Update on HIV and Cardiovascular Disease

February 15th 2017

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AETC AIDS Education & Training Center Program
Southeast

Disclosures

- None

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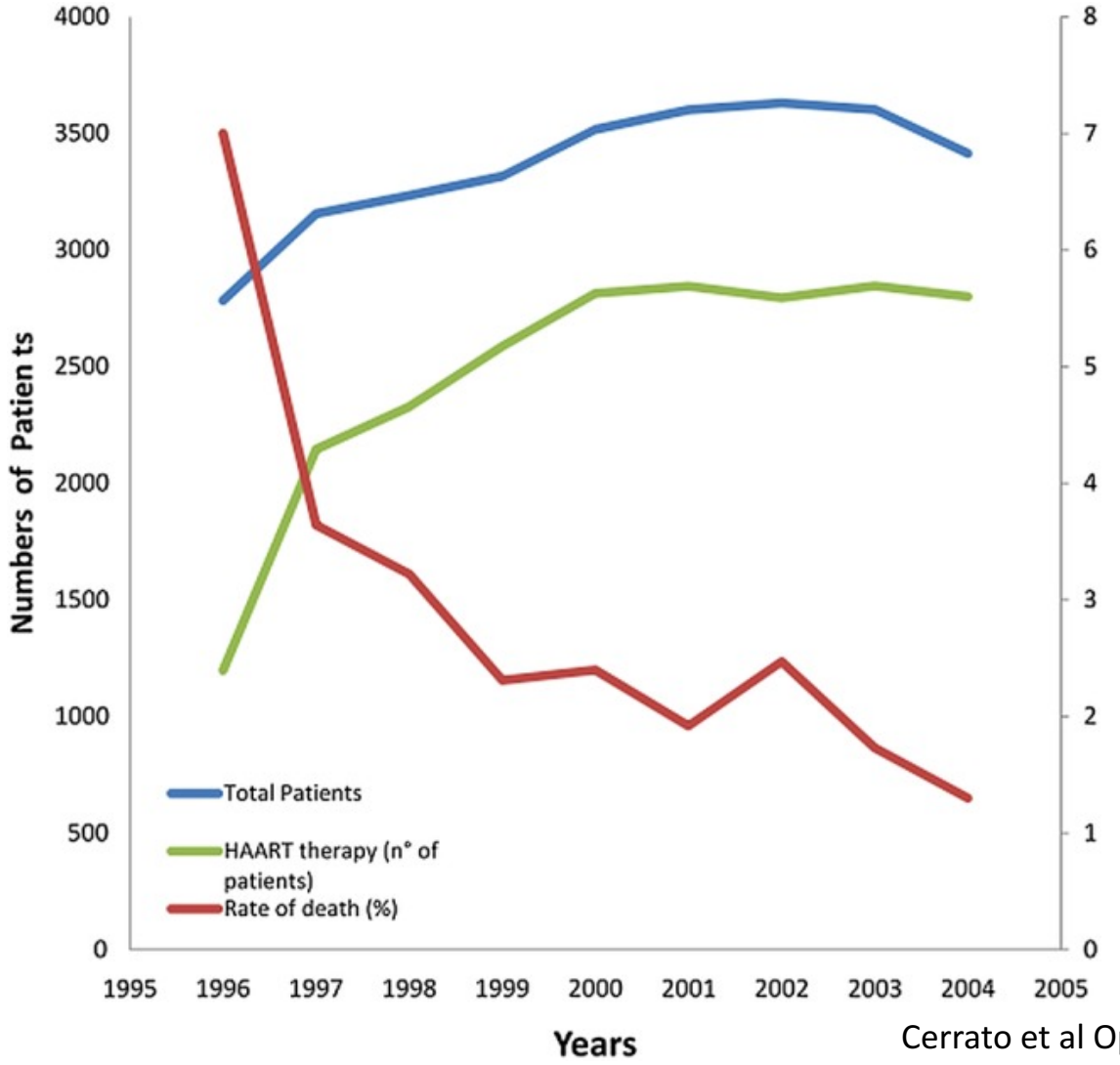
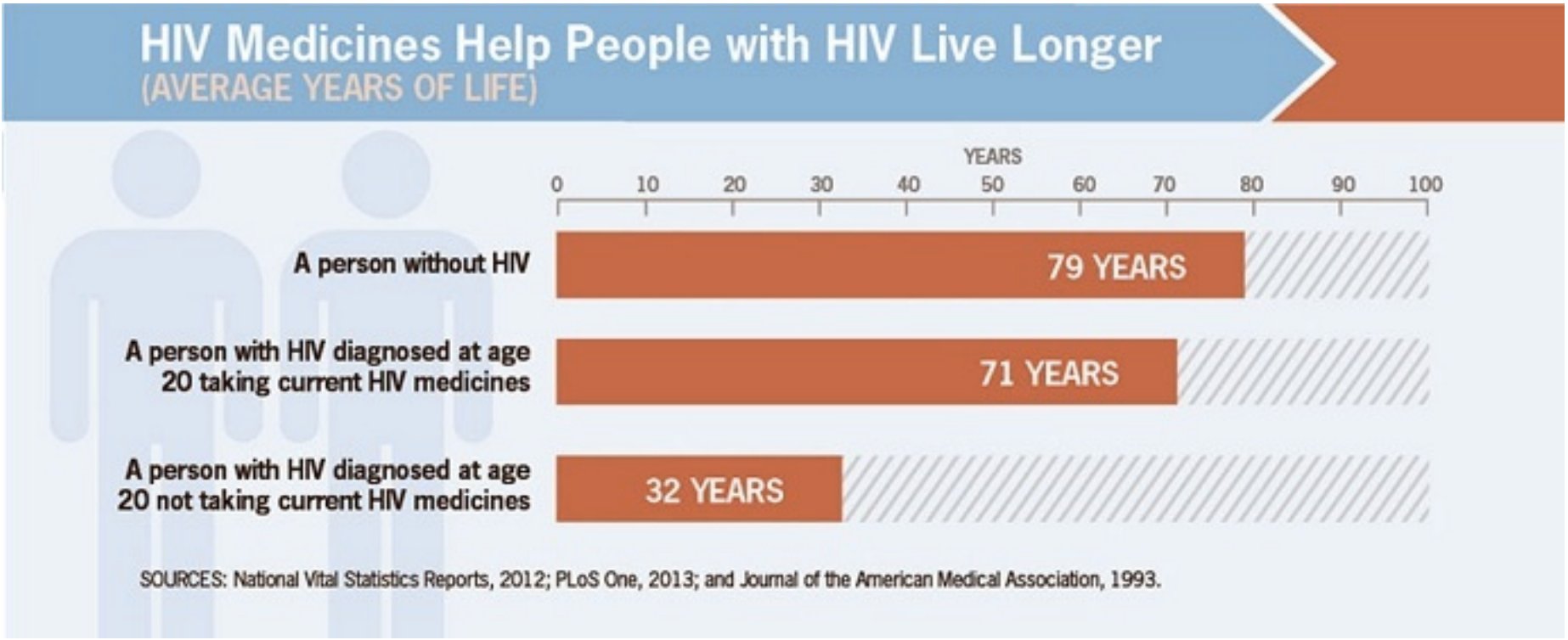
Statistics in patients with HIV



Cerrato et al Open Heart 2015
Kaplan et al Curr HIV/AIDS 2016

Increased Life Expectancy



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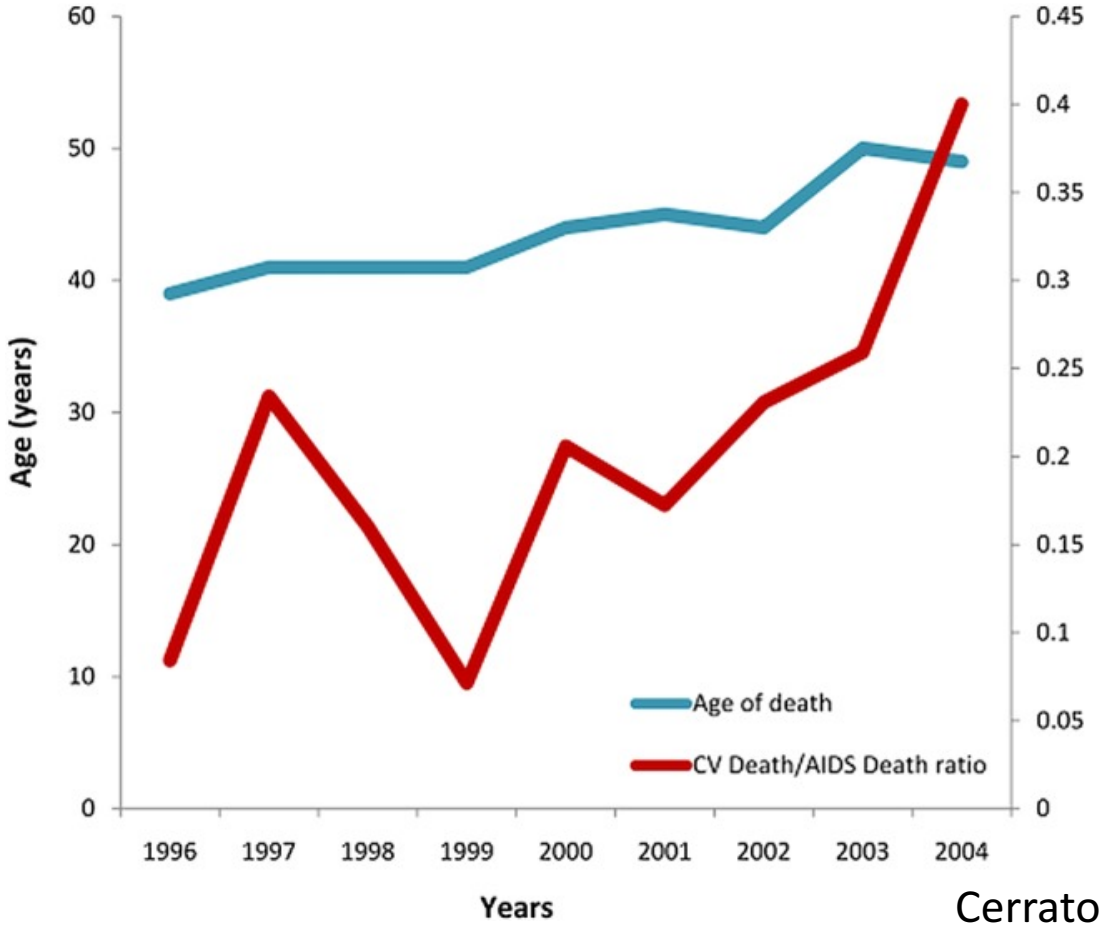
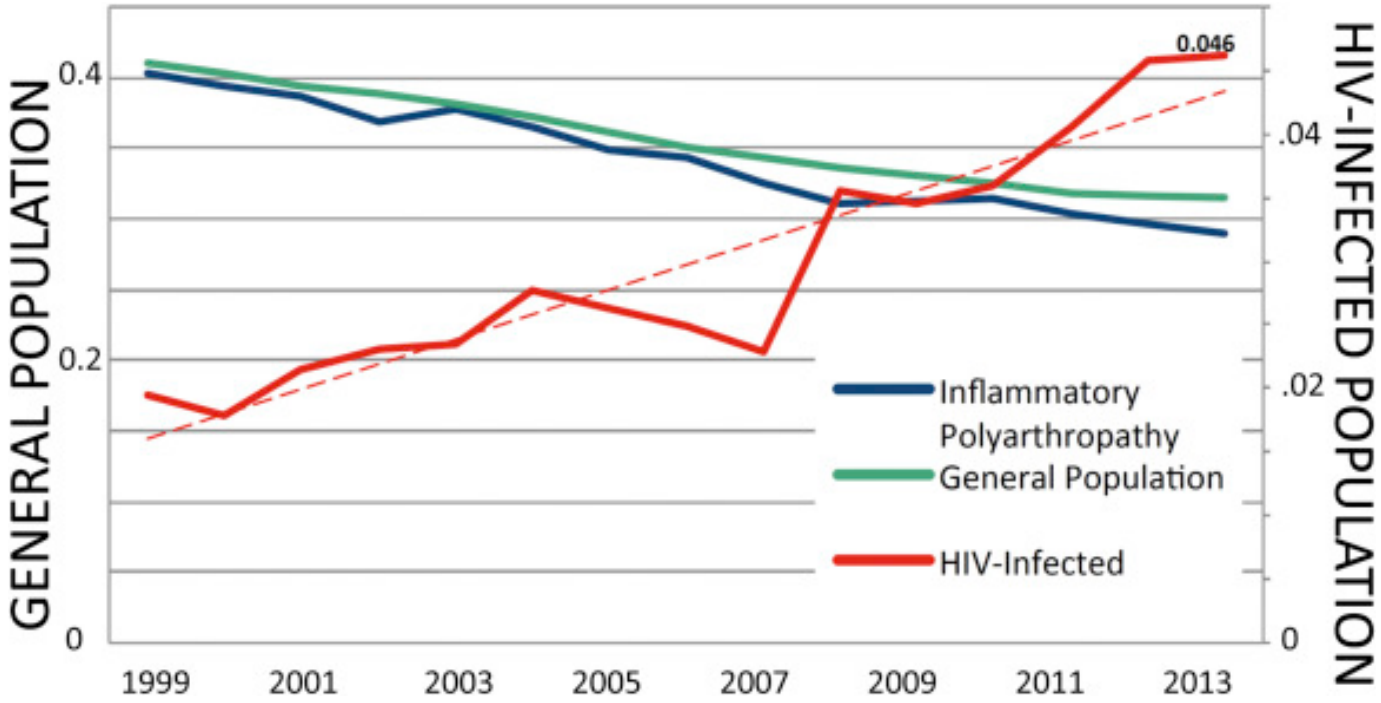
Cardiovascular/AIDS-related death ratio and age of death in the HIV Outpatient Study (HOPS)



Cerrato et al Open Heart 2015

Mortality for CVD general population, inflammatory polyarthropathy population, and HIV



Matthew J. Feinstein, Ehete Bahiru, Chad Achenbach, Christopher T. Longenecker, Priscilla Hsue, Kaku So-Armah, Matthew S. Freiberg, Donald M. Lloyd-Jones

Patterns of Cardiovascular Mortality for HIV-Infected Adults in the United States: 1999 to 2013

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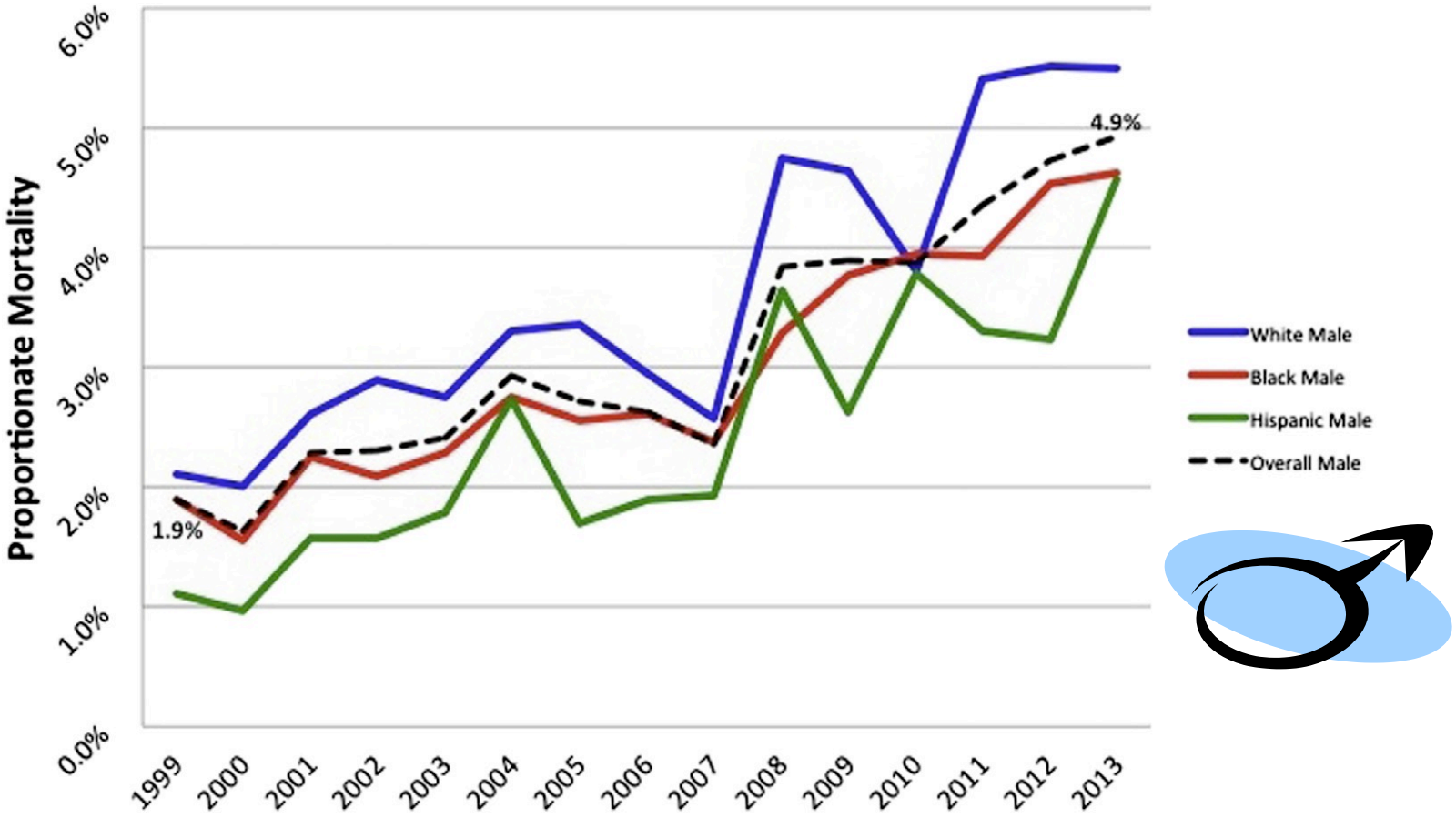
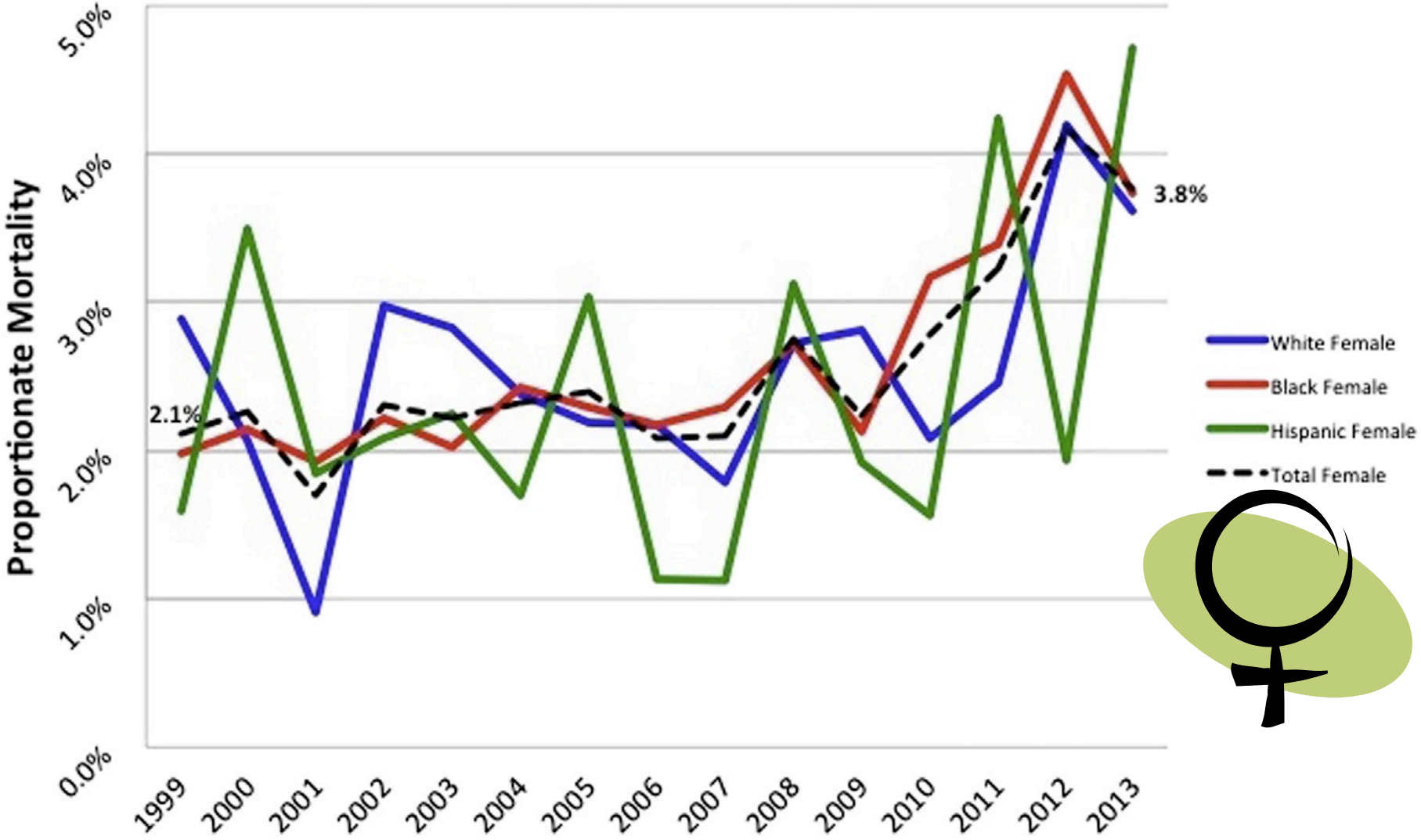
Cardiovascular Mortality for HIV Adults in the US: 1999 to 2013



Feinstein et al Am J Cardiol 2016

Cardiovascular Mortality for HIV Adults in the US: 1999 to 2013



Feinstein et alAm J Cardiol 2016

Cardiovascular Disease Prevalence in HIV-Infected Women at the University of Miami Hospital

Fahim Pyarali, MD, MPH[1]; Claudia Martinez, MD, FSCAI[1]

[1]University of Miami Miller School of Medicine

Introduction

- Since the advent of highly active antiretroviral therapy, the survival of HIV-infected individuals has substantially improved.
- With extended lifespan, there has been an increase in the prevalence of accelerated cardiovascular disease (CVD), and a two-fold increase in the risk of acute myocardial infarction compared to seronegative individuals.
- While
  of CV
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- This s
  CVD
  seron
  Hospit

Antiretroviral Therapy

Methods

- De-identified aggregate-level data was collected through a central data platform at UMH.
- This platform extracts information from medical records for patients seen at UMH from 2011-2015.
- The data environment was queried for patients diagnosed with HIV (ICD9 042) and CVD for both genders.
- We defined CVD as:
  - coronary artery disease (CAD, ICD9 414)

Results – Demographics

- Compared to the overall population of HIV-infected women, those with CVD were disproportionately African American (80% HIV + CVD vs. 72% HIV)
- HIV-infected women with CVD tended to be older compared to the overall population of HIV women (84% over the age of 40 in HIV +CVD vs. 57% in HIV),

Table 2: BMI and CVD in HIV-infected Women

BMI	HIV (-) Females	HIV (-) Females with CVD	HIV (+) Females	HIV (+) Female with CV
Unknown	25.8%	15.3%	51.9%	24.5
<18.5	5.9%	2.3%	5.0%	1.0
18.5 - 24.9	29.2%	20.9%	14.7%	10.8
25.0 - 29.9	20.0%	24.6%	10.6%	19.6
> 30.0	19.1%	36.8%	17.6%	44.1

Women

HIV (+) Females with CVD
47.1%
17.6%
2.9%
29.4%
2.9%

Conclusion:

Approximately 12.5% of HIV-infected women were found to have CVD in this study.

HIV-infection is associated with substantially greater CVD prevalence compared with HIV-seronegative counterparts.

Clinical Problem

- 46 y/o Man with Chest Pain
- PMhx: HIV x 8 years
- Medications: HAART

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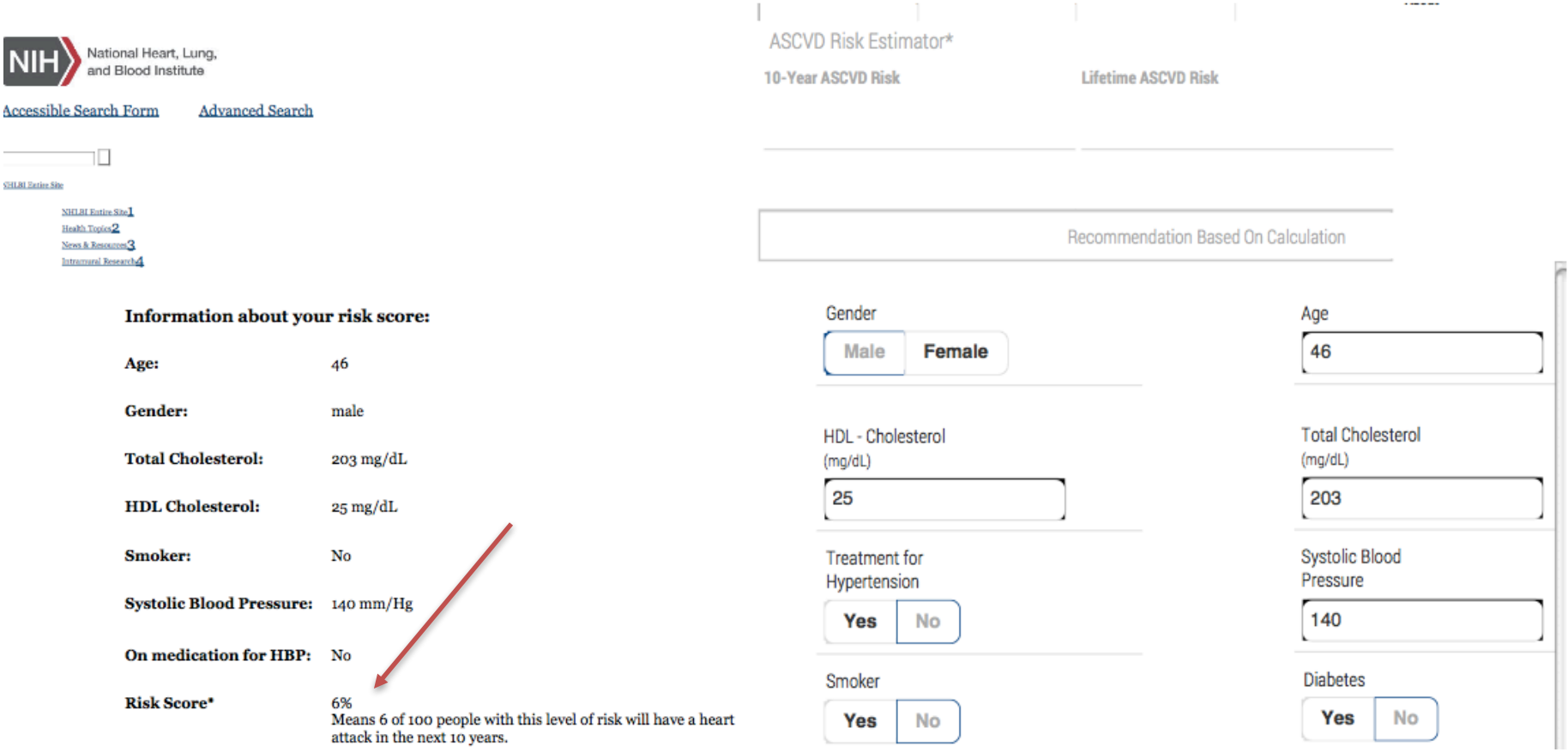
Lipids

Lipid panel	3/2014
TC	203
TGL	225
HDL	25
LDL	133

ASCVD Risk Calculator



NIH National Heart, Lung, and Blood Institute

Accessible Search Form Advanced Search

NHLBI Entire Site
NHLBI Entire Site 1
Health Topics 2
News & Resources 3
Intramural Research 4

Information about your risk score:

Age:	46
Gender:	male
Total Cholesterol:	203 mg/dL
HDL Cholesterol:	25 mg/dL
Smoker:	No
Systolic Blood Pressure:	140 mm/Hg
On medication for HBP:	No
Risk Score*	6% Means 6 of 100 people with this level of risk will have a heart attack in the next 10 years.

ASCVD Risk Estimator*

10-Year ASCVD Risk Lifetime ASCVD Risk

Recommendation Based On Calculation

Gender: Male / Female

Age: 46

HDL - Cholesterol (mg/dL): 25

Total Cholesterol (mg/dL): 203

Treatment for Hypertension: Yes / No

Systolic Blood Pressure: 140

Smoker: Yes / No

Diabetes: Yes / No

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- ECG: normal
- Stress echo: normal

Plan

- Disposition: Home
- Aspirin 81 mg
- Crestor
- Omega 3
- Outpatient f/u
- Diet and exercise

2 months later

STEMI

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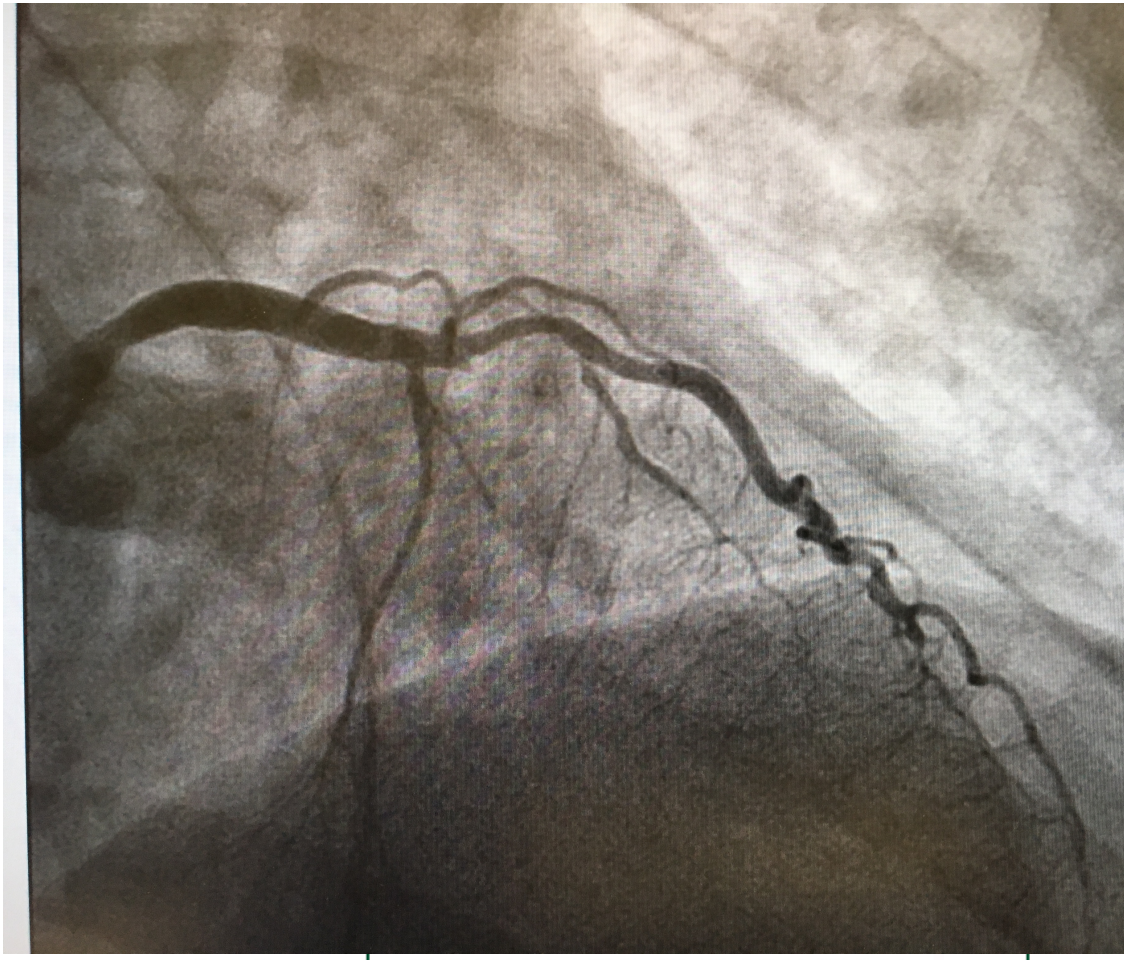
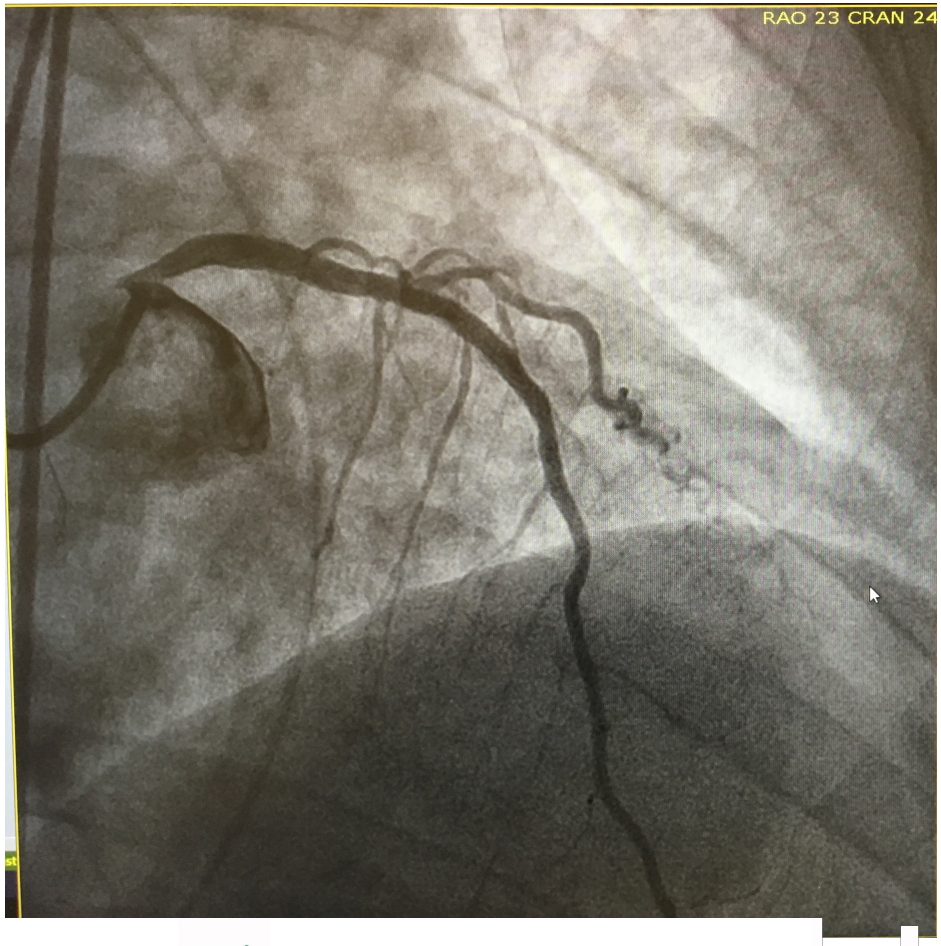
Coronary Angiogram



PCI



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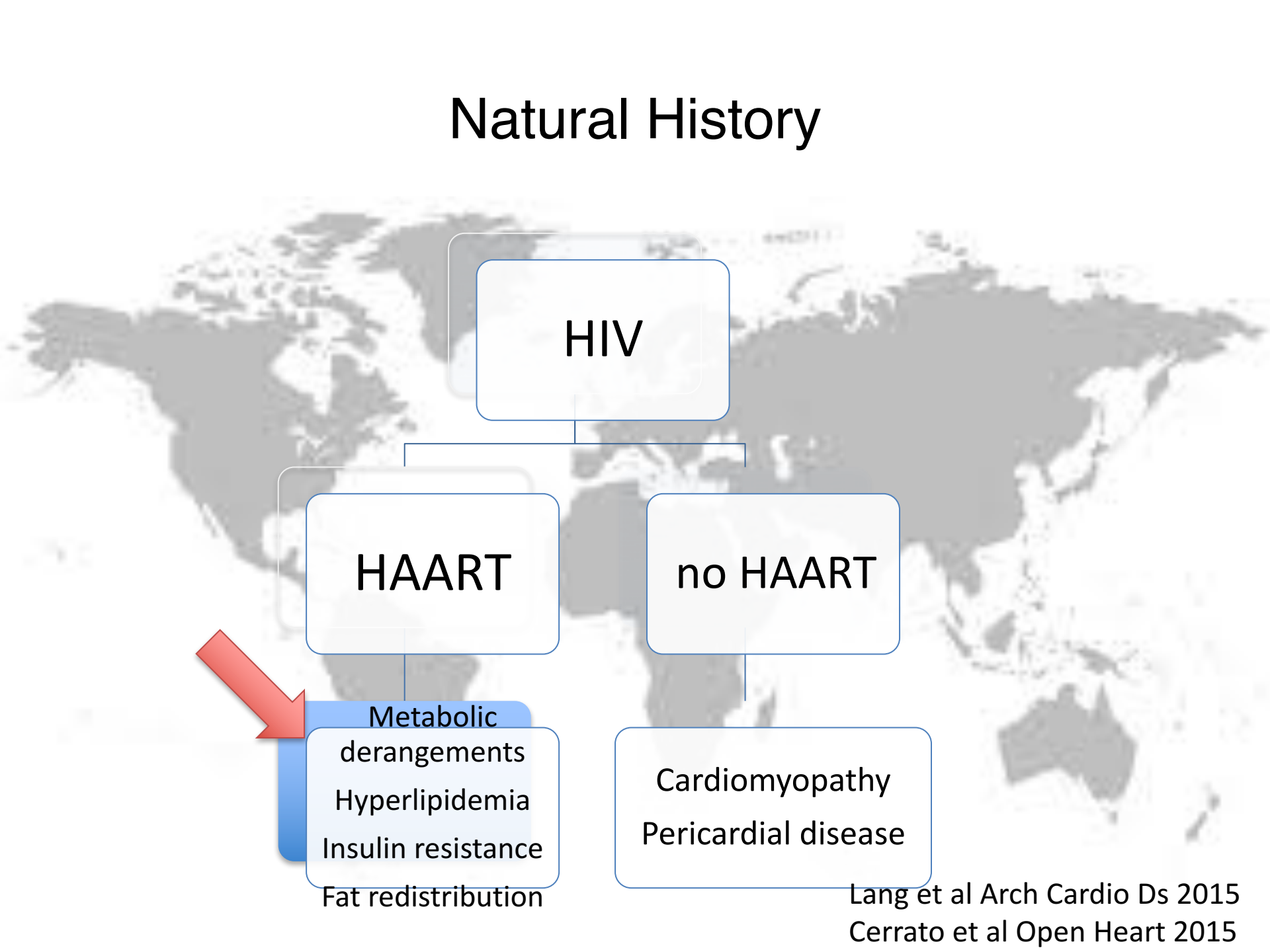
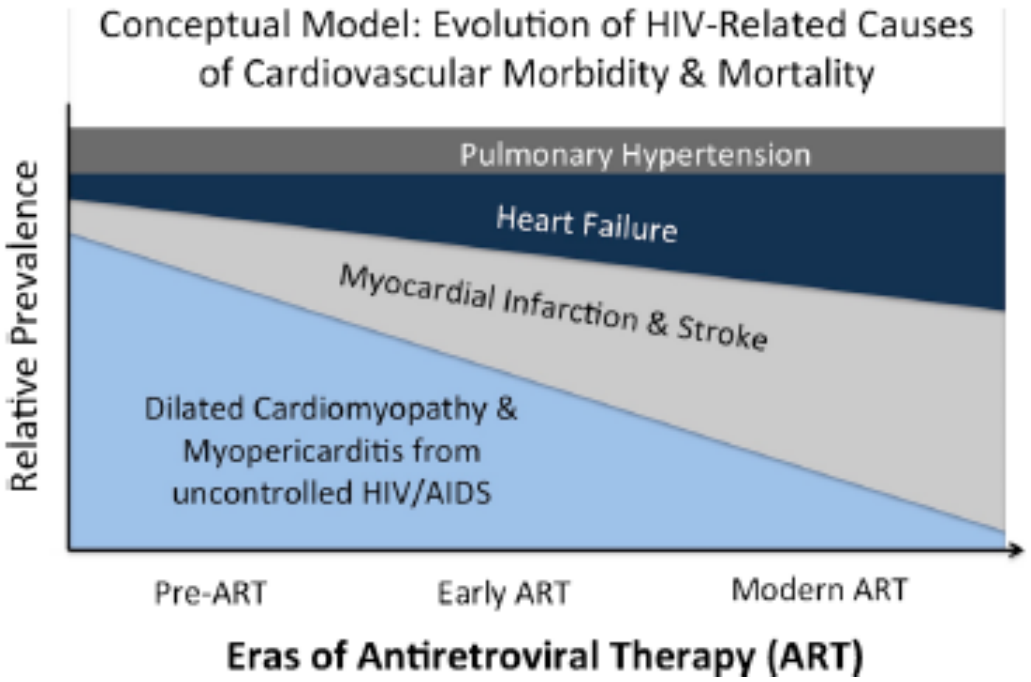
Natural History



Lang et al Arch Cardio Ds 2015
Cerrato et al Open Heart 2015

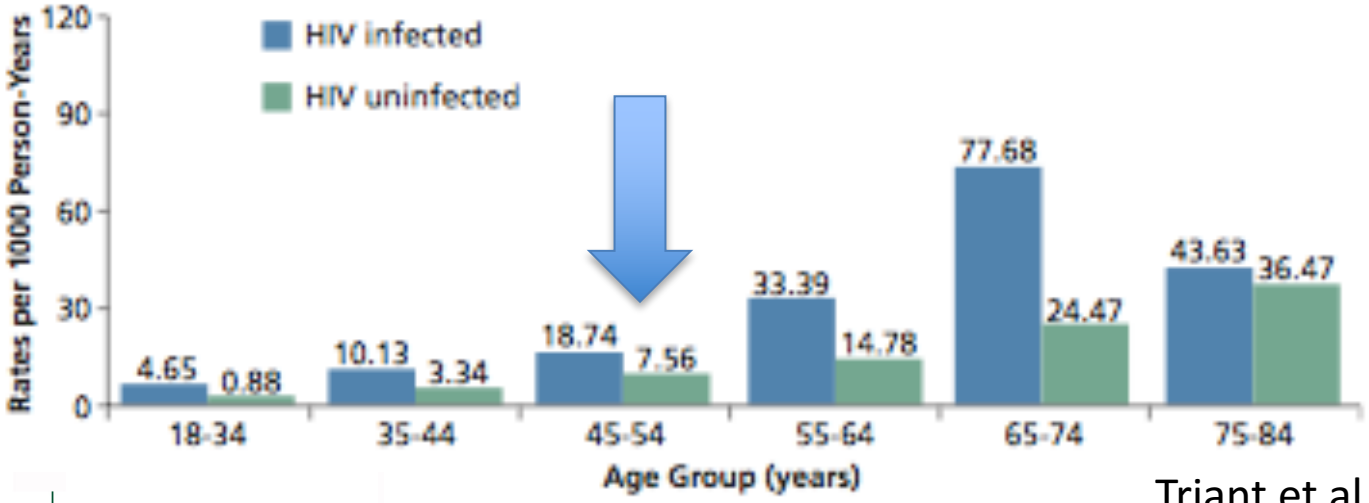
Evolution of HIV and CVD



Feinstein et al 2016

CV Mortality by age group

>50% increased risk



Triant et al 2007
Freiberg JAMA 2013
Lang AIDS 2010

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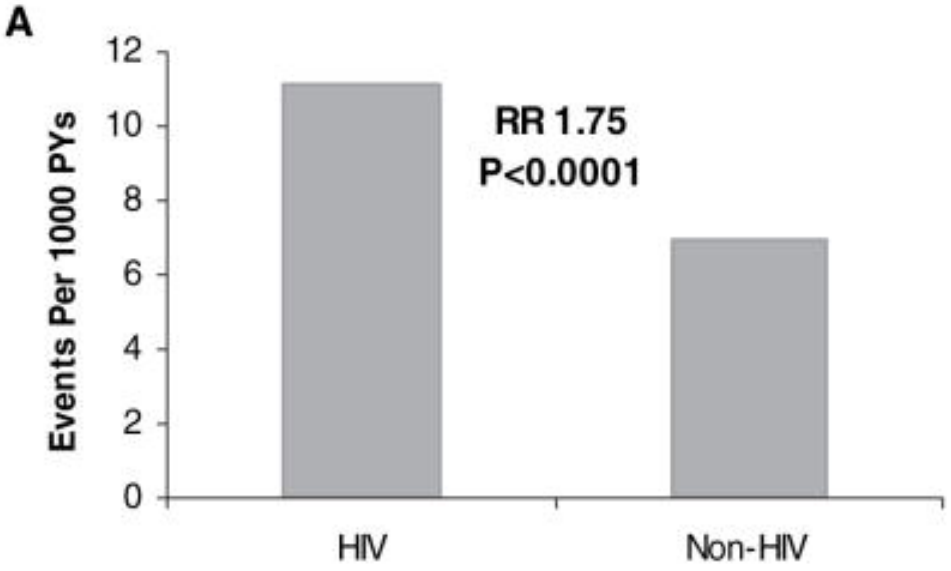
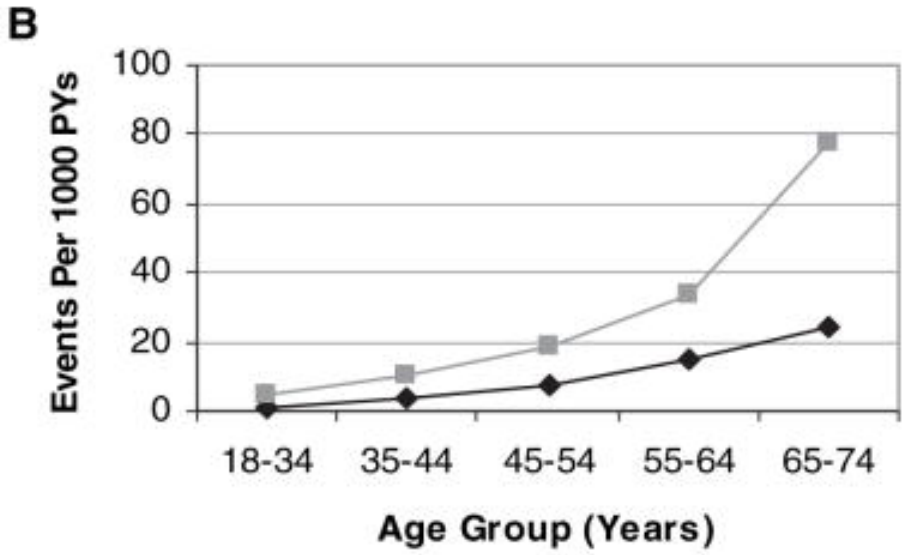
Who is more likely to have an AMI?





Triant et al J Clin Endocrinol Metab. 2007

Why?

Risk factors for CAD in HIV Patients

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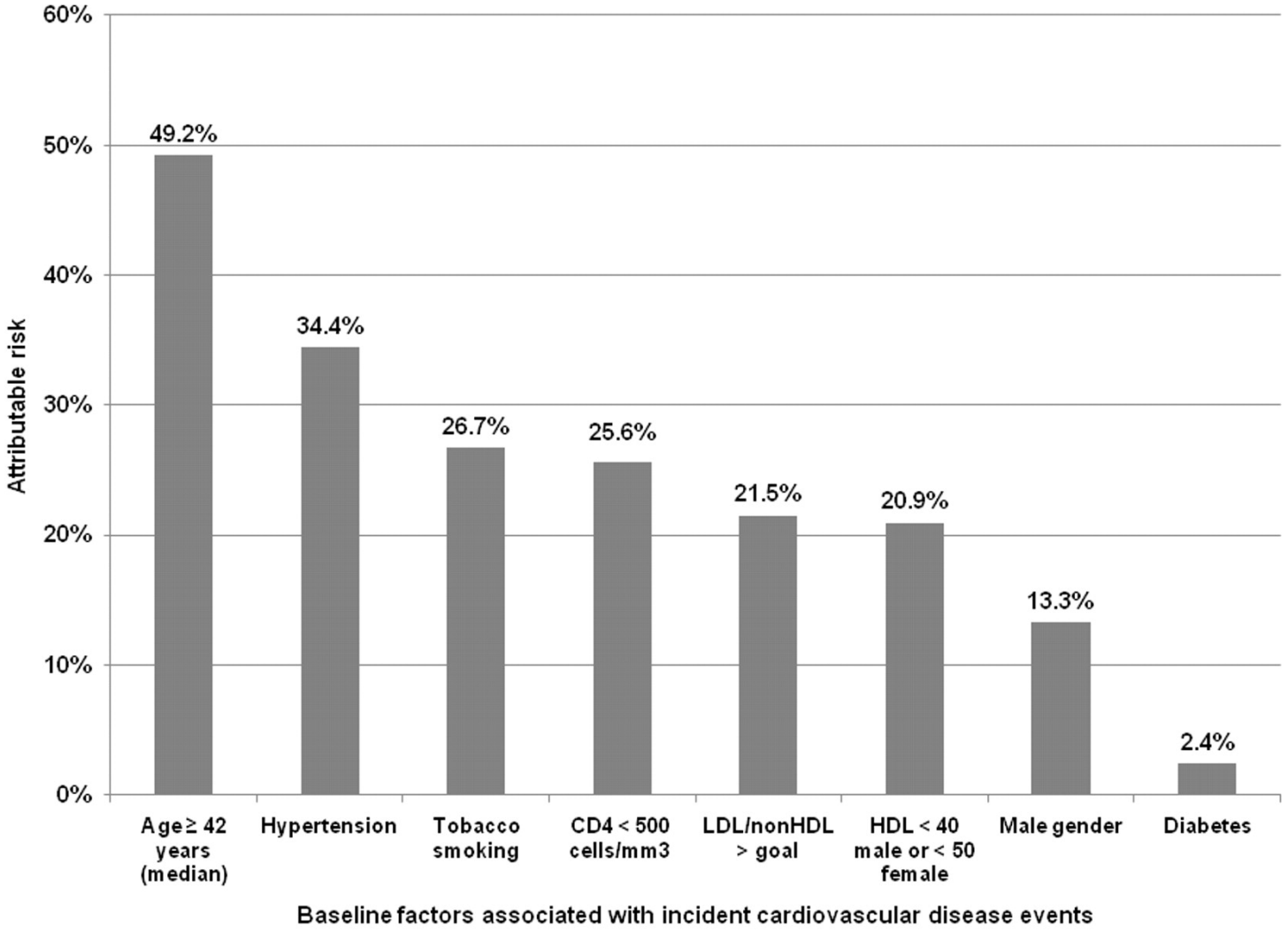
Traditional Risk Factors



Kenneth A. Lichtenstein et al. Clin Infect Dis. 2010;51:435-447

Risk Factors

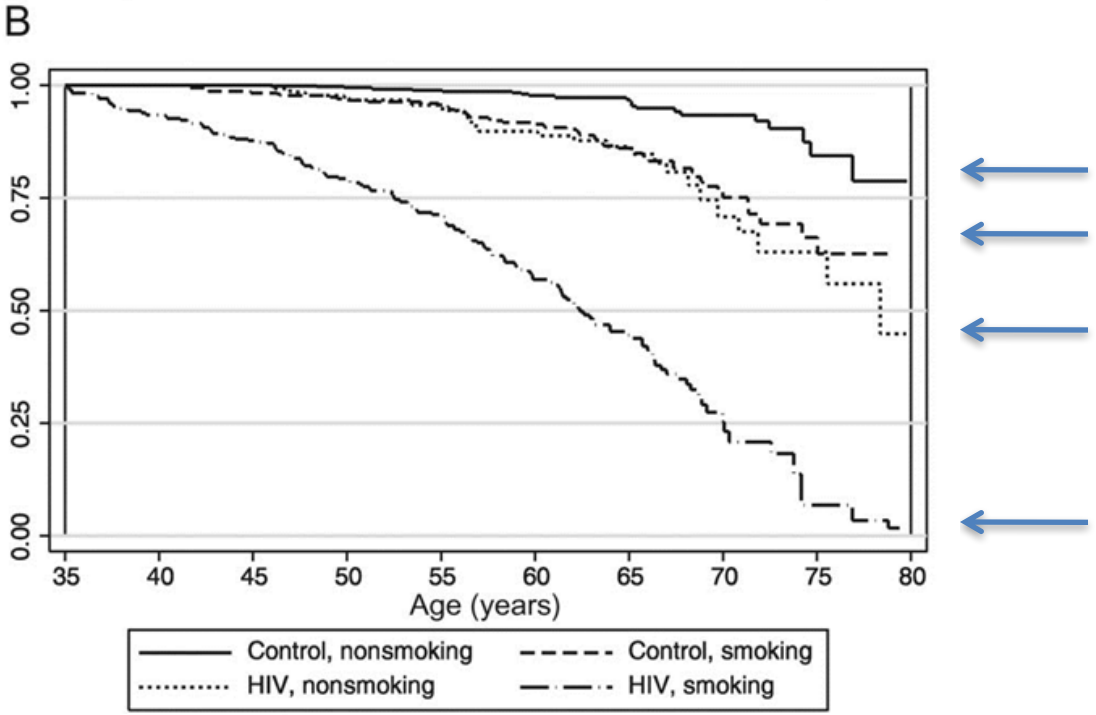
TABLE 2. Cardiac risk factors in HIV and non-HIV cohorts

	HIV (n = 3,851)		Non-HIV (n = 1,044,589)	
	n	Proportion	n	Proportion
Hypertension	818	21.2[a]	165,665	15.9
Females	211	18.0[a]	80,619	13.1
Males	607	22.7[a]	85,046	19.9
Diabetes	443	11.5[a]	68,565	6.6
Females	145	12.4[a]	34,096	5.5
Males	298	11.1[a]	34,469	8.1
Dyslipidemia	896	23.3[a]	184,291	17.6
Females	262	22.4[a]	92,411	15.0
Males	634	23.7[a]	91,880	21.5
Smoking		38%		18%

Triant et al 2007

Smoking

Mortality Attributable to Smoking Among HIV-1–Infected Individuals: A Nationwide, Population-Based Cohort Study



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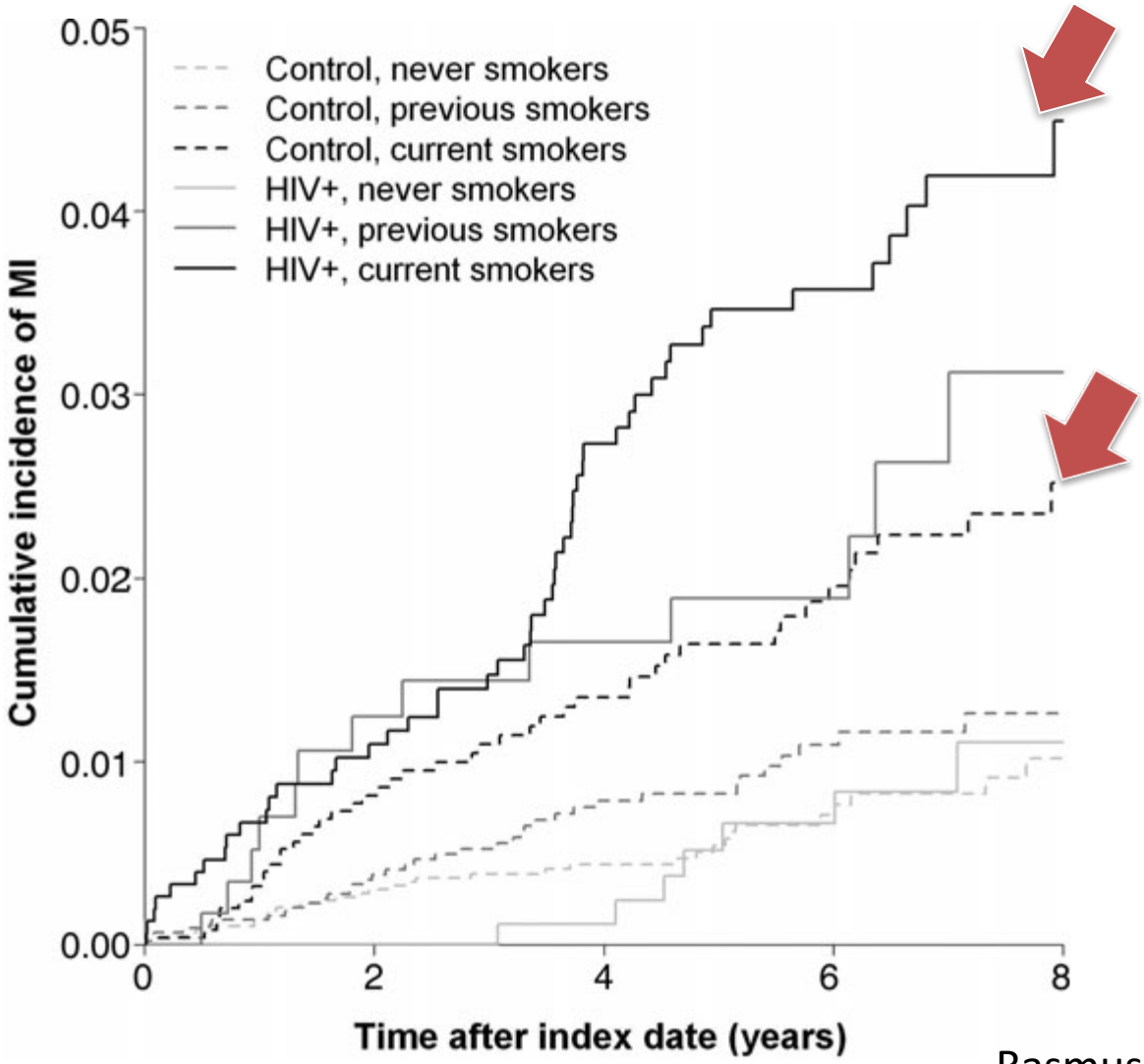
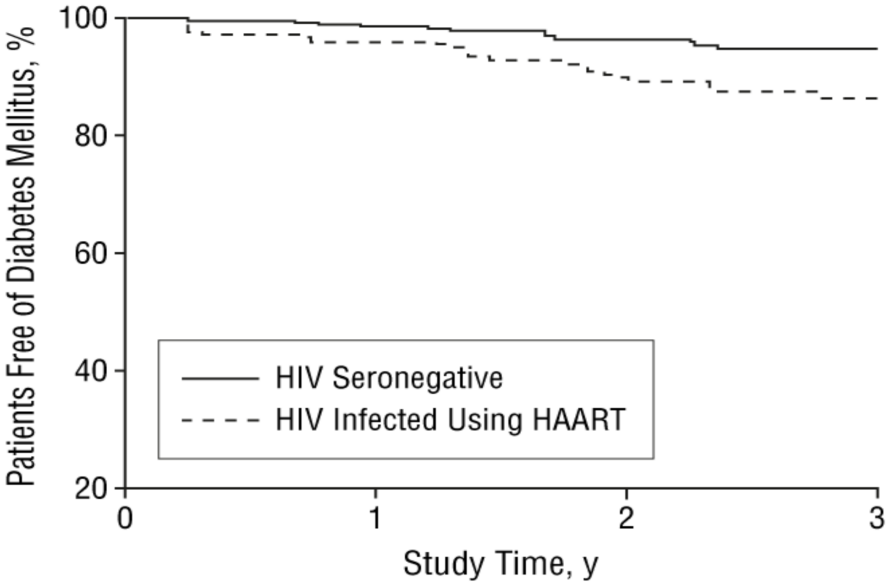
Helleberg et al Clin inf ds 2013

MI & Smoking



Rasmussen et al 2015

Insulin Resistance & DM



No. of Patients				
HIV Seronegative	361	265	177	89
HIV Infected Using HAART	229	204	145	62

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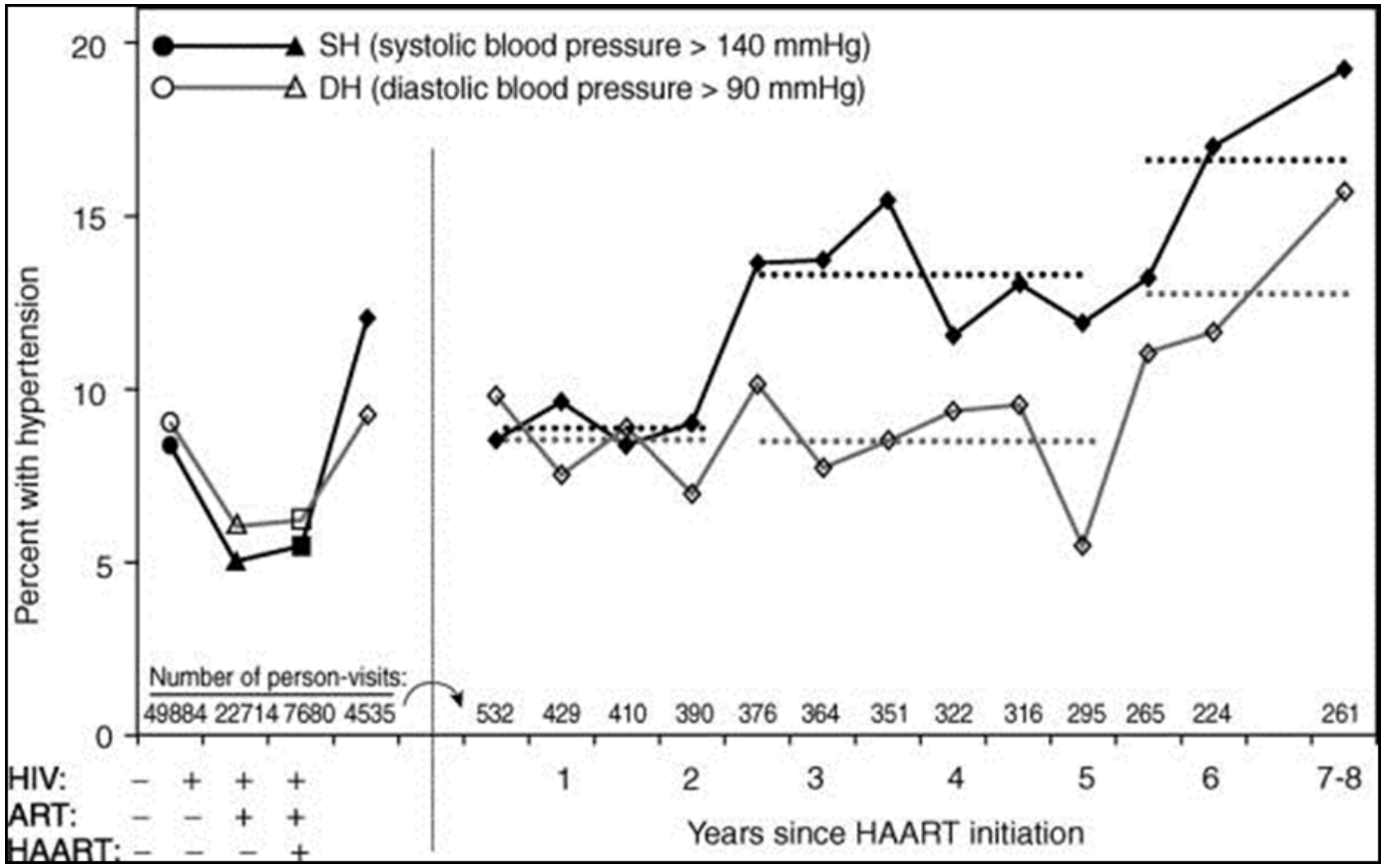
Brown et al Arch Int Med 2005

Hypertension



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Seaberg et al AIdS 2005

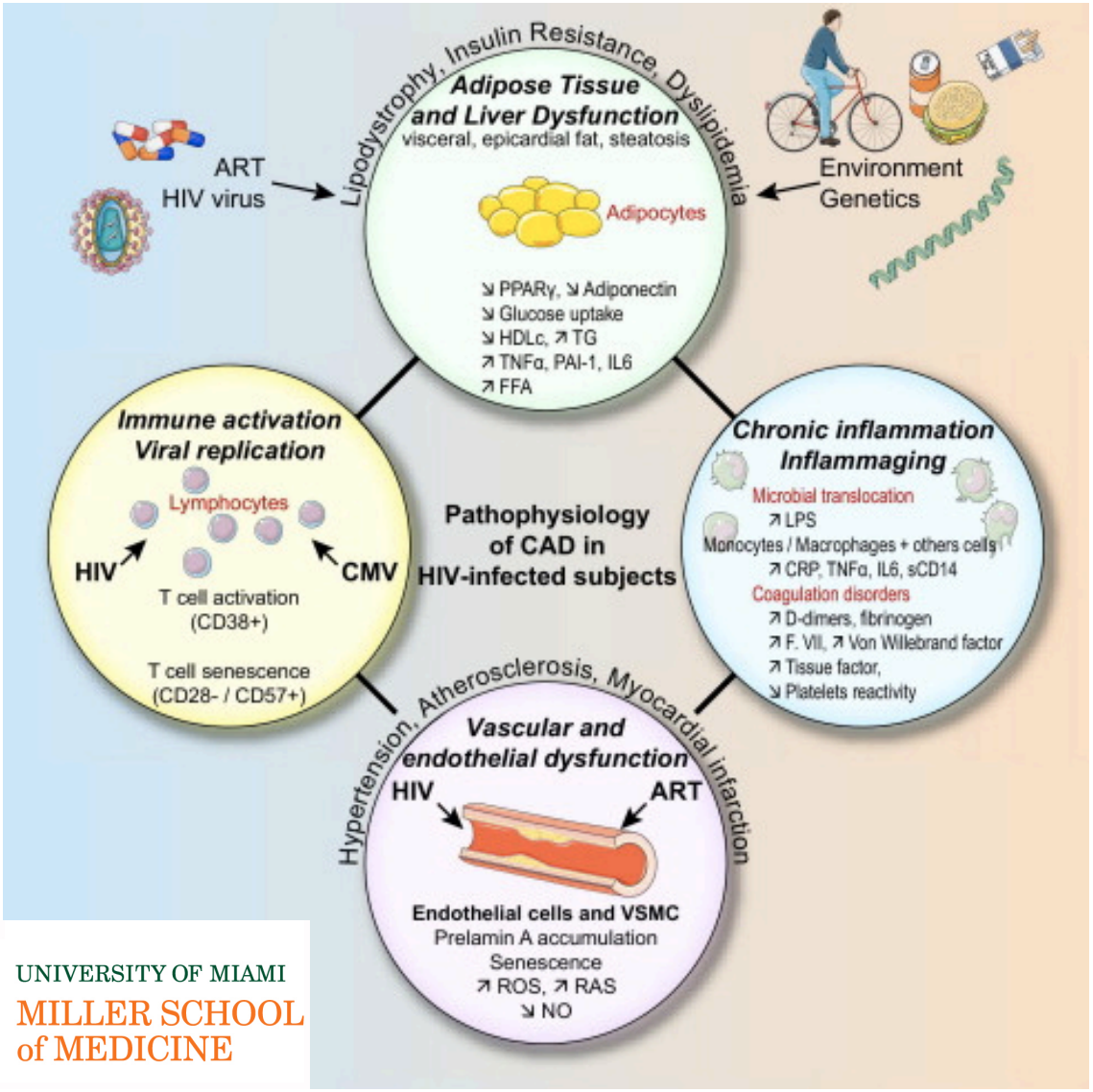
Non Traditional Risk Factors

TABLE 2. *Age-adjusted[a] CHD hospitalization rates by study group*

Study group	Age-adjusted rate (per 1000 person-years)	95% Confidence interval
All HIV-positive cases[b]	6.5[d]	(4.7–8.3)
No PI exposure	6.2	(3.5–8.9)
PI exposure	6.7	(4.4–9.1)
No ART exposure	5.7	(2.1–9.3)
ART exposure	6.8	(4.7–8.8)
HIV-negative controls[c]	3.8[d]	(3.5–4.1)

Klein D J Acquir Immune Defic Syndr 2002

Non Traditional Risk Factors



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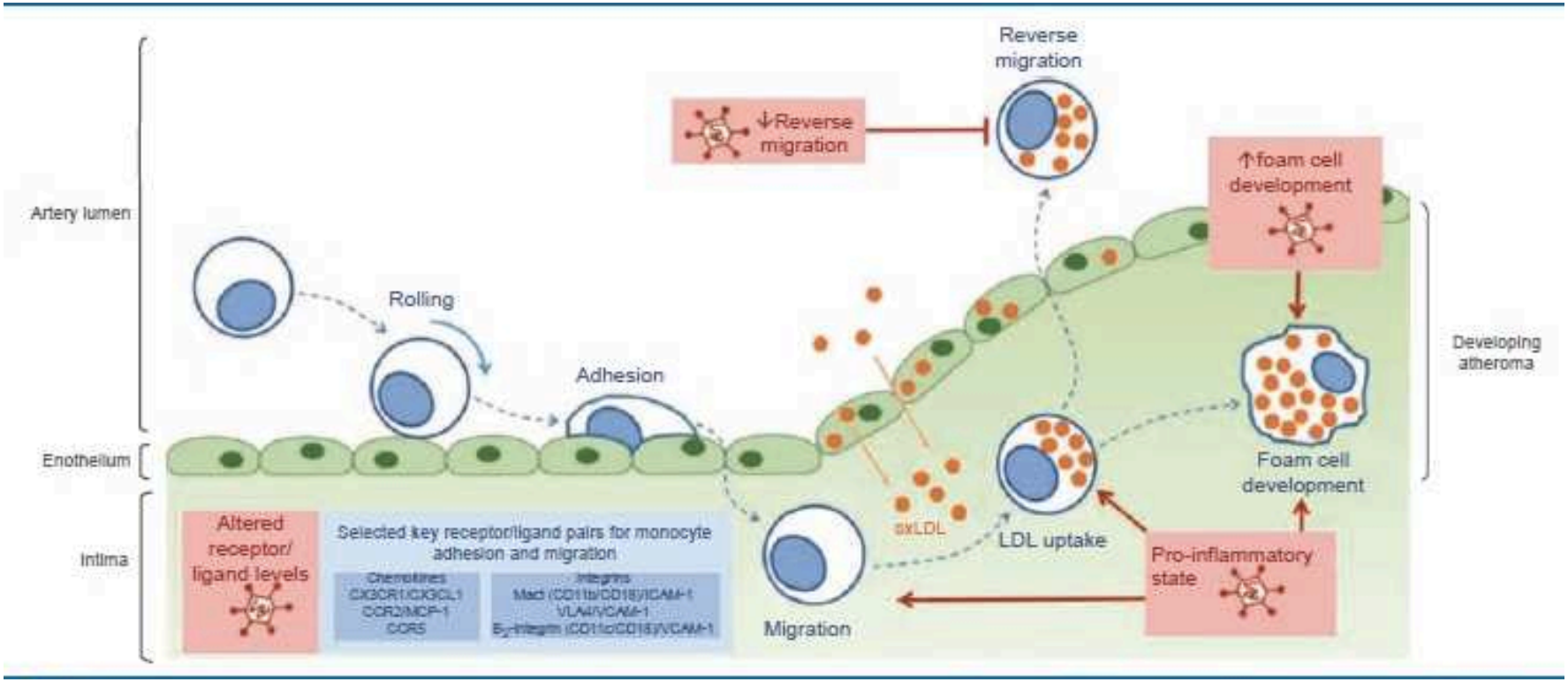
HIV & Lipids



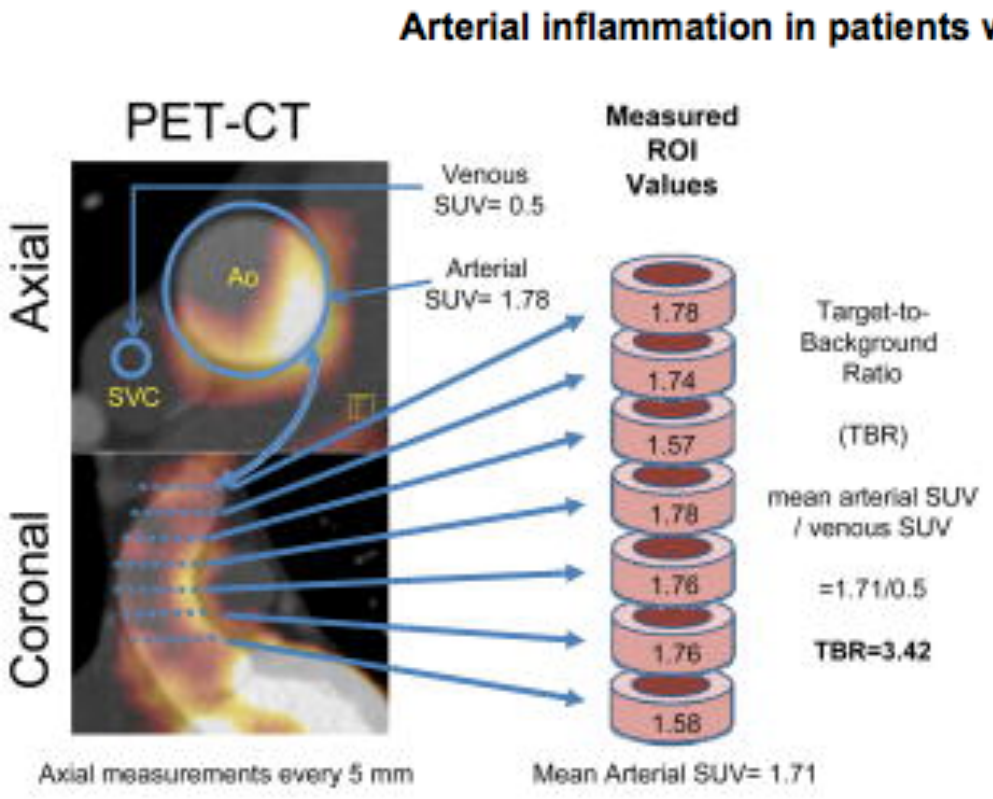
⃠ABCA1

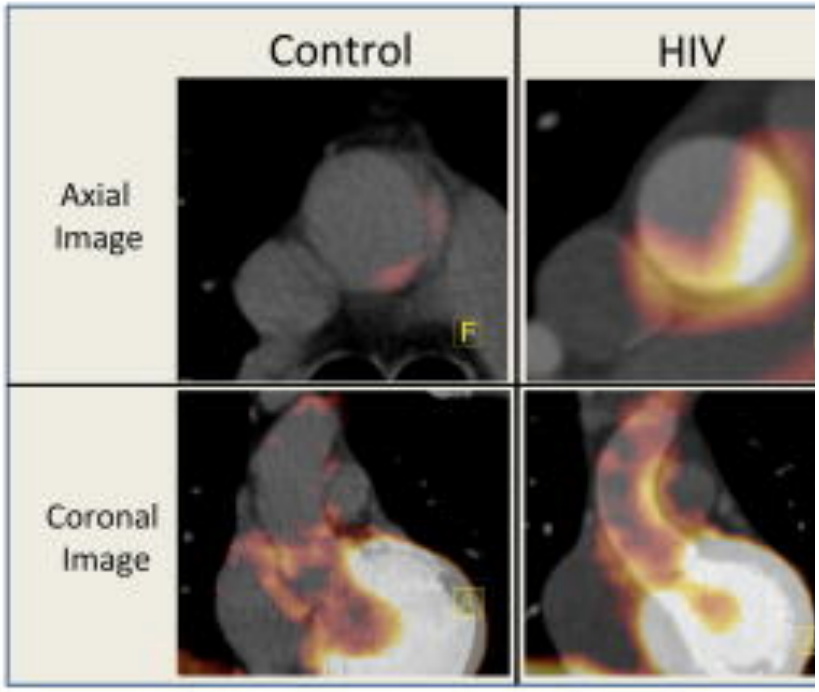
⃠ATP binding cassete transporter A1-dependent cholesterol efflux

Mujawar et al 2006

Riddler et al 2013

Inflammation





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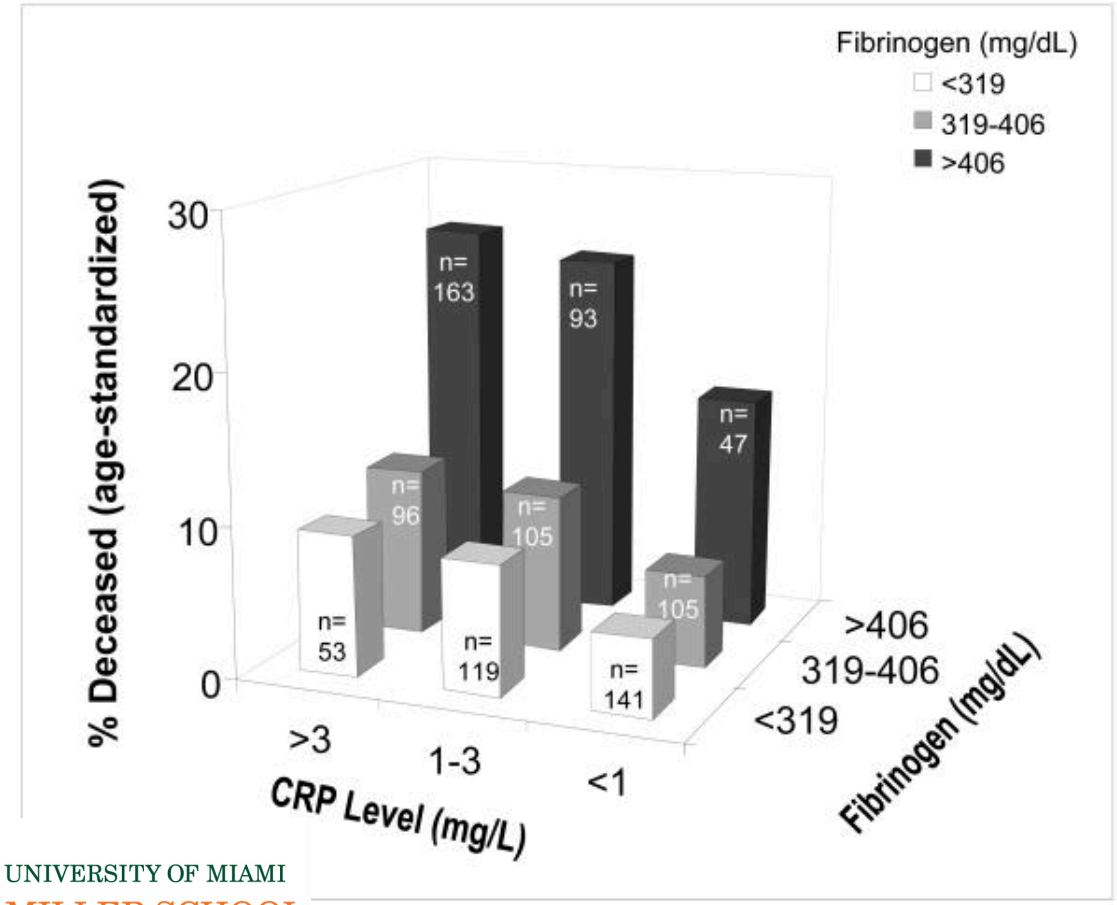
Subramanian JAMA 2012

Inflammation

Inflammation and Mortality in HIV-infected Adults: Analysis of the FRAM Study Cohort



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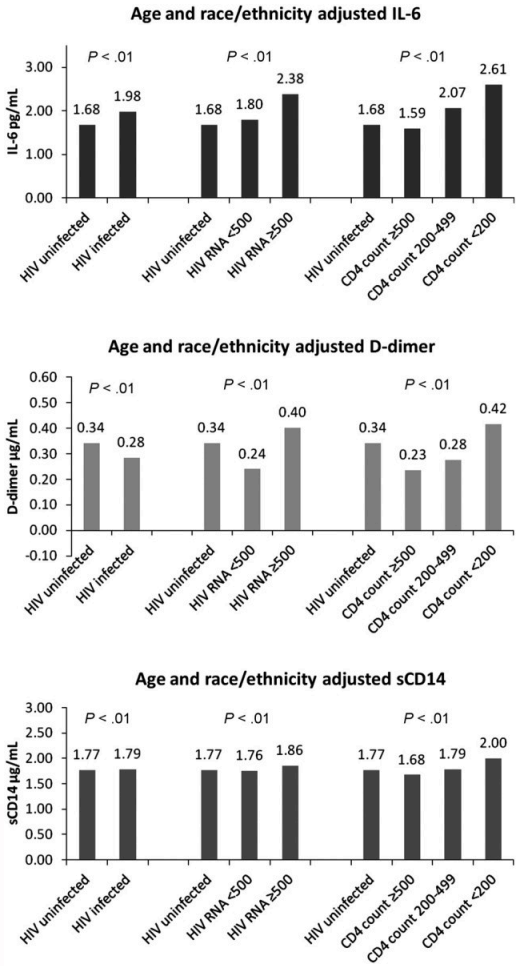
Tien et al J Acq immune 2010

IL-6

IL-6 and D-dimer levels are associated with vascular dysfunction in patients with untreated HIV infection



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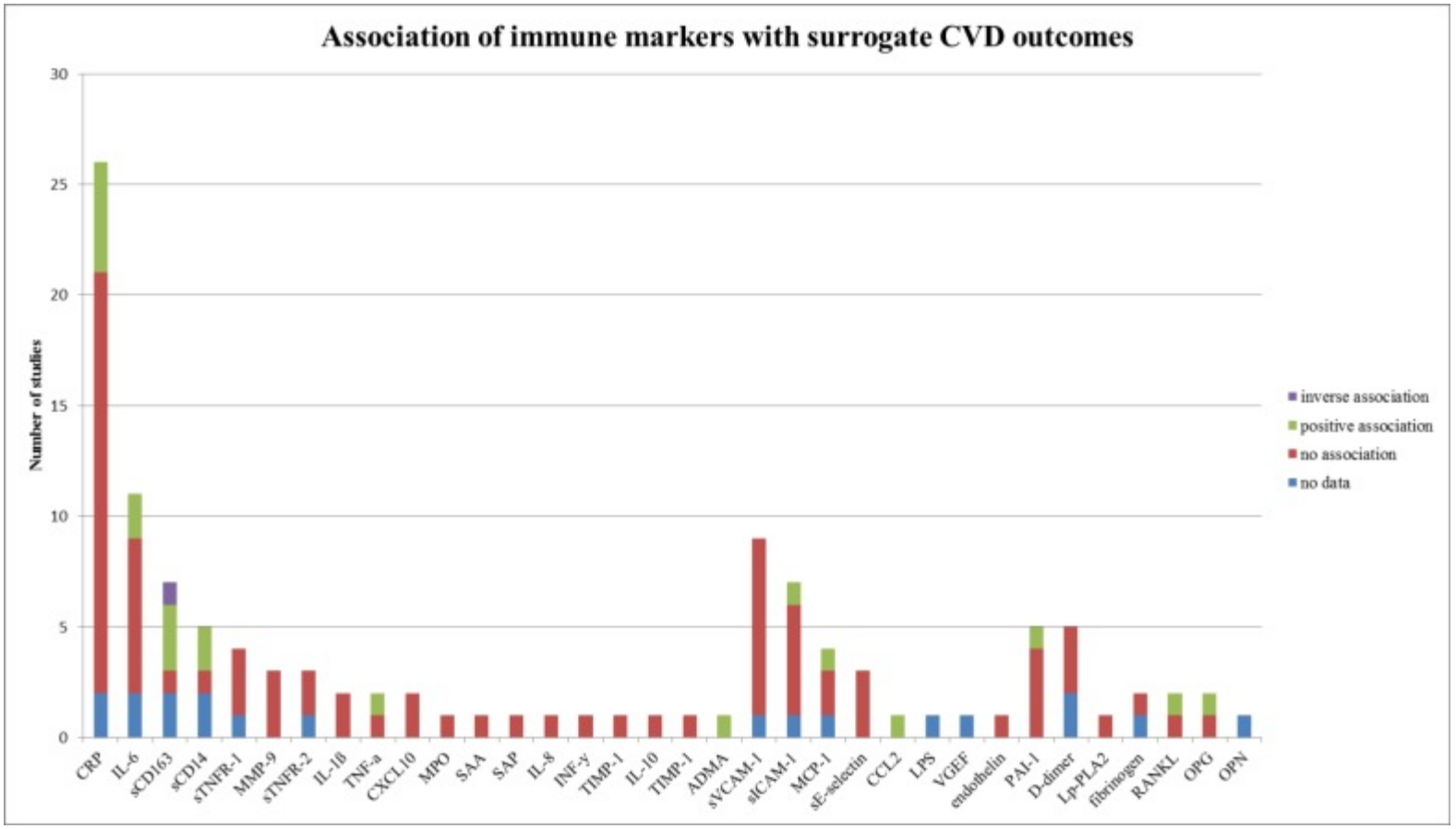
Baker et al HIV med 2010

Immune Markers



A. Vos et al Plos 2017

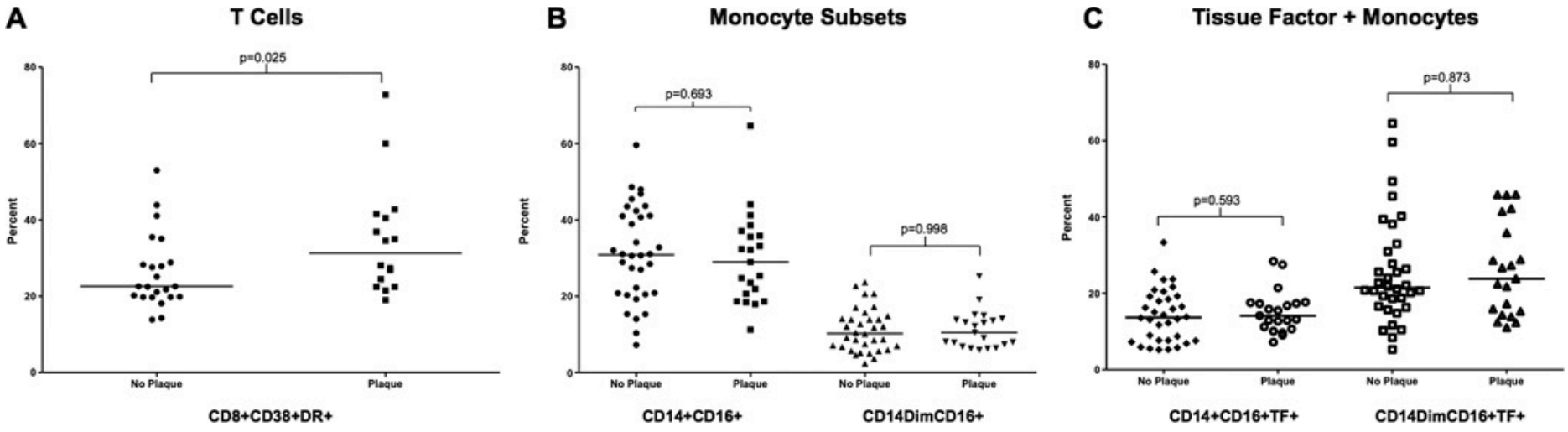
Immune system

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]	
≥500	1.75 (1.40-2.18)	.05
<500	1.39 (1.17-1.66)	
CD4 cell count		
Uninfected	1 [Reference]	
<200	1.88 (1.46-2.40)	.04
≥200	1.43 (1.21-169)	

Freiberg et al JAMA 2013

Activacion Celular



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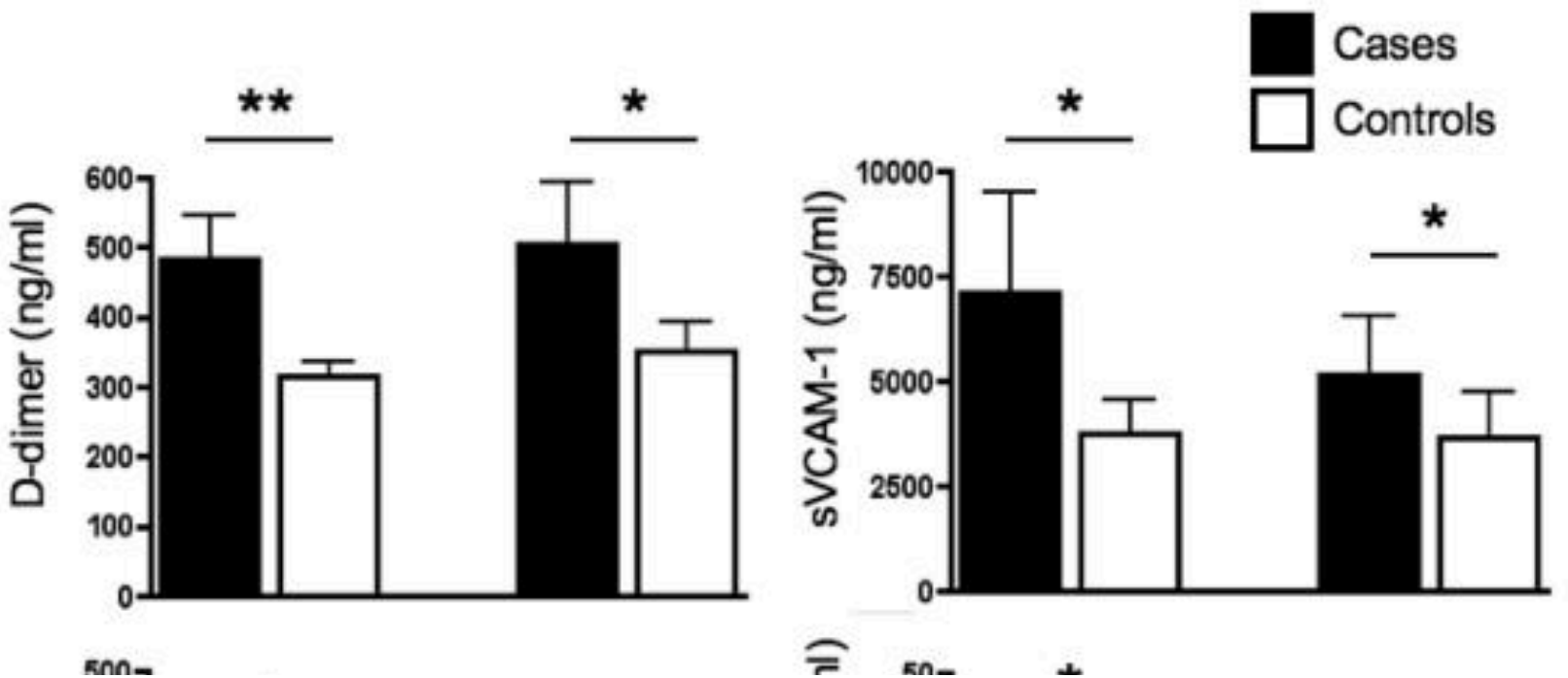
Longenecker et al HIV Med 2013

Coagulation



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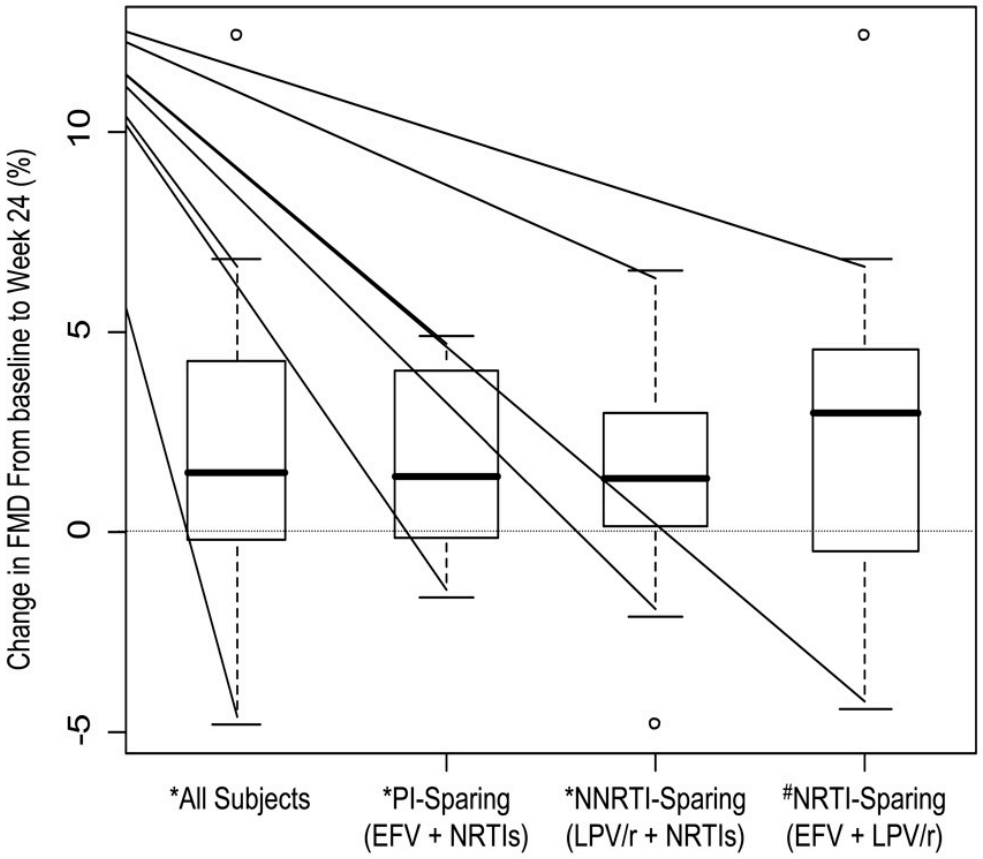
Ford ES AIDS 2010

Endothelial dysfunction



*$p \leq 0.005$, #$p = 0.015$ within arm, compared to baseline (between groups $p = 0.828$)

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Torriani JACC 2008

HAART & CV risk

HAART

- **PI**
  - Indinavir
  - Saquinavir
  - Ritonavir
  - Fosamprenavir
  - Lopinavir
  - Atazanavir
  - Tipranavir
  - Darunavir

N=9

- NNRTI
  - Efavirenz
  - Nevirapina
  - Delavirdina
  - Etravirina
  - Rilpivirina

N=5

- **NRTI**
  - Abacavir
  - Zidovudina
  - Lamivudina
  - Emtricitabina
  - Didanosina
  - Estavudina
  - Zalcitabina
  - Tenofovir

N=8

- **Integrase inhibitors**
  - Raltegravir
  - Elvitegravir
  - Dolutegravir

N=3

- **CCR5 receptor bloquers**
  - Maraviroc

N=1

- **Fusion inhibitors**

N=1

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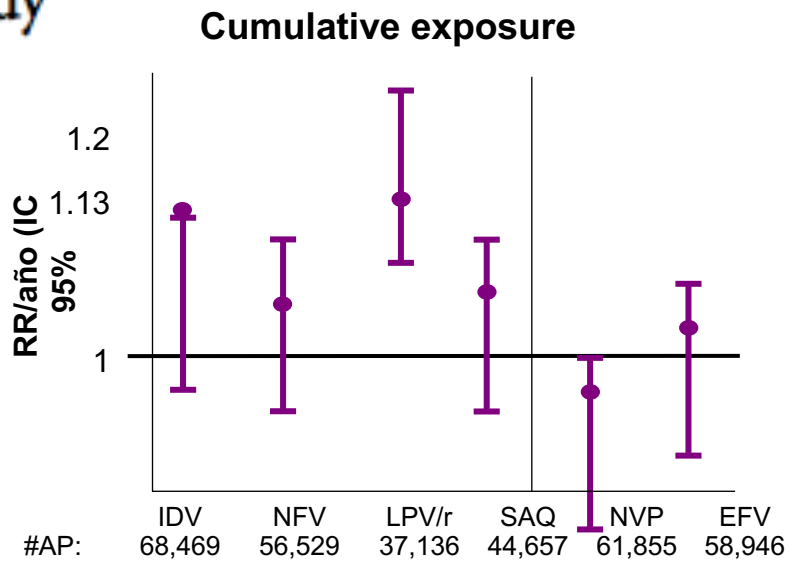
Treatment-Associated Hyperlipidemia

- NRTIs
  - Stavudine > zidovudine > abacavir = tenofovir DF
  - Combinations
    - Stavudine + lamivudine > tenofovir DF + lamivudine
    - Zidovudine/lamivudine > emtricitabine/tenofovir DF
    - Stavudine + didanosine > emtricitabine + didanosine
    - Stavudine + didanosine > abacavir + lamivudine
- Ritonavir-boosted PIs
  - Indinavir, lopinavir, tipranavir > atazanavir, darunavir, fosamprenavir, saquinavir
  - Ritonavir: full dose > boosting dose
- NNRTIs
  - Efavirenz > nevirapine (both increases HDL-C)

1
Gallant JE, et al. *JAMA.* 2004; [2]Pozniak AL, et al. *JAIDS*.; [3]Shlay JC, et al. *JAIDS* [4]Podzamczer D, et al. *JAIDS.* 2007;PW, et al. *AIDS.* 2003 [6]Johnson M, et al. *AIDS.* 2005; [7]Smith K, et al. *AIDS Res Ther*.
2008; [8]Walmsley S, et al. *JAIDS.* 2009;[9]Mills A, et al. *AIDS.* 2009;
[10]Molina J-M, et al. *JAIDS.* 2010;[11]van Leth F, et al. *PLOS Med.* 2004

Protease Inhibitors

Risk of Myocardial Infarction in Patients with HIV Infection Exposed to Specific Individual Antiretroviral Drugs from the 3 Major Drug Classes: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study



Lopinavir-ritonavir
Indinavir
NOT a class effect

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Worm et al J inf Ds 2010
Lundgren JD, et al. CROI 2009
Lang et al Arch int med 2010

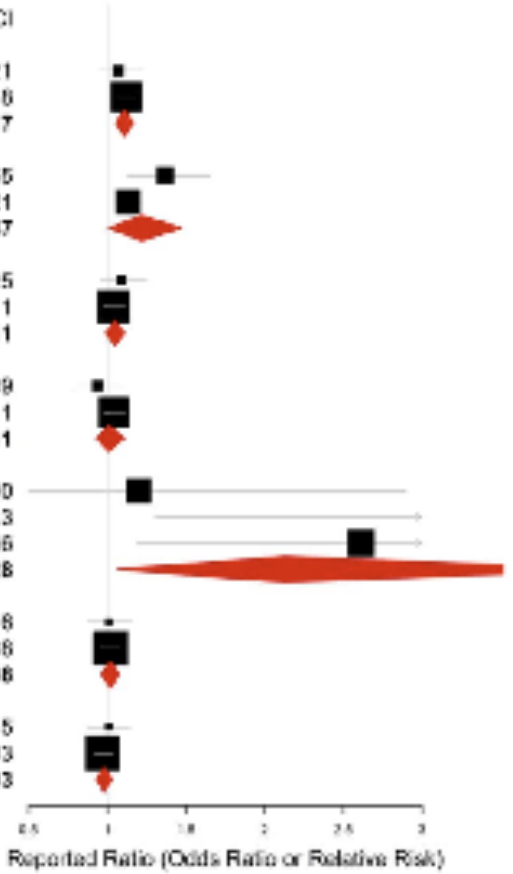
PI & Lipids

Drug Class	Adverse Metabolic Effects	Impact on CHD
PI	Dyslipidemia*; insulin resistance; variable with different drugs	Duration of exposure independently increased risk for MI
Ritonavir	Dyslipidemia+++; insulin resistance+++	This drug is never used alone, but as a pharmacological booster in association with other PIs
Lopinavir + ritonavir	Dyslipidemia+++; insulin resistance++	Cumulative exposure independently increased risk for MI
Atazanavir + ritonavir	Dyslipidemia+; insulin resistance+	No data available (not enough patients exposed)
Darunavir, + ritonavir	Dyslipidemia+; insulin resistance+	No data available (not enough patients exposed)
Indinavir	Dyslipidemia; insulin resistance+++	Controversial results
Saquinavir	Dyslipidemia+; insulin resistance+	No association with risk for MI
Amprenavir + ritonavir	Dyslipidemia+; insulin resistance+	No data available (not enough patients exposed)
Tipranavir + ritonavir	Dyslipidemia++; insulin resistance+	No data available (not enough patients exposed)
Nelfinavir	Dyslipidemia+; insulin resistance+	No association with risk for MI

Bocarra et al JACC 2013

Protease Inhibitors

Author	Class	Drug	Exposure Risk	Outcome	Statistic	Lower CI	Point estimate	Upper CI
Lang	PI	Indinavir	Per Year	MI	OR	0.85	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	0.91	0.94	1.09
DAD 2010	PI	Saquinavir	Per Year	MI	RR	0.96	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
Ricketts	PI	PI	Recent	MI	OR	1.19	2.61	5.66
Summary	**PI**	**PI**	**Recent**	**MI**		**1.06**	**2.13**	**4.26**
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**



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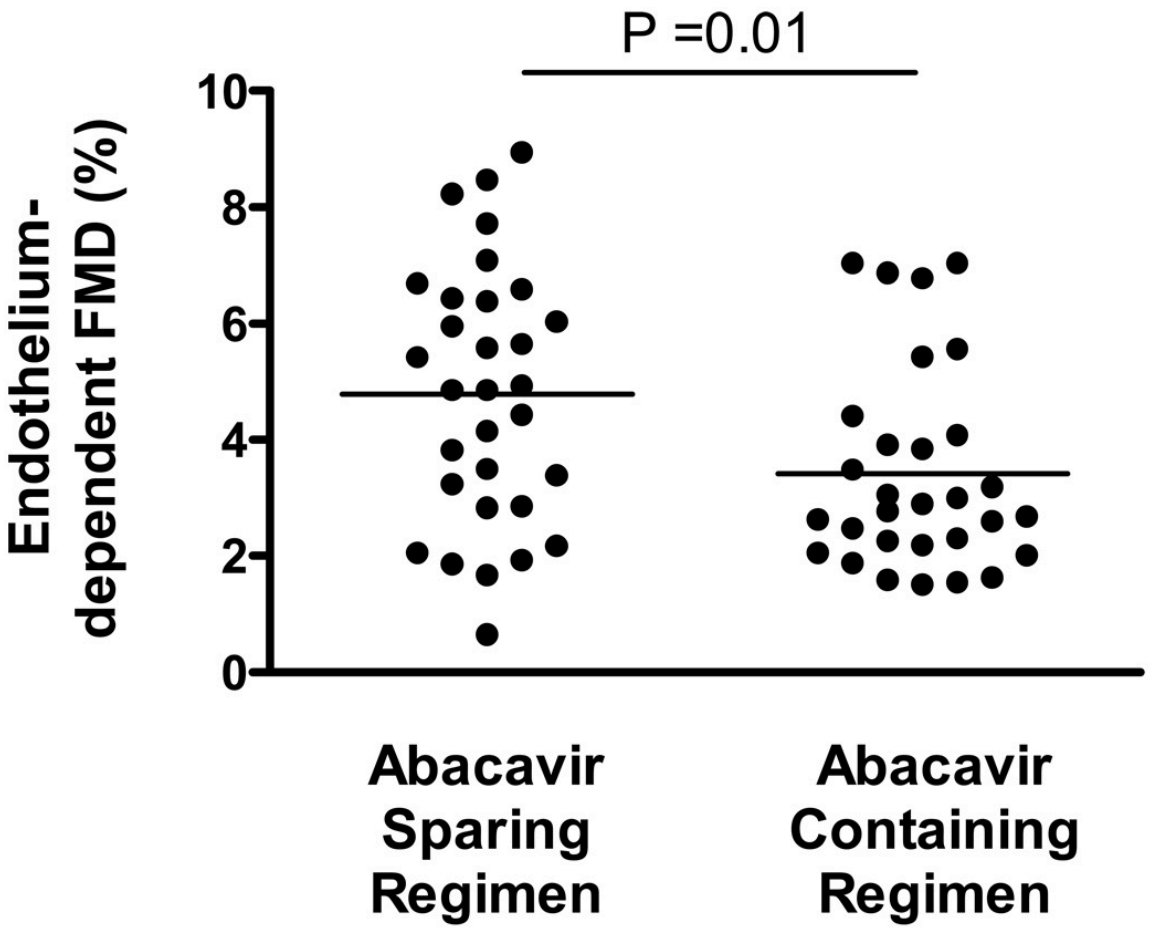
Bavinger et al 2013

NRTI

- Tenofovir & emtricitabine- no lipid effect
  - ↓TC
  - ↓ LDL
  - ↓TGL

Drug Class	Adverse Metabolic Effects	Impact on CHD
NRTI	Insulin resistance+ (stavudine > zidovudine); dyslipidemia with didanosine and stavudine	Two NRTIs (abacavir and didanosine) have been associated with an increased risk for MI but controversial results

Endothelial dysfunction



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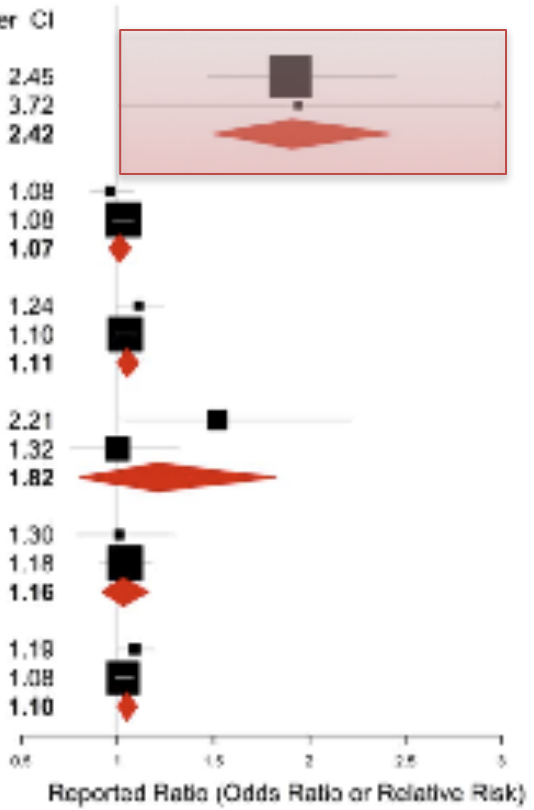
Hsue AIDS 2009

NRTI

a.

Author	Class	Drug	Exposure Risk	Outcome	Statistic	Lower CI	Point estimate	Upper CI
DAD 2008	NRTI	Abacavir	Recent	MI	RR	1.47	1.90	2.45
Obel	NRTI	Abacavir	Recent	MI	RR	1.01	1.94	3.72
Summary	**NRTI**	**Abacavir**	**Recent**	**MI**		**1.50**	**1.91**	**2.42**
Lang	NRTI	Lamivudine	Per Year	MI	OR	0.86	0.96	1.08
DAD 2008	NRTI	Lamivudine	Per Year	MI	RR	0.98	1.03	1.09
Summary	**NRTI**	**Lamivudine**	**Per Year**	**MI**		**0.96**	**1.01**	**1.07**
Lang	NRTI	Stavudine	Per Year	MI	OR	0.99	1.11	1.24
DAD 2008	NRTI	Stavudine	Per Year	MI	RR	0.99	1.04	1.10
Summary	**NRTI**	**Stavudine**	**Per Year**	**MI**		**1.00**	**1.05**	**1.11**
Durand	NRTI	Stavudine	Recent	MI	OR	1.04	1.52	2.21
DAD 2008	NRTI	Stavudine	Recent	MI	RR	0.76	1.00	1.32
Summary	**NRTI**	**Stavudine**	**Recent**	**MI**		**0.80**	**1.21**	**1.82**
Lang	NRTI	Tenofovir	Per Year	MI	OR	0.79	1.01	1.30
DAD 2010	NRTI	Tenofovir	Per Year	MI	RR	0.91	1.04	1.18
Summary	**NRTI**	**Tenofovir**	**Per Year**	**MI**		**0.92**	**1.03**	**1.16**
Lang	NRTI	Zidovudine	Per Year	MI	OR	1.00	1.09	1.18
DAD 2008	NRTI	Zidovudine	Per Year	MI	RR	0.99	1.03	1.08
Summary	**NRTI**	**Zidovudine**	**Per Year**	**MI**		**1.00**	**1.05**	**1.10**



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Bavinger et al 2013

NNTRI

- ↑ LDL
- ↑ TC
- ↑ HDL
- Favorable:Nevirapine ↓ TGL

Drug Class	Adverse Metabolic Effects	Impact on CHD
NNRTI	Dyslipidemia variable with different drugs; efavirenz to a lesser extent than PIs; nevirapine mild dyslipidemia but with increased high-density lipoprotein cholesterol	No association with increased risk for MI

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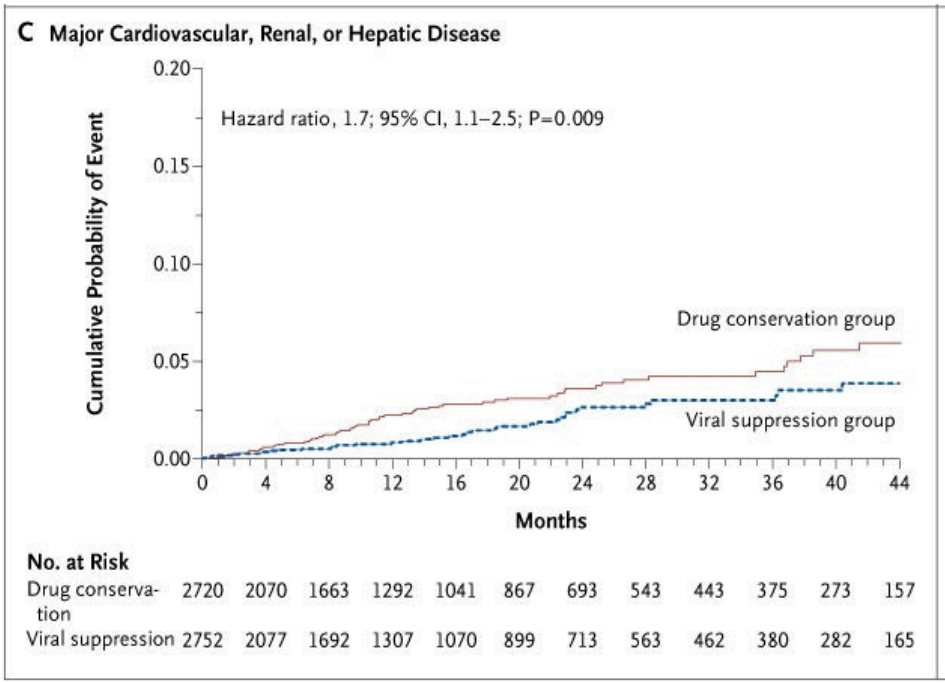
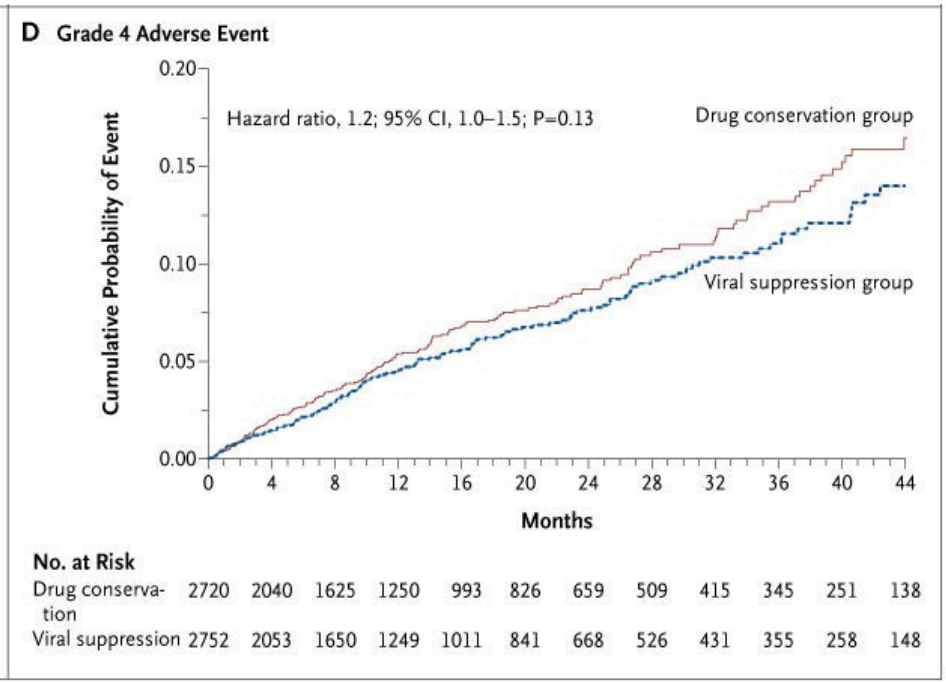
Tebas et al 2014
DUET-I,DUET –II, 2008

Integrase inhibitors

- Favorable lipid profile
  - Raltegravir-neutral
  - Elvitegravir = efavirenz & atazanavir
  - Dolutegravir

SMART study





SMART NEJM 2006

START or SMART? Timing of Antiretroviral Therapy Initiation and Cardiovascular Risk for People With Human Immunodeficiency Virus Infection

Mark J. Siedner

Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston

Table 4. Nadir CD4 Count and Cardiovascular Disease Event Incidence in the SMART and START Studies

Study Group	Nadir CD4	Cardiovascular Events	Event Rate
(per 1000 person-years)			
SMART Treatment Interruption Arm	~200	65	1.8
SMART Continued Therapy Arm	250	39	1.1
START Deferred Initiation Arm	~600	14	0.20
START Immediate Initiation Arm	651	12	0.17

Ofid 2016

Co-infection viral

- CMV
- HSV
- HCV

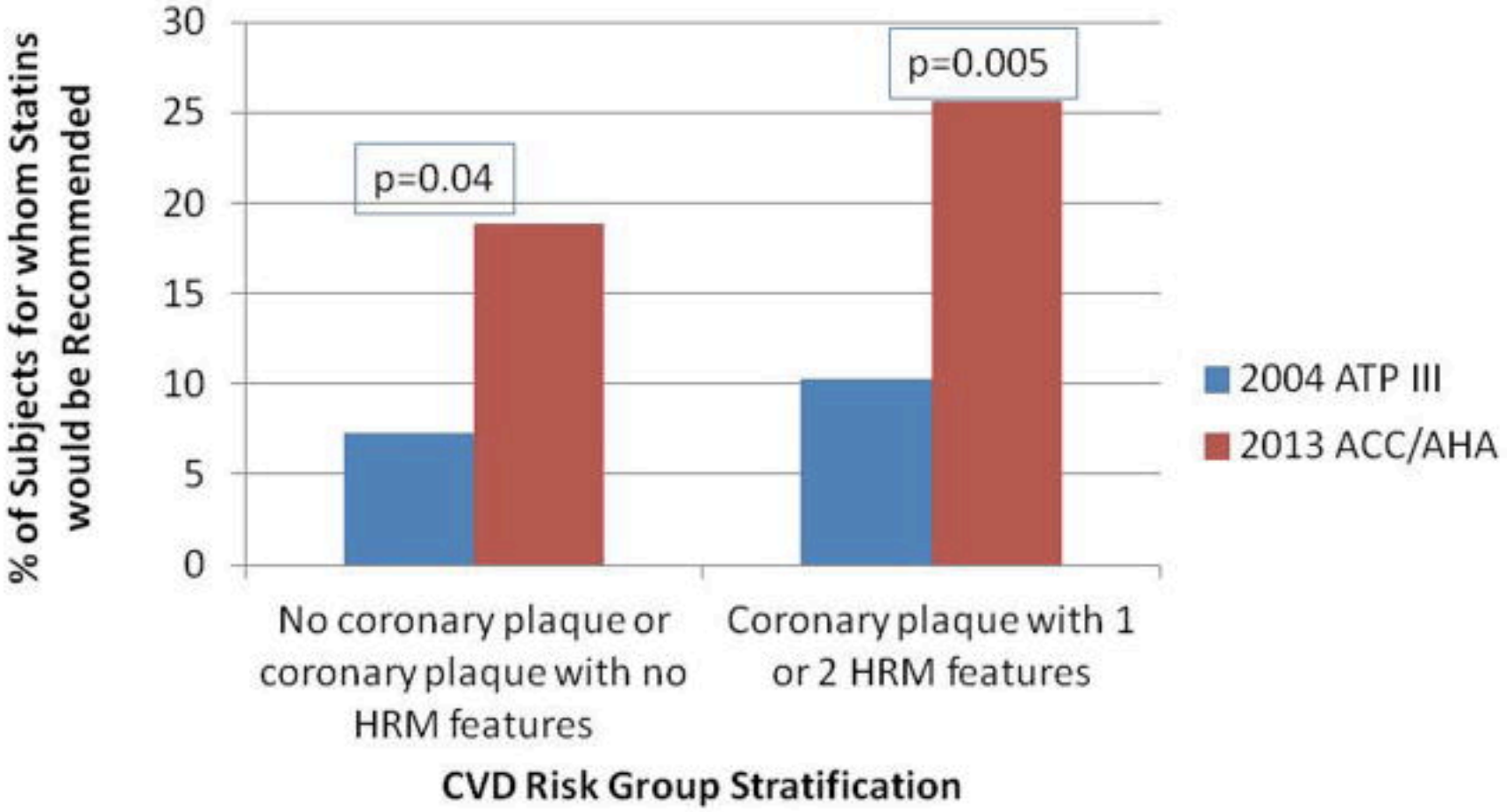
- Clinical translation

How?

Risk calculator

- http://www.cvriskcalculator.com/
- http://www.hivpv.org/
- http://hivpv.org/Home/Tools/tabid/91/ctl/ExamView/mid/500/eid/0/lid/0/Default.aspx

Risk Calculation



Zanni et al AIDS 2014

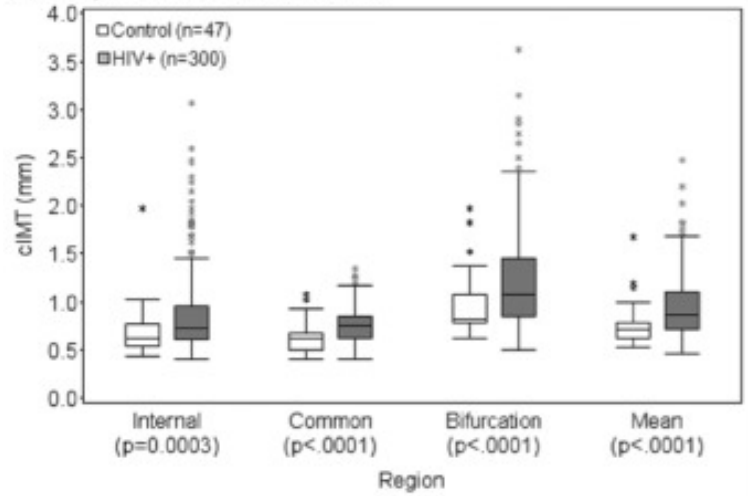
Carotids

RIGINAL RESEARCH

American Heart Association | American Stroke Association

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

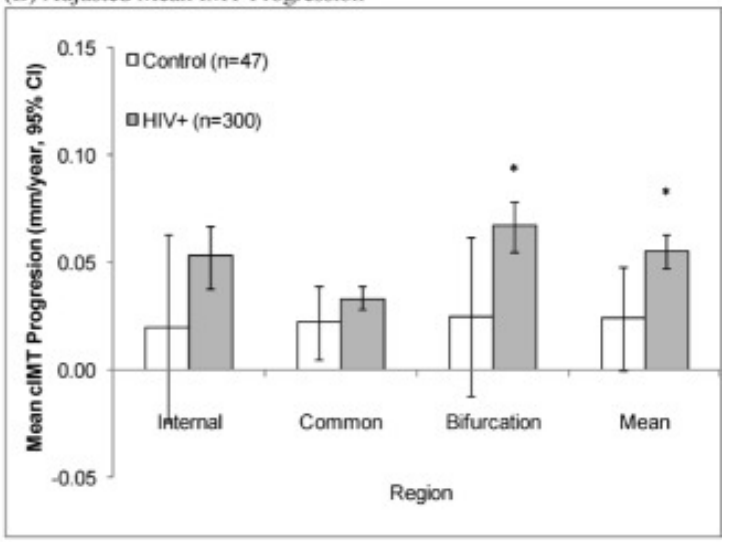
(A) Unadjusted IMT Levels at Baseline



Notes: Median is indicated by black center line, and the IQR (first and third quartiles) are the edges of the box.

xIQR.

(B) Adjusted Mean IMT Progression†



† Adjusted for demographics, traditional CVD risk factors, and hsCRP (full model) , as described in methods.

* denotes p<.05 for comparison with HIV-negative controls

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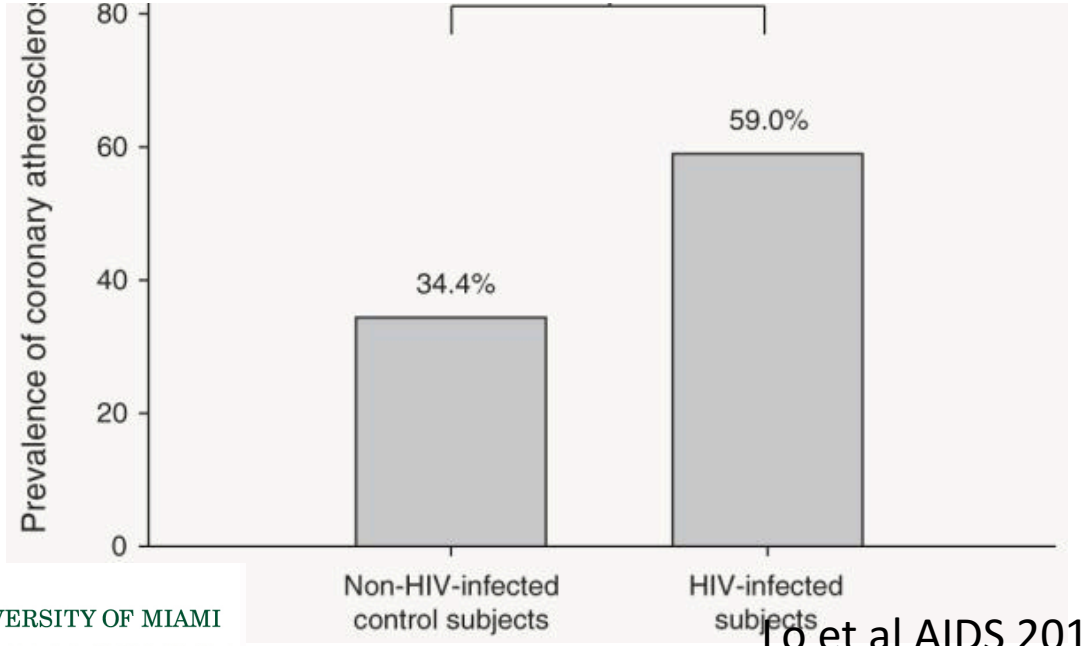
Hsue et al J Am Heart 2012

Grunfeld C AIDS 2009

CTA

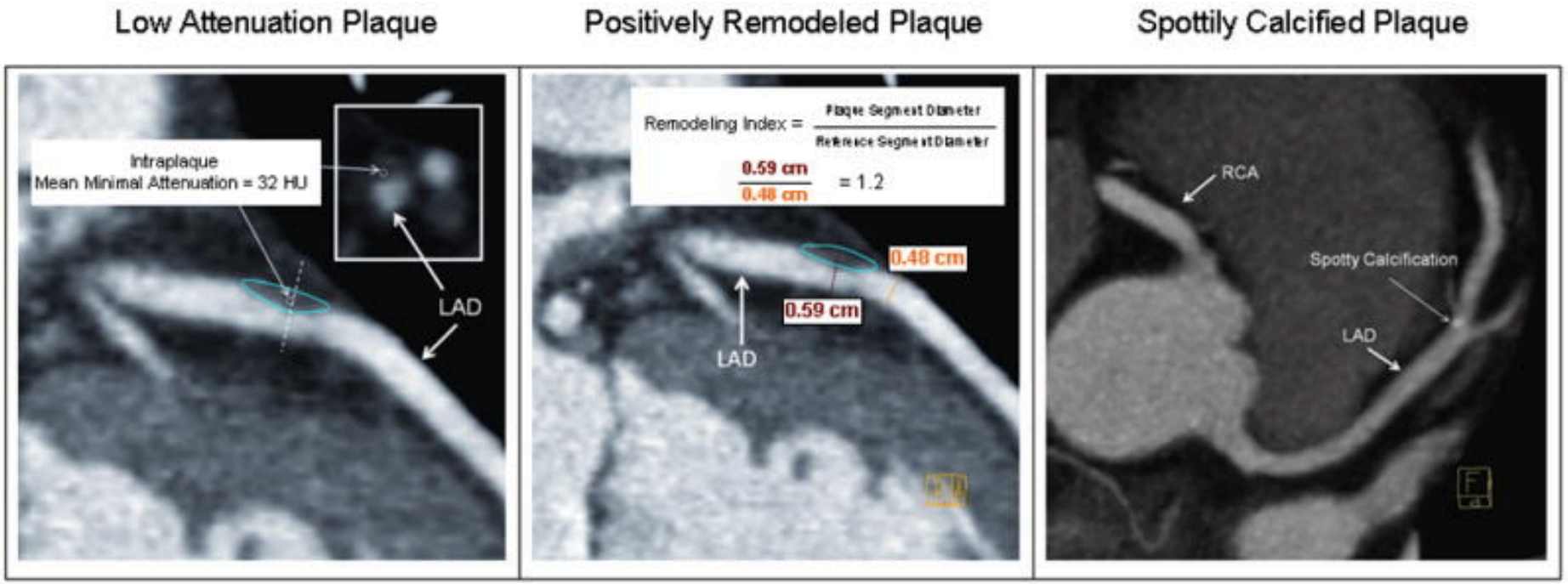
Published in final edited form as:
AIDS. 2010 January 16; 24(2): 243–253. doi:10.1097/QAD.0b013e328333ea9e.

Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men



Lo et al AIDS 2010
D'Ascenzo et al Atherosclerosis. 2015

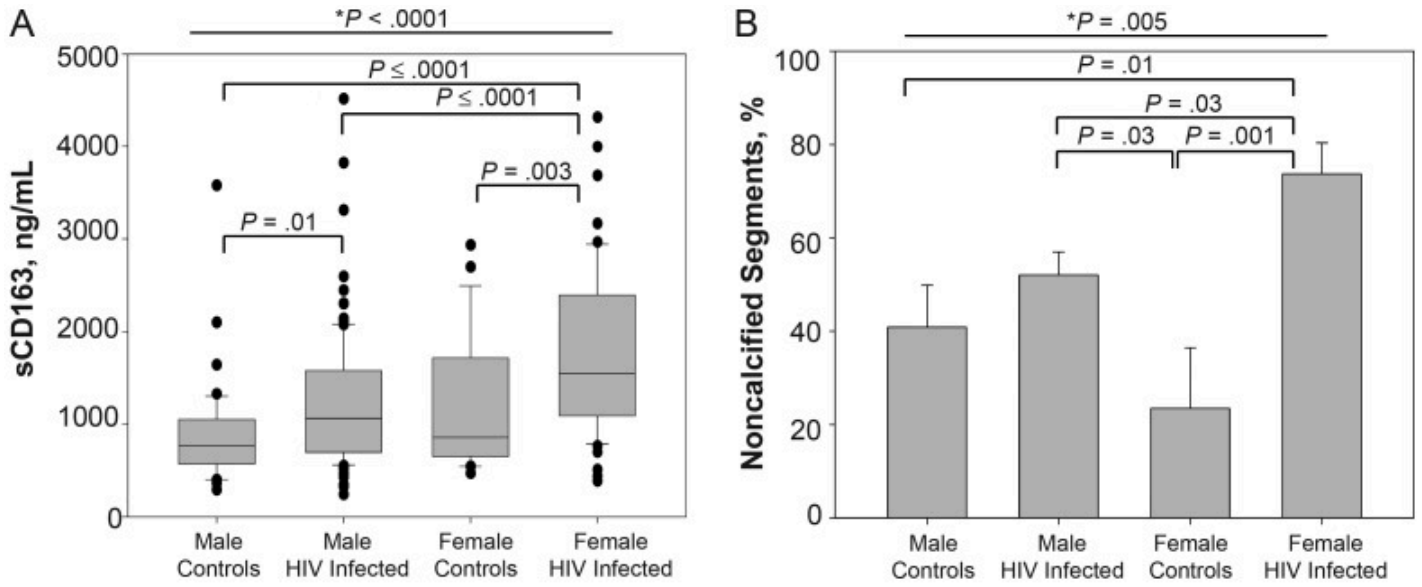
Plaque characterization



Zanni et al AIDS 2013

CAD and Inflammation

Noncalcified Coronary Atherosclerotic Plaque and Immune Activation in HIV-Infected Women



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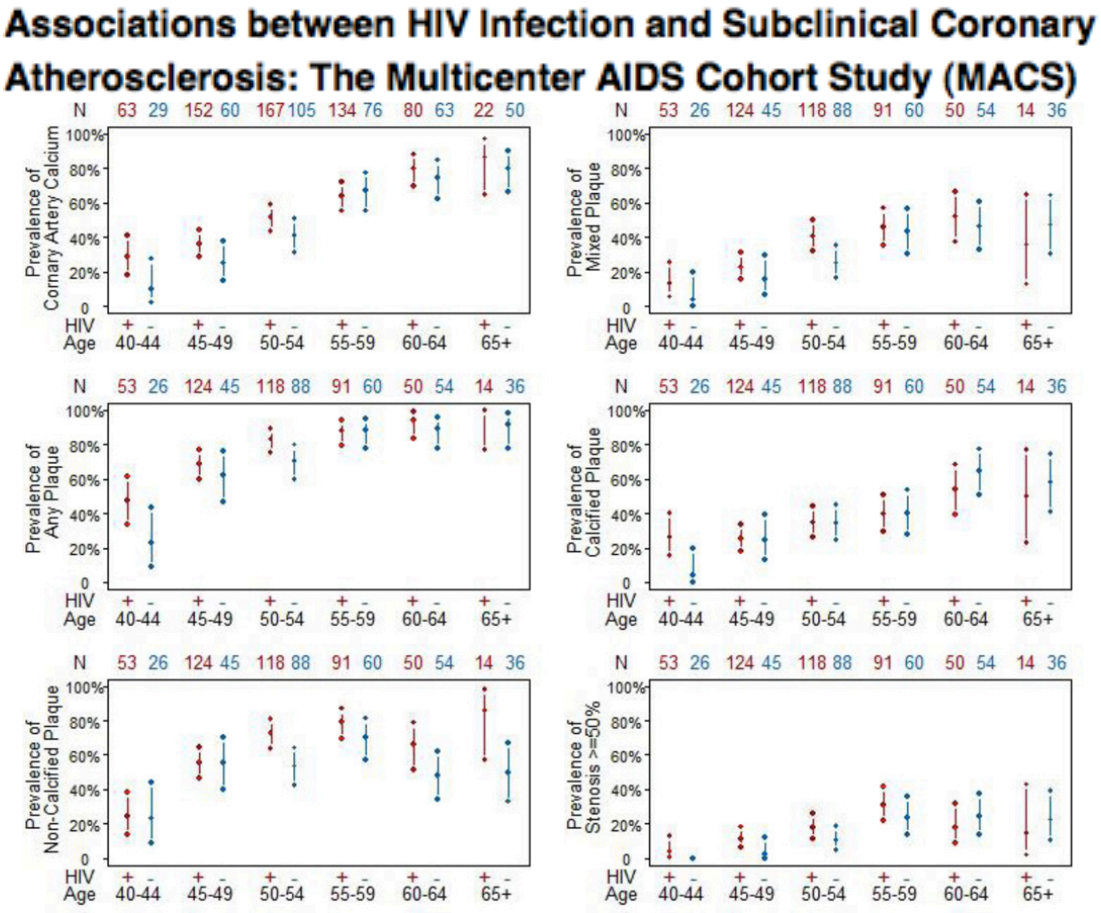
Fitch et al J Inf Dis 2013

CAD



> older, lower nadir CD4, and longer ART

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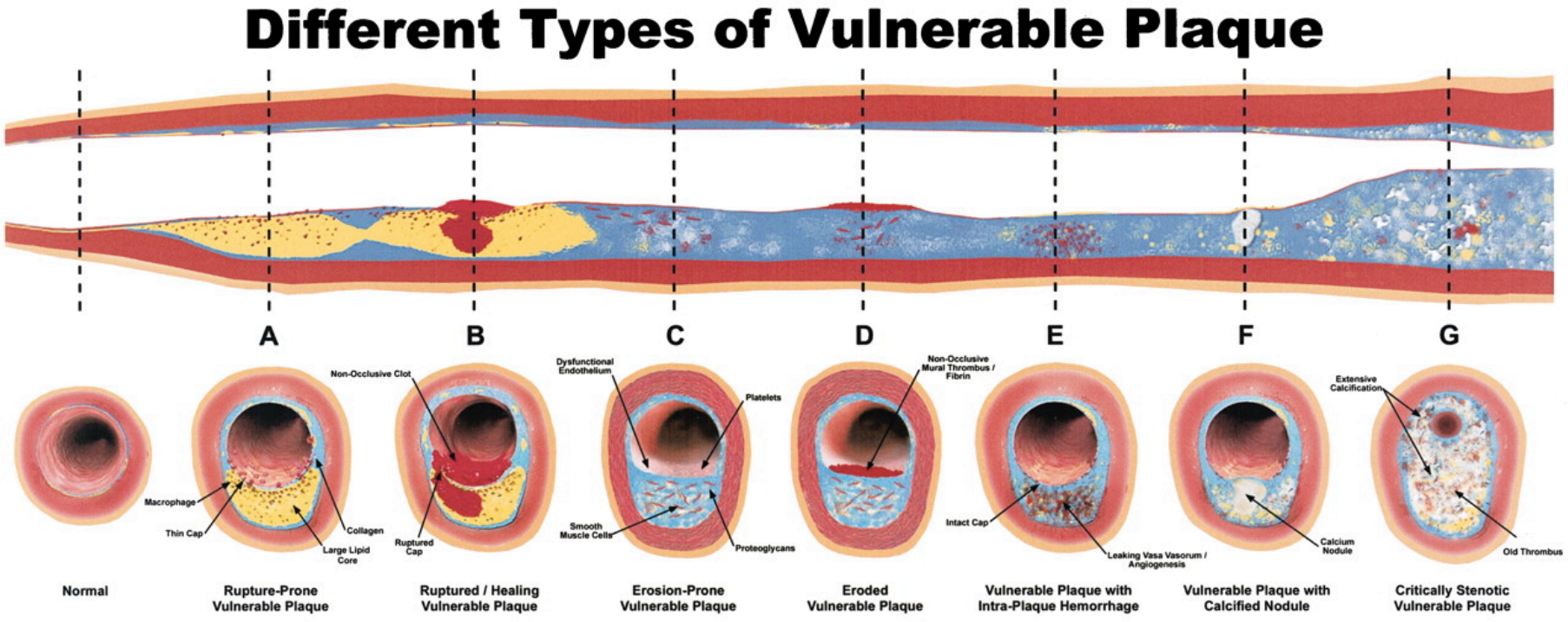
Post et al Ann Int Med 2014

CAD



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Clinical presentation

First Author (Ref. #) HIV Status Period Study Design	n	Age, yrs	Type of ACS
David et al. (21) HIV+ 1999–2000 Retrospective	16	43 (42–66)	STEMI 50;SA 50
Escaut et al. (77) HIV+ 2003	17	46 ± 6	STEMI 64;UA 18;SA 18
Varriale et al. (78) HIV+ 1998–2001 Prospective	29	46 ± 10	STEMI 52;NSTEMI 48
Ambrose et al. (79) HIV+ 1996–2000 Retrospective	51	48 ± 9	STEMI 36;UA 33;NSTEMI 31
Matetzky et al. (80) HIV+ vs. HIV– 1998–2000	24 vs. 48	47 ± 9vs.48 ± 7	STEMI 58;NSTEMI 42;in the entire cohort
Hsue et al. (81) HIV+ vs. HIV– 1993–2003 Database	68 vs. 68	50 ± 8vs61 ± 11	UA 46;STEMI 29;NSTEMI 25;in the entire cohort
Boccara et al. (82) HIV+ vs. HIV– 2003–2006 Prospective	103 vs. 195	48 ± 9vs.50 ± 9	STEMI 49;UA 31;NSTEMI 20;in the entire cohort

Bocarra et al JACC 2013

Angiographic Findings

First Author Year (Ref. #) Population	Age, yrs	Extent of CHD, %	No. of Diseased Vessels	Culprit Vessel, %	Revascularization, %	Clinical Restenosis Rate, %
David 2002 (21) 16 HIV+	43 (42–66)	NR	NR	NR	68% PCI; 13% CABG; 19% Med	ND
Escaut 2003 (77) 17 HIV+	46 ± 6	50% 1 VD	2.56	LAD 82%;LCA 41%;RCA 35%;LMD 6%	100% PCI	18% HIV+
Varriale 2004 (78) 29 HIV+	46 ± 10	NR	NR	NR	35% PCI;10% CABG	ND
Ambrose 2003 (79) 51 HIV+	48 ± 9	47% 1 VD; 22% 2 VD; 20% 3 VD; 11% NSS	NR	NR	49% PCI;18% CABG;12% Med	ND
Matetzky 2003 (80) 24 HIV+, 48 HIV–	47 ± 9	76% ≥2 VD; 14% NSS	NR	NR	71% ATL; 13% CABG	43% HIV+
Hsue 2004 (81) 68 HIV+, 68 HIV–	50 ± 8	NR	HIV+ 1.3 ± 1.0; HIV– 1.9 ± 1.2*	NR	52% PCI;11% CABG	52% HIV+ vs. 14% HIV–*;with stenting (76%): 50% HIV+ vs. 18% HIV–‡
Boccara 2011 (82) 103 HIV+, 195 HIV–	49 ± 9	56% 1 VD;28% 2 VD;13% 3 VD;3% NSS	1.5 ± 0.81.5 ± 0.7*	LAD 51%; LCA 14%; RCA 23%; 12% unknown	76% PCI;4% CABG;20% Med	9% HIV+ vs. 7% HIV–;HR: 1.4 (95% CI: 0.5–3.8)
Mehta 2003 (85)† 129 HIV+	42 ± 10	35% 1 VD;18% 2 VD;47% 3 VD	NR	LAD 62%;LCA 45%;RCA 50%;LMD 6%	25% PCI + CABG	ND
Boccara 2006 (86) 50 HIV+, 50 HIV–	43 ± 6	60% ≥2D	HIV+ 1.74 ± 0.75;HIV– 1.62 ± 0.72‡	NR	100% PCI	14% HIV+ vs. 16% HIV–‡
Ren 2009 (87) 97 HIV+, 97 HIV–	53 ± 9	NR	2 vs. 2	LAD 42%	100% PCI	18% HIV+ vs. 13% HIV–;11% HIV+ DES vs. 2% HIV– DES

Bocarra et al JACC 2013

Revascularizat

First Author Year (Ref. #) Population	Age, yrs	Extent of CHD, %	No. of Diseased Vessels	Culprit Vessel, %	Revascularization, %	Clinical Restenosis Rate, %
David 2002 (21) 16 HIV+	43 (42–66)	NR	NR	NR	68% PCI; 13% CABG; 19% Med	ND
Escaut 2003 (77) 17 HIV+	46 ± 6	50% 1 VD	2.56	LAD 82%;LCA 41%;RCA 35%;LMD 6%	100% PCI	18% HIV+
Varriale 2004 (78) 29 HIV+	46 ± 10	NR	NR	NR	35% PCI;10% CABG	ND
Ambrose 2003 (79) 51 HIV+	48 ± 9	47% 1 VD; 22% 2 VD; 20% 3 VD; 11% NSS	NR	NR	49% PCI;18% CABG;12% Med	ND
Matetzky 2003 (80) 24 HIV+, 48 HIV–	47 ± 9	76% ≥2 VD; 14% NSS	NR	NR	71% ATL; 13% CABG	43% HIV+
Hsue 2004 (81) 68 HIV+, 68 HIV–	50 ± 8	NR	HIV+ 1.3 ± 1.0; HIV– 1.9 ± 1.2*	NR	52% PCI;11% CABG	52% HIV+ vs. 14% HIV–*;with stenting (76%): 50% HIV+ vs. 18% HIV–‡
Boccara 2011 (82) 103 HIV+, 195 HIV–	49 ± 9	56% 1 VD;28% 2 VD;13% 3 VD;3% NSS	1.5 ± 0.81.5 ± 0.7*	LAD 51%; LCA 14%; RCA 23%; 12% unknown	76% PCI;4% CABG;20% Med	9% HIV+ vs. 7% HIV–;HR: 1.4 (95% CI: 0.5–3.8)
Mehta 2003 (85)† 129 HIV+	42 ± 10	35% 1 VD;18% 2 VD;47% 3 VD	NR	LAD 62%;LCA 45%;RCA 50%;LMD 6%	25% PCI + CABG	ND
Boccara 2006 (86) 50 HIV+, 50 HIV–	43 ± 6	60% ≥2D	HIV+ 1.74 ± 0.75;HIV– 1.62 ± 0.72‡	NR	100% PCI	14% HIV+ vs. 16% HIV–‡
Ren 2009 (87) 97 HIV+, 97 HIV–	53 ± 9	NR	2 vs. 2	LAD 42%	100% PCI	18% HIV+ vs. 13% HIV–;11% HIV+ DES vs. 2% HIV– DES

Bocarra et al JACC 2013

Surgical Revascularization

Study/First Author (Ref. #), Period, Mean Age	Patients Undergoing CABG	Hospital Death	Pre- vs. Post-Operative Immune Status	Long-Term Survival
Trachiotis (90), 1994–2000, 41 yrs	27 HIV+	0	No change	81% Event-free at 36 months; no late death
Filsousfi (91), 1998–2004, 47 yrs	7 HIV+	0	No change	No late death at 47 months
Jimenez-Exposito (92), 1997–2004, 35 yrs	7 HIV+, 21 HIV–	0	No change	100% Event-free at 30 months; no difference vs. HIV–
Boccara (93), 1997–2005, 47 yrs	27 HIV+, 54 HIV-	0	15% decrease in CD4 cell count, without clinical complications	54% Event-free at 41 months

Bocarra et al JACC 2013

Hospitalization

Comparison of In-Hospital Mortality from Acute Myocardial Infarction in HIV Sero-Positive Versus Sero-Negative Individuals

Daniel Pearce, DO[a,*], Chizobam Ani, MD[a,b], Yaminah Espinosa-Silva, BS[c], Ryan Clark, BS[c], Khuteja Fatima, BS[d], Munira Rahman, BS[c], Erik Diebolt, DO[c], and Bruce Ovbiagele, MD[e]

Few studies have explored hospitalization outcome differences between patients who are seropositive for human immunodeficiency virus (HIV) compared to HIV-seronegative patients with acute myocardial infarctions (AMIs). The aim of this study was to explore in-hospital AMI mortality risk in seropositive and seronegative patients. A secondary analysis of the Nationwide Inpatient Sample from 1997 to 2006 was conducted. This sample allows the approximation of all United States hospitalizations. All AMI encounters with and without co-occurring HIV were identified using appropriate International Classification of Diseases and procedure codes. Descriptive and Cox proportional-hazards analyses were then conducted to estimate mortality differences between seropositive and seronegative patients while adjusting for demographic, clinical, hospital, and care factors. The results demonstrated higher AMI hospitalization mortality hazard in seropositive compared to seronegative patients after adjustment for age, gender, ethnicity, medical co-morbidities, hospital type, and number of in-hospital procedures (HR 1.38, 95% confidence interval 1.01 to 1.87, p = 0.04). Stratified analysis demonstrated greater although not

66%), and coronary artery bypass graft (6% vs 14%). In conclusion, additional mortality burden and lower procedure rates occur for HIV-seropositive patients receiving AMI care. Health care providers should be alert to the increased mortality burden when treating seropositive patients with AMI. (Am J Cardiol 2012;110:1078–1084)

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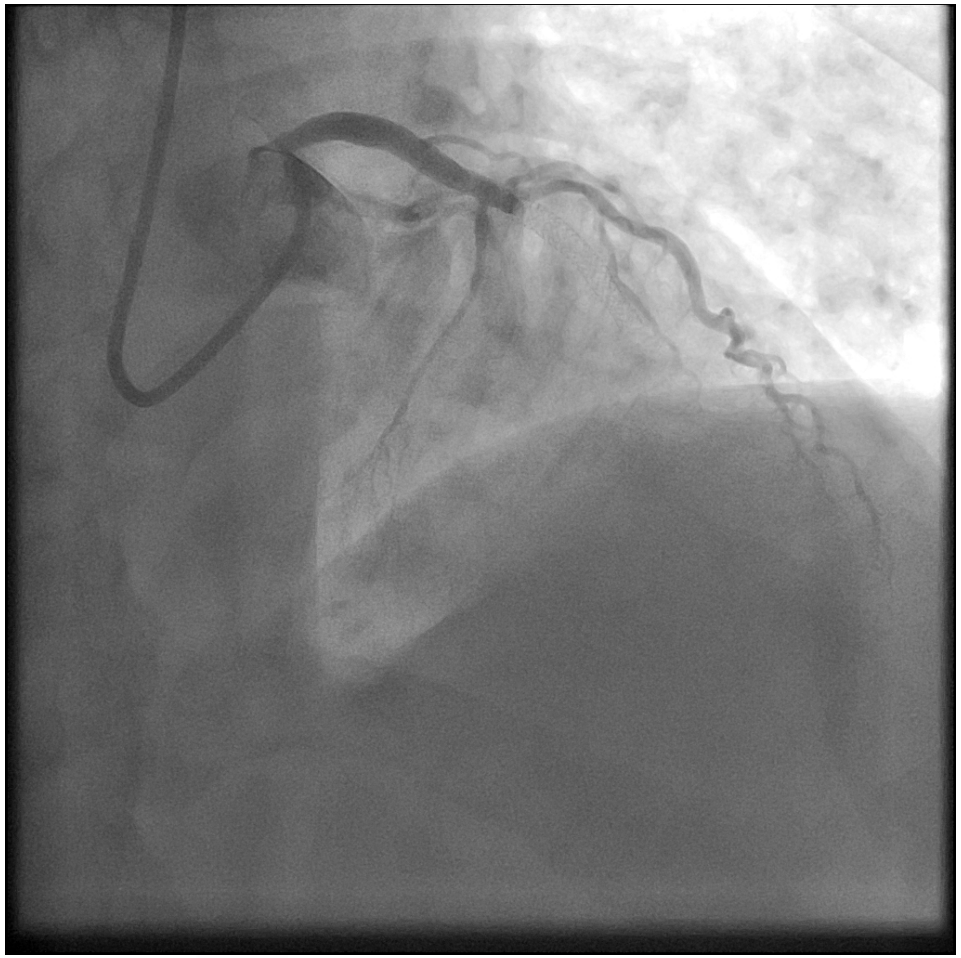
Pearce et al 2012

Management

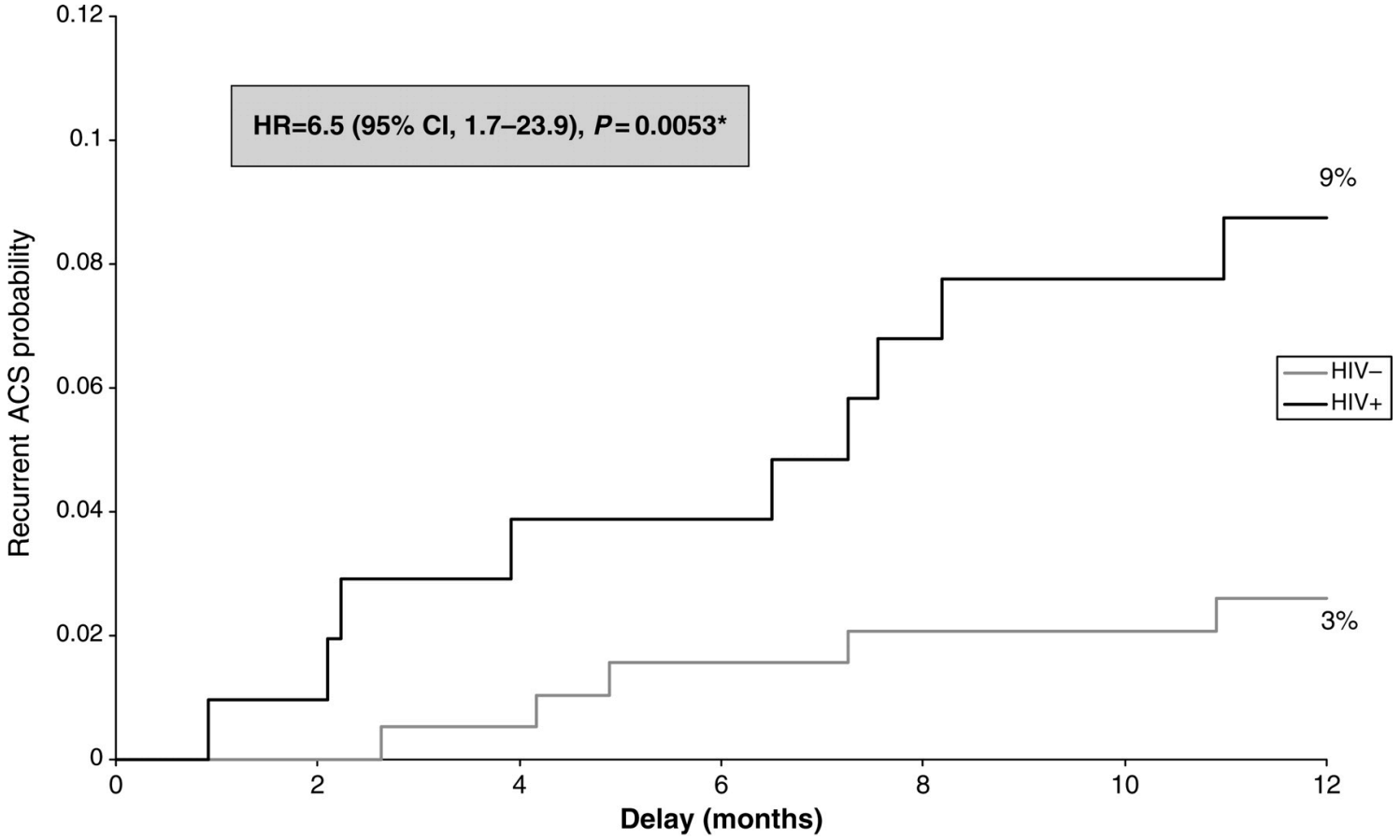
- Lipids (baseline, 1-3 months after HAART, 6-12)
- HbA1c (3-6 months)
- Smoking
- Diet
- Exercise
- Blood pressure
- BMI

Aberg Clin Inf Dis 2014

Clinical Case



Recurrence



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of MEDICINE

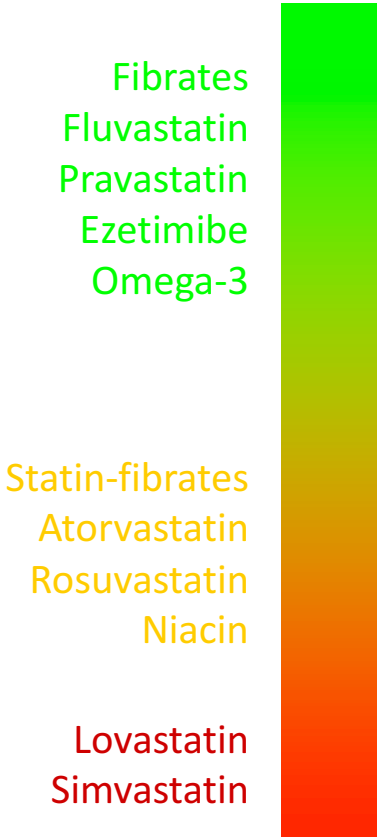
Boccara et al 2011

Follow up

- 4 months later..
- STEMI
- EF 30%

Component *Latest Ref Rng*	3/30/2015
Cholesterol, Total *100 - 199 mg/dL*	91 (L)
Triglycerides *0 - 149 mg/dL*	142
HDL Cholesterol *>39 mg/dL*	26 (L)
LDL Cholesterol *0 - 99 mg/dL*	37
VLDL Cholesterol *5 - 40 mg/dL*	28
Cholesterol/HDL Ratio *< OR = 5.0 (calc)*	

Statins



1. Fitchenbaum CJ et al. *AIDS.* 2002;16:569-577; 2. Hsyu PH et al. *Antimicrob Agents Chemother*. 2001;45:3445-3450;
3. Gerber J et al. 2nd Annual International AIDS Society Meeting; 2003, #870; 4. Carr RA et al. 40th Annual Meeting of Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Canada; 2000, Abstract 1644; 5. Telzir® (fosamprenavir calcium) [prescribing information]. Mississauga, Ontario: GlaxoSmithKline; 2003; 6. Gerber JG et al.
11th Conference on Retroviruses and Opportunistic Infections; 2004, Abstract #603.

Lipid Management

Drug	Cytochrome P450*	Interactions With Other Antiretrovirals	Recommendation
Rosuvastatin	No or weak P450 interactions	Increased AUC with LPV-RTV and ATV-RTV;decreased with NNRTI (efavirenz)	Recommended at 5–10 mg daily
Atorvastatin	3A4	Increased AUC with RTV-SQV;decreased with NNRTI (efavirenz)	Recommended at 10 mg daily
Pravastatin	No P450 interactions	AUC decreased with RTV-SQVand increased with DRV;decreased with NNRTI (efavirenz)	Recommended at 20–40 mg daily
Fluvastatin	2C9	NNRTI (etravirine) could increase plasma level	Recommended at 40 mg daily
Simvastatin	3A4	32-fold increase in AUC with RTV-SQV;decreased with NNRTI (efavirenz)	Possible high toxicity with PI;not recommended
Lovastatin	3A4	Not tested	Possible high toxicity with PI; not recommended
Pitavastatin	No P450 interactions	Not tested	No recommendations at present
Bezafibrate	No P450 interactions	Not tested	Recommended at 400 mg daily
Fenofibrate	No P450 interactions	Not tested	Recommended at 200 mg daily
Gemfibrozil	Interaction with statins	Not tested	Recommended at 900–1,200 mg daily
Ezetimibe	No P450 interactions	Not tested	Recommended with statin, or alone if statin not tolerated

Hypertriglyceridemia

- Fibrates if TGL > 500 mg/d:
  - Gemfibrozil 600 mg BID
  - Fenofibrate 54-160 mg/d
  - Fish Oil 4 grm/d
  - Niacin

Erlandson et al AIDS 2015
Visnegarwala et al J inf 2004
Gerber et al Clin Inf Dis 2004
Wohl DA Clin Inf Dis 2005

www.hiv-druginteractions.org

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What else can we do?

- Omega 3
- Ticagrelor + aspirin
- Modification of HAART
- Platelet activity/Hematology
- Lipidologist→ezetimibe
- Rehab
- BMI < 25, mediterranean diet and exercise
- Meditation

American Journal of Transplantation 2016; 16: 21–28
Wiley Periodicals Inc.

doi: 10.1111/ajt.13496

Minireview

An Update on Heart Transplantation in Human Immunodeficiency Virus–Infected Patients

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Conclusion

- CAD in HIV is real
- Traditional and non traditional risks
- HAART benefits surpass the association with CVD
- Cardiologist have an active responsibility in this rapidly developing field

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EARLY INDICATORS OF INCREASED RISK FOR CARDIOVASCULAR DISEASE IN HIV-INFECTED PATIENTS

Investigator-Initiated Study

Claudia A. Martinez MD FSCAI Principal Investigator

In collaboration with:

Orlando Gomez-Marin PhD
Barry Hurtwitz PhD
Ivonne Schulman MD
Michael Kolber MD

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Take Home Message:

HIV= Cardiovascular evaluation

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Thank you

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Q&A

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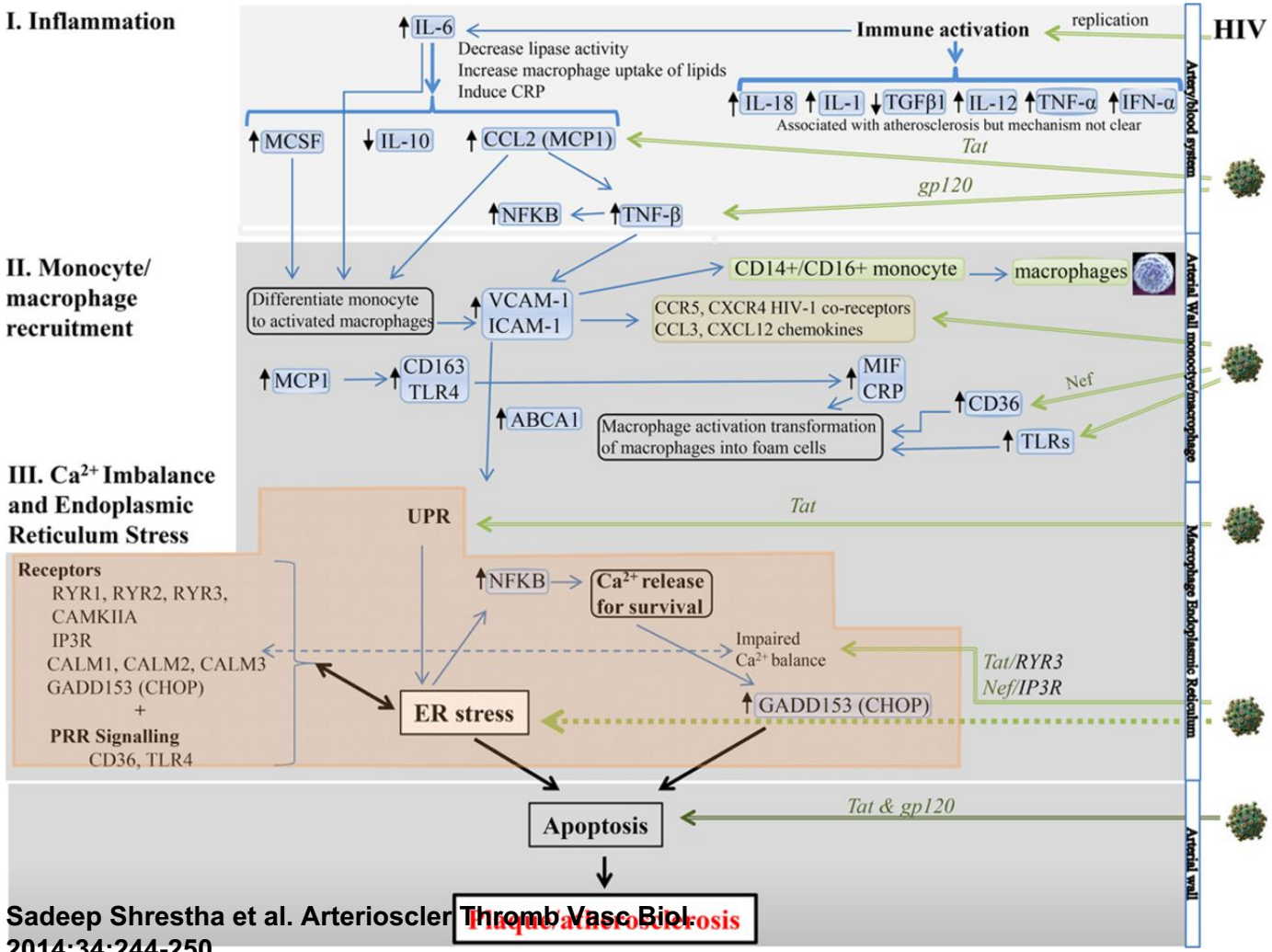
Three mechanisms for atherogenesis in HIV: (I) Inflammation that occurs in the artery and blood system, (II) monocyte/macrophage recruitment that occurs on the arterial wall, and (III) calcium imbalance associated with endoplasmic reticulum (ER) stress and apoptosis of macrophages (foam cells).



Sadeep Shrestha et al. Arterioscler Thromb Vasc Biol. 2014;34:244-250

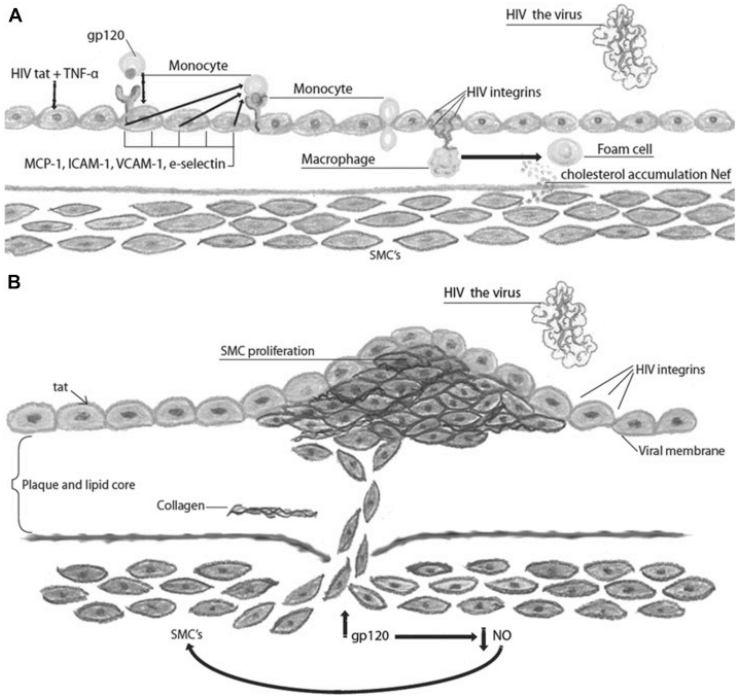


Fig 2. The human immunodeficiency virus (HIV) affects proliferation of smooth muscle cells (SMCs), monocyte, and endothelial cell (EC) activation, and development of foam cells, all contributing to the buildup of atherosclerotic lesions in HIV-infected individ...

Grace C. Haser, Bauer Sumpio

Systemic and cell-specific mechanisms of vasculopathy induced by human immunodeficiency virus and highly active antiretroviral therapy

Journal of Vascular Surgery, 2016, Available online 16 March 2016

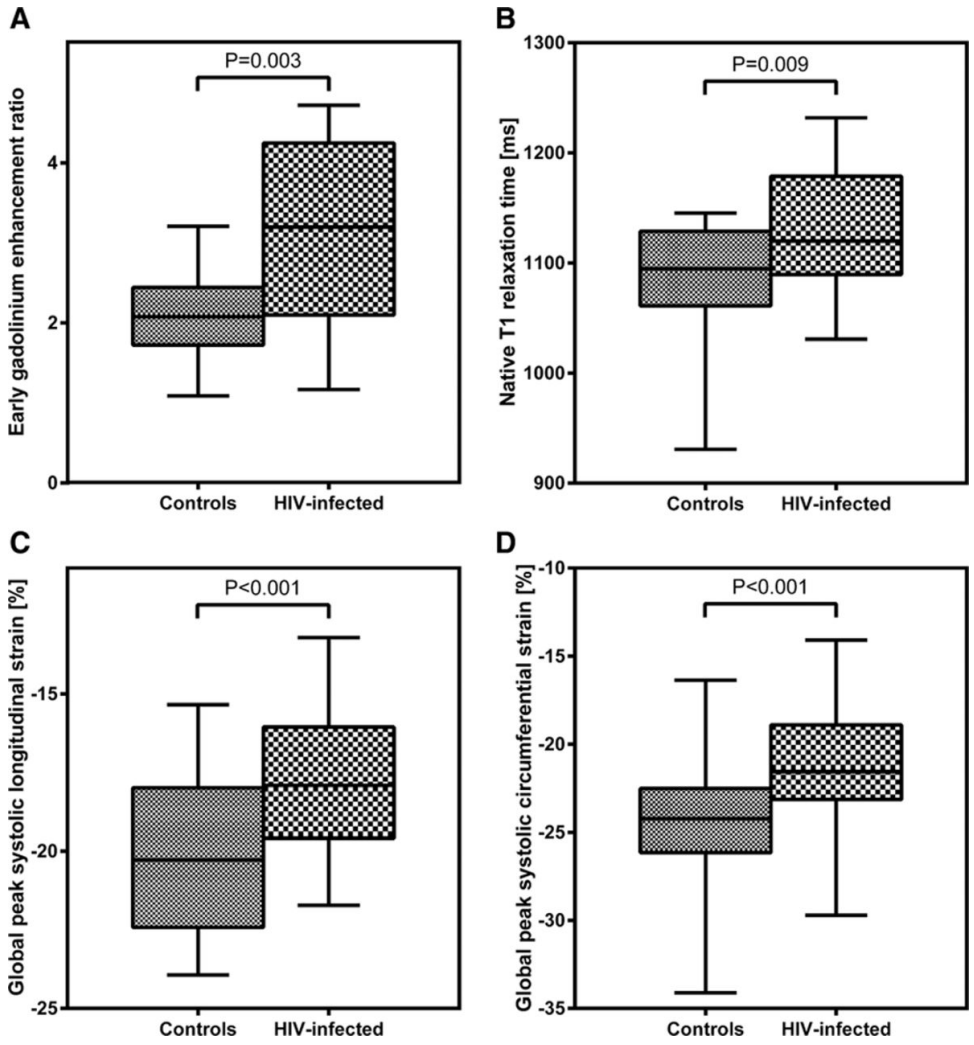
http://dx.doi.org/10.1016/j.jvs.2016.01.036

Cardiac Magnetic Resonance Reveals Signs of Subclinical Myocardial Inflammation in Asymptomatic HIV-Infected PatientsCLINICAL PERSPECTIVE

by Julian A. Luetkens, Jonas Doerner, Carolynne Schwarze-Zander, Jan-Christian Wasmuth, Christoph Boesecke, Alois M. Sprinkart, Frederic C. Schmeel, Rami Homsi, Juergen Gieseke, Hans H. Schild, Jürgen K. Rockstroh, and Claas P. Naehle

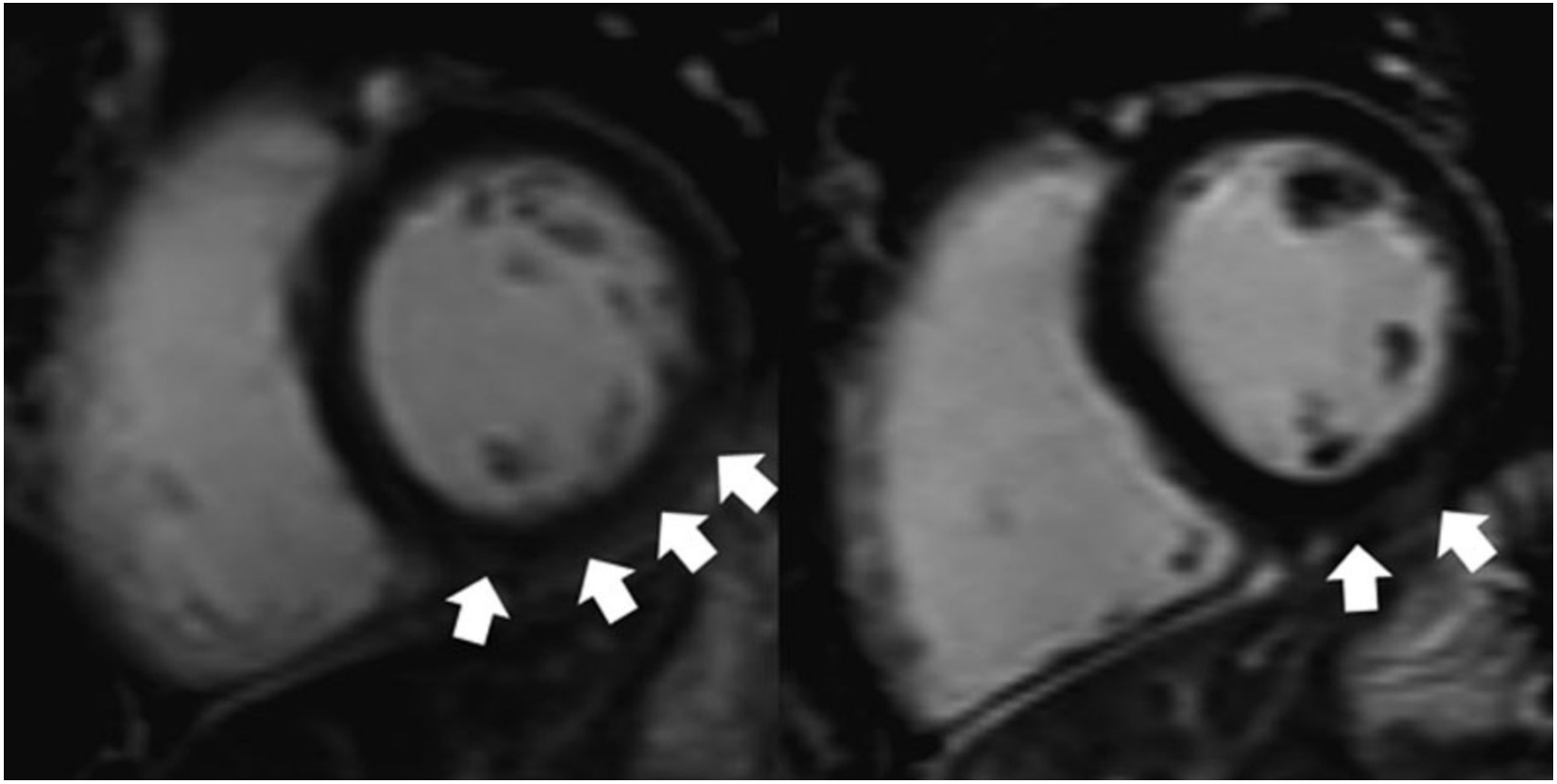
Circ Cardiovasc Imaging
Volume 9(3):e004091
March 7, 2016

Box-whisker plots of different cardiac magnetic resonance parameters in HIV-infected patients and control subjects.



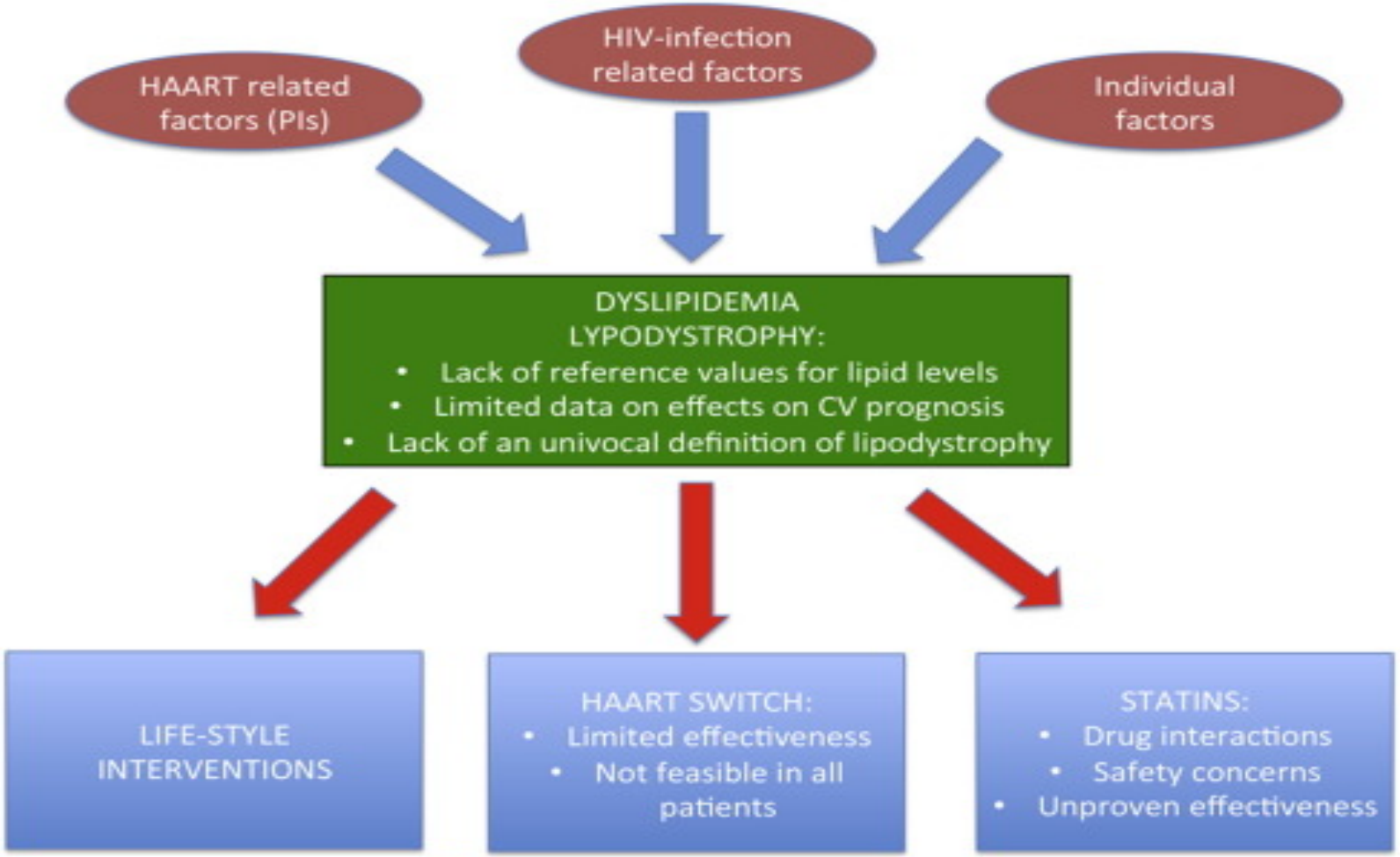
Julian A. Luetkens et al. Circ Cardiovasc Imaging. 2016;9:e004091

Examples of enhanced areas in late gadolinium enhancement short-axis images in 2 HIV-infected patients.



Julian A. Luetkens et al. Circ Cardiovasc Imaging. 2016;9:e004091

HIV Infection and Primary Prevention of Cardiovascular Disease: Lights and Shadows in the HAART Era



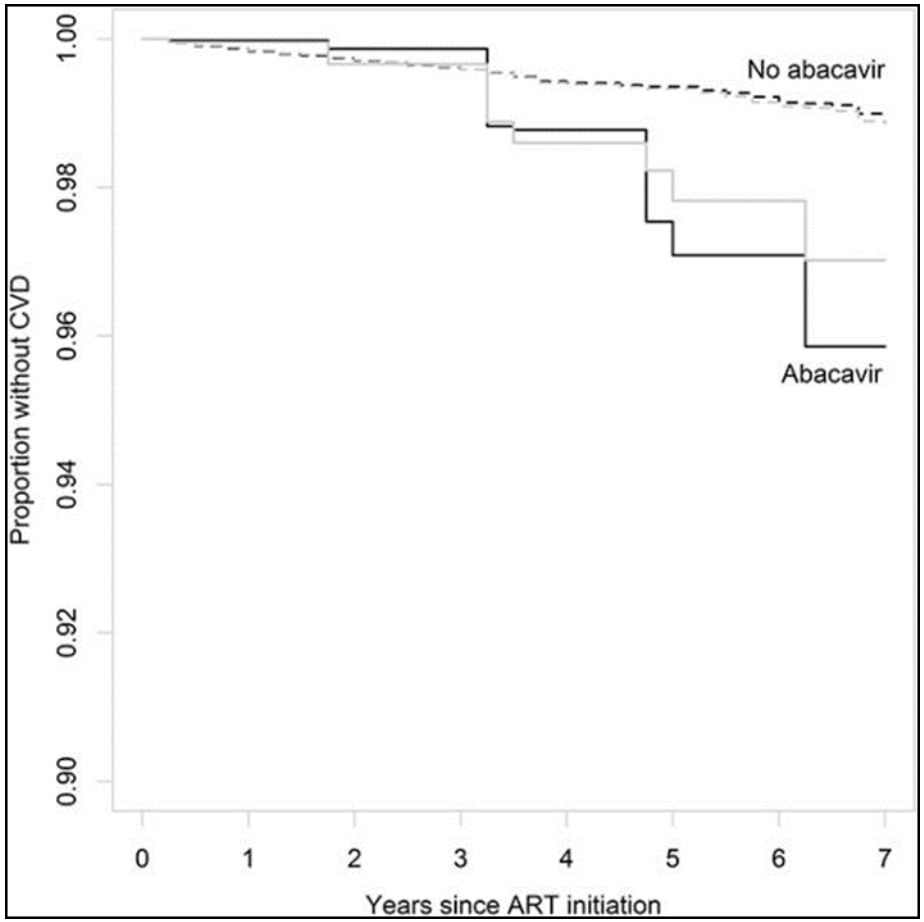
Progress in Cardiovascular Diseases, 2016, Available online 2 March 2016

Flavia Ballocca, Sebastiano Gili, Fabrizio D'Ascenzo, Walter Grosso Marra, Margherita Cannillo, Andrea Calcagno, Stefano Bonora, Andreas Flammer, John Coppola, Claudio Moretti, Fiorenzo Gaita

Use of Abacavir and Risk of Cardiovascular Disease Among HIV-Infected Individuals.

Marcus, Julia; PhD, MPH; Neugebauer, Romain; Leyden, Wendy; Chao, Chun; Xu, Lanfang; Quesenberry, Charles; Klein, Daniel; Towner, William; Horberg, Michael; MD, MAS; Silverberg, Michael; PhD, MPH

JAIDS Journal of Acquired Immune Deficiency Syndromes. 71(4):413-419, April 1, 2016.
DOI: 10.1097/QAI.0000000000000881



Secondary Prevention

- Modification of HAART:
  - PI➔NNRT, raltegravir
  - Substitute: azitothymidine, stavudine, abacavir➔ tenofovir

Statins

- Inflammatory markers:
  - CRP
  - TNFa
  - IL-6
  - CD14

Statins

- Ritonavir- PI➔ pitavastatin 4 mg
- If no Ritonavir-PI➔atorvastatin 10 mg
- Rosuvastatin 10 mg- monitor DM
- Pravastatin 20 mg- less effective

Statins