HIV e infarto miocardico: un problema dimenticato?

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CVD and HIV disease. The current issues

- The real size
- Screening and evaluation
- Clinical management

Italy

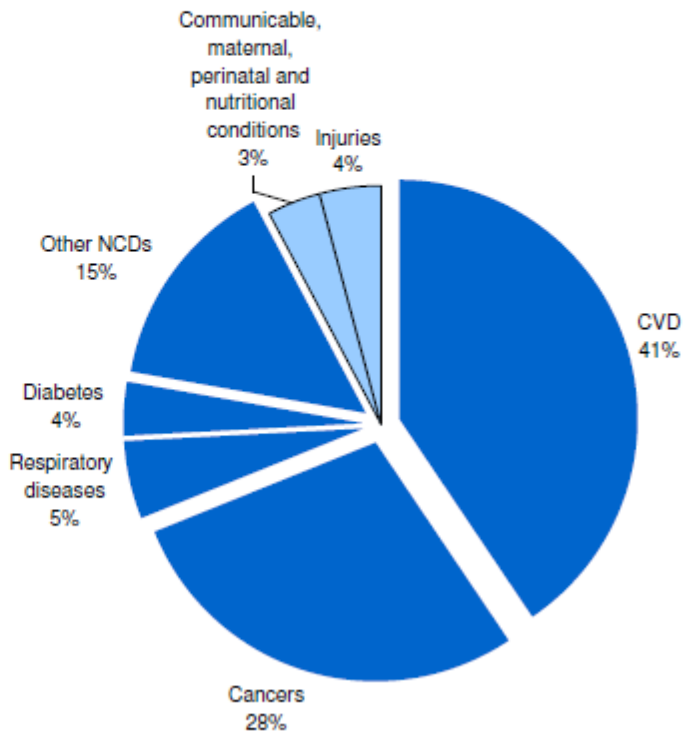
2010 total population: 60 550 848
Income group: High

NCD mortality		
2008 estimates	***males***	***females***
Total NCD deaths (000s)	256.1	280.8
NCD deaths under age 60 (percent of all NCD deaths)	9.8	5.6
Age-standardized death rate per 100 000		
All NCDs	399.8	244.9
Cancers	158.0	90.7
Chronic respiratory diseases	24.6	9.4
Cardiovascular diseases and diabetes	156.3	102.0

Behavioural risk factors			
2008 estimated prevalence (%)	***males***	***females***	***total***
Current daily tobacco smoking	26.3	13.5	19.6
Physical inactivity	51.0	61.8	56.6

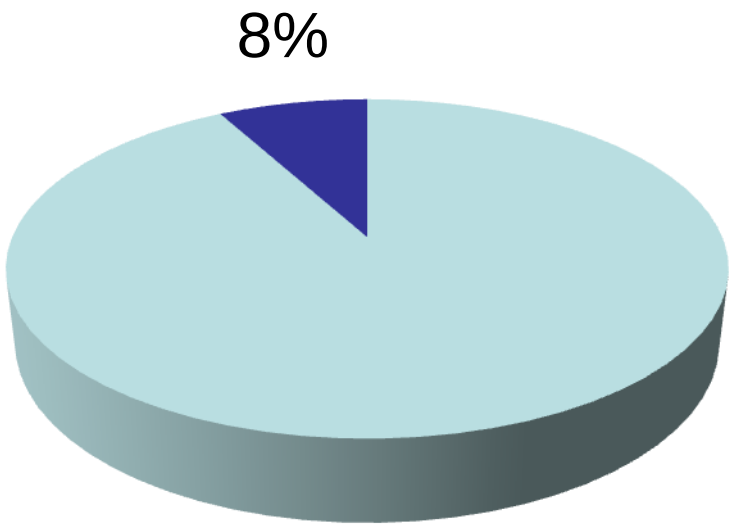
Metabolic risk factors			
2008 estimated prevalence (%)	***males***	***females***	***total***
Raised blood pressure	47.9	44.4	46.1
Raised blood glucose	10.6	7.6	9.1
Overweight	61.8	47.1	54.1
Obesity	21.2	18.5	19.8
Raised cholesterol	63.5	66.8	65.2

Proportional mortality (% of total deaths, all ages)

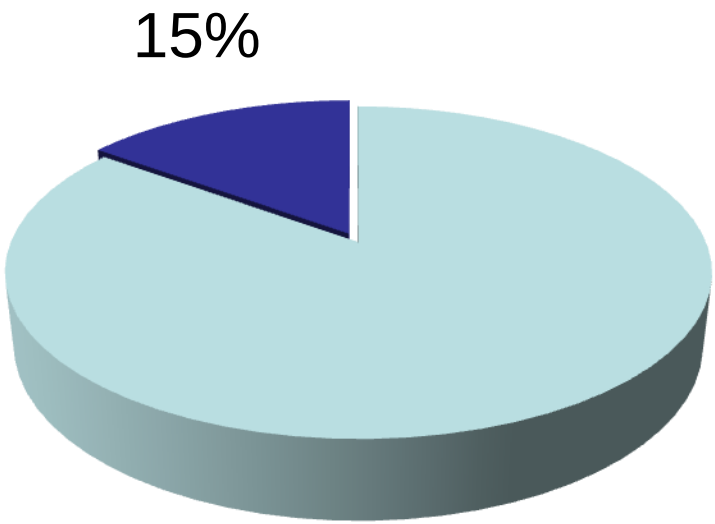


NCDs are estimated to account for 92% of all deaths.

Cardiovascular deaths among HIV-infected patients
(percentage of total deaths)



France



U.S.

(Lewden C et al., J AIDS 2008)
(Palella FJ et al., J AIDS 2006)

Morbidity and Aging in HIV-Infected Persons: The Swiss HIV Cohort Study

- Prospective, observational cohort
- 8,444 HIV-infected patients
- 2008-2010

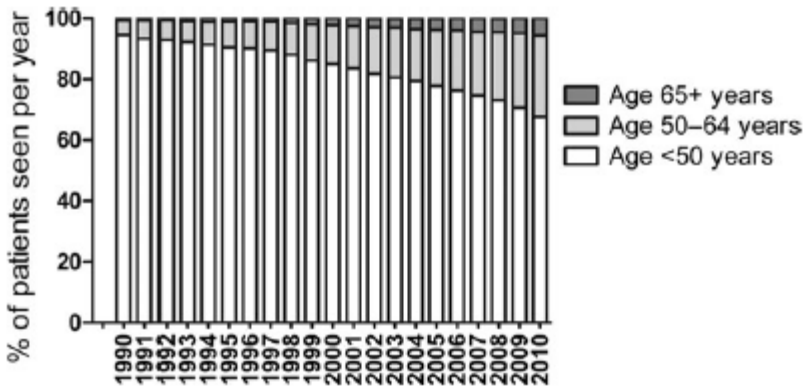
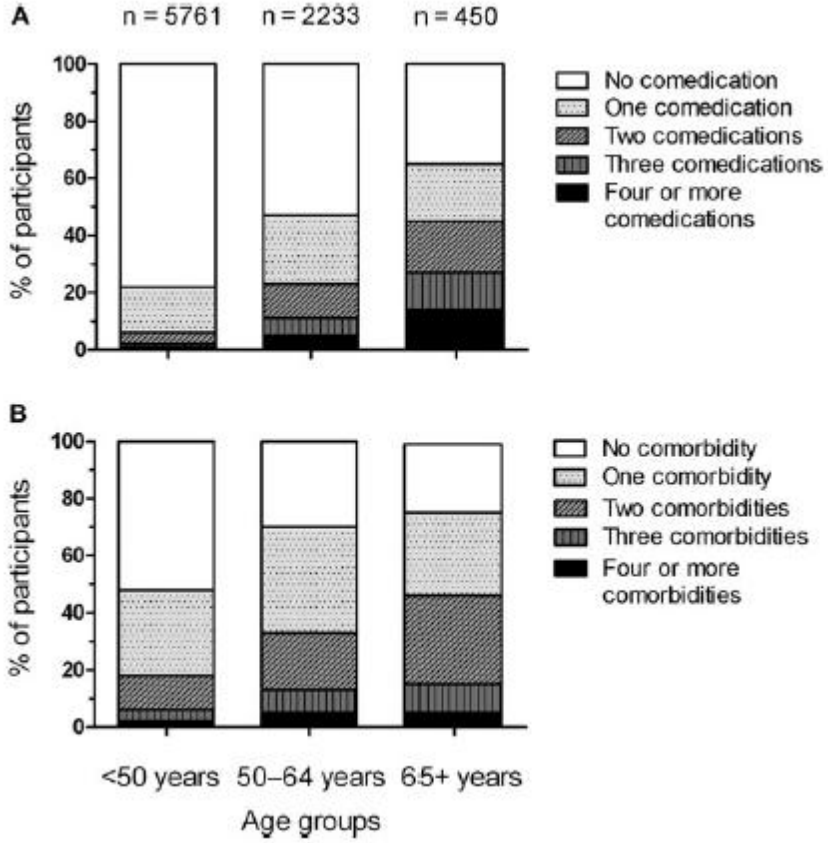


Figure 1. Age distribution among active participants of the Swiss HIV Cohort Study over time.



(Hasse B et al., Clin Infect Dis 2011)

Morbidity and Aging in HIV-Infected Persons: The Swiss HIV Cohort Study

Comorbidities	Rate per 1000 person-years	95% C.I.
Non-AIDS defining malignancies	5.12	4.27-6.15
Coronary angioplasty	3.38	2.7-4.23
Myocardial infarction	2.44	1.88-3.18
Cerebral infarction	1.73	1.26-2.37
Osteoporosis	2.71	2.11-3.48
Liver-associated diseases	2.53	1.95-3.28
Kidney-associated diseases	1.37	0.97-1.95

(Hasse B et al., Clin Infect Dis 2011)

Studies about cardiovascular disease risk in HIV-infected patients compared to the general population

Author	Year	Cohort/ population	N. of HIV+ patients	Results	Effect size
Klein	2002	Kaiser	4,159	↑ MI and CHD vs control	1.5 (MI); 1.7 (CHD)
Currier	2003	CA Medicaid	28,513	↑ CHD vs control	2.06
Triant	2007	Partners	3,851	↑ MI vs control	1.75
Obel	2007	Danish Cohort	3,953	↑ CHD vs control	2.12
Lang	2010	FHDH	74,958	↑ MI vs control	1.5
Durand	2011	Quebec	7,053	↑ MI vs control	2.11
Freiberg	2013	VA	27,350	↑ MI vs control	1.5

HIV Infection and the Risk of Acute Myocardial Infarction

Table 2. Rates of AMI by HIV Status and Age Group[a]

Status	Age Group, y							
	<30	30-39	40-49	50-59	60-69	70-79	80-89	>89
Uninfected								
No. of participants	1175	6783	21 866	19 805	4209	1120	148	3
No. of AMI events	0	19	184	218	66	30	14	0
AMI rates per 1000 person-years (95% CI)	. . .	0.3 (0.2-0.6)	1.5 (1.3-1.7)	2.2 (1.9-2.5)	3.3 (2.6-4.2)	6.7 (4.8-9.2)	21.5 (12.7-36.4)	. . .
HIV Infected								
No. of participants	725	3848	10 575	9342	2065			
No. of AMI events	0	13	105	171	46			
AMI rates per 1000 person-years (95% CI)	. . .	0.7 (0.4-1.2)	2.0 (1.6-2.4)	3.9 (3.3-4.5)	5.0 (3.8-6.7)			
Incidence rate ratio (95% CI)	. . .	2.19 (0.89-5.58)	1.34 (1.04-1.72)	1.80 (1.47-1.21)	1.53 (1.03-2.26)			

- Veterans Aging Cohort Study
- 82,459 HIV-infected patients
- 2003-2009

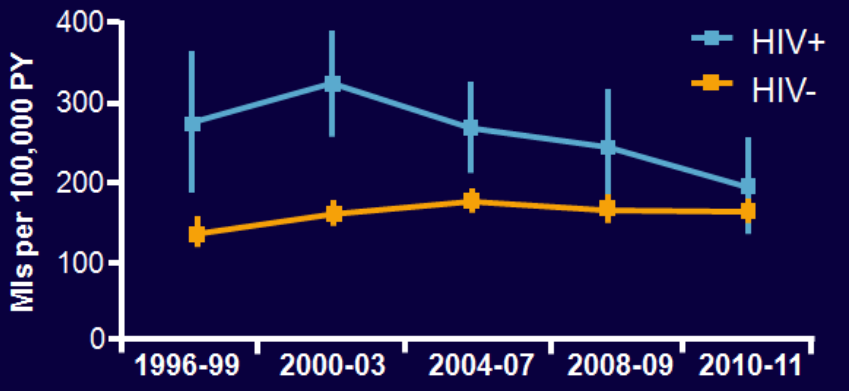
Table 4. Time-Updated Analyses Assessing the Association of HIV-1 RNA and CD4 Cell Count Values and the Risk of AMI in Separate Models[a]

Category	HR (95% CI)	*P* Value[b]
HIV-1 RNA		
Uninfected	1 [Reference]	.05
≥500	1.75 (1.40-2.18)	
<500	1.39 (1.17-1.66)	
CD4 cell count		
Uninfected	1 [Reference]	.04
<200	1.88 (1.46-2.40)	
≥200	1.43 (1.21-169)	

(Freiberg MS et al., JAMA Intern Med 2013)

Incidence of MI in HIV+ vs HIV- Subjects in Kaiser Cohort

- Retrospective analysis of Kaiser cohort EMRs during 1996-2011 for inpatient MI diagnosis
- HIV-/HIV+ pts matched 10:1
- MI rates in HIV+ and HIV- converged over time
  - 40% increased risk of MI in HIV+ pts overall, but difference no longer observed in most recent yrs



Framingham Risk Score Components, 2010-11	HIV+	HIV-	*P* Value
Mean Framingham score, 10-yr risk of MI, %	9.2	9.6	< .001
Male, %	90.7	90.4	.42
Mean age, yrs	47.9	48.5	< .001
TC > 200 mg/dL, %	30.0	39.6	< .001
HDL-C < 40 mg/dL, %	39.4	26.2	< .001
Hx of hypertension, %	28.5	26.2	< .001
Hx of smoking, %	48.7	34.9	< .001

Klein D, et al. CROI 2014. Abstract 737. Reproduced with permission.

Immunodeficiency and Risk of Myocardial Infarction Among HIV-Positive Individuals With Access to Care

(Kaiser Permanente cohort study: 22,081 HIV+ patients, 1996-2009)

TABLE 2. RRs* (95% CI) for MI Comparing HIV+ (Overall and Stratified by Recent and Nadir CD4 Count, and Recent HIV RNA) With HIV− Subjects

	HIV Status (HIV− Reference)			P
Unadjusted	1.72 (1.51–1.94)			<0.001
Adjusted	1.44 (1.27, 1.64)			<0.001
	Recent CD4, cells/μL (HIV− Reference)			
	<200	**200–499**	**≥500**	**P†**
Unadjusted	1.96 (1.46–2.63)	1.92 (1.61–2.28)	1.42 (1.16–1.74)	0.0482
Adjusted	1.76 (1.31–2.37)	1.59 (1.34–1.90)	1.18 (0.96–1.45)	0.030
	Nadir CD4, cells/μL (HIV− Reference)			
	<200	**200–499**	**≥500**	**P†**
~~Unadjusted~~	~~2.28 (1.93–2.69)~~	~~1.50 (1.23–1.81)~~	~~0.82 (0.53–1.28)~~	~~<0.001~~
Adjusted	1.74 (1.47–2.06)	1.30 (1.07–1.58)	0.85 (0.55–1.33)	0.002
	Recent HIV RNA, copies/mL (HIV− Reference)			
	≥10,000	**500–9999**	**<500**	**P†**
Unadjusted	1.46 (1.11–1.93)	1.44 (1.04–2.00)	1.87 (1.61–2.17)	0.1398
Adjusted	1.66 (1.26–2.20)	1.37 (0.98–1.90)	1.41 (1.21–1.64)	0.54

*Unadjusted and adjusted RRs from Poisson regression models with terms for HIV status/CD4/HIV RNA (HIV− reference group). Adjusted model additionally adjusted for age, sex, race/ethnicity, calendar era, SES, smoking, overweight, alcohol/drug abuse, diabetes, hypertension and lipid-lowering therapy.

†*P*-value from the likelihood ratio test of equality across strata.

(Silverberg MJ et al., J AIDS 2014)

Linee guida per il trattamento dell'ipercolesterolemia (*NCEP, 2004*)

Colesterolo LDL (mg/dL)

FATTORI DI RISCHIO PER CHD	Goal	DIETA IPOLIPIDICA	TERAPIA FARMACOLOGICA
Senza CHD:			
0-1 fattori di rischio	**< 160**	**> 160**	**> 190**
> 2 fattori di rischio			
-rischio <10%	**< 130**	**> 130**	**> 160**
-rischio 10-20%	**< 130-100**	**> 130**	**> 130**
Con CHD o equivalenti:			
(diabete, rischio > 20%)	**< 70-100**	**> 100**	**> 100**

(Grundy SM, J Am Coll Cardiol 2004)

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Neil J. Stone, Jennifer Robinson, Alice H. Lichtenstein, C. Noel Bairey Merz, Conrad B. Blum, Robert H. Eckel, Anne C. Goldberg, David Gordon, Daniel Levy, Donald M. Lloyd-Jones, Patrick McBride, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Karol Watson and Peter W.F. Wilson

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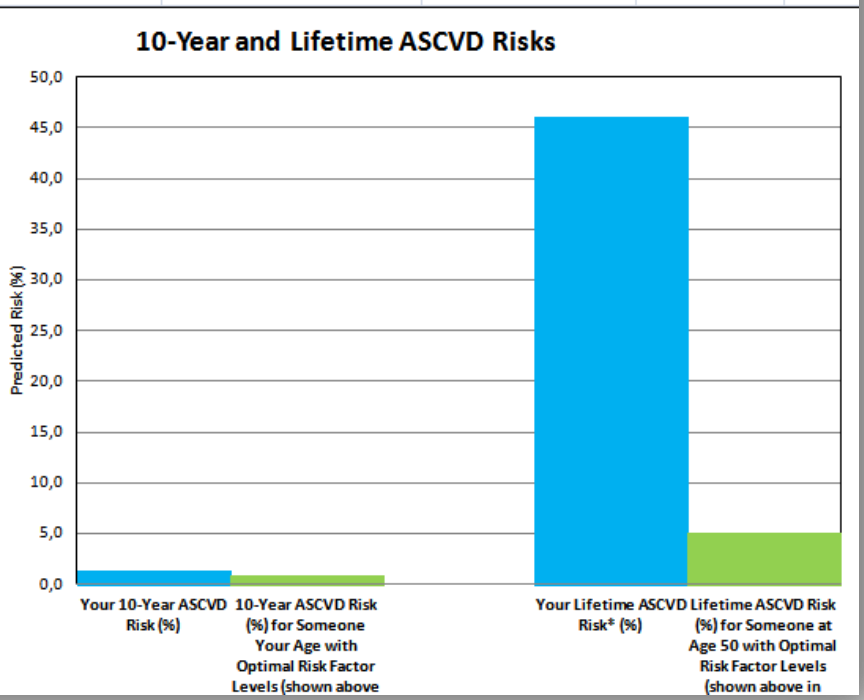
The Pooled Cohort Equations to estimate the 10-year and lifetime risk of ASCVD

Risk Factor	Units	Value	Acceptable range of values	Optimal values
Sex	M (for males) or F (for females)	M	M or F	
Age	years	42	20-79	
Race	AA (for African Americans) or WH (for whites or others)	WH	AA or WH	
Total Cholesterol	mg/dL	210	130-320	170
HDL-Cholesterol	mg/dL	50	20-100	50
Systolic Blood Pressure	mm Hg	120	90-200	110
Treatment for High Blood Pressure	Y (for yes) or N (for no)	N	Y or N	N
Diabetes	Y (for yes) or N (for no)	N	Y or N	N
Smoker	Y (for yes) or N (for no)	N	Y or N	N

Your 10-Year ASCVD Risk (%)	**1,4**
10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)	**0,8**
Your Lifetime ASCVD Risk* (%)	**46,0**
Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (shown above in column E)	**5,0**

***This is the lifetime ASCVD risk for an individual at age 50 years with your risk factor levels. In rare cases, 10-year risks may exceed lifetime risks given that the estimates come from different approaches**

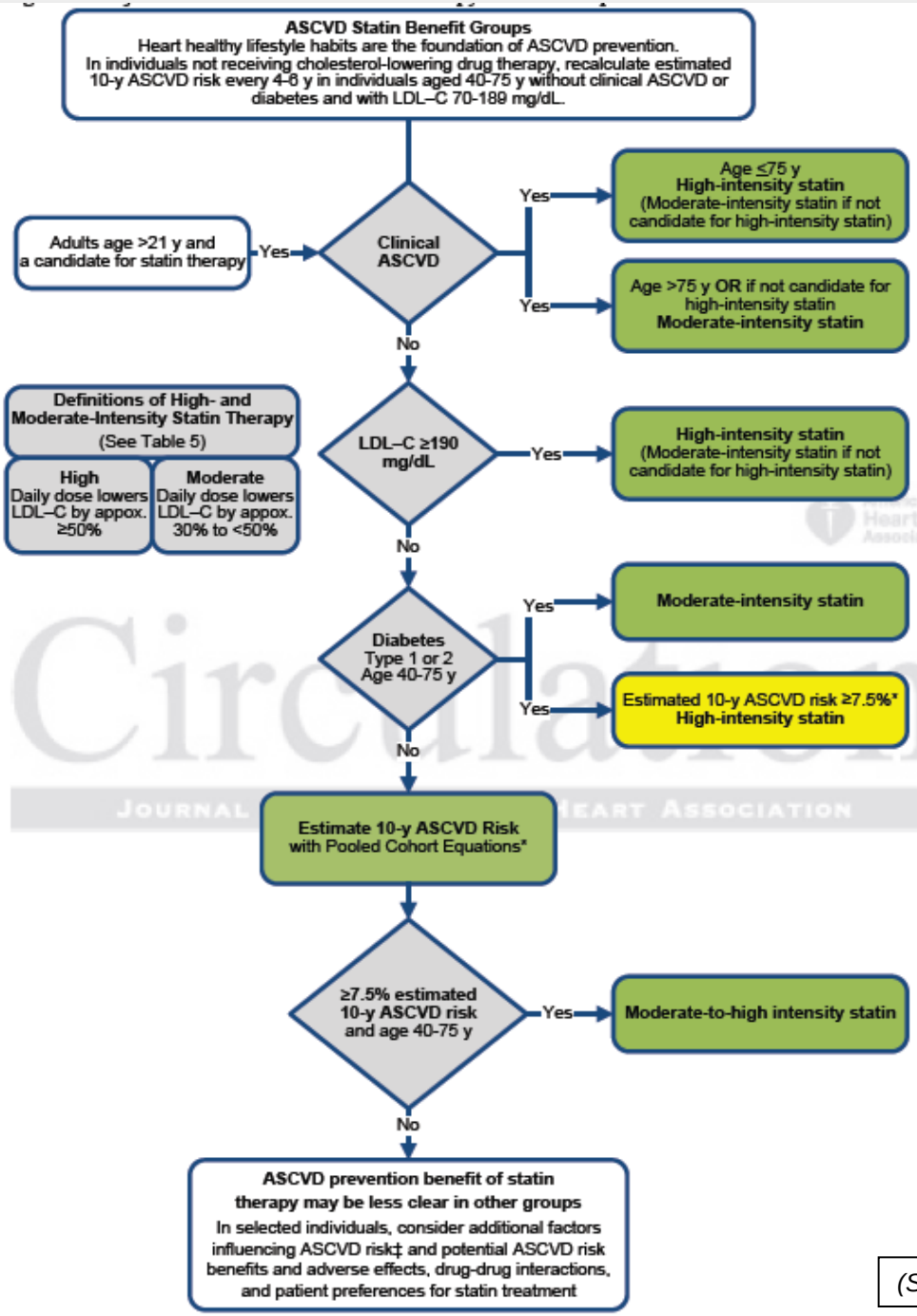


(http://my.americanheart.org/cvriskcalculator)

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** ***(40)*** **mg**	**Atorvastatin 10** ***(20)*** **mg** **Rosuvastatin** ***(5)*** **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** ***(80)*** **mg** **Lovastatin 40 mg** ***Fluvastatin XL 80 mg*** **Fluvastatin 40 mg bid** ***Pitavastatin 2–4 mg***	***Simvastatin 10 mg*** **Pravastatin 10–20 mg** **Lovastatin 20 mg** ***Fluvastatin 20–40 mg*** ***Pitavastatin 1 mg***

(Stone NJ et al., Circulation 2013)



(Stone NJ et al., Circulation 2013)

Enlarge

By Alex Wong, Getty Images for

Moderator Tim Russert is seen
"Meet the Press" at the NBC stu
in Oct. 2007.

NBC's Tim Russert dead at 58

By Jill Lawrence, USA TODAY

WASHINGTON — Tim Russert, the award-winning NBC political pundit who communicated his love of campaigns and

The New York Times U.S.

Tim Russert, 1950-2008 1 of 14

USA TODAY

June 13, 2008

Could Russert's death has been prevented?

He was being treated for high LDL, low HDL and hypertension; he did not smoke; he did not have diabetes.

A stress test in late April was normal.

He had even had a calcium scan in 2006, which yielded a calcium score of 210.

Autopsy has confirmed LV enlargement and plaque rupture in his LAD.

Grady D. A search for answers in Russert's death. New York Times June 17, 2008

The Tim Russert's cardiovascular risk (Framingham score)

Traditional risk factors:

1)Age 2) Hypertension 3) Low HDL cholesterol

NATIONAL CHOLESTEROL EDUCATION PROGRAM
Third Report of the Expert Panel on
Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Risk score results:

Age:	58	
Gender:	male	
Total Cholesterol:	212 mg/dL	**LDL 134 mg/dL**
HDL Cholesterol:	42 mg/dL	
Smoker:	No	
Systolic Blood Pressure:	130 mm/Hg	
On medication for HBP:	Yes	
Risk Score*	13%	

* The risk score shown was derived on the basis of an equation. Other NCEP materials, such as ATP II based system to calculate a risk score that approximates the equation-based one.

To interpret the risk score and for specific information about CHD risk assessment as part of detection, evaluation, blood cholesterol, see ATP III Executive Summary and ATP III At-a-Glance.

The Tim Russert's cardiovascular risk (Mesa score)

Agatston Calcium Score: 210

OPTIONAL (To obtain estimated Framingham 10-year CHD risk)

Age (over 45): 58

Gender: ○ Female ◉ Male

Total cholesterol (mg/dl): 212

HDL cholesterol (mg/dl): 42

Systolic BP (mmHg): 130

Current smoker: ◉ No ○ Yes

Use of meds for hypertension: ○ No ◉ Yes

Calculate

30%

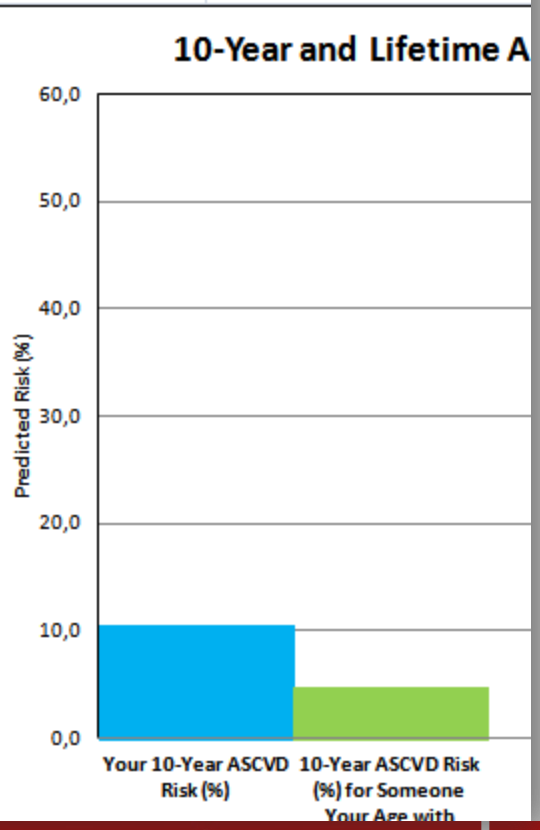
The estimated arterial age for a person with a CAC score of 210 is 78 years (95% CI 75 - 81 years).

The estimated Framingham 10-year Hard CHD Risk is 16 % using observed ag and 30 % using arterial age.

MESA The Multi-Ethnic Study of Atherosclerosis

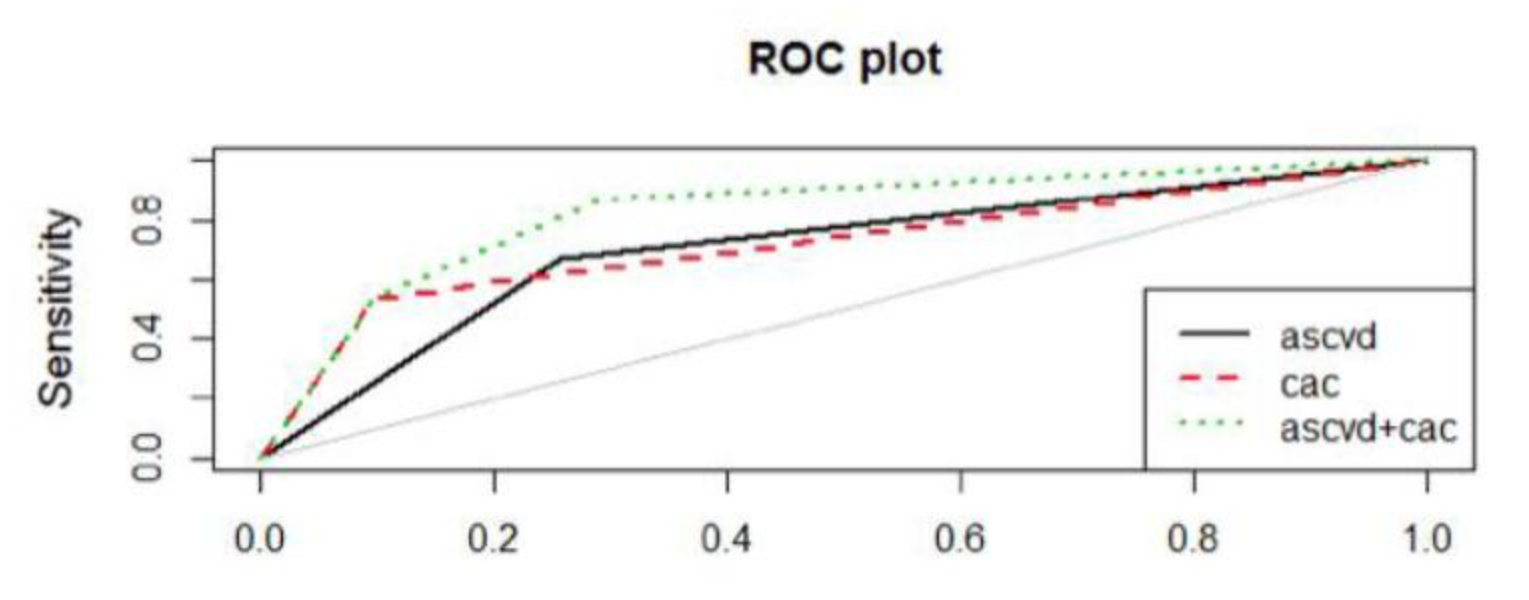
			Enter patient values in this column	
2	**Risk Factor**	**Units**	**Value**	Acceptable range of values
3	**Sex**	M (for males) or F (for females)	**M**	M or F
4	**Age**	years	**58**	20-79
5	**Race**	AA (for African Americans) or WH (for whites or others)	**WH**	AA or WH
6	**Total Cholesterol**	mg/dL	**212**	130-320
7	**HDL-Cholesterol**	mg/dL	**42**	20-100
8	**Systolic Blood Pressure**	mm Hg	**130**	90-200
9	**Treatment for High Blood Pressure**	Y (for yes) or N (for no)	**Y**	Y or N
10	**Diabetes**	Y (for yes) or N (for no)	**N**	Y or N
11	**Smoker**	Y (for yes) or N (for no)	**N**	Y or N

13	**Your 10-Year ASCVD Risk (%)**	**10,6**
14	10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)	**4,8**
16	**Your Lifetime ASCVD Risk* (%)**	**50,0**
17	Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (shown above in column E)	**5,0**



The Pooled Cohort Equations
to estimate the 10-year and lifetime risk of ASCVD

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: the impact in a large HIV cohort

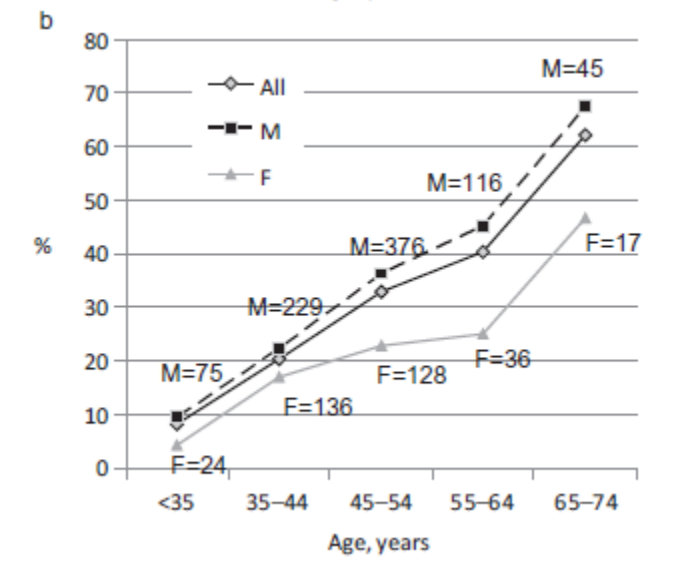


(Guaraldi G et al., Abstract OC73, ICAR 2014)

Prevalence, Awareness, Treatment, and Control Rate of Hypertension in HIV-Infected Patients: The HIV-HY Study

Giuseppe Vittorio De Socio,[1] Elena Ricci,[2] Paolo Maggi,[3] Giustino Parruti,[4] Giacomo Pucci,[5] Antonio Di Biagio,[6] Leonardo Calza,[7] Giancarlo Orofino,[8] Laura Carenzi,[2] Enisia Cecchini,[1] Giordano Madeddu,[9] Tiziana Quirino,[10] and Giuseppe Schillaci;[5] for the CISAI study group

- Multicenter, cross-sectional study
- 1182 HIV-positive patients
- **Overall prevalence of hypertension: 29.3%**

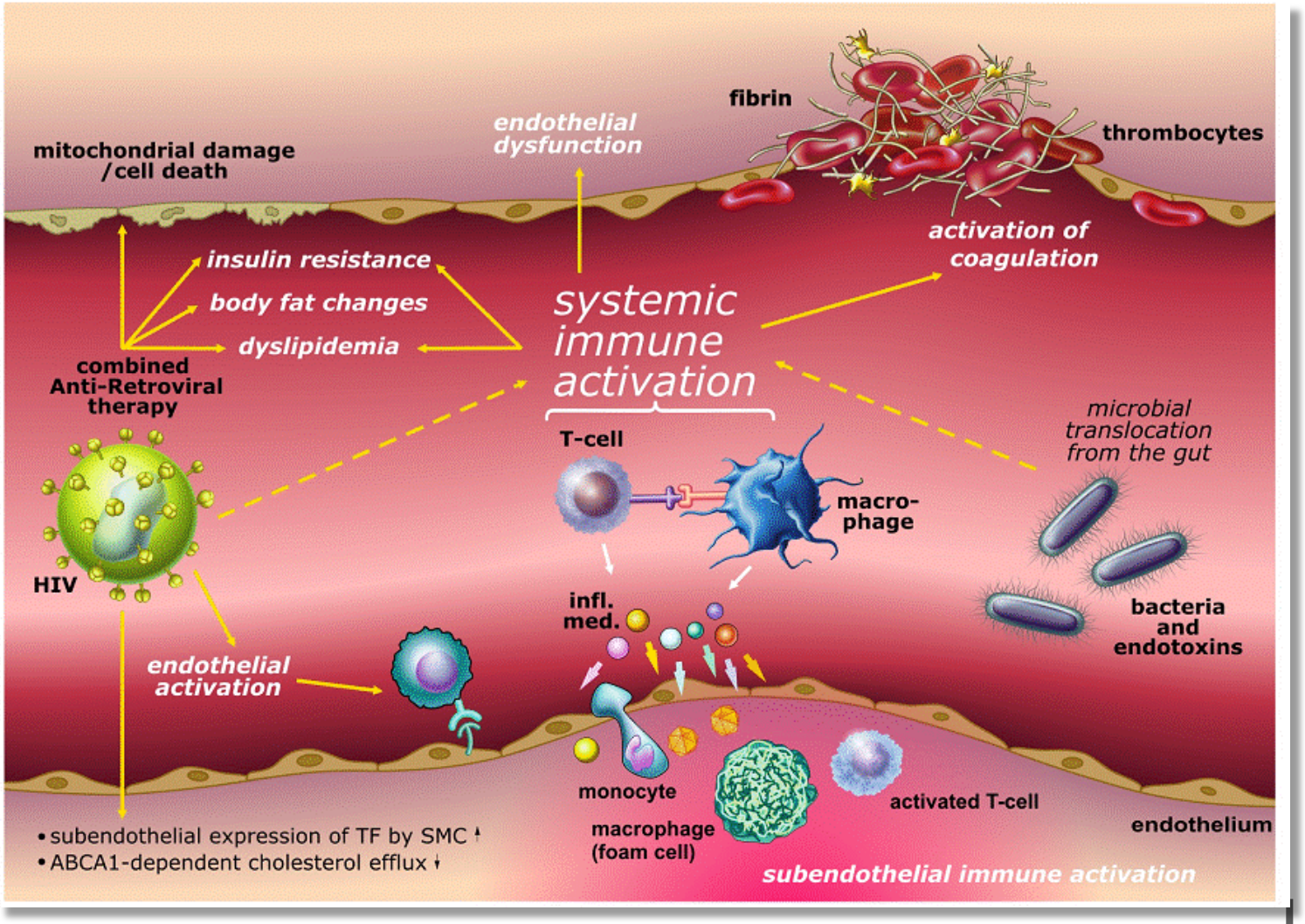


(Am J Hypertens, 2013 Sep 27)

Table 2. Variables associated with hypertension

Variable	Crude Odds ratio (95% CI)	Adjusted[a] Odds ratio (95% CI)
Age ≥50 years	2.39 (1.85–3.09)	1.94 (1.46–2.56)
Men vs. women	1.85 (1.37–2.49)	1.63 (1.18–2.26)
Body mass index ≥25 kg/m²	2.67 (2.06–3.45)	2.52 (1.91–3.33)
Family history of CV disease	1.74 (1.33–2.28)	1.58 (1.18–2.12)
Previous CV events	4.59 (2.54–8.30)	3.14 (1.65–5.99)
Central obesity	1.56 (1.14–2.10)	1.42 (1.03–1.97)
Metabolic syndrome	6.90 (5.18–9.19)	5.67 (4.16–7.73)
Diabetes	3.65 (2.37–5.61)	2.66 (1.65–4.27)
Time since HIV diagnosis, years (by quartile)	1.17 (1.04–1.31)	1.20 (1.05–1.36)
Anti-retroviral treatment duration (by quartile)	1.22 (1.10–1.36)	1.22 (1.08–1.36)
Nadir CD4⁺ cell count/μl (reference: CD4⁺ ≥350)		
<200	1.65 (1.14–2.37)	1.60 (1.05–2.41)
200–349	1.26 (0.85–1.87)	1.31 (0.86–2.00)
Current PI use (reference: no current PI use)	0.93 (0.73–1.20)	0.91 (0.69–1–18)
PastPIuse(reference: no past PI use)	0.73 (0.41–1.29)	0.67 (0.36–1.23)
Current NNRTI use (reference: no currentNNRTIuse)	1.32 (1.02–1.70)	1.25 (0.95–1.64)
Past NNRTI use (reference: no past NNRTI use)	0.57 (0.25–1.31)	0.74 (0.31–1.75)

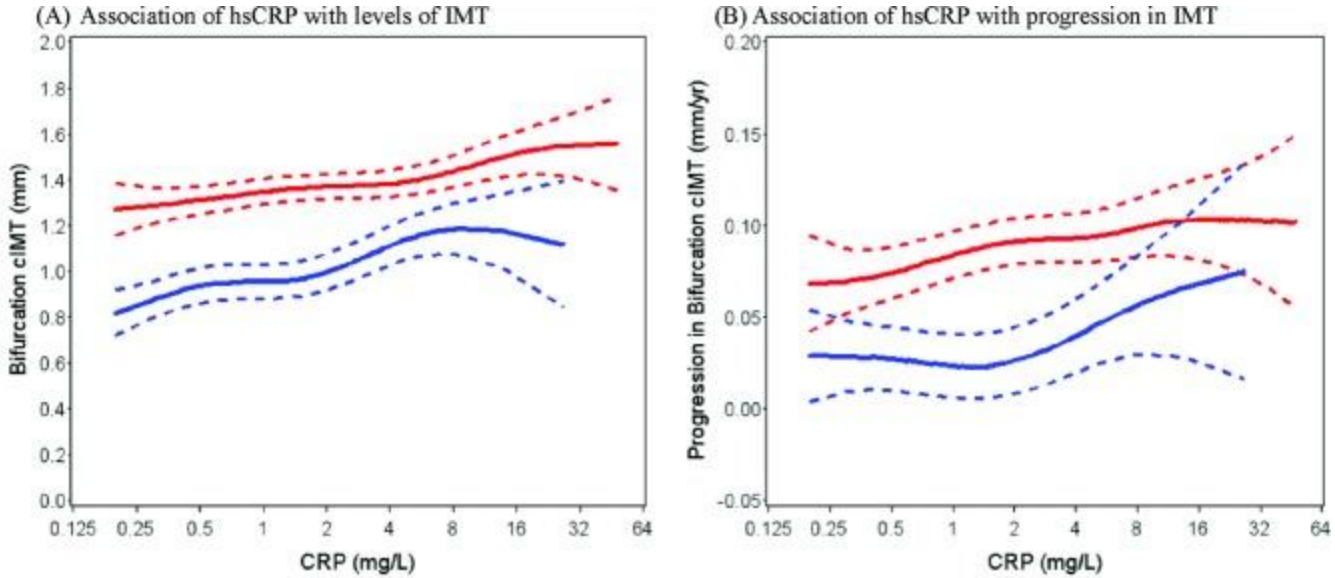
HIV, systemic immune activation and endothelial damage



(van Leuven SI et al., Current Opin HIV/AIDS 2007)

Carotid Intima-Media Thickness Progression in HIV-Infected Adults Occurs Preferentially at the Carotid Bifurcation and Is Predicted by Inflammation

(Case-control study, 347 patients, mean follow-up 2.4 years)



Higher Solid line denotes predicted IMT (with dotted 95%CI confidence bounds) calculated from unadjusted generalized additive model (GAM). P-values are from spline and linear portion of the fit:

HIV: Spline: p=0.090; linear: p=0.0008;
Control: Spline: p=0.0081; linear: p<.0001

HIV: Spline: p=0.29; linear: p=0.017
Control: Spline: p=0.016; linear: p=0.21

(Hsue PY et al., J Am Heart Assoc 2012)

The association of high-sensitivity c-reactive protein and other biomarkers with cardiovascular disease in patients treated for HIV: a nested case–control study

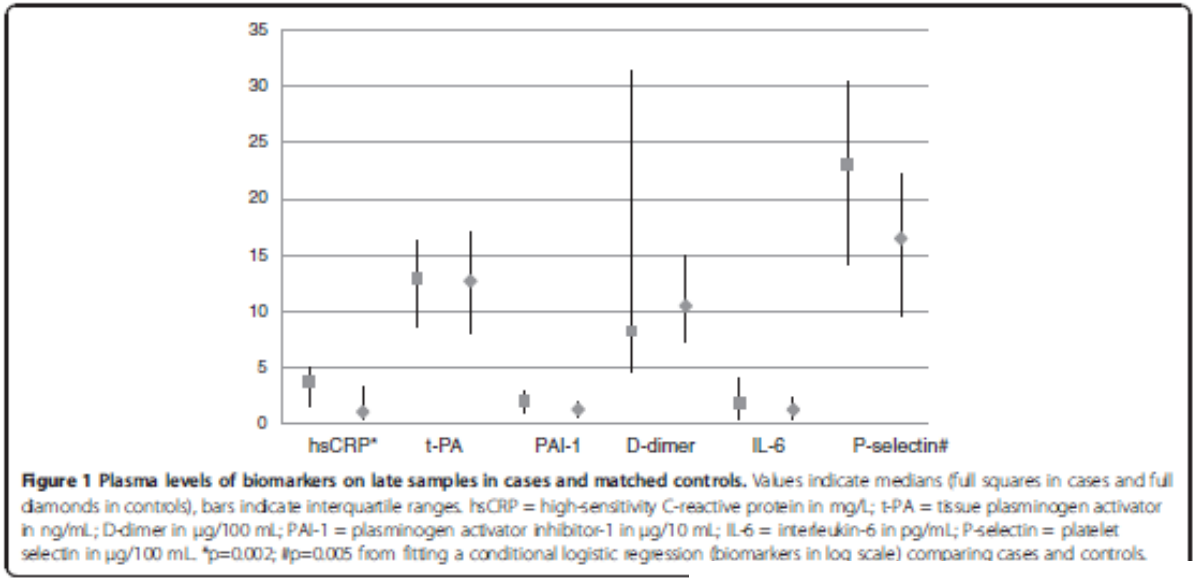


Figure 1 Plasma levels of biomarkers on late samples in cases and matched controls. Values indicate medians (full squares in cases and full diamonds in controls), bars indicate interquartile ranges. hsCRP = high-sensitivity C-reactive protein in mg/L; t-PA = tissue plasminogen activator in ng/mL; D-dimer in µg/100 mL; PAI-1 = plasminogen activator inhibitor-1 in µg/10 mL; IL-6 = interleukin-6 in pg/mL; P-selectin = platelet selectin in µg/100 mL. *p=0.002; #p=0.005 from fitting a conditional logistic regression (biomarkers in log scale) comparing cases and controls.

- Retrospective, nested, case-control study
- 109 HIV-infected patients
- 5-year follow-up

Table 2 Univariable and multivariable odds ratios for cardiovascular events according to biomarkers in late samples *(Continued)*

hsCRP, mg/L				
Per log2 higher	1.61 (1.18, 2.18)	0.002	1.69 (1.09, 2.64)	0.020
IL-6, pg/ml				
Per log2 higher	1.09 (0.81, 1.45)	0.568	1.05 (0.72, 1.53)	0.799
P-selectin, ng/ml				
Per log2 higher	2.88 (1.38, 6.02)	0.005	3.14 (1.04, 9.45)	0.042

Estimate performed by a Conditional Logistic Regression Model; CI = confidence interval; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; IQR = interquartile range; OR = odds ratio; PAI-1 = plasminogen activator inhibitor-1; t-PA = tissue plasminogen activator. *Adjusted for duration of time between the date of samples and the analysis time, age, total cholesterol, HDL.

(De Luca A et al., BMC Infect Dis 2013)

Soluble CD14 is independently associated with coronary calcification and extent of subclinical vascular disease in treated HIV infection

(Cross-sectional study, 147 HIV-positive patients on cART with HIV RNA <1000 copies/mL and LDL-cholesterol <130 mg/dL)

Table 2. Biomarkers of inflammation and immune activation by coronary artery calcium category.

	CAC = 0 (n = 93)	CAC >0 (n = 54)	P
$CD8^+CD38^+HLA\text{-}DR^+$ T cells (%)	13 (9–18)	11 (7.4–17)	>0.1
$CD4^+CD38^+HLA\text{-}DR^+$ T cells (%)	5.1 (3.8–6.9)	4.9 (3.4–6.2)	>0.1
$CD14^+CD16^+$ monocytes (%)	22 (17–32)	26 (19–38)	>0.1
$CD14_{dim}CD16^+$ monocytes (%)	12 (7.8–15)	9.9 (7.8–14)	>0.1
$CD14^+CD16^+TF^+$ monocytes (%)	13 (7.9–18)	10 (6.9–15)	0.03
$CD14_{dim}CD16^+TF^+$ monocytes (%)	21 (14–29)	18 (14–24)	>0.1
Soluble CD14 (ng/ml)	2057 (1677–2413)	2246 (1927–2781)	0.03
Soluble CD163 (ng/ml)	651 (487–829)	630 (476–904)	>0.1
Interleukin-6 (pg/ml)	2.5 (1.9–4.4)	3.0 (2.2–5.7)	0.08
TNF-α receptor I (pg/ml)	1581 (1297–2330)	1581 (1191–2208)	>0.1
High sensitivity CRP (μg/ml)	1.7 (0.8–4.8)	2.0 (0.6–5.3)	>0.1
Soluble VCAM (ng/ml)	638 (530–795)	687 (575–839)	>0.1
D-dimer (μg/ml)	0.17 (0.11–0.32)	0.16 (0.13)-0.29	>0.1
Fibrinogen (mg/dl)	394 (334–513)	367 (339–477)	>0.1
OPG (pmol/l)	3.7 (3.1–4.8)	4.1 (3.0–5.1)	>0.1
RANKL (pg/ml)	10 (3.0–29)	8.2 (2.0–29)	>0.1

Data presented as median (interquartile range). CRP, C-reactive protein; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor kappa-B ligand; TNF, tumour necrosis factor; VCAM, vascular cell adhesion molecule.

(Longenecker CT et al., AIDS 2014)

Plasma plasminogen activator inhibitor-1 predicts myocardial infarction in HIV-1-infected individuals

(Matched case-control study of 54 cases and 54 controls)

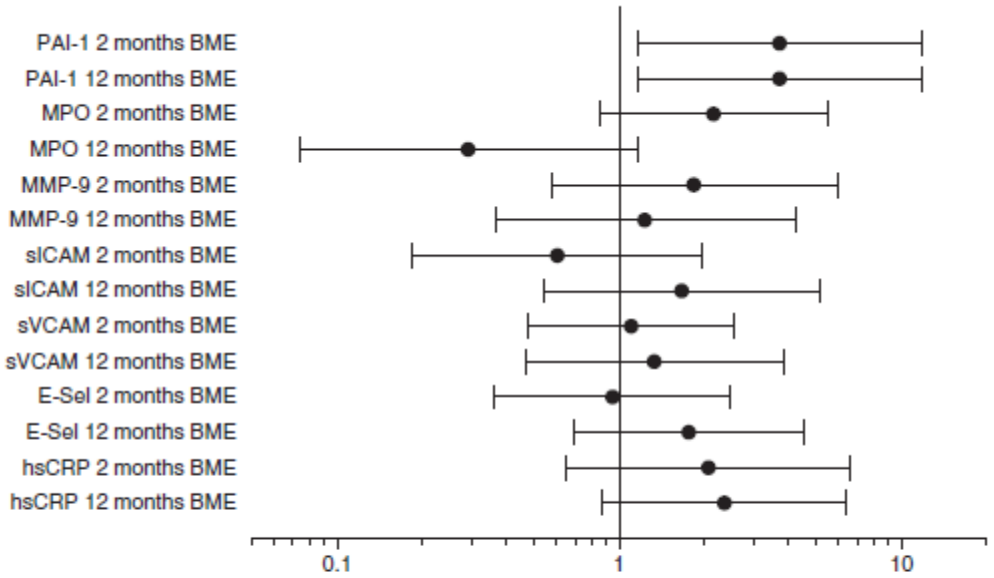


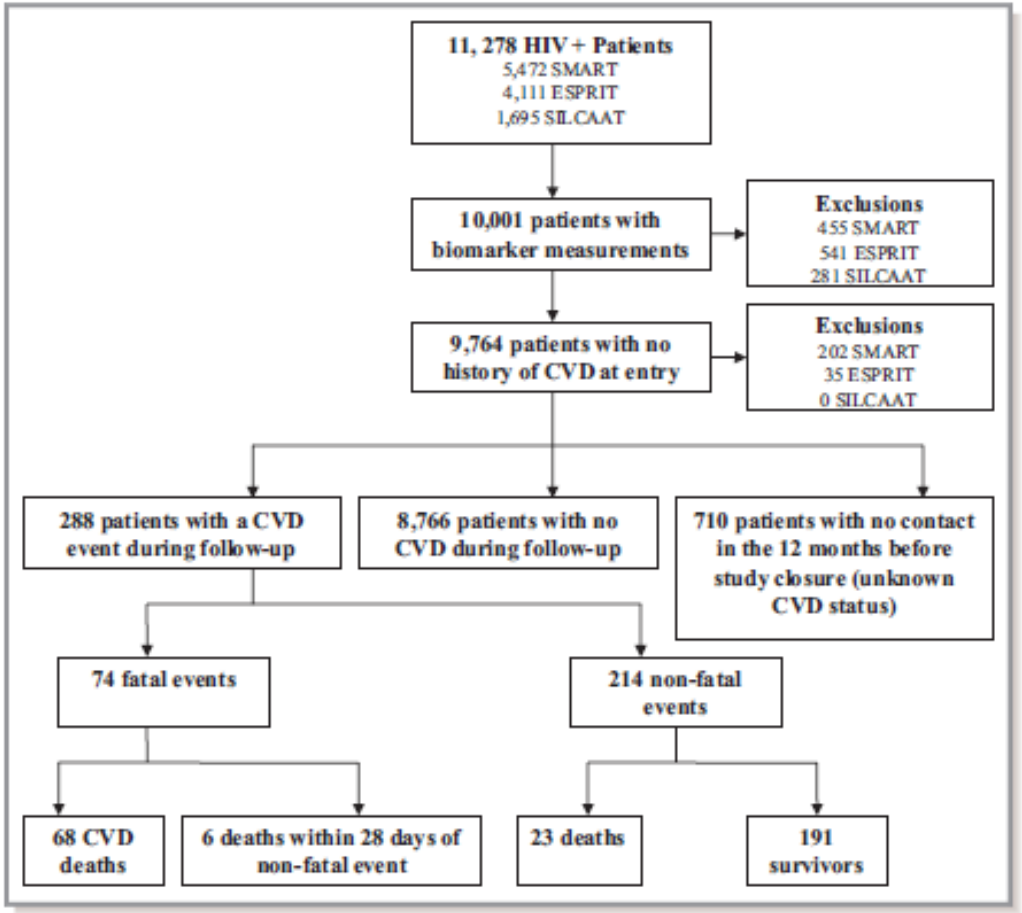
Fig. 2. Risk of myocardial infarction (odds ratio, 95% CI) when having plasma levels in the highest quartile 12 months before matching event (BME) and 2 months BME adjusted for high HIV viral load (>400 copies/ml) and high D:A:D risk score (>10% 5-year risk). BME, before matching event; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; MMP-9, matrix metalloprotease 9; MPO, myloperoxidase; PAI-1, plasminogen activator inhibitor 1; sE-selectin, soluble endothelial selectin; sICAM-1, soluble intercellular adhesion molecule 1; sVCAM-1, soluble vascular adhesion molecule 1.

(Knudsen A et al., AIDS 2014)

ORIGINAL RESEARCH

Severity of Cardiovascular Disease Outcomes Among Patients With HIV Is Related to Markers of Inflammation and Coagulation

- Observational, cohort study
- 9,764 HIV-positive patients with no history of CVD
- Follow-up: 5 years



(Nordell AD et al., J Am Heart Assoc 2014)

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

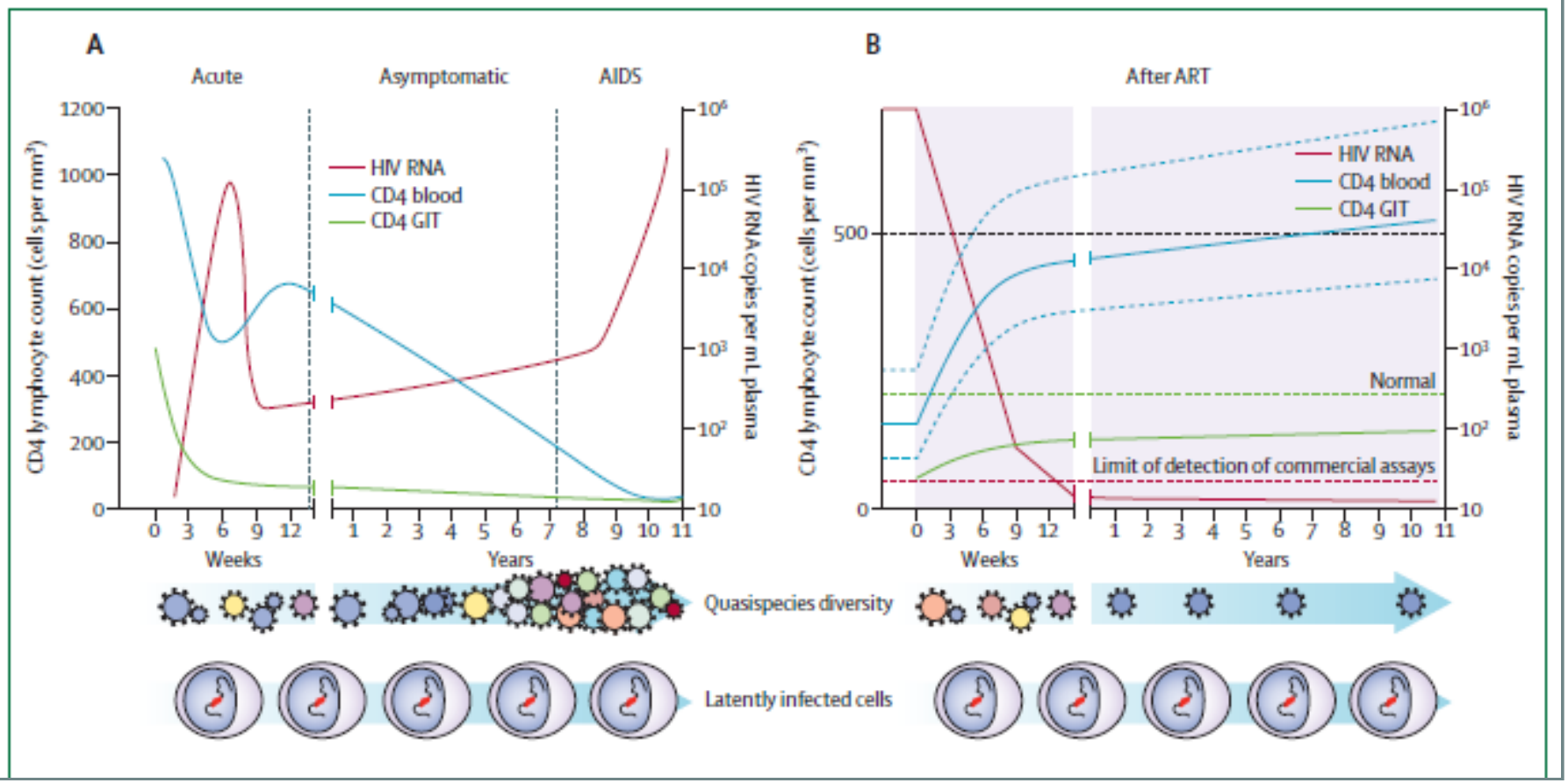
Severity of Cardiovascular Disease Outcomes Among Patients With HIV Is Related to Markers of Inflammation and Coagulation

Table 3. Unadjusted and Covariate Adjusted* Odds Ratios for Fatal CVD† (Versus Nonfatal CVD‡) According to Tertile and Associated With a Doubling of Each Biomarker or 1-Unit Increase of IL-6 and D-Dimer Score

	Lowest Tertile	Middle Tertile			Highest Tertile				OR Associated With Doubling of Biomarker		
Biomarker	OR	OR	95% CI	*P* Value	OR	95% CI	*P* Value	Omnibus *P* Value§	OR	95% CI	*P* Value
IL-6, pg/mL											
Univariate	1.0	1.32	(0.66 to 2.64)	0.44	2.46	(1.25 to 4.87)	0.01	0.02	1.39	(1.07 to 1.79)	0.01
Adjusted	1.0	1.41	(0.69 to 2.88)	0.34	2.62	(1.26 to 5.46)	0.01	0.02	1.41	(1.07 to 1.86)	0.01
D-dimer (μg/mL)											
Univariate	1.0	1.63	(0.80 to 3.33)	0.18	2.47	(1.25 to 4.85)	0.009	0.03	1.40	(1.10 to 1.78)	0.007
Adjusted	1.0	1.74	(0.80 to 3.75)	0.16	2.70	(1.27 to 5.75)	0.01	0.05	1.45	(1.10 to 1.92)	0.008
hsCRP (μg/mL)											
Univariate	1.0	1.17	(0.60 to 2.29)	0.65	1.49	(0.77 to 2.88)	0.24	0.49	1.09	(0.93 to 1.28)	0.31
Adjusted	1.0	1.17	(0.59 to 2.33)	0.65	1.55	(0.78 to 3.10)	0.21	0.39	1.10	(0.93 to 1.30)	0.29
IL-6 and D-dimer score											
Univariate	1.0	1.15	(0.56 to 2.38)	0.71	3.07	(1.57 to 6.00)	0.001	0.001	1.51	(1.15 to 1.97)	0.003
Adjusted	1.0	1.20	(0.57 to 2.54)	0.64	3.67	(1.74 to 7.72)	<0.001	<0.001	1.58	(1.17 to 2.13)	0.003

(Nordell AD et al., J Am Heart Assoc 2014)

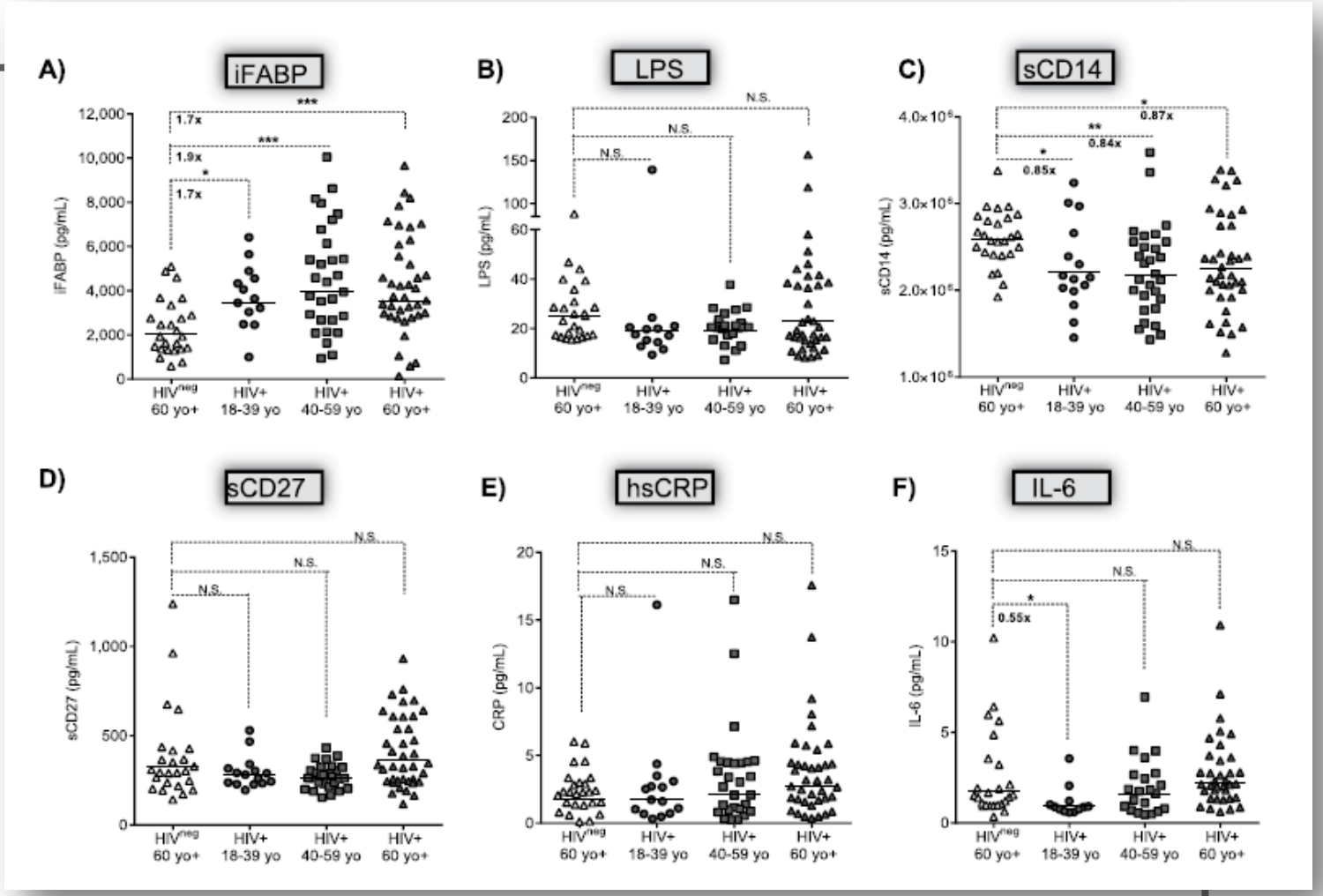
Gastrointestinal tract T CD4+ cell depletion



(Maartens G et al., Lancet 2014)

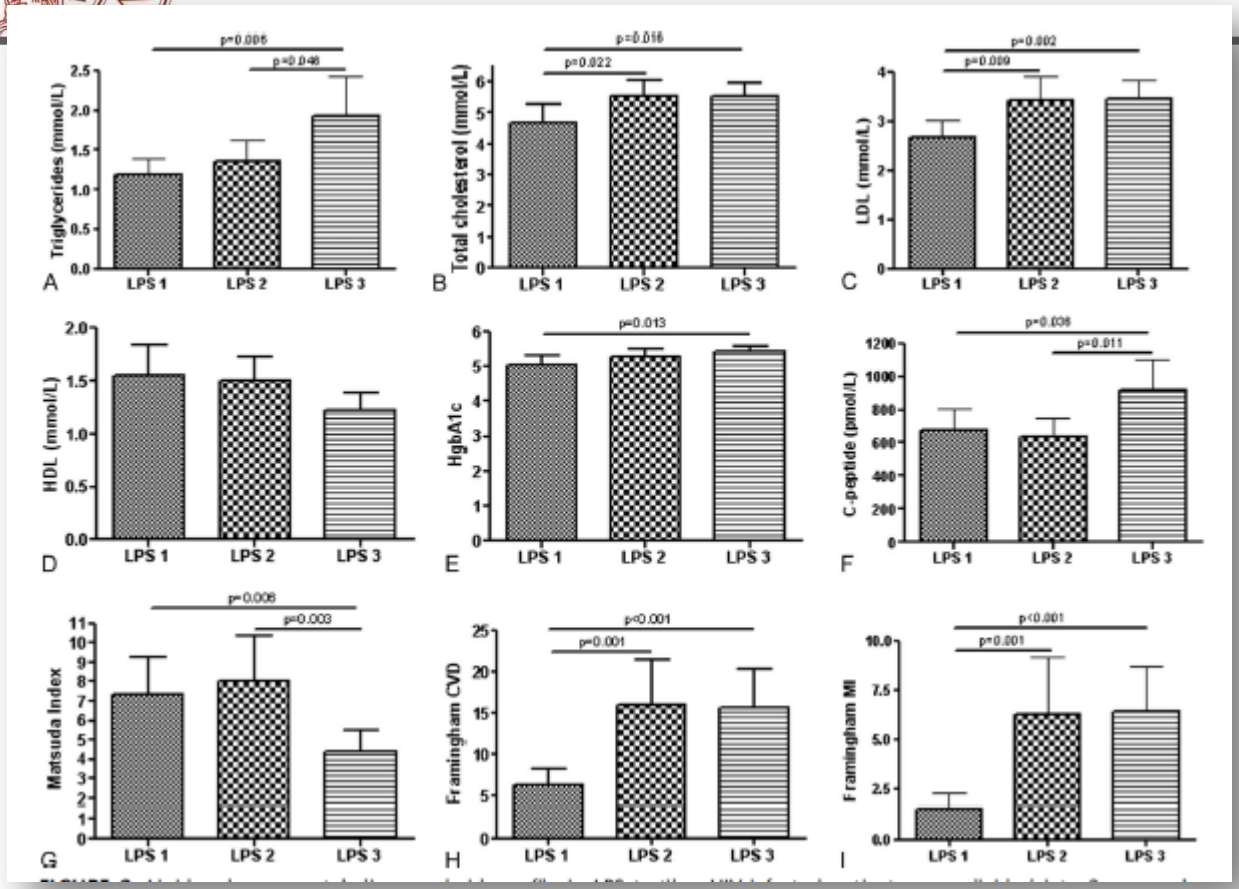
Contribution of Intestinal Barrier Damage, Microbial Translocation and HIV-1 Infection Status to an Inflammaging Signature

- Case-control study
- 83 HIV-positive patients on HAART *vs* 88 HIV-negative subjects
- Age: 20-100 years



(Steele AK et al., PLoS One 2014)

Microbial Translocation in HIV Infection Is Associated With Dyslipidemia, Insulin Resistance, and Risk of Myocardial Infarction



- Cross-sectional study
- 60 HIV-positive patients on HAART with viral suppression *vs* 31 HIV-negative subjects

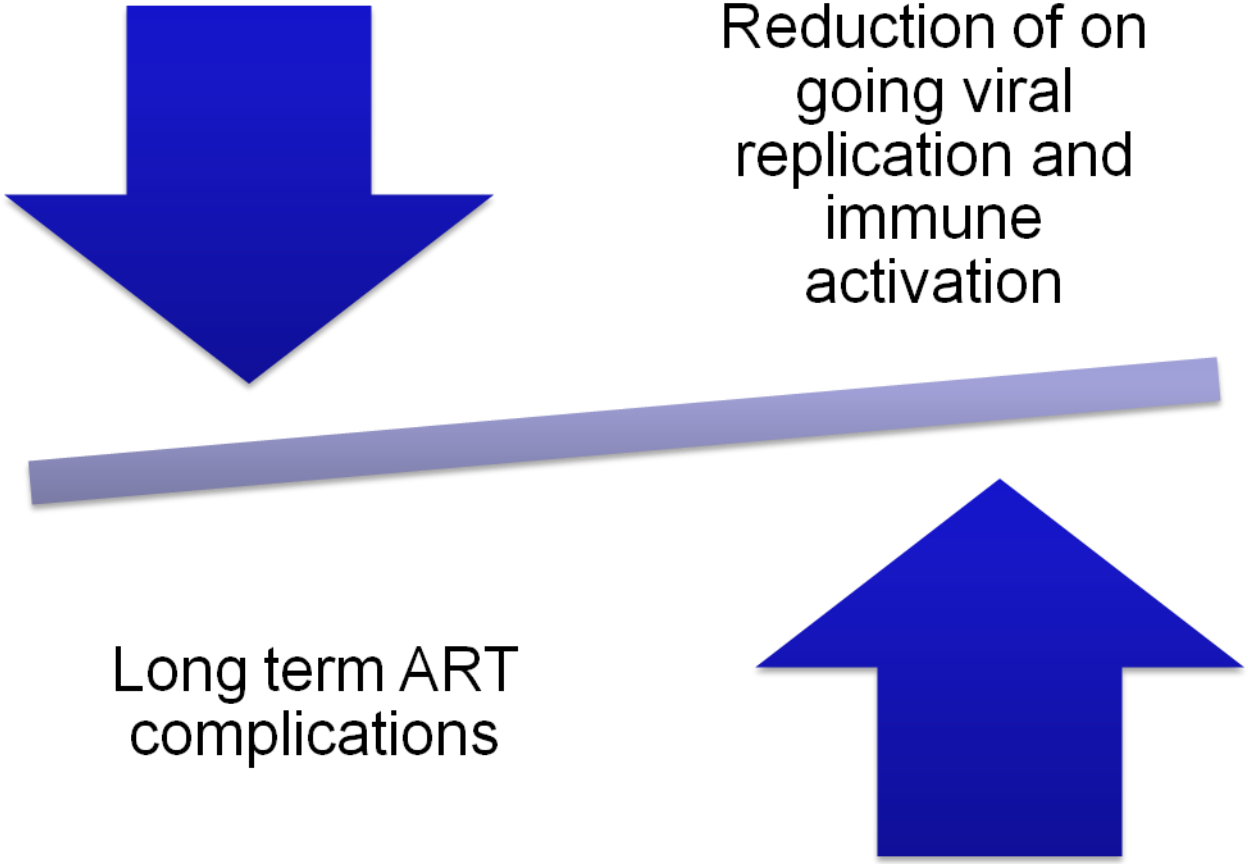
LPS mean level (pg/mL):

HIV+	64
HIV-	50

(p=0.002)

(Pedersen KK et al., J AIDS 2013)

Antiretroviral therapy and cardiovascular disease



Effects of Combination Antiretroviral Therapies on the Risk of Myocardial Infarction Among HIV Patients

(North Carolina new-user, active-comparator cohort study, 3481 HIV-positive patients)

TABLE 3. Unadjusted and Inverse Probability–weighted Incidence Rates (IRs) per 1000 Person-years and Hazard Ratios (HRs) for the Rate of Myocardial Infarction Events Among HIV-infected North Carolina Medicaid Patients Receiving New Combination Antiretroviral Therapy Regimens

	No.	Myocardial Infarction Events No.	Person-Time at Risk (years)	Unadjusted		Inverse Probability Weighted	
				IR (95% CI)	HR (95% CI)	IR (95% CI*)[a]	HR (95% CI)[a]
Backbone: Nucleoside reverse transcriptase inhibitors[b]							
Abacavir	611	15	1,263.8	11.9 (7.2–19.7)	2.70 (1.24–5.91)	9.4 (3.9–22.5)	2.05 (0.72–5.86)
Tenofovir[c]	1,605	11	2,433.4	4.5 (2.5–8.2)	1.0	4.6 (2.5–8.3)	1.0
Anchor antiretrovirals: Protease inhibitors/nonnucleoside reverse transcriptase inhibitors[d]							
Atazanavir	543	<11	786.5	5.1 (1.9–13.6)	1.13 (0.36–3.51)	5.1 (1.9–13.7)	1.12 (0.35–3.62)
NNRTI[c]	1,511	13	2,603.9	5.0 (2.9–8.6)	1.0	4.7 (2.5–8.8)	1.0
Lopinavir-ritonavir	654	<11	1,325.4	3.8 (1.6–9.1)	0.77 (0.27–2.18)	3.8 (1.6–9.1)	0.92 (0.26–3.22)
NNRTI[c]	1,511	13	2,603.9	5.0 (2.9–8.6)	1.0	4.3 (1.8–10.1)	1.0

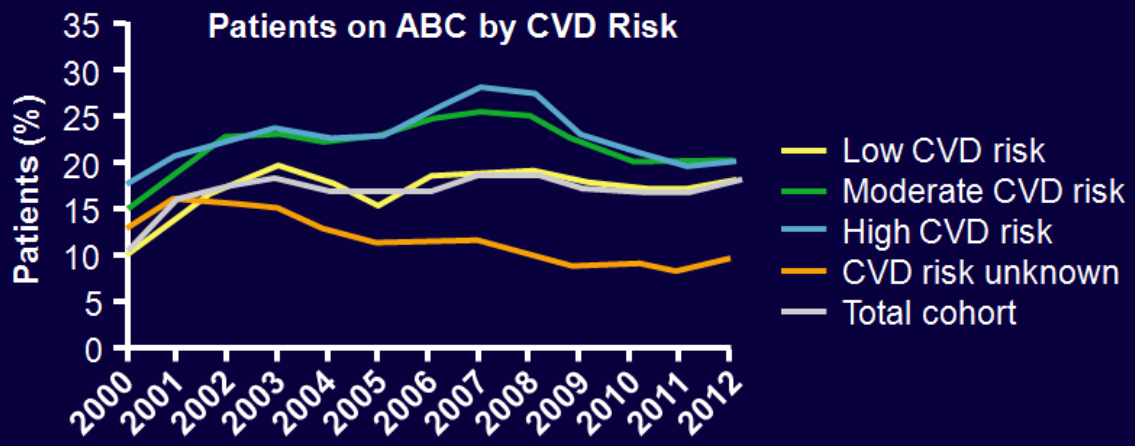
[a]Robust variance estimator used to calculate variance for inverse probability–weighted data

(Brouwer ES et al., Epidemiology 2014)

D:A:D: Abacavir Remains Associated With Elevated Risk of MI

- Update of analysis of ABC and risk of acute MI in pts with low, medium, and high CVD risk
- After initial D:A:D report in March 2008, decline in ABC initiations in pts with higher CVD risk

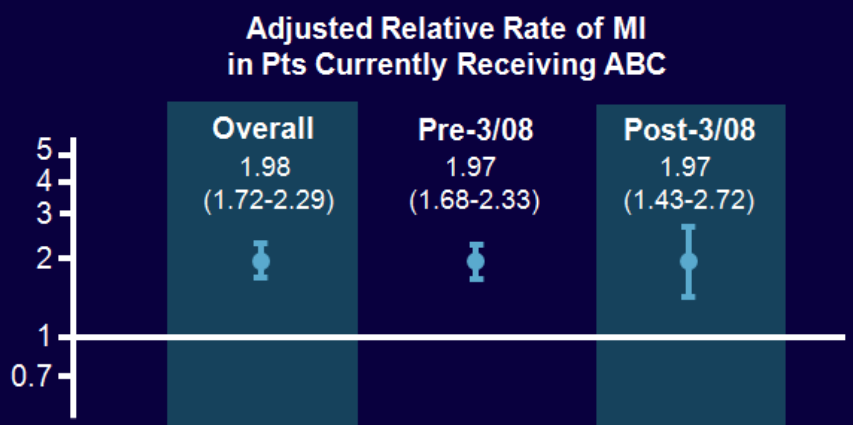
Framingham Risk Group	ABC Use as Proportion of All ART Initiations, %
Before March 2008	
▪ Low/unknown CVD risk	13.6
▪ Moderate/high CVD risk	17.1
After March 2008	
▪ Low/unknown CVD risk	7.6
▪ Moderate/high CVD risk	5.3



Sabin C, et al. CROI 2014. Abstract 747LB. Reproduced with permission.

D:A:D: Current Abacavir Use Associated With 98% Increase in Acute MI Risk

- Current ABC use remained associated with increased risk of acute MI
  - Similar RR in post-3/08 group vs pre-3/08 group, despite decrease in ABC use in pts with high CVD risk
  - Absolute risk in the post 2008 small: 6 cases /2000 PY vs 3 cases/2000 PY or absolute risk ↑ 0.15%
- Overall cohort: 941 MI events during 367,599 PYs
  - 0.47/100 PYs (95% CI: 0.42-0.52) with current ABC
  - 0.21 (95% CI: 0.19-0.22) with no current ABC



	Overall	Pre-3/08	Post-3/08
No Current ABC			
Events/PYs	600/295,642	425/169,417	175/126,225
Rate/100 PYs	0.20 (0.19-0.22)	0.25 (0.23-0.28)	0.14 (0.12-0.16)
Current ABC			
Events/PYs	341/71917	247/40833	94/31084
Rate/100 PYs	0.47 (0.42-0.52)	0.61 (0.53-0.68)	0.30 (0.24-0.36)

Sabin C, et al. CROI 2014. Abstract 747LB. Reproduced with permission.

744 Abacavir Induces Leukocyte Accumulation Through the Interaction of ATP and $P2X_7$ Receptors

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Background: The use of abacavir has been linked to cardiovascular disease. We have demonstrated (using a flow chamber system in vitro) that cyclic purine analogues (abacavir and didanosine) induce leukocyte-endothelial cell interactions through Mac-1/ICAM-1 interaction, and that this effect is not produced by pyrimidine analogues (lamivudine, zidovudine, emtricitabine) or the acyclic nucleotide tenofovir. However, the molecular mechanism underlying these interactions remains elusive. Given the chemical structure of abacavir, we have explored whether its proinflammatory effects are a result of the interference of its structure with the purine signalling pathway.

Methodology: Human umbilical vein endothelial cells (HUVEC) and polymorphonuclear leukocytes (PMN) were treated with abacavir (0.5-15 µmol/L) to determine: 1) intracellular ATP levels by a luciferase bioluminescence assay; and 2) expression of CD73 (the enzyme responsible for ATP degradation) by western blotting. To analyse the role of ATP and its receptors in the leukocyte accumulation induced by abacavir, HUVEC and PMN were pre-treated with antagonists of $P2X_7$ ATP receptors [oxATP (600 µmol/L) or BGG (5 µmol/L)] prior to abacavir (10 µmol/L, 4h) administration and leukocyte-endothelium interactions were then measured using a flow chamber system. Data are expressed as mean±SEM. Statistical analysis was performed with one-way ANOVA and a Newman-Keuls post-hoc test, with significance set at $^{**}p<0.01$ (vs. control), $n \geq 3$.

Results: Clinical concentrations of abacavir (0.5-15 µmol/L, 4h) produced an increase in intracellular ATP levels on HUVEC (abacavir 10 µmol/L: 197.6±22.4** vs. 100% control) and PMN (abacavir 10 µmol/L: 158.1±15.4** vs. 100% control) and a decrease in CD73 expression on HUVEC (abacavir 10 µmol/L: 52.2±10.2** vs. 100% control) and PMN (abacavir 10 µmol/L: 18.7±14.7** vs. 100% control). Abacavir-induced leukocyte-endothelial cell interactions were absent following pre-treatment with $P2X_7$ receptor antagonists.

Conclusions: Our results suggest a structure-activity relationship in the effects of abacavir on leukocyte accumulation through the interaction of ATP with its $P2X_7$ receptors. This proinflammatory mechanism may be especially relevant for understanding the vascular damage observed in abacavir-treated patients.

Original article

Abacavir (Ziagen®) use between 2003 and 2008 in France according to the electronic medical record NADIS®

Utilisation de l'abacavir (Ziagen®) entre 2003 et 2008 en France selon le dossier médical informatisé NADIS®

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Received 17 December 2012; received in revised form 27 July 2013; accepted 27 September 2013
Available online 18 November 2013

Summary

Objective. – The authors had for objective to describe HIV-infected patients treated with ABC (Ziagen®, ABC), and the immune, virological, and clinical treatment outcome between 2003 and 2008.

Patients and methods. – We performed a retrospective analysis of the Dat'AIDS database on patients who were treated with ABC for the first time between 2003 and 2008.

Results. – Eight hundred and thirty-six patients were included. Before initiation of ABC, 26.3% has stopped the previous treatment because of immuno-virological failure, 30.5% because of adverse events, and 29.8% for other reasons. Thirteen percent were antiretroviral naive. One third of patients were ranked as CDC class C, and more than 2/3 had a viral load < 5 log copies/mL or a CD4 count ≥ 200 mm^3. ABC was mainly included in a combination containing 2 NRTI and 1 PI (63%), or 1 non-NRTI (16%). Thirty-two percent of patients were still treated with ABC after 2 years of treatment and the median of ABC treatment was 11 months (IQ 84 days–2 years). The main causes for stopping ABC were therapeutic simplification (47.4% of patients), intolerance (19.0%), and immuno-virological failure (9.8%). Suspected hypersensitivity reactions were the main cause of discontinuation due to intolerance (27.6%); the rate was 3.8% when ABC had been introduced before the routine use of the screening test HLA-B*5701. The incidence of myocardial infarction was 3.8 per 1000 patient-years; 70.6% of patients received a fixed combination including ABC after discontinuation of ABC as a single agent (Ziagen®).

Conclusion. – This retrospective analysis confirmed the effectiveness and the good tolerance of ABC in the therapeutic strategy, between 2003 and 2008.

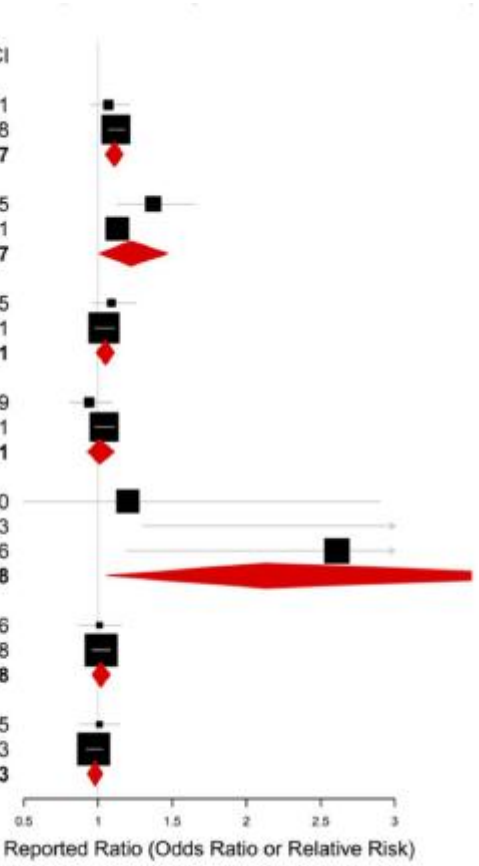
(Med Mal Infect 2013)

Risk of Cardiovascular Disease from Antiretroviral Therapy for HIV: A Systematic Review

(Meta-analysis of 27 studies)

b.

Author	Class	Drug	Exposure Risk	Outcome	Statistic	Lower CI	Point estimate	Upper CI
Lang	PI	Indinavir	Per Year	MI	OR	0.95	1.07	1.21
DAD 2010	PI	Indinavir	Per Year	MI	RR	1.07	1.12	1.18
Summary	**PI**	**Indinavir**	**Per Year**	**MI**		**1.05**	**1.11**	**1.17**
Lang	PI	Lopinavir	Per Year	MI	OR	1.13	1.37	1.65
DAD 2010	PI	Lopinavir	Per Year	MI	RR	1.05	1.13	1.21
Summary	**PI**	**Lopinavir**	**Per Year**	**MI**		**1.01**	**1.22**	**1.47**
Lang	PI	Nelfinavir	Per Year	MI	OR	0.96	1.09	1.25
DAD 2010	PI	Nelfinavir	Per Year	MI	RR	0.98	1.04	1.11
Summary	**PI**	**Nelfinavir**	**Per Year**	**MI**		**0.99**	**1.05**	**1.11**
Lang	PI	Saquinavir	Per Year	MI	OR	0.81	0.94	1.09
DAD 2010	PI	Saquinavir	Per Year	MI	RR	0.98	1.04	1.11
Summary	**PI**	**Saquinavir**	**Per Year**	**MI**		**0.93**	**1.01**	**1.11**
Daftary	PI	PI	Recent	MI	OR	0.5	1.20	2.90
Holmberg	PI	PI	Recent	MI	OR	1.3	4.92	32.3
Rickerts	PI	PI	Recent	MI	OR	1.19	2.61	5.66
Summary	**PI**	**PI**	**Recent**	**MI**		**1.06**	**2.13**	**4.28**
Lang	NNRTI	Efavirenz	Per Year	MI	OR	0.87	1.01	1.16
DAD 2010	NNRTI	Efavirenz	Per Year	MI	RR	0.96	1.02	1.08
Summary	**NNRTI**	**Efavirenz**	**Per Year**	**MI**		**0.96**	**1.02**	**1.08**
Lang	NNRTI	Nevarapine	Per Year	MI	OR	0.88	1.01	1.15
DAD 2010	NNRTI	Nevarapine	Per Year	MI	RR	0.92	0.97	1.03
Summary	**NNRTI**	**Nevarapine**	**Per Year**	**MI**		**0.93**	**0.98**	**1.03**



(Bavinger C et al., PLoS One 2013)

Atazanavir is not associated with an increased risk of cardio or cerebrovascular disease events

(D:A:D Study)

Table 2. Rates of MI and stroke according to the cumulative duration of exposure (years) to atazanavir (ATV), ATV boosted with ritonavir (ATV-RT) and ATV unboosted.

	Events	PYFU[a]	Rate (/100 PYFU)	95% CI
Myocardial infarction				
Any ATV (years)				
None	740	264901	0.279	0.259, 0.299
>0, ≤1	41	13323	0.308	0.214, 0.402
>1, ≤2	29	8307	0.349	0.222, 0.476
>2, ≤3	15	5974	0.251	0.141, 0.414
>3	19	9401	0.202	0.122, 0.316
ATV-RT (years)				
None	751	270676	0.277	0.258, 0.297
>0, ≤1	41	12039	0.341	0.236, 0.445
>1, ≤2	24	7110	0.338	0.203, 0.473
>2, ≤3	10	4863	0.206	0.099, 0.378
>3	18	7220	0.249	0.148, 0.394
ATV unboosted (years)				
None	821	292295	0.281	0.262, 0.300
>0, ≤1	15	4686	0.320	0.179, 0.528
>1, ≤2	4	1967	0.203	0.055, 0.521
>2, ≤3	3	1227	0.244	0.050, 0.715
>3	1	1731	0.058	0.001, 0.322

(d'Arminio Monforte A et al., AIDS 2013)

Effects of Combination Antiretroviral Therapies on the Risk of Myocardial Infarction Among HIV Patients

(North Carolina new-user, active-comparator cohort study, 3481 HIV-positive patients)

TABLE 3. Unadjusted and Inverse Probability–weighted Incidence Rates (IRs) per 1000 Person-years and Hazard Ratios (HRs) for the Rate of Myocardial Infarction Events Among HIV-infected North Carolina Medicaid Patients Receiving New Combination Antiretroviral Therapy Regimens

		Myocardial Infarction Events		Unadjusted		Inverse Probability Weighted	
	No.	No.	Person-Time at Risk (years)	IR (95% CI)	HR (95% CI)	IR (95% CI*)[a]	HR (95% CI)[a]
Backbone: Nucleoside reverse transcriptase inhibitors[b]							
Abacavir	611	15	1,263.8	11.9 (7.2–19.7)	2.70 (1.24–5.91)	9.4 (3.9–22.5)	2.05 (0.72–5.86)
Tenofovir[c]	1,605	11	2,433.4	4.5 (2.5–8.2)	1.0	4.6 (2.5–8.3)	1.0
Anchor antiretrovirals: Protease inhibitors/nonnucleoside reverse transcriptase inhibitors[d]							
Atazanavir	543	<11	786.5	5.1 (1.9–13.6)	1.13 (0.36–3.51)	5.1 (1.9–13.7)	1.12 (0.35–3.62)
NNRTI[c]	1,511	13	2,603.9	5.0 (2.9–8.6)	1.0	4.7 (2.5–8.8)	1.0
Lopinavir-ritonavir	654	<11	1,325.4	3.8 (1.6–9.1)	0.77 (0.27–2.18)	3.8 (1.6–9.1)	0.92 (0.26–3.22)
NNRTI[c]	1,511	13	2,603.9	5.0 (2.9–8.6)	1.0	4.3 (1.8–10.1)	1.0

[a]Robust variance estimator used to calculate variance for inverse probability–weighted data

(Brouwer ES et al., Epidemiology 2014)

Research interventions to reduce inflammation in HIV patients on cART

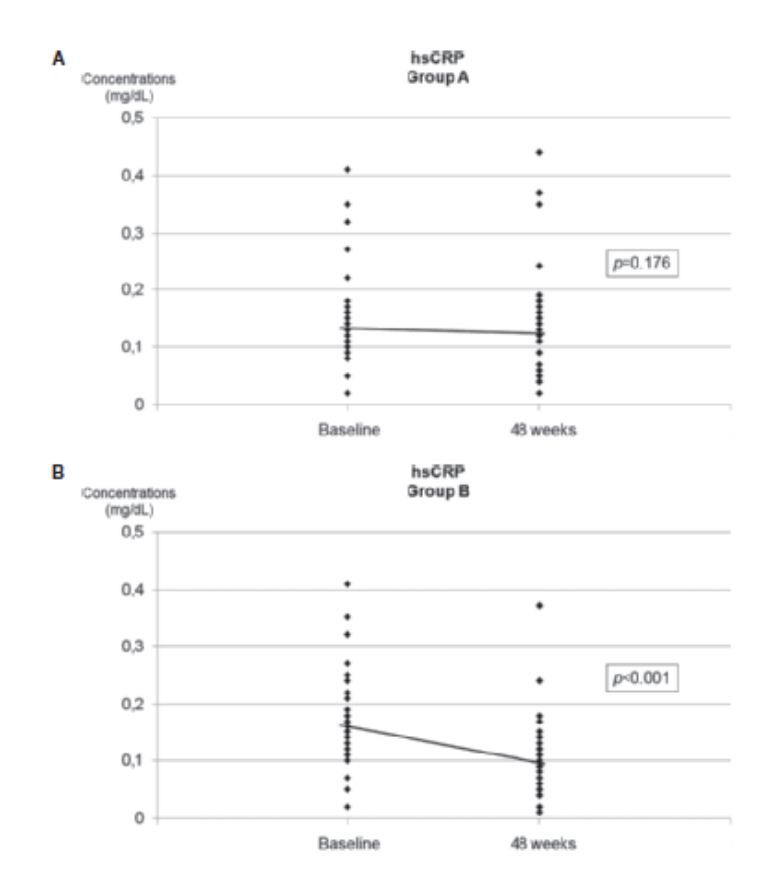
- **Chemokine receptor inhibitors:** maraviroc, TB-652
- **Anti-infective therapy:** CMV, EBV, HSV, HBV, HCV
- **Microbial translocation:** sevelamer, colostrum, rifaximin, pre-biotics, pro-biotics, isotretinoin
- **Enhance T cell renewal:** growth hormone, IL-7
- **Anti-fibrotic drugs:** perfenidone, ACE-inhibitors, ARBs
- **Anti-aging:** caloric restriction, diet,sirtuin activators, vitamin D, omega-3 fatty acids, sirolimus, exercise
- **Anti-inflammatory drugs**
- **Anti-coagulants:** low dose warfarin, dabigatran, aspirin, clopidogrel

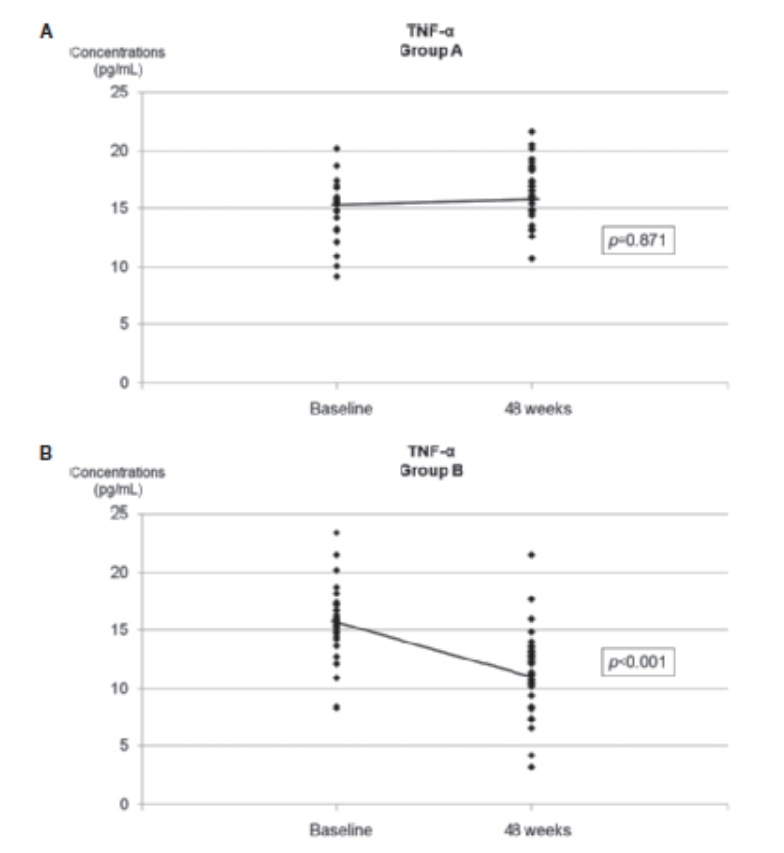
Anti-inflammatory drugs

- Chloroquine, hydroxychloroquine
- Minocycline
- NSAIDs (COX-2 inhibitors), aspirin
- Statins
- Methotrexate (low-dose; CIRT)
- Talidomide, lenalidomide, pentoxyfylin

Tenofovir/Emtricitabine/Efavirenz Plus Rosuvastatin Decrease Serum Levels of Inflammatory Markers More Than Antiretroviral Drugs Alone in Antiretroviral Therapy-Naive HIV-Infected Patients

(Observational, cohort study, 86 patients, 12-month follow-up)





(Calza L et al., HIV Clin Trials 2014)

Two-Year Treatment with Rosuvastatin Reduces Carotid Intima-Media Thickness in HIV Type 1-Infected Patients Receiving Highly Active Antiretroviral Therapy with Asymptomatic Atherosclerosis and Moderate Cardiovascular Risk

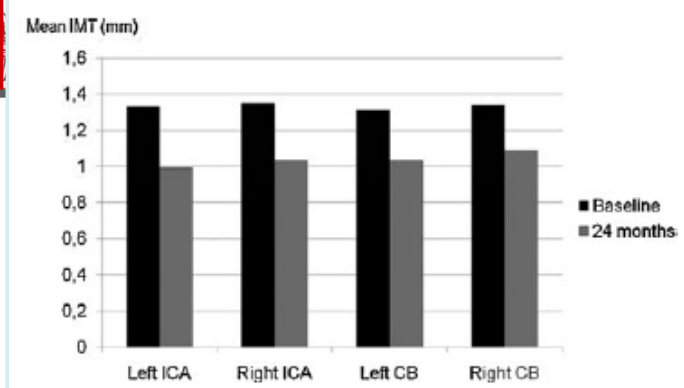


FIG. 1. Changes in mean values of carotid intima-media thickness after the 24-month treatment with rosuvastatin among the 36 patients who completed the follow-up (IMT, intima-media thickness; ICA, internal carotid artery; CB, carotid bifurcation).

-Observational, cohort study
-36 patients
-2-year follow-up

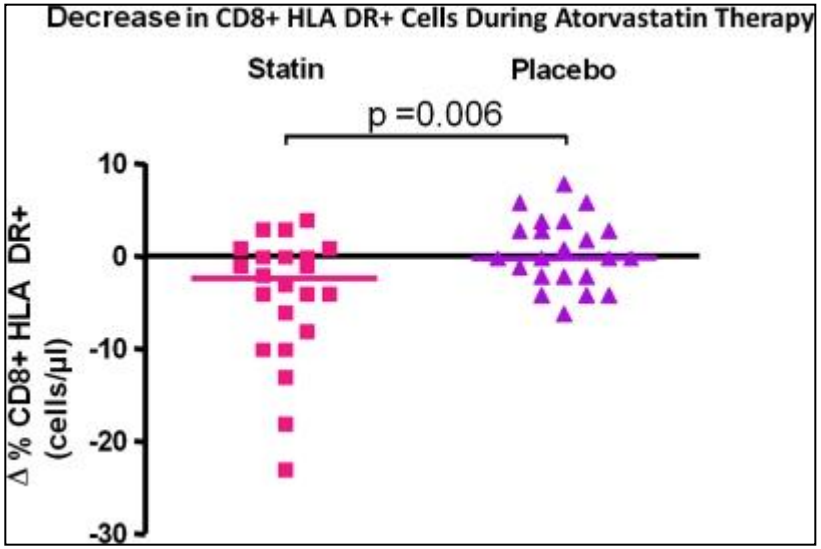
5. Plasma Levels of Lipid Parameters, Cardiovascular Risk, and Carotid Intima-Media Thickness es at Baseline and After 24 Months of Lipid-Lowering Therapy with Rosuvastatin (10 mg Daily) Among the 42 Enrolled Patients (Intent-to-Treat Analysis)

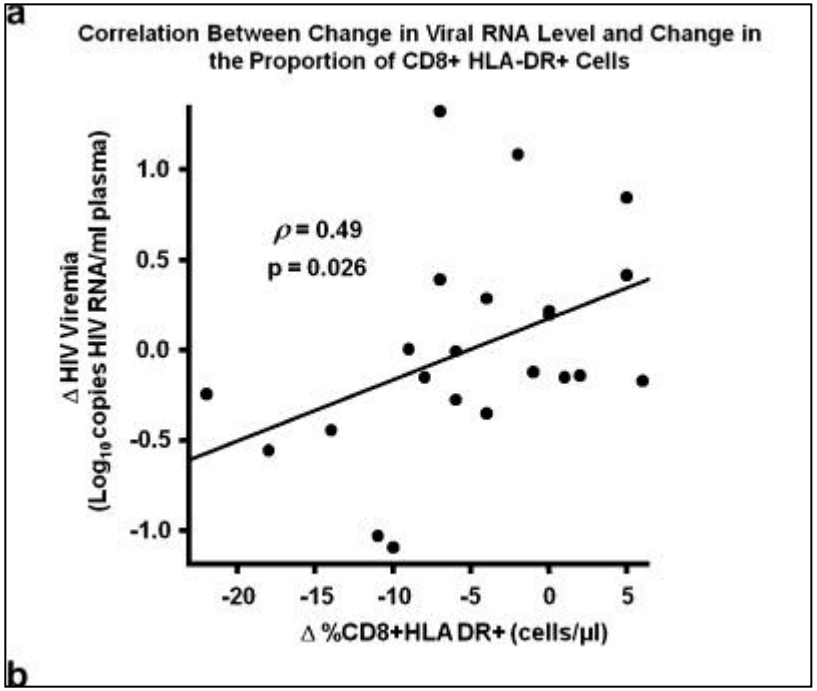
	Baseline	*After 24 months of treatment*	*Mean change[a] ± SD*	*Mean percentage of change[a]*	*p value[b]*
Mean serum concentration of total cholesterol ± SD (mg/dl)	267.1 ± 54.2	198.3 ± 46.8	−65.5 ± 20.1	−25.1%	<0.001
Mean serum concentration of LDL cholesterol ± SD (mg/dl)	175.6 ± 38.8	122.7 ± 28.9	−50.3 ± 15.1	−29.5%	<0.001
Mean serum concentration of HDL cholesterol ± SD (mg/dl)	44.2 ± 19.6	49.3 ± 16.7	+5.4 ± 2.2	+11.3%	0.065
Mean serum concentration of triglycerides ± SD (mg/dl)	186.2 ± 75.2	156.8 ± 35.2	−30.4 ± 12.5	−16.1%	0.029
Patients who met NCEP LDL cholesterol goal, no. (%)	0	26 (61.9)	n.a.	n.a.	0.033
Mean calculated 10-year risk of MI ± SD (%)[c]	17.7 ± 9.8	10.6 ± 5.9	−7.9 ± 3.5	−42.3%	<0.001
Mean IMT ± SD (mm)					
Right common carotid artery	1.26 ± 0.49	1.07 ± 0.24	−0.22 ± 0.14	−16.1%	0.003
Left common carotid artery	1.25 ± 0.47	1.03 ± 0.22	−0.22 ± 0.17	−17.9%	0.011
Right carotid bifurcation	1.33 ± 0.38	1.09 ± 0.21	−0.26 ± 0.11	−18.2%	0.012
Left carotid bifurcation	1.31 ± 0.41	1.05 ± 0.18	−0.26 ± 0.14	−20.9%	0.002
Right internal carotid artery	1.34 ± 0.31	1.04 ± 0.25	−0.29 ± 0.16	−22.8%	<0.001
Left internal carotid artery	1.33 ± 0.38	1.01 ± 0.32	−0.34 ± 0.27	−24.2%	<0.001
N. of patients (%) with carotid plaques	22 (52.4)	10 (23.8)	n.a.	n.a.	<0.001

(Calza L et al.,
AIDS Res Hum Retroviruses 2012)

High Dose Atorvastatin Decreases Cellular Markers of Immune Activation Without Affecting HIV-1 RNA Levels: Results of a Double-blind Randomized Placebo Controlled Clinical Trial

(Double-blind, randomized trial: 24 naive patients)

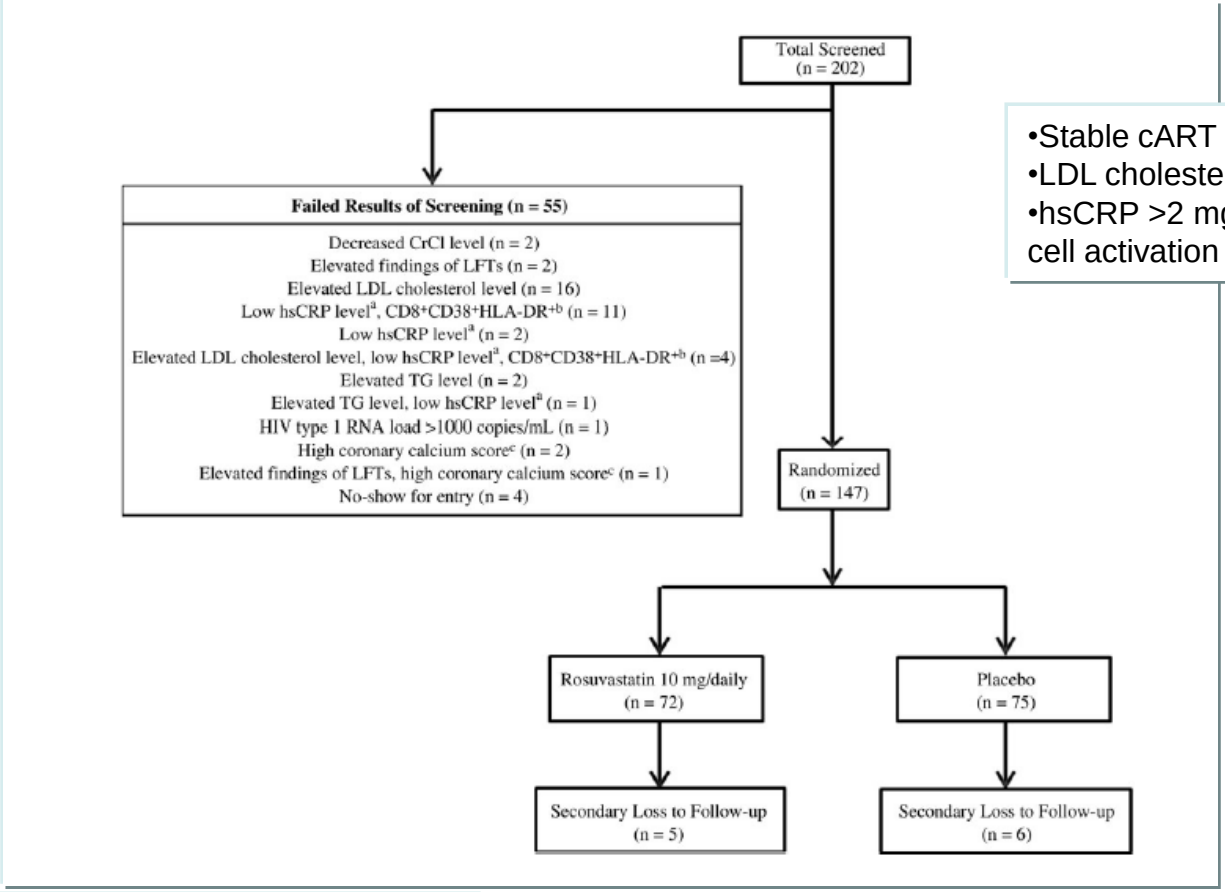




(Ganesan A et al., J Infect Dis 2011)

Effect of 24 Weeks of Statin Therapy on Systemic and Vascular Inflammation in HIV-Infected Subjects Receiving Antiretroviral Therapy

(SATURN-HIV randomized, double-blinded, placebo-controlled trial; 147 HIV+ patients)



- Stable cART (>12 weeks)
- LDL cholesterol ≤130 mg/dL
- hsCRP >2 mg/L and/or CD8+ cell activation

(Eckard AR et al., J Infect Dis 2014)

Effect of 24 Weeks of Statin Therapy on Systemic and Vascular Inflammation in HIV-Infected Subjects Receiving Antiretroviral Therapy

Table 2. Percentage Change in Markers of Inflammation, Cellular Adhesion, Coagulation, and Low-Density Lipoprotein (LDL) Cholesterol, by Study Group

Marker	Statin, Percentage Change (n = 72[a])	Placebo, Percentage Change (n = 75[a])	*P*
hsCRP level	−12.5 (−54.6 to 22.2)	0.0 (−42.4 to 54.7)	.14
IL-6 level	−24.2 (−42.4 to 29.4)	−2.1 (−39.5 to 32.9)	.24
sTNFR-I level	−7.1 (−41.7 to 6.3)[b]	−13.5 (−38.3 to 7.2)[b]	.77
sTNFR-II level	5.6 (−23.3 to 78.7)[b]	22.5 (−9.9 to 63.4)[b]	.27
sVCAM-1 level	3.8 (−11.5 to 15.3)	1.9 (−7.4 to 11.4)	.72
sICAM-1 level	6.2 (−8.2 to 19.0)[b]	4.6 (8.1–20.7)	.56
IP-10 level	−22 (−34.3 to −4.2)[b]	−12.1 (34.7–4.0)	.34
D-dimer level	6.9 (43.8 to −35.0)	21.9 (−9.1 to 73.3)[b]	.23
Fibrinogen level	0.2 (−20.1 to 22.2)	9.8 (−6.4 to 23.5)[b]	.16
Lp-PLA_2 level	−9.9 (−20.1 to −1.0)[b]	−1.9 (−8.6 to 13.3)	<.01
LDL cholesterol level	−28 (−43 to −16)[b]	3.8 (−0.7% to 17.2)[b]	<.01

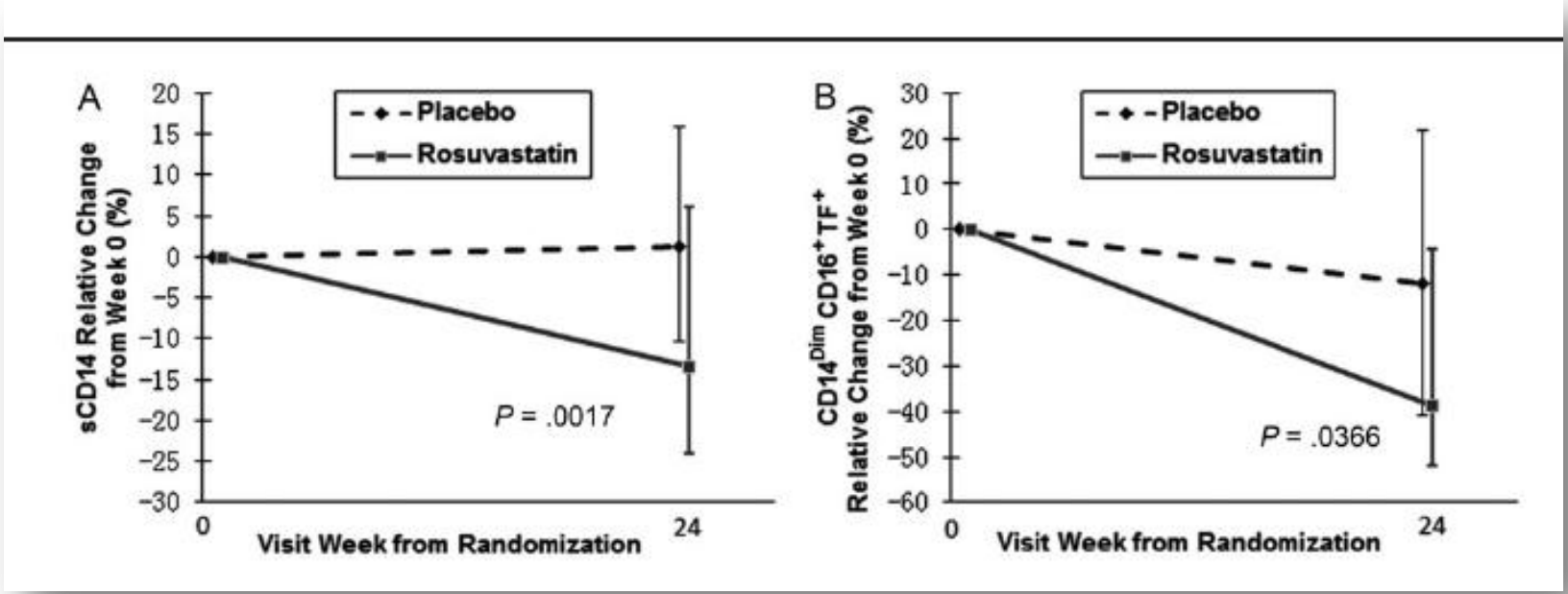
Abbreviations: hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; IP-10, interferon γ–inducible protein 10; Lp-PLA_2, lipoprotein-associated phospholipase A_2; sTNFR-I, soluble tumor necrosis factor receptor I; sTNFR-II, soluble tumor necrosis factor receptor II; sICAM-1, soluble intercellular adhesion molecule I; sVCAM-1, soluble vascular cellular adhesion molecule I.

[a] Baseline numbers. At 24 weeks, 5 subjects in the statin group and 6 in the placebo group had withdrawn or were lost to follow-up.

[b] $P < .05$ for within-group changes.

(Eckard AR et al., J Infect Dis 2014)

Rosuvastatin Treatment Reduces Markers of Monocyte Activation in HIV-Infected Subjects on Antiretroviral Therapy



(Fundferburg NT et al., Clin Infect Dis 2014)

Will Statins Be an Effective Anti-inflammatory Intervention for Prevention of Cardiovascular Disease in Patients With HIV?

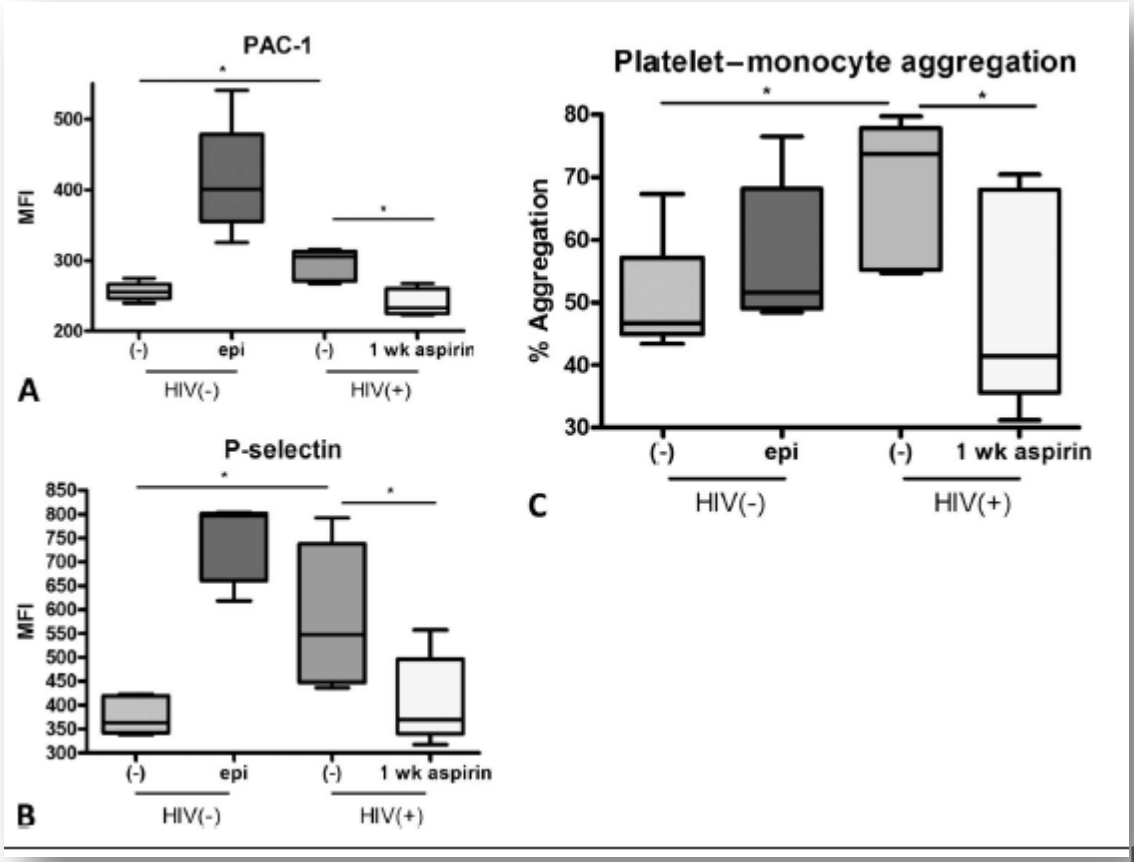
Michael P. Dubé

Department of Medicine and Division of Infectious Diseases, University of Southern California Keck School of Medicine, Los Angeles, California

(J Infect Dis 2014; 209: 1149-50)

Aspirin Attenuates Platelet Activation and Immune Activation in HIV-1-Infected Subjects on Antiretroviral Therapy: A Pilot Study

-Case-control study
-25 HIV-positive patients with HIV RNA <50 copies/mL and 44 healthy controls



(O'Brien M et al., J AIDS 2013)

Underutilization of Aspirin for Primary Prevention of Cardiovascular Disease Among HIV-Infected Patients

(Cross-sectional study, 397 patients)

Patients in need receiving aspirin: 17%

Table 2. Factors Associated With Aspirin Prescription Among HIV-Infected Patients at the University of Alabama at Birmingham 1917 Clinic Meeting 2009 United States Preventive Services Task Force Criteria [16] for Aspirin for Primary Prevention of Cardiovascular Disease Events

Characteristic	Unadjusted OR (95% CI) for ASA Prescription[a]	*P* Value	Adjusted OR (95% CI) for ASA Prescription[a,b]	*P* Value
Age (per 10 years)	1.44 (.94–2.19)	.09	1.25 (.75–2.09)	.40
Male sex	0.61 (.23–1.59)	.31	0.58 (.18–1.86)	.36
Race/ethnicity				
White	1.0	…	1.0	…
African American	0.62 (.34–1.11)	.11	0.55 (.27–1.11)	.10
CD4 count (cells/μL)				
>350	1.0	…	1.0	…
200–350	0.81 (.41–1.60)	.54	0.79 (.37–1.66)	.53
<200	**0.22 (.05–.96)**	**.04**	0.34 (.08–1.51)	.16
Obesity (BMI ≥30 kg/m^2)[c]	1.12 (.58–2.15)	.73	0.94 (.45–1.95)	.86
Hypertension	**1.81 (1.01–3.25)**	**.046**	1.39 (.72–2.71)	.33
Diabetes mellitus	**3.30 (1.79–6.09)**	**<.001**	**2.60 (1.28–5.27)**	**.01**
Hyperlipidemia	**3.53 (1.78–6.99)**	**<.001**	**3.42 (1.55–7.56)**	**.002**
Current smoking	1.26 (.74–2.15)	.40	**1.87 (1.03–3.41)**	**.04**
Length of time in care (per year)	**1.10 (1.02–1.18)**	**.02**	1.03 (.95–1.12)	.46
Plasma HIV-1 RNA <50 copies/mL	0.77 (.45–1.31)	.33	…	…
10-year risk for CVD event (per 5% increase)[d,e]	**1.35 (1.13–1.62)**	**.001**	…	…
CVD-related comorbidity count (per increase of 1)[e,f]	**2.15 (1.57–2.95)**	**<.001**	…	…

(Burkholder GA et al., Clin Infect Dis 2012)

Table 1. Guideline Recommendations for Aspirin Use in Primary Prevention of Cardiovascular Disease

Guideline	Cardiovascular Disease Risk	Sex	Age	Dose
AHA[2]	Higher coronary heart disease risk (especially those with a 10-yr risk of CHD ≥ 10%)	No specification	No specification	75–160 mg/day
CHEST[20]	For persons aged ≥ 50 yrs without symptomatic cardiovascular disease	No specification	≥ 50 yrs	75–100 mg/day
USPSTF[7]	Myocardial infarction when 10-yr CHD risk ≥ 4%	Men	45–59 yrs	No recommendation
	Myocardial infarction when 10-yr CHD risk ≥ 9%	Men	60–69 yrs	No recommendation
	Myocardial infarction when 10-yr CHD risk ≥ 12%	Men	70–79 yrs	No recommendation
	Stroke when 10-yr stroke risk ≥ 3%	Women	55–59 yrs	No recommendation
	Stroke when 10-yr stroke risk ≥ 8%	Women	60–69 yrs	No recommendation
	Stroke when 10-yr stroke risk ≥ 11%	Women	70–79 yrs	No recommendation
ESC[21]	10-yr risk score of CVD > 10%	No specification	No specification	75 mg/day
CCS[22]	Not recommended at any level of CVD risk[a]	—	—	—

AHA = American Heart Association; CHD = coronary heart disease; CHEST = American College of Chest Physicians; USPSTF = U.S. Preventive Services Task Force; ESC = European Society of Cardiology; CVD = cardiovascular disease; CCS = Canadian Cardiovascular Society.
[a]In special circumstances where vascular risk is considered high and bleeding risk is low, aspirin 75–162 mg/day may be considered.

(Nemerovski CW et al., Pharmacotherapy 2012)

Conclusions.
The current challenges

- The correct assessment of CDV risk in HIV+ patients
- The best markers for chronic inflammation and CVD risk in HIV
- The best treatment to reduce HIV-associated inflammation and CVD risk

Assess, prevent and treat

Grazie per l'attenzione.