

Cardiovascular Disease in the HIV-infected Patient: A Primer

Mark J. Siedner

Harvard Medical School

Massachusetts General Hospital

Mbarara University of Science and Technology

Key Topics

- Epidemiology of CVD in HIV Infection
- Screening and Primary Prevention
- Secondary Prevention and Management

Question 1:

Which of the following do you have consistently available at your facility?

I. Blood Pressure Monitor

II. Aspirin

III. Metformin

IV. Statins

V. Smoking Cessation Support

A. All of the above

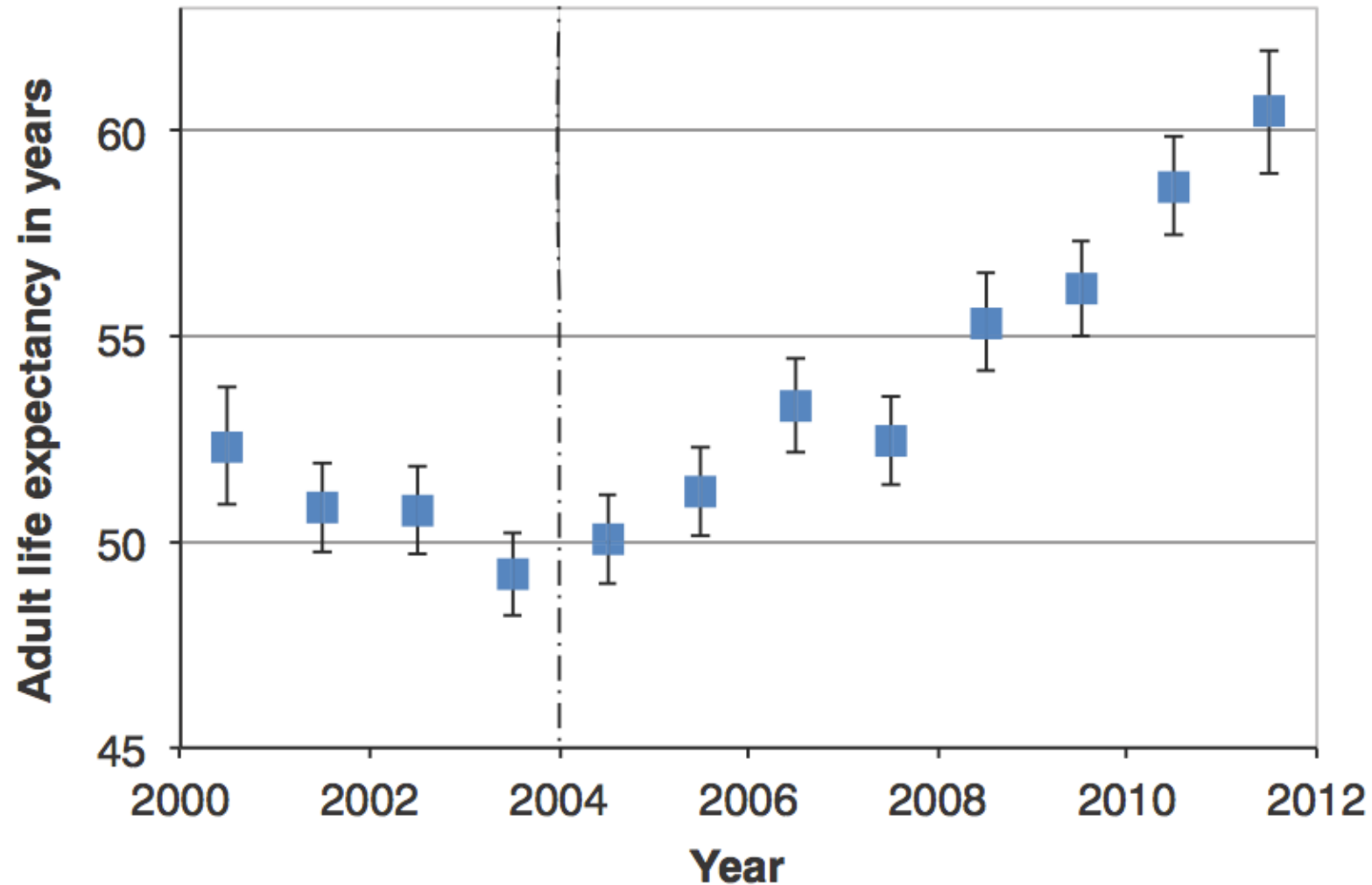
B. None of the above

C. I only

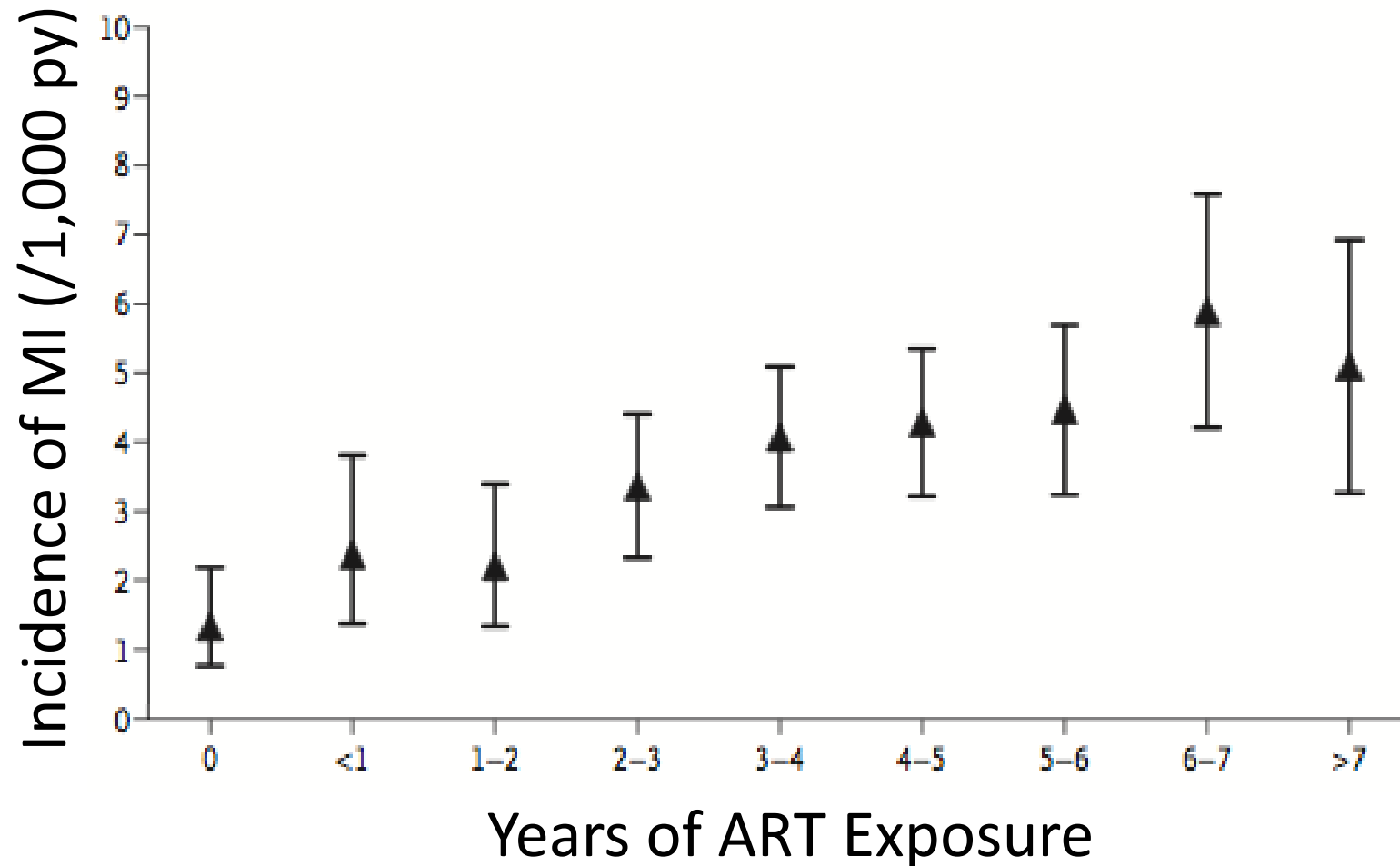
D. I, II, III, IV

E. Why is this question so complicated?

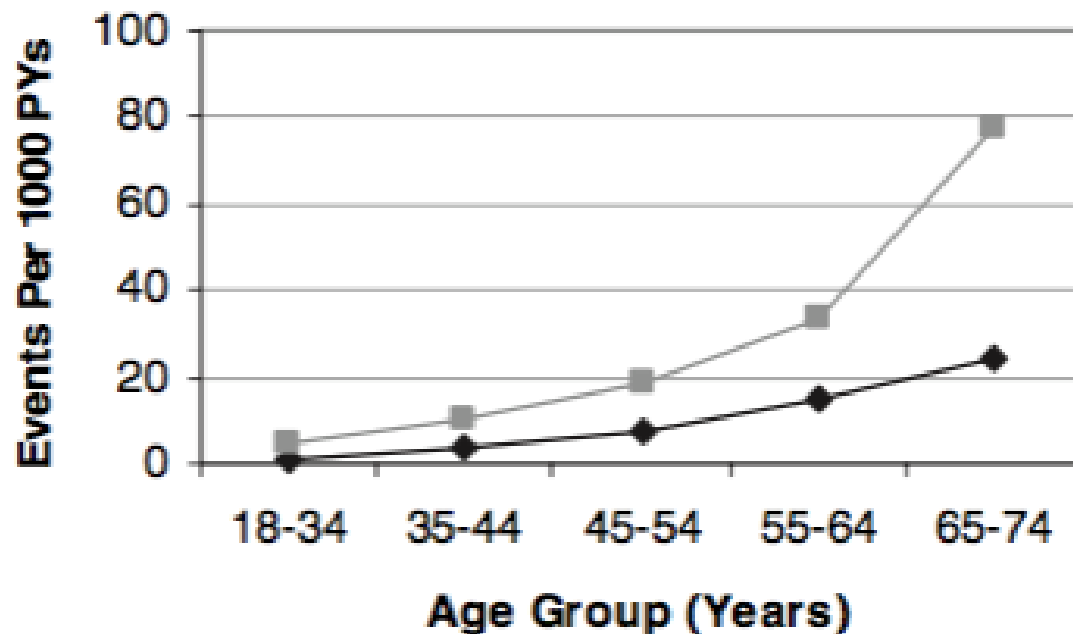
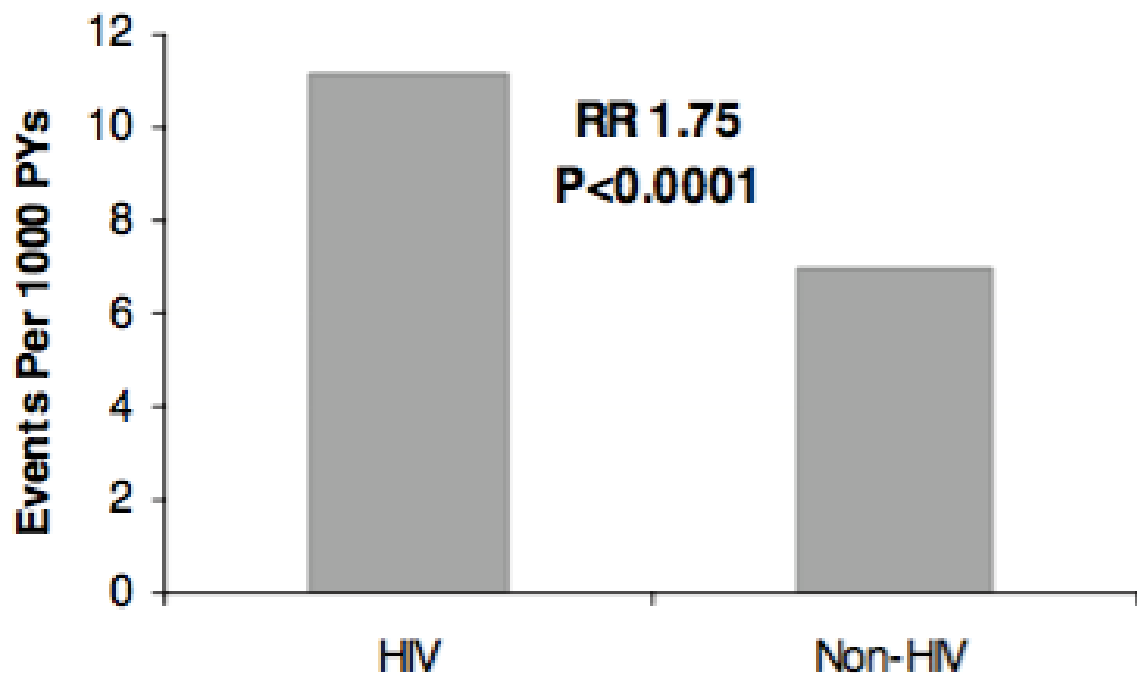
ART and Life Expectancy in South Africa



Myocardial Infarction Risk in the ART Era



Increased Risk of Myocardial Infarction in HIV



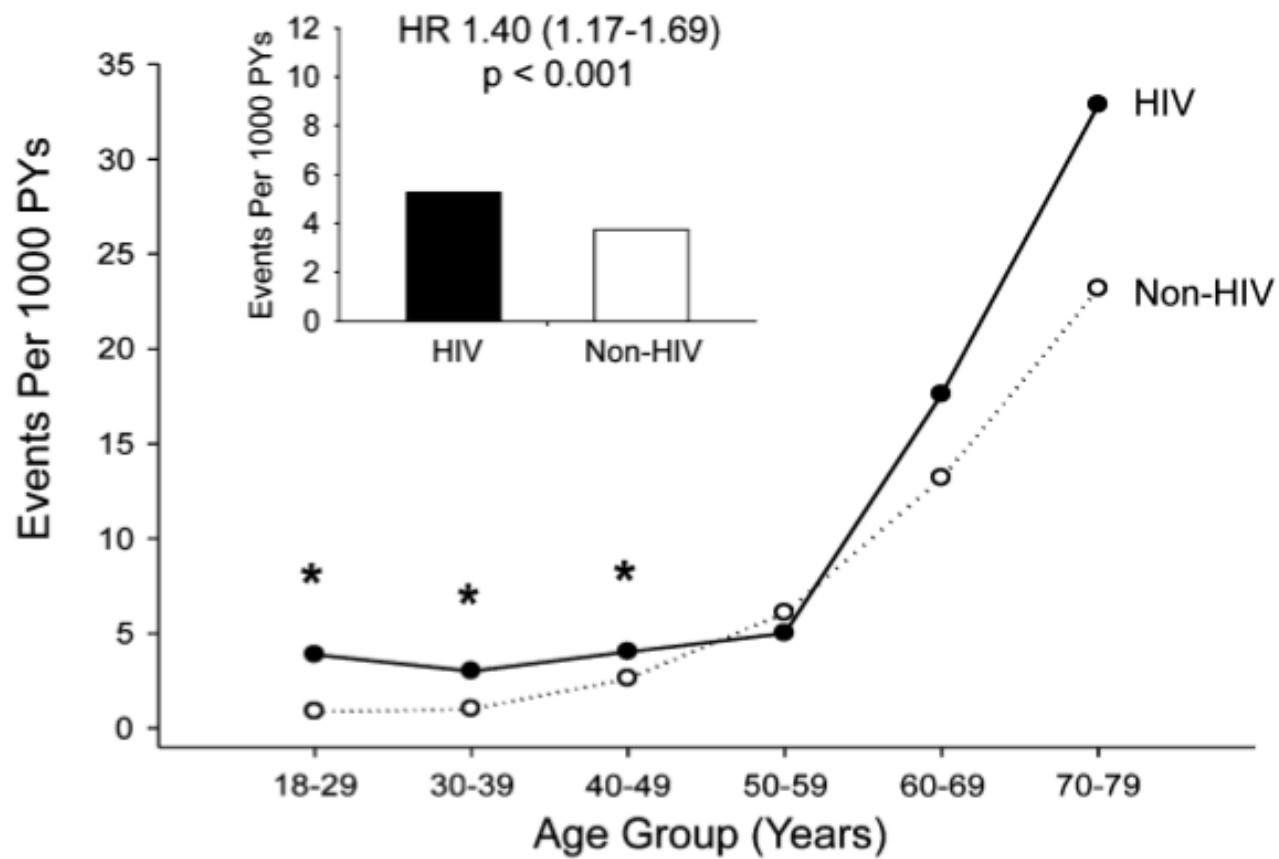
Triant et al, J Clin Endo, 2007

Currier et al, JAIDS, 2003

Friberg et al, Ann Int Med, 2013

Althoff et al, Clin Inf Dis, 2015

Increased Risk of Stroke in HIV



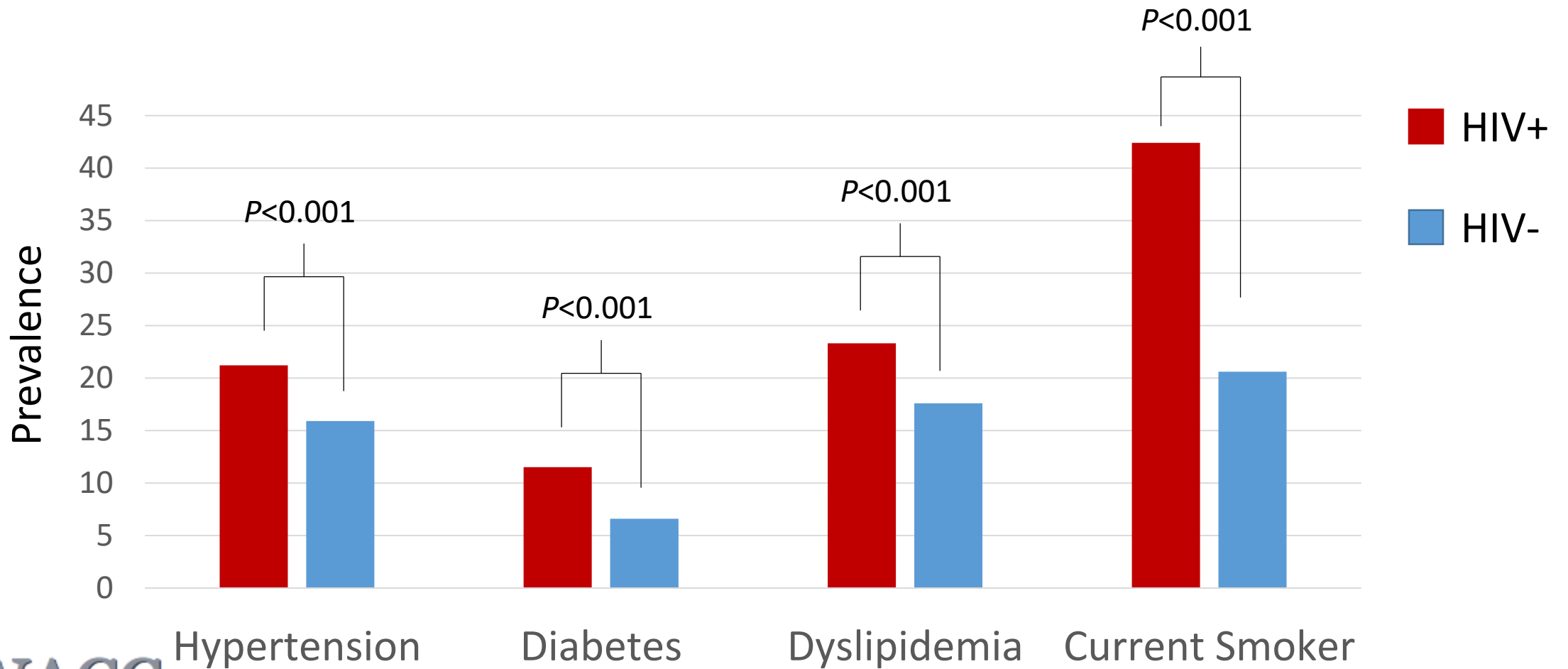
HIV Infection and Stroke Risk in Malawi

Characteristic	Adjusted Odds Ratio*	P-value	Population Attributable Fraction
Hypertension	5.01 (3.02 – 8.29)	<0.001	46%
Diabetes	3.41 (1.45 - 8.01)	0.005	3%
Current Smoker	2.36 (1.34 - 4.13)	0.003	6%
HIV Infection	3.28 (2.05 – 5.25)	<0.001	15%

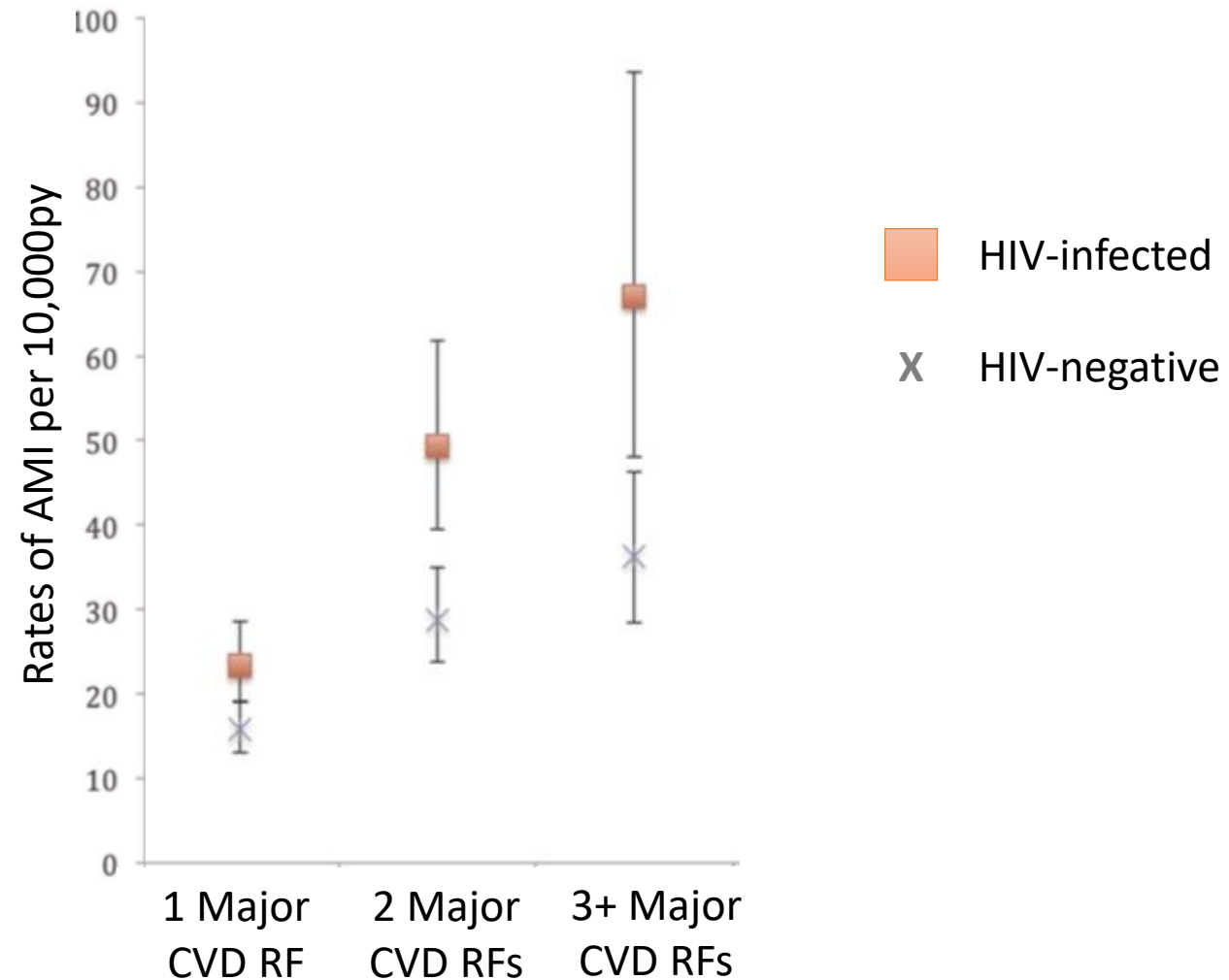
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Current Smoker	2.36 (1.34 - 4.13)	0.003	6%
HIV Infection	3.28 (2.05 – 5.25)	<0.001	15%
Untreated	4.48 (2.44 – 8.24)	<0.001	
ART >6 months	1.49 (0.72 – 3.07)	0.23	

HIV and Traditional Risk Factors in the US



Traditional Risk Factors Not the Whole Story



Question 2

Does initiation of antiretroviral therapy increase the risk of cardiovascular events in HIV infection?

- A. Yes
- B. No**
- C. I came to this conference so I could learn new information, not be asked questions
- D. When is tea?

ART and CVD risk: SMART Study

Outcome	Relative Risk*	P-value	Total Events
Death	1.8 (1.2-2.9)	0.007	55

***Relative risk comparing those with ART treatment interruption versus those who remained on therapy**

ART and CVD risk: SMART Study

Outcome	Relative Risk*	P-value	Total Events
Death	1.8 (1.2-2.9)	0.007	55
Serious OI	6.6 (1.5 – 29)	0.01	13

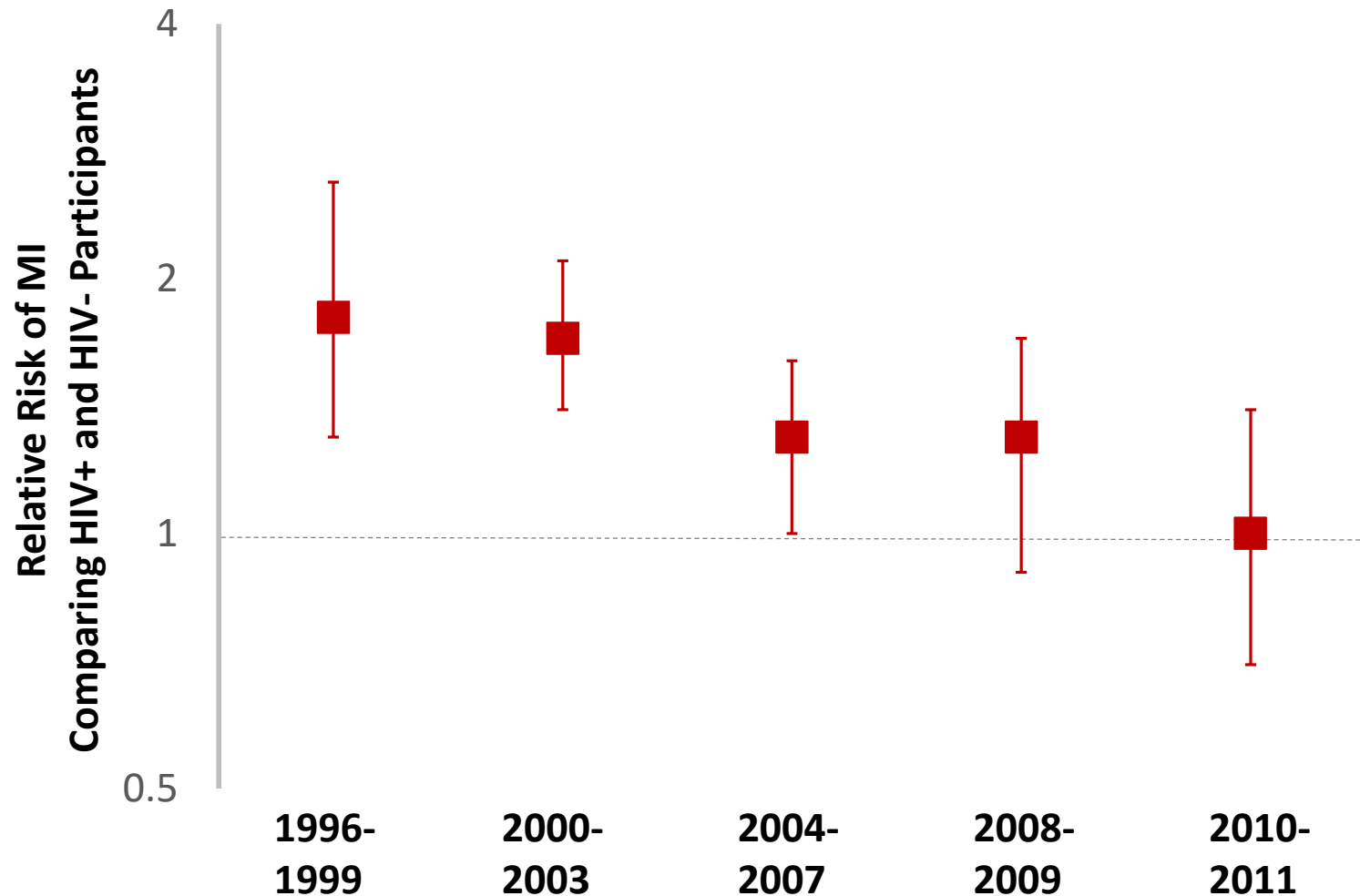
***Relative risk comparing those with ART treatment interruption versus those who remained on therapy**

ART and CVD risk: SMART Study

Outcome	Relative Risk*	P-value	Total Events
Death	1.8 (1.2-2.9)	0.007	55
Serious OI	6.6 (1.5 – 29)	0.01	13
Major CV Event	1.7 (1.1-2.5)	0.009	65

***Relative risk comparing those with ART treatment interruption versus those who remained on therapy**

Trends in Risk of MI over Calendar Time



CD4, Viral Load and CVD Risk

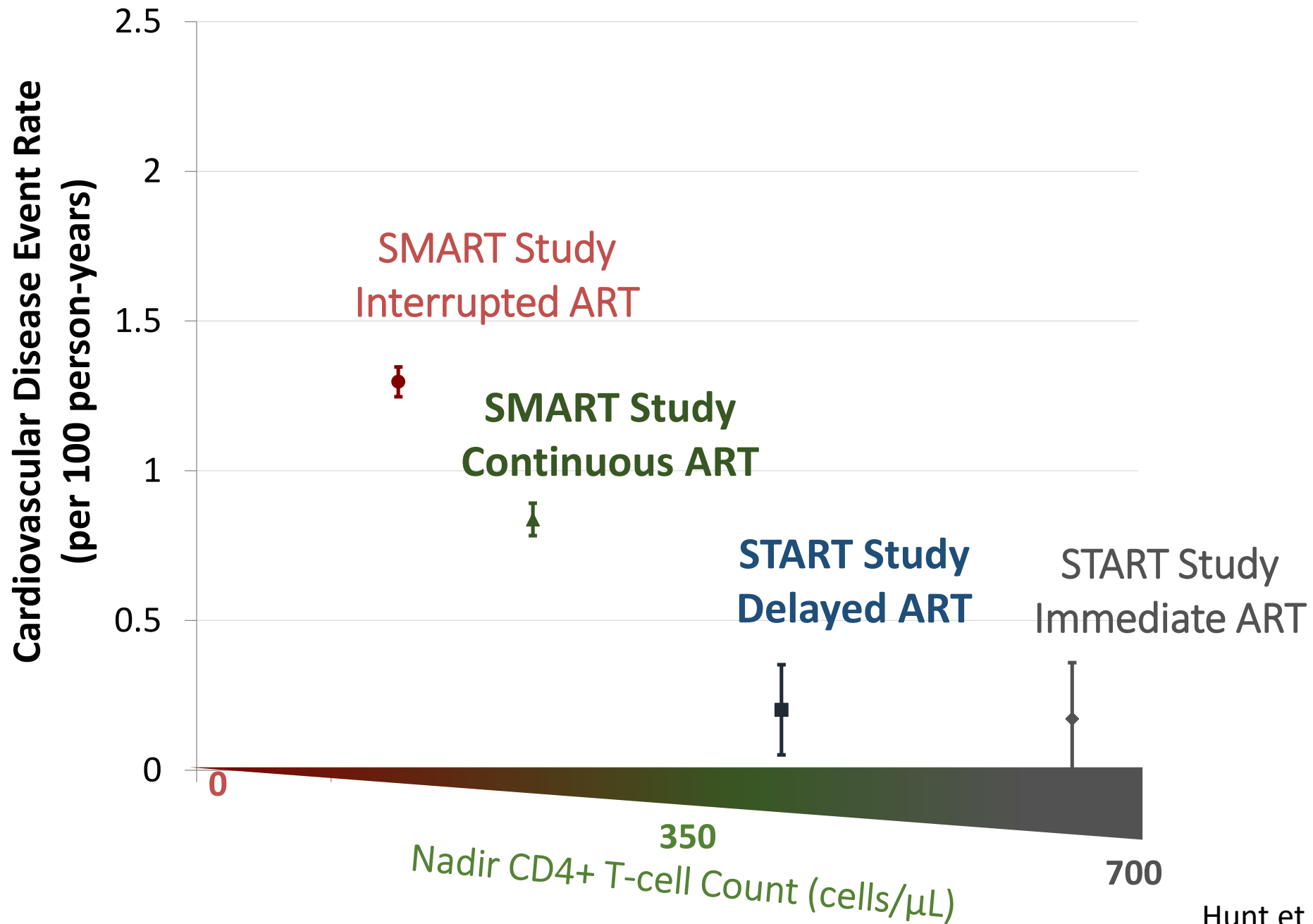
Risk of Acute Myocardial Infarction by HIV Viral Load and CD4 Count Category

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)	

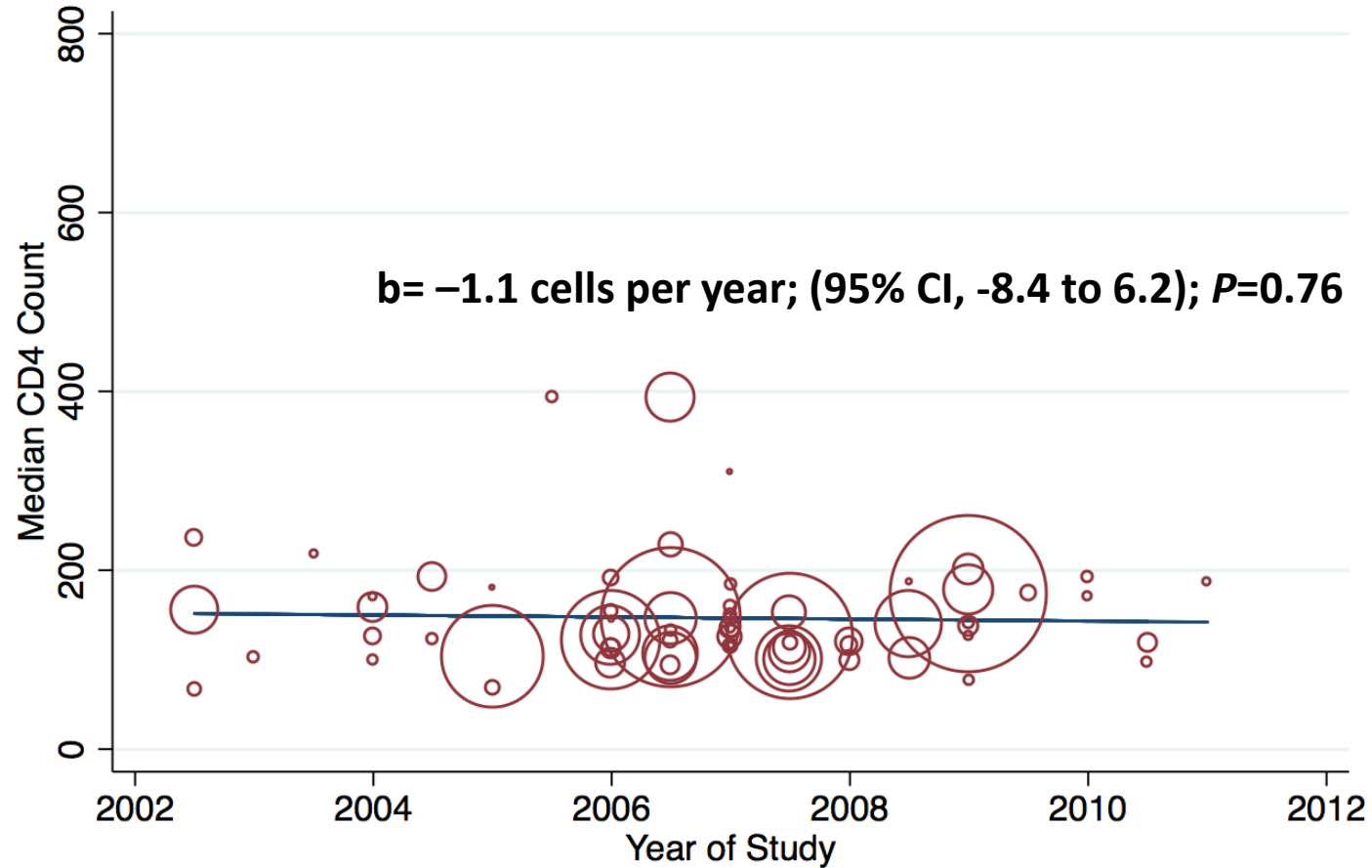
CD4, Viral Load and CVD Risk

Risk of Acute Myocardial Infarction by HIV Viral Load and CD4 Count Category

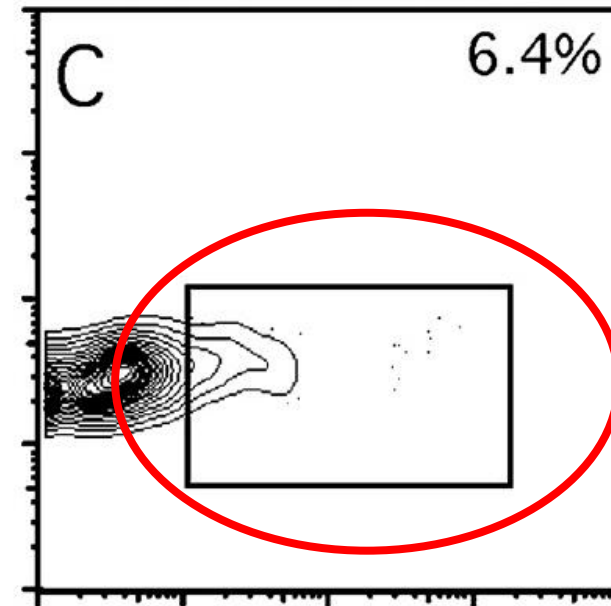
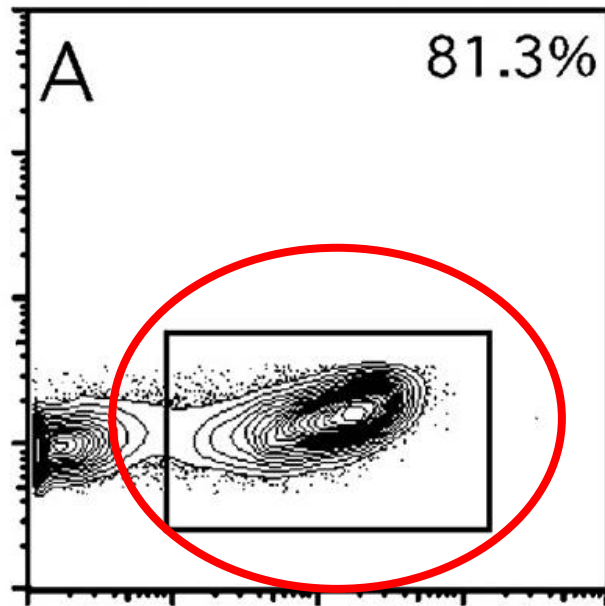
Category	HR (95% CI)	P Value ^b
CD4 cell count		
Uninfected	1 [Reference]	.04
<200	1.88 (1.46-2.40)	
≥200	1.43 (1.21-1.69)	



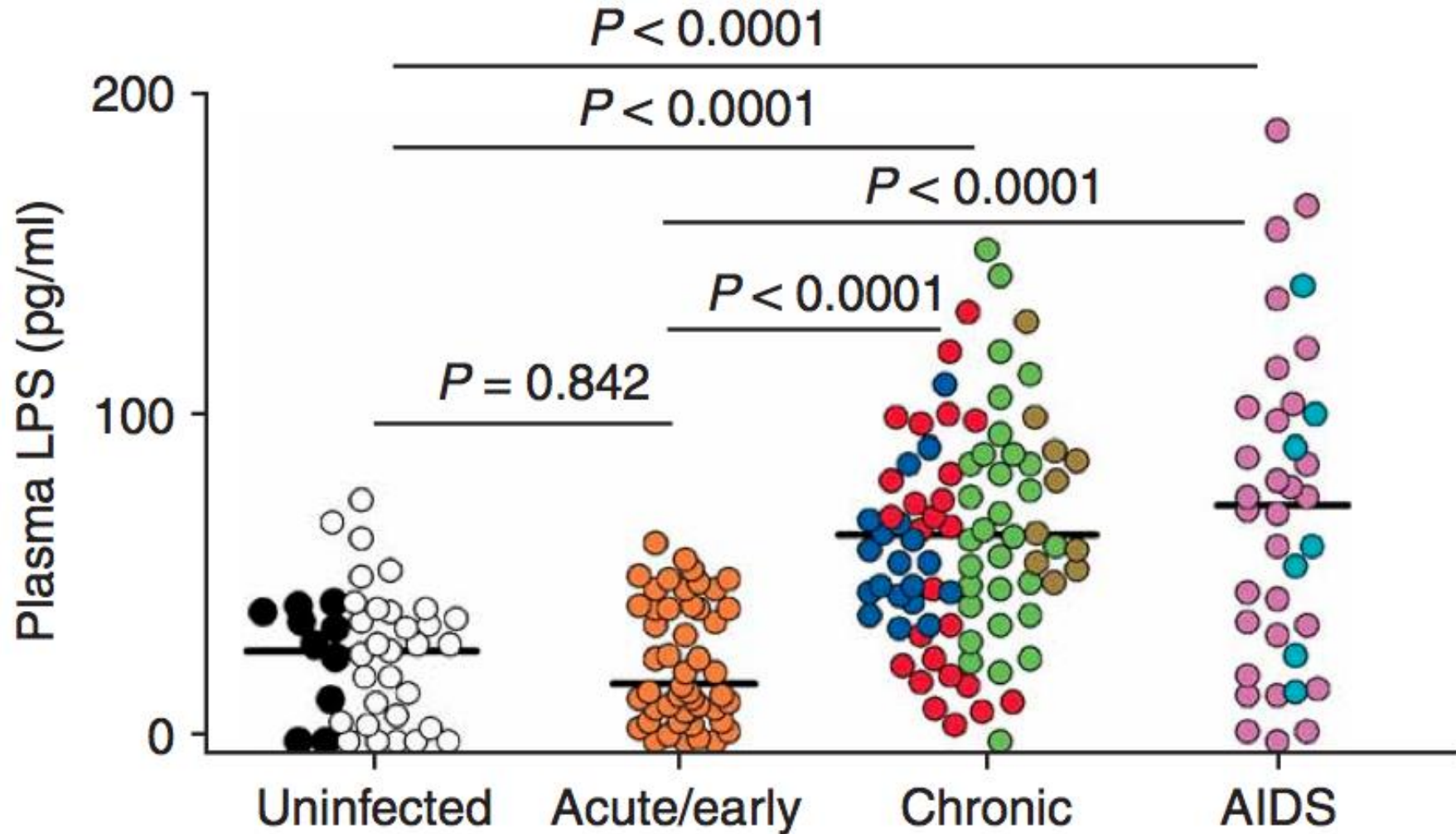
Trends in CD4 Count at ART Initiation in SSA

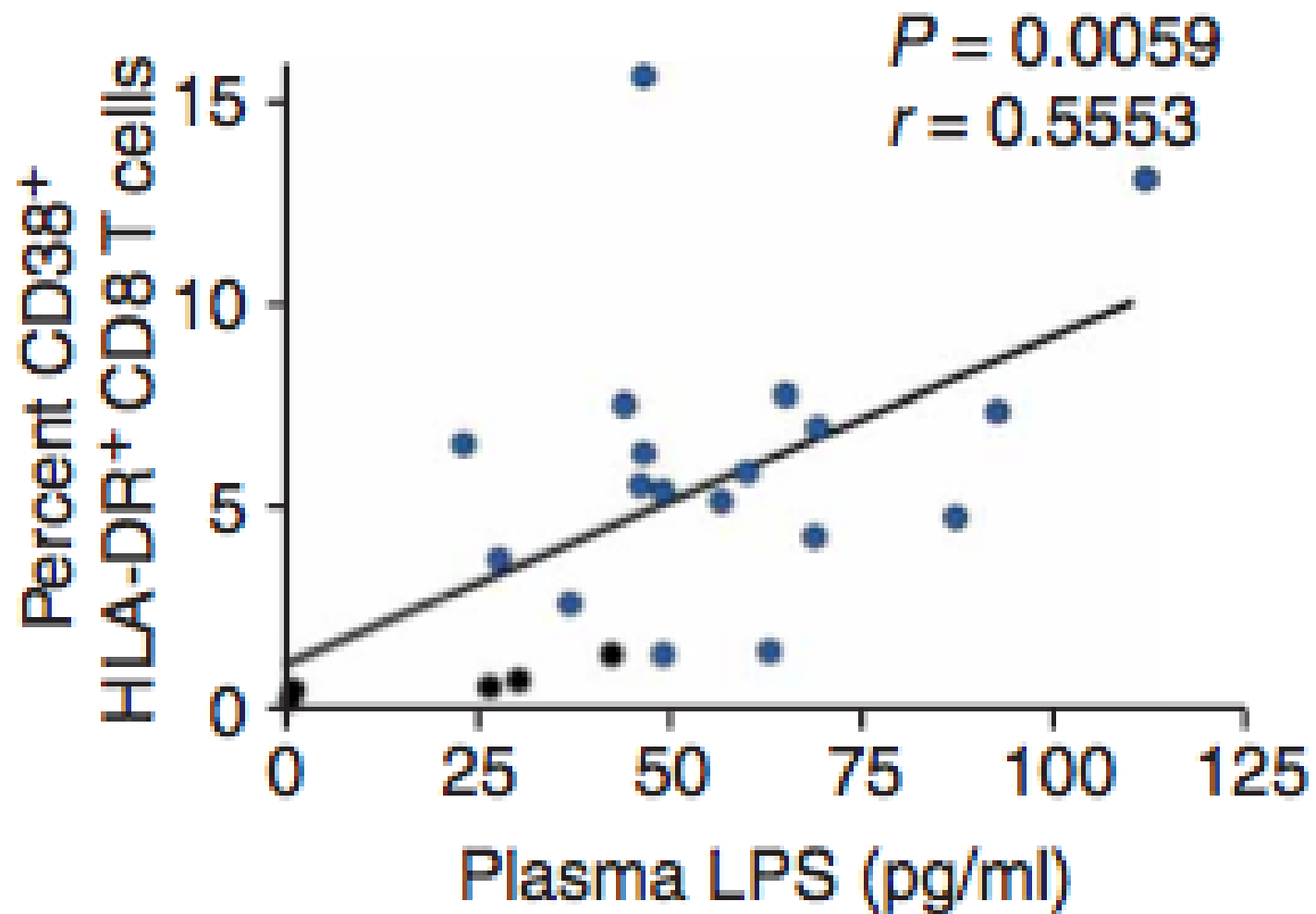


Gut goes first (and remains gone)



Chronic HIV Infection and Plasma LPS

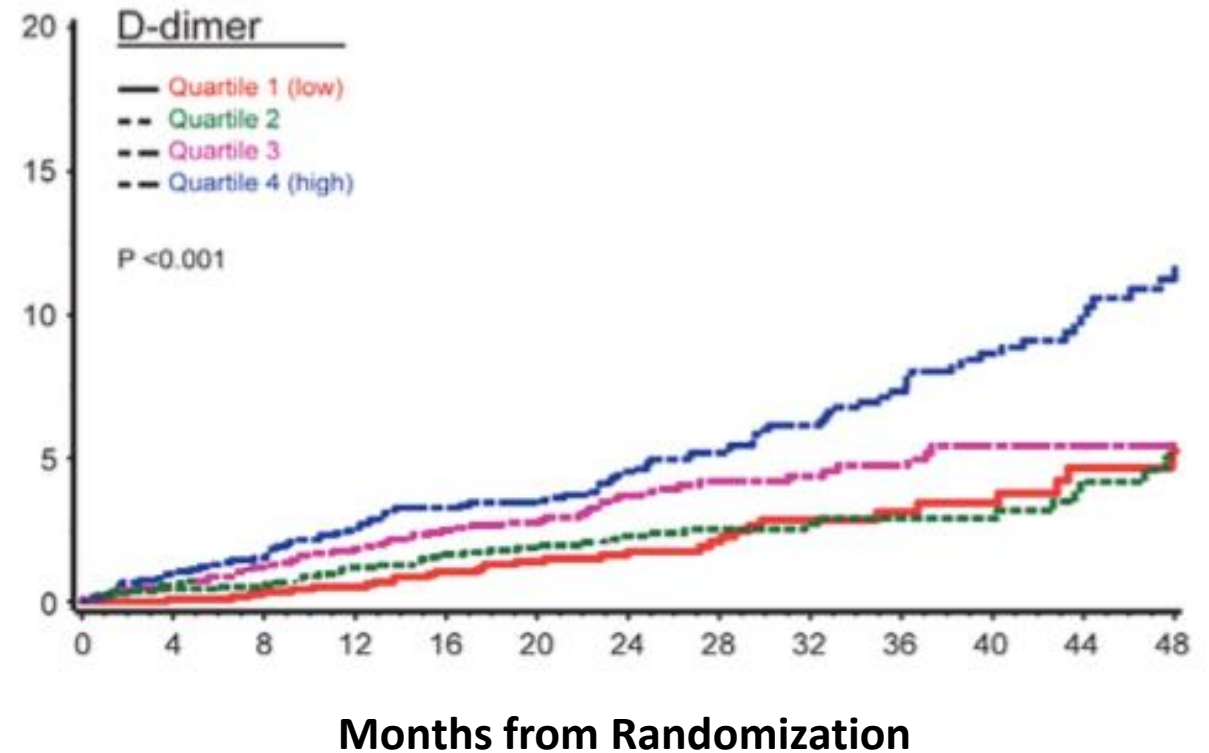
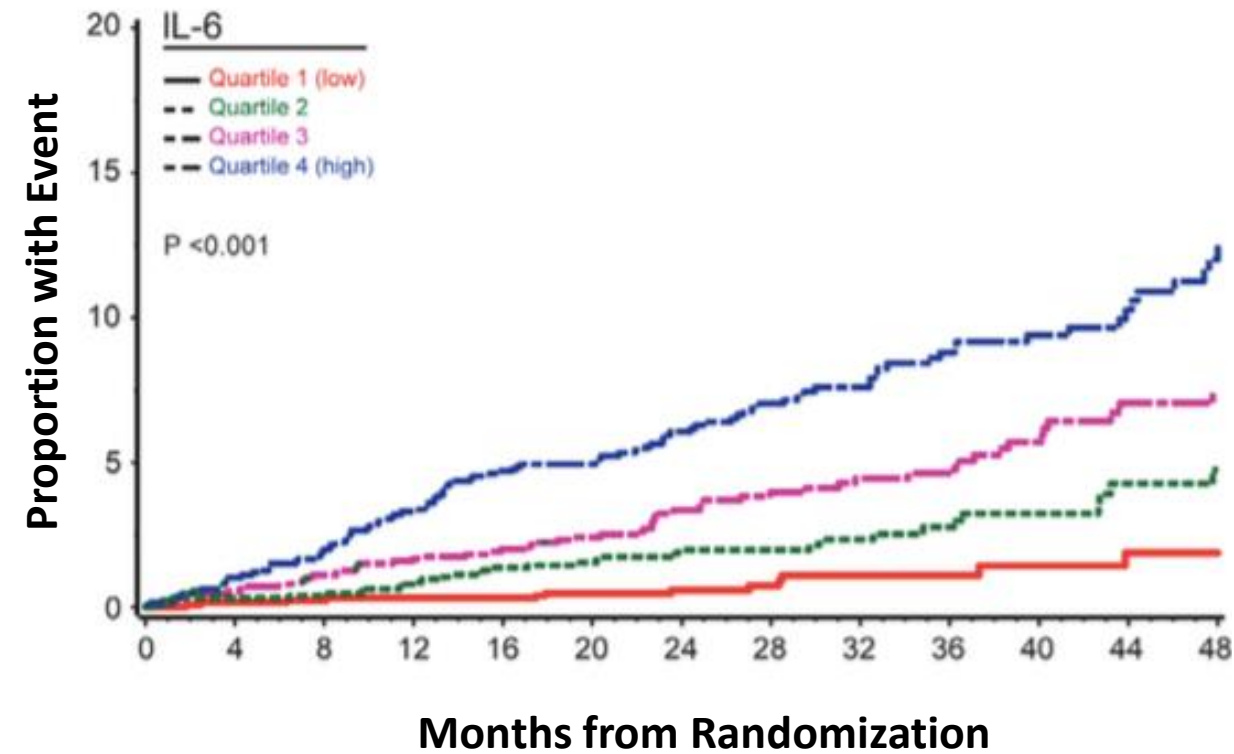




HIV and Immune Activation

Biomarker	Median among HIV+	Median among HIV-	P-value
sCD163	680 (519-879)	547 (430-693)	<0.001
sCD14	1619 (1406 – 1899)	1282 (1114-1458)	<0.001

Immune Activation and CVD Events in SMART



Traditional Cardiovascular Risk Factors

Female Gender

Demographics & Family History

Smoking

Diet

Hypertension

Diabetes

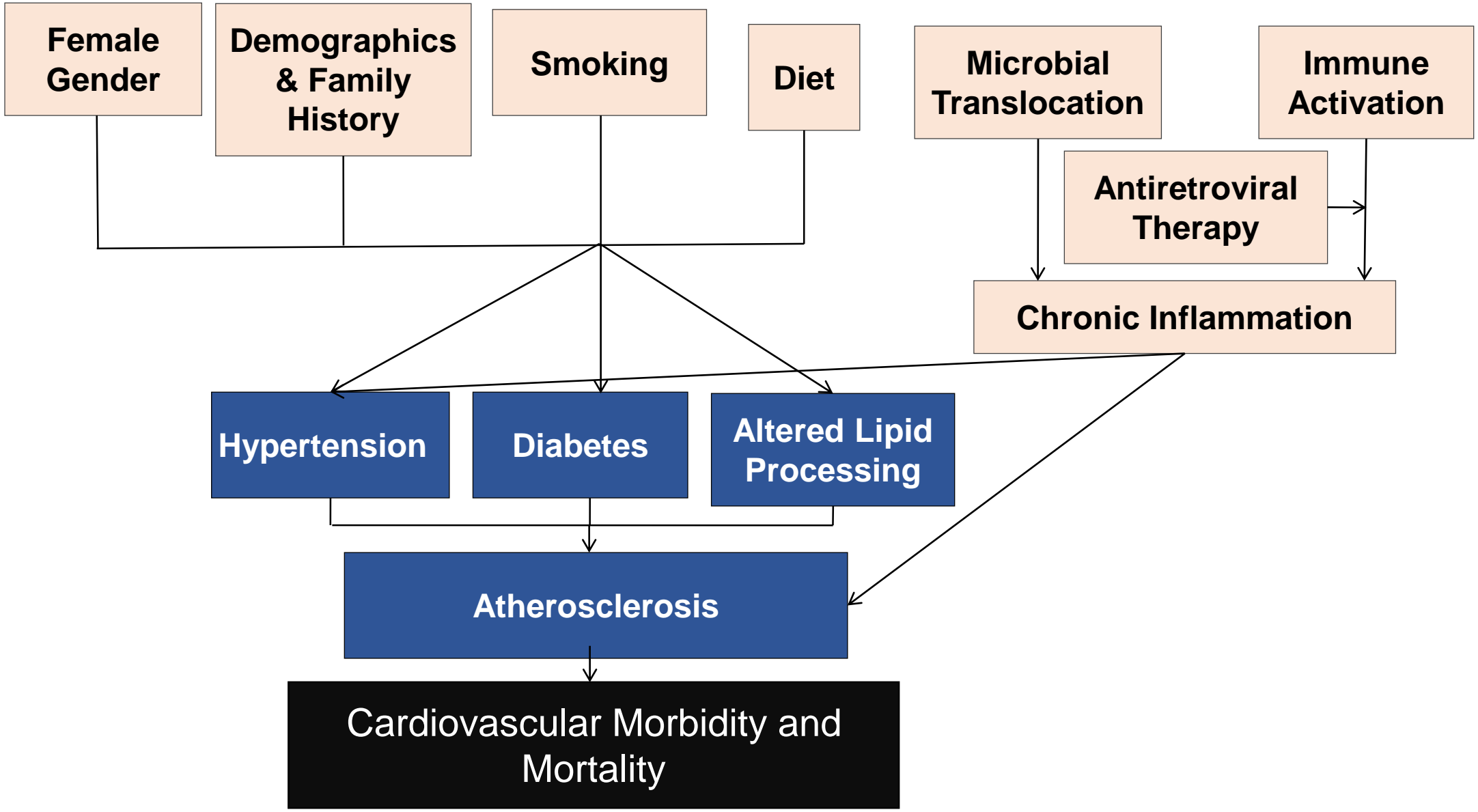
Altered Lipid Processing

Atherosclerosis

Cardiovascular Morbidity and Mortality

Traditional Cardiovascular Risk Factors

HIV-Infection Associated Cardiovascular Risk Factors



Gender, HIV, and CVD Risk

- Multiple cohort studies suggest that **women** with HIV have relatively increased risk of CVD (over uninfected counterparts) of CVD than men
- Women have higher rates of traditional risk factors
- Women appear to have less decreases in immune activation than men after ART initiation

Triant et al, J Clin Endo, 2007

Lang et al, AIDS, 2010

Womack et al, CROI, 2014

Hessamfar, PLoS One, 2014

Mathad et al, JAIDS, 2016



Question 3:

Which of these factors contributes to CVD risk in HIV-infected persons?

- A. Smoking
- B. Hypertension
- C. CD4 count nadir
- D. Virologic failure
- E. Female gender
- F. All of the above**
- G. When is tea?

HIV and CVD: Screening and Primary Prevention

- ART Regimens, metabolic disorders, and CVD Risk
- Screening for CVD risk factors
- Screening for CVD

HIV and Dyslipidemia

Treatment Status	Low Density Lipoprotein	High Density Lipoprotein	Total Cholesterol	Triglycerides
HIV Negative	REF	REF	REF	REF
Untreated	↓	↓↓	↓↓	↑
After ART Initiation	↑	↓	--	↑

ART and Dyslipidemia

Treatment Status	Low Density Lipoprotein	High Density Lipoprotein	Total Cholesterol	Triglycerides
HIV Untreated	REF	REF	REF	REF
Zidovudine	↑	↑	↑↑	↑
Tenofovir	↓	↓	↓↓	--

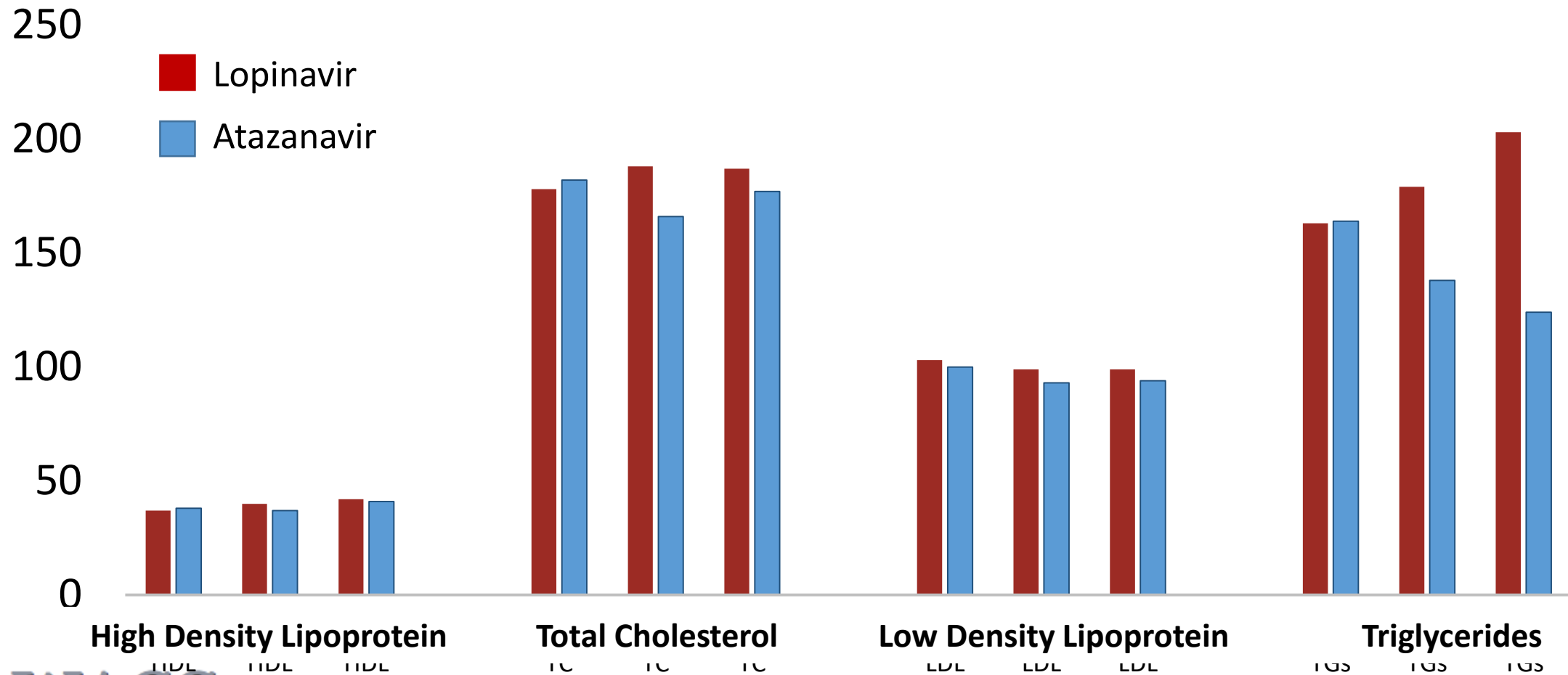
ART and Dyslipidemia

Treatment Status	Low Density Lipoprotein	High Density Lipoprotein	Total Cholesterol	Triglycerides
HIV Untreated	REF	REF	REF	REF
Zidovudine	↑	↑	↑↑	↑
Tenofovir	↓	↓	↓↓	--
Efavirenz	↑	↑	↑	↑
Nevirapine	↑	↑↑	↑	--

ART and Dyslipidemia

Treatment Status	Low Density Lipoprotein	High Density Lipoprotein	Total Cholesterol	Triglycerides
HIV Untreated	REF	REF	REF	REF
Zidovudine	↑	↑	↑↑	↑
Tenofovir	↓	↓	↓↓	--
Efavirenz	↑	↑	↑	↑
Nevirapine	↑	↑↑	↑	--
Ritonavir	↑↑	--	↑↑	↑
Lopinavir	↑↑	--	↑↑	↑
Atazanvir	↑	--	↑	↓

Lopinavir, Atazanavir, and Lipid Alterations



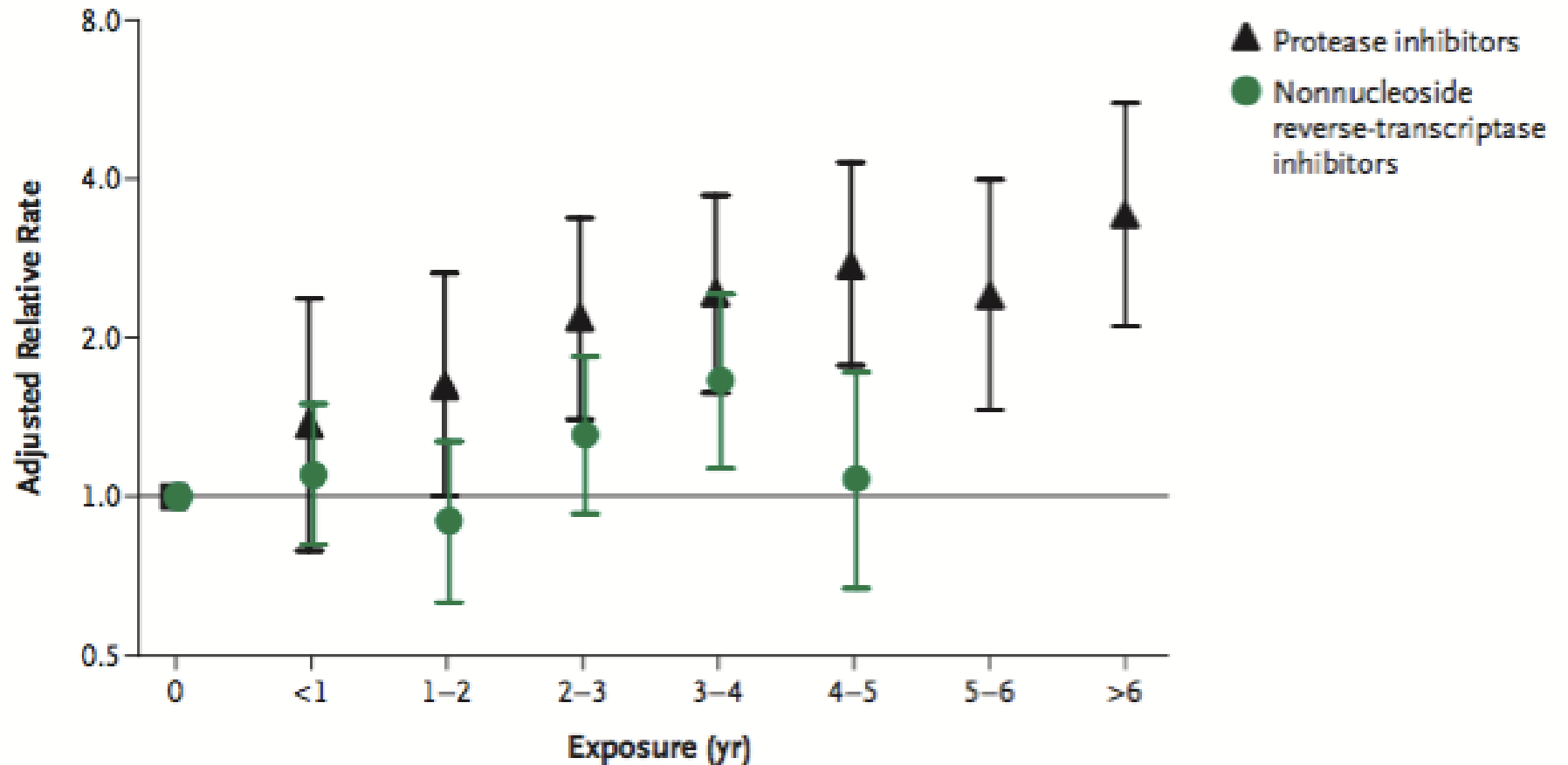
Question 4:

Which of these ART medications is least likely to cause increases in levels of cholesterol?

- A. Zidovudine
- B. Ritonavir
- C. Lopinavir
- D. Nevirapine
- E. Tenofovir
- F. Seriously, is this still going on?

Do ARVs or ARV classes increase CVD risk?

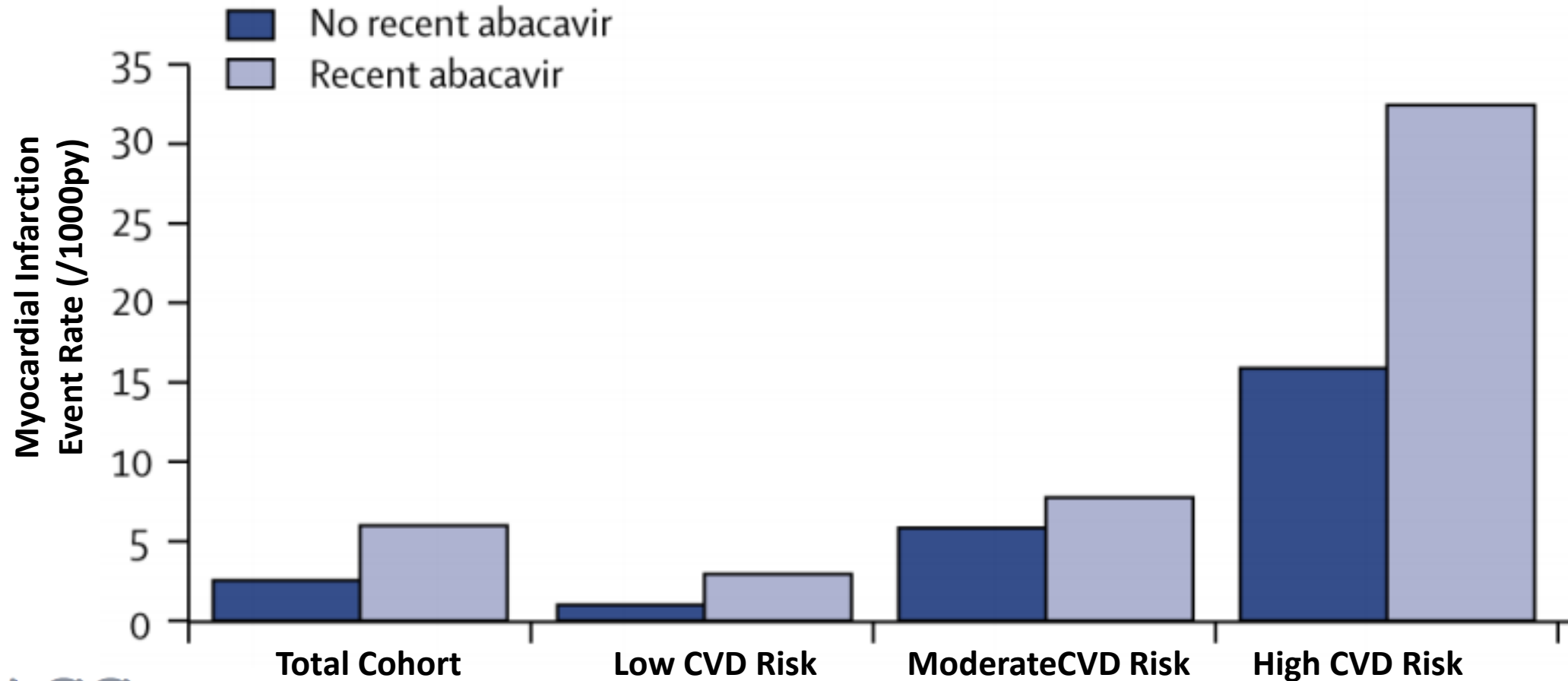
Class of Antiretroviral Therapy and CVD Risk



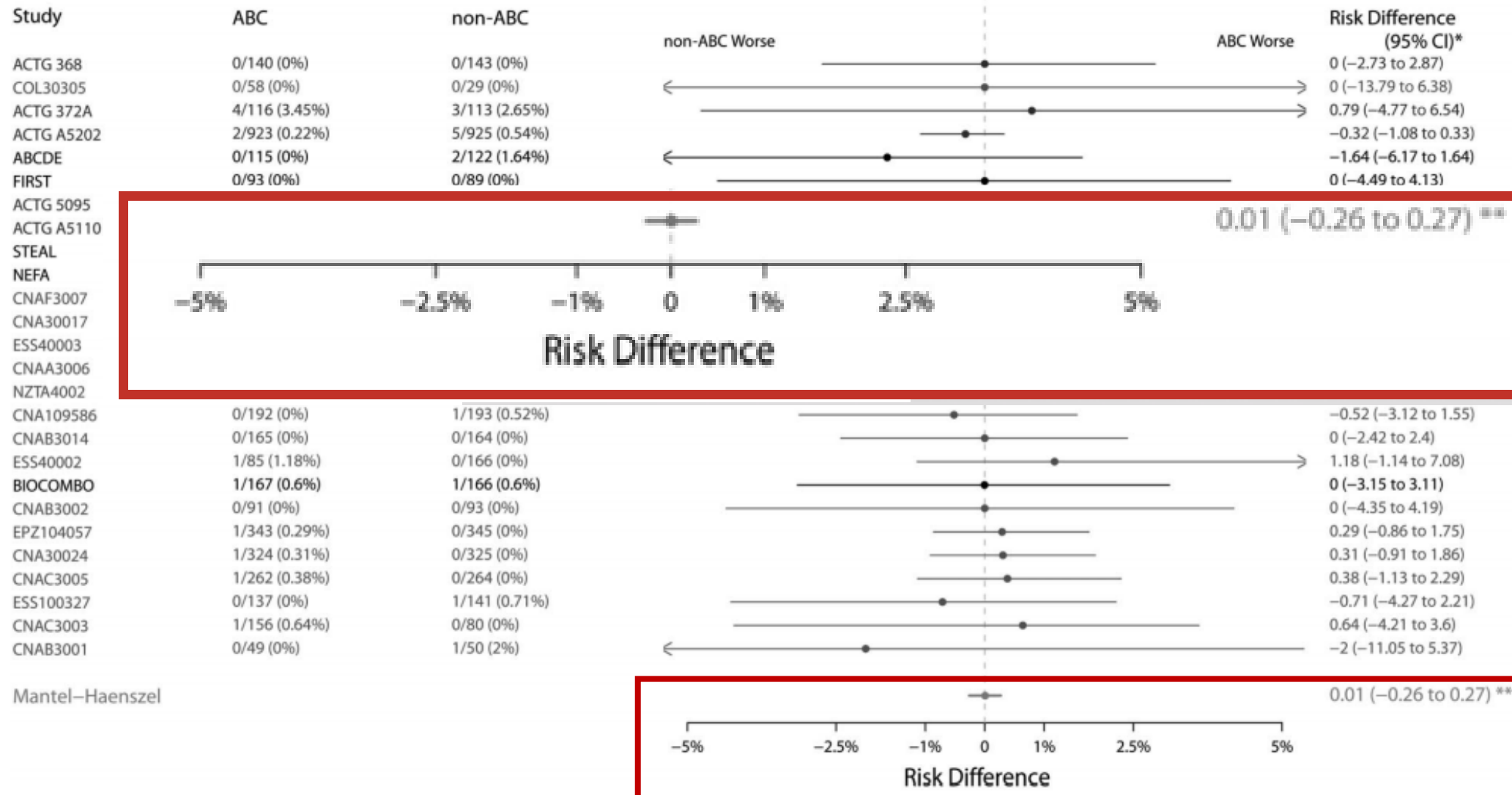
Class of Antiretroviral Therapy and CVD Risk

- Protease inhibitors and CVD risk
 - Lopinavir and other older PIs associated with increased risk
 - Atazanvir *not* associated with CVD risk in follow-up D:A:D Study analysis

Abacavir and Risk of Myocardial Infarction



Abacavir and Risk of Myocardial Infarction



Question 5:

Are you ready for tea?

- A. Yes, and I mentally left this room about 30 minutes ago
- B. Yes, but I can wait for this guy to finish I suppose (I might as well get my money's worth for the conference fee)
- C. Why would he ask that? Does tea increase the risk of CVD?

Screening for CVD Risk in HIV Infection



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Screening for CVD Risk in HIV Infection

IDSA GUIDELINES

Primary Care Guidelines for the Management of Persons Infected With HIV: 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America

Judith A. Aberg,¹ Joel E. Gallant,^{2,3} Khalil G. Ghanem,³ Patricia Emmanuel,⁴ Barry S. Zingman,⁵ and Michael A. Horberg⁶

¹Division of Infectious Diseases and Immunology, New York University School of Medicine, Bellevue Hospital Center, New York; ²Southwest CARE Center, Santa Fe, New Mexico; ³Johns Hopkins University School of Medicine, Baltimore, Maryland; ⁴Department of Pediatrics, University of South Florida Health, Tampa; ⁵Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York; and ⁶Mid-Atlantic Permanente Research Institute, Rockville, Maryland



Screening for CVD Risk in HIV Infection

Measurement	Initial Evaluation	Monitoring Frequency
Height/Weight (BMI)	Baseline	Annually
Smoking, diet, exercise	Baseline	Each Visit
Lipid profile	Baseline and 1-3 months after initiation	q6-12 months
Fasting Blood Sugar or A1c	Baseline and 1-3 months after initiation	q6-12 months
Blood Pressure Measurement	Baseline	Each Visit
Cardiovascular Disease Risk Assessment	Baseline	Annually

Hemoglobin A1c and HIV Infection

- A1c might underestimate mean glucose in HIV-infected populations
 - ~1.7 mmol/L (30 mg/dL) difference in mean glucose between HIV+/HIV-
- Some have advocated for a lower threshold (5.8%) in HIV
- ADA recommends for discordant results between FBG and A1c:
 - Repeat the test that was below the threshold (FBG >126 or A1c > 6.5%)
 - If repeat remains below threshold, monitor
 - If repeat is above threshold, manage as if a diagnosis of DM

CVD Risk Scores

- Scores
 - Framingham Risk Score Calculator
 - <https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php#>
 - Lab-based: using lipid panel
 - Non-lab based: using BMI (no laboratory tests needed)
 - ATP III Guidelines for Statin Therapy
 - <https://www.nhlbi.nih.gov/files/docs/guidelines/atglance.pdf>

ATP III Guidelines At-A-Glance

Quick Desk Reference

5

Step 5

Determine risk category:

- Establish LDL goal of therapy
- Determine need for therapeutic lifestyle changes (TLC)
- Determine level for drug consideration

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

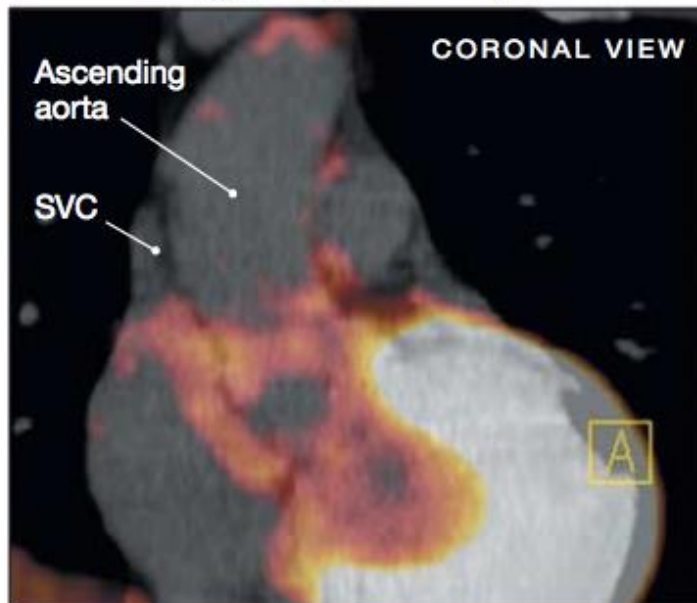
Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor [†]	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

CVD Risk Scores in HIV Infection

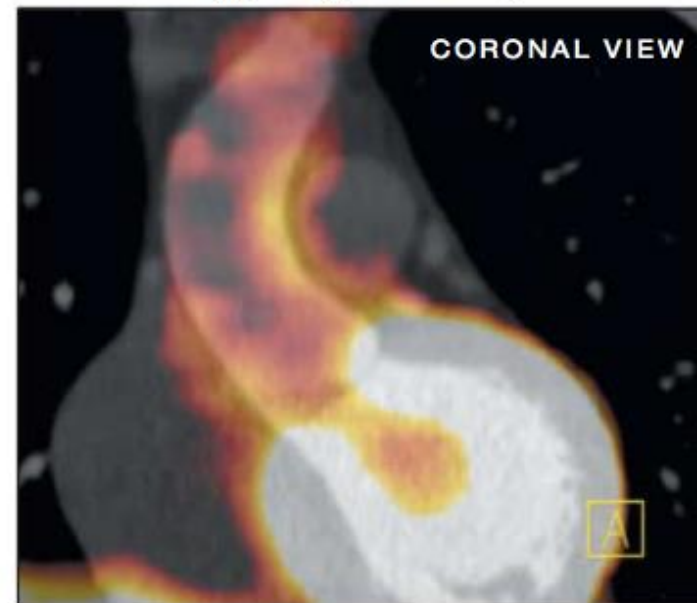
- Do standard CVD risk scores under-predict risk in HIV-infected populations?

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

Non-HIV FRS-matched control participant
(Age 43 y, TBR=2.01)



Participant with HIV
(Age 42 y, TBR=3.42)

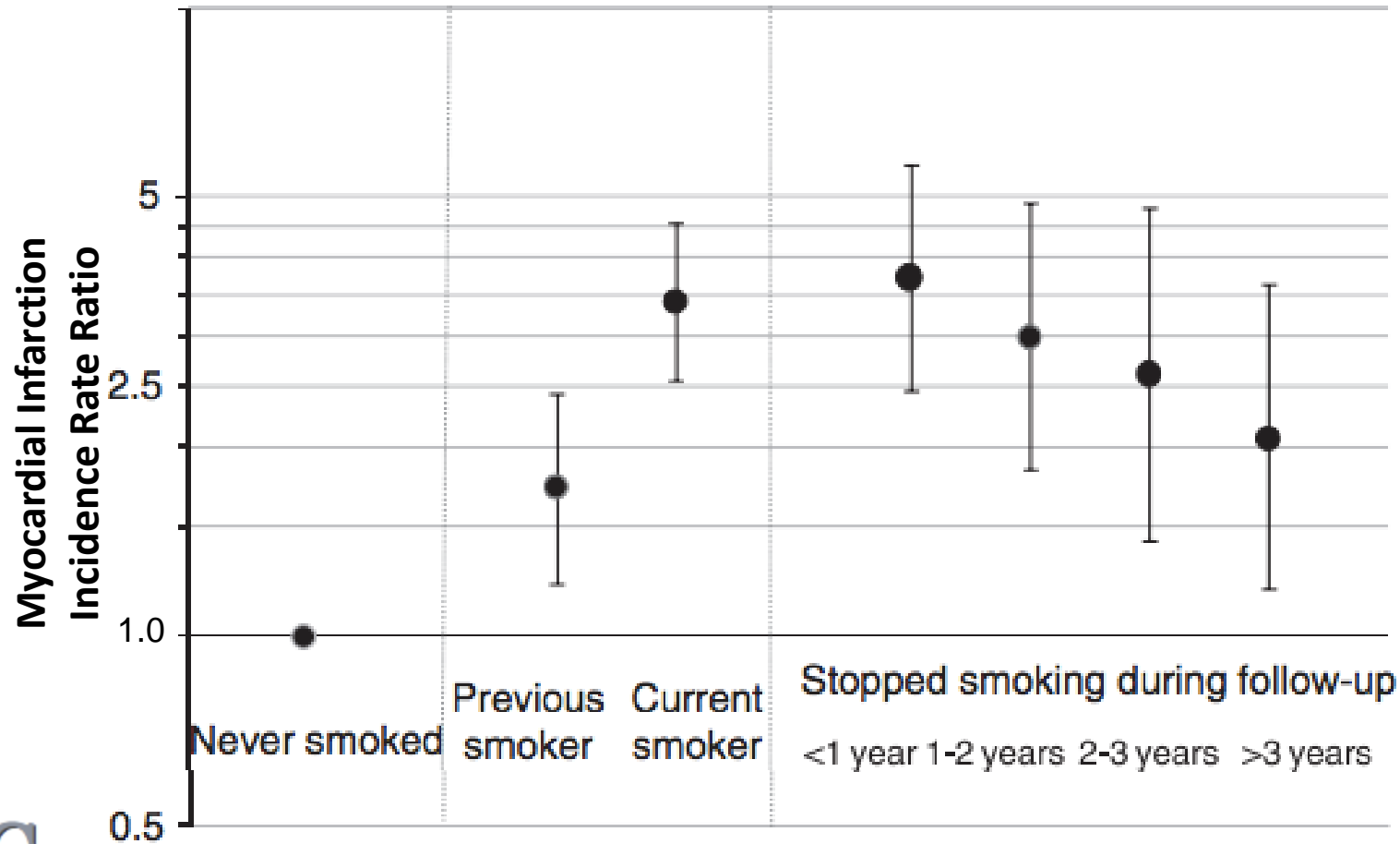


Management of CVD Risk Factors in HIV

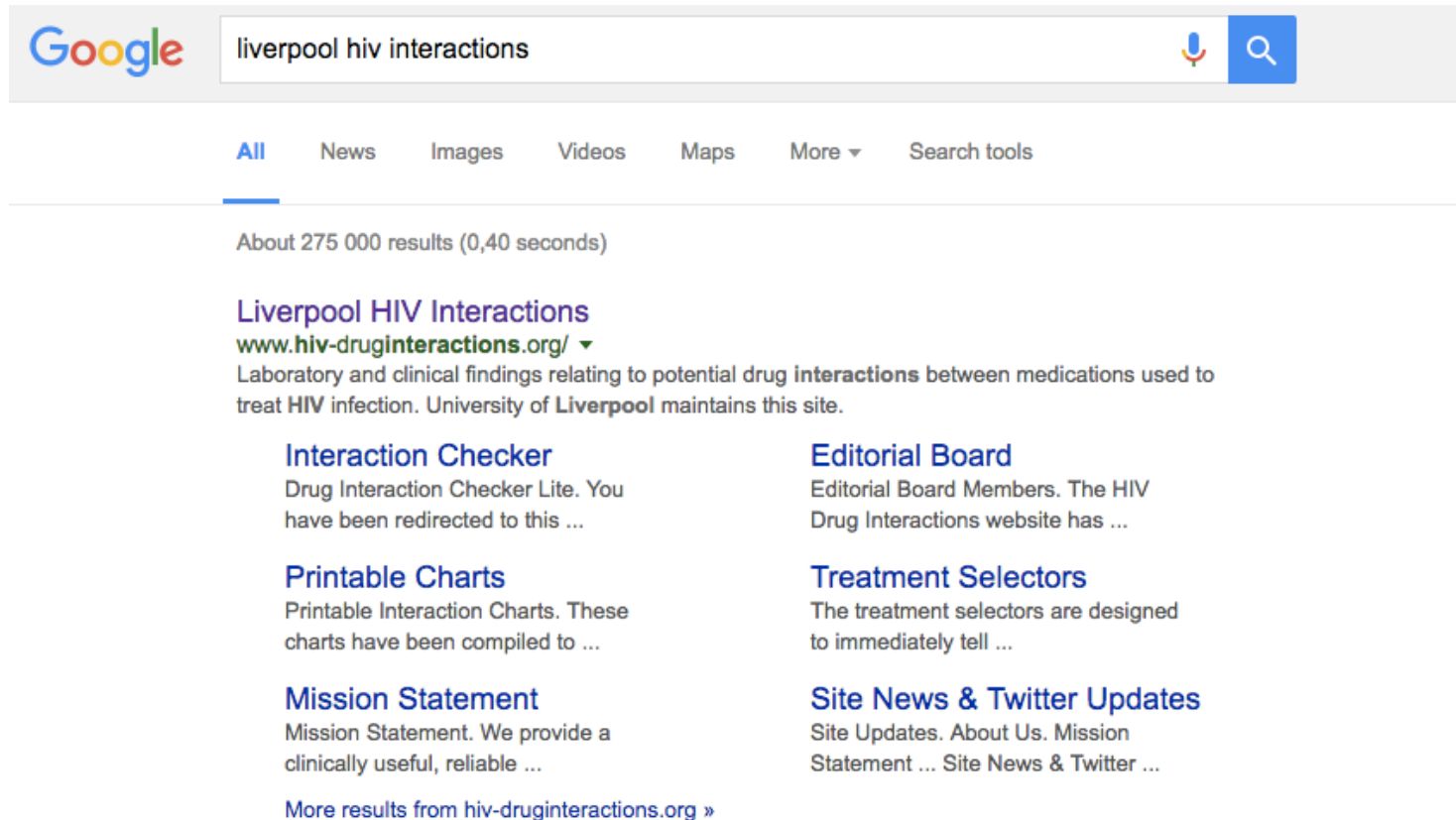


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Smoking Cessation and CVD Risk in HIV



HIV Drug Interactions



The image shows a Google search interface. The search bar contains the text "liverpool hiv interactions". Below the search bar, there are navigation tabs for "All", "News", "Images", "Videos", "Maps", "More", and "Search tools". The "All" tab is selected. Below the tabs, it says "About 275 000 results (0,40 seconds)". The first search result is titled "Liverpool HIV Interactions" with the URL "www.hiv-druginteractions.org/". Below the title, there is a brief description: "Laboratory and clinical findings relating to potential drug interactions between medications used to treat HIV infection. University of Liverpool maintains this site." Below the description, there are several links to different sections of the website: "Interaction Checker", "Printable Charts", "Mission Statement", "Editorial Board", "Treatment Selectors", and "Site News & Twitter Updates". Each link has a short description. At the bottom of the search results, there is a link that says "More results from hiv-druginteractions.org »".

Google liverpool hiv interactions

All News Images Videos Maps More Search tools

About 275 000 results (0,40 seconds)

Liverpool HIV Interactions
www.hiv-druginteractions.org/
Laboratory and clinical findings relating to potential drug interactions between medications used to treat HIV infection. University of Liverpool maintains this site.

Interaction Checker
Drug Interaction Checker Lite. You have been redirected to this ...

Printable Charts
Printable Interaction Charts. These charts have been compiled to ...

Mission Statement
Mission Statement. We provide a clinically useful, reliable ...

Editorial Board
Editorial Board Members. The HIV Drug Interactions website has ...

Treatment Selectors
The treatment selectors are designed to immediately tell ...

Site News & Twitter Updates
Site Updates. About Us. Mission Statement ... Site News & Twitter ...

[More results from hiv-druginteractions.org »](#)

HIV Drug Interactions: Liverpool Database



HIV Drug Interactions



Apps



[Interaction Charts](#)

[Site Updates](#)

[About Us](#)

[Pharmacology Resources](#)

[Contact Us](#)

	ATV	Cobi	DRV	FPV	IDV	LPV	NFV	RTV	SQV	TPV
Lipid Lowering Agents										
Atorvastatin	■	■	■	■	■	■	■	■	■	■
Bezafibrate	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Clofibrate	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Ezetimibe	■	◆	◆	◆	◆	◆	◆	◆	◆	◆
Fenofibrate	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Fish oils	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Fluvastatin	■	■	◆	◆	■	◆	◆	◆	■	◆
Gemfibrozil	■	◆	■	■	■	■	■	■	■	■
Lovastatin	●	●	●	●	●	●	●	●	●	●
Pitavastatin	■	■	◆	◆	◆	◆	◆	◆	◆	◆
Pravastatin	■	■	■	◆	■	◆	■	◆	■	■
Rosuvastatin	■	■	■	■	■	■	■	■	■	■
Simvastatin	●	●	●	●	●	●	●	●	●	●



ART and Lipid Interaction Pearls

- Most statins are generally tolerated with NRTIs and NNRTIs
- For patients on PIs
 - **Avoid simvastatin, lovastatin,** and high dose atorvastatin
 - **Pravastatin and pitavastatin generally safe** with boosted PIs
 - Caution with darunavir + pravastatin. Combination increases pravastatin levels by ~80%
 - Starting at lower doses (particularly with atorvastatin) and monitor for myalgias and other statin-related side effects

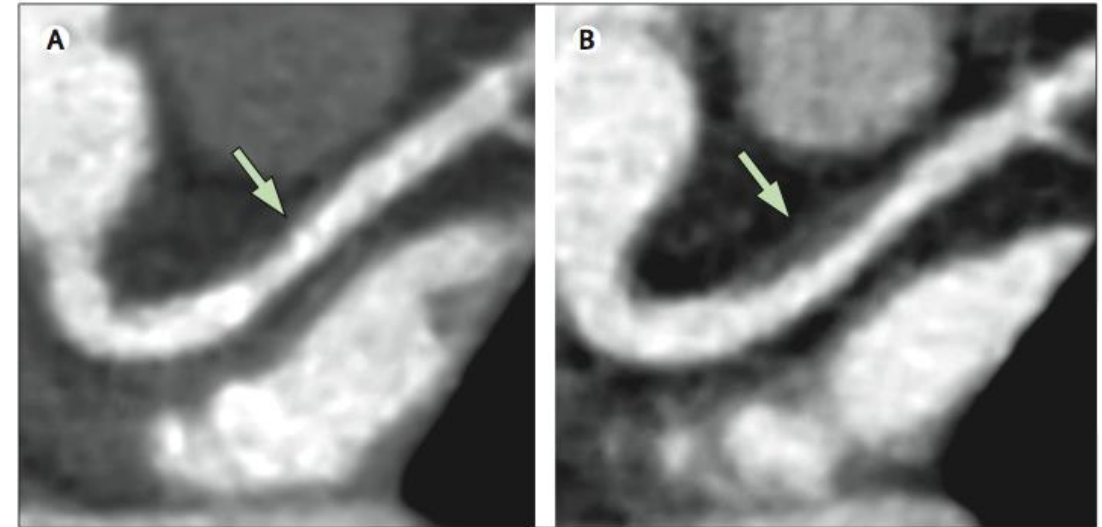
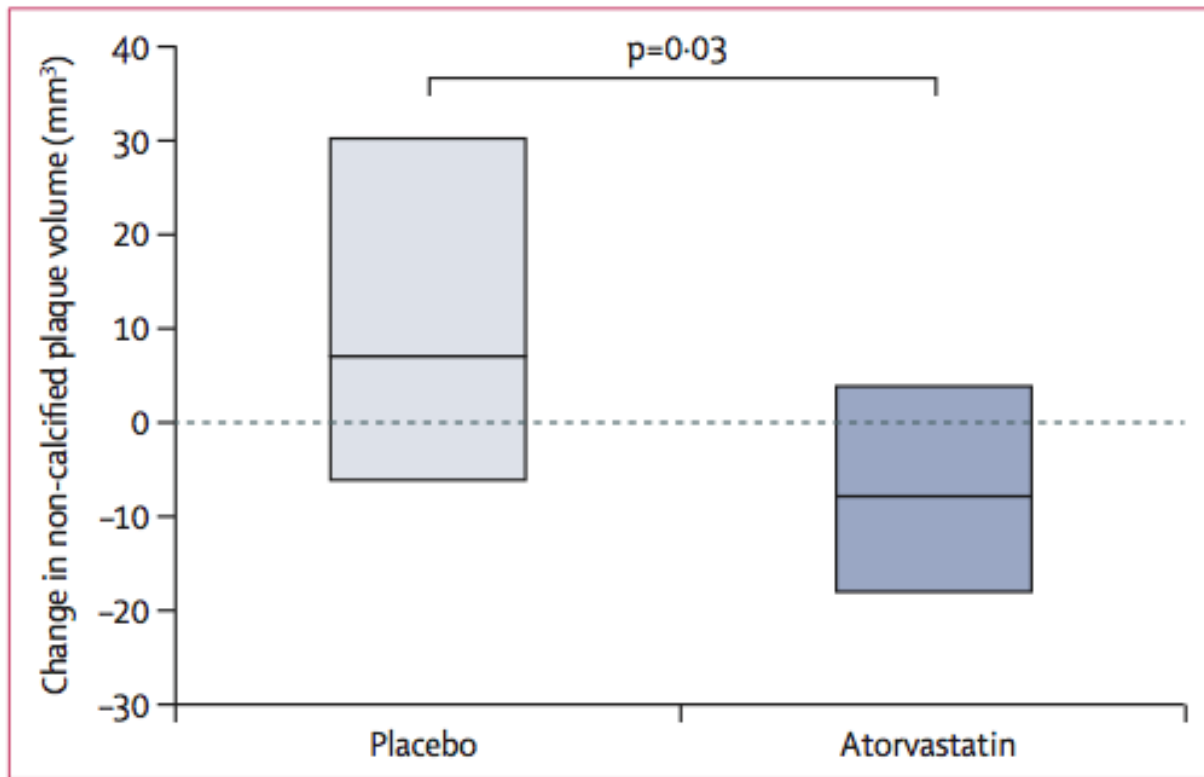
ART and Diabetes Interaction Pearls

- Dolutegravir and metformin interaction
 - Single dose dolutegravir raises metformin AUC levels 60-80%
 - Double dose dolutegravir raises metformin AUC levels 100-120%
 - Consider starting with low dose metformin (500mg) and using maximum dose of 1,000mg

Aspirin in HIV infection

- Standard guidelines for use of aspirin apply
 - Typically indicated for patients with a known history of CVD
 - Risks of bleeding and benefits must be balanced
- Of note, preliminary data suggest aspirin might have limited anti-inflammatory effects in HIV infection

Statins as primary prevention?



REPRIEVE

Randomized Trial to Prevent Vascular Events in HIV



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Lo et al, Lancet HIV, 2015

Summary 1: HIV and CVD Epidemiology

- In US/Europe **HIV+ have ~50% increased risk of CVD events**
 - Limited data about similar relationships in sub-Saharan Africa
- Both **traditional and HIV-specific risk factors** play a role
 - Smoking, diabetes, hyperlipidemia play similar role as in HIV-
 - HIV-associated immune activation, inflammation also appear to contribute
 - **Females with HIV** appear to have increased risk of CVD events
- **ART is associated with a significant decrease risk of CVD events**
 - Initiation when CD4 >350 cells/uL appears to offer additional benefit

Summary 2: ART, Metabolic Disorders and CVD

- Treated HIV infection is associated with modest **decrease in HDL**, and **increases in LDL and triglycerides**
- Protease inhibitors are associated with metabolic syndrome
 - **Ritonavir > Lopinavir > Atazanavir/Darunavir**
- Mixed data on abacavir and MI risk
 - Many providers **avoid use of abacavir in those with known CVD** or high risk of CVD events when other options available

Summary 3: Screening and Management of CVD

- Screen for obesity, hypertension, smoking, diabetes (A1c or FBG), and hypercholesterolemia regularly
- Management is **similar to that of the HIV-infected** populations
- Special considerations
 - Emphasis on behavioral risk factors including smoking
 - Consider **drug-drug interactions** when initiating statins
 - HIV-specific anti-inflammatory interventions are actively being investigated

Case 1

44 year old man with untreated HIV infection, presents to initiate care. CD4 325, viral load 100,000 copies/mL. No evidence of opportunistic infections. Other data include: BMI 31, former smoker, A1c 6.3%, LDL 4.0 mmol/L (155 mg/dL). Which of these interventions is most likely to reduce his CVD risk?

- A. Additional smoking cessation counseling
- B. Addition of metformin
- C. Initiation of antiretroviral therapy
- D. Addition of pravastatin

Case 2

52 year old woman with well controlled HIV infection, CD4 680, viral load below limit of detection of ABC/3TC/LPV/R (history of first-line failure without resistance). She presents to HIV clinic after suffering a recent myocardial infarction. She was initiated on aspirin in the hospital, but takes no other medicines. Her current evaluation notable for BP 128/67, BMI 35, non-smoker, A1c 5.5%, LDL 3.5mmol/L (135mg/dL). How would you adjust her HIV regimen?

- A. No change, she is virologically suppressed
- B. Change to TDF/3TC/ATV/R
- C. Change to ABC/3TC/ATV/R
- D. Discontinue ART for a treatment holiday given likely ART-related CVD

Case 2, continued

What else would you suggest for this patient?

- A. Diet, exercise, and lifestyle counseling
- B. Initiate pravastatin
- C. A and B
- D. No other interventions at this time
- E. Enough is enough. I'm calling the police to end this talk.

Thank you for your attention!

Please do not hesitate with any questions.

Mark Siedner MD MPH
Massachusetts General Hospital
msiedner@mgh.harvard.edu



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