Neurocognitive impairment and cardiovascular disease

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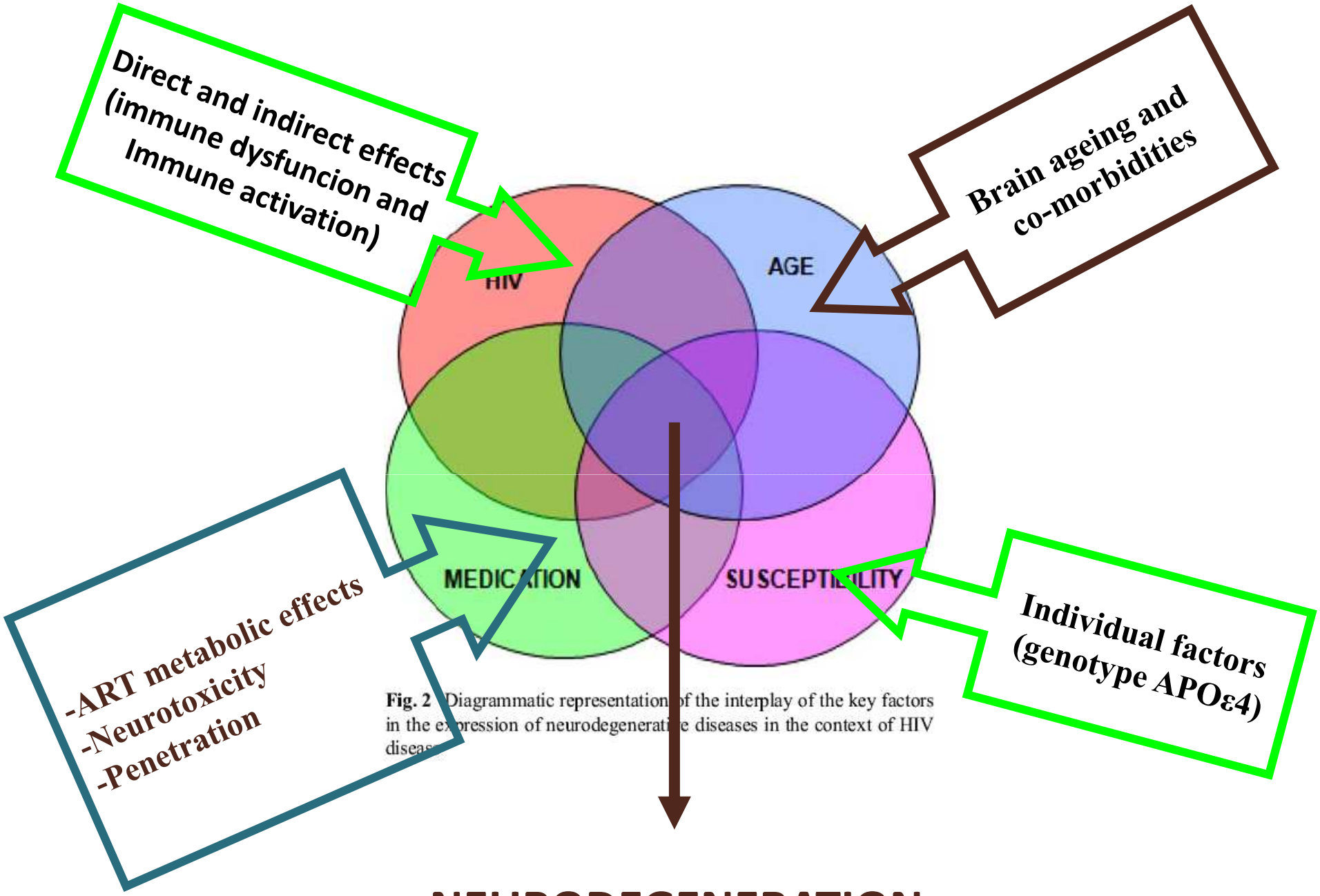
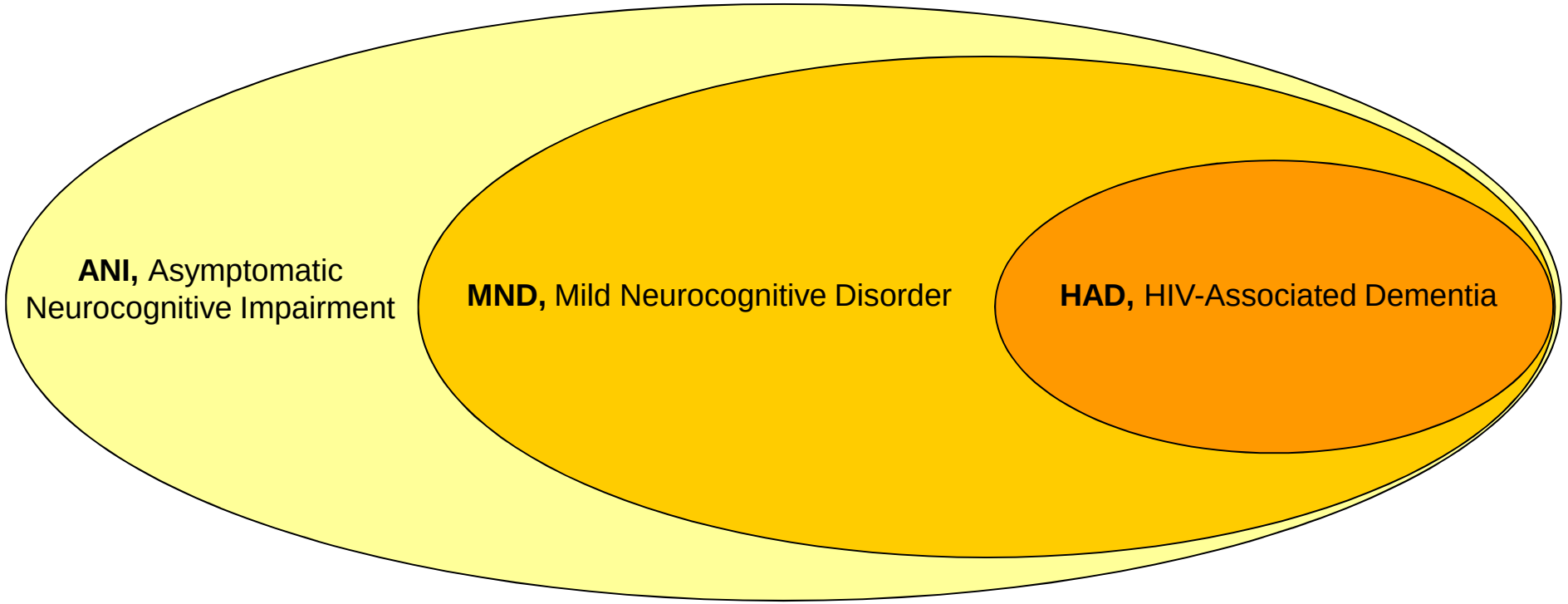


Fig. 2 Diagrammatic representation of the interplay of the key factors in the expression of neurodegenerative diseases in the context of HIV disease

HIV-Associated Neurocognitive Disorders, HAND

Reduction of the performance (<1 SD) involving >=2 cognitive domains



NB: exclusion of other causes of neurocognitive impairment

Updated **RESEARCH** nosology for HIV-associated neurocognitive disorders. Neurology 2007; 69: 1789-99

Outline

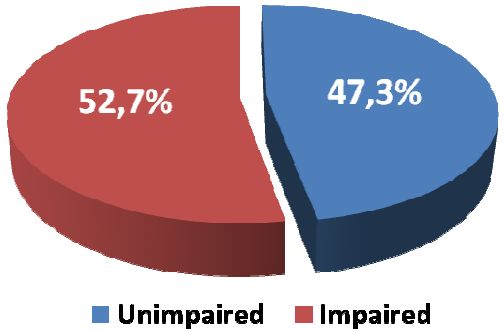
- Evidence linking metabolic abnormalities /atherosclerosis to neurocognitive impairment in HIV+ patients
- (Differences/similarities with the general population)
- Risk factors and pathogenetic mechanisms
- Influence of the type of antiretroviral therapy?
- How to prevent or treat this complication

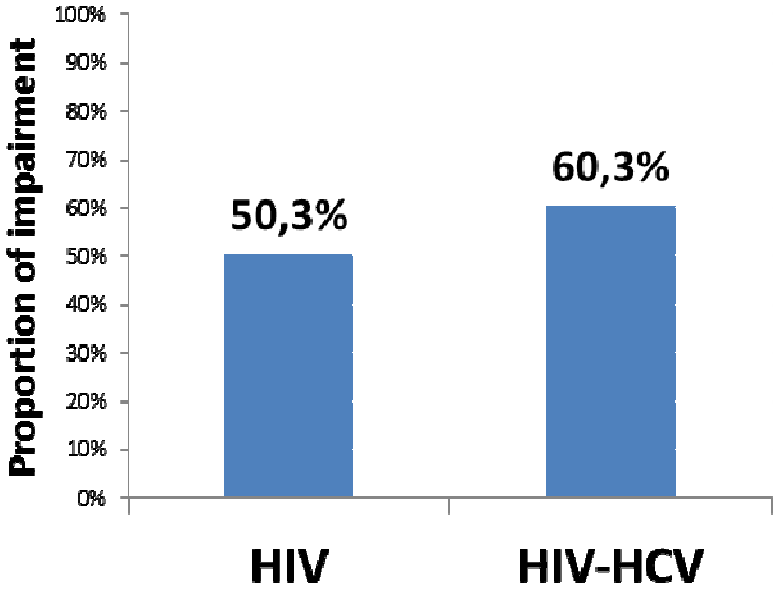
Conditions/disorders associated with neurocognitive impairment (general population)

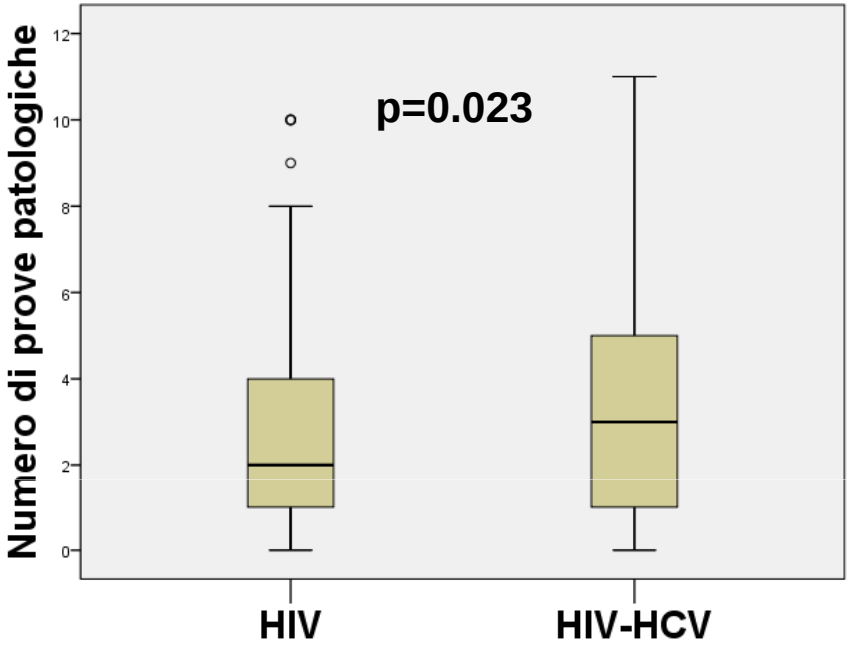
- Dementia (Alzheimer, vascular…)
- Depression, anxiety, psychosis
- Drug abuse and drug dependence (current, previous)
- Alcoholism
- CNS infections or cancers (and their sequelae)
- Cerebrovascular disorders
- Metabolic encephalopathies
- HCV co-infection, decompensated cirrhosis

Prevalence of HAND Coorte UCSC

Total patients (n=245)







Median (IQR) nr impaired tests:

- **HIV** **2 (1 – 4)**
- **HIV-HCV** **3 (1 – 5)**

Fabbiani M et al. HIV Med 2013

Infection (2013) 41:1103–1109
DOI 10.1007/s15010-013-0503-2

CLINICAL AND EPIDEMIOLOGICAL STUDY

Comparison of cognitive performance in HIV or HCV mono-infected and HIV–HCV co-infected patients

N. Ciccarelli · M. Fabbiani · P. Grima · K. Falasca · M. Tana · E. Baldonero · M. Colafigli · M. C. Silveri · J. Vecchiet · R. Cauda · S. Di Giambenedetto

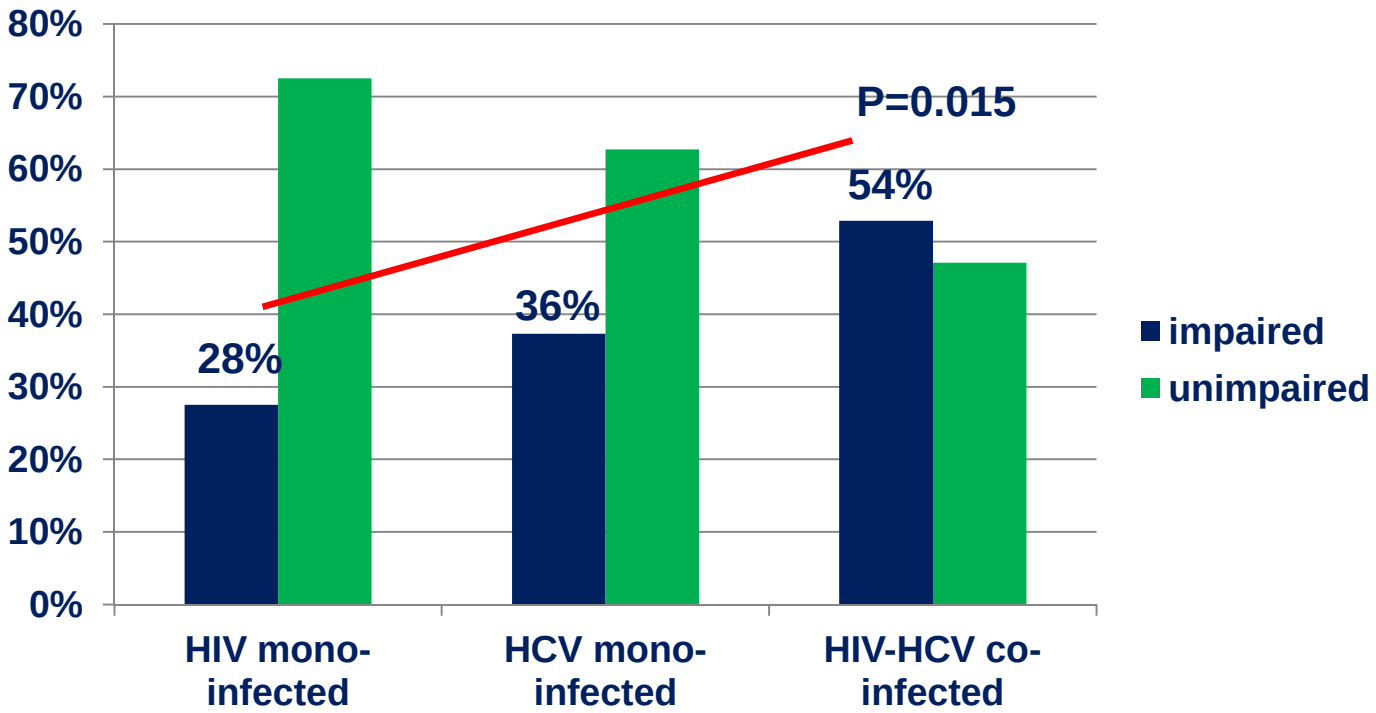
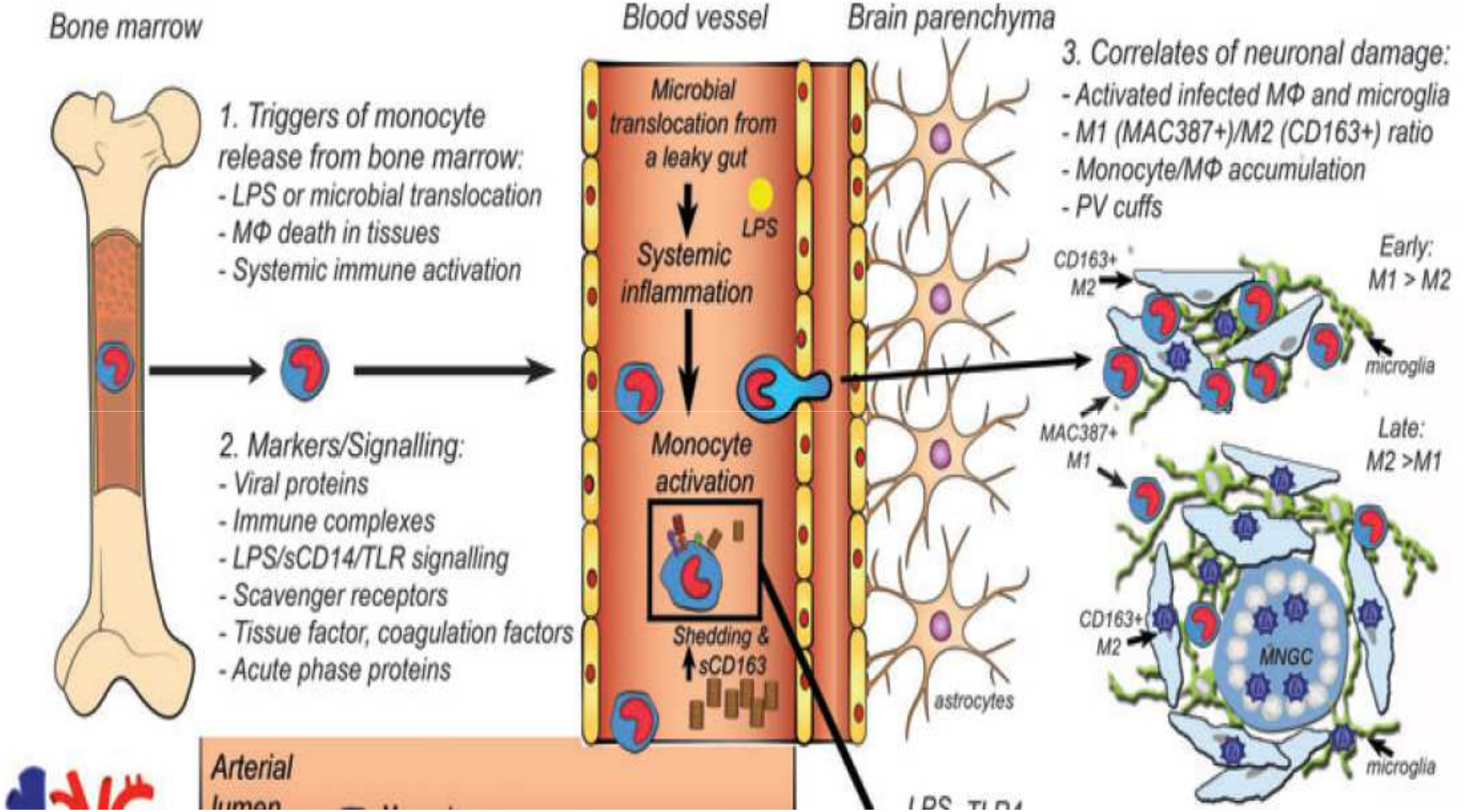


Table 3 Factors associated with cognitive impairment

	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	*p* Value	OR (95 % CI)	*p* Value
Variables explored in the total population				
Sex (male vs. female)	0.86 (0.42–1.77)	0.688		
Age	1.01 (0.97–1.06)	0.544		–
Education (per 1 year more)	0.78 (0.69–0.89)	**<0.001**	0.78 (0.68–0.89)	**<0.001**
Past injection drug users	2.10 (1.07–4.12)	**0.030**	0.83 (0.32–2.14)	0.698
Zung depression scale (per 1 point more)	1.054 (1.02–1.09)	**0.002**	1.05 (1.01–1.08)	**0.017**
Groups				
HIV mono-infected	**1 (ref)**		**1 (ref)**	
HCV mono-infected	1.45 (0.62–3.37)	0.392	1.37 (0.51–3.66)	0.528
HIV–HCV co-infected	3.02 (1.32–6.93)	**0.009**	3.35 (1.07–10.52)	**0.038**
Variables explored in the total HIV population (groups 1 and 3)				
Duration of HIV infection (per 1 year longer)	1.04 (0.98–1.10)	0.166		
Time on antiretroviral therapy (per 1 year longer)	1.03 (0.93–1.13)	0.594		
Past AIDS-defining events	1.79 (0.66–4.90)	0.256		
HIV-RNA <50 copies/mL	1.24 (0.44–3.48)	0.683		
CD4 cells count nadir	0.10 (0.1–1.00)	0.129		
CD4 cells count	0.10 (0.1–1.00)	0.154		
CPE rank ≥6	1.37 (0.49–3.81)	0.543		
Variables explored in the total HCV population (groups 2 and 3)				
Duration of HCV infection	1.07 (0.98–1.16)	0.124		
HCV-RNA (log_{10}UI/L)	1.255 (0.88–1.78)	0.205		


Bone marrow
Blood vessel
Brain parenchyma
1. Triggers of monocyte release from bone marrow:
- LPS or microbial translocation
- MΦ death in tissues
- Systemic immune activation
2. Markers/Signalling:
- Viral proteins
- Immune complexes
- LPS/sCD14/TLR signalling
- Scavenger receptors
- Tissue factor, coagulation factors
- Acute phase proteins
Microbial translocation from a leaky gut
LPS
Systemic inflammation
Monocyte activation
Shedding & sCD163
astrocytes
Arterial
3. Correlates of neuronal damage:
- Activated infected MΦ and microglia
- M1 (MAC387+)/M2 (CD163+) ratio
- Monocyte/MΦ accumulation
- PV cuffs
CD163+
M2
Early:
M1 > M2
microglia
MAC387+
M1
Late:
M2 >M1
CD163+
M2
MNGC
microglia

Monocytes/macrophages (M/M) activation markers

- CD16 is a surface markers implicated in BBB transmigration:
  - Three phenotypes can be distinguished on the basis of CD14 and CD16 expression:
    - **Classic** CD14++CD16-
    - **Intermediate** CD14++CD16+
    - **Nonclassic** CD14+CD16++
  - HIV infection is associated with an increase in Intermediate and Nonclassic phenotypes
  - CD16 is expressed in activated monocytes
  - CD16+ cells express higher levels of cell migration markers (e.g. CXCR5, CX3CR1)
- CD163 is a haptoglobin-haemoglobin scavenger receptor expressed by M/M
  - Cleaved by proinflammatory stimuli and released as soluble receptor (sCD163)
- CD11b is a surface marker indicating a high tissue migratory property
- HLADR, CD38, CD69 are other markers implicated in M/M activation

M/M activation markers and cognitive impairment

- sCD14:
  - elevated in plasma and CSF samples
- sCD163:
  - elevated plasma and CSF samples
- Most data are from patients with HIV-RNA >50 copies/mL
- Most studies are cross sectional
- Paucity of data on specific M/M phenotypes involved in immune activation

Cognitive disorders in HIV-infected patients: are they HIV-related?

Fabrice Bonnet[a,b,c], Hélène Amieva[a], Fabienne Marquant[a,b], Charlotte Bernard[d,e], Mathias Bruyand[a,b], Frédéric-Antoine Dauchy[b,f], Patrick Mercié[a,b,c], Carine Greib[g], Laura Richert[a], Didier Neau[f], Gwenaelle Catheline[d], Patrick Dehail[b,h], Francois Dabis[a,b], Philippe Morlat[a,b,c], Jean-François Dartigues[a], Geneviève Chêne[a,b], for the ANRS CO3 Aquitaine Cohort

Objectives: Large unselected studies on representative samples of HIV-infected patients with a whole battery of neuropsychological tests and cerebral MRI scan are required to assess the frequency of neurocognitive impairment (NCI), the determinants of mild neurocognitive disorders (MNDs), or HIV-associated dementia (HAD) and the relationship between NCI and MRI scan findings.

Methods: Investigation of 400 consecutively enrolled HIV-1-infected adults from the ANRS CO3 Aquitaine Cohort, using standardized neurocognitive tests chosen to achieve consistency with Frascati's criteria. Half of the patients had a cerebral MRI scan allowing gray and white matter volume measurement. Factors associated with NCI were studied by logistic regression models.

Results: Median age of participants was 47 years, 79% were male and 89% received combination antiretroviral treatment (cART), of whom 93% had plasma HIV RNA below 500 copies/ml. Median CD4 cell count was 515 cells/μl. Prevalence of NCI was 59%, including 21% of asymptomatic NCI, 31% of MND, and 7% of HAD. A low level of education, prior neurologic AIDS-defining disorders event, anxiety, depressive symptoms, and prior history of brain damage were independently associated with MND or HAD, but neither HIV nor cART-related variables. The presence of NCI was significantly associated with lower gray matter fraction.

Interpretation: In this large unselected cohort, a high prevalence of symptomatic neurocognitive disorders was mainly related to its traditional determinants and associated with gray matter atrophy at early stages of the disease.

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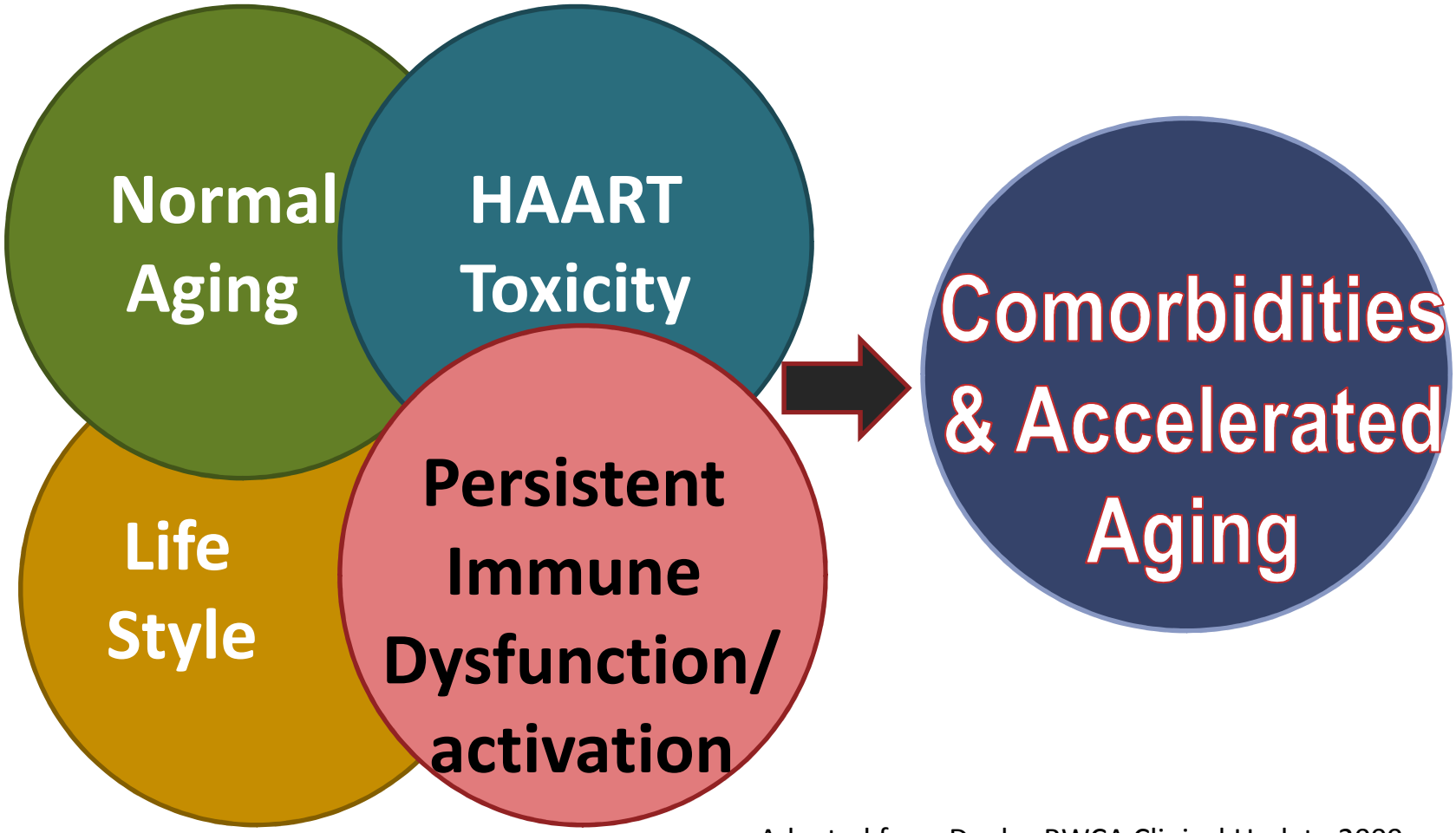
AIDS 2013, **27**:391–400

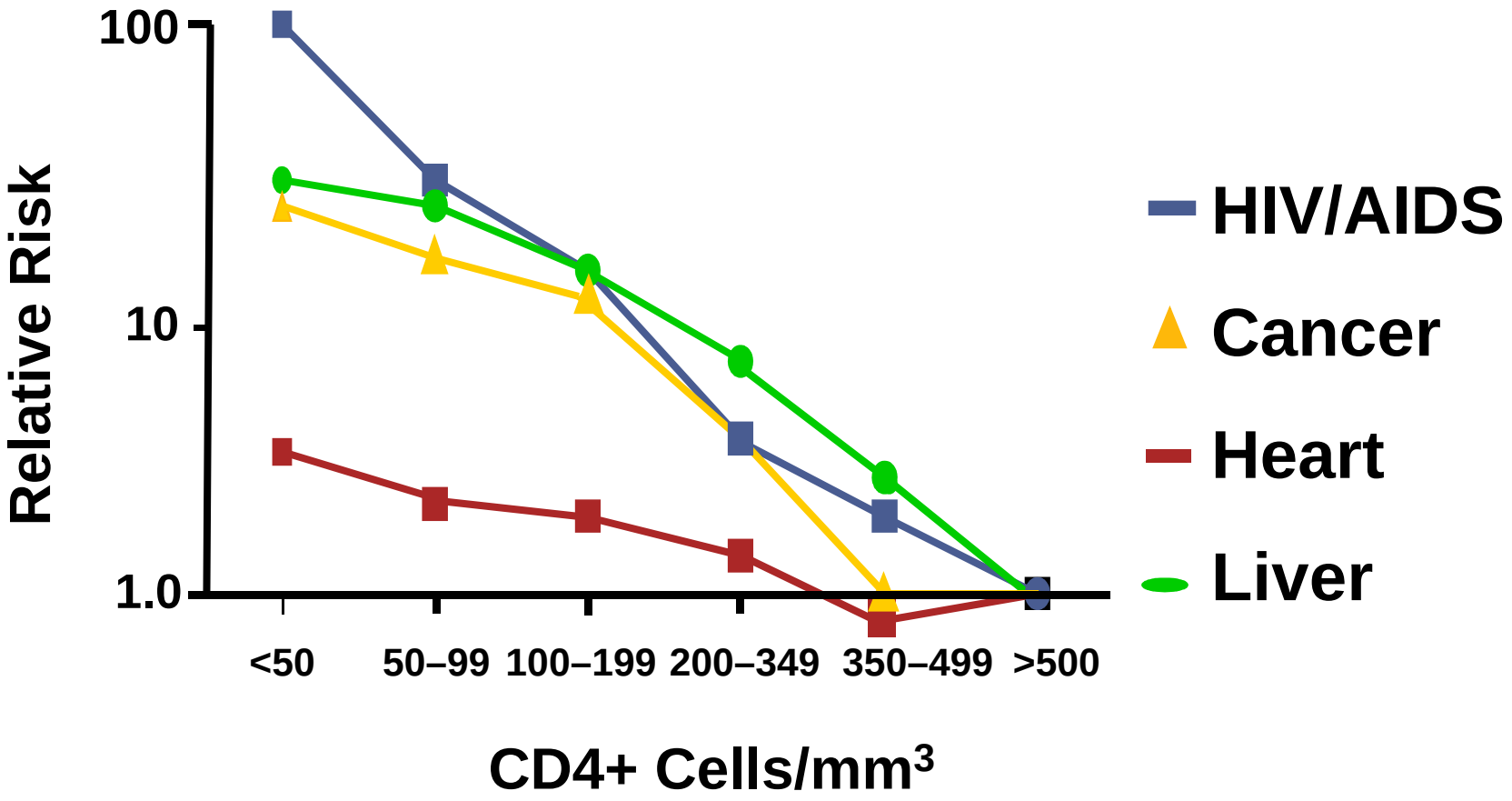
↑Comorbidities & Premature Aging

Even After Adjusting for Age, HAART Exposure & Traditional Risk Factors



Adapted from Deeks, RWCA Clinical Update 2009

Low CD4 On-Therapy Predicts Risk of AIDS & Non-AIDS Events (D:A:D)



Weber R, et al. CROI 2005, #595. Weber R, et al Arch Int Med 2006; 166:1632-1641. Philips AN. AIDS 2008; 22:2409-2418. Baker JV, et al AIDS 2008; 22:841-848.

Normalization of CD4/CD8 Ratio and Non-AIDS Events in ICONA Cohort

- Analysis of 3236 pts with virologic suppression on ART and CD4/CD8 ratio ≤ 0.8
  - 458 pts reached CD4/CD8 ≥ 1
  - Median time to normalization: 10.1 yrs
  - Younger pts, those starting ART in recent yrs, those with higher CD4+ counts and negative CMV IgG more likely to normalize
- Current CD4/CD8 ratio predicted incidence of clinical progression (serious non-AIDS–related events or all-cause death)
  - Remained predictive after adjusting for current CD4+ cell count

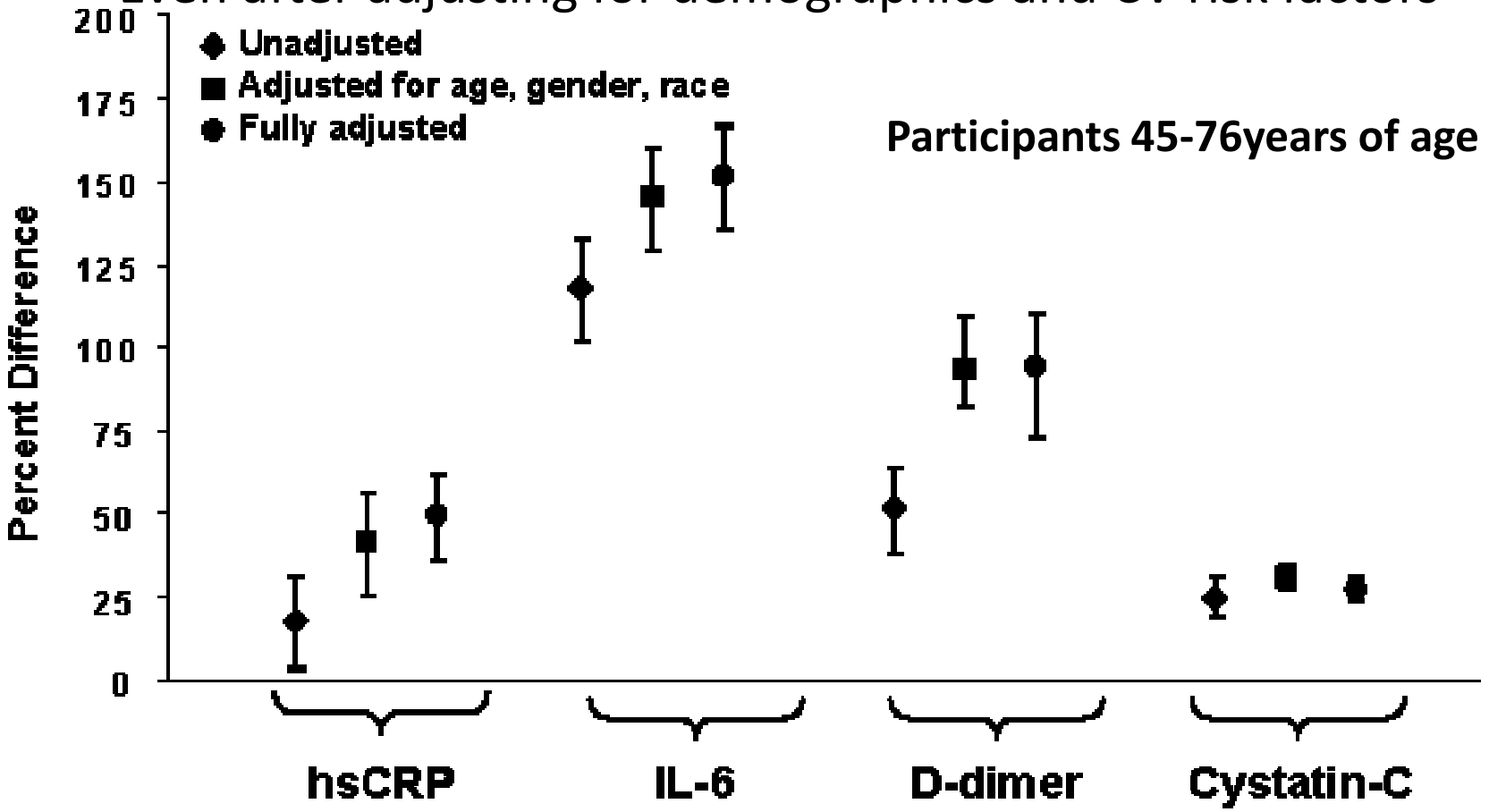
Time	Probability of CD4/CD8 Normalization (95% CI)
1 yr	4.4 (3.7-5.2)
2 yrs	11.5 (10.2-13.0)
5 yrs	29.4 (26.7-32.4)

Current CD4/CD8 Ratio	Incidence of Clinical Progression (95% CI)
< 0.30	4.8 (3.9-5.9)
0.30-0.45	2.4 (1.9-3.1)
> 0.45	2.0 (1.7-2.3)

Mussini C, Lancet HIV 2015

Elevated Inflammatory Markers in Treated HIV-Infected Patients

Even after adjusting for demographics and CV risk factors

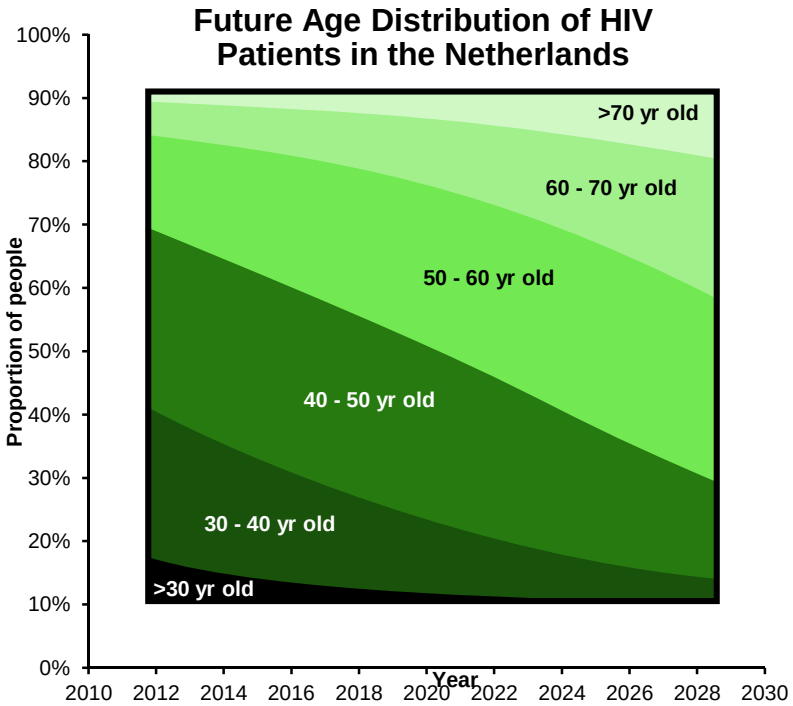


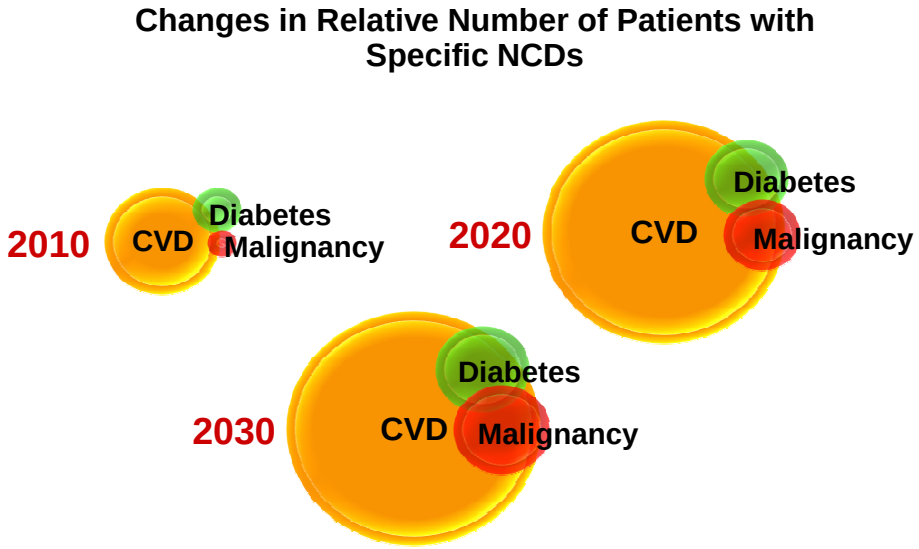
Neuhaus J, et al. CROI 2009 Abstract O-140.

Clinical Implications of an Ageing HIV Population: ATHENA Cohort

Increased Burden of Non-Communicable Diseases (NCDs) and Polypharmacy

An individual-based model of an ageing HIV-population following patients on treatment as they age, develop NCDs and start co-administered medications





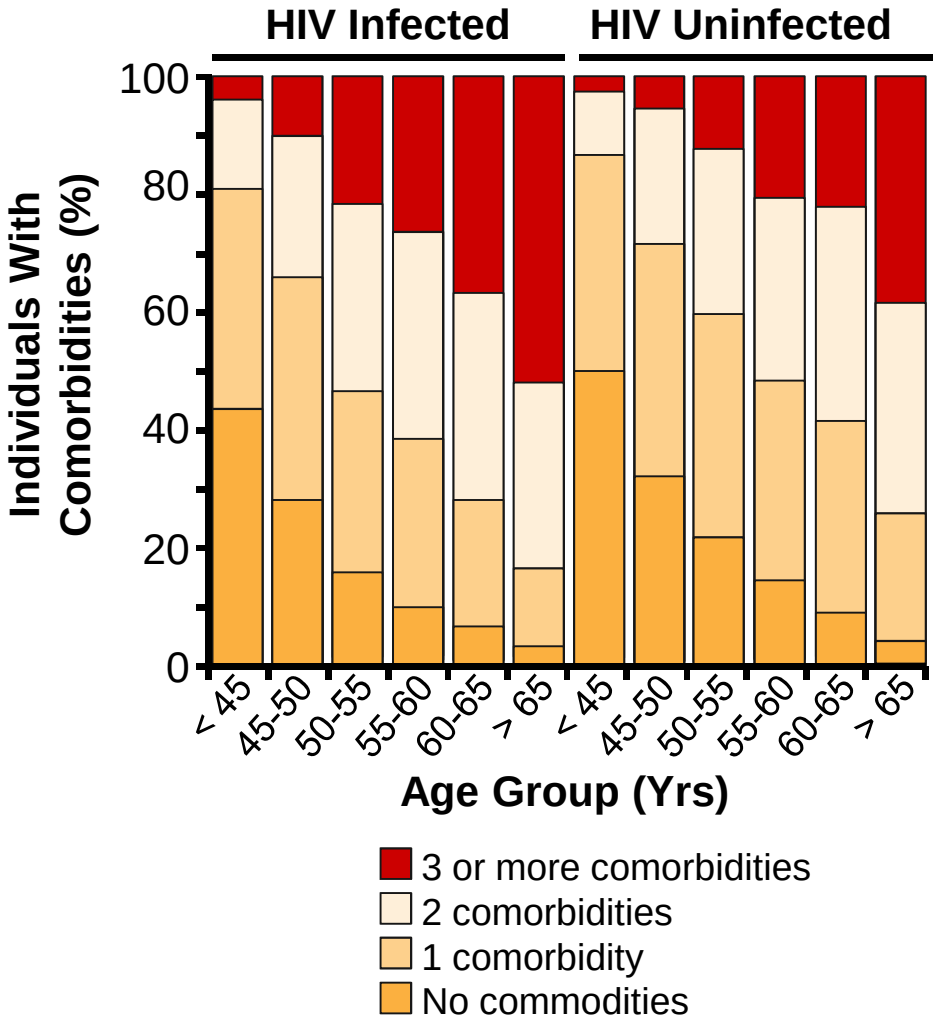
- **In the ATHENA cohort, proportion of patients on ART aged ≥50 years old will increase from 28% to 73% between 2010 and 2030**
- **Burden of NCDs mostly driven by larger increases in cardiovascular disease compared with increases in other comorbidities**
- **Polypharmacy is being driven by increase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

Smit M, et al. IAC 2014. Melbourne, Australia. #MOPE107

ATHENA: Comorbidities Increase With Age and With HIV Infection

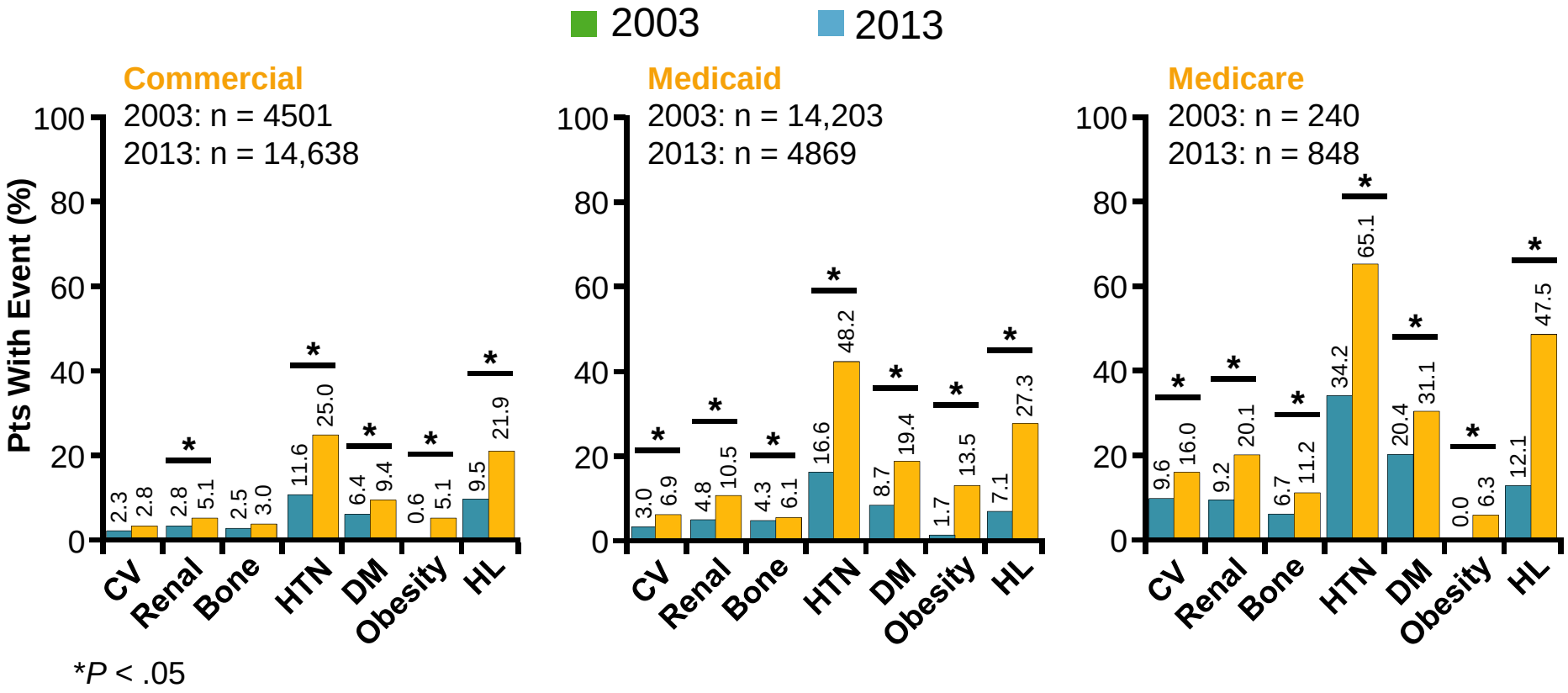
Modeling study suggests that in 2030:

- 84% of HIV+ pts will have ≥ 1 NCD
  - Increased from 29% in 2010
  - Pts with comorbidities higher in every age group in HIV+ pts vs uninfected
- 28% of HIV+ pts will have ≥ 3 NCDs
- 54% of HIV+ pts will be prescribed meds other than ART
  - Increased from 13% in 2010
- 20% will take ≥ 3 meds besides ART
  - Mostly driven by increase in CVD



Smit M, et al. Lancet Infect Dis. 2015;15:810-818.

Comorbidity Prevalence Increased 2003-2013 in Commercial and Public Settings



*$P < .05$

- In 5-yr trend analysis, HTN, DM, hyperlipidemia, and renal dysfunction rates increased for all 3 payer groups

Meyer N, et al. ICAAC 2015. Abstract.

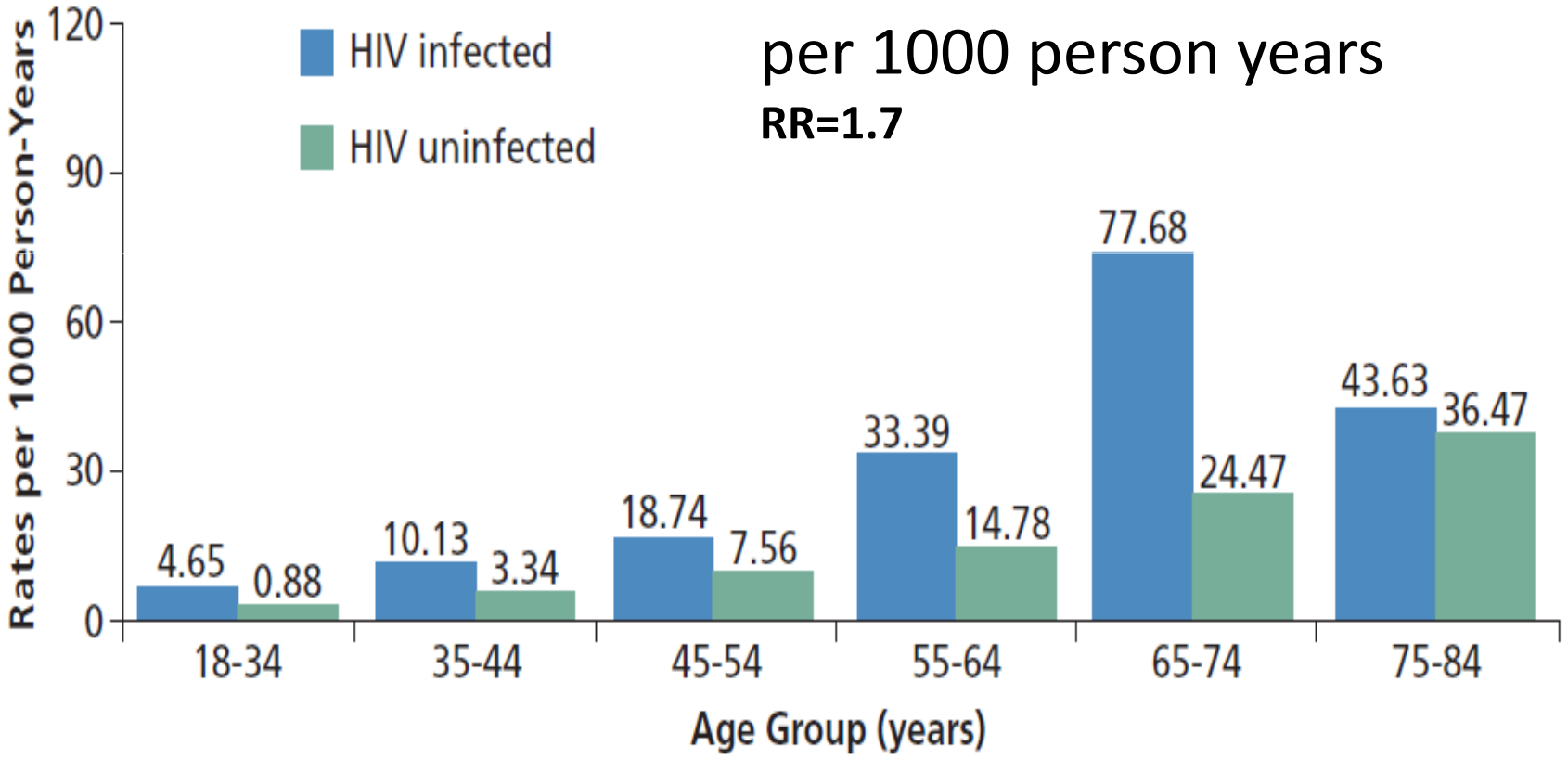
Insulin Resistance and Diabetes in the HIV Positive Population

- An increased prevalence of insulin resistance, glucose intolerance and diabetes has been reported in HIV infections in the HAART era[1]
- Diabetes in HIV positive men with HAART exposure > 4X HIV-seronegative men[2]
- Risk factors for HIV positive individuals developing diabetes include[3]:
  - Certain ARVs (PIs, d-drugs)
  - Older age
  - Ethnic background (African American)
  - HCV co-infection

[1]Florescu, D. *Antiretroviral Therapy.* 2007. 12:149-162.
[2]Brown, TT. *Arch Intern Med.* 2005. 165:1179-1184.
[3]DeWit, D. *Diabetes Care.* 2008. 31(6):1224-1229 De Luca A EACS 2015.

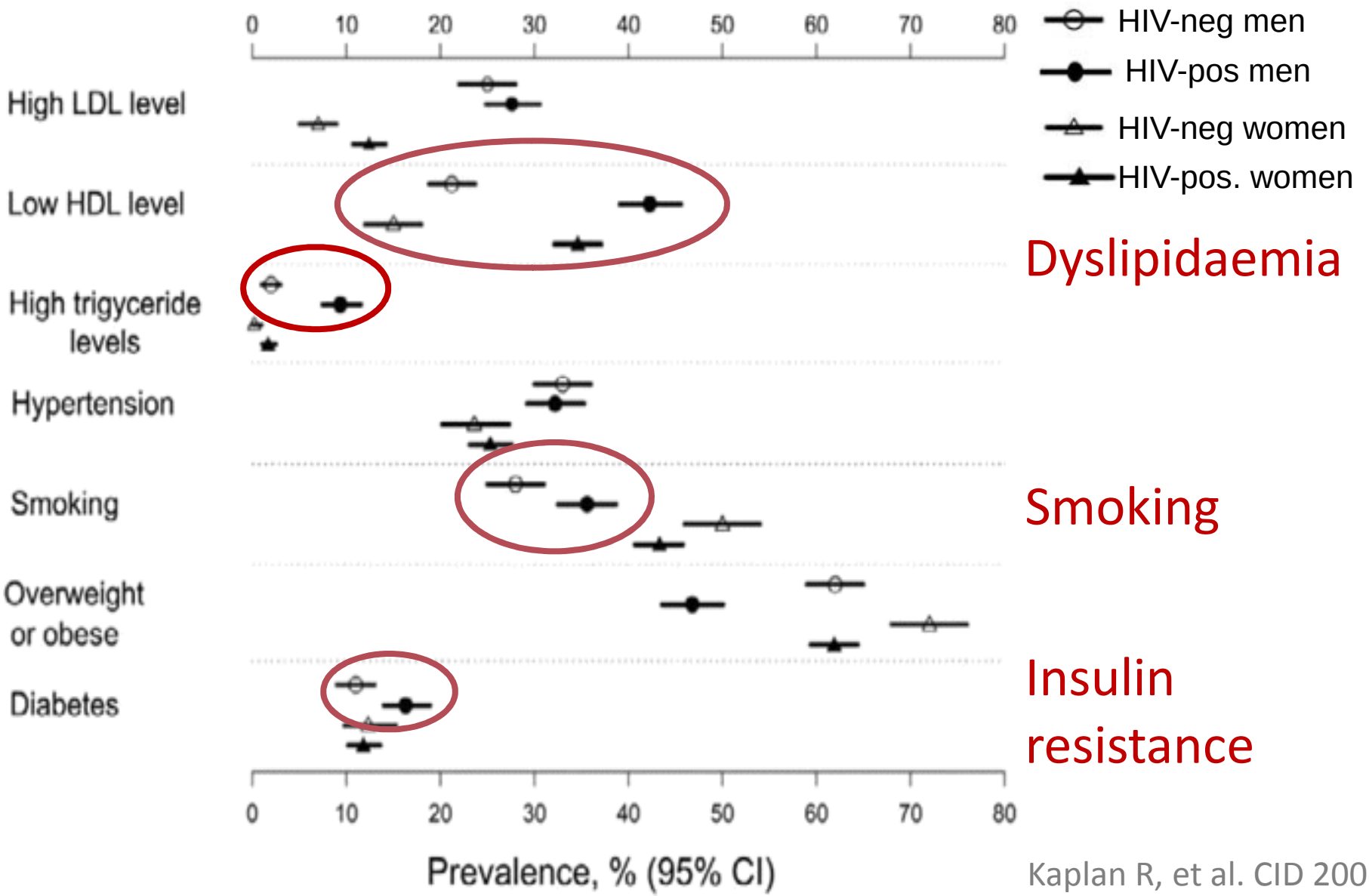
Myocardial Infarction rates in HIV+ versus HIV-

Mean MI rate = 11 v 7
per 1000 person years
RR=1.7



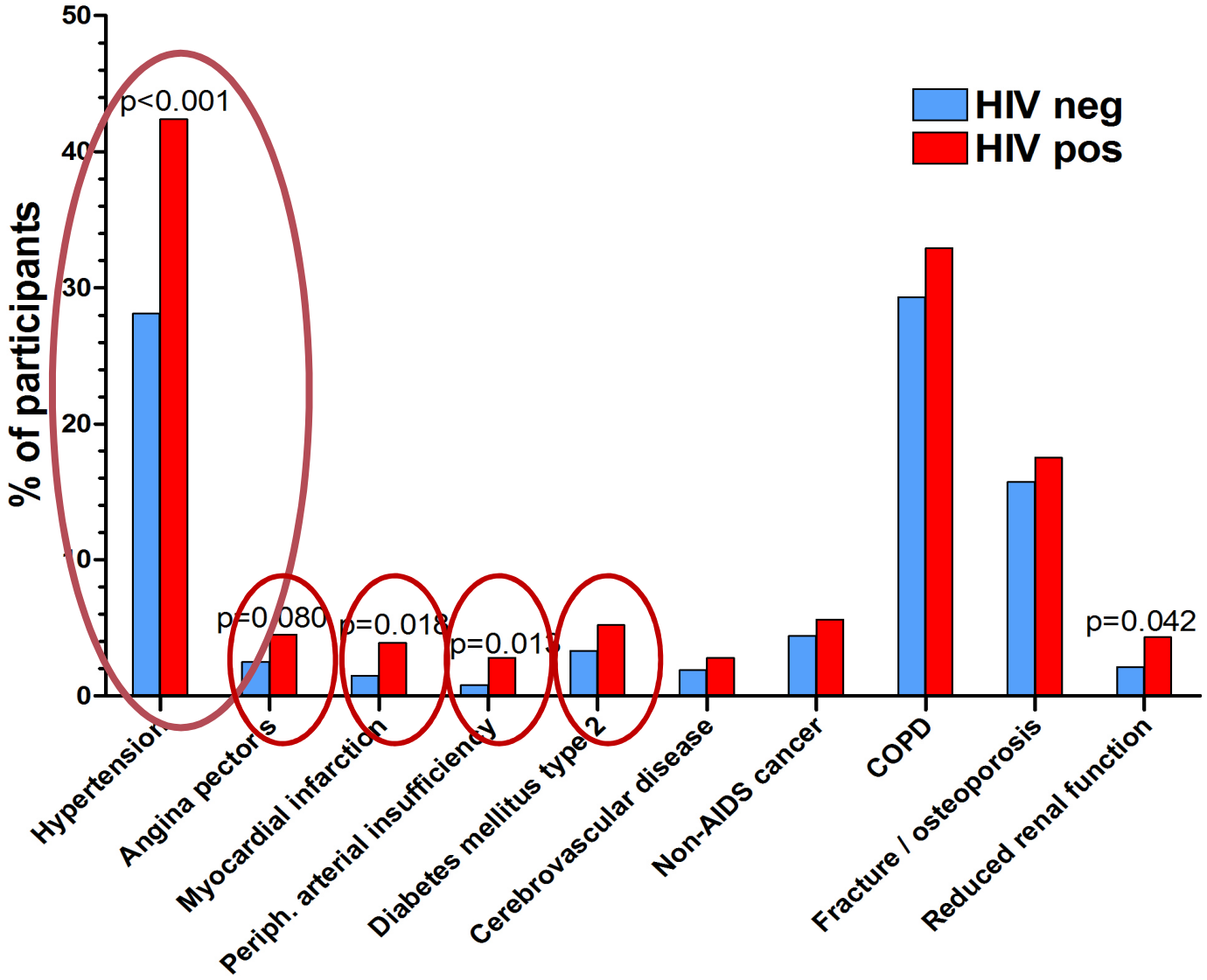
Triant J, et al. Clin Endocrinol Metab. 2007.

Risk factors CVD HIV+ vs HIV-



Kaplan R, et al. CID 2007

Comorbidity distribution

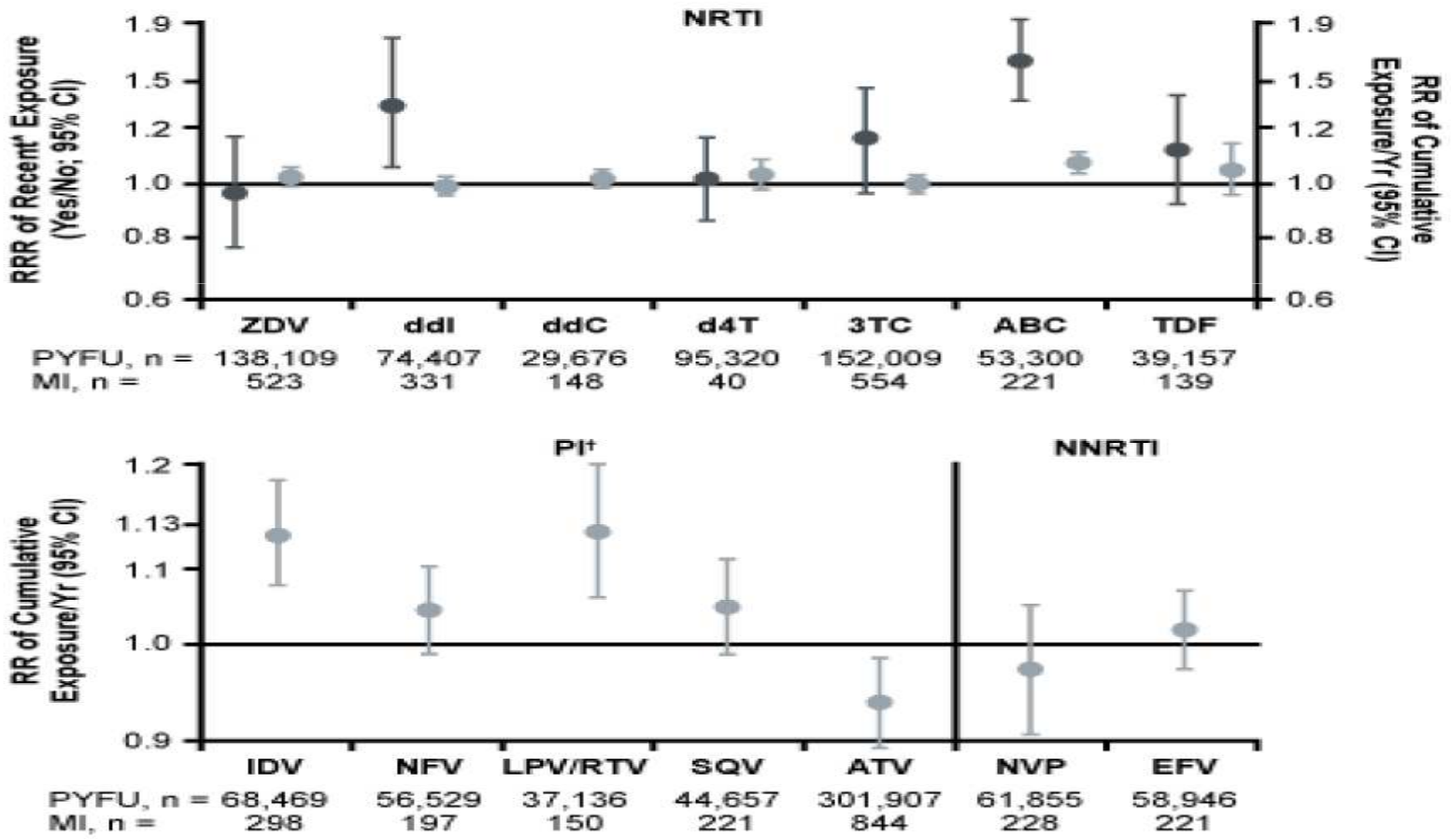


Schouten J et al. World AIDS Conference July 2012;
updated May 2013 (personal communication, Reiss P)

*

Cardiovascular complications of HIV

MI risk disease by ARV exposure in D:A:D

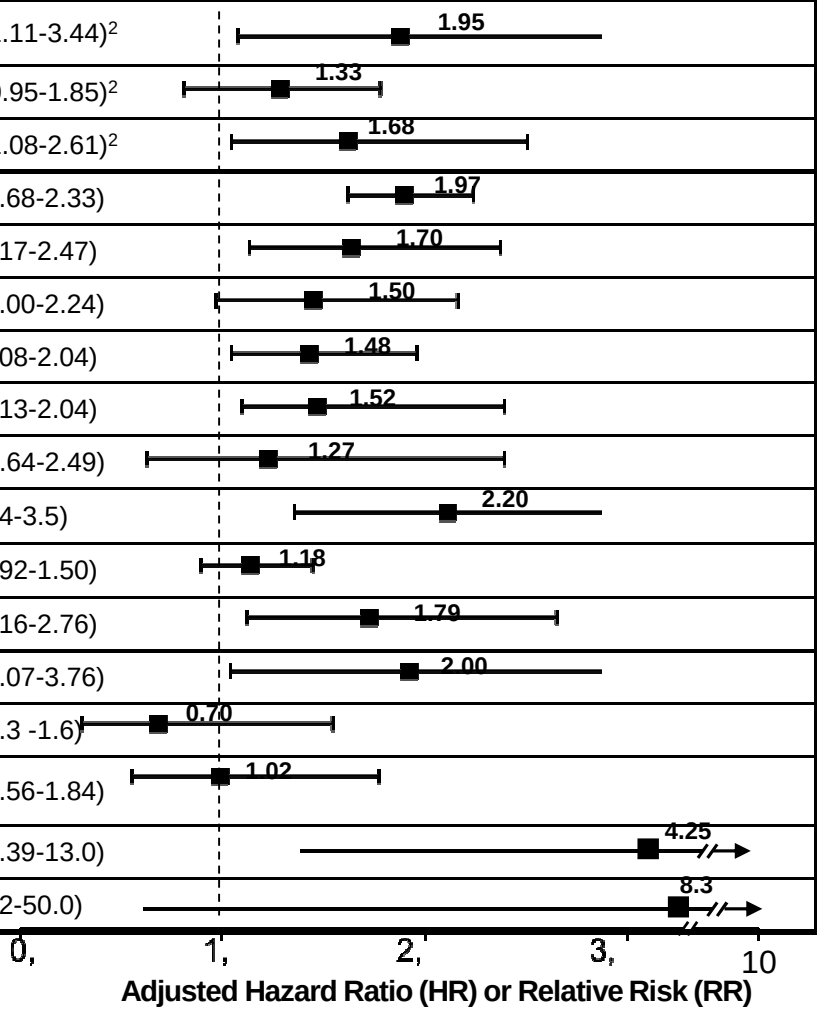


Worm S, et al. D:A:D. JID 2012.

Association of ABC Exposure with Risk of CV Events

(separate trials – not a direct head-to-head comparison)

			ABC Association, Risk[d] of MI (95%CI)
NA ACCORD	**Restricted Population (20,998)[1,2]**	MI (93)	1.95[1] (1.11-3.44)[2]
	Full Population (64,607)[1,2]	MI (301)	1.33[1] (0.95-1.85)[2]
	D:A:D Replication (>64,607)[1,2]	MI (>301)	1.68[1] (1.08-2.61)[2]
Studies >100 MI	**D:A:D 2014 (367,559)[3]**	MI (941)	1.97 (1.68-2.33)
	D:A:D (178,835)[4]	MI (580)	1.70 (1.17-2.47)
	D:A:D 2016 (3,863)[17]	Second MI (102)	1.50 (1.00-2.24)
	VA - Choi (59,578)[6]	CVD Event[c] (501)	1.48 (1.08-2.04)
	Swiss (NA)[7]	CVD Event[e] (350)	1.52 (1.13-2.04)
	French HD (298,156)[8]	MI (289)	1.27[e] (0.64-2.49)
	Kaiser (34,472)[16]	CVD (178)	2.20 (1.4-3.5)
	VA - Bedimo (76,376)[9]	MI (278)	1.18 (0.92-1.50)
	QPHID (35,851)[10]	MI (125)	1.79 (1.16-2.76)
Studies < 100 MI	**Danish (19,124)[11]**	MI (67)	2.00 (1.07-3.76)
	ALLRT/ACTG (17,404)[12]	MI (36)	0.70 (0.3 -1.6)
	FDA (range: 42 to 1257)[13]	MI (24)	1.02 (0.56-1.84)
	SMART (NA)[14]	MI (19)	4.25 (1.39-13.0)
	STEAL (NA)[15]	MI (3)	8.3 (1.02-50.0)



QPHID = Quebec's public health insurance database; French HD – French Hospital Database

aAll or majority of patients were treatment-experienced at ABC initiation; bAll or majority of pts were treatment-naïve at ABC inclusion; cMI, unstable angina, CVA, CHF, PVD; dRisk reported is the adjusted risk as presented by each study; e MI, unstable angina, PCI, CABG, fatal CAD

1. Palella F, et al. CROI 2015; Seattle, WA. #749; 2. Personal Communication - Investigator. March 2015; 3. Sabin C, et al. CROI 2014. Boston, MA. #LB747; 4. Worm SW, et al. JID 2010; 5. Rotger M et al, CID 2013; 6. Choi AI, et al. AIDS. 2011; 7. Young J, et al. IAS 2013. MOPE070; 8. Lang S, et al. Arch Intern Med 2010; 9. Bedimo RJ, et al. CID 2011; 10. Durand M, et al. JAIDS 2011; 11. Obel N, et al. HIV Medicine 2010; 12. Ribaudo HJ, et al. CID 2011; 13. Ding X, et al. JAIDS 2012; 14. SMART/INSIGHT Study Group. AIDS 2008; 15. Martin A, et al. CID 2009 (full citations located in slide notes); 16. Marcus, JL, et al, JAIDS 2015; 17. Sabin, et al. CROI 2016, #661

Possible Non-Cholesterol Causes of CVD Risk With Protease Inhibitor Therapy in HIV

- Endothelial dysfunction
- Increased endothelial permeability
- Insulin resistance
- Accelerated lipid accumulation in vessel wall
- Inflammation
- Impaired response to vascular injury
- Increased oxidative stress
- Lipoatrophy / reduced adiponectin

M/ Dube, AAHIVM-AHA CVD Conference Chicago June 2007

FRAM 2 carotid Intima Media Thickness: HIV Infection is an Independent Risk for Atherosclerosis

- Cross-sectional study
- Evidence of pre-clinical atherosclerosis
  Internal cIMT (mm)

HIV+ (n=433)	Controls (n=5479)	P value
1.17	1.06	<.0001

- After adjusting for demographics and CVD risk factors, HIV infection has more atherosclerosis than controls
  - Difference 0.15 mm (*P* =.0001)
- **HIV infection similar to traditional CV risk factors**

Multivariable Analysis of Associated Factors	
Estimated Effect of	**Difference in Internal cIMT (mm)[a]**
HIV infection	**0.15**
Current smoker Past smoker	**0.17** 0.09
Age *(per 10 yr)*	**0.16**
Male[b]	**0.13**
Diabetes	**0.12**
Systolic BP	0.05

[a]*P* <.001 for all values.
[b]Significant gender interaction (women > men).

"Independent association of HIV infection with atherosclerosis should be taken into account when counseling HIV-infected patients with regard to their CVD risk factors."

Grunfeld C, et al. 16th CROI; 2009; Montreal. Abstract #146.

Factors associated with carotid distensibility (n=2789)

Table 2. Carotid Arterial Distensibility by HIV Adjusted for Demographic, Behavioral, and Clinical Cofactors

	Overall		MACS (males)		WIHS (females)	
	Percent Difference	95% CI	Percent Difference	95% CI	Percent Difference	95% CI
WIHS (vs MACS)	−0.2	(−17.2, 20.3)				
Age per 10 years	−17.1†	(−19.4, −14.7)	−12.1†	(−13.7, −10.5)	−19.1†	(−21.5, −16.6)
Race/ethnicity						
White and other races*	0		0		0	
Black	−10.4†	(−12.7, −8.1)	−5.8†	(−9.2, −2.4)	−11.0†	(−14.3, −7.6)
Hispanic	−8.9†	(−11.0, −6.8)	−6.6	(−14.4, 1.8)	−9.2†	(−12.8, −5.4)
More than high school education	1.2	(−2.3, 4.7)	5.6	(−6.5, 19.6)	−0.1	(−2.8, 2.7)
Smoking status						
Never smoked*	0		0		0	
Former smoker	−0.9	(−5.2, 3.6)	3.6	(−2.2, 9.9)	−3.5	(−8.3, 1.5)
Current smoker	−0.1	(−3.5, 3.5)	−0.6	(−4.1, 3.0)	0.2	(−5.0, 5.6)
History of injection drug use	−2.6	(−5.7, 0.6)	−3.3	(−8.3, 1.9)	−0.1	(−4.7, 4.0)
Family history of myocardial infarction	0.3	(−2.8, 3.5)	−3.8	(−8.1, 0.6)	2.9	(−1.7, 7.7)
Body mass index per 5 kg/m^2	−4.4†	(−5.5, −3.3)	−5.9†	(−9.3, −2.3)	−4.1†	(−5.3, −3.0)
LDL-c per 0.52 mmol/L (20 mg/dL)	−0.9†	(−1.4, −0.3)	−1.0	(−2.2, 0.2)	−0.5	(−1.2, 0.3)
HDL-c per 0.13 mmol/L (5 mg/dL)	0.5†	(0.1, 1.0)	−0.2	(−1.2, 0.9)	0.8†	(0.4, 1.1)
Systolic blood pressure per 10 mm Hg	−8.1†	(−9.4, −7.1)	−8.8†	(−10.1, −7.5)	−8.0†	(−9.4, −6.7)
Diabetes	−2.1	(−5.1, 1.0)	−3.0	(−7.8, 2.1)	−1.7	(−5.7, 2.5)
HIV positive vs negative	−4.3†	(−7.4, −1.1)	−5.5†	(−9.9, −1.0)	−1.9	(−6.2, 2.6)

*Reference.
†$P<0.05$.

Seaberg Stroke 2010

Factors associated with NCI (SMART study, n=292)

Factors[b]	% of population	NCI[c]	QNPZ-5
Age (per 10 y)		NS	NS
Gender (female vs male)	41.7	NS	p=0.05[e] −0.21
Race/ethnicity (black vs other)	19.7	p=0.08 2.25	p<0.001[e] −0.48
Education (>12 y)	46.6	NS	NS
Location		NS	NS
Brazil[d]	15.2		
Thailand[d]	50.0		
Prior AIDS	20.7	p=0.08 0.41	p=0.05[e] 0.24
Hepatitis B	2.1	—	p=0.05[e] −0.66
Prior CVD	3.5	p=0.01[a] 6.17	p=0.02[e] −0.65
Blood pressure-lowering drugs	11.0	—	p=0.03[e] −0.37
Total cholesterol (per 10 mg/mL)		p=0.06 1.08	p=0.02[e] −0.03
HDL (per 10 mg/mL)		—	—
Depression (CES-D ≥ 16)	23.8	—	p=0.07 −0.21

Wright EJ Neurology 2010

Cardiovascular risk factors and carotid intima-media thickness are associated with lower cognitive performance in HIV-infected patients

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DOI: 10.1111/j.1468-1293.2012.01044.x

HIV Medicine (2012)

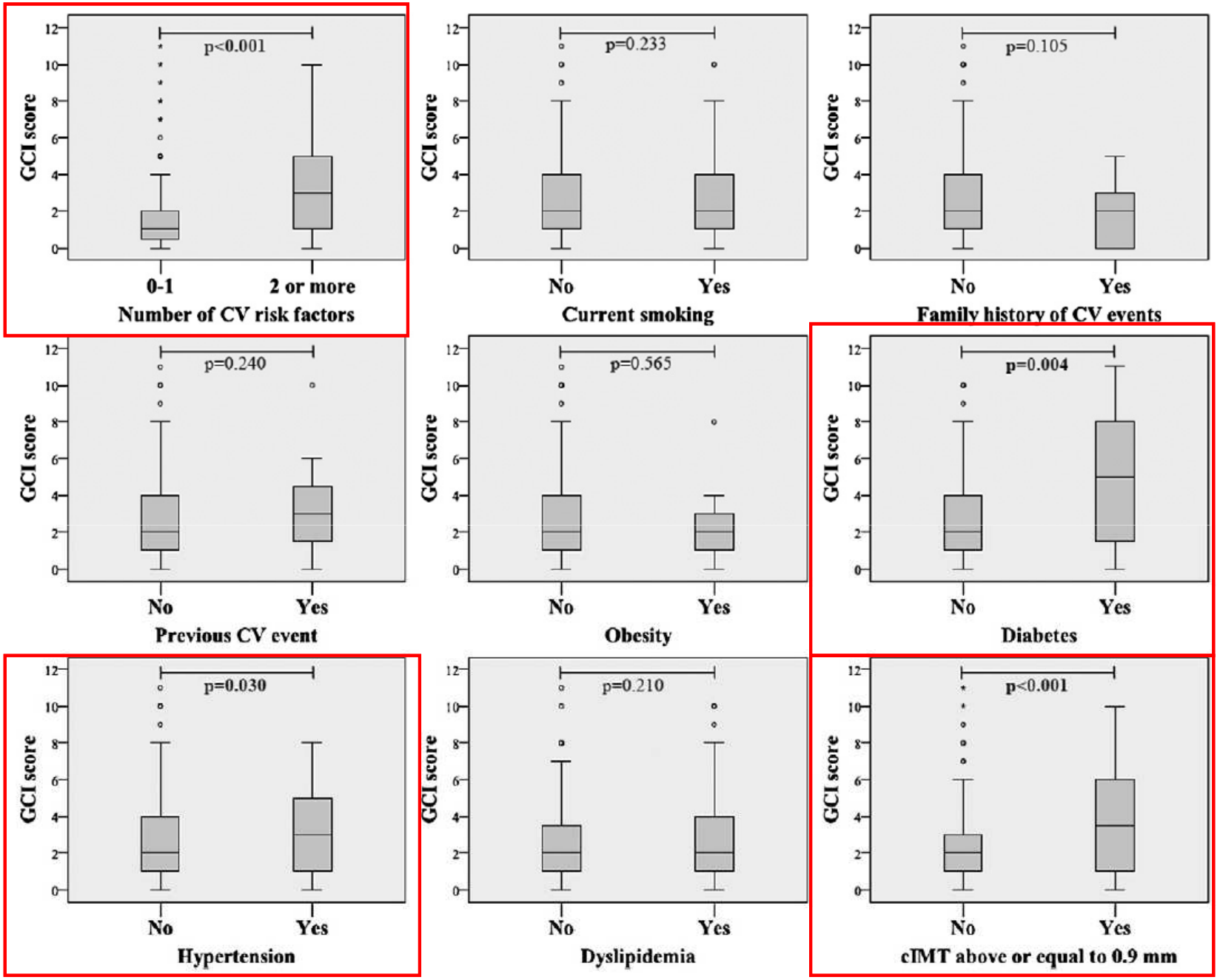


Fig. 1 Global cognitive impairment (GCI) score according to each cardiovascular (CV) risk factor. cIMT, carotid intima-media thickness.

Fabbiani M HIV Medicine 2012

Table 3 Predictors of global cognitive performance

	Univariate analysis		Multivariate analysis	
	Mean (95% CI) change in GCI score	*P*	Mean (95% CI) change in GCI score	*P*
Male sex	−0.41 (−0.75; 0.67)	0.911		
Age (per 10-year increase)	0.59 (0.31; 0.88)	**<0.001**	0.15 (−0.15; 0.44)	0.323
Education (per 1-year increase)	−0.29 (−0.37; −0.22)	**<0.001**	−0.24 (−0.31; −0.16)	**<0.001**
Non-Italian born	−0.12 (−1.30; 1.05)	0.837		
Past injecting drug user	0.76 (0.03–1.49)	**0.043**	−0.07 (−1.108; 0.96)	0.894
Past AIDS-defining events	0.76 (−0.03; 1.55)	0.059		
HCV coinfection	0.77 (0.06–1.49)	**0.034**	0.13 (−0.89; 1.14)	0.808
Time from HIV diagnosis (per 1-year increase)	0.03 (−0.01; 0.07)	0.124		
CD4 count at nadir (per 100 cells/μL increase)	−0.25 (−0.48; −0.03)	**0.029**	−0.05 (−0.27; 0.17)	0.639
PI experience	1.00 (0.28–1.73)	**0.007**	0.45 (−0.23; 1.12)	0.193
Current cART	1.42 (0.16–2.69)	**0.027**	0.66 (−0.53; 1.85)	0.275
CPE rank ≥ 7	0.01 (−0.81; 0.81)	0.998		
CD4 count (per 100 cells/μL increase)	−0.09 (−0.22; 0.04)	0.154		
HIV RNA < 50 copies/mL	0.16 (−0.68; 0.99)	0.714		
Zung depression score	0.04 (0.01; 0.07)	**0.010**	0.02 (−0.01; 0.05)	0.148
Cardiovascular risk factor				
Current smoking	0.10 (−0.51; 0.71)	0.753		
Family history of CV events	−0.88 (−1.79; 0.04)	0.060		
Previous CV event	0.79 (−0.63; 2.20)	0.275		
Obesity	−0.50 (−1.78; 0.78)	0.440		
Diabetes	2.32 (1.24; 3.40)	**<0.001**	1.38 (0.38, 2.38)	**0.007**
Hypertension	0.84 (−0.01; 1.68)	0.054		
Dyslipidaemia	0.37 (−0.26; 1.00)	0.244		
cIMT ≥ 0.9 mm	1.60 (0.97; 2.22)	**<0.001**	0.66 (0.02; 1.31)	**0.044**

Bold values represent statistically significant *P* values.
cART, combined antiretroviral therapy; CI, confidence interval; cIMT, carotid intima-media thickness; CPE, central nervous system penetration effectiveness score; CV, cardiovascular; GCI, global cognitive impairment; HCV, hepatitis C virus; PI, protease inhibitor.

Fabbiani M HIV Medicine 2012

Ophtalmic artery resistance index and cognitive impairment
(n=116)

Table 3 Factor associated with cognitive impairment (logistic regression analysis).

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Male sex	1.82 (0.69–4.77)	0.218		
Age (per 10 years increase)	2.03 (1.29–3.20)	**0.002**	1.25 (0.72–2.15)	0.415
Education (per 1 year increase)	0.76 (0.67–0.86)	**<0.0001**	0.84 (0.73–0.97)	**0.017**
Non Italian born	0.25 (0.02–2.35)	0.220		
Past injecting drug users	1.00 (0.99–1.01)	0.402		
Past AIDS-defining events	1.96 (0.66–5.88)	0.224		
HCV coinfection	1.20 (0.54–2.63)	0.645		
Time from HIV diagnosis (per 1 year increase)	1.05 (0.99–1.11)	**0.072**	1.02 (0.95–1.10)	0.541
CD4 at nadir (per 100 cells increase)	0.87 (0.64–1.19)	0.405		
PI experience	2.10 (0.95–4.60)	**0.060**	1.10 (0.42–2.86)	0.835
CPE rank ≥7	2.6 (0.66–10.62)	0.164		
CD4 cells count (per 100 cells increase)	0.99 (0.86–1.13)	0.893		
HIV-RNA <20 copies/mL	1.93 (0.70–5.30)	0.190		
Chronic renal impairment	1.64 (0.26–10.23)	0.590		
Zung depression score	1.05 (1.01–1.1)	**0.020**	1.02 (0.96–1.07)	0.410
Current smoking	1.56 (0.74–3.29)	0.237		
Familiarity for CV events	0.28 (0.05–1.41)	0.123		
Previous CV event	3.34 (0.33–33.17)	0.302		
Obesity (BMI ≥ 30 kg/m^2)	0.52 (0.04–5.99)	0.606		
Diabetes	1.46 (0.31–6.85)	0.628		
Hypertension	2.07 (0.75–5.72)	0.159		
Dyslipidemia	1.50 (0.71–3.18)	0.181		
OARI >0.72	7.83 (3.39–18.07)	**<0.0001**	4.70 (1.81–12.14)	**0.001**

Abbreviations: HCV, hepatitis C virus; PI, protease inhibitors; CPE, central nervous system penetration effectiveness score; CV, cardiovascular; BMI, body mass index; OARI, opthalmic artery resistance index; OR, odds ratio; CI, confidence interval.

Grima P J Infect 2012

Table 3. Baseline factors associated with the risk of cognitive impairment at 2-year follow-up examination (n=150)

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Variables at baseline				
Male sex	1.3 (0.6, 2.9)	0.556	–	–
Age (per 10 years higher)	1.5 (1.0, 2.9)	**0.030**	0.9 (0.6, 1.5)	0.792
Non-Italian born	1.0 (0.2, 5.8)	0.972	–	–
Past injecting drug users	2.2 (0.9, 5.2)	0.062	–	–
Past AIDS-defining events	1.2 (0.5, 2.9)	0.602	–	–
HCV coinfection	1.3 (0.5, 3.0)	0.593	–	–
Time from HIV diagnosis (per 1 year higher)	1.0 (0.9, 1.1)	0.586	–	–
Time from first cART (per 1 year higher)	1.1 (0.9, 1.1)	0.174	–	–
Cumulative PI exposure (per 1 year higher)	1.2 (1.0, 1.4)	**0.008**	1.2 (1.0, 1.4)	0.081
CD4+ T-cell count at nadir (per 100 cells higher)	0.7 (0.5, 0.9)	**0.023**	0.9 (0.6, 1.3)	0.579
CPE rank ≥6	1.0 (0.9, 5.7)	0.990	–	–
CD4+ T-cell count (per 100 cells higher)	0.8 (0.7, 1.0)	**0.026**	0.9 (0.8, 1.1)	0.199
HIV RNA<50 copies/ml	0.7 (0.3, 2.0)	0.550	–	–
Zung Depression Score	1.00 (0.98, 1.04)	0.550	–	–
CV factors				
Current smoker	1.3 (0.7, 2.7)	0.385	–	–
Previous CV events	0.4 (0.0, 3.5)	0.409	–	–
Familiarity for CV events	0.4 (0.1, 1.6)	0.219	–	–
BMI≥30 kg/m^2	2.2 (0.5, 9.0)	0.293	–	–
Diabetes	2.8 (0.8, 10.8)	0.145	–	–
HDL (per 1 mg/dl higher)	0.99 (0.97, 1.02)	0.810	–	–
Dyslipidaemia	3.2 (1.4, 7.2)	**0.006**	2.6 (1.0, 7.1)	0.053
cIMT (per 0.1 mm higher)	51.4 (7.4, 355.6)	**0.001**	14.5 (1.2, 174.6)	**0.035**
Baseline presence of ANI	8.3 (3.8, 18.3)	**<0.001**	9.5 (3.9, 23.3)	**<0.001**

Significant *P*-values are in bold. ANI, asymptomatic neurocognitive impairment; BMI, body mass index; cART, combined antiretroviral therapy; cIMT, carotid intima-media thickness; CPE, central nervous system penetration effectiveness score; CV, cardiovascular; HDL, high-density lipoprotein cholesterol; PI, protease inhibitor.

Ciccarelli N Antivir Ther 2015

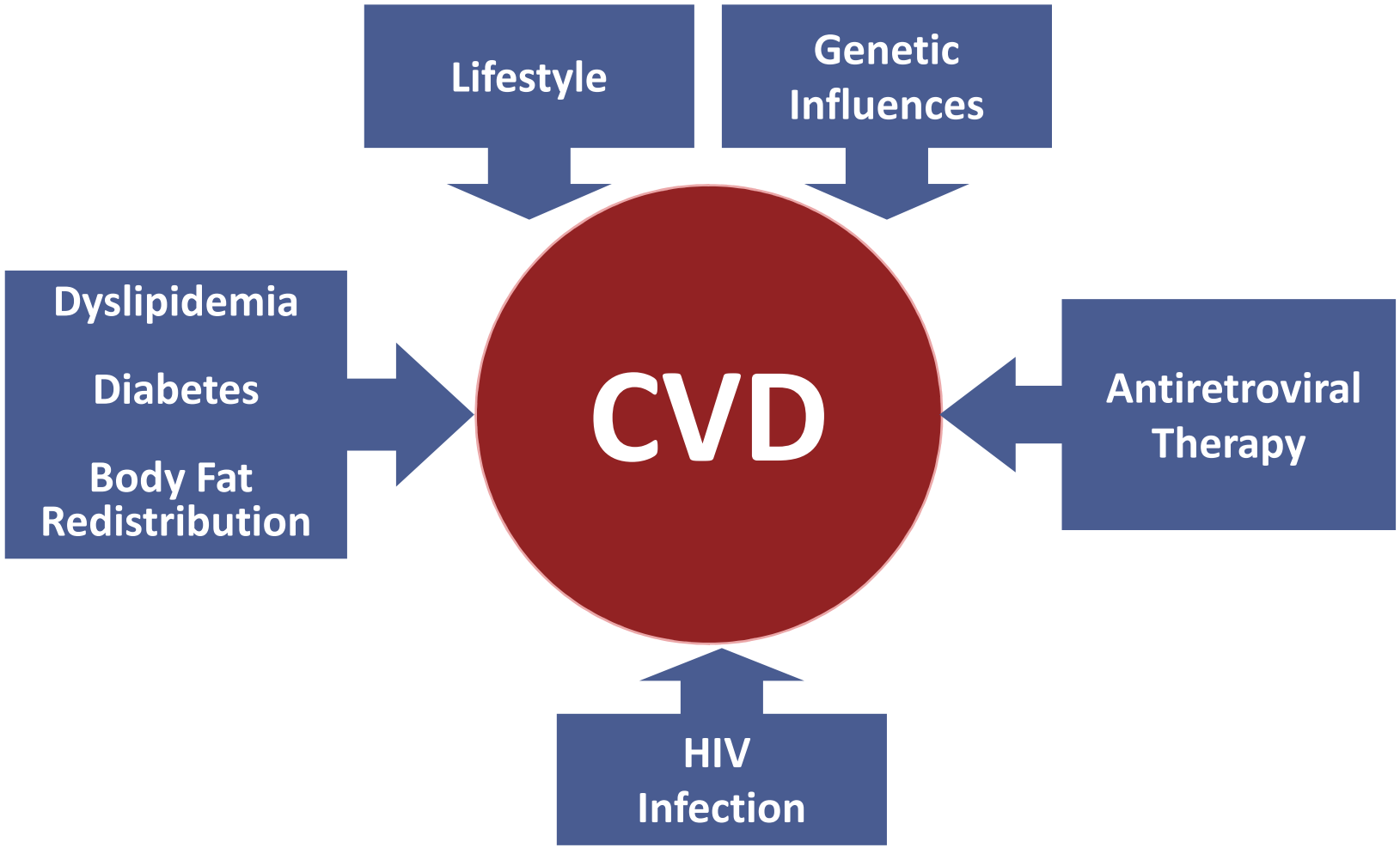
Table 4. Baseline factors associated with a higher risk of impaired long-term memory performance (mean z score ≤-1) at 2-year follow-up examination (n=150)

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Variables at baseline				
Male sex	1.6 (0.7, 3.7)	0.259	–	–
Age (per 10 years higher)	1.0 (0.7, 1.4)	0.878	–	–
Non-Italian born	0.9 (0.1, 4.9)	0.863	–	–
Past injecting drug users	1.8 (0.8, 4.2)	0.175	–	–
Past AIDS-defining events	1.0 (0.4, 2.3)	1.000	–	–
HCV coinfection	1.2 (0.5, 2.9)	0.628	–	–
Time from HIV diagnosis (per 1 year higher)	1.0 (0.9, 1.0)	0.508	–	–
Time from first cART (per 1 year higher)	1.0 (0.9, 1.1)	0.679	–	–
PI exposure	1.1 (1.0, 1.3)	0.134	–	–
CD4⁺ T-cell count at nadir (per 100 cells higher)	1.4 (0.7, 2.8)	0.403	–	–
CPE rank	1.0 (0.7, 1.3)	0.862	–	–
CD4⁺ T-cell count (per 100 cells higher)	0.83 (0.71, 0.97)	**0.019**	0.80 (0.66, 0.97)	**0.026**
HIV RNA<50 copies/ml	0.6 (0.2, 1.4)	0.216	–	–
Zung Depression Score	1.00 (0.97, 1.04)	0.681	–	–
CV factors				
Current smoker	1.1 (0.5, 2.1)	0.865	–	–
Previous CV events	0.0 (0.0-NC)	0.999	–	–
Familiarity for CV events	1.4 (0.5, 4.0)	0.535	–	–
BMI	1.0 (0.9, 1.2)	0.400	–	–
Diabetes	2.3 (0.6, 8.6)	0.236	–	–
HDL (per 1 mg/dl higher)	0.99 (0.96, 1.01)	0.295	–	–
Dyslipidaemia	2.9 (1.3, 6.3)	**0.007**	2.7 (1.1, 7.1)	**0.037**
cIMT (per 0.1 mm higher)	13.0 (2.3, 73.7)	**0.004**	4.16 (0.7, 32.1)	0.122
Baseline pathological long-term memory performance	13.8 (5.9, 32.2)	**<0.001**	13.6 (5.4, 33.9)	**<0.001**

Significant *P*-values are in bold. BMI, body mass index; cART, combined antiretroviral therapy; CPE, central nervous system penetration effectiveness score; cIMT, carotid intima-media thickness; CV, cardiovascular; HDL, high-density lipoprotein cholesterol; NC, not calculable; PI, protease inhibitor.

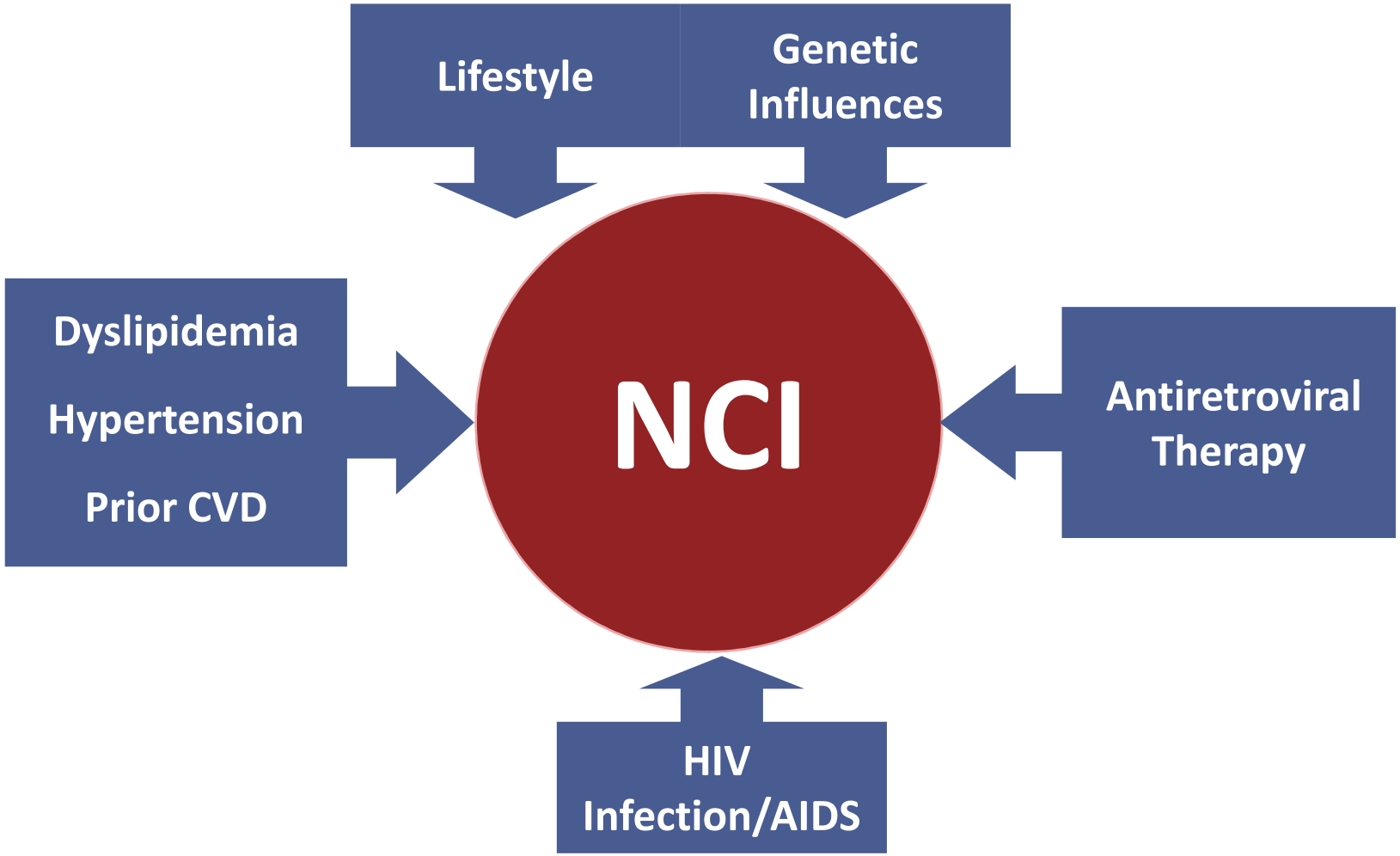
Ciccarelli N Antivir Ther 2015

Factors Affecting Risk for CVD in Patients With HIV



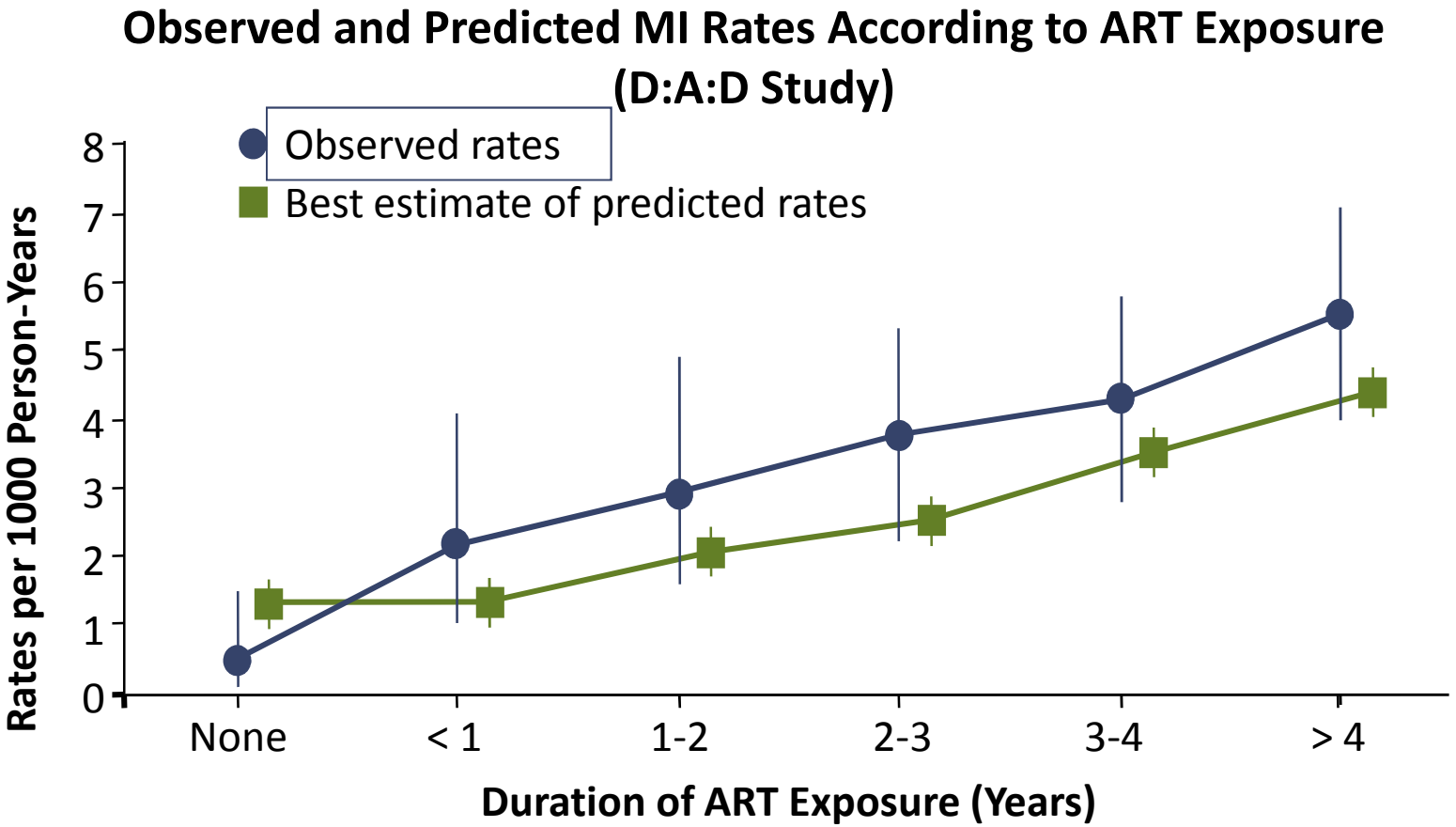
Adapted from Grinspoon S et al. *N Engl J Med.* 2005;352:348.

Factors Affecting Risk for NCI in Patients With HIV



Adapted from Grinspoon S et al. *N Engl J Med.* 2005;352:348.

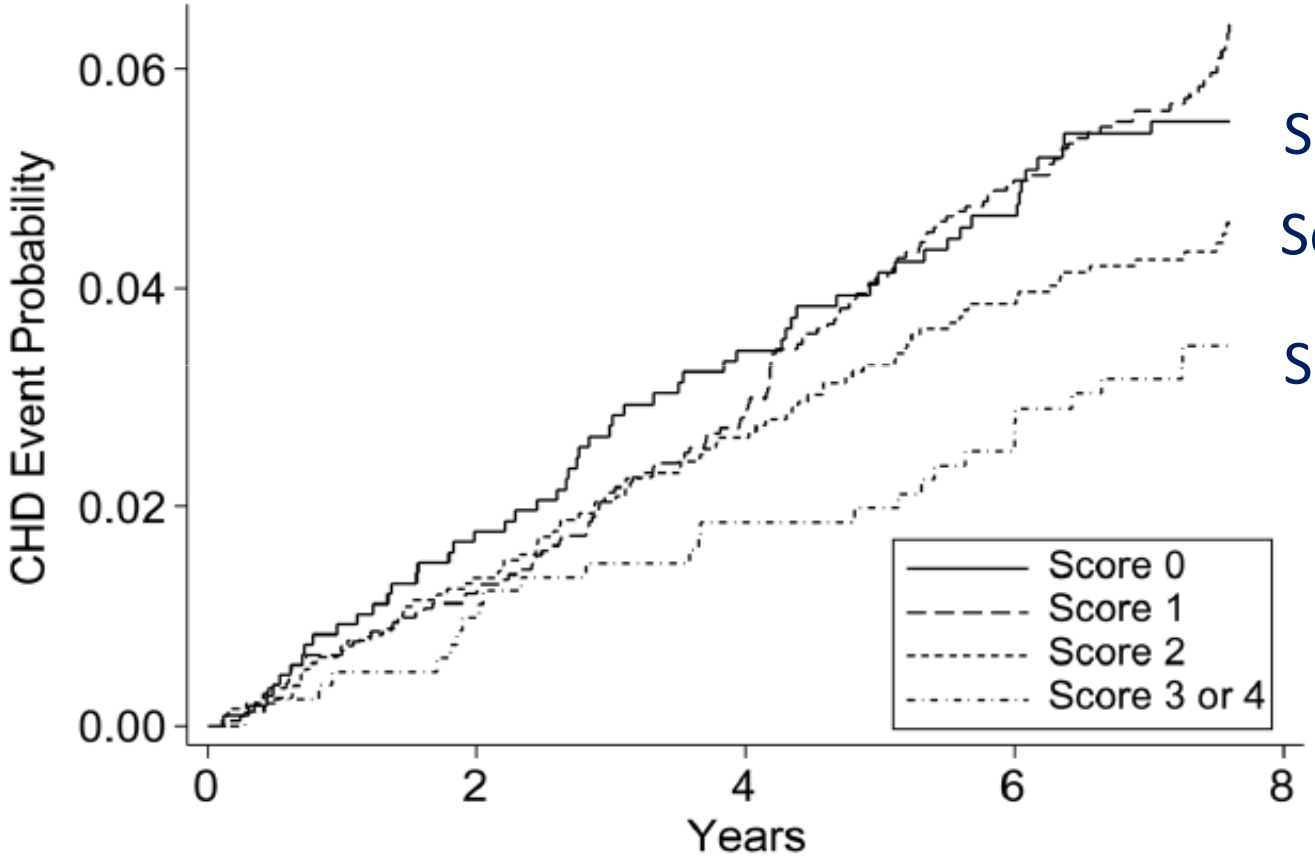
Framingham Risk Score: Underestimates CVD Risk in HIV+ Patients



Law MG et al. *HIV Med*. 2006;7:218-230.

CVD complications of HIV

Prevention: adopt a healthy lifestyle



Score 0

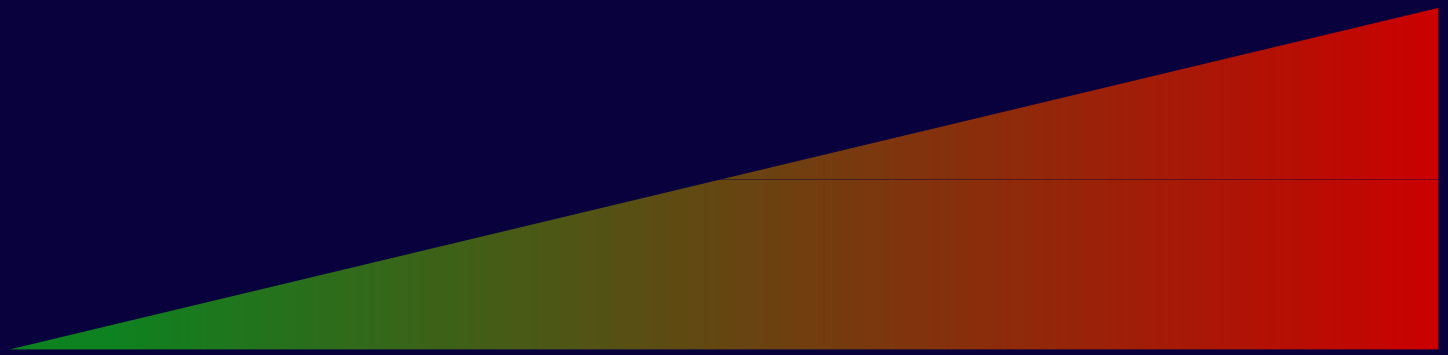
Score 2

Score 3 & 4

Probability of CHD according to health score

Ahmed H et al. MESA. Am J Epi 2013.

ART and Effects on Lipids



TDF

RAL
DTG

RPV

ABC

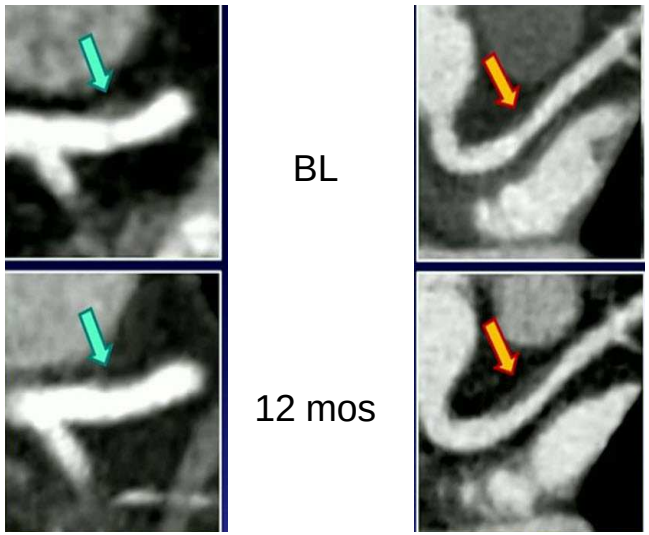
EFV

ATV/RTV or ATV/COBI
DRV/RTV or DRV/COBI
EVG/COBI

Randomized Trial of Statin Therapy and Coronary Plaque Progression

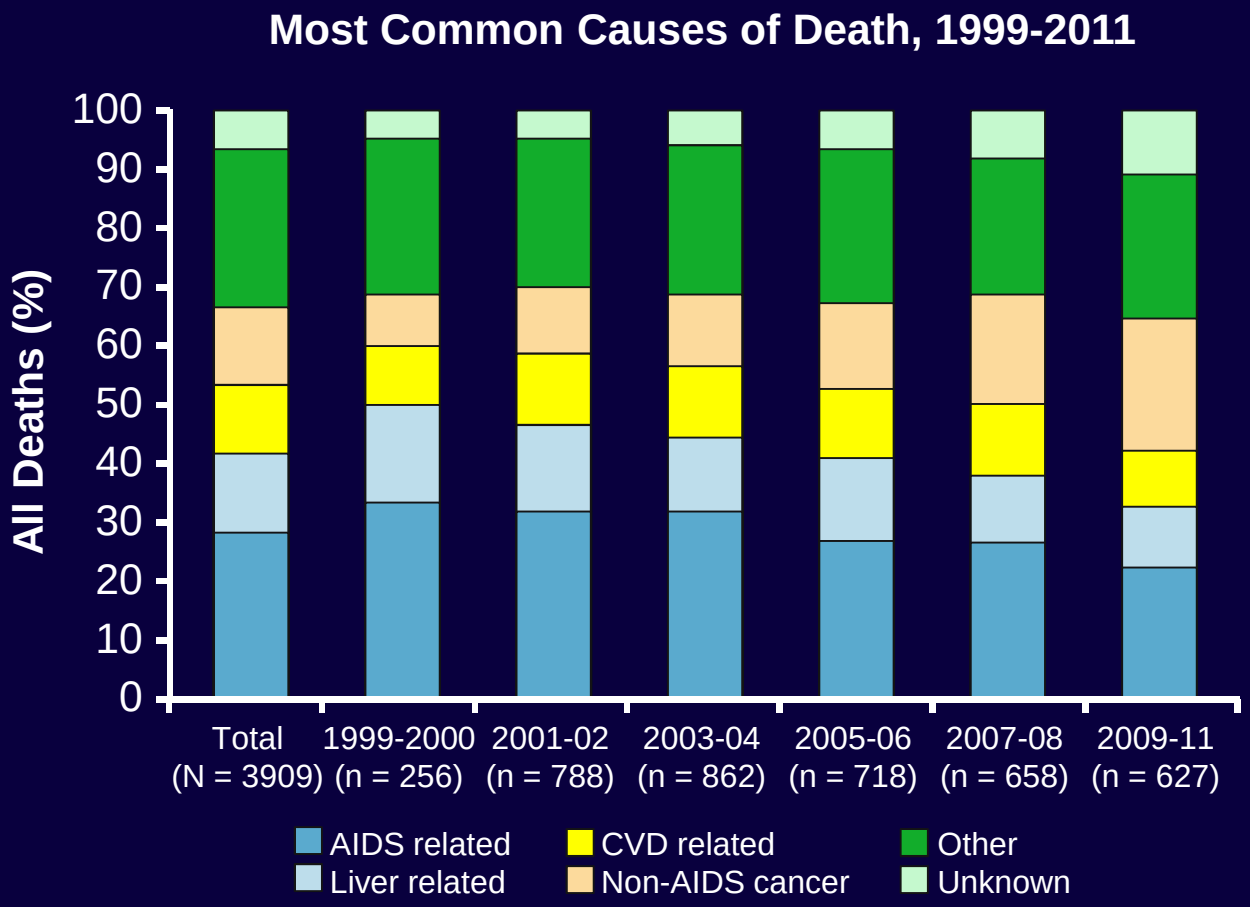
- Randomized 12-mo trial in HIV+ pts on stable ART with LDL-C < 130 and ≥ 1 coronary plaque
  - Atorvastatin 20 mg (↑ to 40 mg at 3 mos) (n = 19) vs
  - Placebo (n = 21)
- Statin therapy reduced progression of coronary plaques
  - Reduced overall plaque volume, including lipid-laden plaques
  - Reduced high-risk morphology plaques
- Statin therapy safe and well tolerated

Plaque Progression in Proximal Left Anterior Descending Coronary Artery With Atorvastatin or Placebo



Lo J, et al. CROI 2015. Abstract 136.

D:A:D: CVD Deaths Decreased in Era of Modern ART



Smith C, et al Lancet. 2014:384:241-248.

Overall Conclusions

- Virologic suppression and immune restoration remain the most important goals of HIV disease management
  - Will certainly reduce HIV-associated NCI
- With increasing longevity of HIV-infected patients, focus is shifting toward whole health patient care
  - Management of age-related comorbidities is critical in order to optimize long-term outcomes
    - Lifestyle changes (diet, exercise, smoking, alcohol)
    - Statins
    - Treatment of hypertension
    - Optimization of ART
  - Optimal management of these co-morbidities will likely reduce the risk of NCI