



HIV Care Beyond Viral Suppression: Focus on Cardiovascular Disease

DUKE  CFAR
Duke Center for AIDS Research

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Disclosures/COI

- Nothing to disclose



CM: 48 y.o M with recent PCI to right coronary artery

- 48 y.o Caucasian male; store manager for home improvement outlet
- 1/2017: reports insidious onset of exertional dyspnea and decreased exercise capacity
- 5/2017: new onset of exertional chest pain
 - Referred for myocardial perfusion scanning by PCP
- 5/26/2017: new onset chest pain at rest
 - Cardiac enzymes negative
- Stress test on admission revealed reversible ischemia in RCA distribution
- Cardiac catheterization: **90% RCA, 50% LCx, 30% LAD**
 - **PCI: DES to RCA**

C.M. continued...

- Diagnosed with HIV in 2001
 - 2004-2009: LPV/r + FTC/TDF
 - 2009-2015: EFV/FTC/TDF
 - 2015- : DTG/ABC/3TC
- PMH otherwise negative
- No family history of CAD
- Quit smoking 5 years prior to event (12.5 pack-year history)
 - No substance abuse
- Lifts weights once a week, walks on treadmill for 20-30 min once a week
- “Eats well” because of his spouse

C.M continued . . .

- BP 113/72, 6'0", 207 lbs
- BMI 28.1 kg/m²
- CD4 796 (nadir 82 (7%)); no history of OI
- VL undetectable
- Tchol 102, LDL 48, HDL 27, TG 135
- hsCRP 0.10
- Meds: Rosuvastatin 20mg, Metoprolol 25mg, Lisinopril 10mg, Aspirin 81mg, Clopidogrel 75mg, Triumeq

C.M continued . . .

- BP 113/72, 6'0", 207 lbs

- BMI 29.4

- CD

- VL

- To

- hs

- Me

10

Does HIV have anything to do with this presentation?

inopril

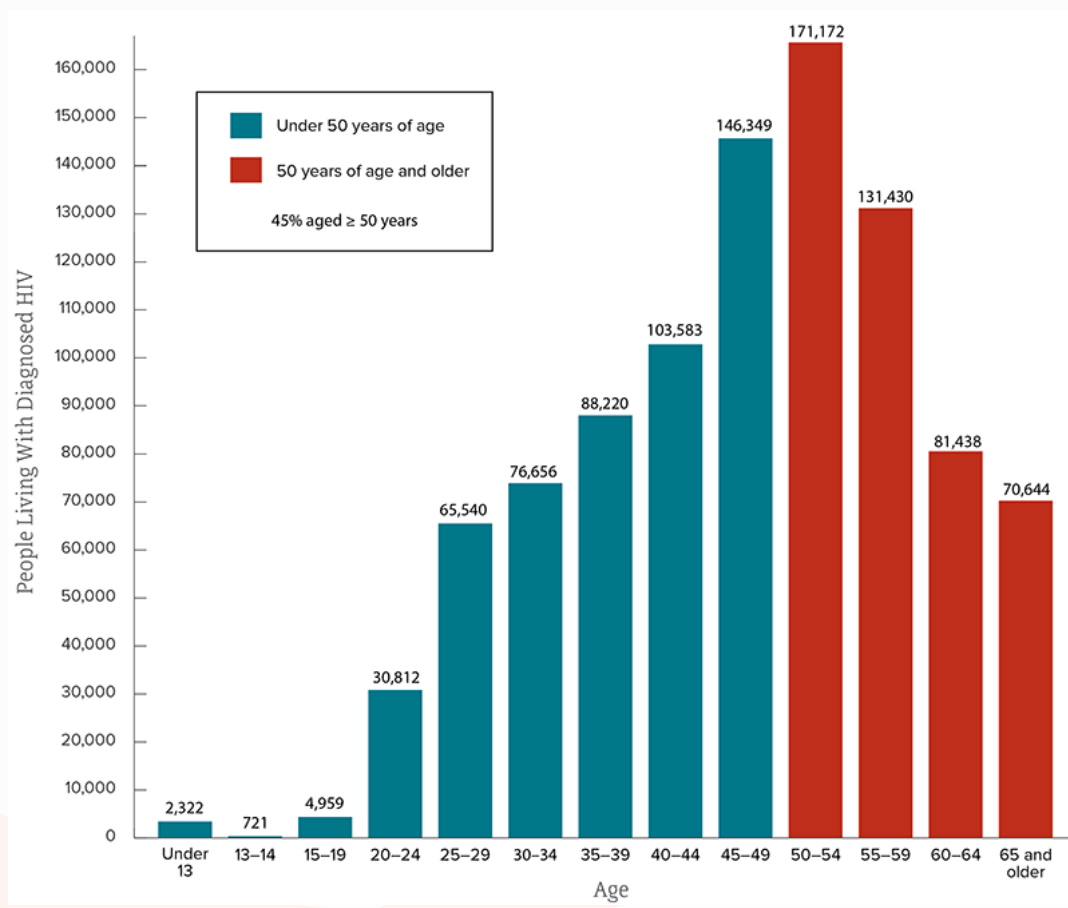


Overview

- Epidemiology of Cardiovascular Disease in Persons with HIV (PWH)
- Pathogenesis of Atherosclerosis in Chronic HIV Infection
- Determinants of Cardiovascular Risk among PWH
- Cardiovascular Disease Care Delivery in PWH

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CDC, 2018



Study	Cohort Size	CV-Related Mortality
D:A:D	49731	11.6%
HOPS	7338	23%
ANRS EN20	Not Reported	14%
SMART/ESPR IT	9583	6.1%

Lancet. 2014 Jul 19;384(9939):241-8.

J Acquir Immune Defic Syndr. 2006 Sep;43(1):27-34.

AIDS. 2014 May 15;28(8):1181-91.

AIDS. 2013 Mar 27;27(6):973-9.



ORIGINAL INVESTIGATION

HIV Infection and the Risk of Acute Myocardial Infarction

Matthew S. Freiberg, MD, MSc; Chung-Chou H. Chang, PhD; Lewis H. Kuller, MD, DrPH; Melissa Skanderson, MSW; Elliott Lowy, PhD; Kevin L. Kraemer, MD, MSc; Adeel A. Butt, MD, MS; Matthew Bidwell Goetz, MD; David Leaf, MD, MPH; Kris Ann Oursler, MD, ScM; David Rimland, MD; Maria Rodriguez Barradas, MD; Sheldon Brown, MD; Cynthia Gibert, MD; Kathy McGinnis, MS; Kristina Crothers, MD; Jason Sico, MD; Heidi Crane, MD, MPH; Alberta Warner, MD; Stephen Gottlieb, MD; John Gottdiener, MD; Russell P. Tracy, PhD; Matthew Budoff, MD; Courtney Watson, MPH; Kaku A. Armah, BA; Donna Doebler, DrPH, MS; Kendall Bryant, PhD; Amy C. Justice, MD, PhD

Veterans Aging Cohort Study

- 82,459 veterans
 - 55,109 uninfected
 - 27,350 HIV-infected
 - 2003-2009
- Median follow up: 5.9 years
- **Primary outcome**: Acute MI
- Adjudicated MI:
 - Appropriate billing code
 - Documentation of AMI in discharge summary
 - Evidence of elevated cardiac enzymes

JAMA Intern Med.2013;173:614-622



VACS Study

- 871 AMI Events
 - 363 (41.6%) in persons with HIV
- Median age at event
 - HIV +: 56.2 years
 - HIV - : 56.4 years (p = 0.42)
- Current Smokers: HR 1.78 (95% CI 1.47-2.16)
- Uncontrolled HTN: HR 1.64 (95% CI 1.41-1.91)
- Diabetes Mellitus: HR 1.74 (95% CI 1.50-2.02)
- **HIV Positive: HR 1.48 (95% CI 1.27-1.72)**
 - **VL > 500: HR 1.75 (95% CI 1.40-2.18)**
 - **VL < 500: HR 1.39 (95% CI 1.17-1.66)**

PLH have a higher risk of MI than the general population

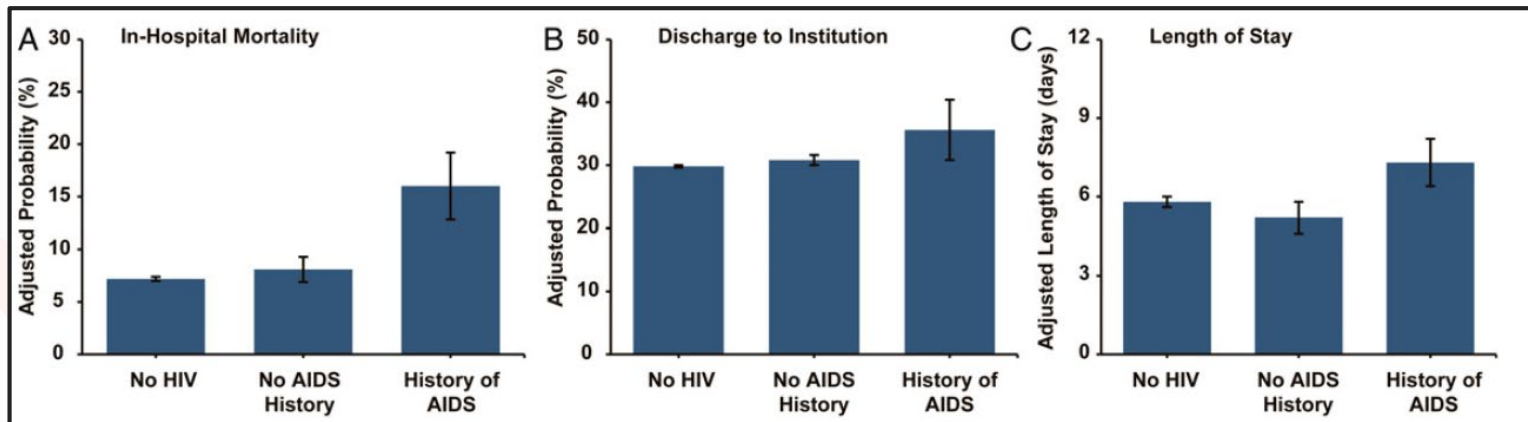
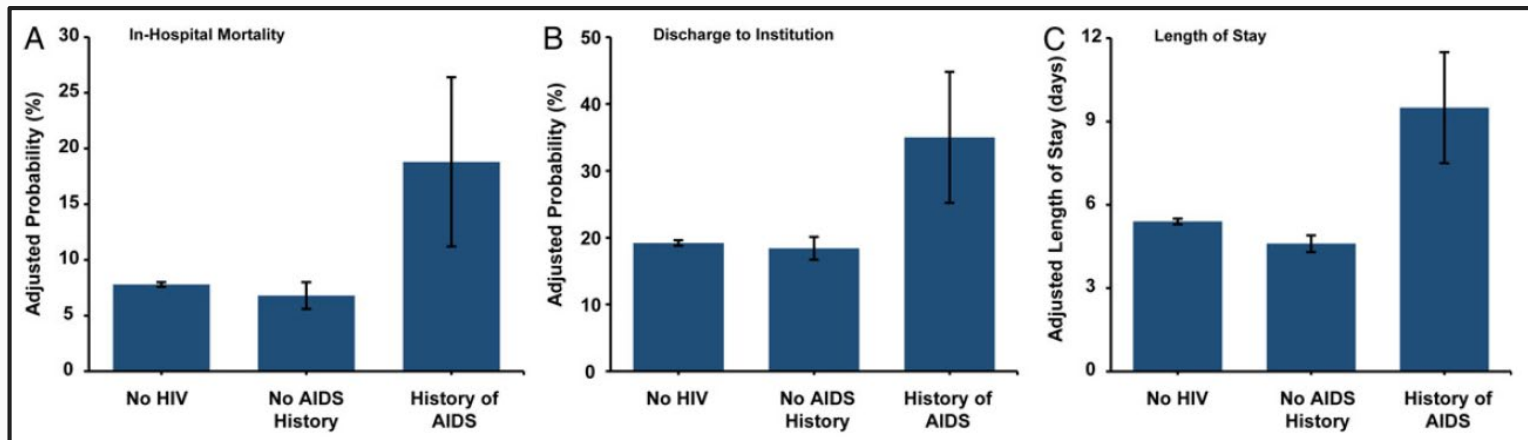
Study	Sample Size	Adjusted Point-Estimate MI PLH (95% CI)
Kaiser (2014)	252,150	IRR 1.4 (1.3,1.6)
VACS Women (2014)	2,187	HR 2.8 (1.7,4.6)
NA-ACCORD (2017)	43477	IRR 1.21 (1.02,1.45)
Shah et al. (2018)	793,635	RR 2.16 (1.68,2.77)



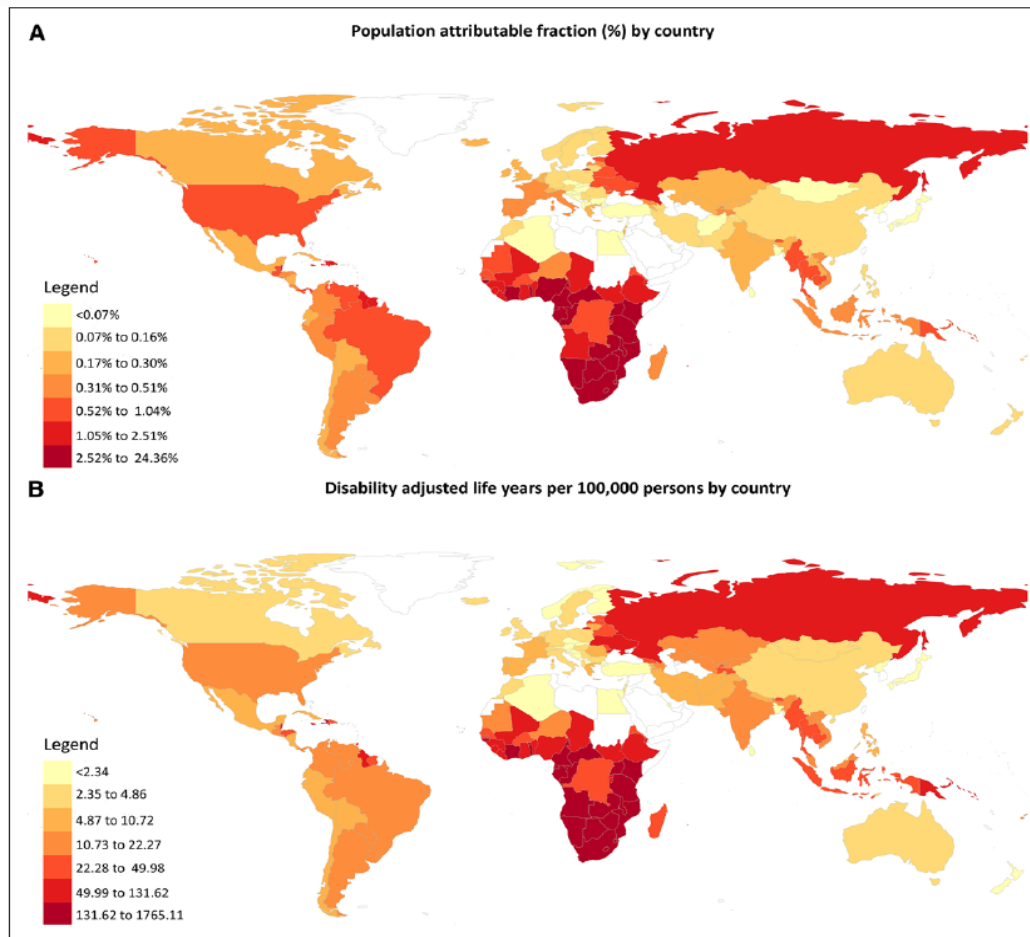
PLH have a higher risk of stroke than the general population

Study	Sample Size	Adjusted Point-Estimate MI PLH (95% CI)
Partners Health (2012)	36,731	HR 1.21 (1.01-1.46)
Kaiser (2014)	282,000	HR 1.4 (1.2-1.7)
VACS Men (2015)	76835	HR 1.17 (1.01-1.36)
Partners Health Women (2018)	13,256	HR 2.39 (1.62-3.43)

... and they do worse when hospitalized for AMI and stroke



J Infect Dis 2016; 1955-61



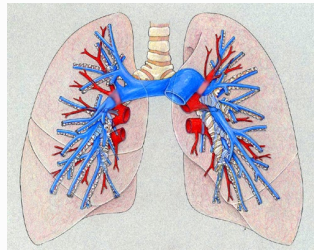
Circulation 2018; 138: 1100-1112

ASCVD in PLH: Epidemiology

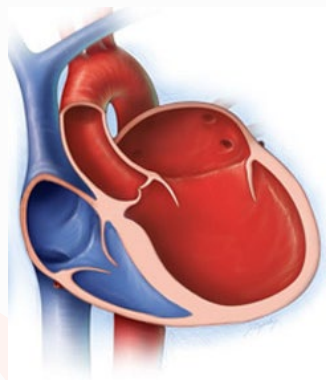
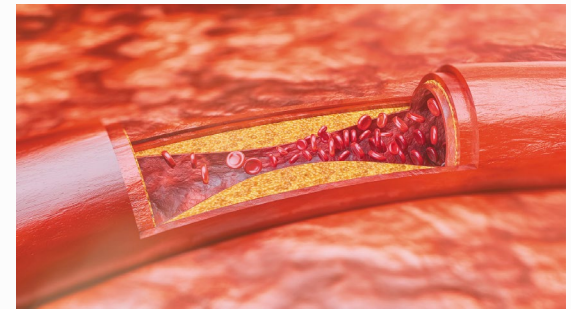
- Rapidly aging HIV population
- Cardiovascular disease incidence predictably increasing
- HIV is an independent risk determinant for major atherosclerotic events
- Increased risk of ASCVD persists in PWH who have achieved viral suppression
- Poorer inpatient outcomes for PWH hospitalized with AMI or stroke
- HIV contributes more to the burden of cardiovascular disease in sub-Saharan Africa than anywhere else in the world

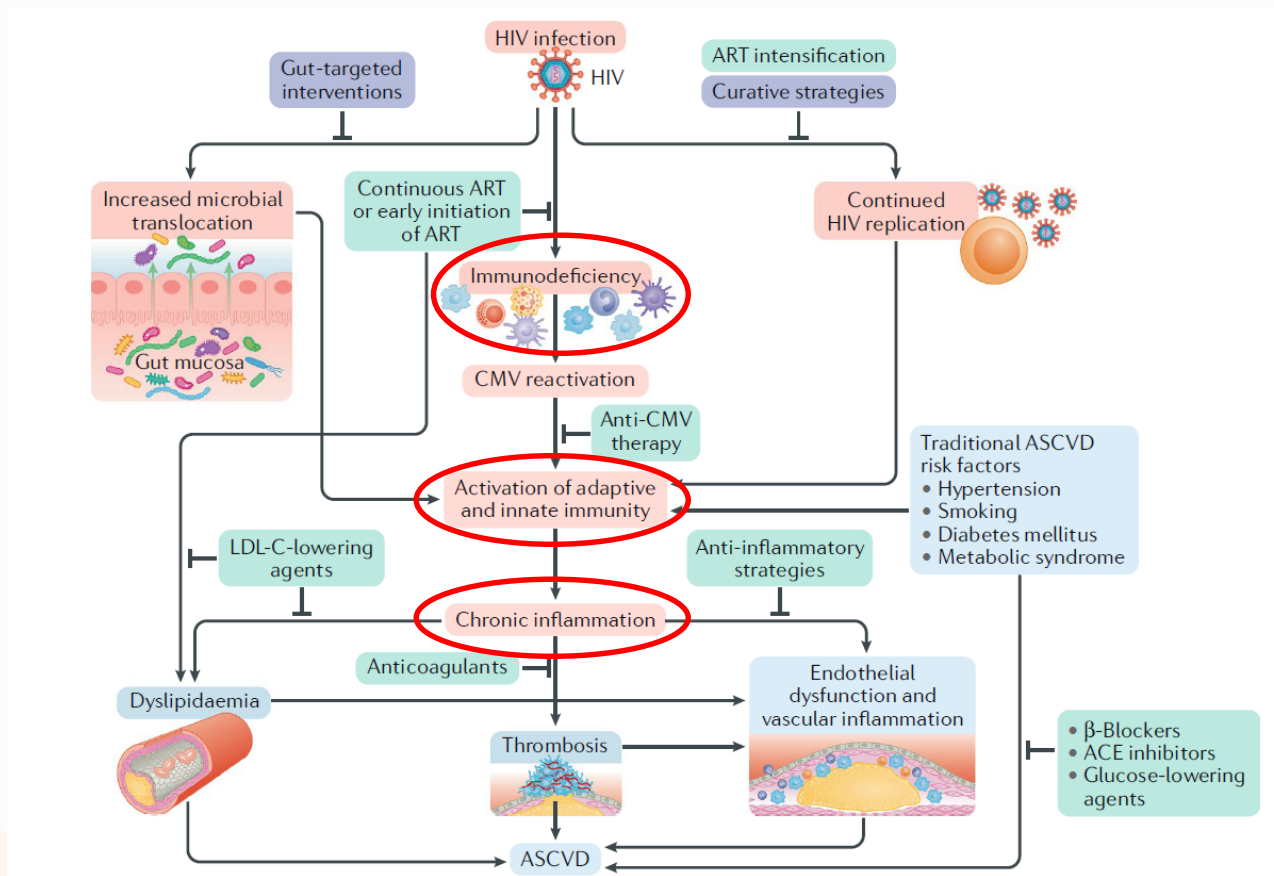
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Antiretroviral Therapy
Aging





Nature Card Rev, 2019

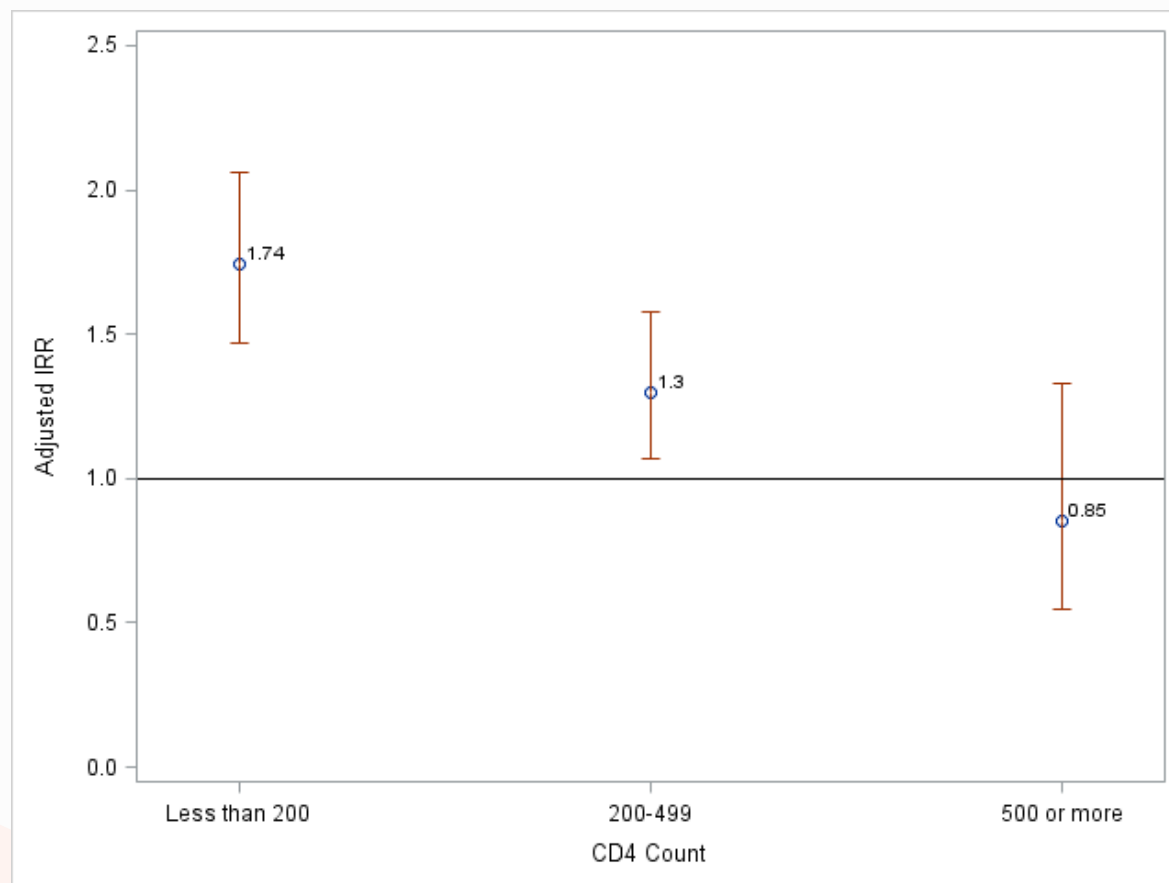
Kaiser Northern California, 2014

- Prospective cohort: 1996-2009
- 22081 HIV+, 230069 matched uninfected
- Restricted to HIV+ persons with complete ART history
- Cohort Demographics
 - 90.5% men, 55% White, 43% current/former smokers
 - 3% diabetes, 5% statin, 7% hypertension, mean CD4 400 cells/mL
- 39% with “history of clinical AIDS”
- 80% on ART by the end of study period
- **IRR for MI: 1.44 (95% CI 1.27,1.64)**

J Acquir Immune Defic Syndr 2014;65:160–166



Adjusted Incidence Rate Ratio (IRR) for MI by CD4 Nadir





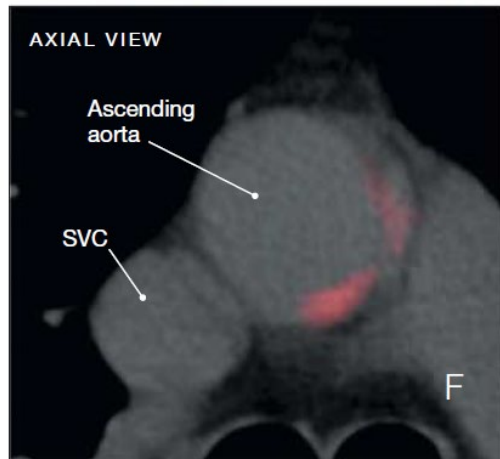
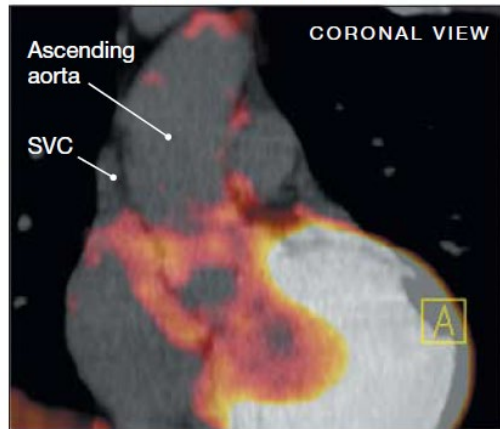
Immunodeficiency and Chronic Inflammation

- Increased T-cell activation
 - ↑ CD38+ T-cells
- Increased T-cell senescence
 - ↑ CD28- and/or CD57 + T-cells
- Increased peripheral markers of monocyte activation
 - sCD163 and CD14
- Increased circulating “intermediate” monocytes
 - CD14⁺⁺CD16⁺ monocytes, pro-secretory in response to LPS
- Increased circulating levels of IL-6, CRP, sTNFR, D-Dimer

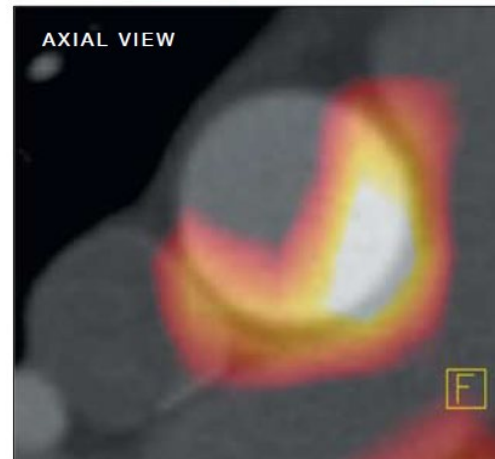
J Infect Dis. 2012 Jun;205 Suppl 3:S375-82



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



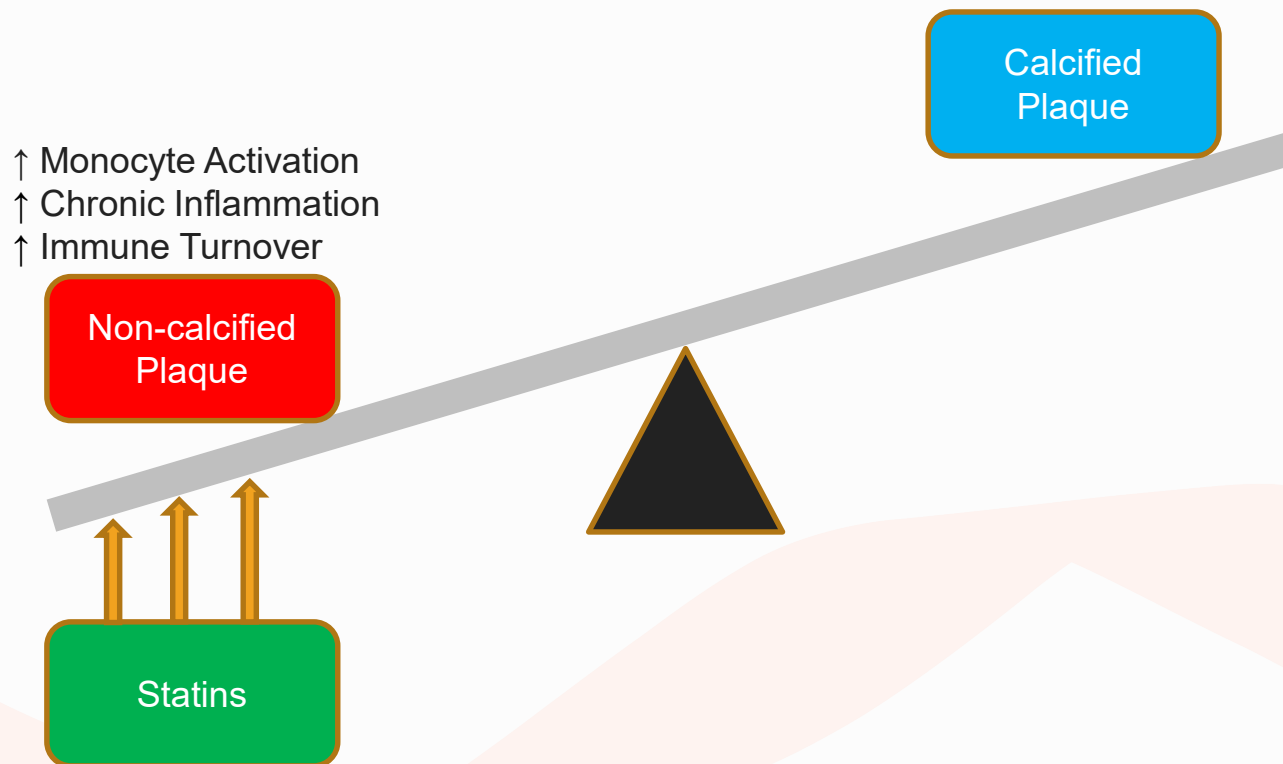
Participant with HIV
(Age 42 y, TBR=3.42)



JAMA. 2012 Jul 25;308(4):379-86.



Presence of non-calcified plaque:
58% v. 17%



Atherosclerosis 240, 197–204 (2015).

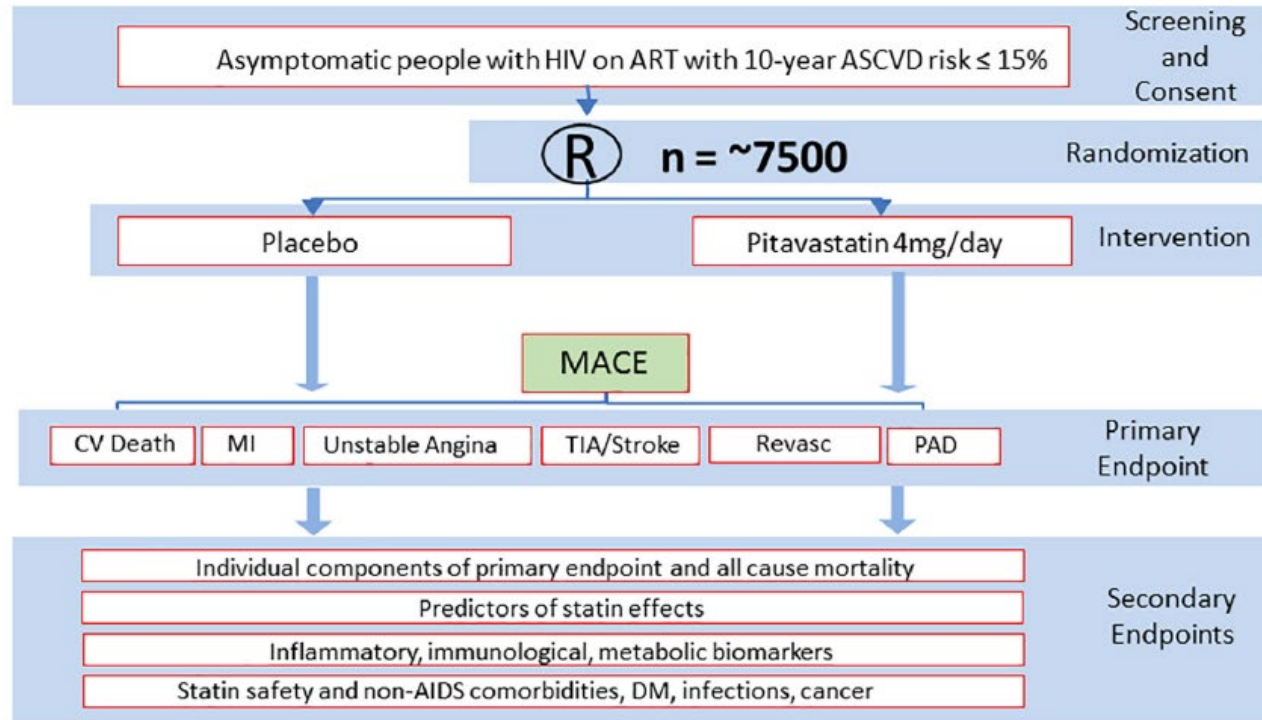


REPRIEVE

Randomized Trial to Prevent Vascular Events in HIV

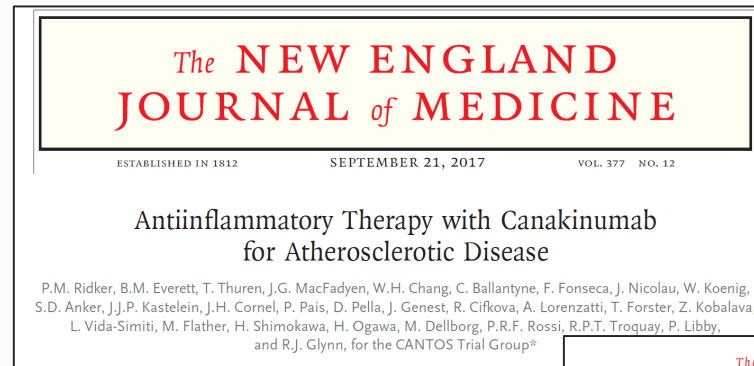
Time

Up to 8 yrs



Inflammation and ASCVD in HIV: Investigational Approaches

- Aspirin
- Methotrexate
- Canakinumab



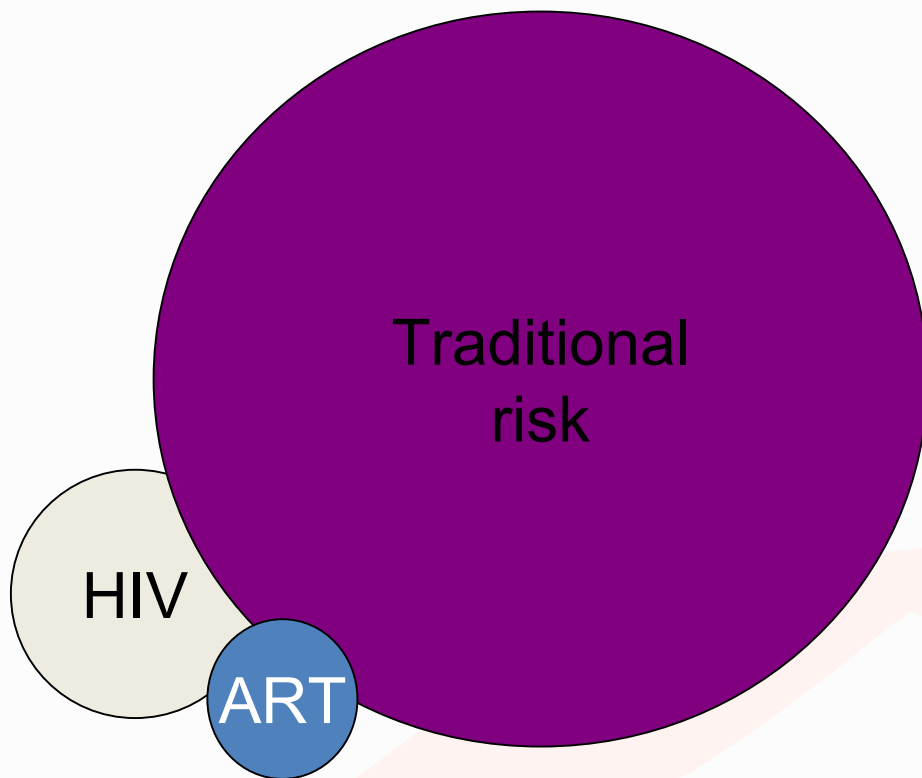
J. Am. Coll. Cardiol. 72, 2809–2811 (2018)
Clin Infect Dis. 2019 May 17;68(11):1877-1886

ASCVD in PLH: Pathophysiology

- Immunosuppression (current and historic) is associated with ASCVD risk in PLH
- Convergence of sequelae of immunodeficiency, increased immune turnover, increased microbial translocation and viral co-infections lead to a pro-inflammatory state promoting atherosclerosis progression
- Pro-inflammatory state leads to predominance of non-calcified, less-stable coronary plaque which may contribute to increased events
- Statins may be more beneficial in attenuating CVD risk in PLH than uninfected persons

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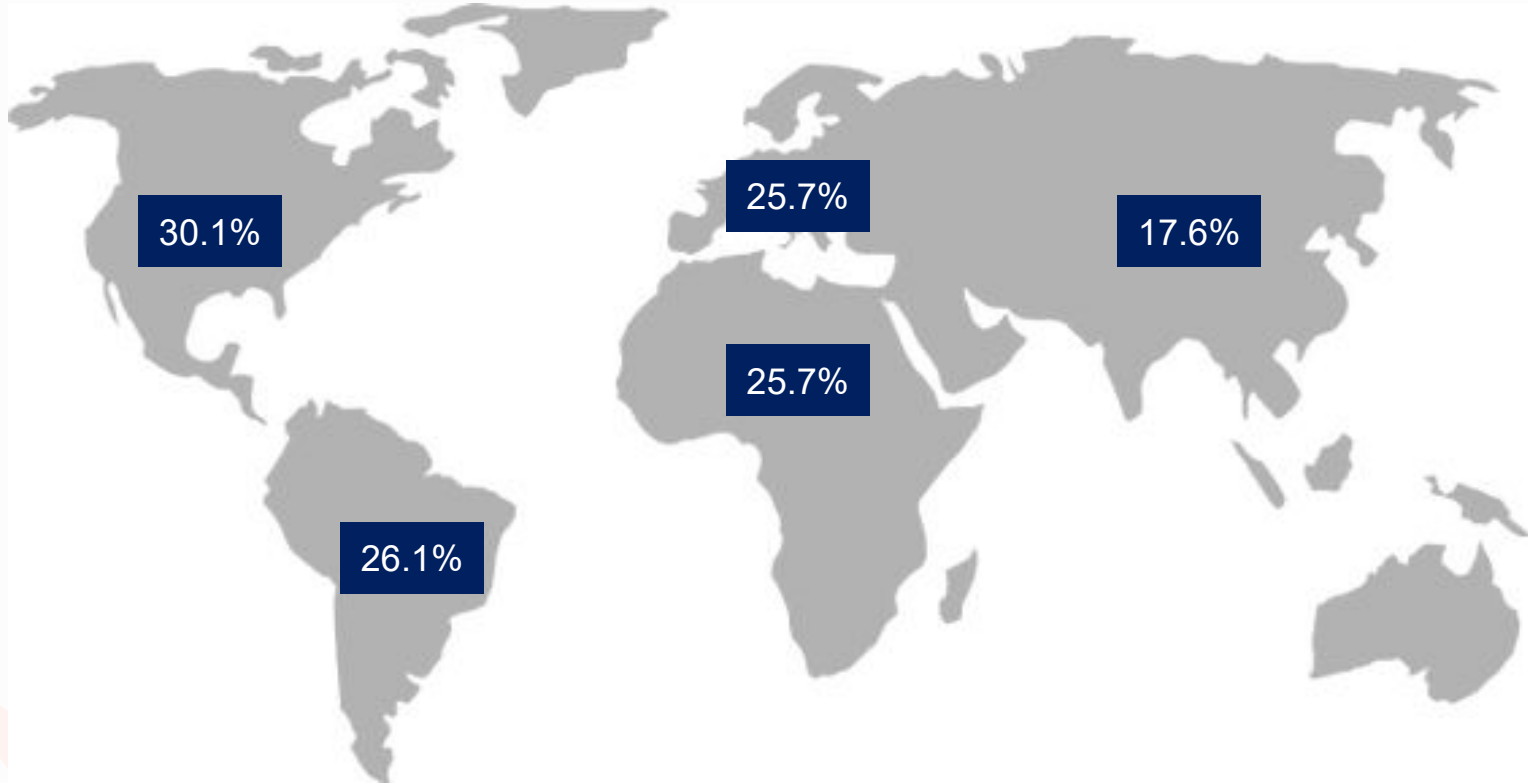
Traditional ASCVD Risk Factors

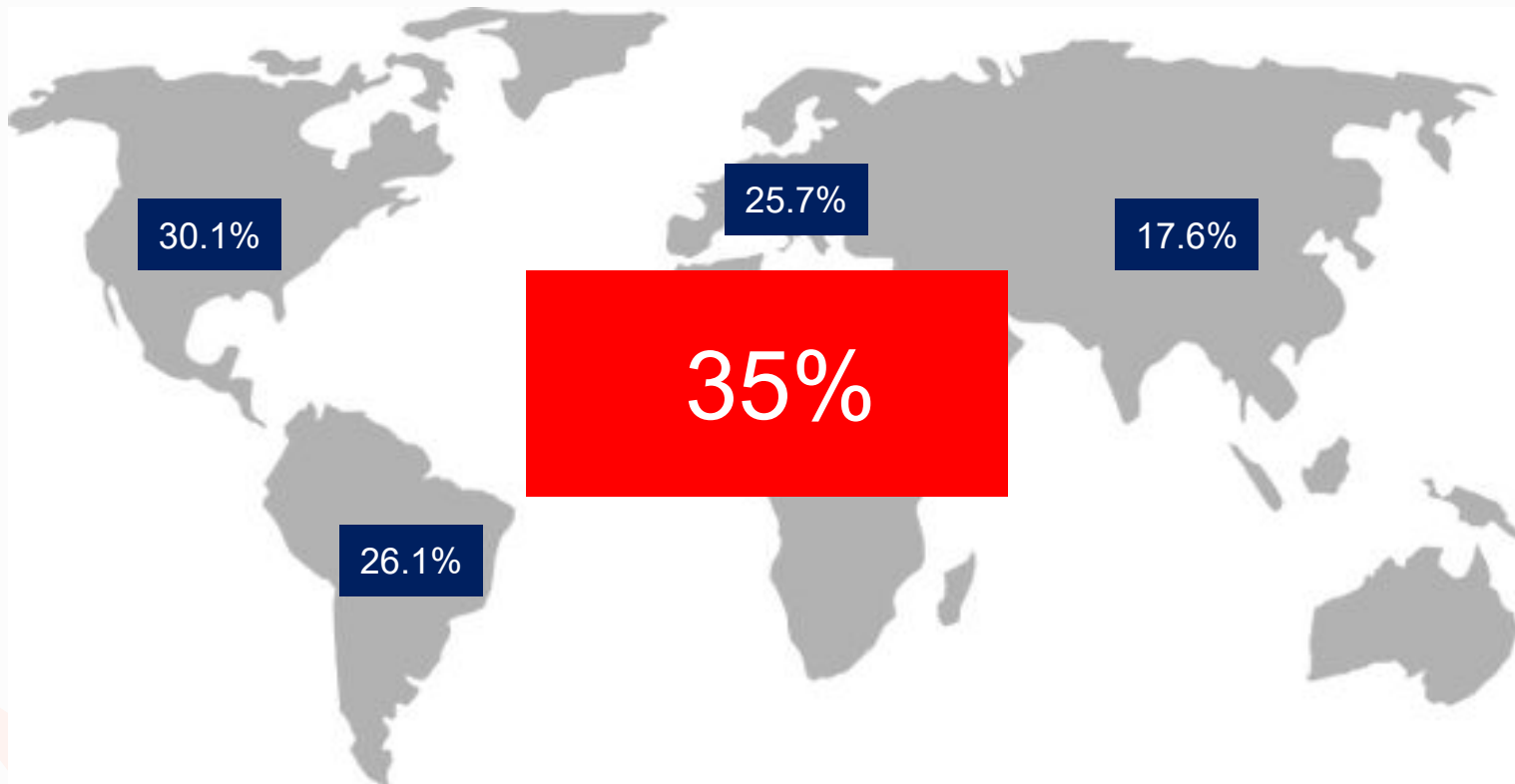
- Hypertension
- Dyslipidemia
- Tobacco Use
- Obesity
- Antiretroviral Therapy

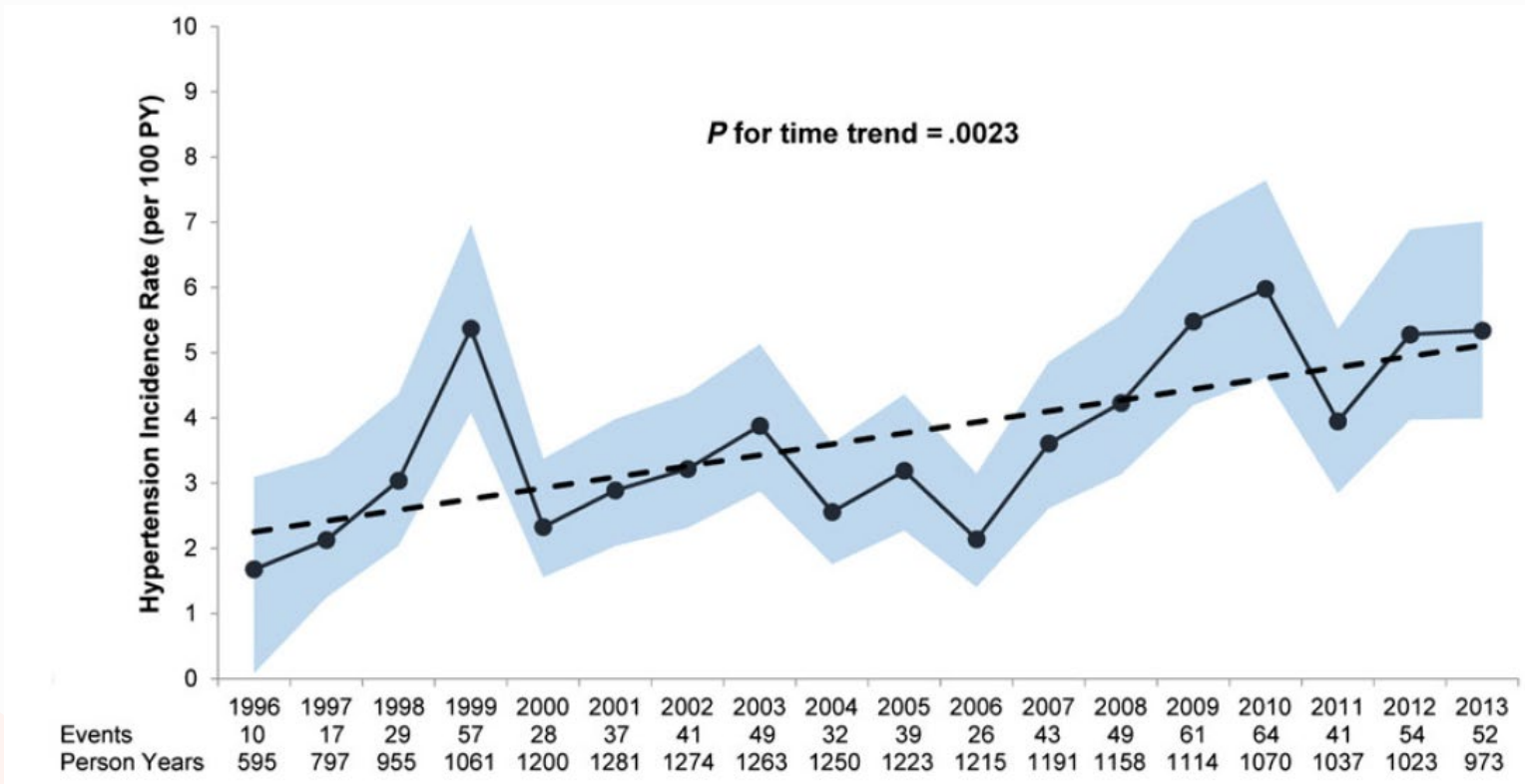
Hypertension in Persons with HIV

- Metanalysis of 49 studies (2018)
 - 25 from North and South America
 - 13 from Europe
 - 10 from Africa
 - 1 from Asia
- 63,554 people with HIV between 1996-2014

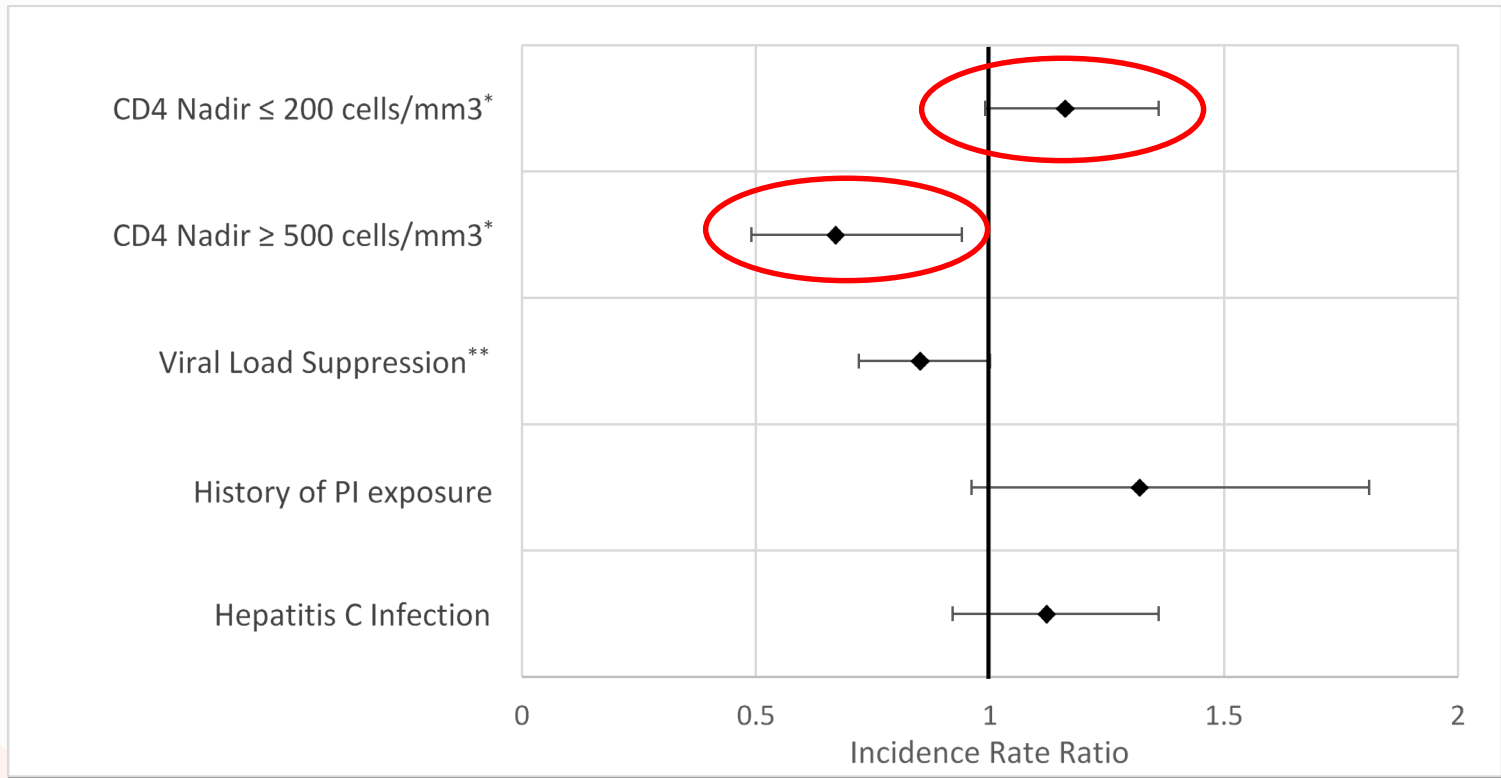
J Am Soc Hypertens.2017;11:530-540.







Clin Infect Dis (63): 242-248



Point estimates for association of HIV biomarkers and incident hypertension

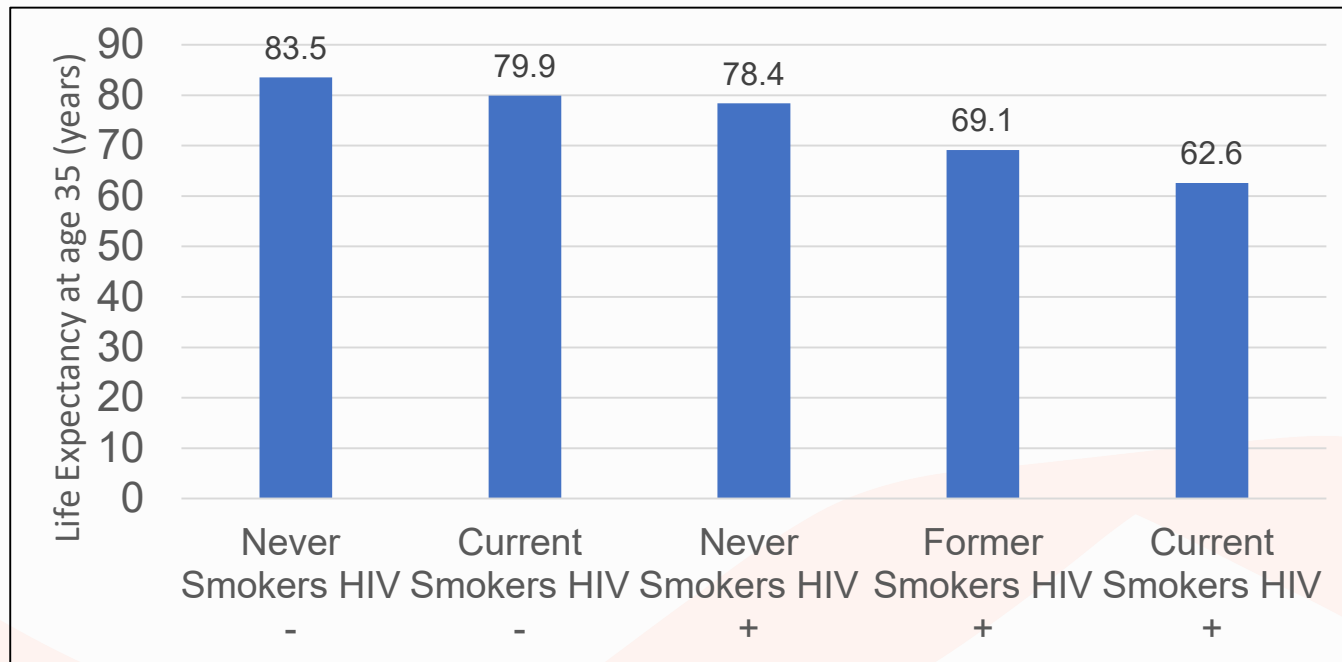
HIV, ASCVD and Tobacco Use

- Approximately 40% of PWH use tobacco
- Tobacco use appears to account for more of the attributable risk of MI in HIV+ than in HIV-
- The interactions between smoking-induced vascular inflammation and chronic HIV infection are not well established

Nature Card Rev, 2019



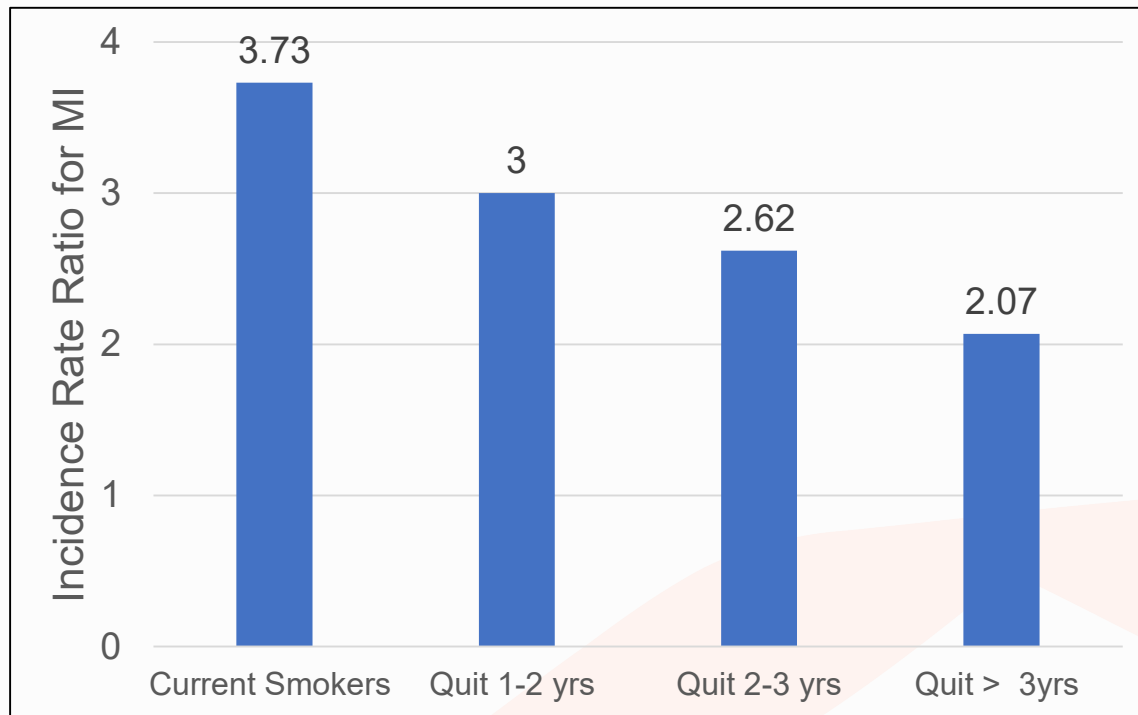
Danish HIV Cohort Study/Copenhagen General Population Study, 1995-2010 (n = 13563)



Clin. Infect. Dis. 56,727-734 (2013).

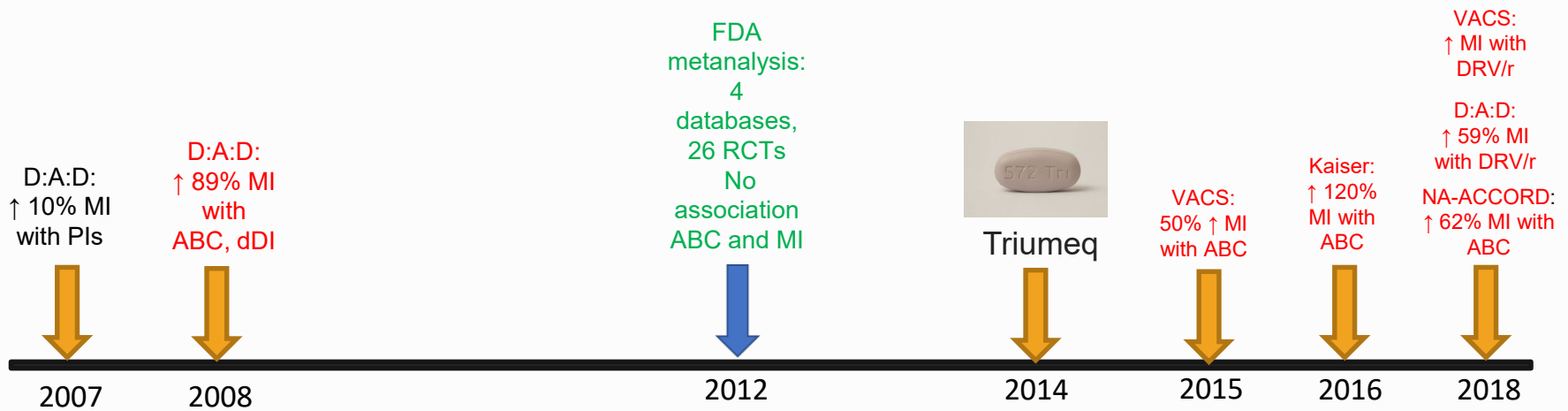


D:A:D Study Cohort (n = 11951)



HIV Med.12, 412-421 (2011).





N. Engl. J. Med. 356,1723–1735 (2007)
 Lancet 371, 1417–1426 (2008).
 J Acquir Immune Defic Syndr. 2012 Dec 1;61(4):441-7
 Clin Infect Dis. 2015 Aug 1;61(3):445-52
 Lancet HIV 5, e291–e300 (2018).
 J Acquir Immune Defic Syndr. 2016 Apr 1;71(4):413-9.
 J. Acquir. Immune Defic. Syndr. 78, 62–72 (2018).



Recommended Initial Regimens, DHHS 2018

- BIC/TAF/FTC (AI)
- **DTG/ABC/3TC (AI)**
- DTG + TDF/FTC or TAF/FTC
- RAL + TDF/FTC or TAF/FTC

DHHS, 2018

Bourgi et al. 2019

- 1152 ART- naïve PWH at Vanderbilt HIV Clinic
- Followed for 18 months
- Weight gain at 18 months
 - Elvitegravir – 0.5kg
 - NNRTI – 2.6kg
 - Raltegravir - 3.4kg
 - Protease Inhibitors – 4.1kg
 - **Dolutegravir – 6.0kg**

Clin Infect Dis. 2019 May 17.

Recommended Initial Regimens, DHHS 2019

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- DTG/ABC/3TC (AI)
- DTG + TDF/FTC or TAF/FTC
- RAL + TDF/FTC or TAF/FTC
- DTG + 3TC

ASCVD in PLH: Traditional Risk Factors

- Increased prevalence of tobacco use, dyslipidemia, hypertension among PWH then uninfected population
- Hypertension incidence increasing and their may be a physiologic basis for this observation
- Tobacco use may be disproportionately deleterious in PWH but mechanisms unknown
- The role of contemporary ART in metabolic dysfunction and MI risk is being elucidated

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Likelihood for Medication Prescription HIV v. Matched non-HIV (n = 1697)

Medication	Adjusted OR (95% CI)	p-value
Aspirin	0.53 (0.40-0.71)	<0.000 1
Statin	0.70 (0.53-0.92)	0.01
Antihypertensives	0.63 (0.50-0.79)	<0.000 1

AIDS Care. 2016;28(4):475-82



CVD care in PLWH

- PLH are less likely to receive evidence-based medications for CVD primary prevention
- Ladapo et al. (2017)
 - Guideline-indicated prescription of primary prevention medications
 - National Hospital Ambulatory Medical Care Survey
 - Aspirin 5.1% v. 13.8% ($p = 0.03$)
 - Statin 23.6% v. 35.8% ($p < 0.01$)
 - Antihypertensives 53.4% v. 58.6%

J Am Heart Assoc. 2017 Nov 14;6(11)

CVD care in PLWH

- PLH are less likely to receive evidence-based medications for CVD primary prevention

- Ladhani et al (2017)

- G

m

- N

Higher CVD risk patients, less comprehensive CVD preventative care

- Antihypertensives 53.4% v. 58.6%

J Am Heart Assoc. 2017 Nov 14;6(11)

Relative Risk for meeting JNC-8 Blood Pressure Goals among Persons Living with HIV (n = 1296)

Variable	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Female	0.98 (0.85-1.15)	1.02 (0.92-1.13)
Black	0.90 (0.77-1.04)	0.89 (0.81-0.99)
Hispanic	0.98 (0.62-1.55)	0.96 (0.71-1.29)
Age (per 10 year increase)	1.01 (0.92-1.11)	1.00 (0.99-1.01)
Medicaid/Medicare	1.01 (0.87-1.17)	0.88 (0.55-1.40)
Self Pay	0.95 (0.76-1.18)	0.85 (0.53-1.35)
Antihypertensive Prescribed by ID Clinic	0.79 (0.66-0.94)	0.80 (0.70-0.91)

Okeke et al., CROI 2019, Poster 666

Relative Risk for meeting NLA non HDL-c Goals
among Persons Living with HIV (n = 889)

Variable	Unadjusted RR (95% CI)	Adjusted RR (95%CI)
Female	0.92 (0.72-1.16)	0.97 (0.75-1.24)
Black	0.97 (0.78-1.21)	1.02 (0.81-1.30)
Hispanic	1.16 (0.71-1.88)	1.56 (0.99-2.46)
Age (per 10 year increase)	1.23 (1.08-1.40)	1.18 (1.04-1.35)
Medicaid/Medicare	1.13 (0.91-1.40)	1.01 (0.22-1.53)
Self Pay	0.98 (0.73-1.32)	1.02 (0.68-1.51)
Statin Prescribed by ID Clinic	0.72 (0.53-0.97)	0.75 (0.59-0.94)

Okeke et al., CROI 2019, Poster 666



How might we support HIV providers to provide the best primary preventative CVD care possible?

Clinic Visit with C.M.

- Diagnosed with HIV in 2001
 - 2004-2009: LPV/r + FTC/TDF
 - 2009-2015: EFV/FTC/TDF
 - **2015- : DTG/ABC/3TC**
- PMH otherwise negative
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Lisinopril 10mg, Aspirin 81mg, Clopidogrel 75mg,
Triumeq

Take Home Points

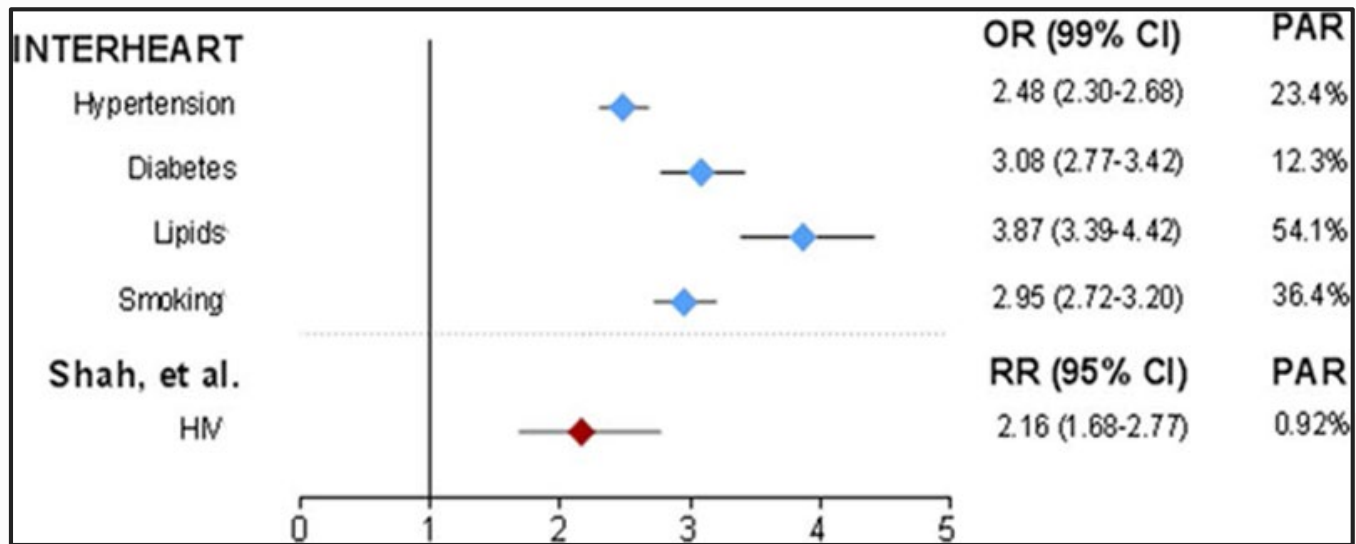
- Persons living with HIV are twice as likely to suffer MI or stroke even after viral suppression
- Atherosclerosis in PWH has a unique pathobiology; investigations of mechanisms and potential interventions are ongoing
- Modifiable ASCVD risk factors have a higher prevalence in PWH than the general population
- Improving modifiable ASCVD risk factors remains **by far** the best way to reduce ASCVD risk in persons with HIV

Circulation

AHA SCIENTIFIC STATEMENT

Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV

A Scientific Statement From the American Heart Association



Feinstein et al., 2019