Non-Communicable Diseases in People Living with HIV: A Review

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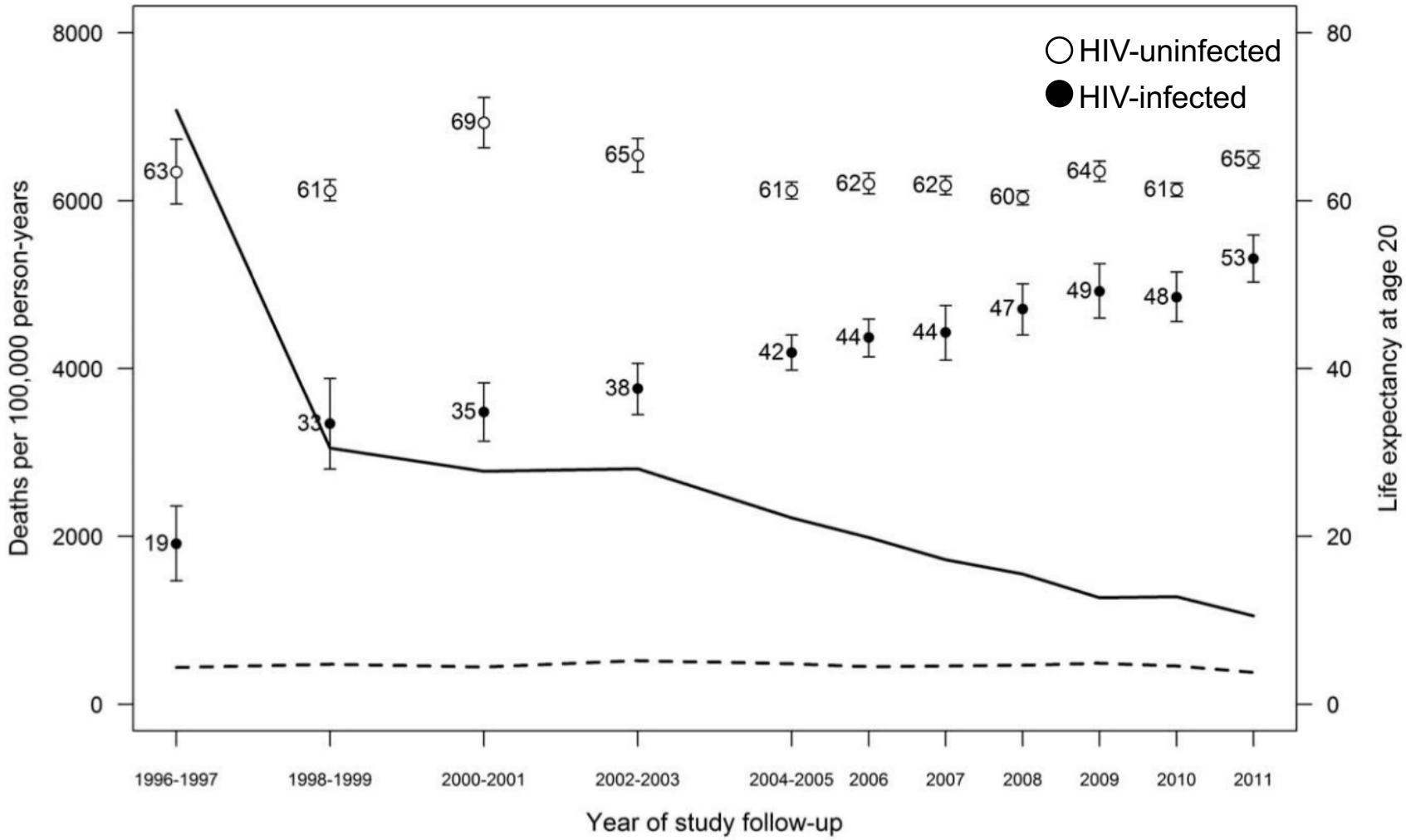
Key Topics

- Epidemiology of NCDs in HIV Infection
  - Data from the United States and Europe
  - Emerging data from sub-Saharan Africa
- Screening and Primary Prevention
- Secondary Prevention and Management

ART and Life Expectancy in the US

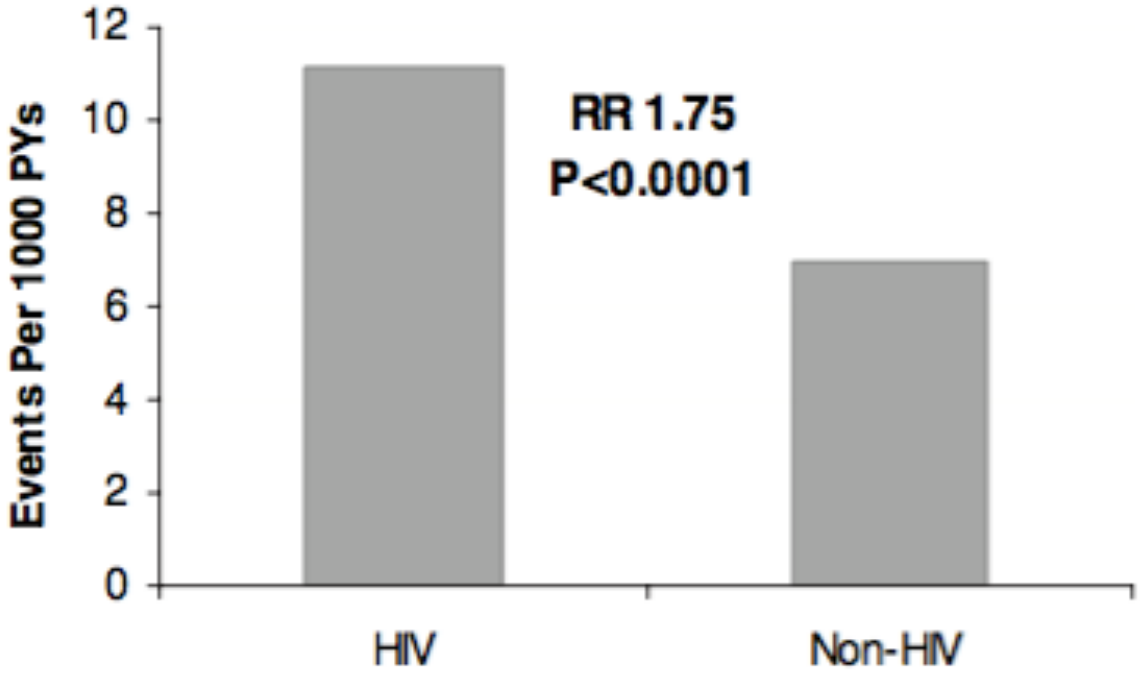


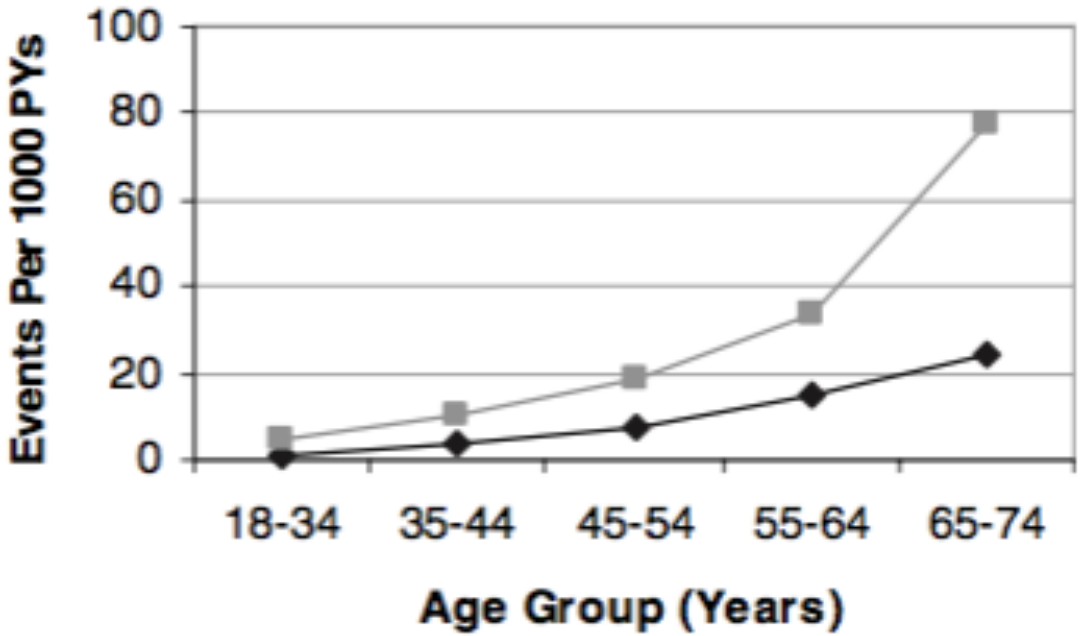
Marcus et al, JAIDS, 2016

Myocardial Infarction Risk in the ART Era

DAD Study Group, NEJM, 2007

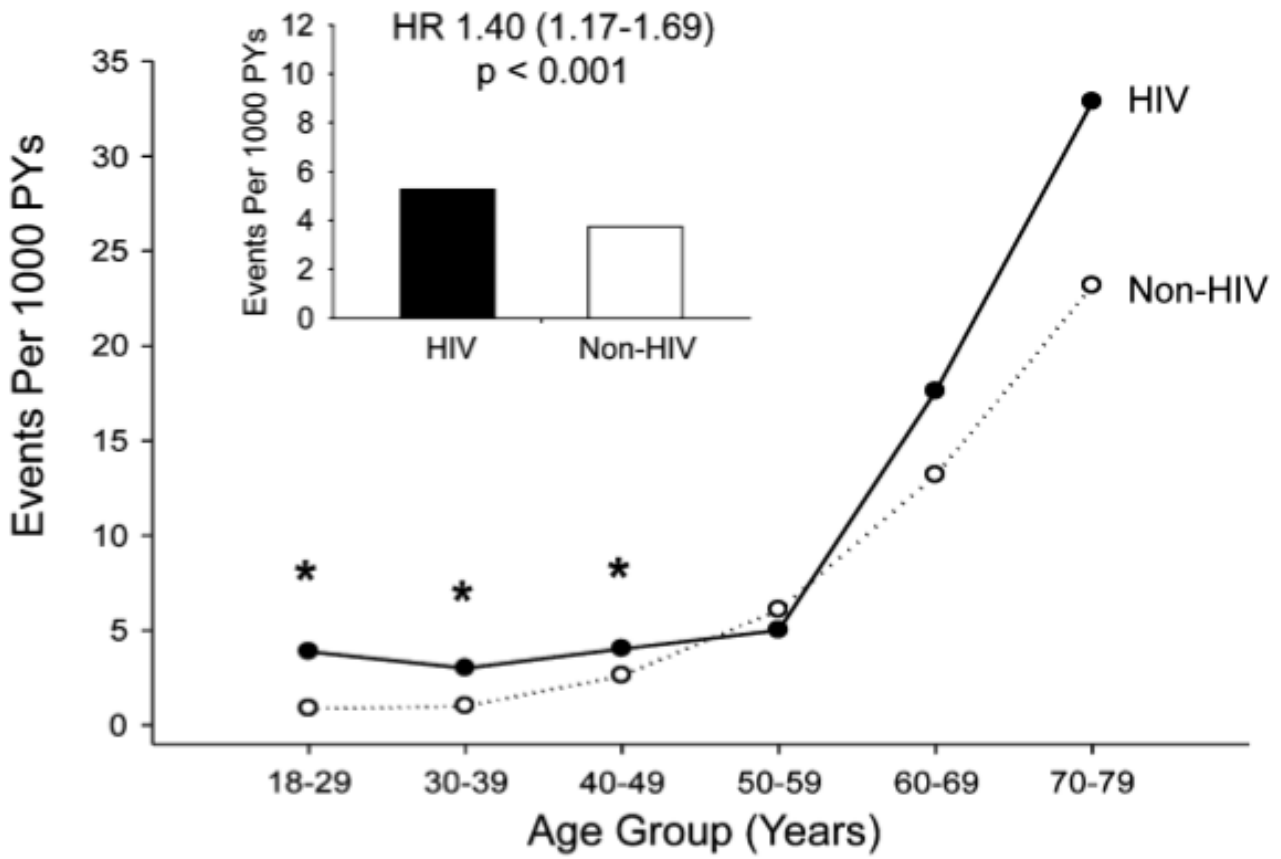
Increased Risk of Myocardial Infarction in HIV





Triant et al, J Clin Endo, 2007
Currier et al, JAIDS, 2003
Frieberg et al, Ann Int Med, 2013
Althoff et al, Clin Inf Dis, 2015

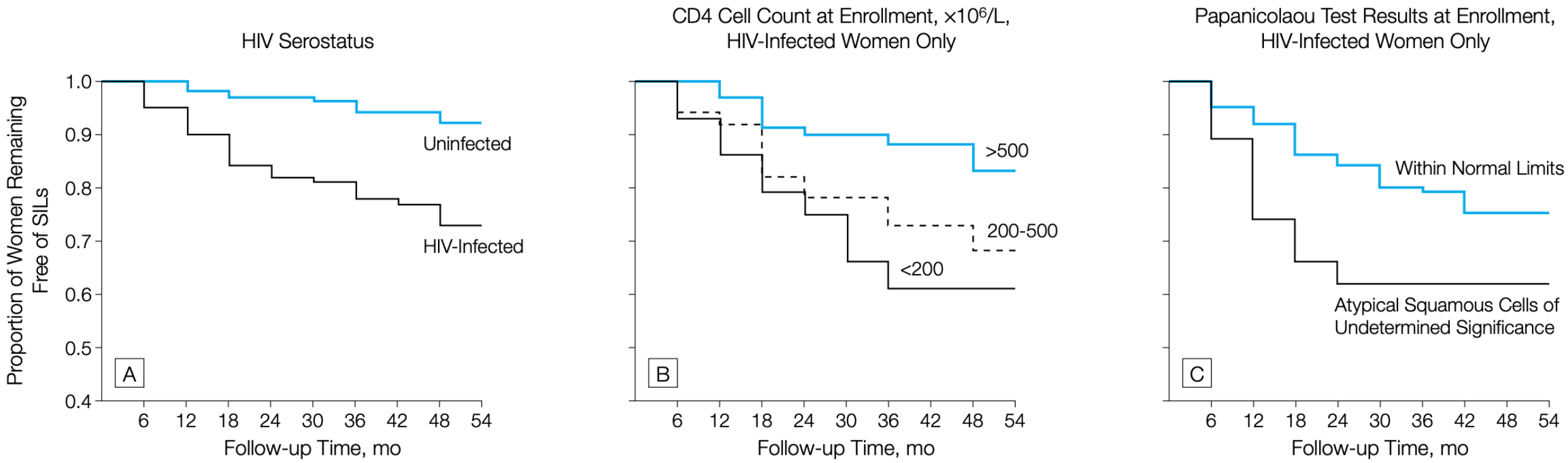
Increased Risk of Stroke in HIV



Chow et al, AIDS, 2012

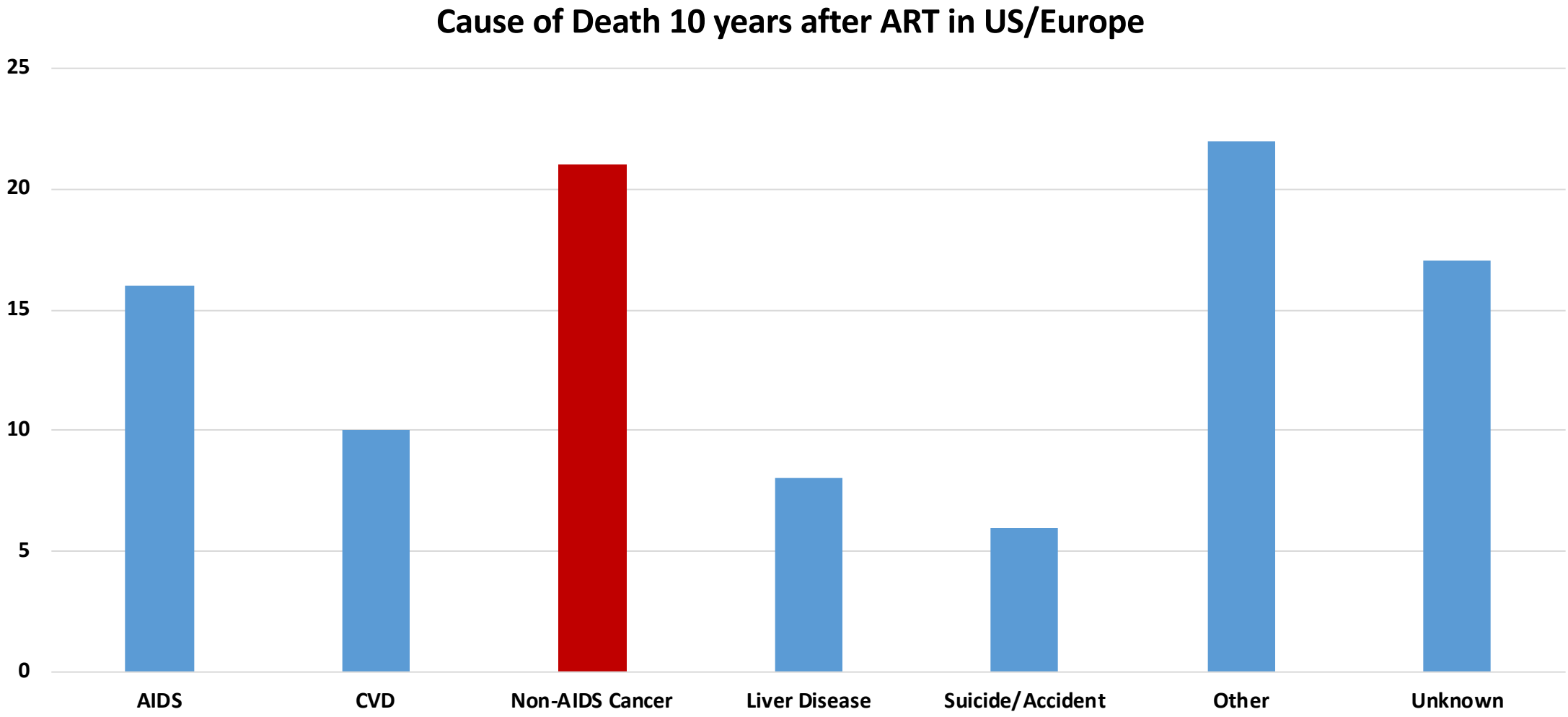
HIV and Cancer Risk

Figure 1. Kaplan-Meier Curves of Proportions of Women Remaining Free of Squamous Intraepithelial Lesions (SILs)



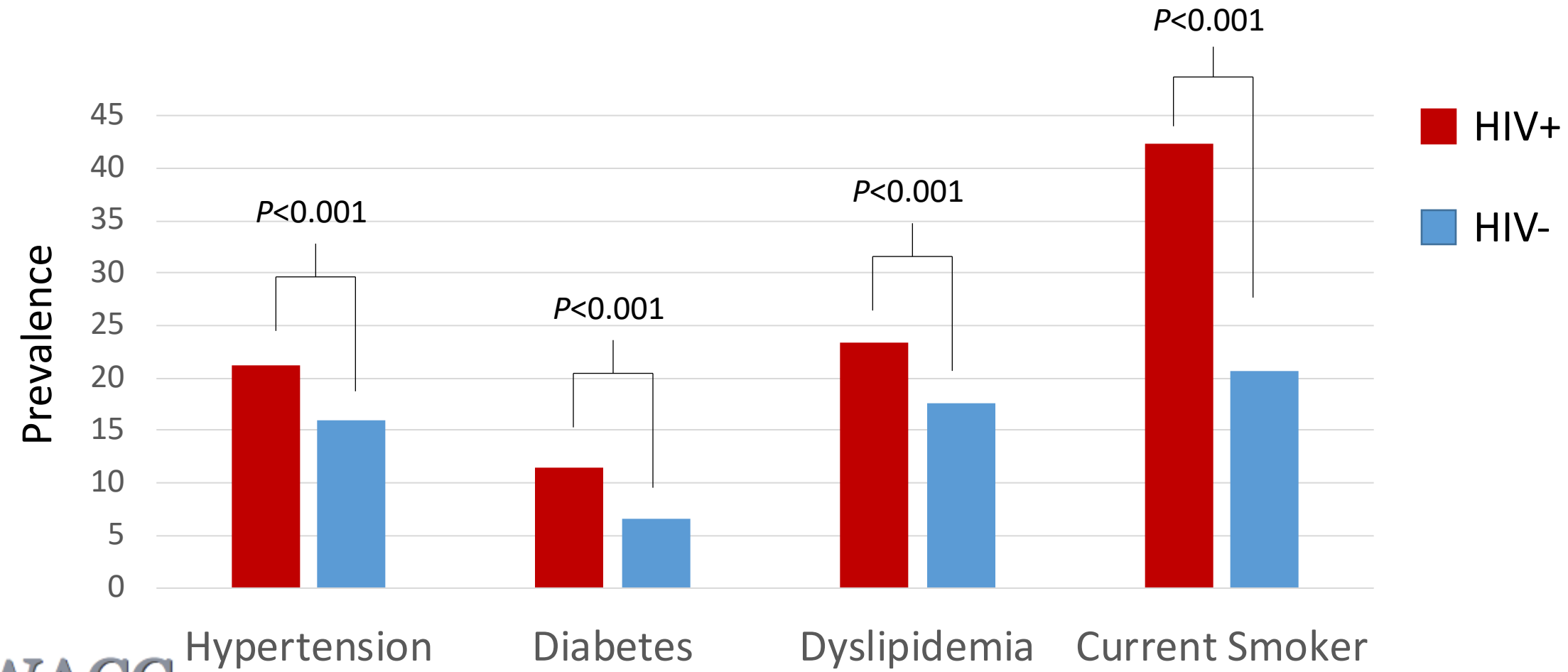
Ellerbrock et al, JAMA, 2000

HIV and Cancer Risk



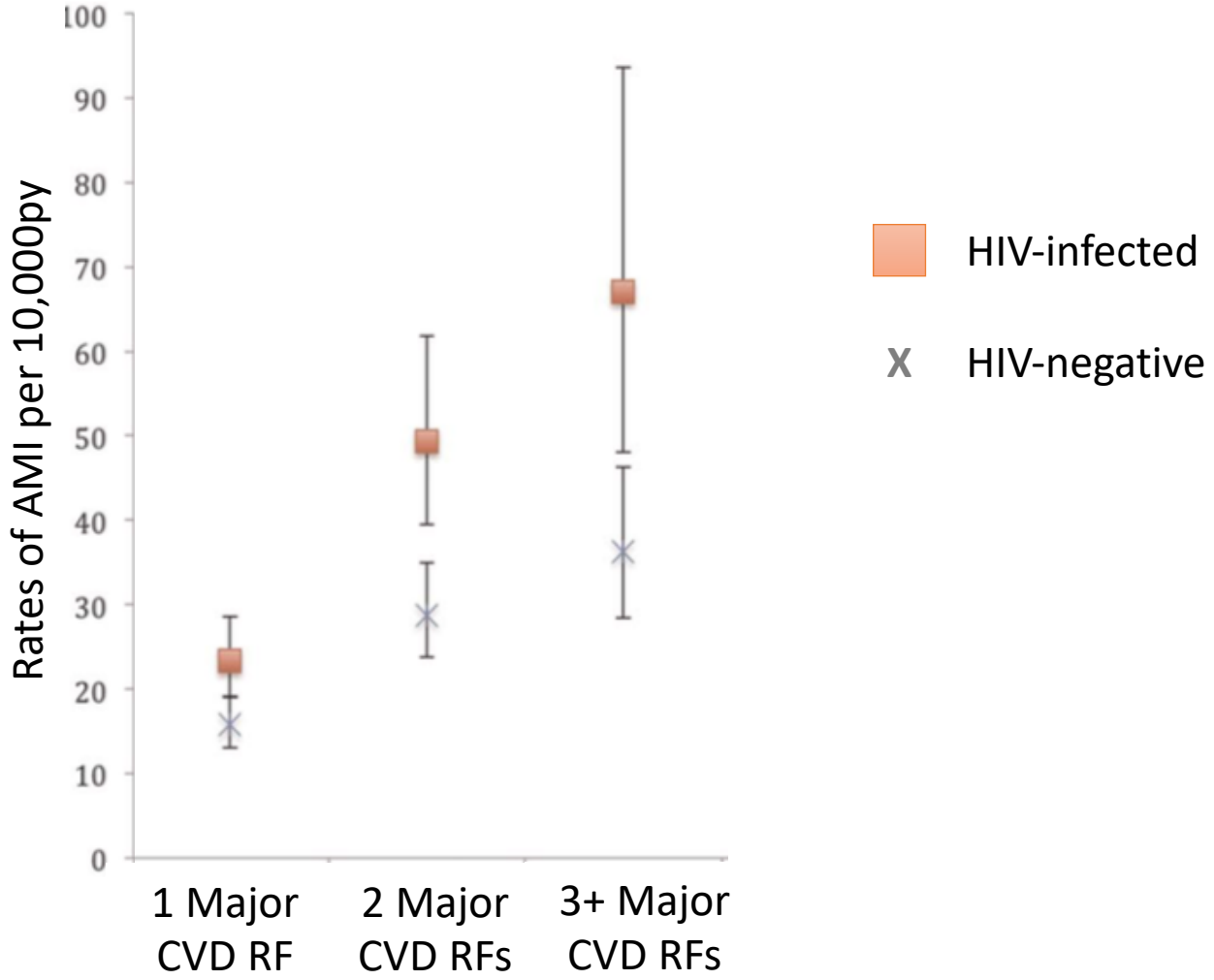
Trickey et al, PLoS One, 2016

HIV and Traditional Risk Factors in the US



Triant et al, J Clin Endo, 2007
Mdodo, Ann Int Med, 2015

Traditional Risk Factors Not the Whole Story



Paisable et al, JAIDS, 2015

Question 1

Does treated HIV infection increase risk of CVD events in sub-Saharan Africa?

A. Yes
B. No
C. Who knows?

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A. Yes
B. No
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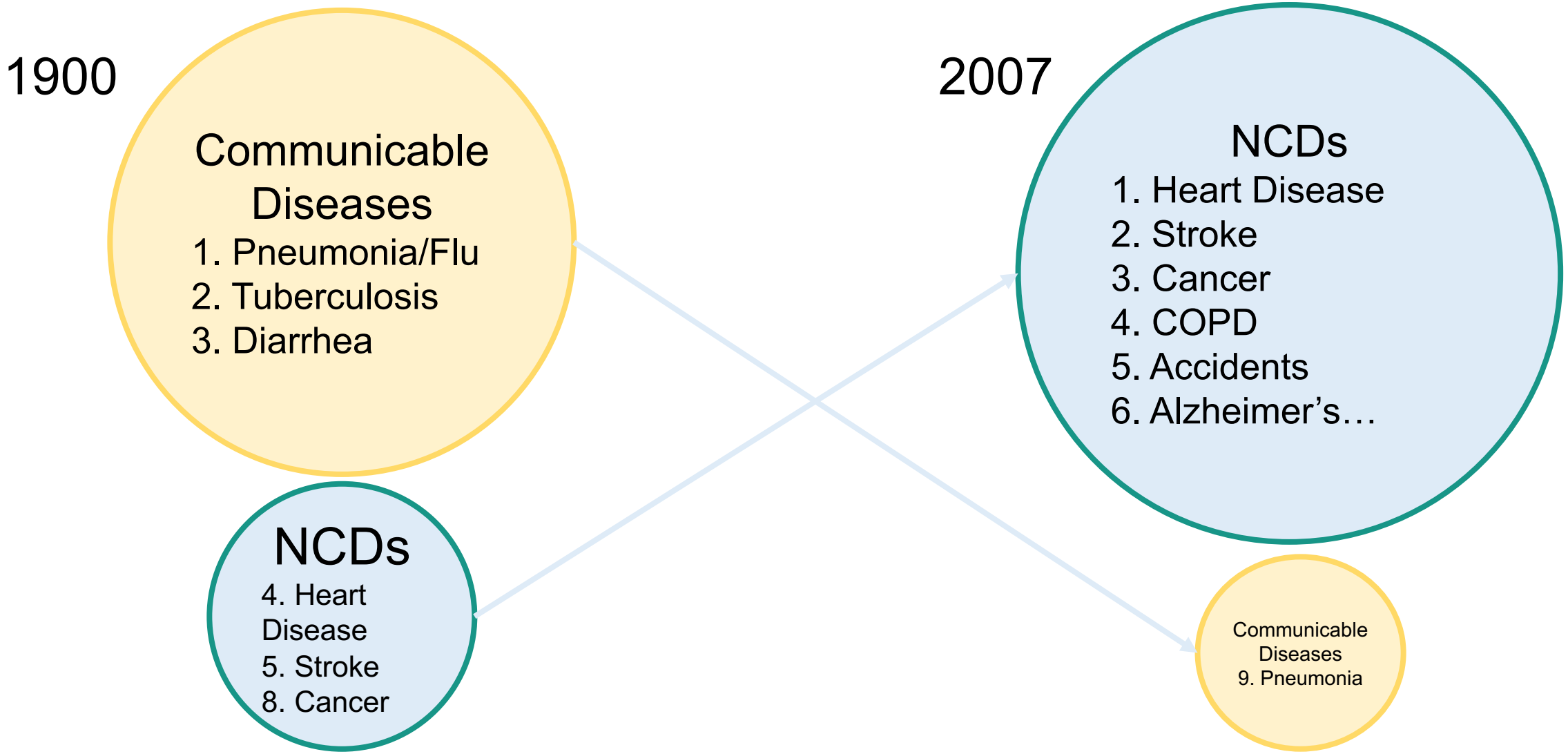
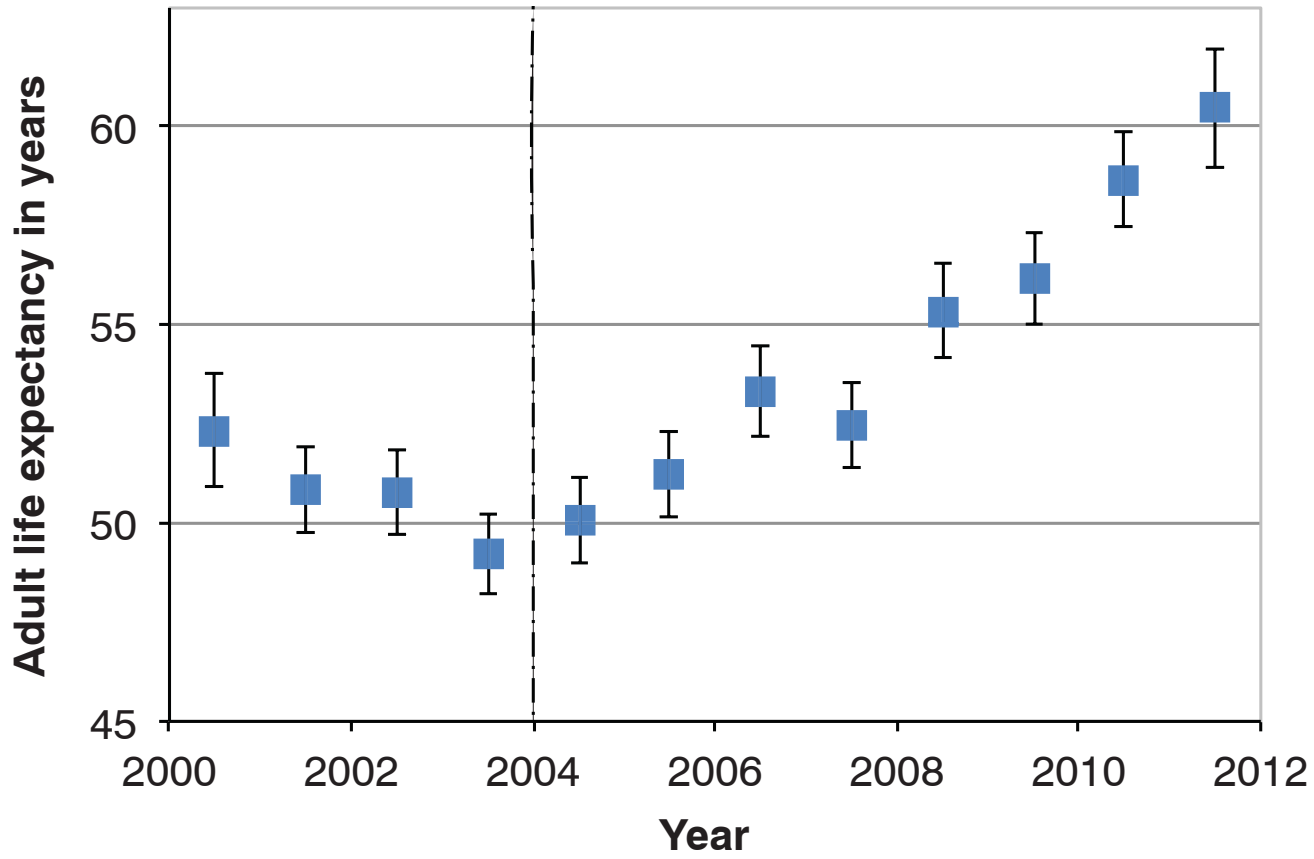
United States and Europe

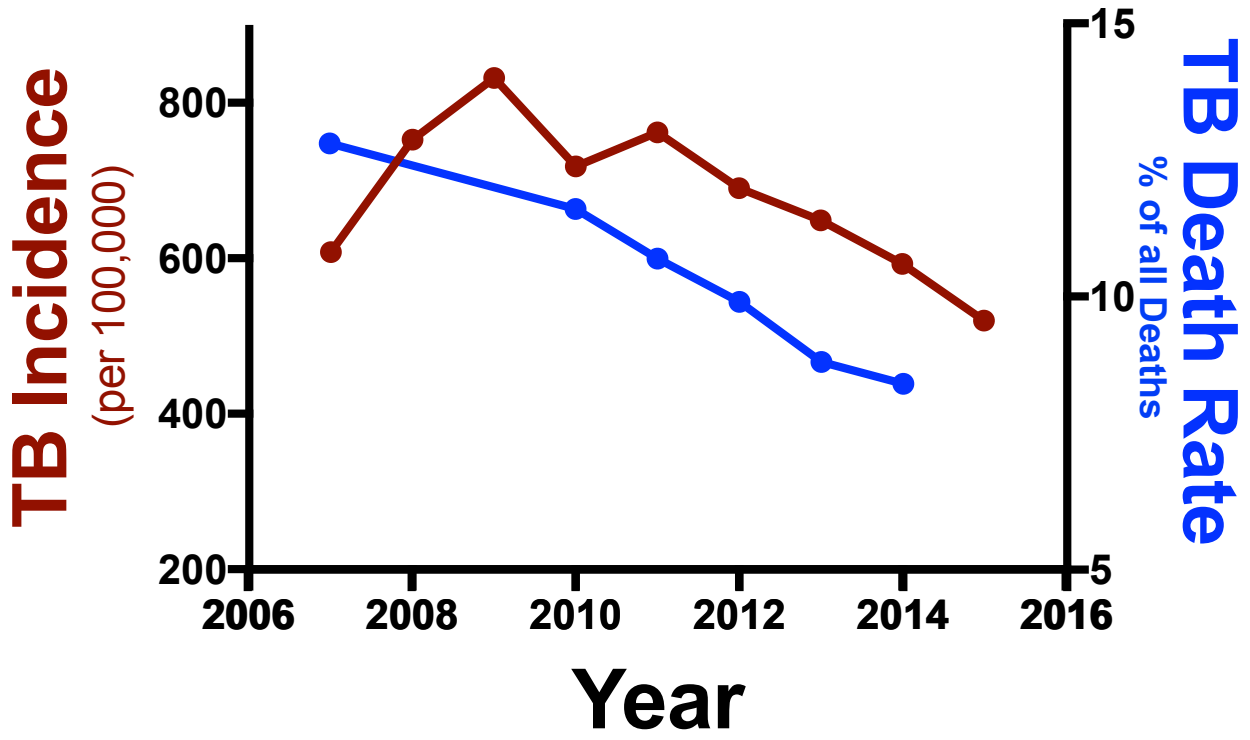


Umkhanyakude District



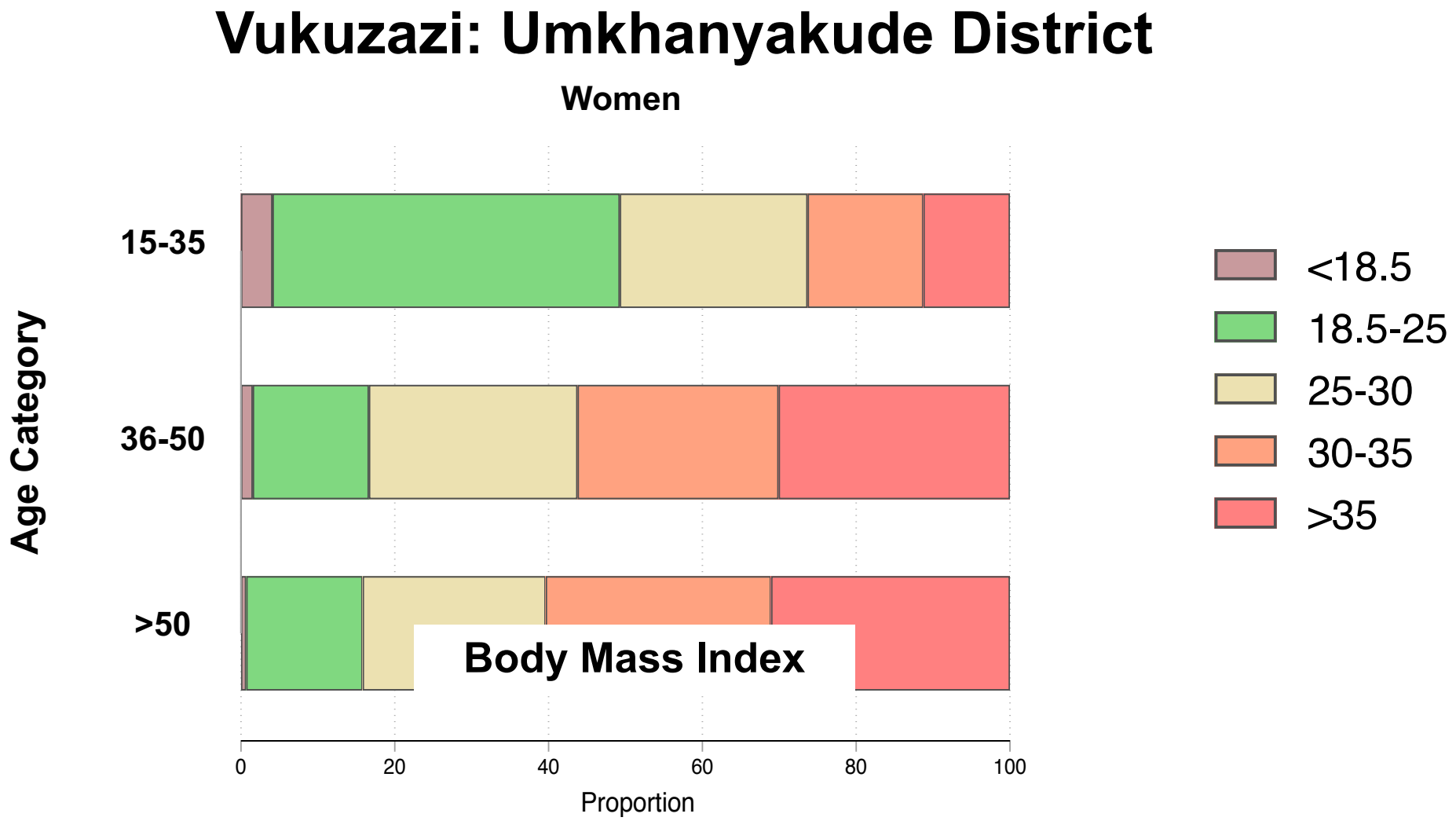
Bor et al, Science 2013

TB Epidemiology in South Africa

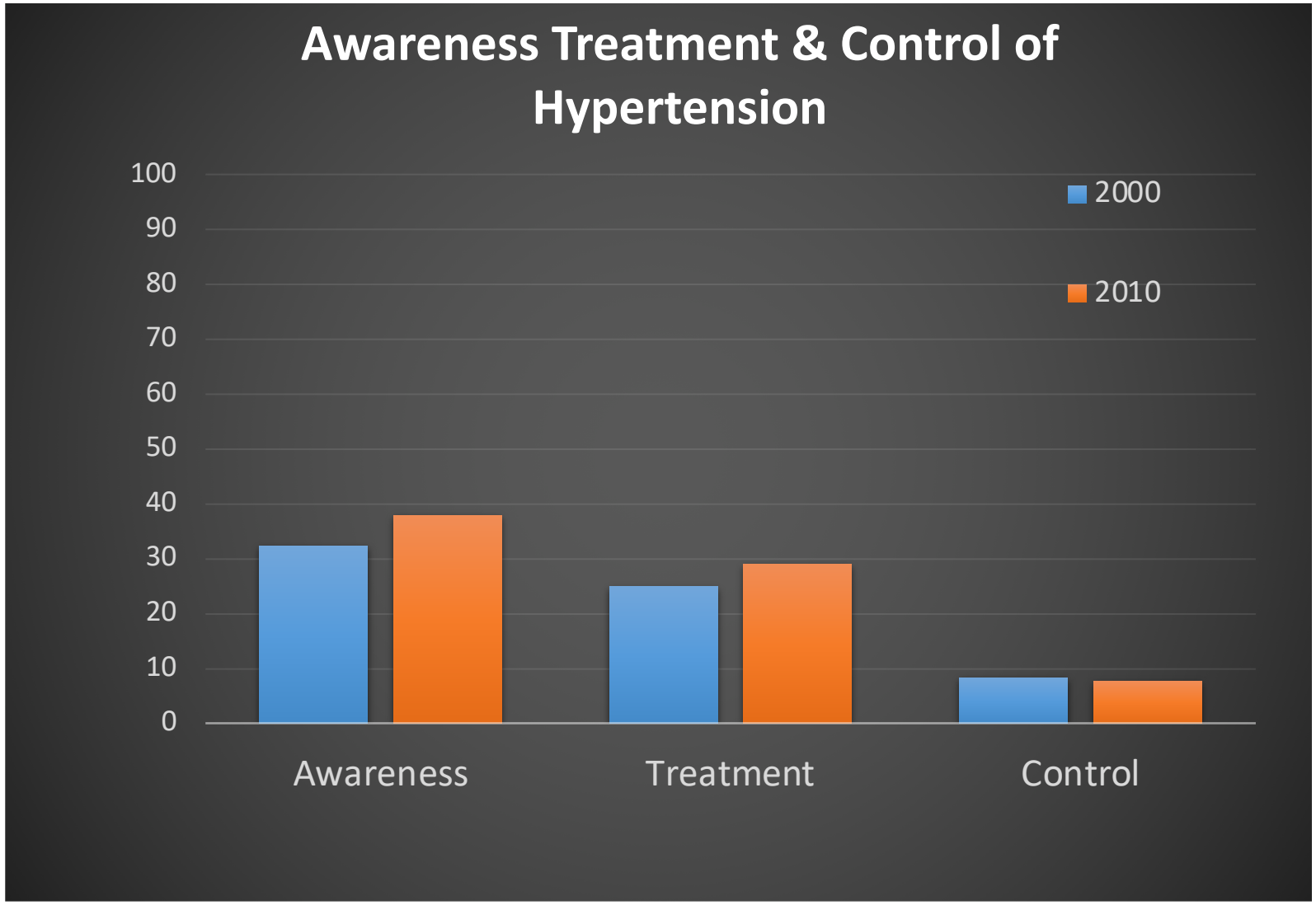


Global Tuberculosis Control 2016, WHO

Obesity in Rural KwaZulu-Natal

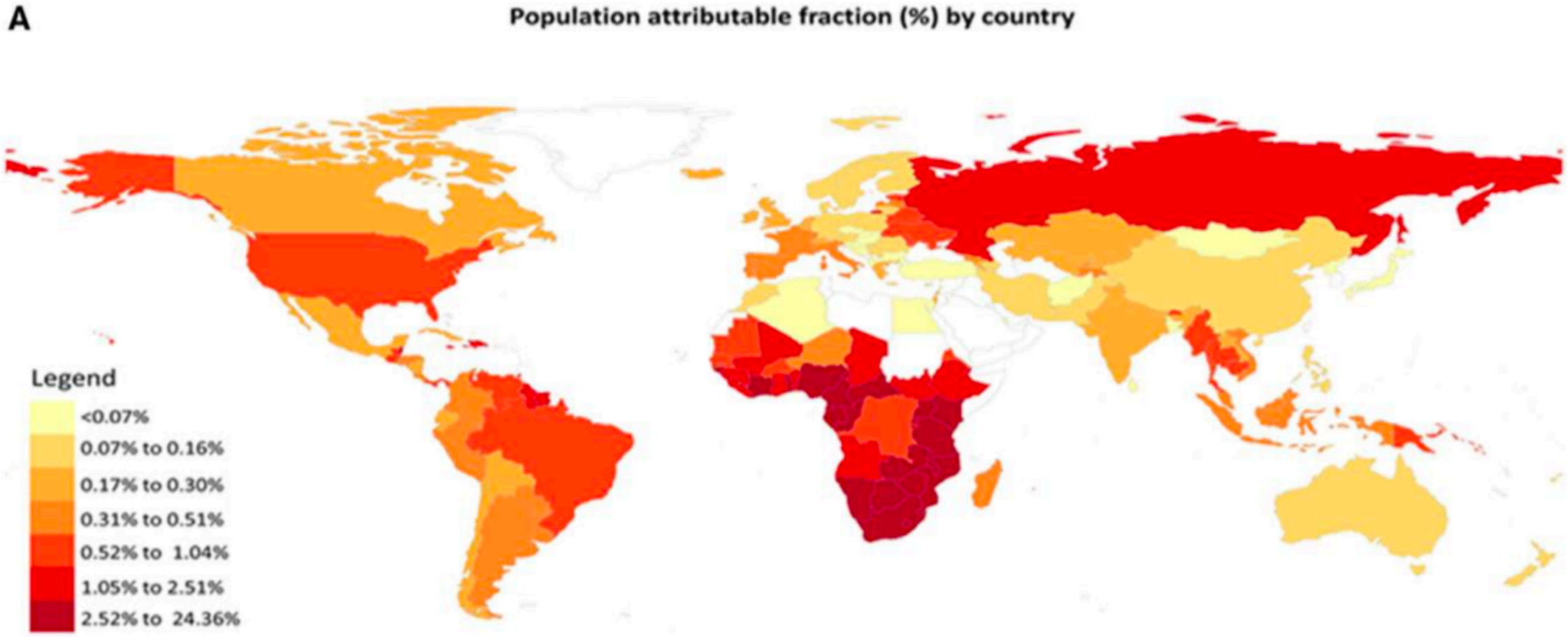


Awareness & Control of Hypertension in SA



Mills et al, Circulation, 2016

HIV and CAD Attributable Risk

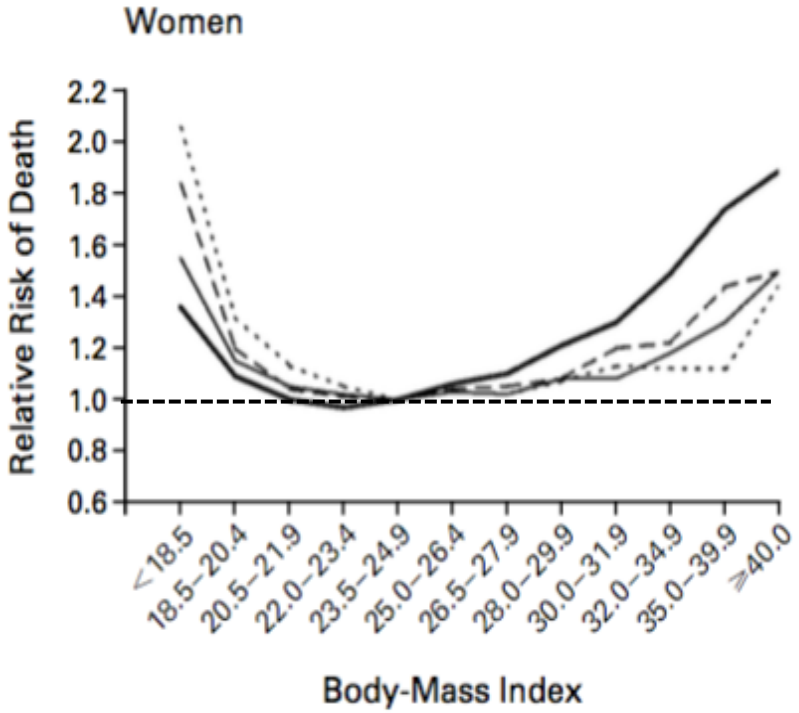


Shah et al, Circulation, 2018

Do NCD Risk Scores Apply in South Africa

Obesity and All-Cause Mortality

United States



Calle et al, NEJM 1999

Obesity and All-Cause Mortality

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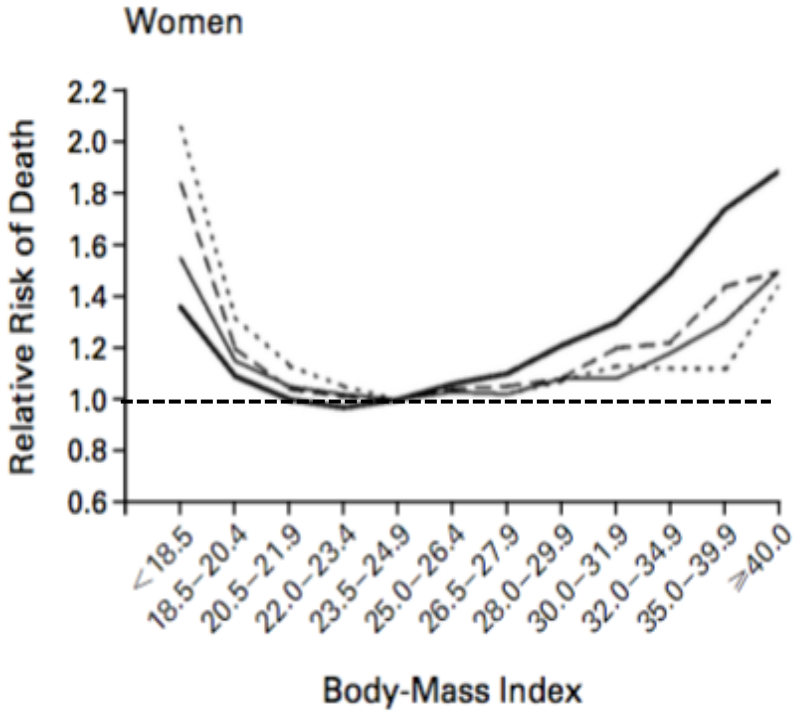
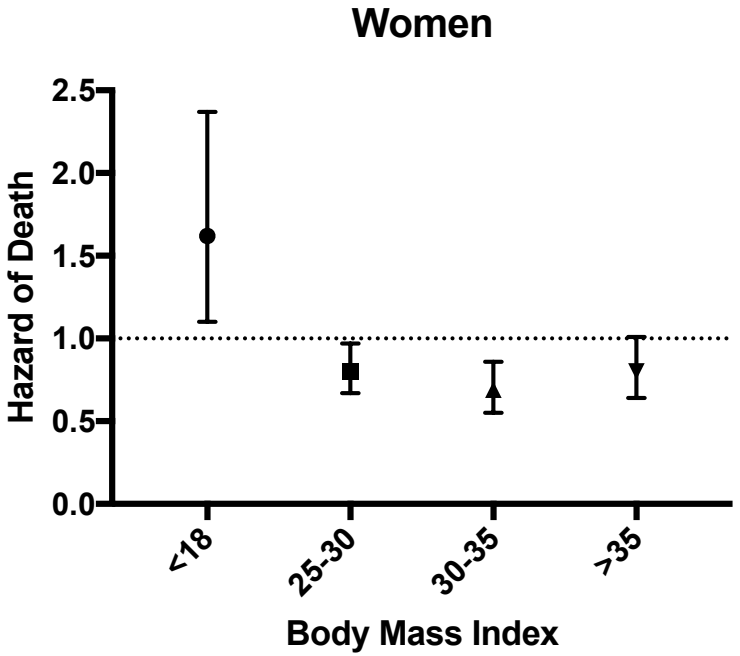
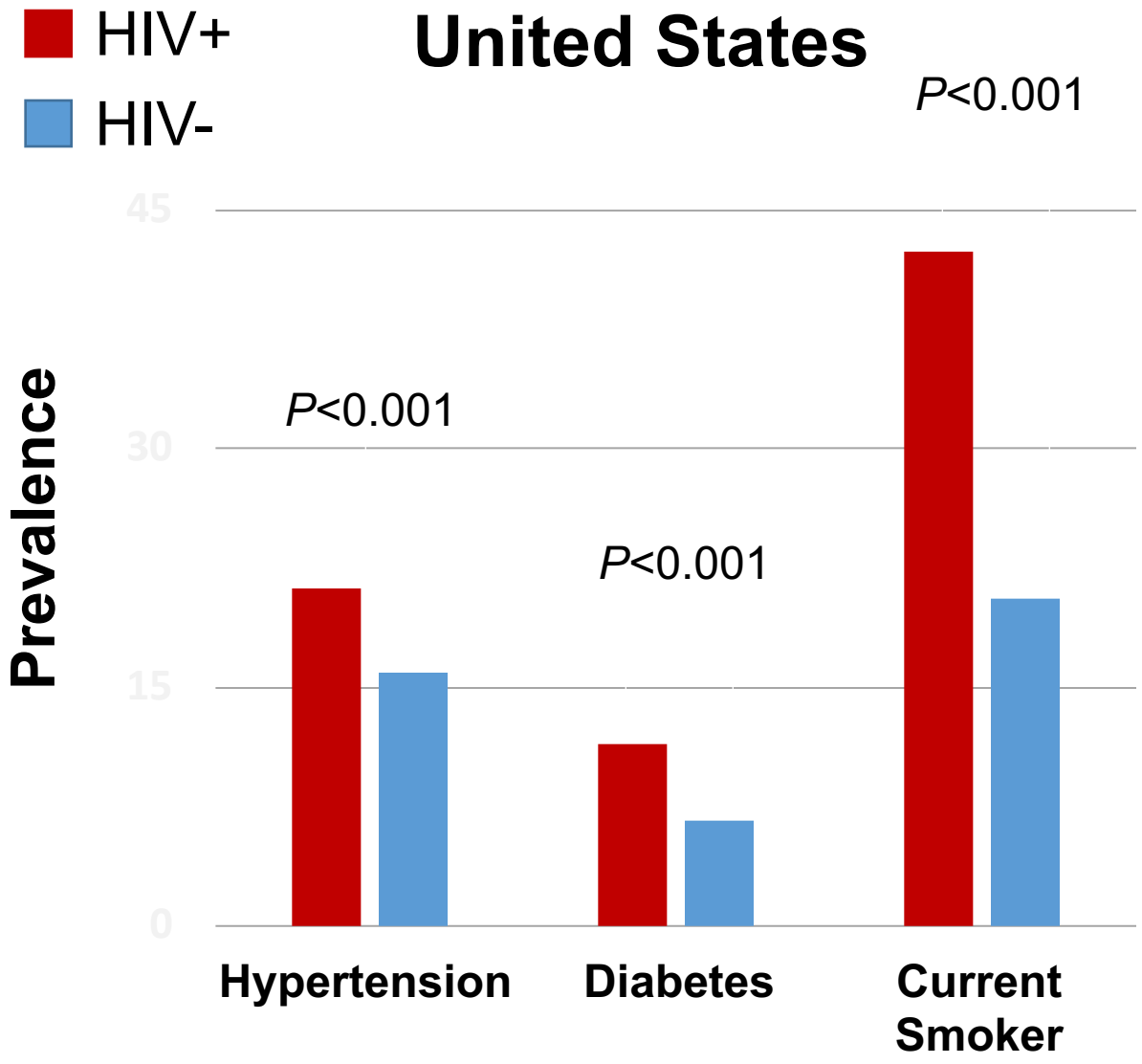


Vukuzazi: Umkhanyakude District



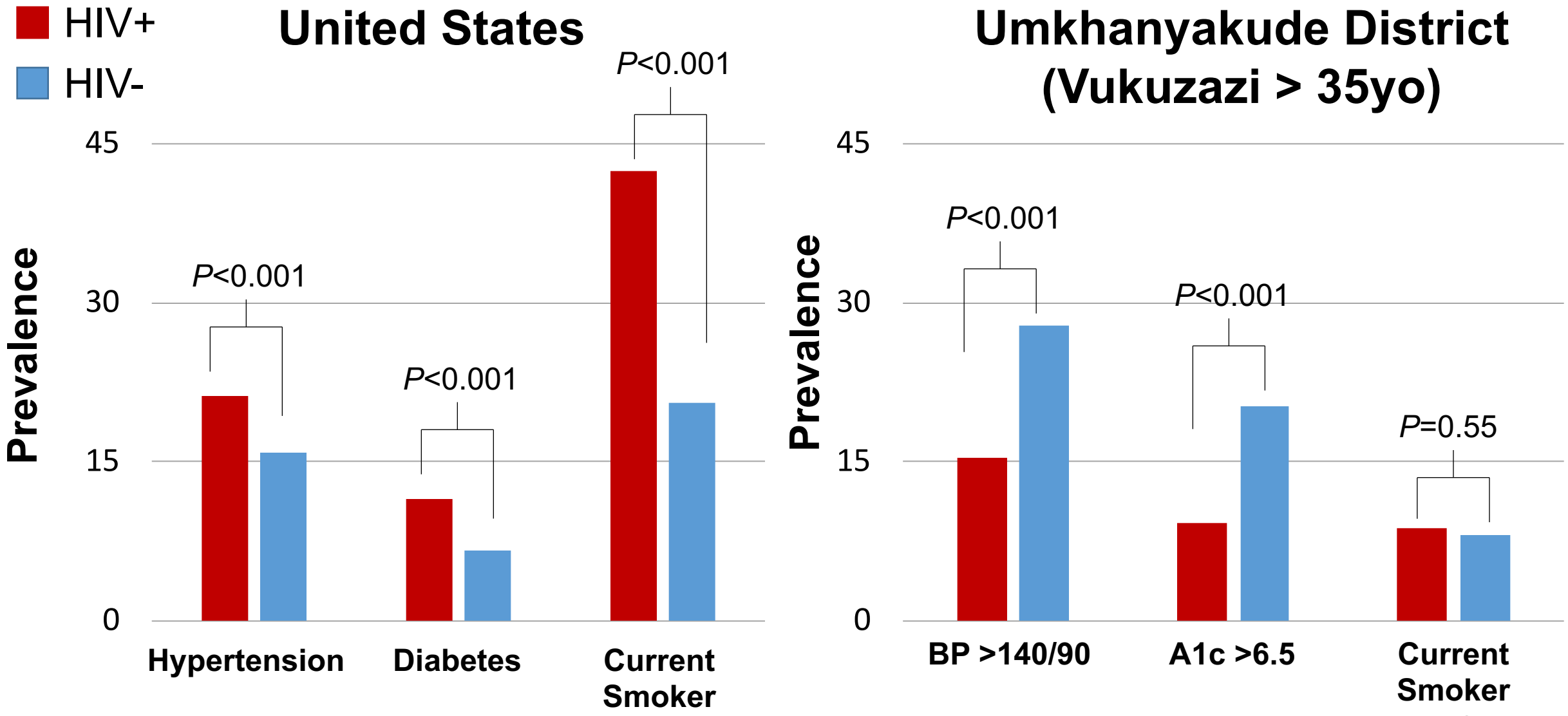
Calle et al, NEJM 1999
Siedner et al, *in preparation*

HIV and CVD Risk Factors



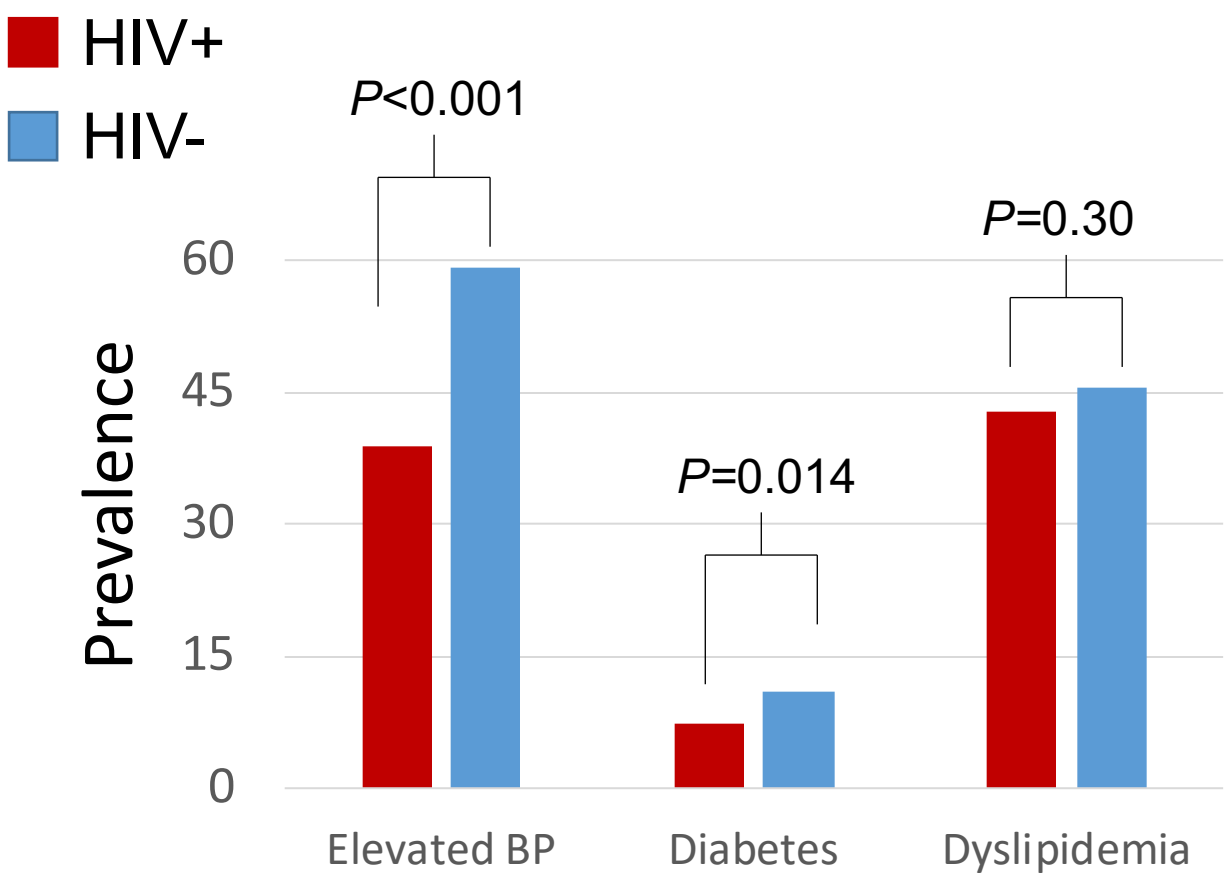
Triant et al, J Clin Endo, 2007
Mdodo, Ann Int Med, 2015

HIV and CVD Risk Factors

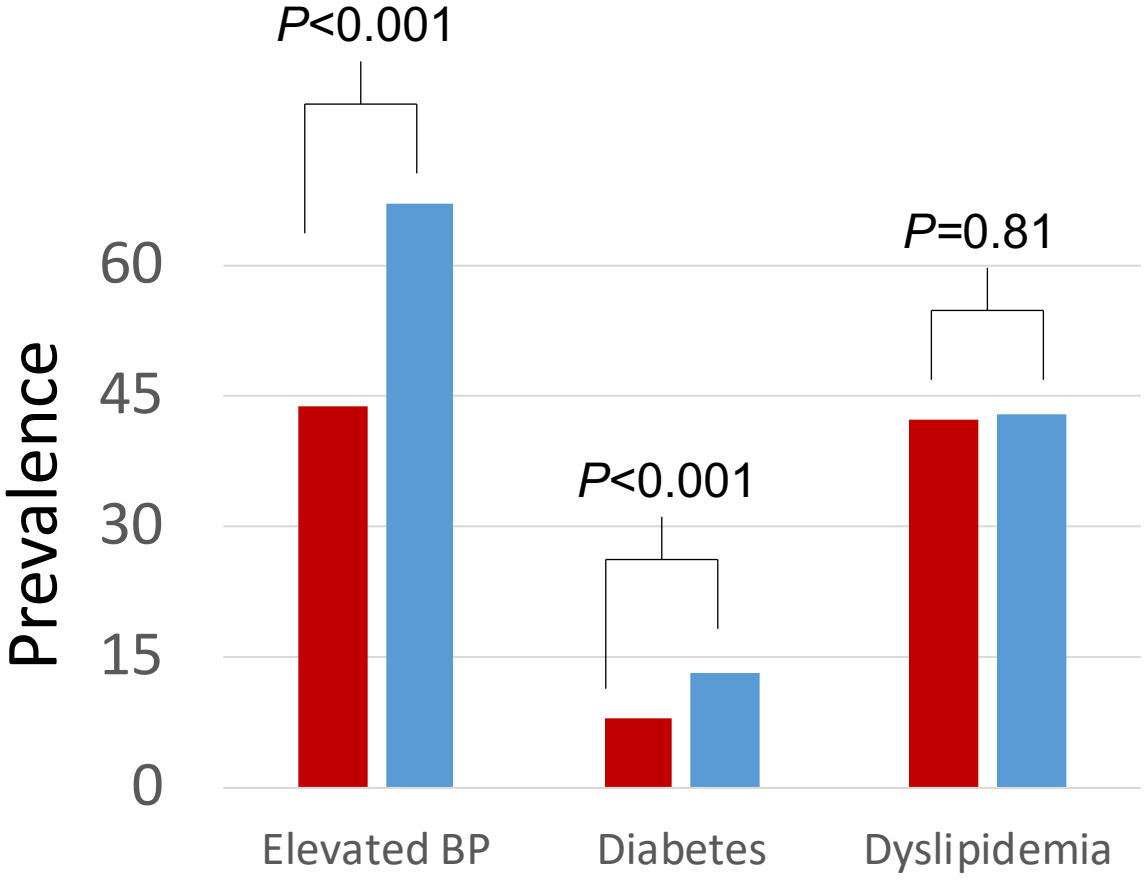


Triant et al, J Clin Endo, 2007
Mdodo, Ann Int Med, 2015

HIV and CVD Risk



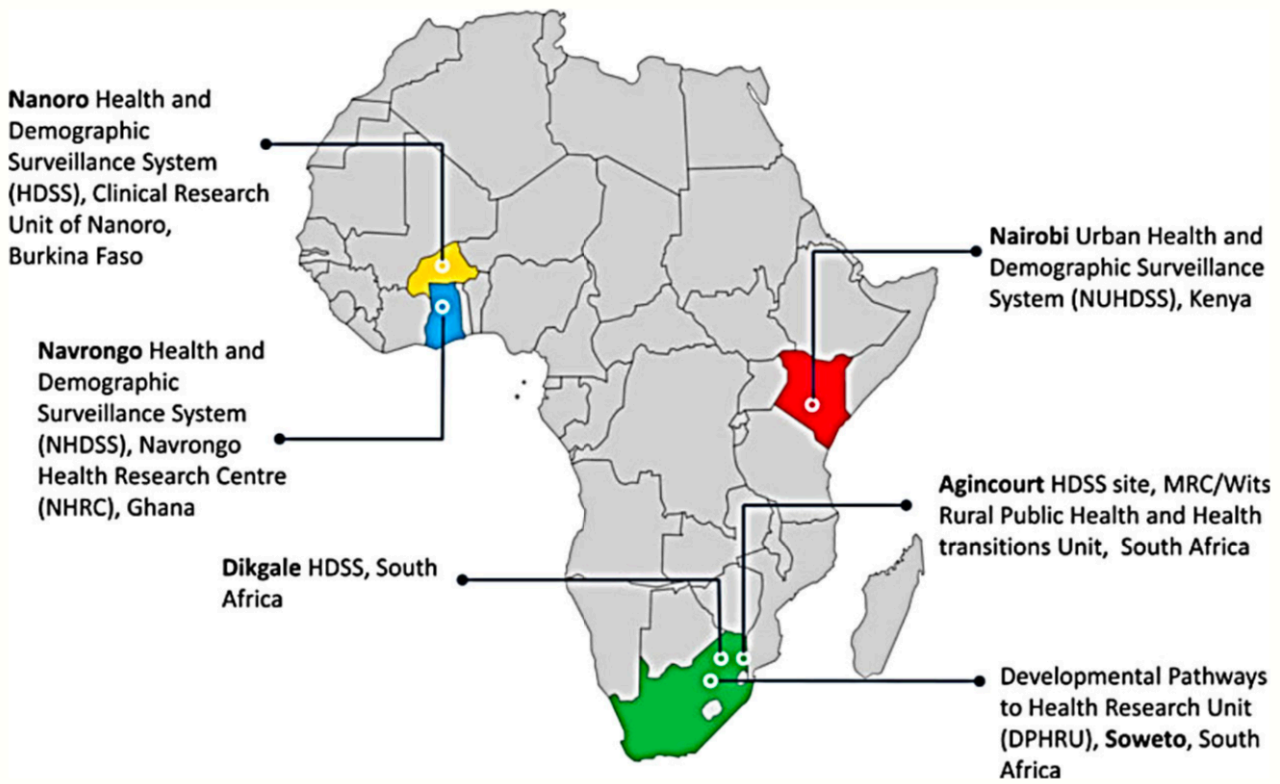
Males



Females

Gaziano et al, BMC Public Health, 2017

HIV and Carotid Intima Media Thickness

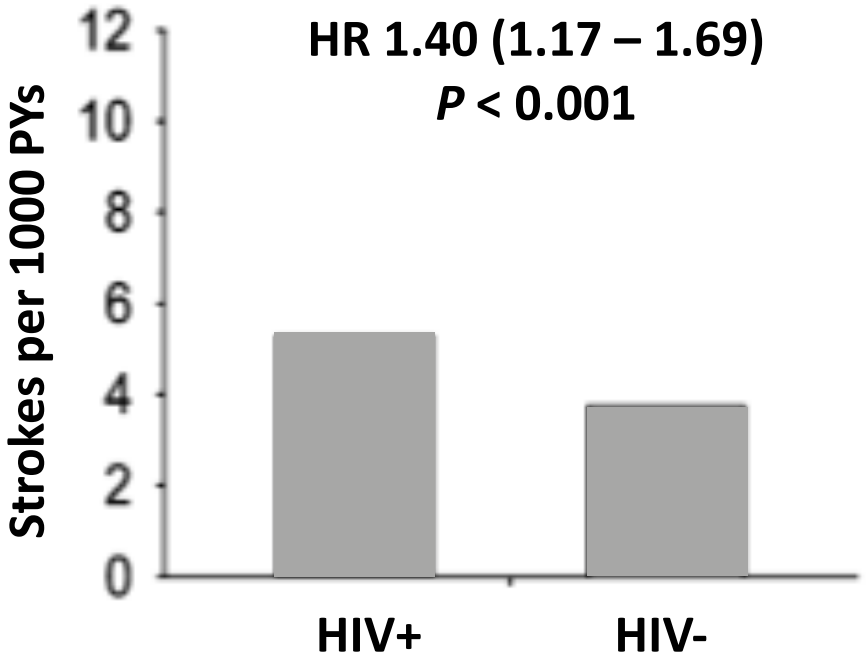


Risk Factors	Model 4	
	ß-Coefficients (95% CI)	*P* Value
Age in y	6.77 (6.34, 7.19)	<0.001
Men vs women	10.32 (4.75, 15.90)	<0.001
Current vs never/previous smoking	6.26 (−0.83, 13.35)	0.084
SBP per 10 mm Hg	7.52 (6.21, 8.83)	<0.001
Glucose per 1 mmol/L	0.94 (−0.67, 2.56)	0.252
HDL per 1 mmol/L	−12.15 (−17.88, −6.41)	<0.001
HIV+ vs HIV−	−8.86 (−15.70, −2.03)	0.011
Primary	−4.03 (−11.29, 3.24)	0.625
Secondary	−7.77 (−8.66, 7.11)	
Tertiary	−3.81 (−18.60, 10.98)	
Household SES		
Poorest	Ref (0)	Ref (0)
Poorer	−0.11 (−8.27, 8.04)	0.096
Poor	−2.77 (−10.98, 5.44)	
Less poor	−7.18 (−15.20, 0.85)	
Least	1.78 (−6.29, 9.85)	
HIV+ vs HIV−	−8.86 (−15.70, −2.03)	0.011

Nantero et al, J AHA, 2019

HIV and Stroke Risk

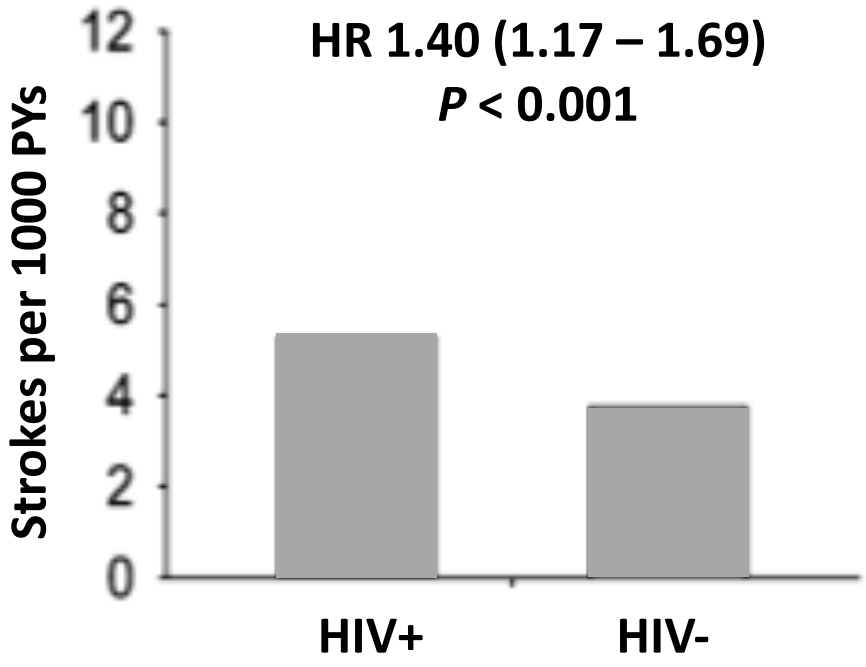
United States
HIV and Stroke Incidence



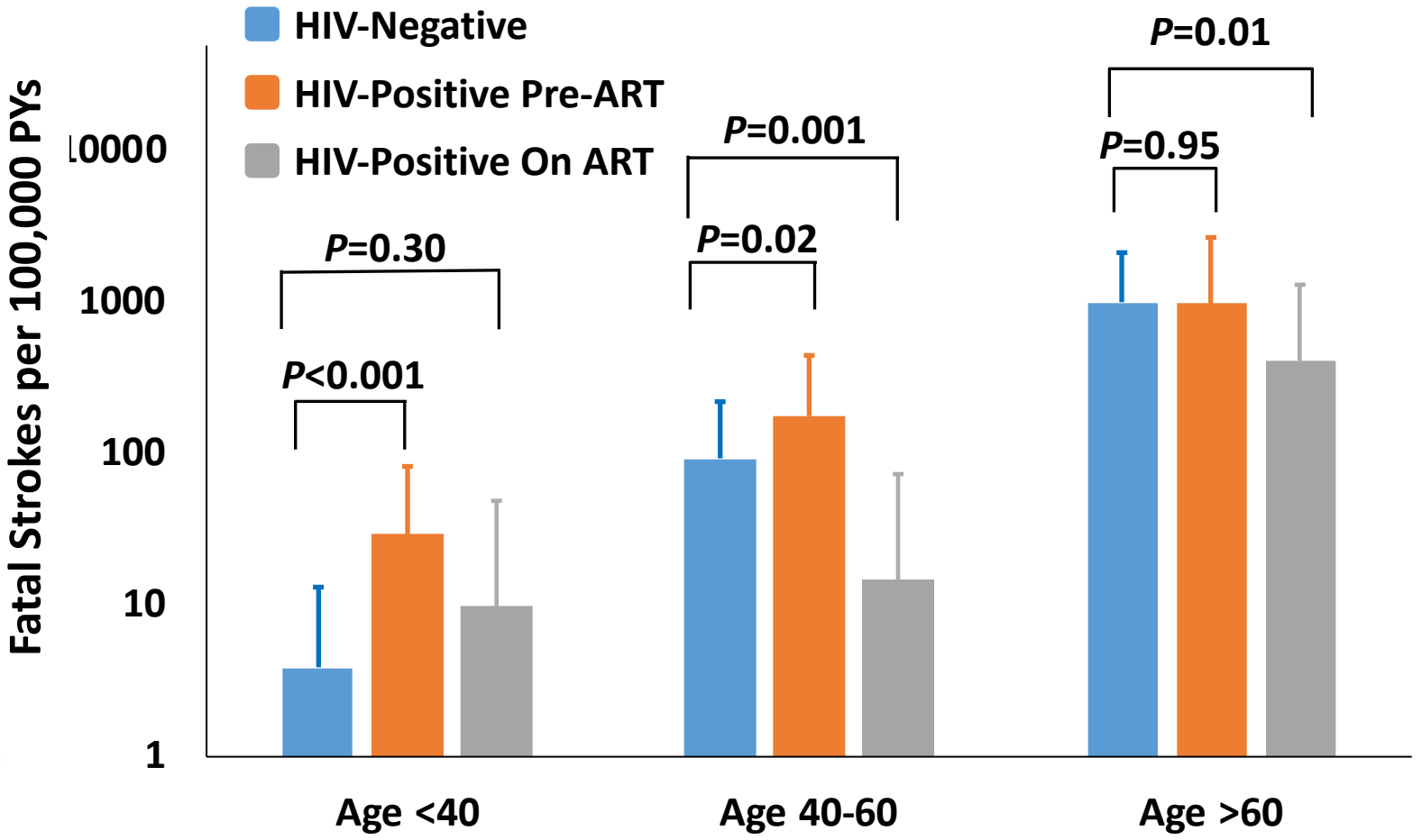
Chow et al, AIDS, 2012

HIV and Stroke Risk

United States
HIV and Stroke Incidence



Umkhanyakude District
HIV and Fatal Stroke Incidence



Chow et al, AIDS, 2012
Siedner et al, 2018 *IAS Conference*

HIV 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%**

Benjamin et al, Neurology, 2016

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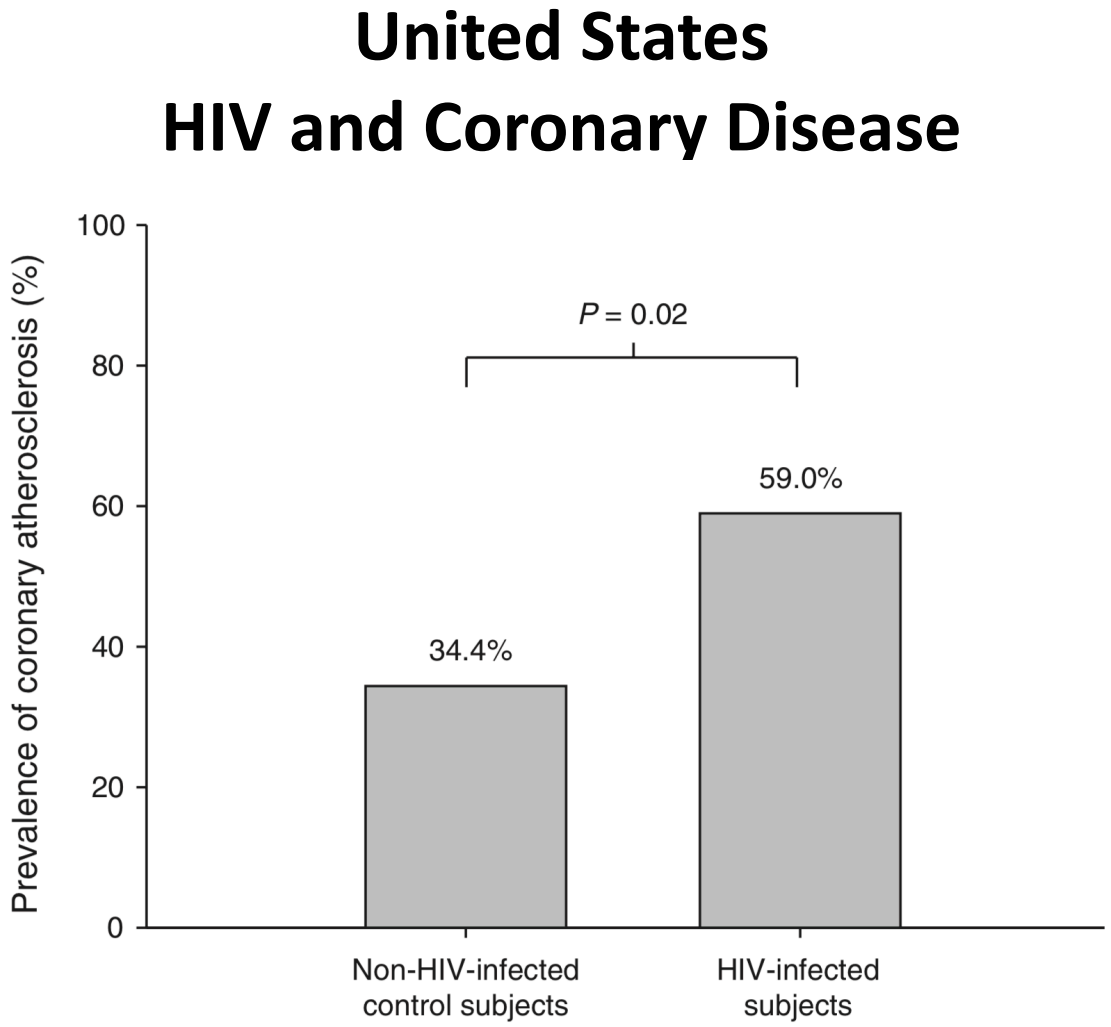
Current Smoker	2.36 (1.34 - 4.13)	0.003	6%
HIV Infection	3.28 (2.05 – 5.25)	<0.001	15%
Untreated	**4.48 (2.44 – 8.24)**	**<0.001**	
ART >6 months	**1.49 (0.72 – 3.07)**	**0.23**	

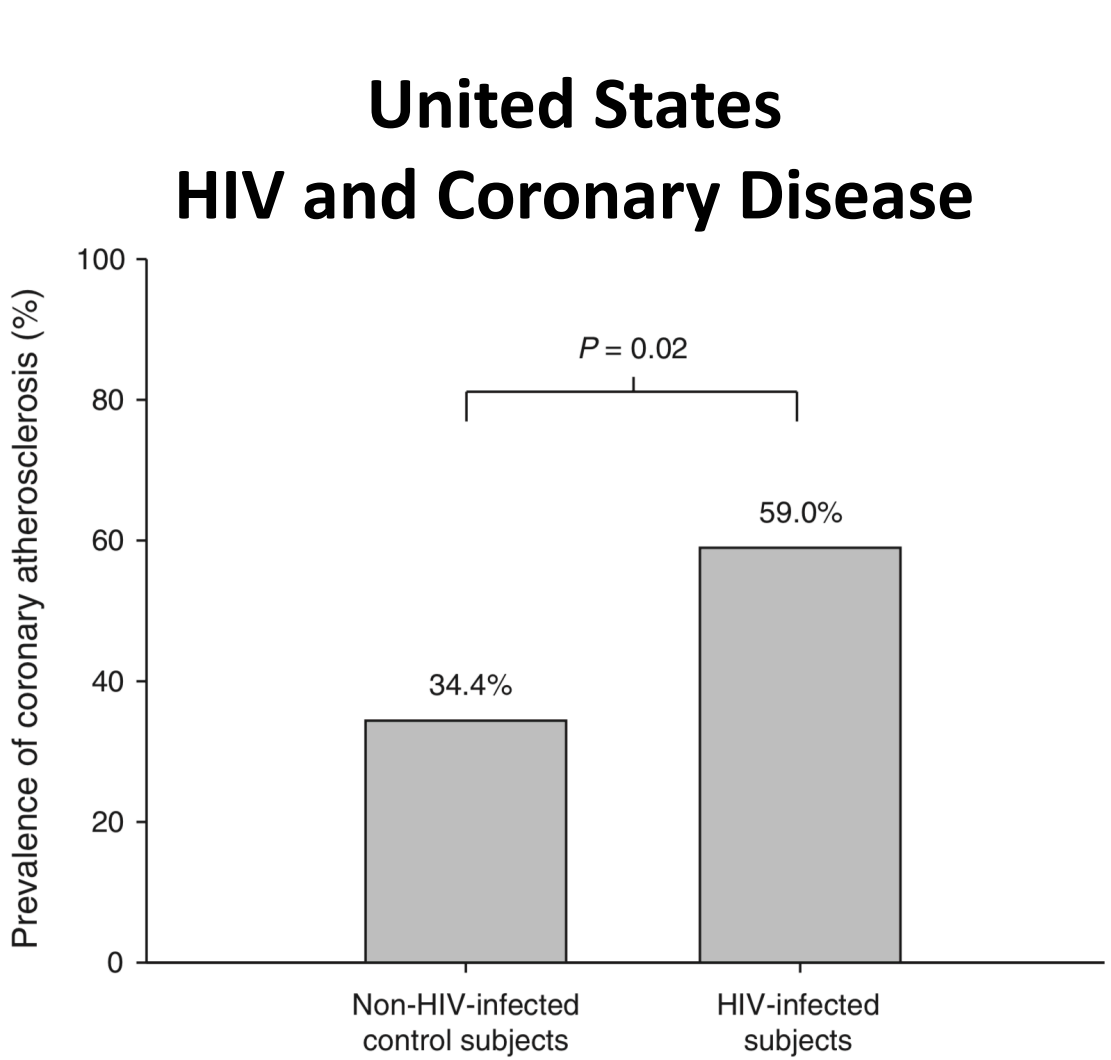
Benjamin et al, Neurology, 2016

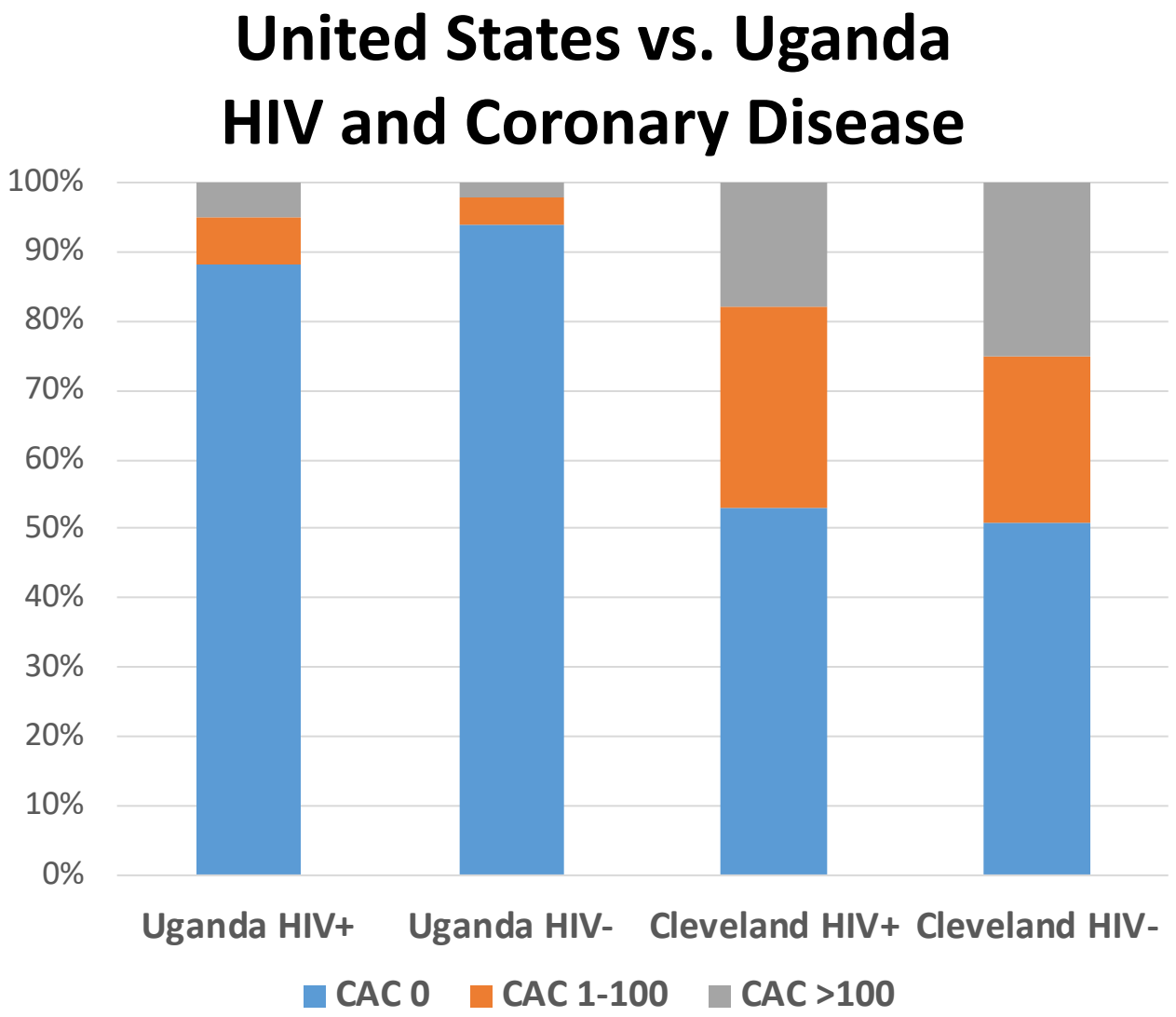
HIV and MI Risk



Lo et al, AIDS, 2010

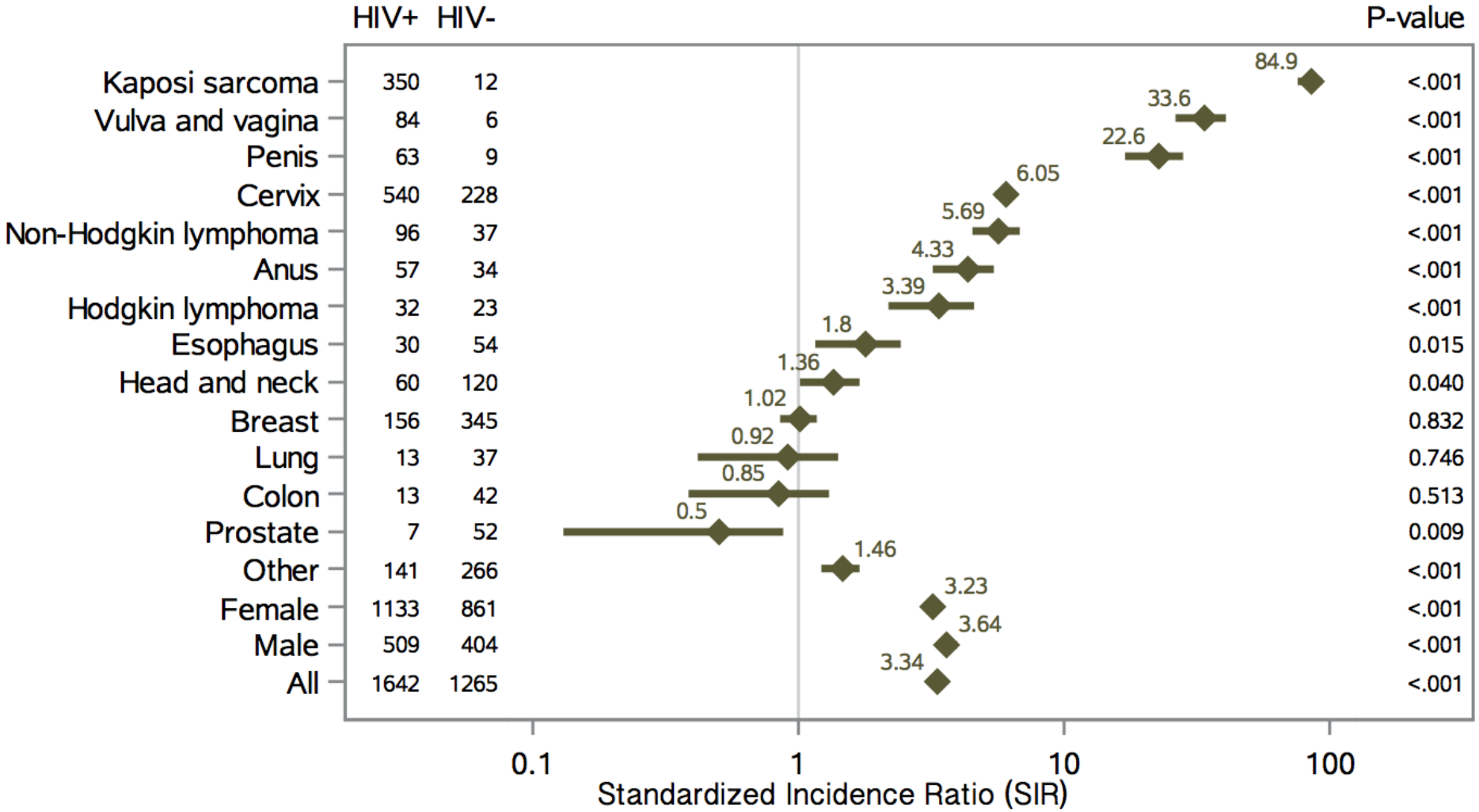
HIV and MI Risk





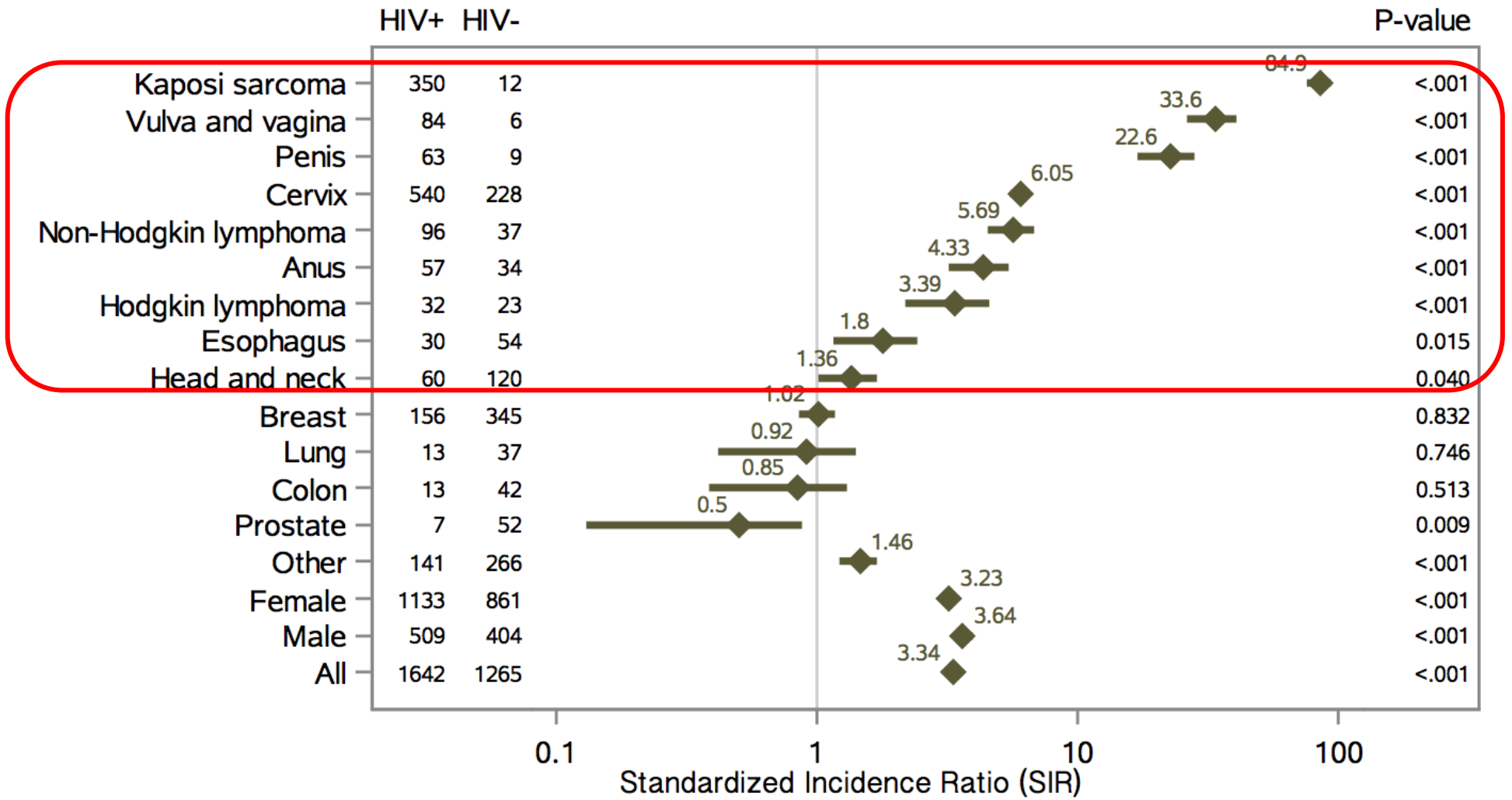
Lo et al, AIDS, 2010
Longenecker et al, Open Heart, 2019

HIV and Cancer Risk in Botswana



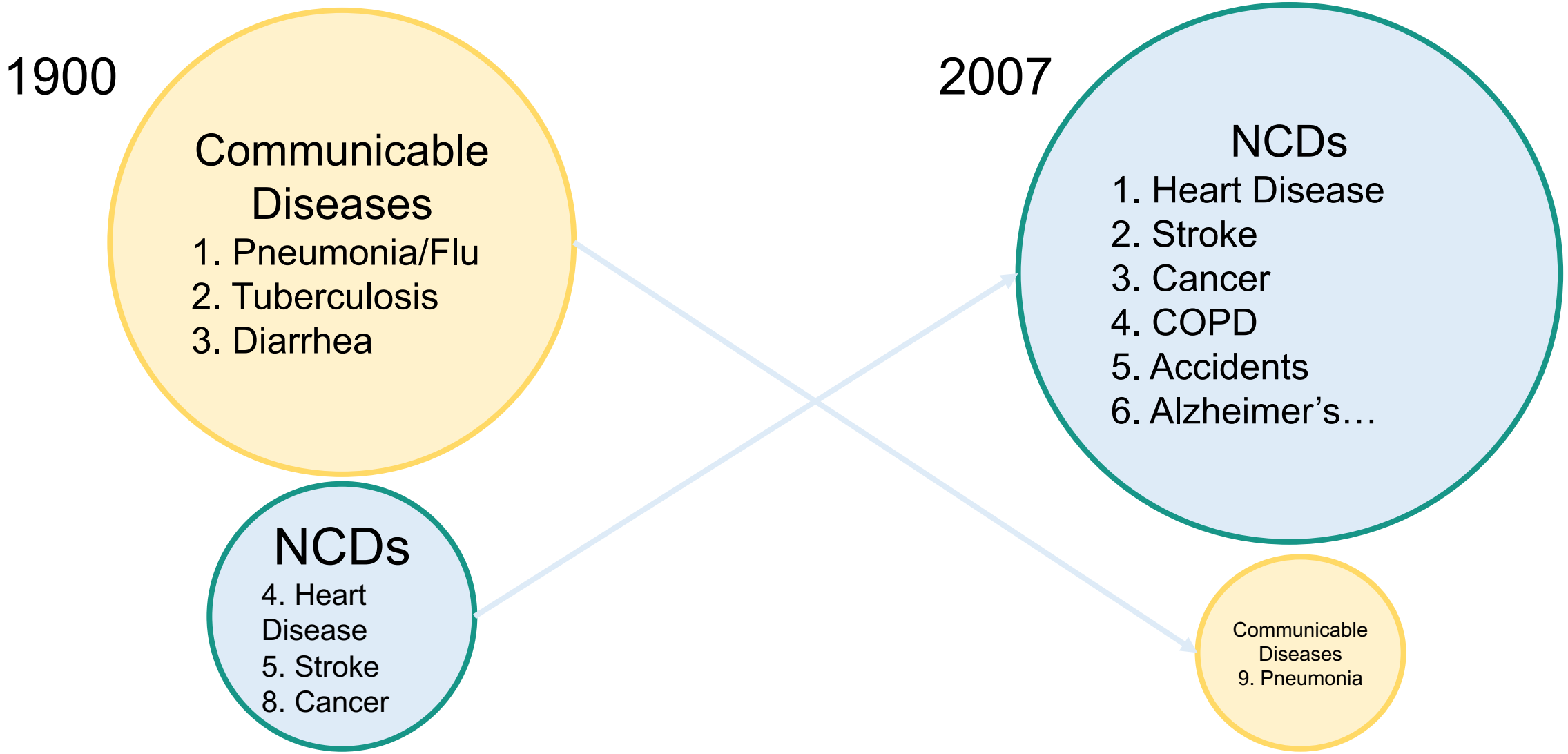
Dryden-Petersen et al, CROI, 2018

HIV and Cancer Risk in Botswana



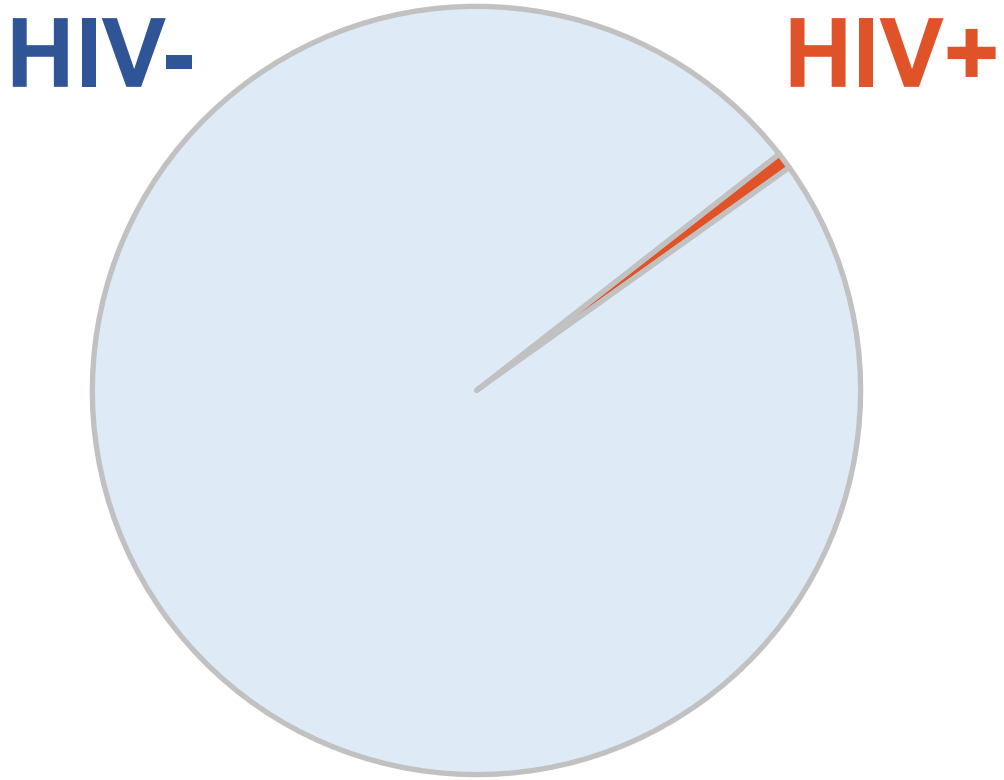
Dryden-Petersen et al, CROI, 2018

United States and Europe



HIV Prevalence Ages 35-54

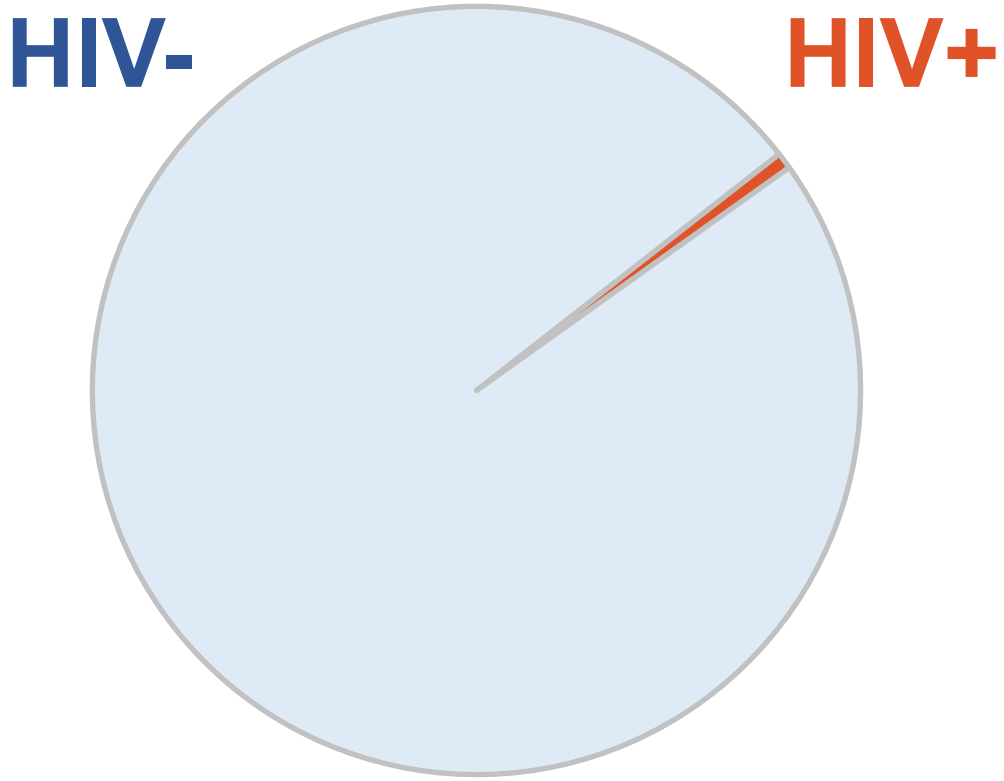
United States



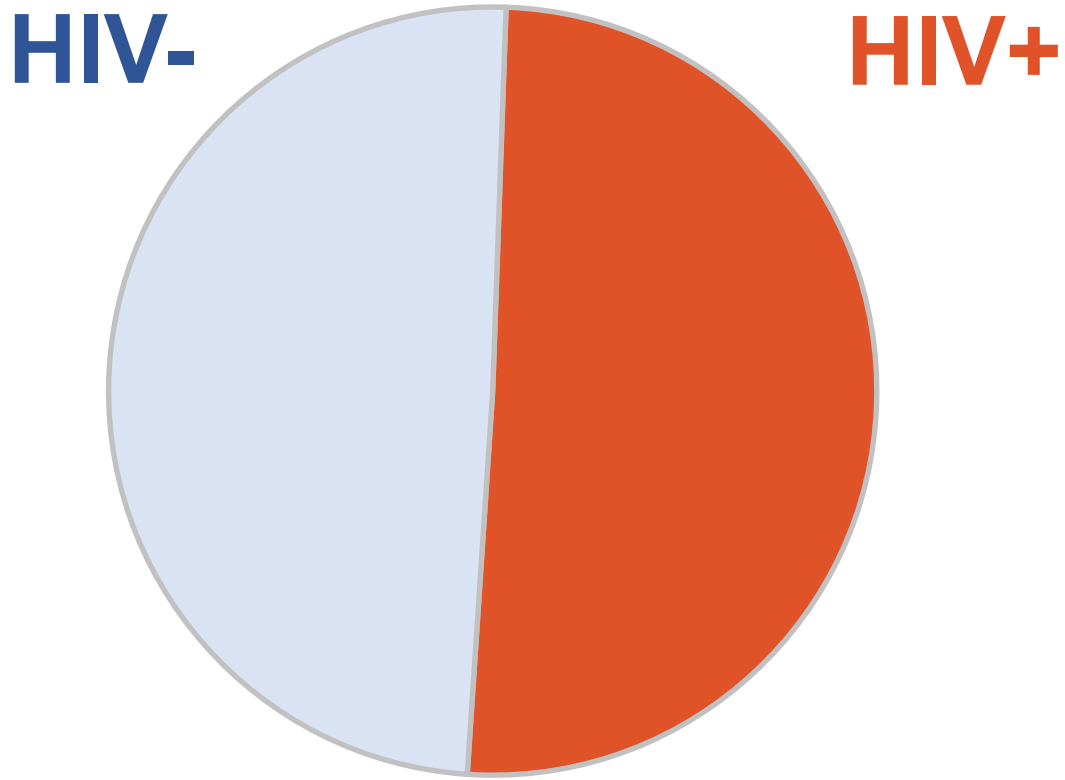
Source: CDC Surveillance Report 2018
Vukuzazi Study (through March 2019)

HIV Prevalence Ages 35-54

United States

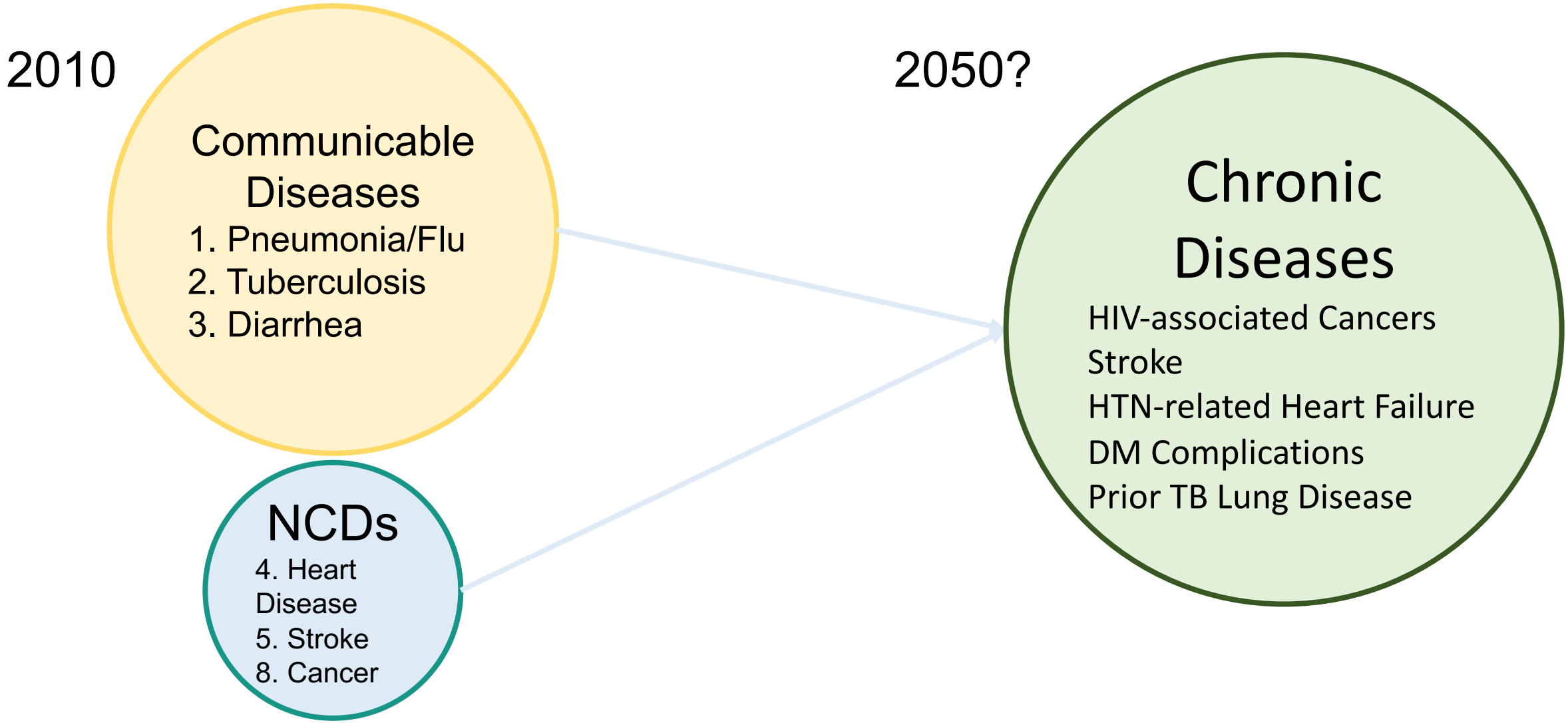


Vukuzazi: Umkhanyakude District



Source: CDC Surveillance Report 2018
Vukuzazi Study (through March 2019)

Sub-Saharan Africa?



Current Rural SA Health System

- Strong HIV treatment program

- Remainder of the chronic disease response
  - **0 Oncologists** in the public sector in uMkhanyakude District
  - **0 Cardiologists** in the public sector in uMkhanyakude District
  - **0 Neurologists** in the public sector in uMkhanyakude District
  - **0 CT scanners** in uMkhanyakude District

Question 2

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

A. Yes
B. No
C. 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**

SMART Study Group, NEJM, 2006

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

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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**

SMART Study Group, NEJM, 2006

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]	
≥500	1.75 (1.40-2.18)	.05
<500	1.39 (1.17-1.66)	

Freiberg et al, Ann Int Med, 2013

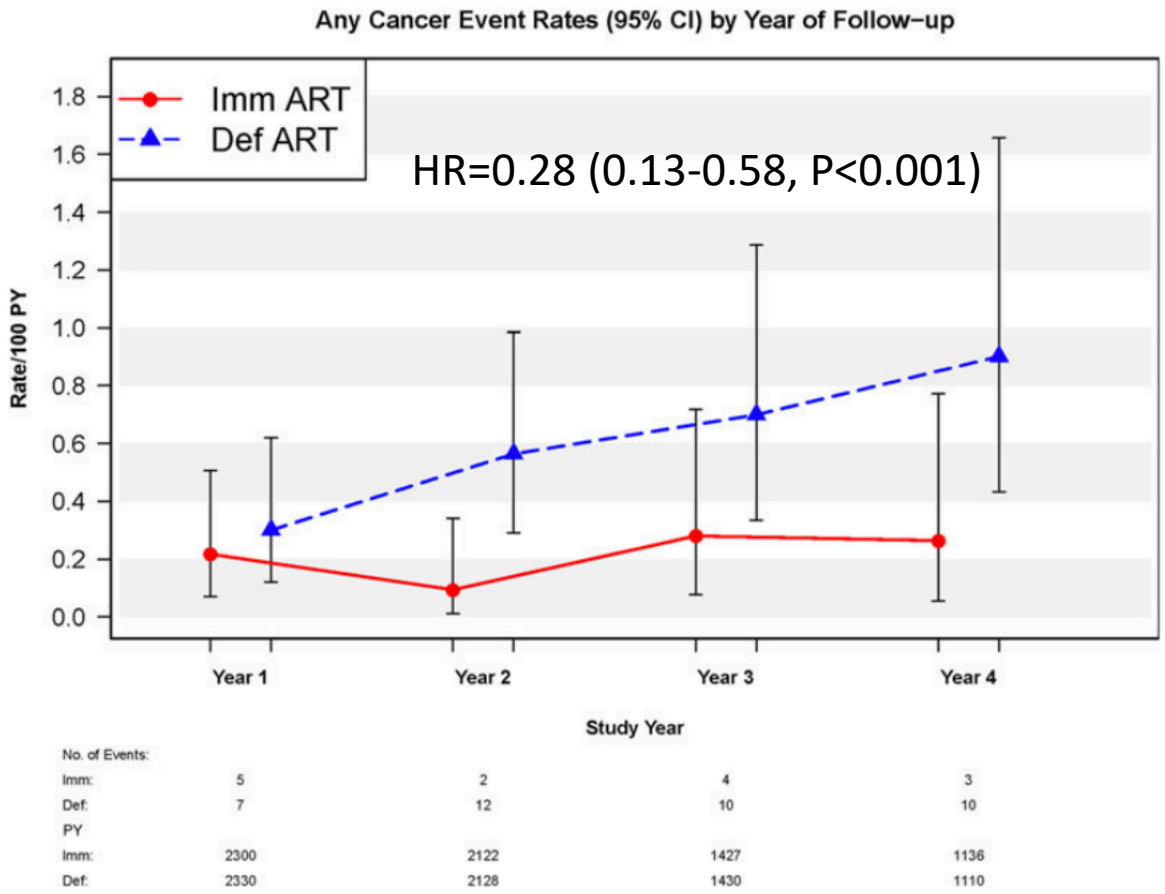
CD4, Viral Load and CVD Risk

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]	
<200	1.88 (1.46-2.40)	.04
≥200	1.43 (1.21-169)	

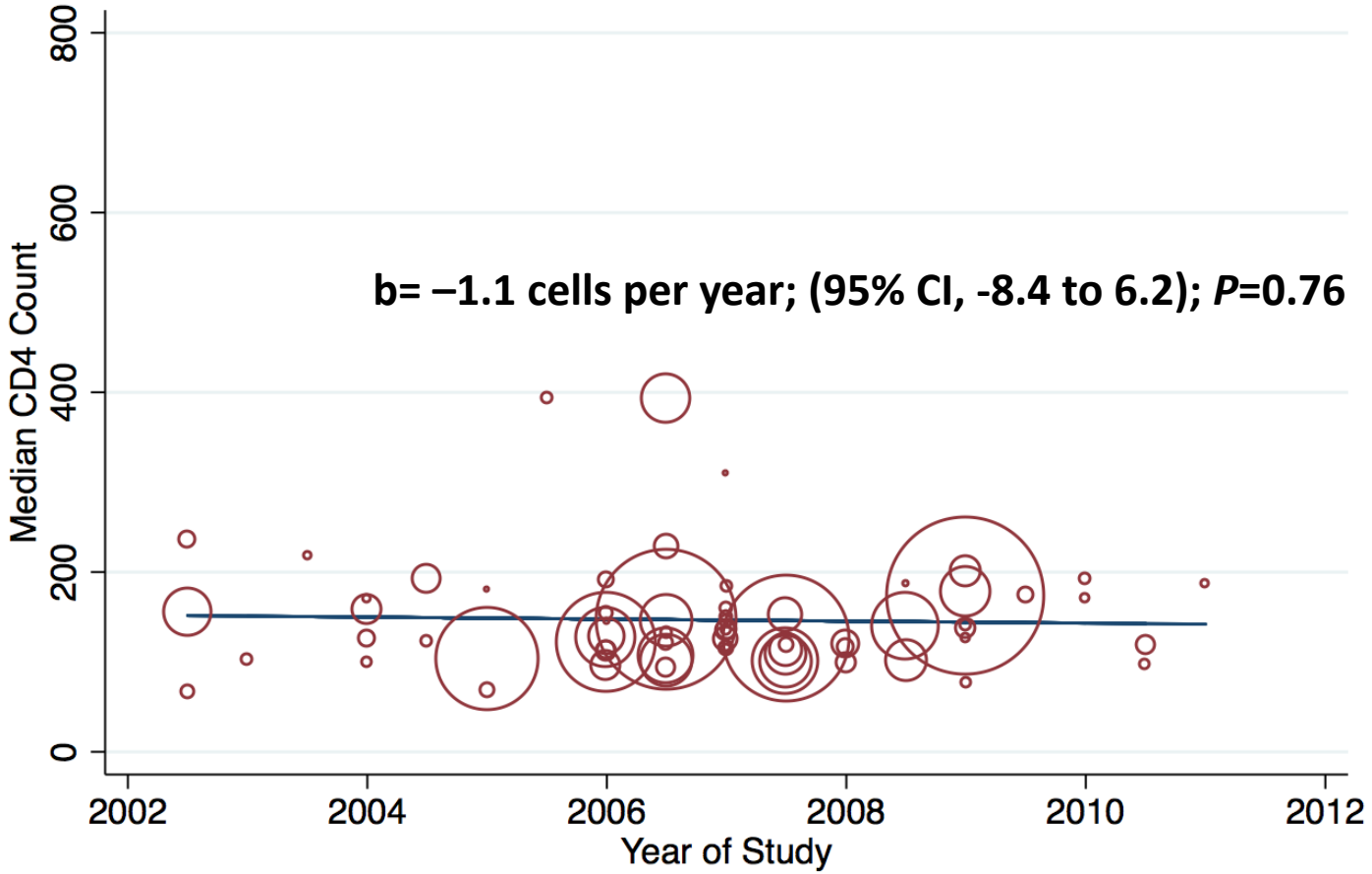
Freiberg et al, Ann Int Med, 2013

ART Timing and Cancer Risk



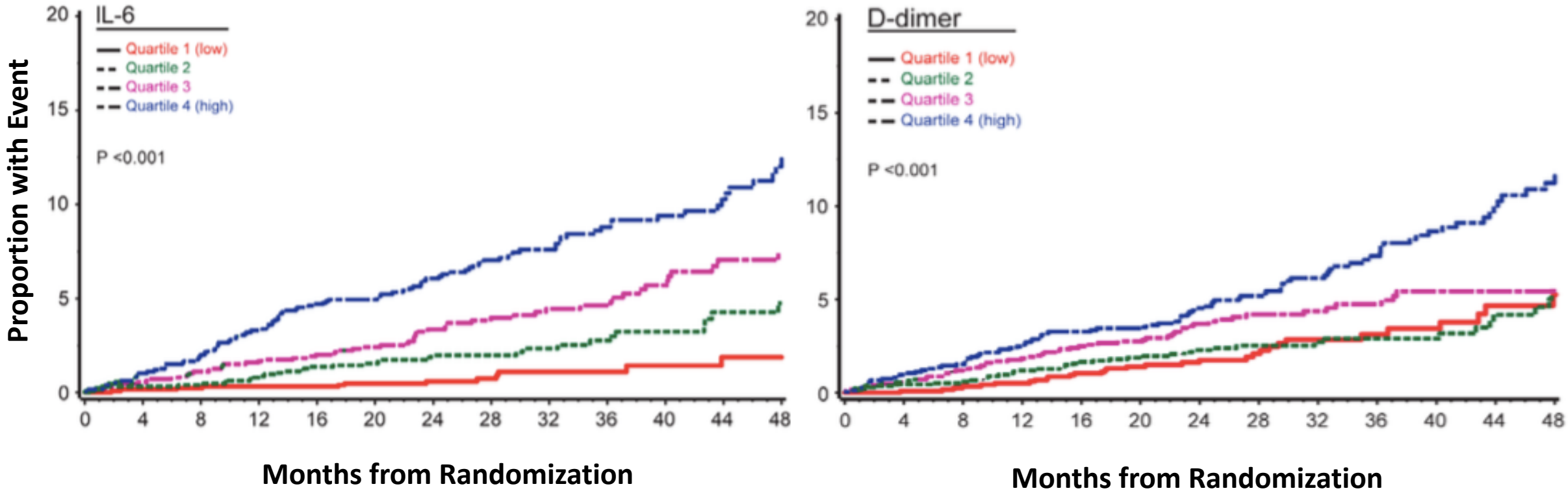
Borges et al, Clin Inf Dis, 2016

Trends in CD4 Count at ART Initiation in SSA



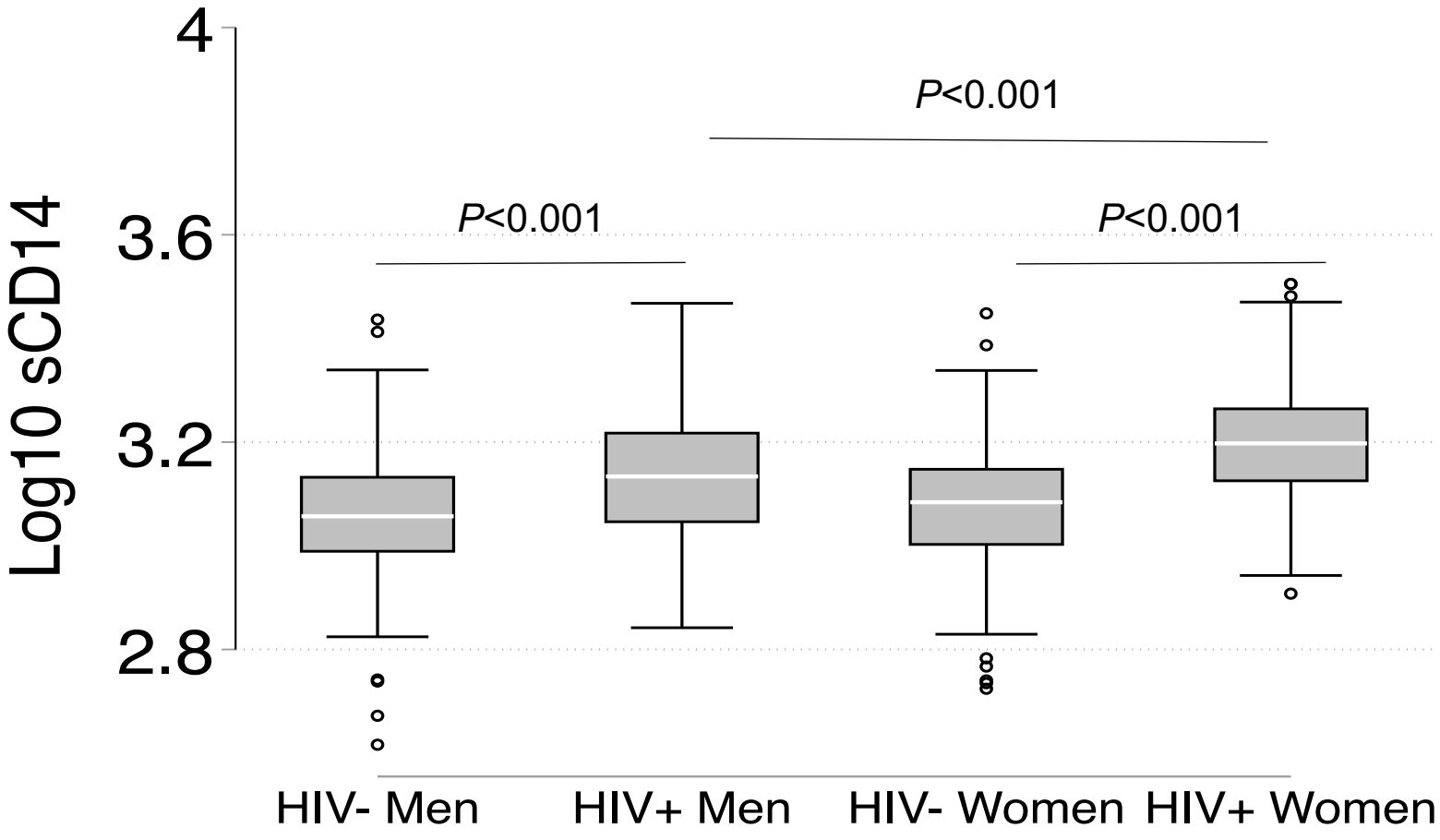
Siedner et al, Clin Inf Dis, 2015

Immune Activation and CVD Events in SMART

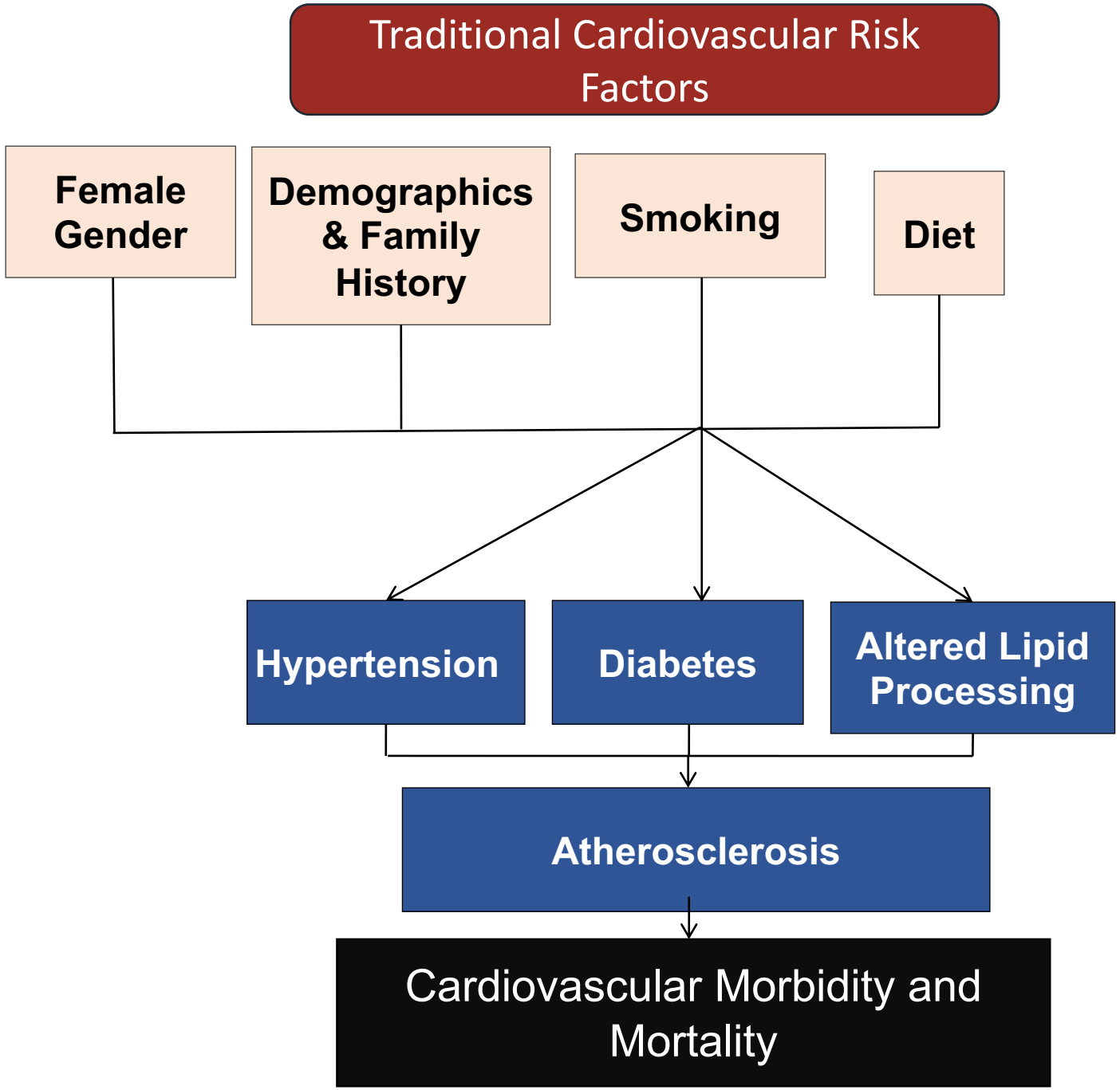


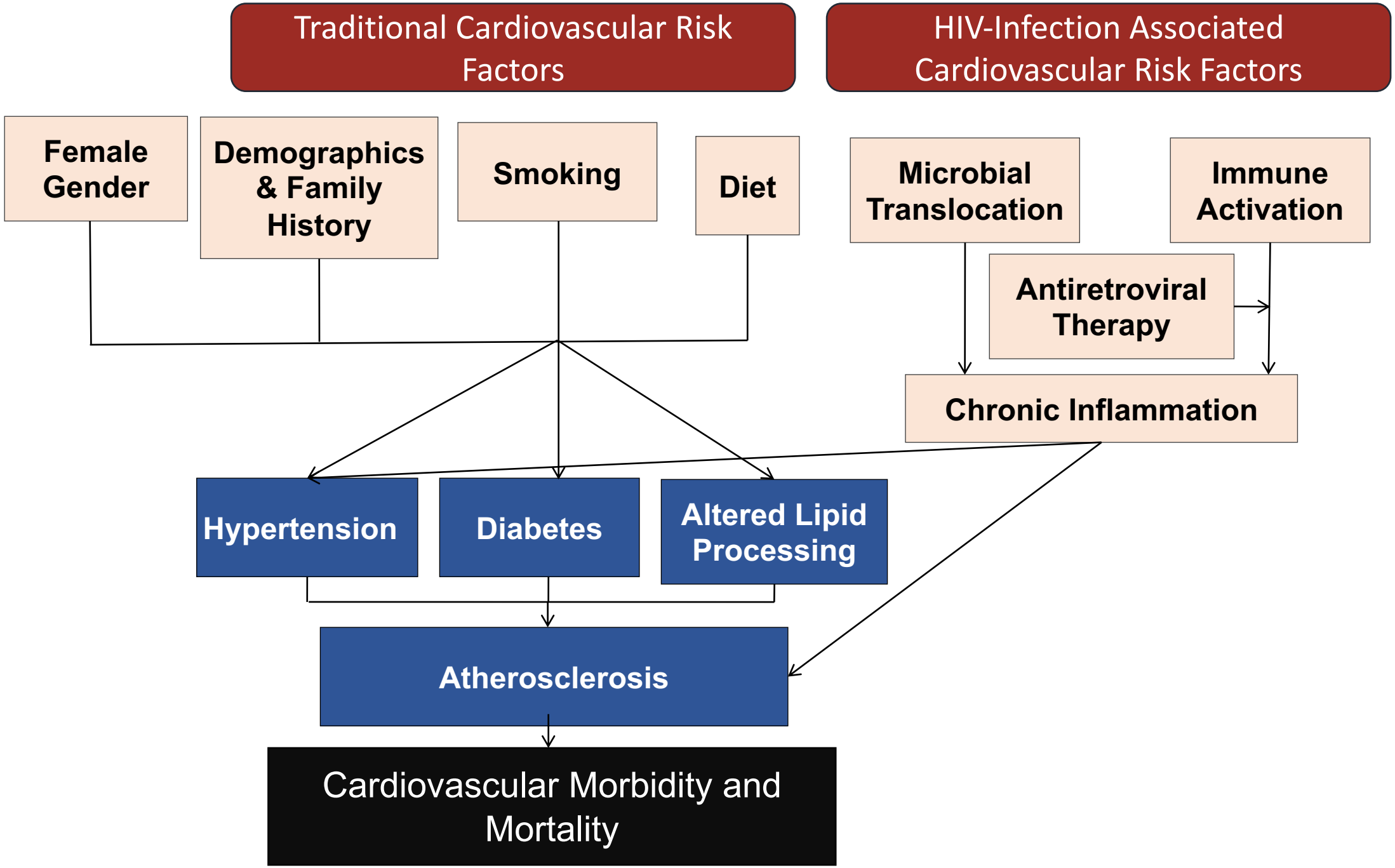
Duprez et al, Plos One, 2012

HIV, Gender and Inflammation in Uganda



Siedner et al, *J Infect Dis*, 2018


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
Female Gender
Demographics & Family History
Smoking
Diet
Microbial Translocation
Immune Activation
Antiretroviral Therapy
Chronic Inflammation
Hypertension
Diabetes
Altered Lipid Processing
Atherosclerosis
Cardiovascular Morbidity and Mortality

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
Siedner et al, JID, 2018

Question 3:

Which of these factors appear to contribute to CVD risk in peole with HIV?

A. Smoking
B. Hypertension
C. CD4 count nadir
D. Virologic failure
E. Female gender
F. All of the above
G. He wasn't kidding about talking for two hours

Question 3:

Which of these factors appear to contribute to CVD risk in peole with HIV?

A. Smoking
B. Hypertension
C. CD4 count nadir
D. Virologic failure
E. Female gender
F. All of the above
G. He wasn't kidding about talking for two hours

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			--	

Ridker et al, JAMA, 2003

ART and Dyslipidemia

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

Estrada et al, AIDS Rev, 2011
Gallant et al, NEJM, 2006
Santos et al, Clin Inf Dis, 2015
Tebas et al, Clin Inf Dis, 2014
Grunfeld, Top HIV Med, 2010

ART and Dyslipidemia

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

Estrada et al, AIDS Rev, 2011
Gallant et al, NEJM, 2006
Santos et al, Clin Inf Dis, 2015
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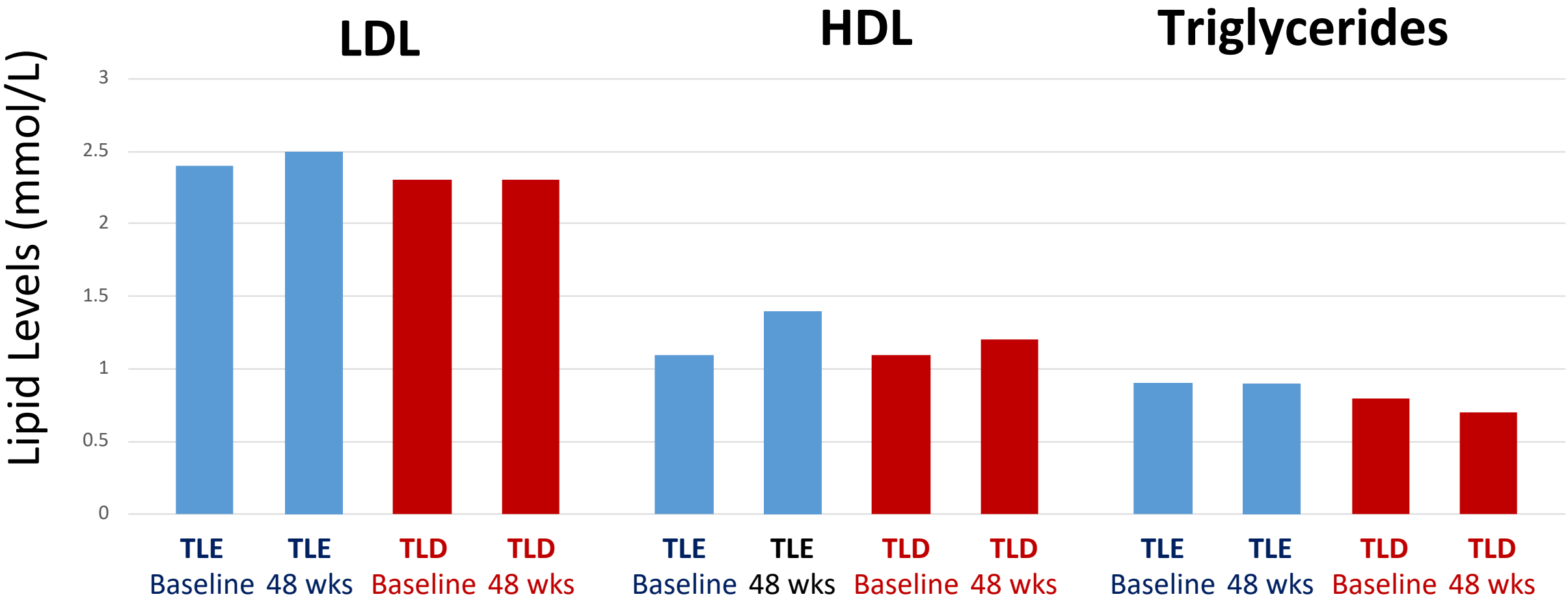
Grunfeld, Top HIV Med, 2010

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		--		

Estrada et al, AIDS Rev, 2011
Gallant et al, NEJM, 2006
Santos et al, Clin Inf Dis, 2015
Tebas et al, Clin Inf Dis, 2014
Grunfeld, Top HIV Med, 2010

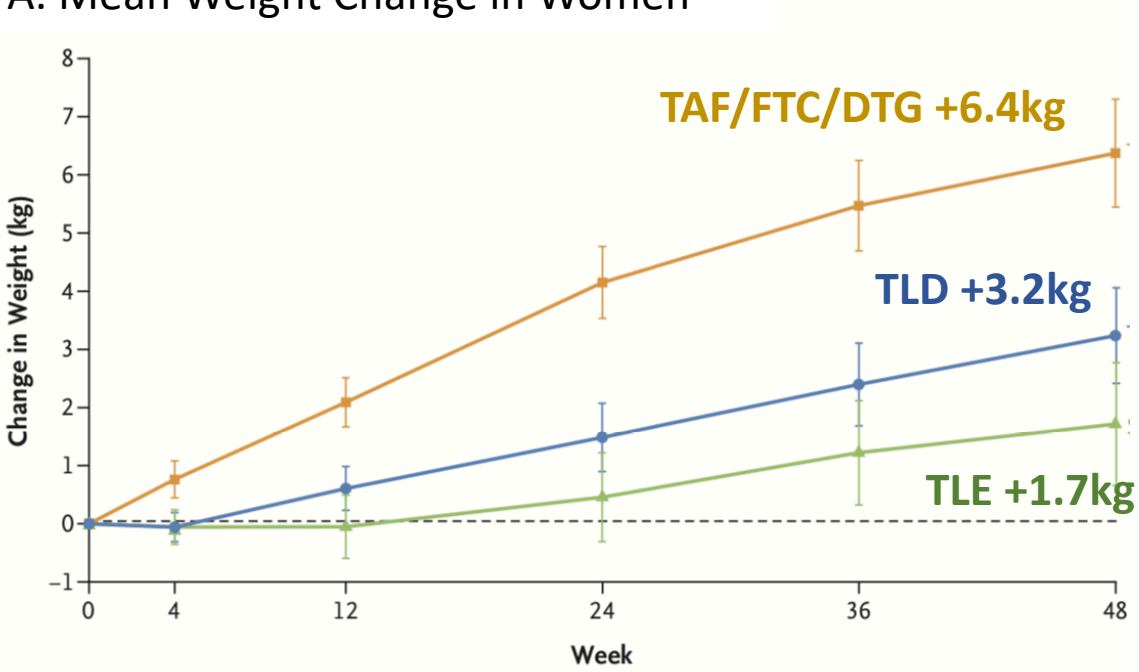
Dolutegravir vs Efavirenz and Lipid Levels



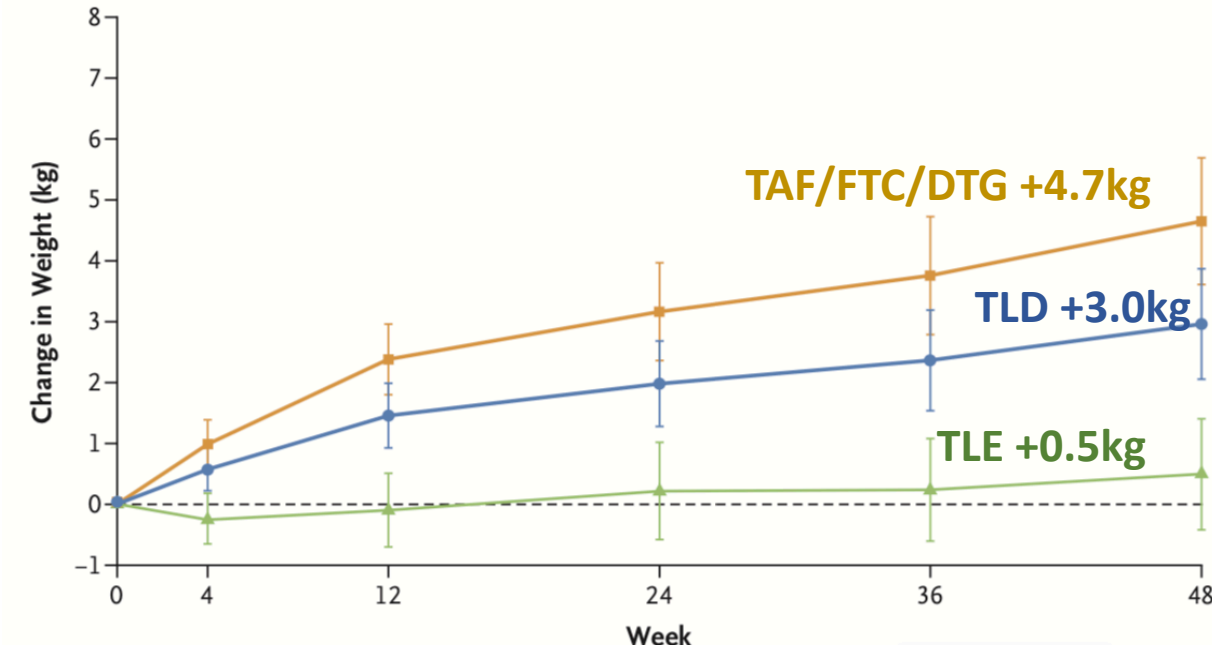
Venter et al, NEJM, 2019

ART and Weight Gain?

A. Mean Weight Change in Women



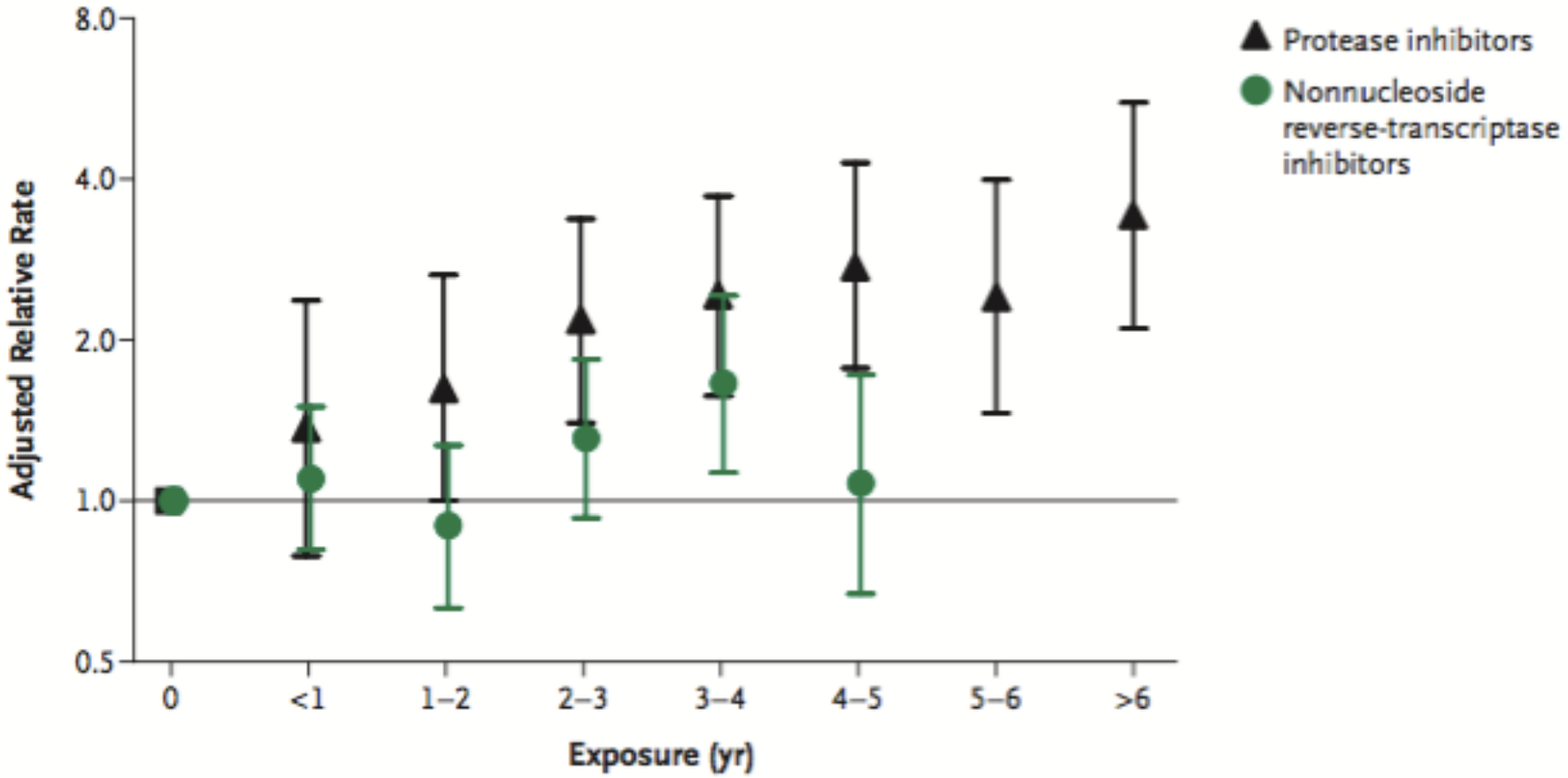
B. Mean Weight Change in Women



Venter et al, NEJM, 2019

Do ARVs or ARV classes increase CVD risk?

Class of Antiretroviral Therapy and CVD Risk



Friis-Møller et al, NEJM, 2007

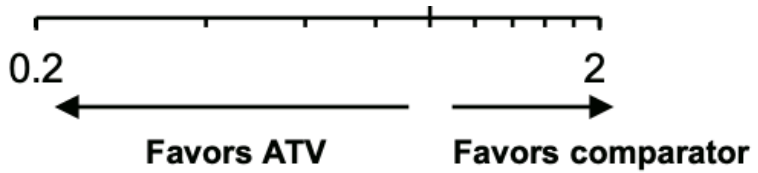
Class of Antiretroviral Therapy and CVD Risk

- 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

Monforte et al, AIDS, 2013
Lang et al, JAMA Int Med, 2010

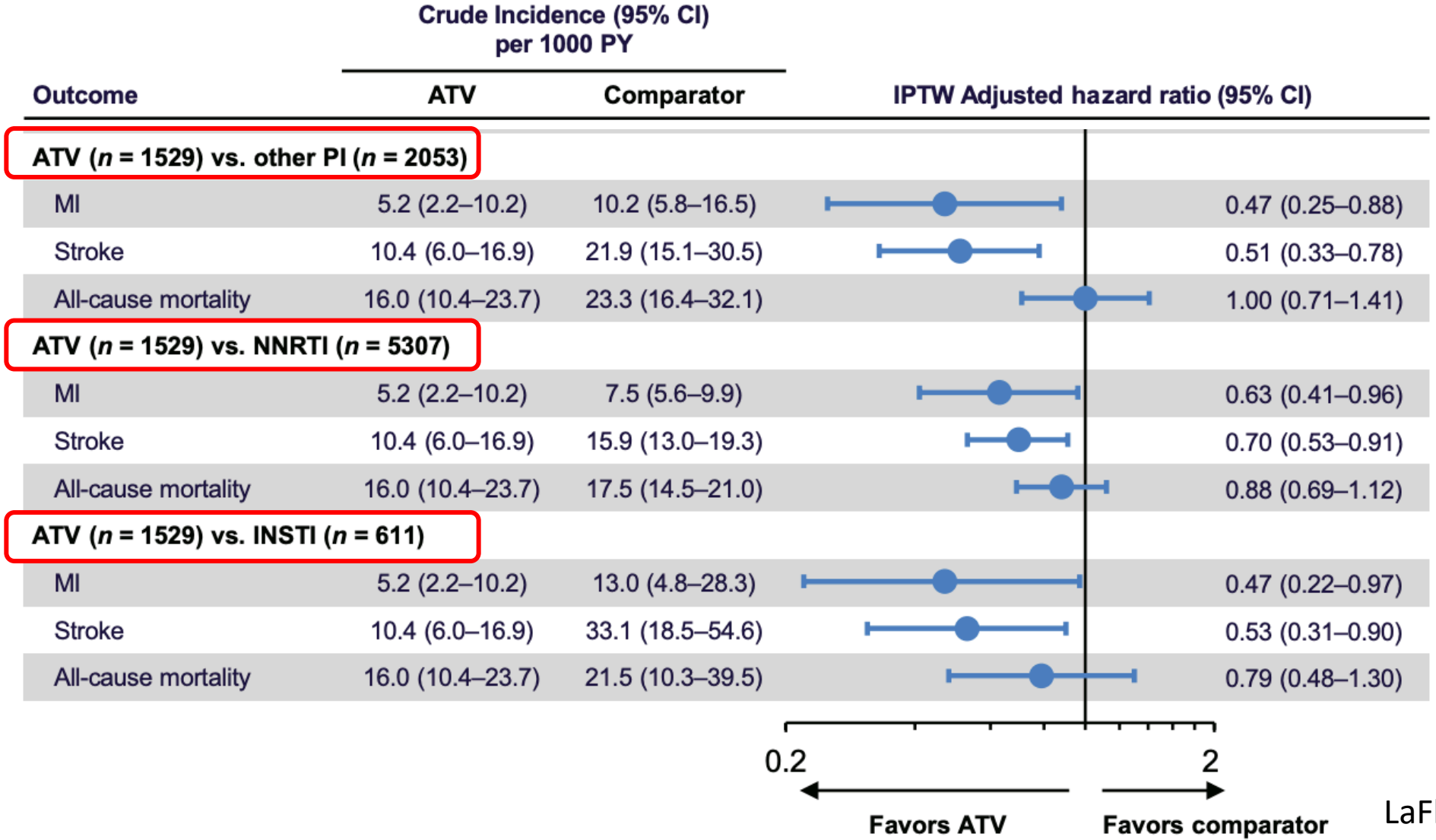
Atazanavir and MI risk

Outcome	Crude Incidence (95% CI) per 1000 PY: ATV	Crude Incidence (95% CI) per 1000 PY: Comparator	IPTW Adjusted hazard ratio (95% CI)
ATV (*n* = 1529) vs. non-ATV (*n* = 7971)			
MI	5.2 (2.2–10.2)	8.3 (6.5–10.4)	0.59 (0.41–0.84)
Stroke	10.4 (6.0–16.9)	17.9 (15.2–21.0)	0.64 (0.50–0.81)
All-cause mortality	16.0 (10.4–23.7)	18.8 (16.0–21.9)	0.90 (0.73–1.11)



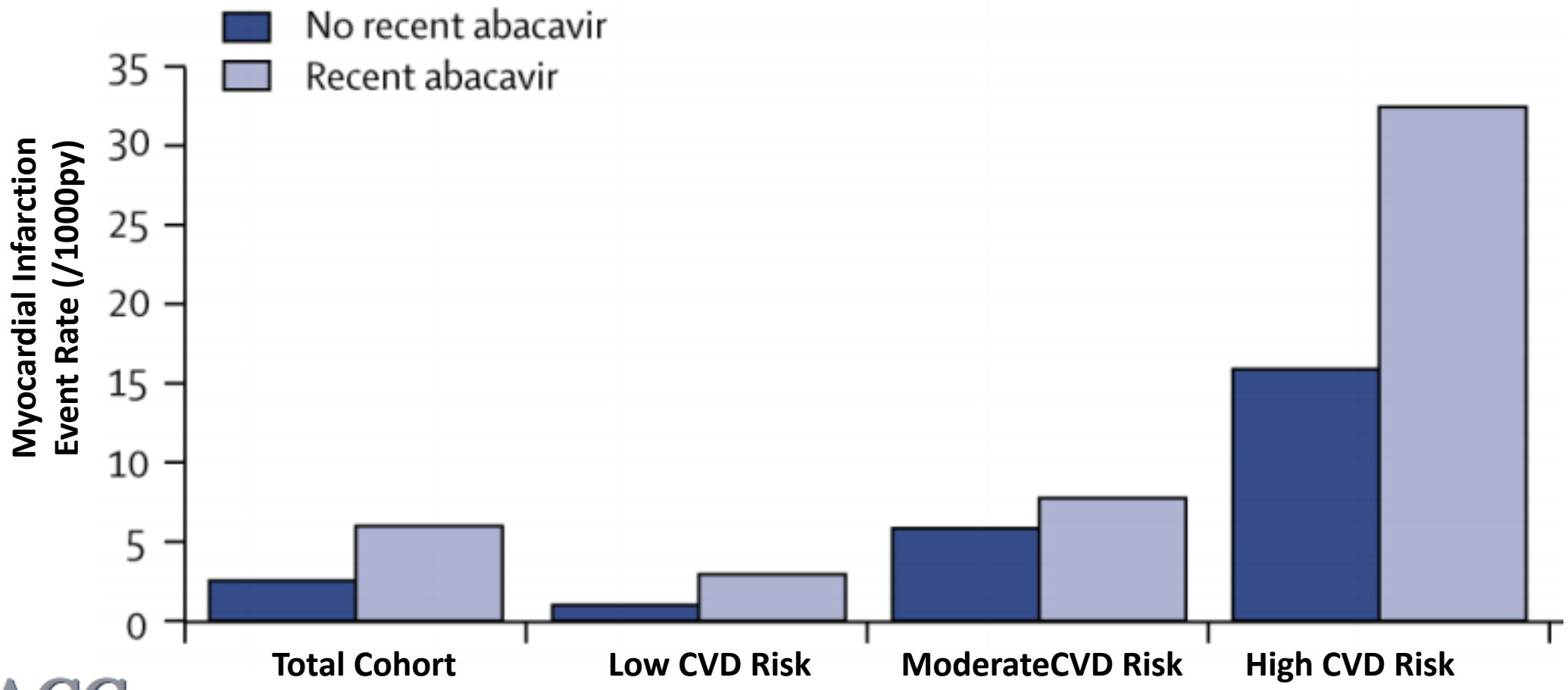
LaFleur et al, JAIDS 2017

Atazanavir and MI risk



LaFleur et al, JAIDS 2017

Abacavir and Risk of Myocardial Infarction



Monforte et al, AIDS, 2013
Lang et al, JAMA Int Med, 2010

Screening for CVD Risk in HIV Infection

Screening for CVD Risk in HIV Infection

Standard Treatment Guidelines and Essential Medicines List for South Africa

Primary Healthcare Level
2018 Edition

Screening for CVD Risk in HIV Infection

Standardised national monitoring for adults and adolescents with HIV

At initial diagnosis of HIV	Purpose
Confirm HIV result with rapid antibody test.	Ensure that national testing algorithm has been followed.
If HIV-infected: Do CD4 count and WHO clinical staging.	To assess eligibility for OI prophylaxis and management. To assess eligibility for fast-tracking.
Screen for pregnancy or ask if planning to conceive.	See Section: 6.8: HIV in pregnancy.
Screen for TB symptoms (See Section 17.4: Pulmonary tuberculosis).	To identify TB/HIV co-infected.
If CD4 < 100 cells/mm^3: Do cryptococcal antigen test (CrAg).	To identify asymptomatic patients who need pre-emptive fluconazole treatment.
If AZT required: Do FBC.	To detect anaemia or neutropaenia.
If TDF required: Do creatinine.	To detect renal insufficiency.
If NVP required: Do ALT.	To exclude liver disease.

Screening for CVD Risk in HIV Infection

On ART	Purpose
CD4 at 1 year on ART.	To monitor immune response to ART and see if OI prophylaxis is still necessary.
VL at month 6, 1 year and then every 12 months.	To identify treatment failures and problems with adherence.
If on NVP and develops rash or symptoms of hepatitis: Do ALT.	To identify NVP toxicity.
If on AZT: Do FBC at month 1, 2, 3 and 6.	To identify AZT toxicity.
If on TDF: Do creatinine at month 3 and 6, 1 year and then every 12 months.	To identify TDF toxicity.
If on LPV/r: Do fasting cholesterol and triglycerides at month 3.	To identify LPV/r toxicity.

Screening for CVD Risk in HIV Infection

Protease inhibitor-induced dyslipidaemia:

» Certain antiretroviral medication, particularly protease inhibitors, can cause dyslipidaemia. Fasting lipid levels should be done 3 months after starting lopinavir/ritonavir. Lopinavir/ritonavir is associated with a higher risk of dyslipidaemia (specifically hypertriglyceraemia) than atazanavir/ritonavir.

» Patients at high risk (> 20% risk of developing a CVS event in 10 years) should switch to atazanavir/ritonavir and repeat the fasting lipid profile in 3 months.

» Patients with persistent dyslipidaemia despite switching, qualify for lipid lowering therapy. Criteria for initiating lipid lowering therapy are the same as for HIV-uninfected patients. Many statins (including simvastatin) cannot be used with protease inhibitors, as protease inhibitors inhibit the metabolism of the statin resulting in extremely high blood levels.

» Patients who fail to respond to lifestyle modification and have dyslipidaemia treat with:

- Atorvastatin, oral, 10 mg at night.

Screening for CVD Risk in HIV Infection

Southern African Journal of HIV Medicine
ISSN: (Online) 2078-6751, (Print) 1608-9693

Adult antiretroviral therapy guidelines 2017

The following investigations are recommended prior to initiating ART:

- alanine transaminase (ALT)
- full blood count (FBC) if AZT being considered: avoid AZT if haemoglobin (Hb) is < 8 g/dL
- serum creatinine and calculation of CrCl: avoid TDF if CrCl is < 50 mL/min; other nucleoside reverse transcriptase inhibitors (NRTIs), except abacavir (ABC), require dose adjustment if CrCl is < 50 mL/min (either by using the estimated glomerular filtration rate [eGFR] provided by the laboratory or calculating by using the modified Cockgraft–Gault equation, Table 11)
- hepatitis B surface antigen (HBsAg – see the section 'Hepatitis B co-infection')
- CD4+ count
- baseline VL
- syphilis serology
- serum cryptococcal antigen test in patients starting ART at a CD4+ count < 100 cells/μL (to screen for early cryptococcal disease and to initiate pre-emptive treatment if positive)

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. Horberg[6]

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

Aberg et al, Clin Inf Dis, 2014

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

Adapted from Aberg et al, Clin Inf Dis, 2014

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 recommendations for discordant results between FBG and A1c:
  - Repeat the test below the threshold (FBG >126 or A1c > 6.5%)
  - If repeat below threshold, monitor
  - If repeat above threshold, manage as if a diagnosis of DM

Kim et al, Diabetes Care, 2009
Eckhardt et al, AIDS Pt Care STDs, 2012
Slama et al, J Antimicr Chemo, 2014

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)
  - Atherosclerotic Cardiovascular Disease Risk Estimator
    - http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/
  - ATP III Guidelines for Statin Use
    - https://www.nhlbi.nih.gov/files/docs/guidelines/atglance.pdf

AMERICAN COLLEGE of CARDIOLOGY

ASCVD Risk Estimator Plus

Estimate Risk | Therapy Impa

26.6% High — **Current 10-Year ASCVD Risk****

Lifetime ASCVD Risk: **69%** Optimal ASCVD Risk: **5.5%**

Current Age * — 58 — *Age must be between 20-79*

Sex * — ✔ Male | Female

Race * — White | ✔ African American | Other

Systolic Blood Pressure (mm Hg) * — 170 — *Value must be between 90-200*

Diastolic Blood Pressure (mm Hg) — 95 — *Value must be between 60-130*

Total Cholesterol (mmol/L) * — 8 — *Value must be between 3.367 - 8.288*

HDL Cholesterol (mmol/L) * — 1 — *Value must be between 0.518 - 2.59*

LDL Cholesterol (mmol/L) — 4.9 — *Value must be between 0.777-7.770*

History of Diabetes? * — ✔ Yes | No

Smoker? * — Current | ✔ Former | Never

How long ago did patient quit smoking? * — 2.5-3.5 years ago

On Hypertension Treatment? * — Yes | ✔ No

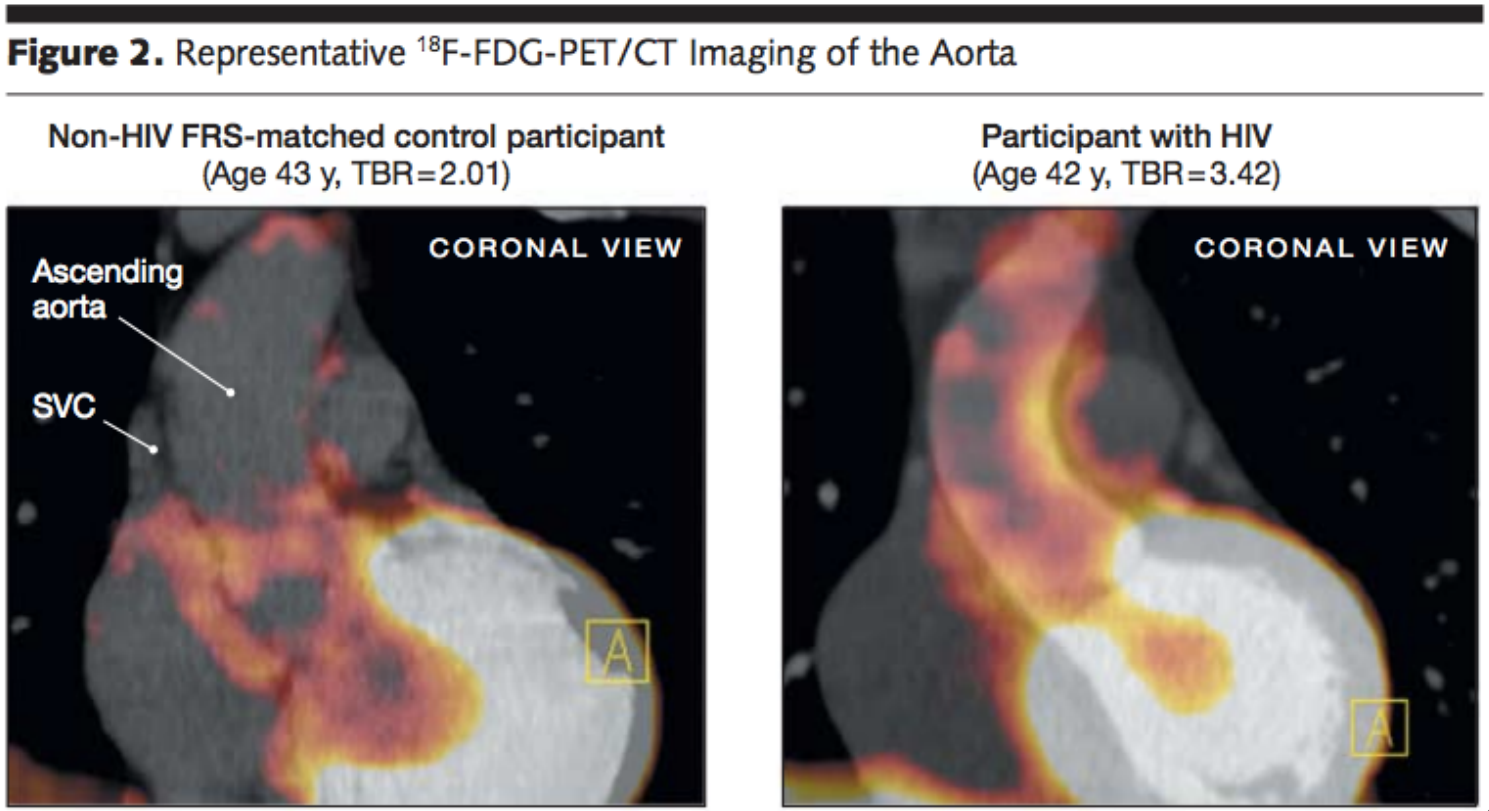
On a Statin? — Yes | ✔ No

On Aspirin Therapy? — Yes | ✔ No

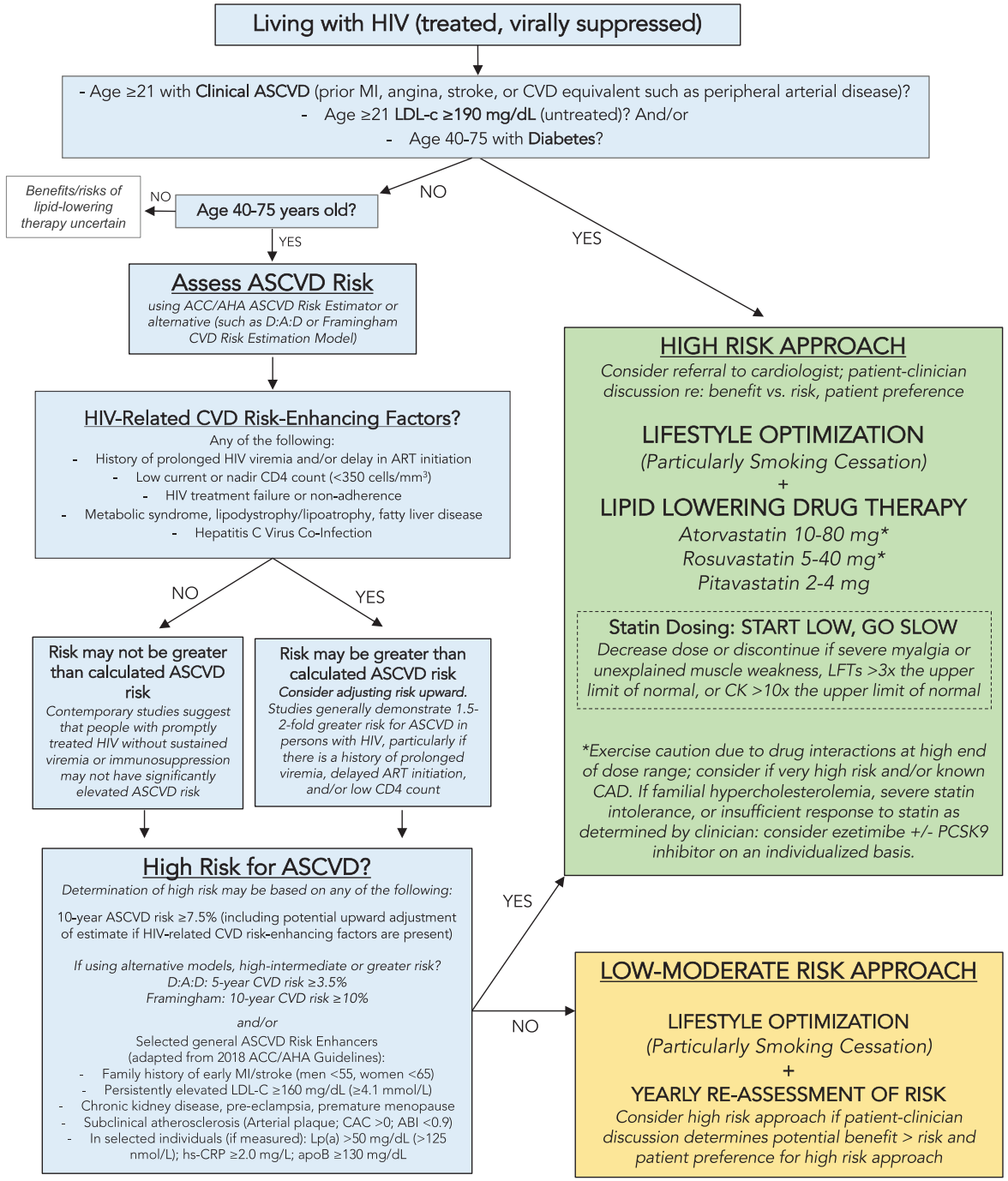
CVD Risk Scores in HIV Infection

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

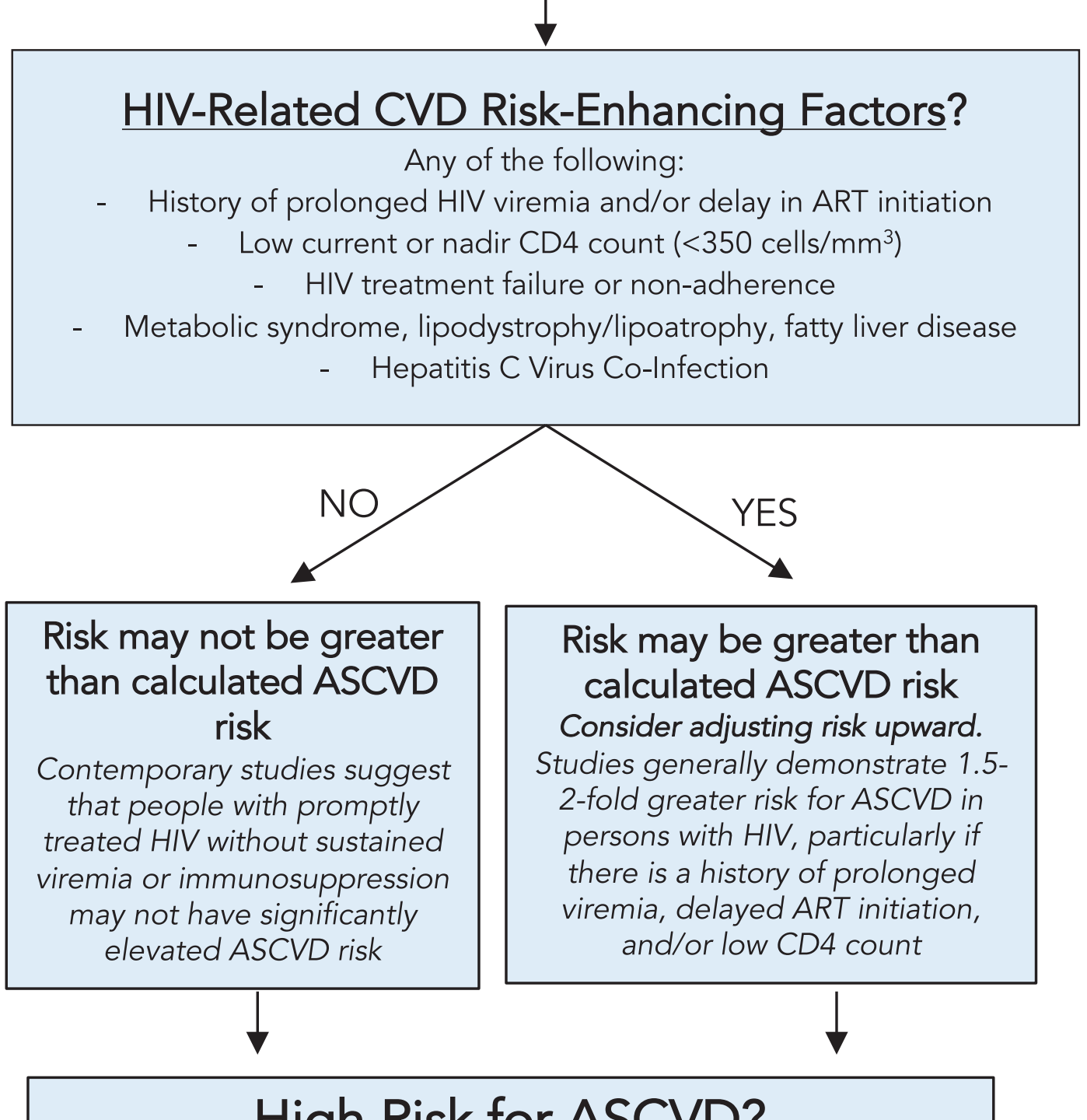
Figure 2. Representative ^{18}F-FDG-PET/CT Imaging of the Aorta



Subramanian et al, JAMA 2012
Law et al, HIV Medicine, 2006
Mateen et al, Neurology, 2013



Feinstein et al, Circulation, 2018



Feinstein et al, Circulation, 2018

Consider referral to cardiolo
discussion re: benefit vs. risk

LIFESTYLE OPTI

(Particularly Smokin

+

LIPID LOWERING D

Atorvastatin 10
Rosuvastatin 5
Pitavastatin 2

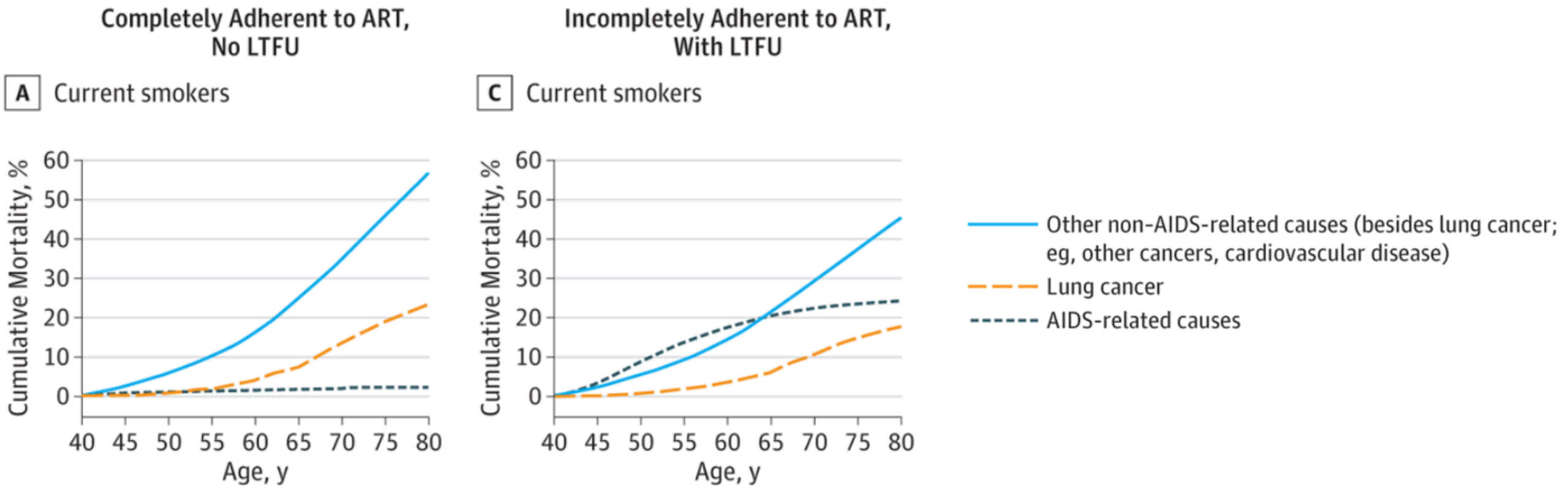
Statin Dosing: START L

Decrease dose or discontinu
unexplained muscle weaknes
limit of normal, or CK >10x th

**Exercise caution due to drug*
of dose range; consider if very
CAD. If familial hypercholeste
intolerance, or insufficient r
determined by clinician: consid
inhibitor on an indivi

Screening for Cancer Risk in HIV Infection

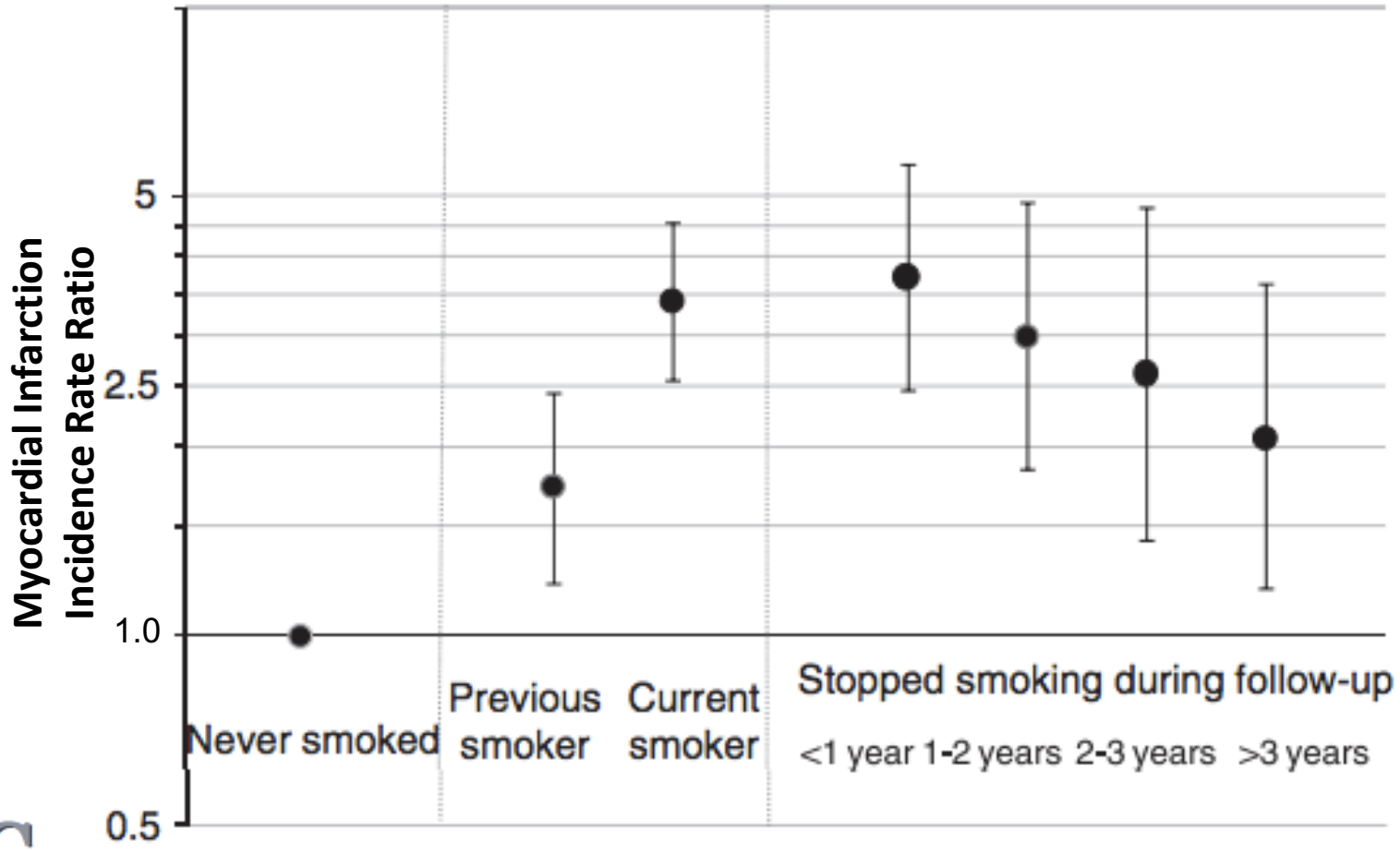
Smoking, HIV, Cancer and CVD Risk



"ART-adherent individuals who continued to smoke were 6 to 13 times more likely to die from lung cancer than from traditional AIDS-related causes, depending on sex and smoking intensity."

Reddy et al, JAMA IM, 2017

Smoking Cessation and CVD Risk in HIV



Petoumonos, HIV Medicine, 2011

Cervical Cancer Prevention

	A	B	C
	Relative risks according to number of the doses received among women who were HPV16/18- at enrolment		
		HPV16/18 DNA-	
	Outcome	3 doses	≥1 dose	1 to 2 doses
	Age group 15-26			
	High-grade intraepithelial neoplasia due to HPV16/18			
1	CIN2+	0.07 (0.03 to 0.15)[b4q2] [2.1.1 ⊕⊕⊕⊕	0.05 (0.03 to 0.10)[b4q2] [2.2.1 ⊕⊕⊕⊕	0.10 (0.04 to 0.26)[b3q2] [2.3.1 ⊕⊕⊕
2	CIN3+	0.07 (0.02 to 0.29)[b1q2] [2.7] ⊕⊕⊕⊕	0.05 (0.02 to 0.14)[b1q2] [2.8] ⊕⊕⊕⊕	0.06 (0.01 to 0.24)[b1q2] [2.9] ⊕⊕⊕
3	AIS+	0.12 (0.02 to 0.70)[b1q2] [2.10] ⊕⊕⊕	0.09 (0.01 to 0.72)[q2] [2.11] ⊕⊕⊕	0.15 (0.01 to 2.97)[q2] [2.12] ⊕⊕
	High-grade intraepithelial neoplasia irrespective of HPV or due to whatever HPV type			
4	CIN2+	0.40 (0.25 to 0.64)[b2q1] [2.13] ⊕⊕⊕⊕	0.41 (0.32 to 0.52)[b3] [2.14] ⊕⊕⊕⊕	0.71 (0.15 to 3.38)[b1] [2.15] ⊕⊕
5	CIN3+	-	-	-
		-	-	-
6	AIS+	-	-	-
	Persistent HPV16/18 infection			
7	6M persisting	0.06 (0.05 to 0.08)[b4] [5.4.1] ⊕⊕⊕⊕	0.10 (0.08 to 0.12)[b4] [5.5.1] ⊕⊕⊕⊕	0.12 (0.03 to 0.42)[b2] [5.6.1] ⊕⊕
	Age group 24-45			
	High-grade intraepithelial neoplasia due to HPV16/18			
8	CIN2+	0.16 (0.04 to 0.74)[b1q1] [2.1.2 ⊕⊕⊕	0.30 (0.11 to 0.81)[b1q1] [2.2.2 ⊕⊕⊕	0.61 (0.14 to 2.67)[b1q1] [2.3.2 ⊕⊕
9	CIN3+	-	-	-
10	AIS+	-	-	-

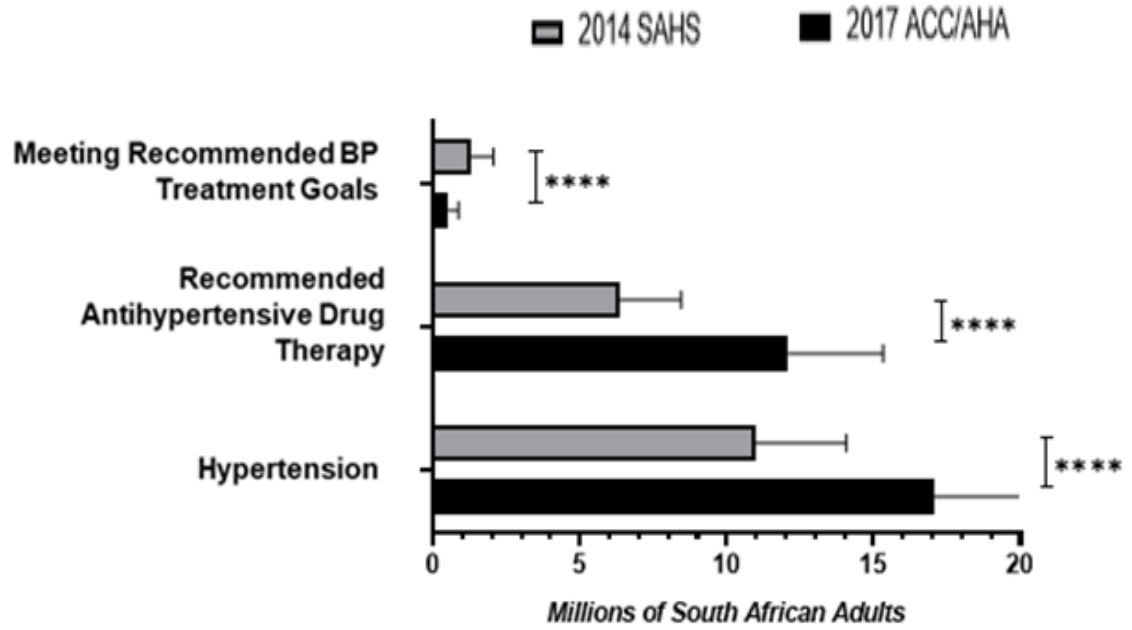
Arbyn et al, Cochrane Database, 2018

Therapy of CVD Risk Factors with ART Use

Hypertension Management

- Similar recommendations to HIV-uninfected patients
- PIs expected to ,modestly increase levels of amlodipine and beta-blockers marginally

- BP threshold controversy:
  - SA Guidelines >140 sys or >90 dias
  - 2017 AHA >130 sys or > 80 dias

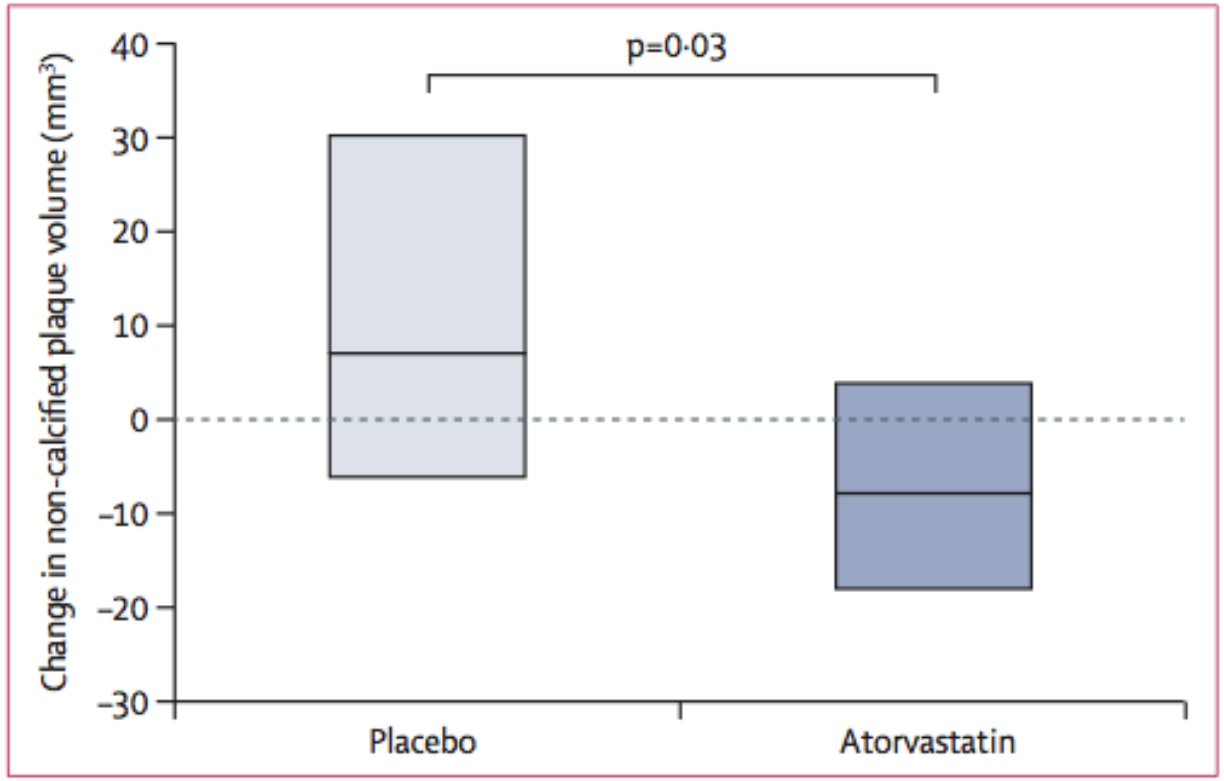


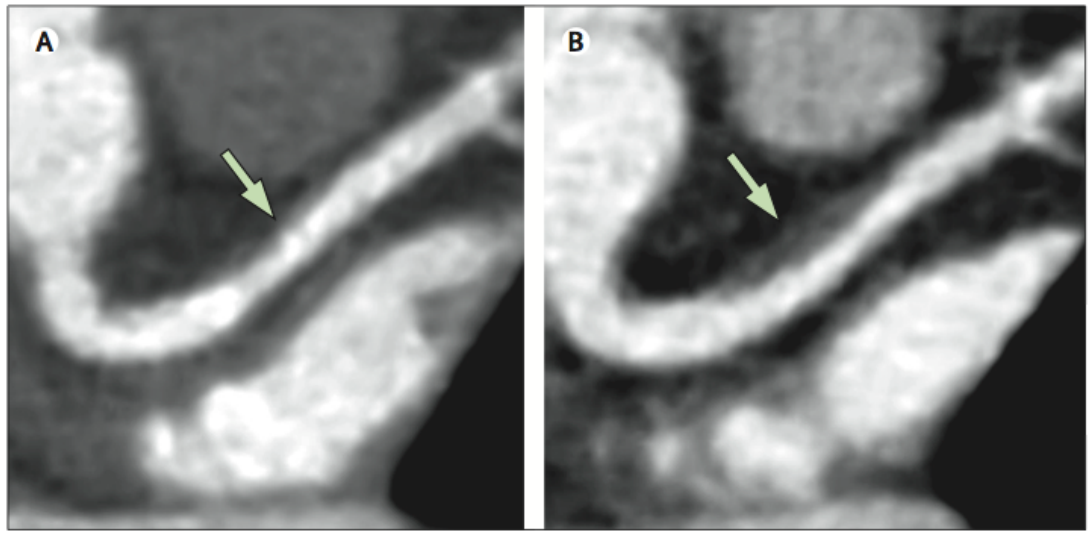
Magodoro et al, under review

ART and Lipid Interaction Pearls

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

Statins as primary prevention?





REPRIEVE

Randomized Trial to Prevent Vascular Events in HIV

Lo et al, Lancet HIV, 2015

ART and Diabetes Interaction Pearls

- Dolutegravir and metformin interaction
  - Single dose dultegravir raises metformin AUC levels 60-80%
  - Double dose dultegravir 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

O'Brien et al, CROI Abstract 44LB, 2016

Summary 1: HIV and CVD Epidemiology

- In US/Europe **HIV+ have ~50% increased risk of CVD events and cancer**
  - 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 in 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
- **Dolutegravir associated with increased weight gain** but similar lipid changes compared to EFV in treatment naïve

Summary 3: Screening and Management of CVD

- **Screen** for obesity, hypertension, smoking, diabetes (A1c or FBG), and hypercholesterolemia prior to treatment and at least once annually
  - Conduct annual CVD risk assessments
  - Assess role for lifestyle interventions and statin indications

- Management of CVD risk is **similar to that of the HIV-infected** populations
  - BP and DM control, weight loss, lipid targets
  - Secondary prevention (statins, aspirin)
  - This might change after REPREIVE study published

- Special considerations
  - Emphasis on behavioral risk factors including smoking and cervical cancer screening
  - Consider **drug-drug interactions** when initiating statins

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

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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

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Case 2, continued

What else would you suggest for this patient?

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

Case 2, continued

What else would you suggest for this patient?

A. Diet, exercise, and lifestyle counseling
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C. A and B
D. No other interventions at this time
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Case 3

36 year old man is changed from TDF/FTC/EFV with a suppressed VL to TDF/3TC/DTG during routine programmatic switch as recommended by DoH guidelines sometime in the future. Prior to change, he has a BMI of 32, a fasting blood glucose of 7.5, and is a former smoker. He works as a truck driver and is mostly sedentary. 8 months after change to DTG-based regimen his viral load is undetectable and he has gained 12 kilograms. How would you manage this patient?

A. No change, he is virologically suppressed
B. Change back to TDF/FTC/EFV
C. Initiate diet and exercise regimen
D. Call Francois

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C. Initiate diet and exercise regimen
D. Call Francois

Thank you for your attention!

Thanks to Dr. Sunpath, Moosa, Gandhi, the SA DoH and all the people who make this conference possible.

Please do not hesitate with any questions.

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