/cobi <u>Perpetrator</u> – enzyme and transporter inhibition <u>Victim</u> - absorption; induction	(Maraviroc) <u>Victim</u> of enzyme inhibition and induction.	Most NRTIs <u>Victim</u> of transporter mediated interactions.
Efavirenz, (Nevirapine, Etravirine) <u>Perpetrators</u> – enzyme and transporter induction		<div>← TDF & TAF</div> Dolutegravir <u>Victim</u> of enzyme induction and absorption interactions <u>Perpetrator</u> of renal interaction

Check for DDIs between HCV and HIV drugs!

- **Drug interactions**
 - http://www.drugs.com/drug_interactions.html
 - <http://www.medscape.com/druginfo/druginterchecker>
 - <http://www.drugstore.com/pharmacy/drugchecker/>
 - <http://drugchecker.aol.com>
 - <http://hcvdruginfo.ca>
- **List of CYP substrates, inhibitors, inducers**
 - <http://medicine.iupui.edu/clinpharm/ddls>
- **HIV drug interactions**
 - <http://www.hiv-druginteractions.org>
 - <http://www.hep-druginteractions.org>



J. Rockstroh

Khoo S. 15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, May 2014 [oral presentation].

CYP, cytochrome



Low potential for drug–drug interactions with some HCV DAA and HIV antiretrovirals

		SOF	SOF/LDV	SOF/VEL	3D	GZR/EBR	DCV	SIM
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir	◆	■	■	◆	◆	◆	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	■	●
	Etravirine	◆	◆	●	●	●	■	●
	Nevirapine	◆	◆	●	●	●	■	●
	Rilpivirine	◆	◆*	◆*	■	◆	◆	◆
Protease inhibitors	Atazanavir; atazanavir/r; atazanavir/cobicistat	◆	◆*	◆*	■†	●	■	●
	Darunavir/r; darunavir/cobicistat	◆	◆*	◆*	■†	●	◆	●
	Lopinavir/r	◆	◆*	◆*	●	●	◆	●
Entry/integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	◆	■*	■*	●	●	■	●
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	◆	◆	◆	●	●	■	●
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

◆ No clinically significant interaction expected.
 ■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.
 ● These drugs should not be co-administered.

Regularly updated Information on DDIs can be found at:
<http://www.hep-druginteractions.org>

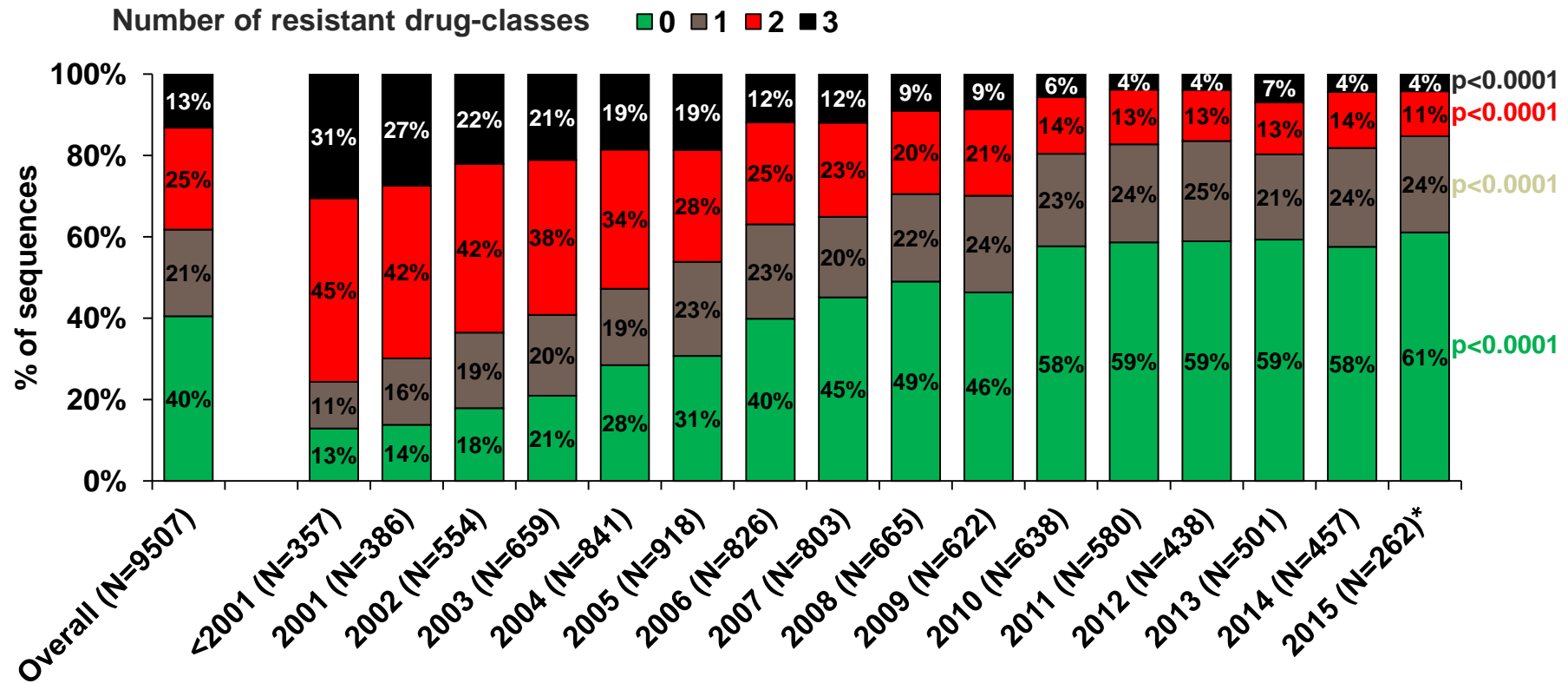
J. Rockstroh

EASL Recommendations on treatment of hepatitis C. Available at:
<http://www.easl.eu/medias/cpg/HCV2016/English-report.pdf> (accessed September 2016)

DDI: drug–drug interaction; NNRTI: non-nucleoside reverse transcriptase inhibitor;
 NRTI: nucleoside reverse transcriptase inhibitor

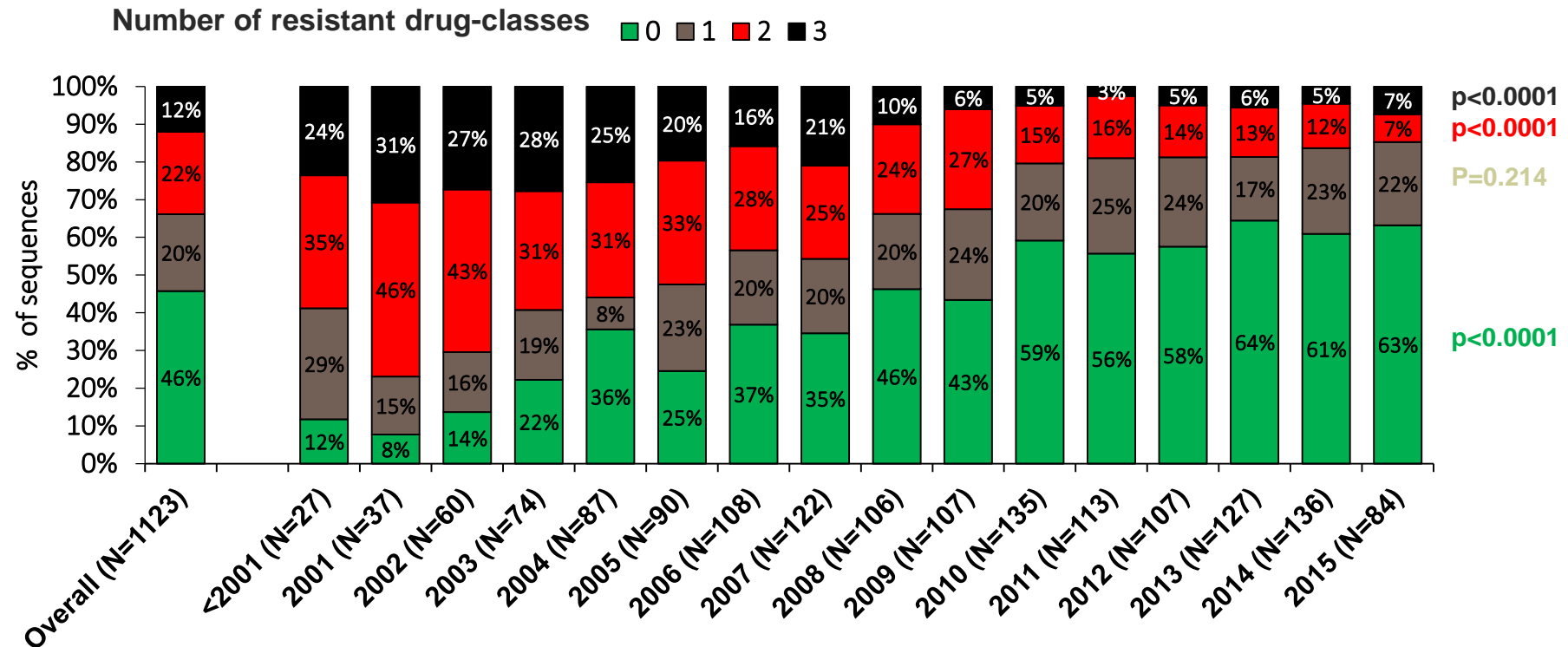


The prevalence of resistance to 3 classes significantly decreased over the years, from 30.5% before 2001 to 4.2% in 2015, while the prevalence of sequences without resistance significantly increased from 12.9% before 2001 to 61.1% in 2015.



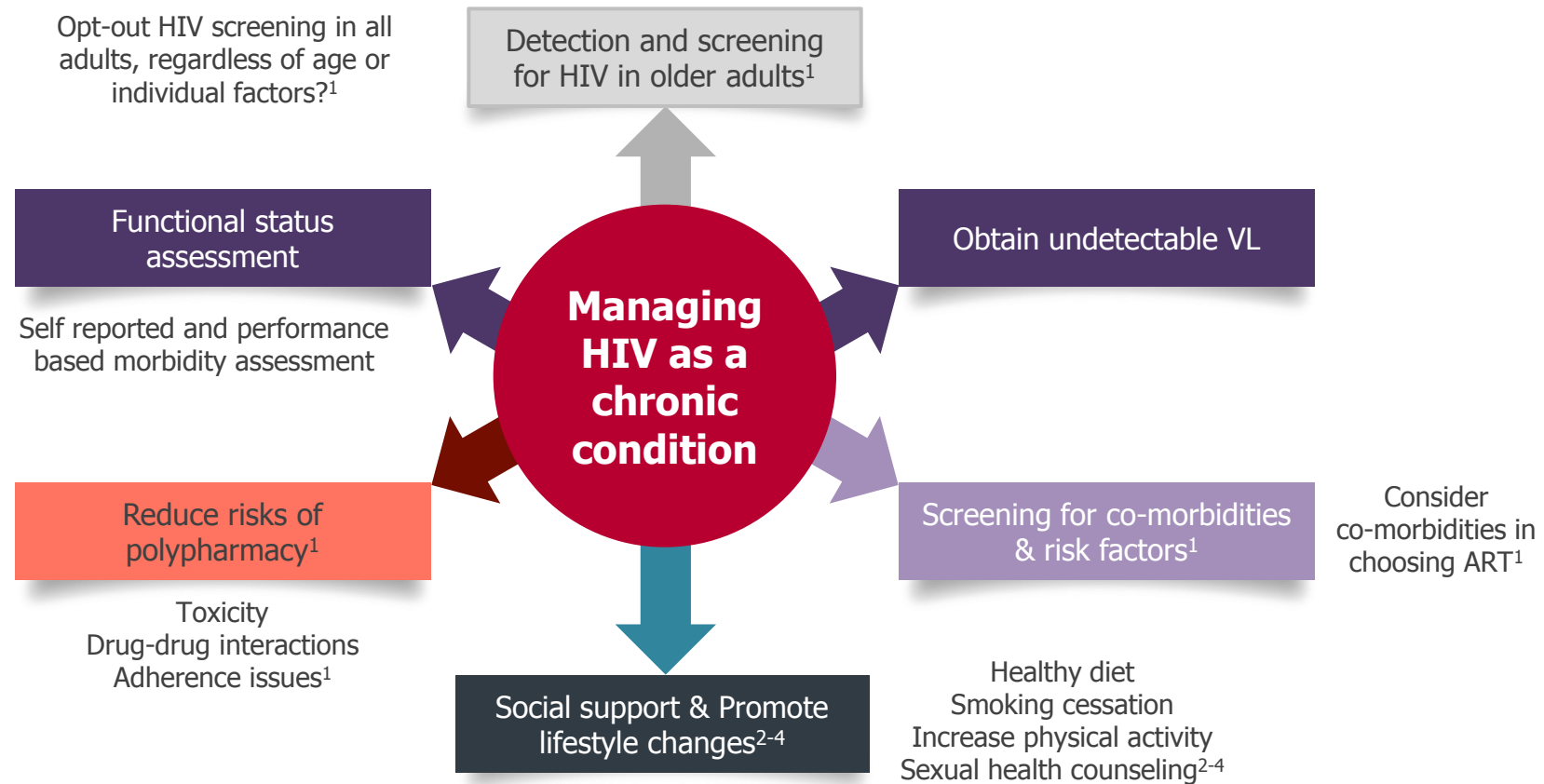
Analysis performed on 9,507 sequences of treated HIV-1 infected patients from protease and reverse transcriptase genes. P-values by Chi-squared test for trend. *Update July 2015.

A similar trend of class resistance prevalence was observed in sequences from patients older than 50 year with the exception of 1 class resistance which is stable over time



Analysis performed on 1123 sequences of treated HIV-1 infected patients (age >50 years) from protease and reverse transcriptase genes. P-values by Chi-squared test for trend. *Update July 2015.

How to manage HIV as a chronic condition



*if plasma HIV RNA levels > 50,000 copies/ml, greater than 100-point decline in CD4 count in prior 12 months, or risk factors for CVD.

Aging and HIV: Some final considerations

- Sexual activity has no age limits
- The “grey generation” goes for a 2nd round
- Older patients don’t feel at risk
- Elderly patients show up later
- HCW are less prone to discuss sexual activity with older patients.
- HIV testing is not part of regular screening in elderly
- Symptoms are initially attributed to other diseases, both by patients and HCW



As time goes by....

- HIV is the major driver of M&M, but other bugs are also involved
- Immunosenescence strongly correlated with inflammation
- Aging does not necessarily equal frailty
- Frailty is the pathway to disability, but not all those with frailty are disabled
- But frailty is correlated with mortality
- HIV may accelerate and/or accentuate aging
- Being old is bad
- Having HIV infection is bad
- Being old and HIV+ is certainly worst !!!
- Exercise, diet, lifestyle changes should be reinforced at each visit

Take home message

- Comorbidities are the prevalent clinical picture of contemporary HIV disease
- The association of comorbidities into complex multi-morbidity pictures describe patient complexity
- When Multi-morbidity is the norm, frailty and disability turn to be relevant clinical outcomes and allows patient risk stratification beyond the CD4 and HIV VL assessment
- **Total patient care** allows to integrate the need for reaching un-detectability with the need to take care of comorbidities.

The new target

90-90-90-90-90

90% diagnosed


90% on treatment

90% virally suppressed

90% fit at 90 years



Thank you....
...and stay fit!

- 
- “No es cierto que la gente deje de perseguir sus sueños por envejecer. Envejecen porque dejan de perseguir sus sueños”.
 - It is not true that people stop pursuing dreams because they grow old, they grow old because they stop pursuing dreams.”

Gabriel García Marquez

The real drama of aging for Ventura....



Acknowledgments

- Omar Sued
- Eugenia Negredo
- And the Aging symposium faculty



"You've got the blood pressure of a teenager – who lives on junk food, TV and the computer."