

An Integrative Approach to Cardiovascular Disease Prevention for People Living with HIV

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Disclosures

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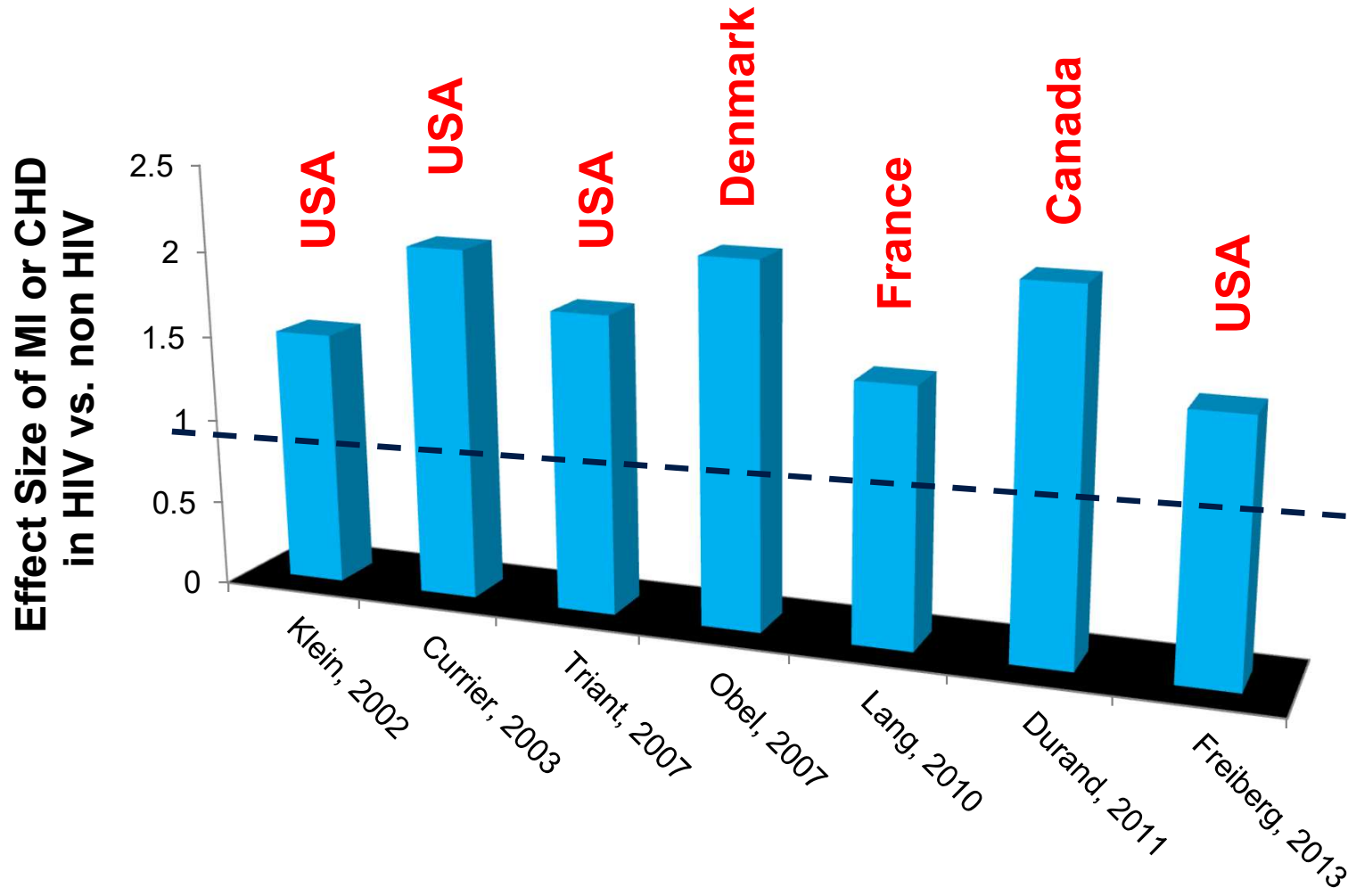
Gilead Pharmaceuticals (research grant)

All relevant financial relationships have been mitigated.

Outline

- **Epidemiology of CVD risk in people living with HIV**
- **Part 1: Mechanisms of CVD risk in PLWH**
 - Inflammation
 - Traditional risk factors
 - (ART)
- **Part 2: An integrated approach to CVD prevention for PLWH**
 - Two cases
 - Management pearls
 - Nurse-led management of CVD prevention care
- **Conclusions**

PLWH have a higher risk of coronary disease



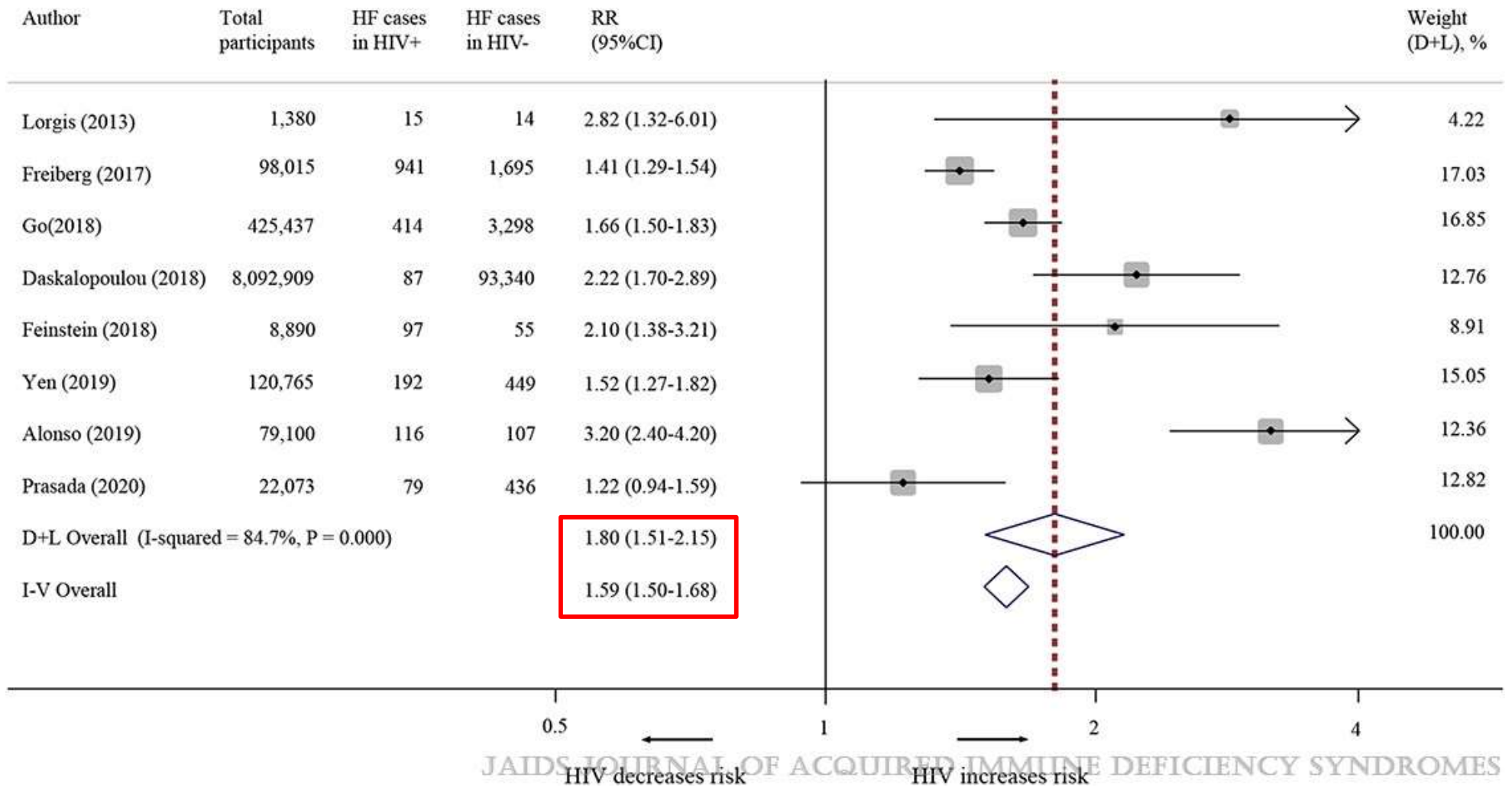
Association Between HIV Infection and the Risk of Heart Failure With Reduced Ejection Fraction and Preserved Ejection Fraction in the Antiretroviral Therapy Era

Results From the Veterans Aging Cohort Study

Matthew S. Freiberg, MD, MSc; Chung-Chou H. Chang, PhD; Melissa Skanderson, MSW; Olga V. Patterson, PhD; Scott L. DuVall, PhD; Cynthia A. Brandt, MD, MPH; Kaku A. So-Armah, PhD; Ramachandran S. Vasan, MD; Kris Ann Oursler, MD, ScM; John Gottdiener, MD; Stephen Gottlieb, MD; David Leaf, MD, MPH; Maria Rodriguez-Barradas, MD; Russell P. Tracy, PhD; Cynthia L. Gibert, MD, MS; David Rimland, MD; Roger J. Bedimo, MD, MS; Sheldon T. Brown, MD; Matthew Bidwell Goetz, MD; Alberta Warner, MD; Kristina Crothers, MD; Hilary A. Tindle, MD, MPH; Charles Alcorn, MA; Justin M. Bachmann, MD, MPH; Amy C. Justice, MD, PhD; Adeel A. Butt, MD, MS

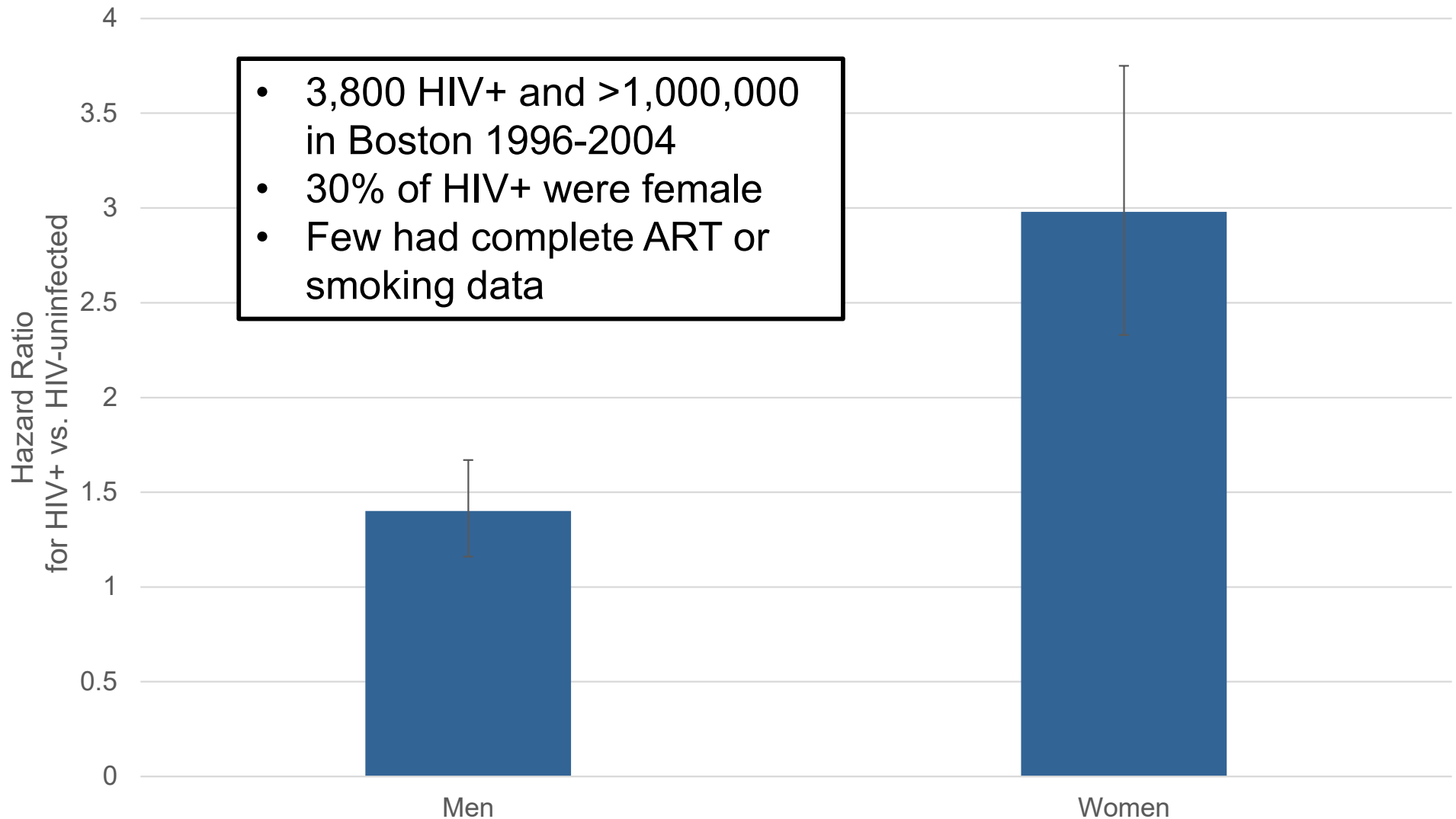
	HFpEF (EF >50%)	Borderline (EF 40-49%)	HFrEF (EF <40%)
Overall HIV	HR 1.2 (1.0-1.4)	1.4 (1.1-1.7)	1.6 (1.4-1.9)
White race	1.1 (0.9-1.5)	1.4 (1.0-2.1)	1.5 (1.2-2.0)
Black race	1.2 (0.9-1.4)	1.3 (1.0-1.8)	1.6 (1.4-1.9)
Age <40	1.2 (0.5-2.8)	2.1 (0.6-7.0)	3.6 (2.0-6.6)

Meta-analysis of heart failure risk

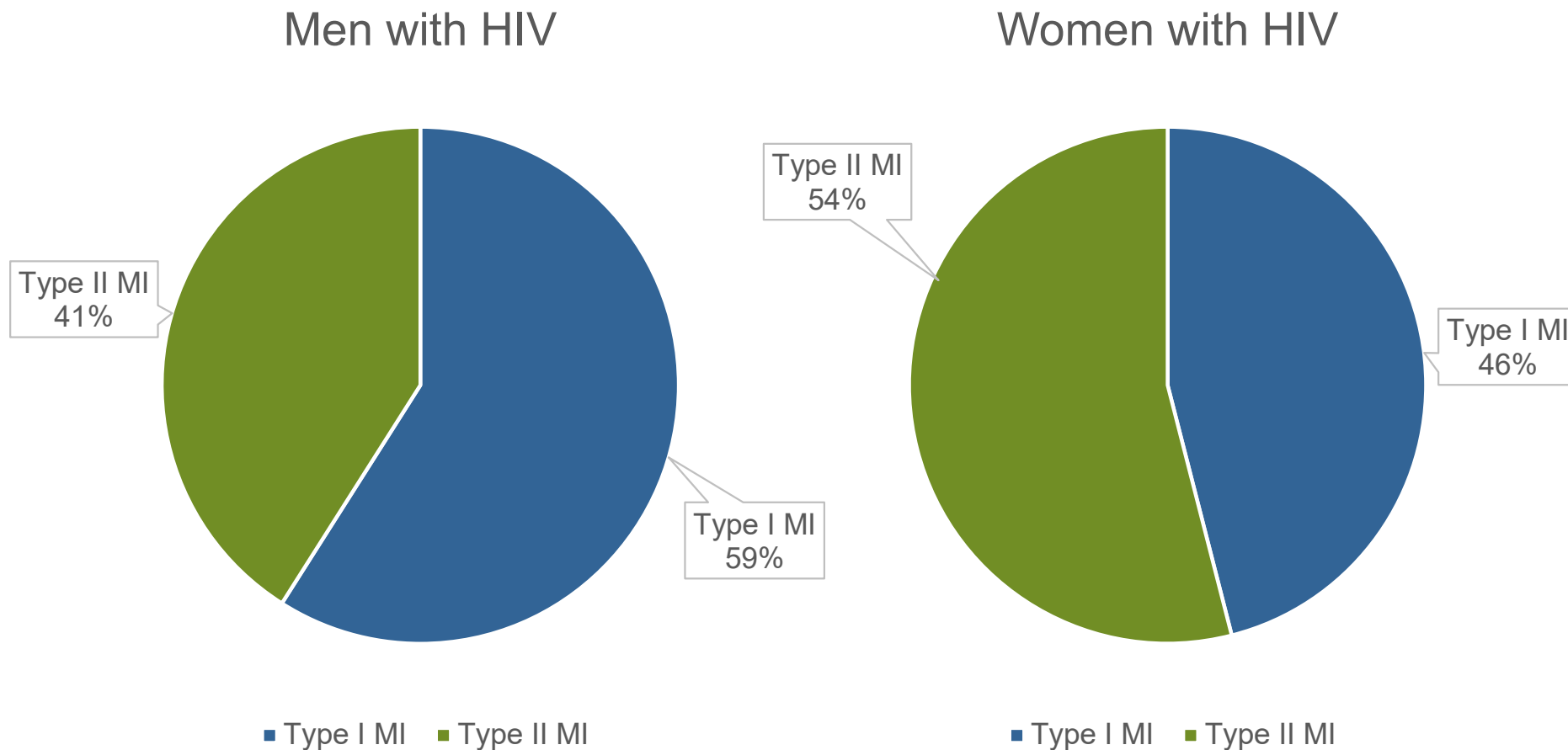


JAIDS JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES

HIV related risk of myocardial infarction is higher in women

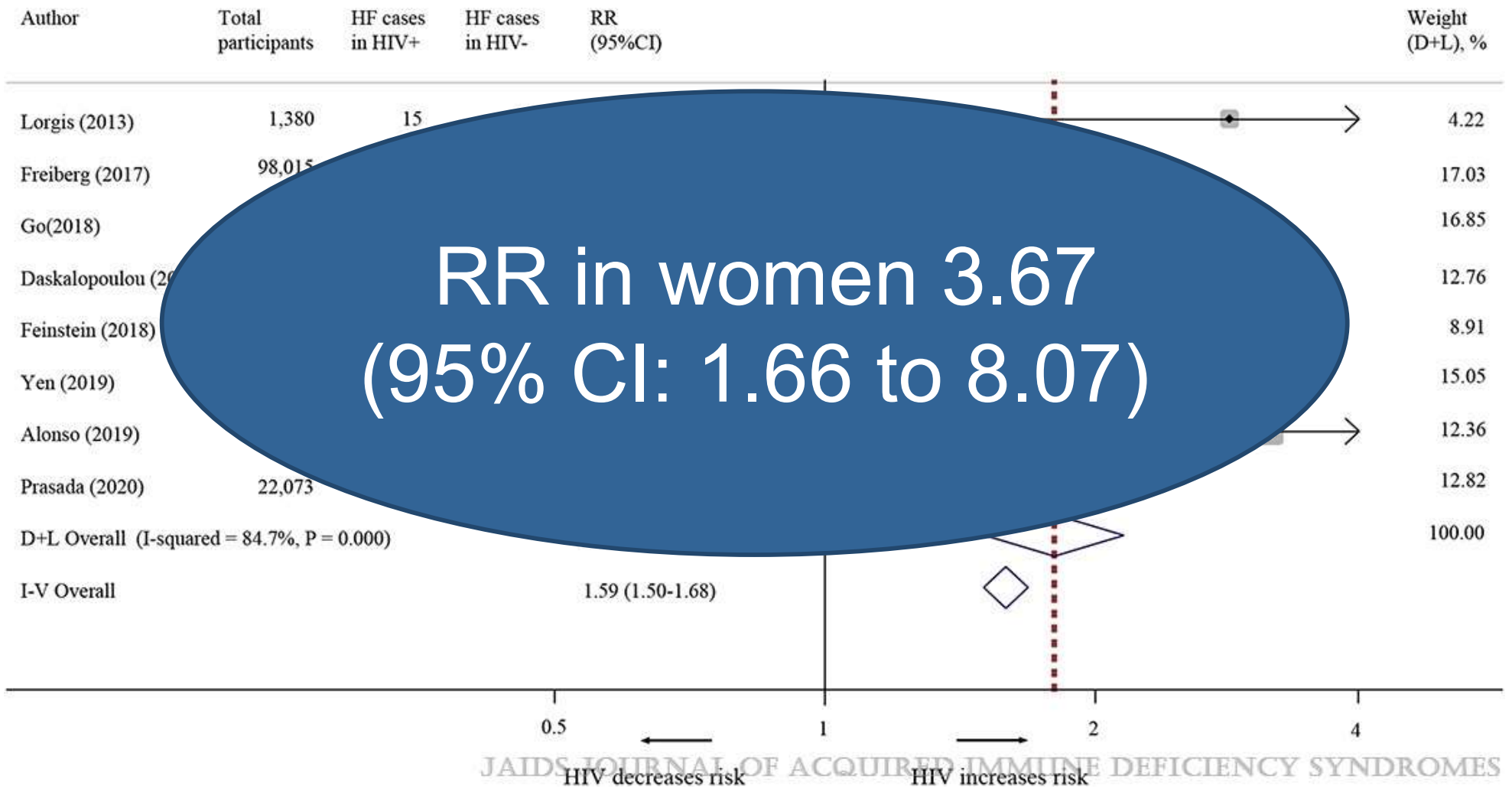


Type II MI more common in women than men

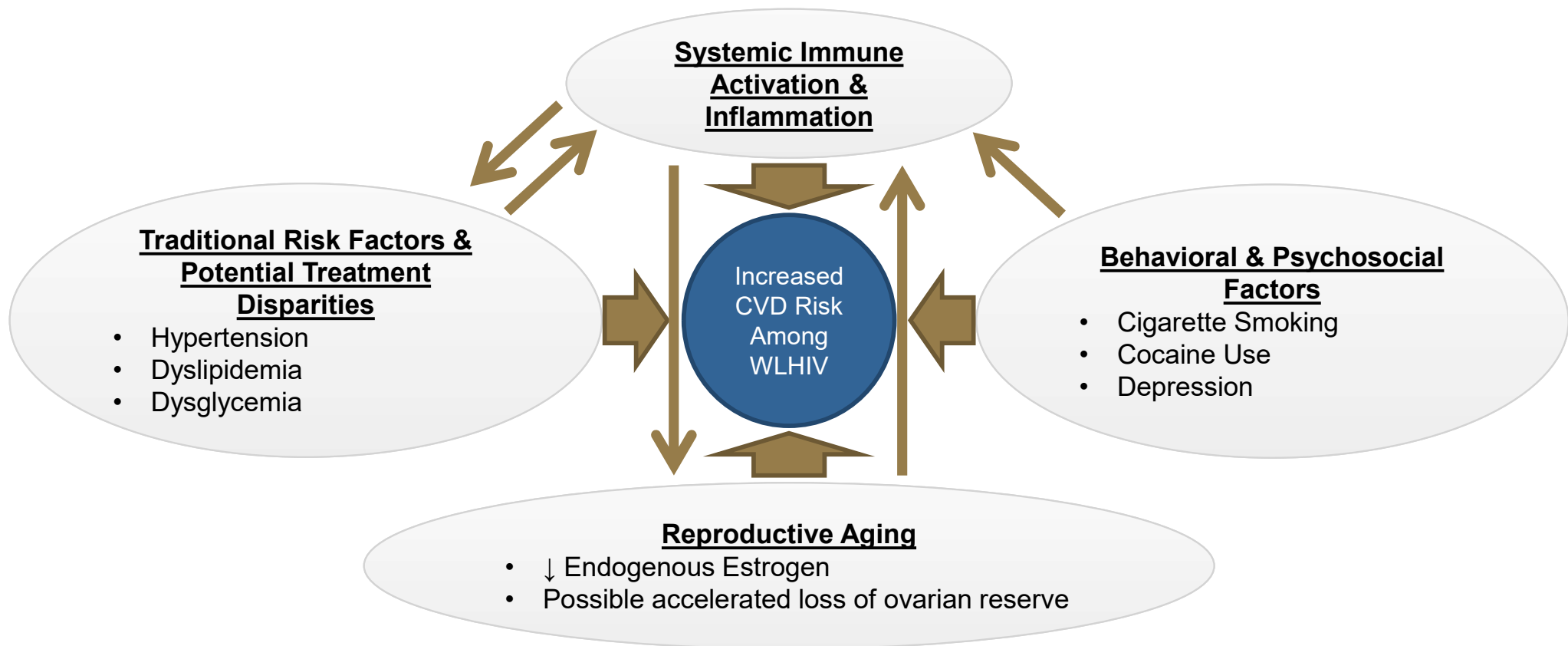


* Data from the CFAR Network of Integrated Clinical Systems (CNICS). No HIV-negative controls

HIV Heart Failure risk higher in women

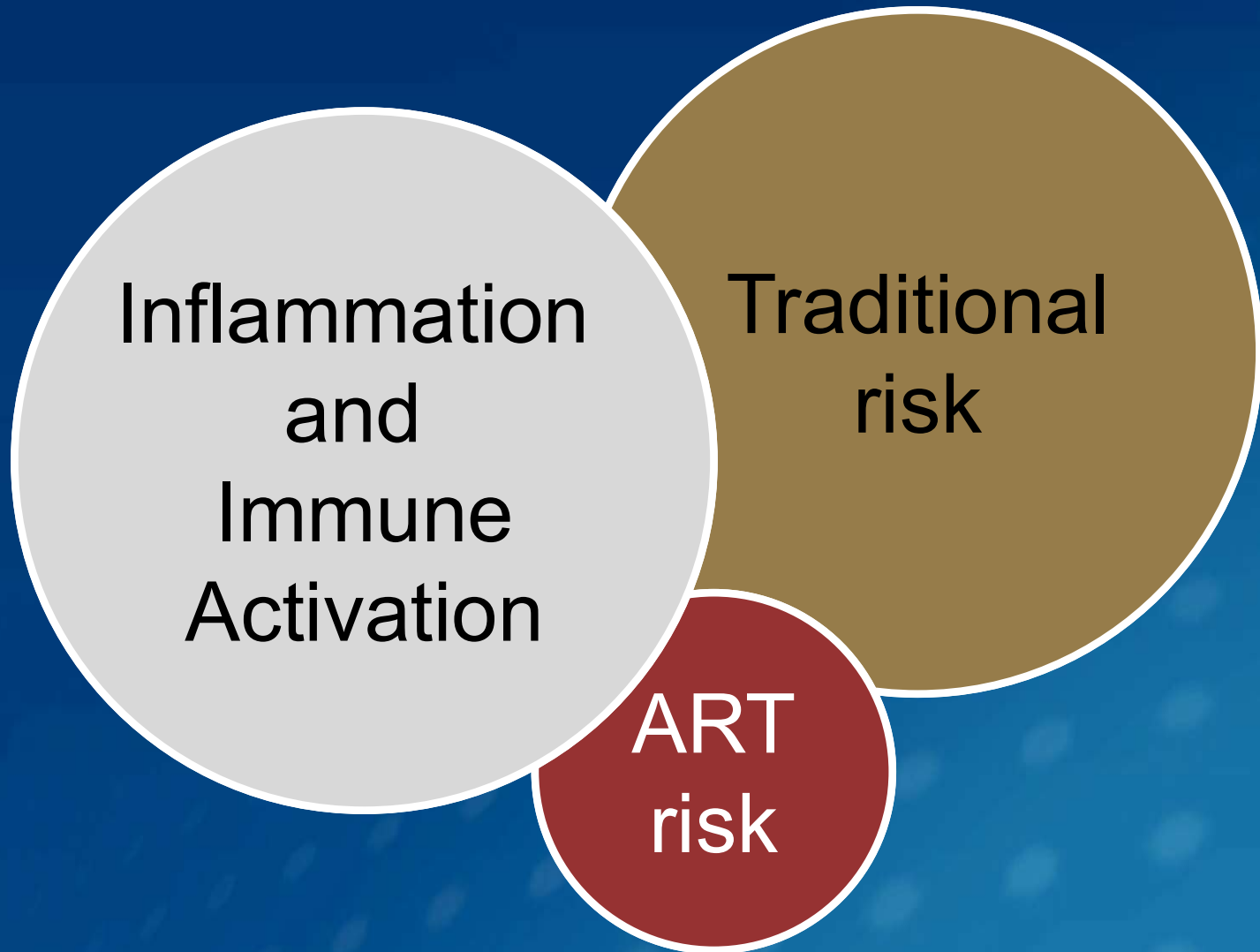


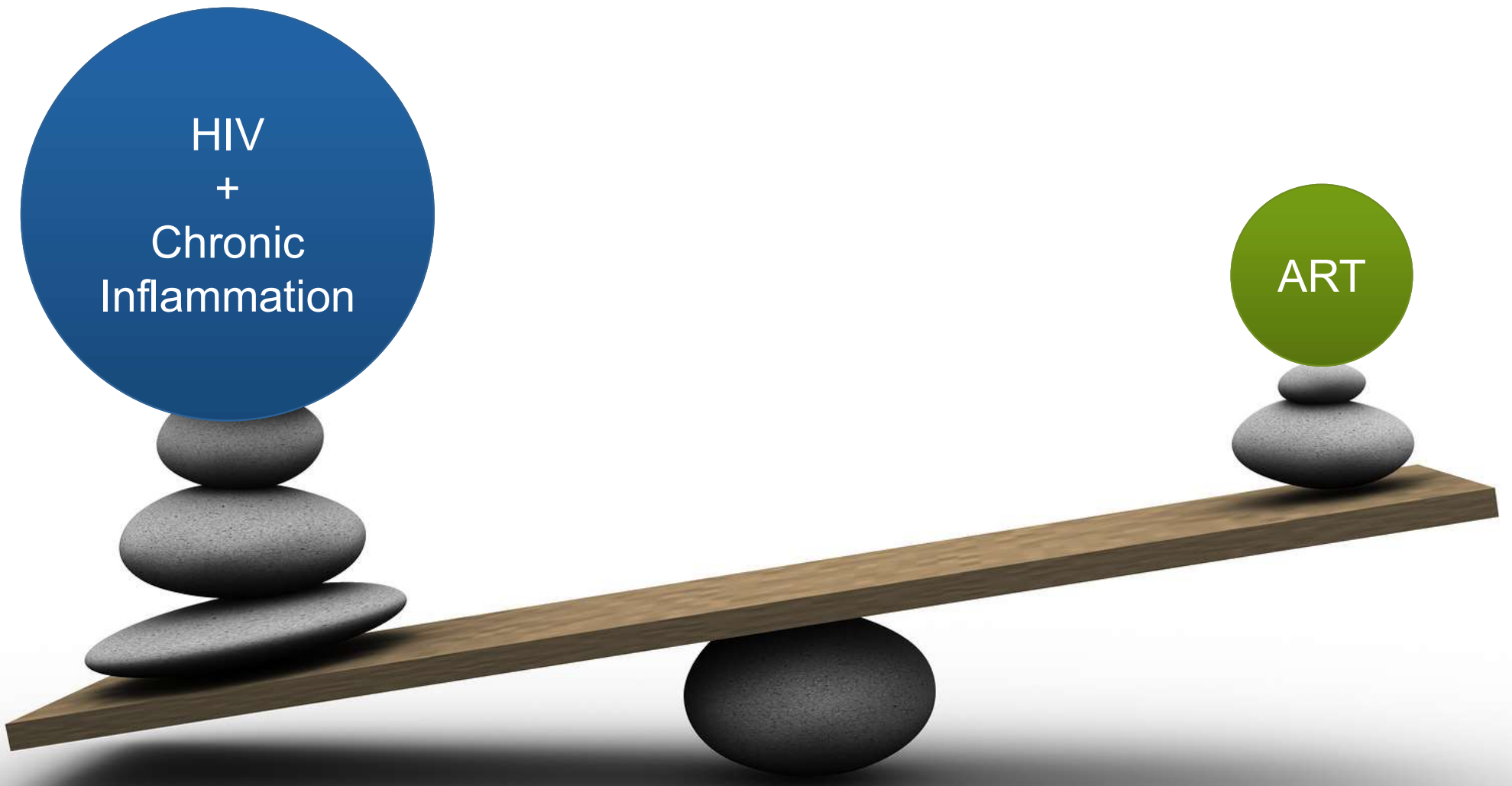
Mechanisms of risk in women with HIV



PART 1

Mechanisms of residual risk





START: No Difference in Cardiovascular Outcomes with Early vs. Delayed ART

Cardiovascular Events

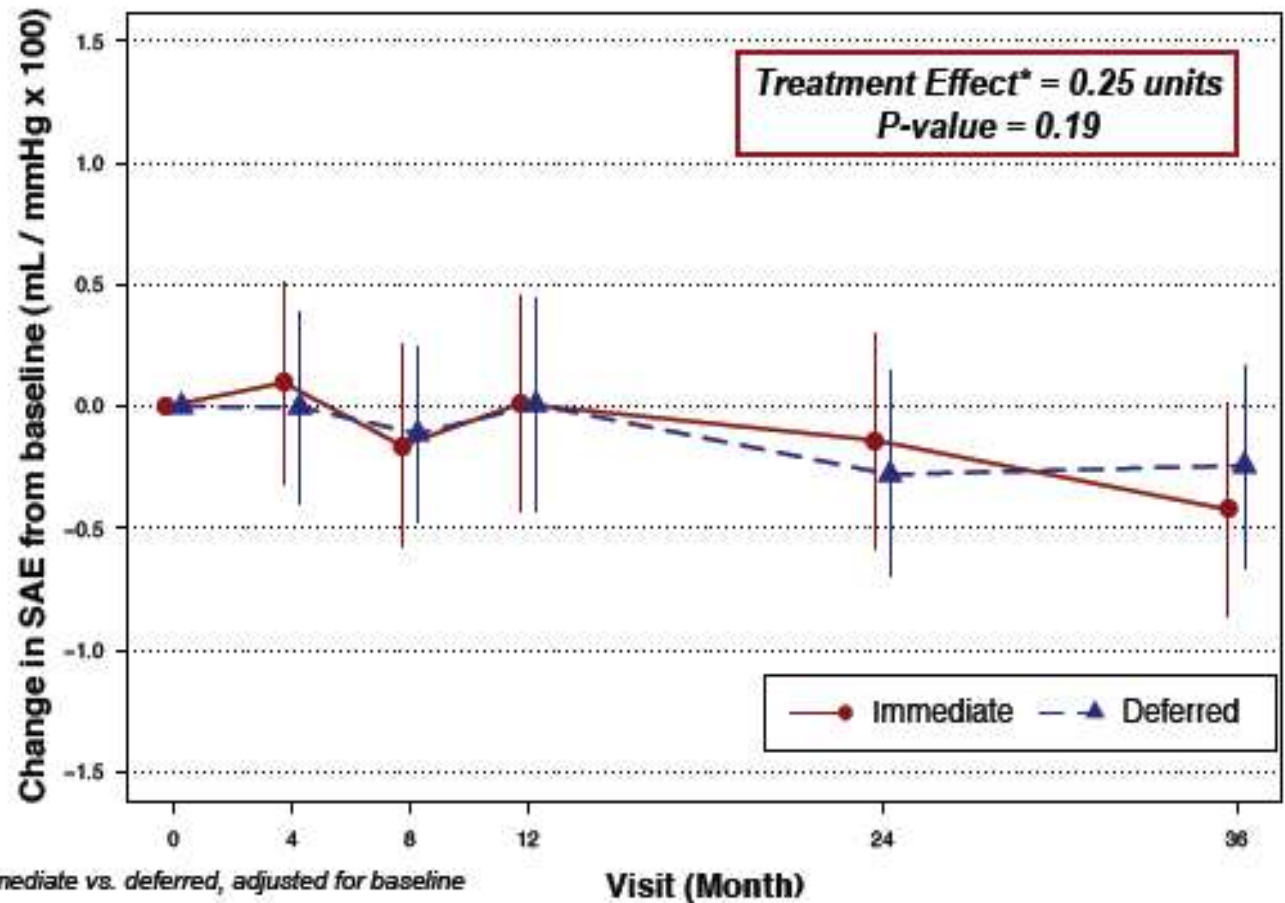
(Early vs. Delayed):

HR 0.84 (0.4-1.8)

P=0.65

Why?

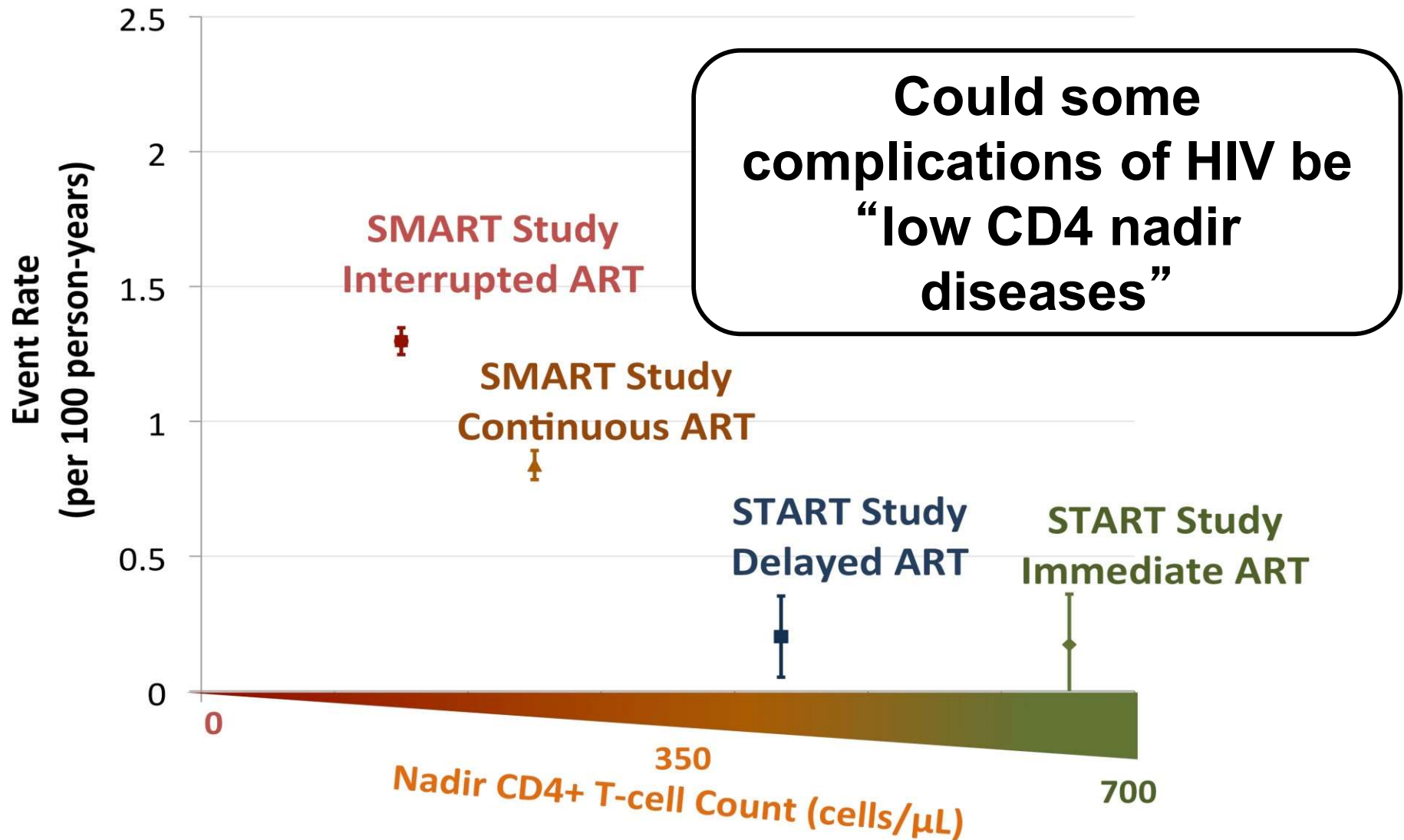
Small Artery Elasticity (higher better)



START

insight

Cardiovascular Complications Much Lower in START than SMART: Role of CD4 nadir



Canakinumab: IL-1 β Inhibition

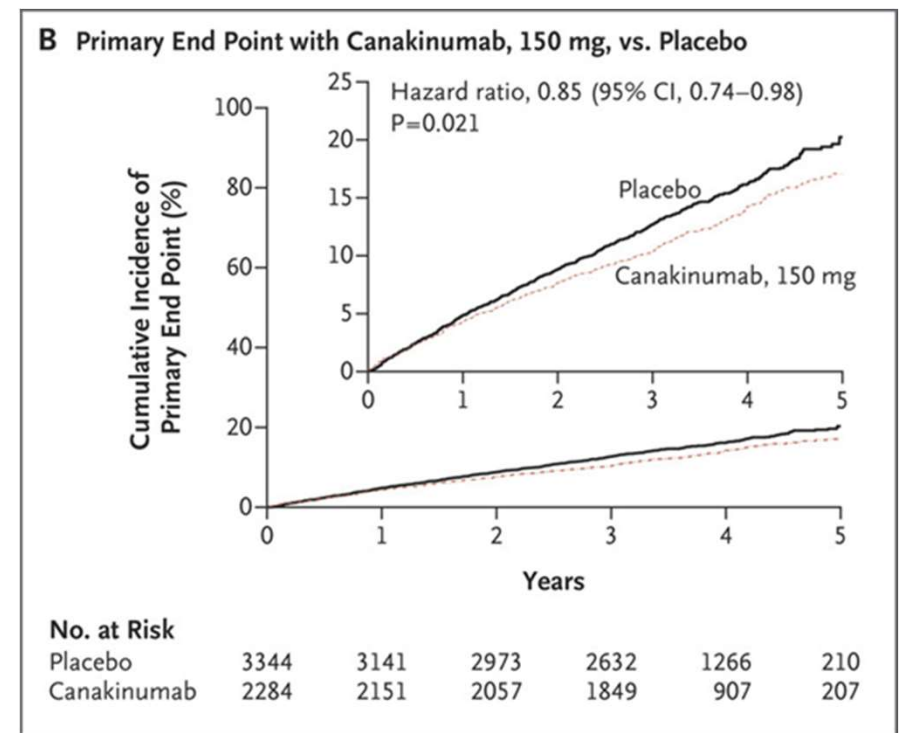
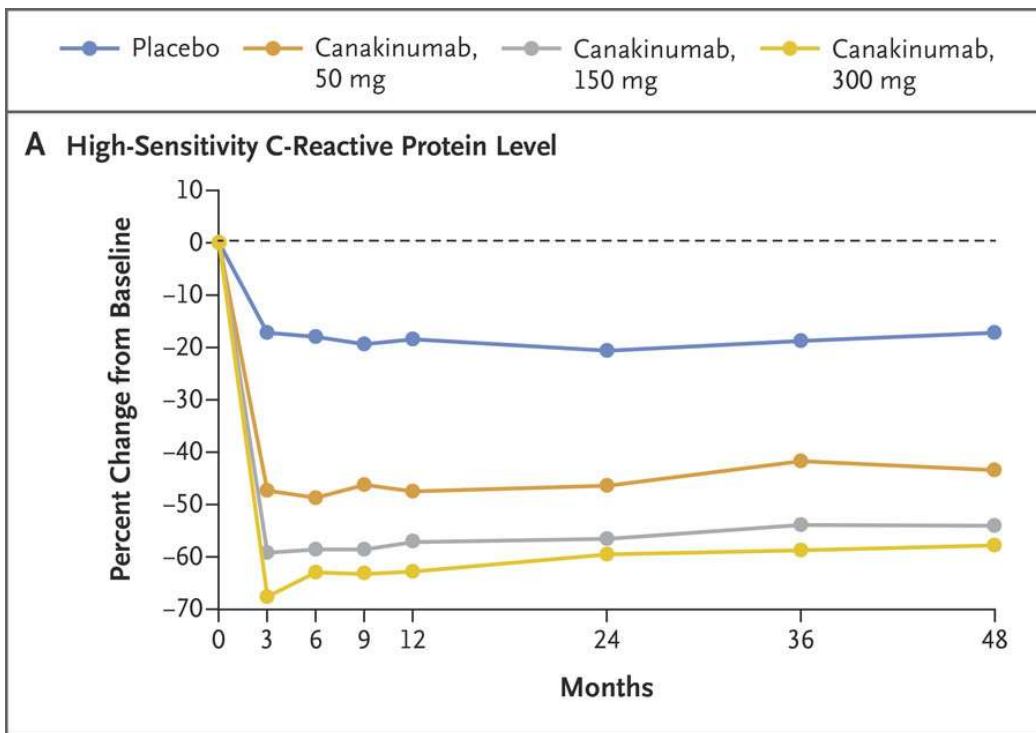
- N=110 HIV+ (40 enrolled as of 3/2/2020); Study completion Dec 2022
- >40 years on ART with high CVD risk
- **1° outcome: safety**– AEs @ week 1, 2, 4, 8, 12, 18
- **Co-2° outcome:** 0-12 week change in (A) FMD and (B) aortic FDG uptake by PET/CT
- Similar to **CANTOS** trial in the general population



CANTOS

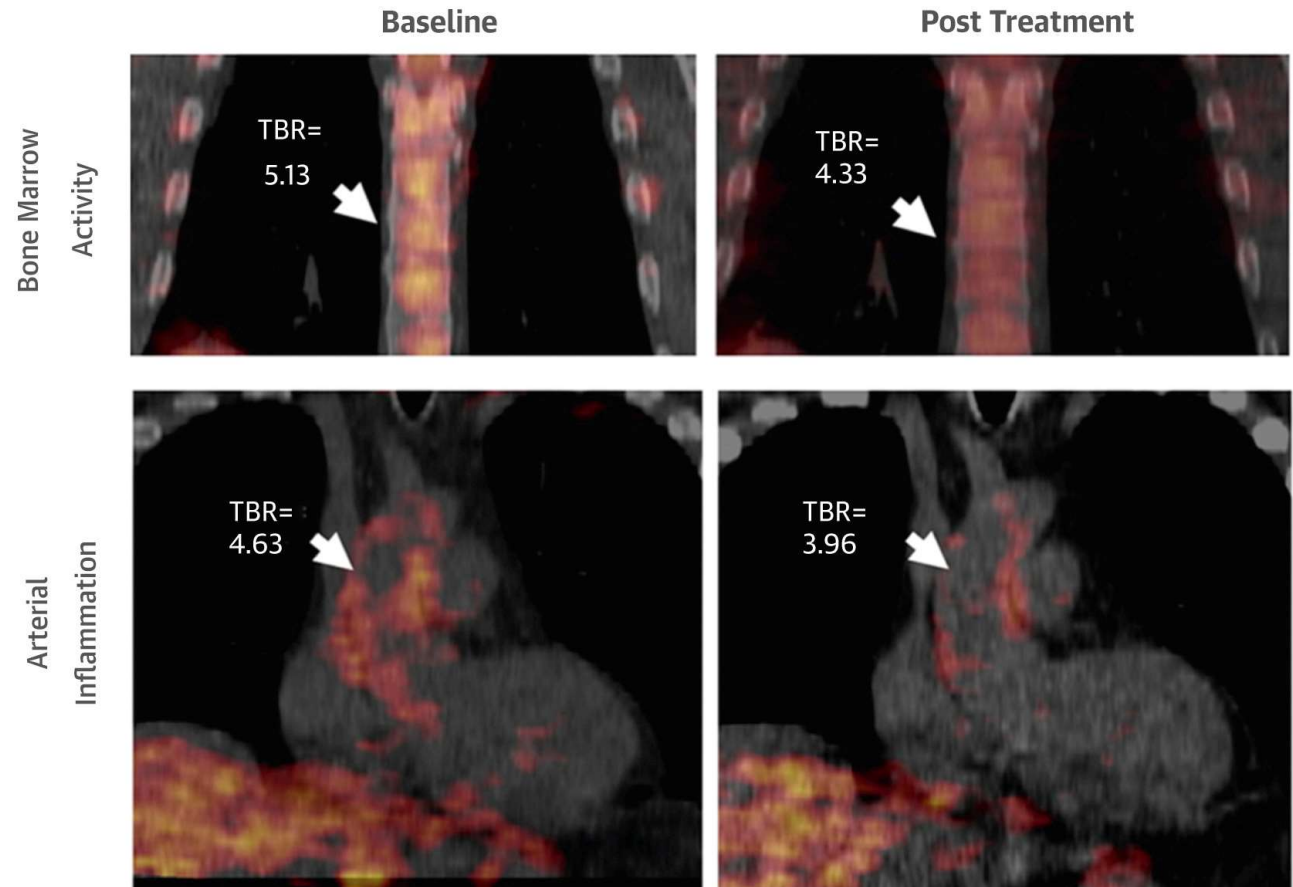
Canakinumab **Anti-inflammatory Thrombosis Outcomes Study**

CANTOS Trial Results

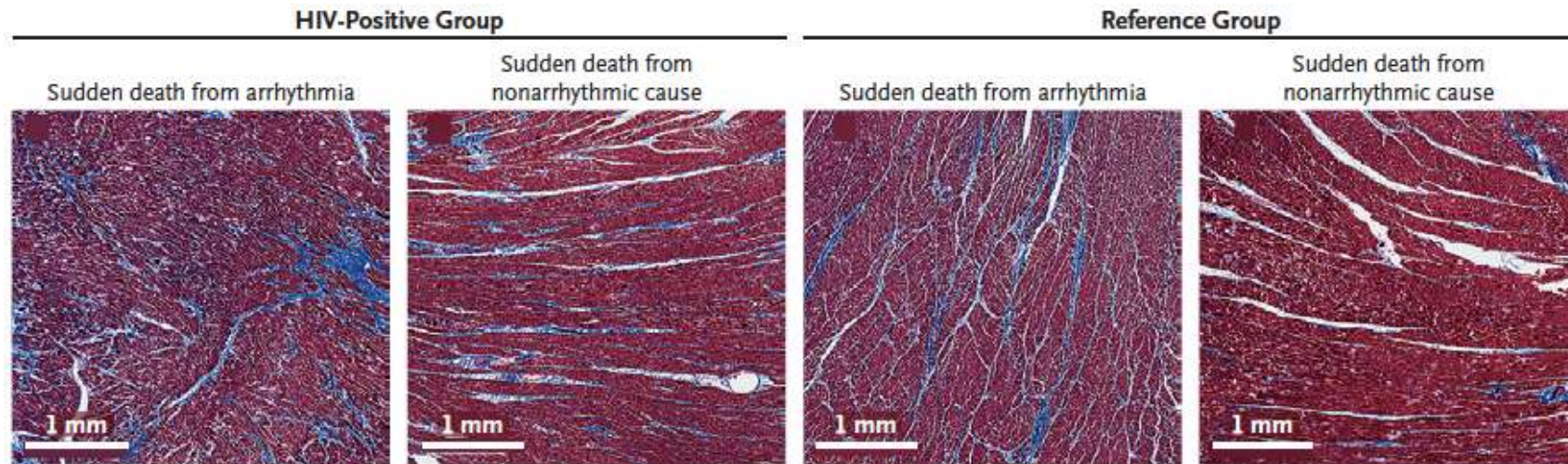


Effect of Canakinumab on Aortic Inflammation

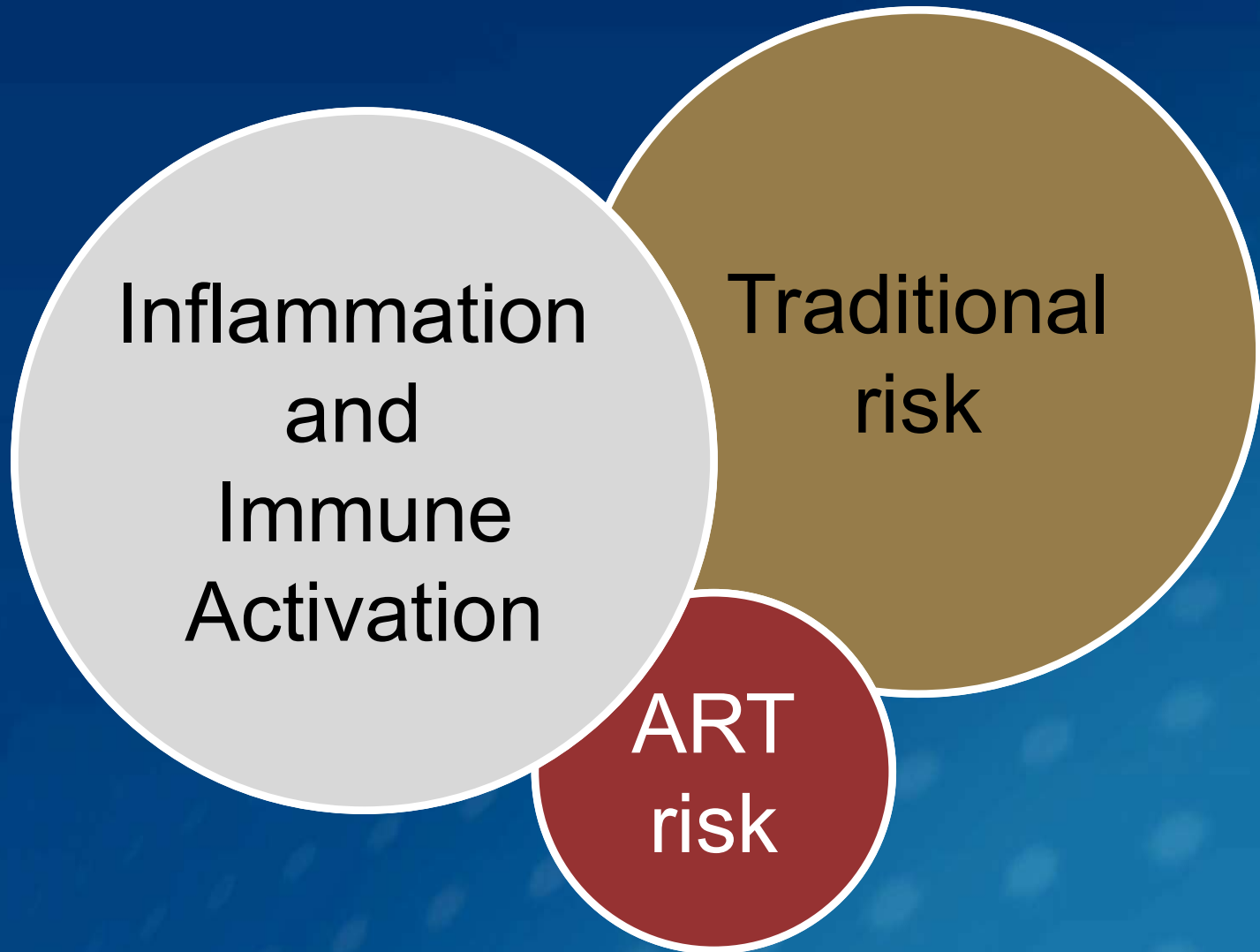
- First 10 patients
- Single dose of 150mg
- Aortic uptake of 18-FDG PET decreased by ~10%
- Bone marrow uptake decreased by ~11%



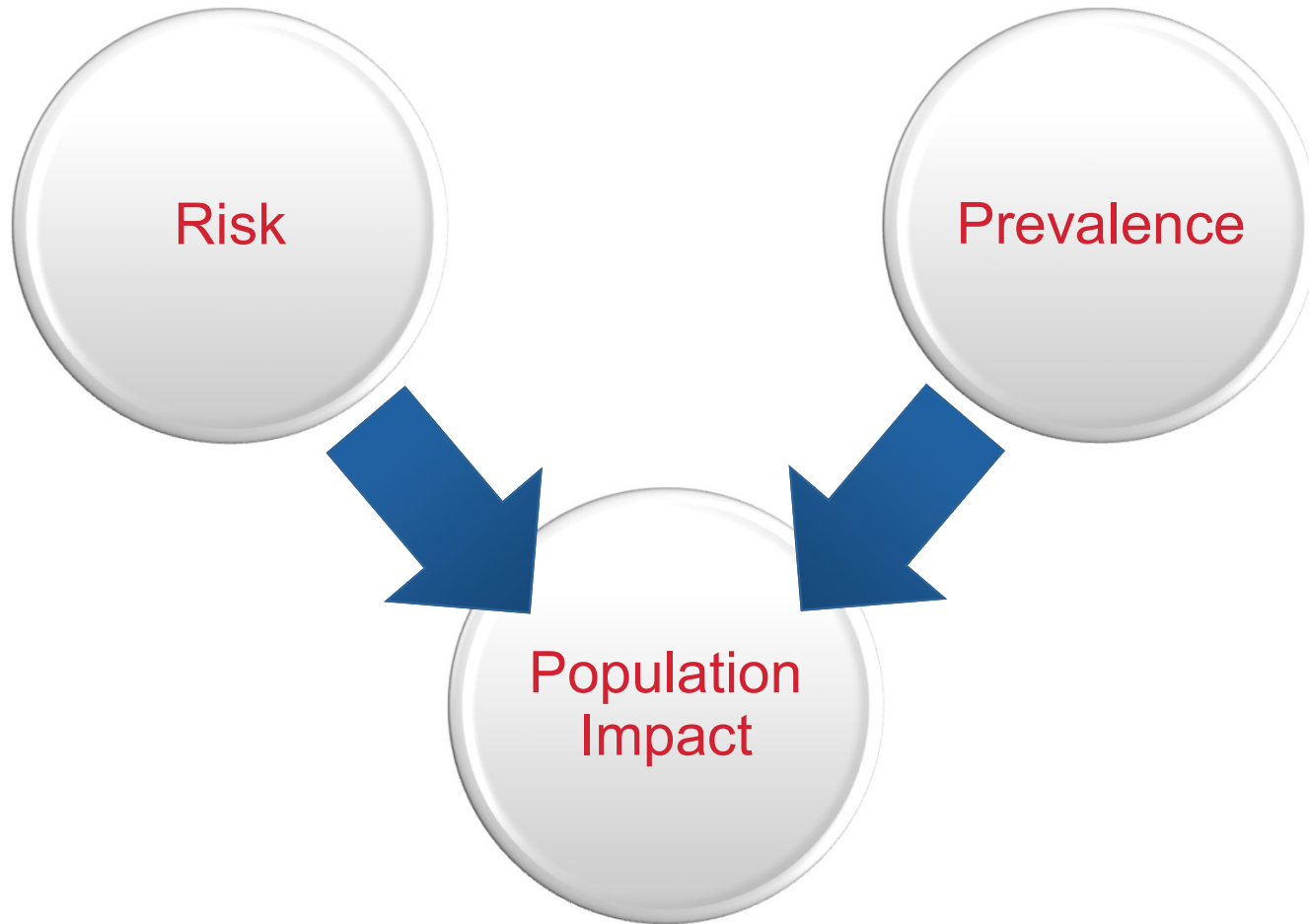
Inflammation leads to cardiac fibrosis and sudden cardiac death



	HIV-Positive Group, Presumed Sudden Cardiac Death (N=24)		Reference Group, Presumed Sudden Cardiac Death (N=164)		HIV-Positive Group vs. Reference Group, Presumed Sudden Cardiac Death	
	Sudden death from arrhythmia (N=12)	Sudden death from nonarrhythmic cause (N=12)	Sudden death from arrhythmia (N=100)	Sudden death from nonarrhythmic cause (N=64)	Sudden death from arrhythmia	Sudden death from nonarrhythmic cause
	<i>mean percent fibrosis</i>				<i>percent difference (95% CI)</i>	
Total Fibrosis	12.5±6.4		8.7±7.5		72 (23 to 142)	
	13.8±7.1	11.3±5.7	9.7±8.2	7.0±5.9	76 (9 to 184)	79 (7 to 198)
Interstitial and Perivascular Fibrosis	10.9±5.4		7.7±6.5		67 (20 to 131)	
	11.9±5.4	9.9±5.4	8.6±7.3	6.2±4.7	69 (6 to 170)	76 (8 to 185)
Replacement Fibrosis	1.6±2.8		1.0±1.9		25 (-4 to 63)	
	1.9±3.4	1.4±2.2	1.1±1.8	0.9±2.2	25 (-14 to 80)	18 (-20 to 75)

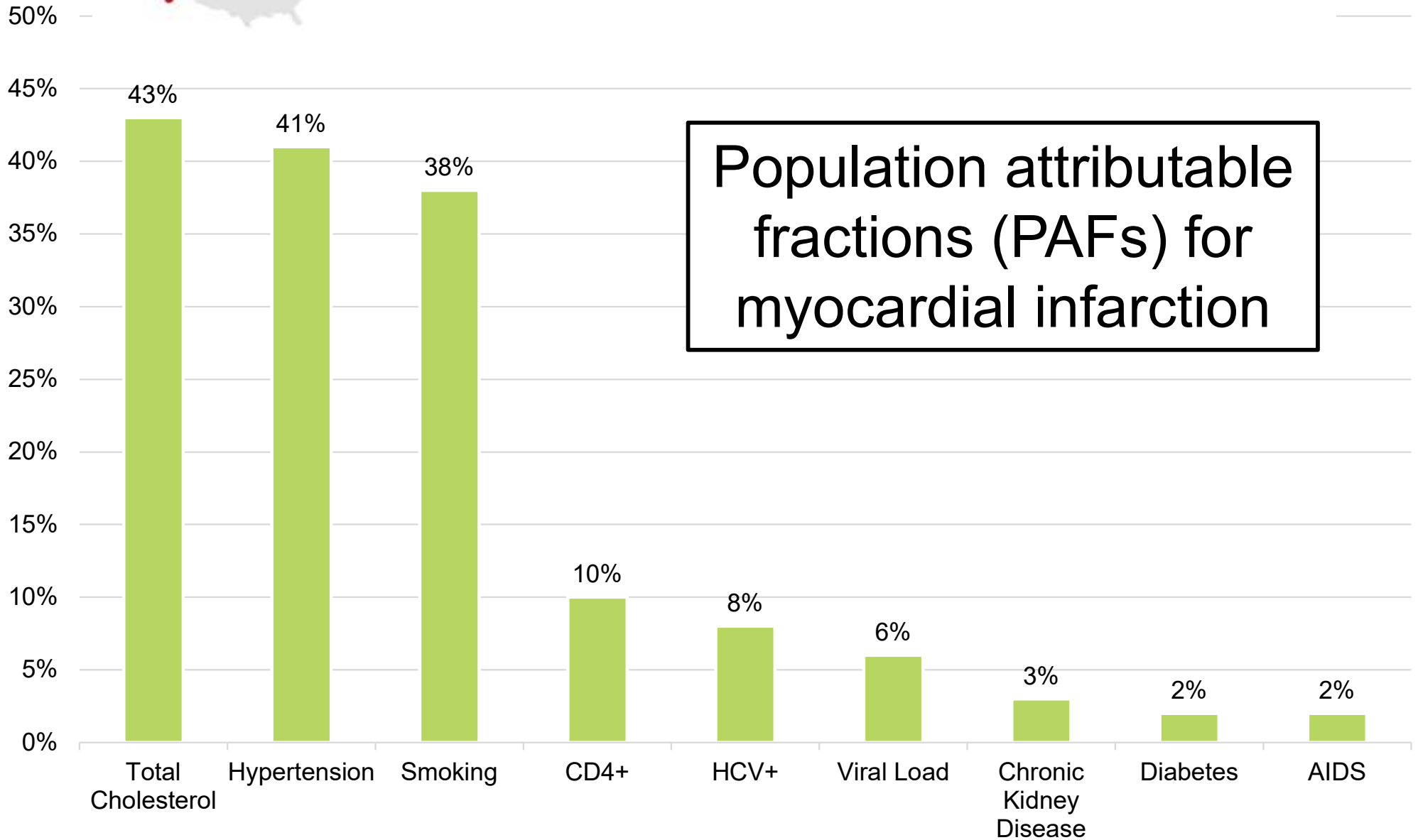


Population impact of HIV on CVD Burden

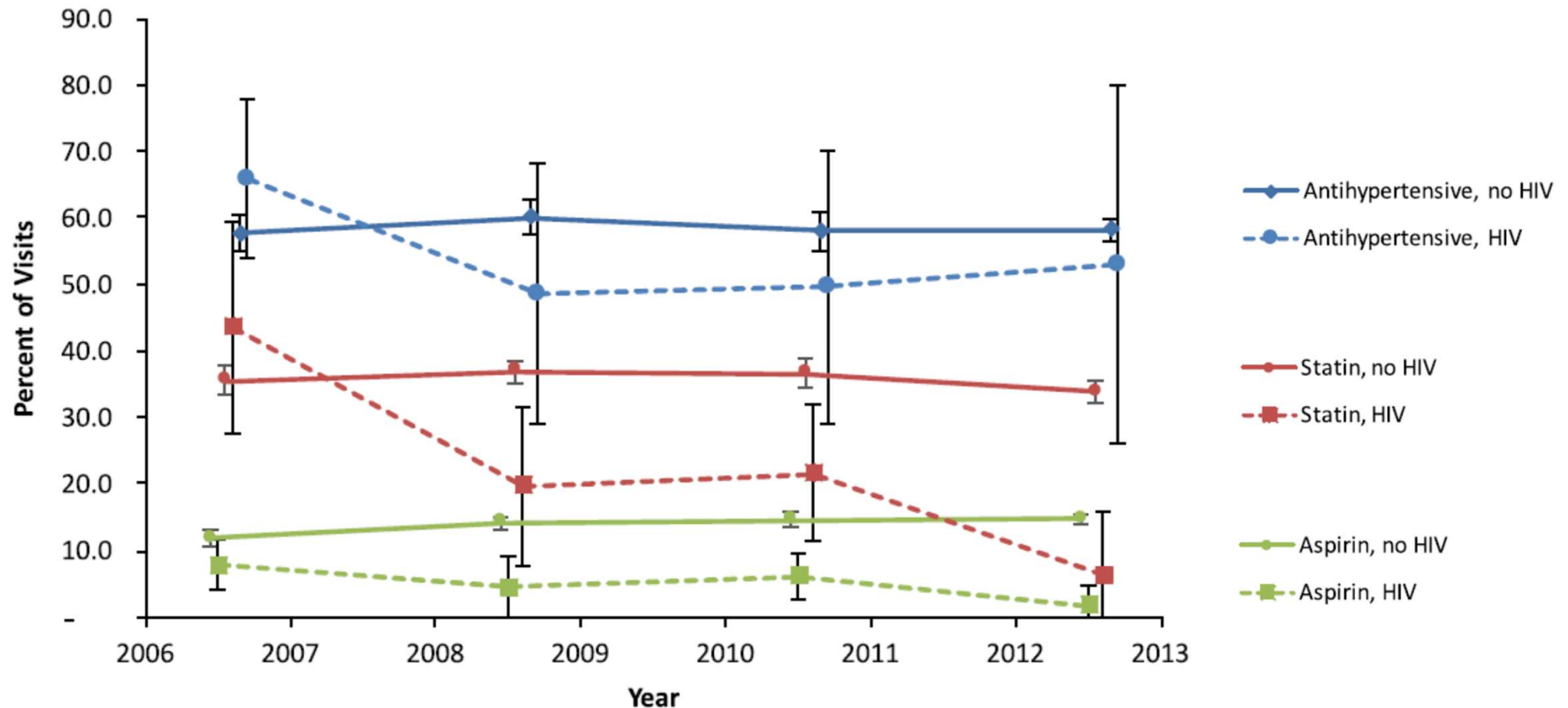




North American AIDS Cohort Collaboration on Research and Design



Guideline directed medical therapy is prescribed less often for PLWH



AHA SCIENTIFIC STATEMENT

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

A Scientific Statement From the American Heart Association

ABSTRACT: As widespread, HIV-related chronic, manageable diseases, including myocardial infarction, heart failure, pulmonary hypertension, and stroke, are higher for people living with HIV, even in the setting of antiretroviral therapy. These clinical risk factors, along with chronic inflammation, increase CVD outcomes. The transition of HIV from a chronic to an acute CVD pathogen, as observed in observational studies, are underpowered. This document is to provide recommendations on HIV-associated myocardial infarction and stroke) and heart failure, as well as pragmatic recommendations on how to approach CVD prevention and treatment in HIV in the absence of large-scale randomized controlled trial data. This statement is intended for clinicians caring for people with HIV, individuals living with HIV, and clinical and translational researchers interested in HIV-associated CVD.

... There are **many opportunities for implementation research** aimed at leveraging the HIV care infrastructure to deliver integrated cardiovascular preventive and therapeutic care for PLWH. Such structures could include improving health insurance access to specialists, **strengthening specialist referral pathways, nurse management**, clinical pharmacist engagement, team-based approaches, electronic medical record–based approaches to targeting high-risk patients, **co-located clinics**, and other approaches that consider the specific vulnerabilities in this population.

Prevention and Council
on Cardiovascular and
Stroke Nursing; Council
on Clinical Cardiology;
and Stroke Council

PART 2

Implementing cardiovascular disease prevention in HIV clinic care

Our opportunity to improve CVD prevention care for PLWH



- 50 years old
- AIDS in 2002; on ART since
- Nadir/Current CD4+ 20/600
- BP 140/70 on amlodipine 10mg daily
- LDL 100mg/dl on atorvastatin 40mg daily



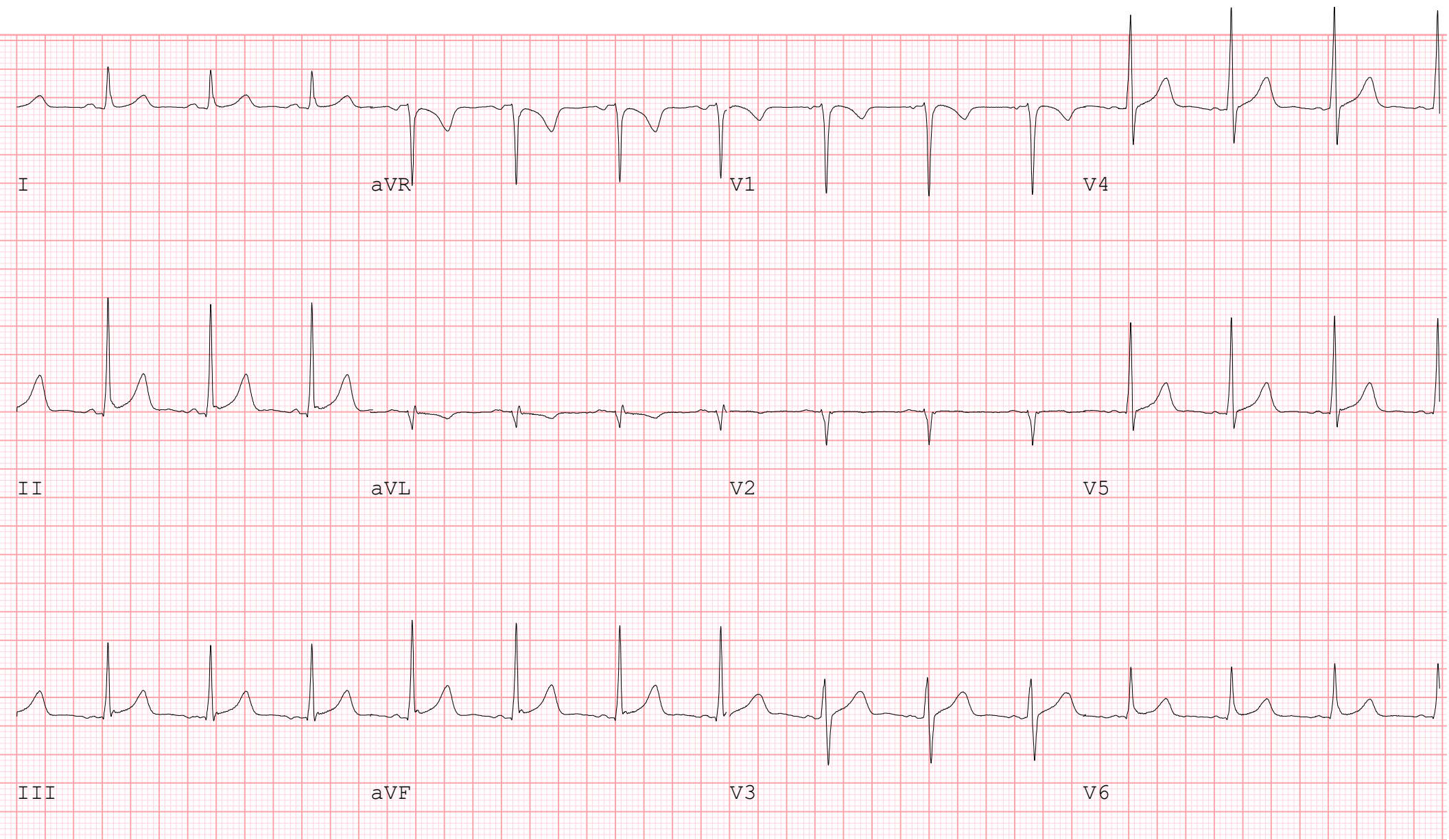
- 50 years old
- HIV-negative
- BP 150/90
- LDL 160mg/dl



- 50 years old
- HIV+ 2010; on ART since
- Nadir/Current CD4+ 600/1000
- BP 120/70
- LDL 100mg/dl on atorvastatin 40mg daily

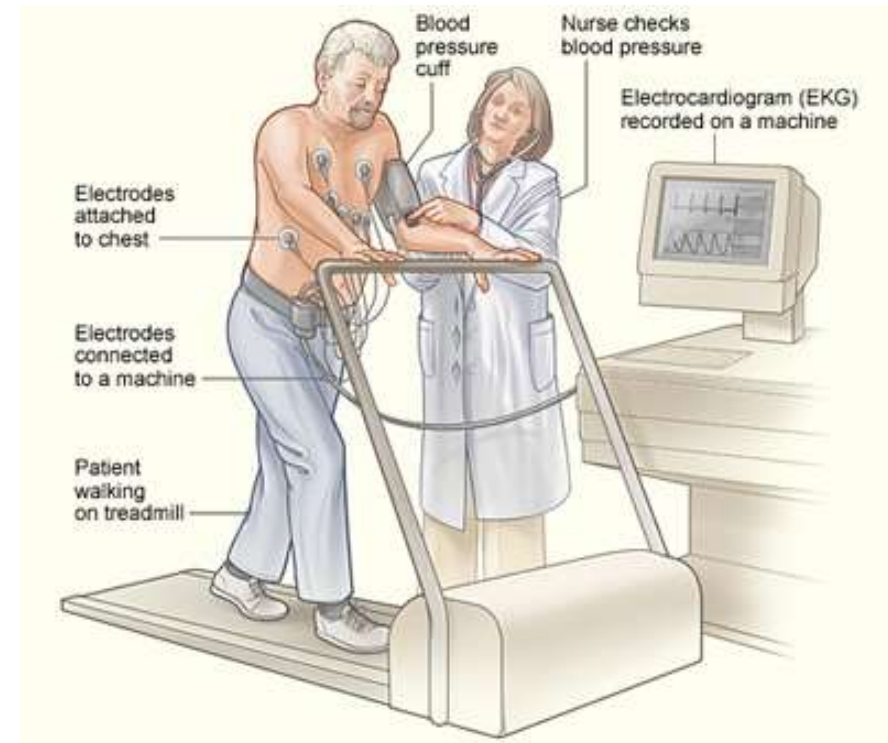
Case 1 – High risk CAD

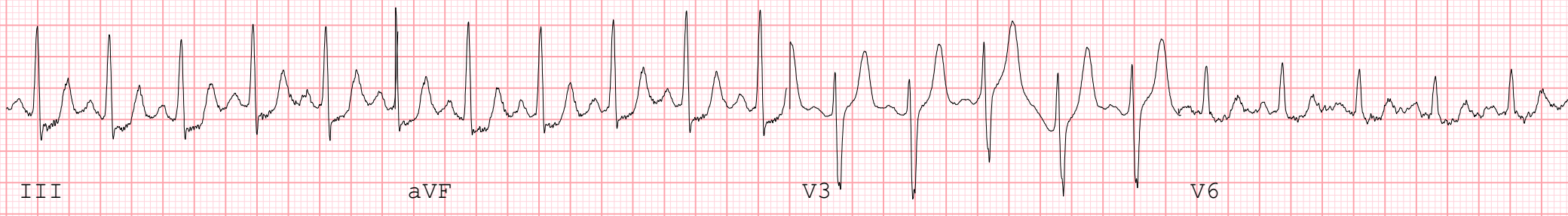
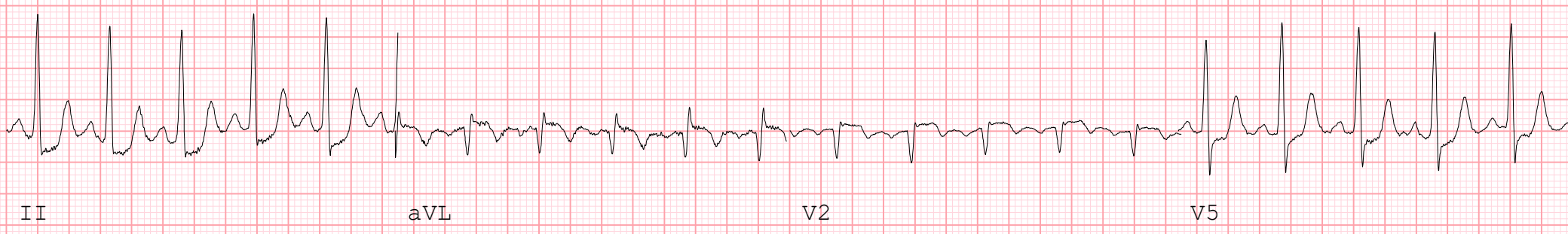
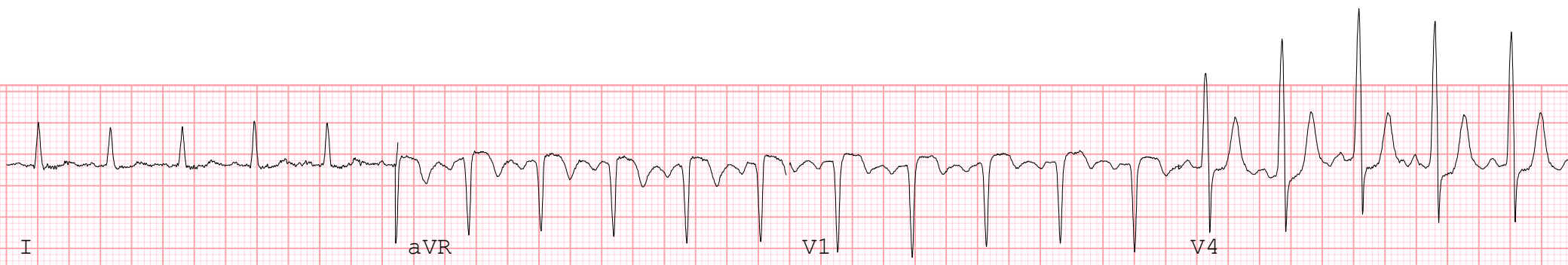
- 54 yo AA man with HIV (CD4+ 871, nadir 258, viral load <50 on DRV/c/FTC/TAF).
- 1 month h/o dyspnea on exertion accompanied by a “stabbing sensation” in his chest, relieved with rest. No relationship to dietary patterns or body position. No cough/fever/chills.
- Risk factors:
 - Cigarette smoker
 - Brother died of MI at 52
 - No hypertension, diabetes
- Medications: DRV/c/FTC/TAF, multivitamin
- Lipids:
 - Total cholesterol 167, HDL 58, LDL 98, triglycerides 55 OFF statin

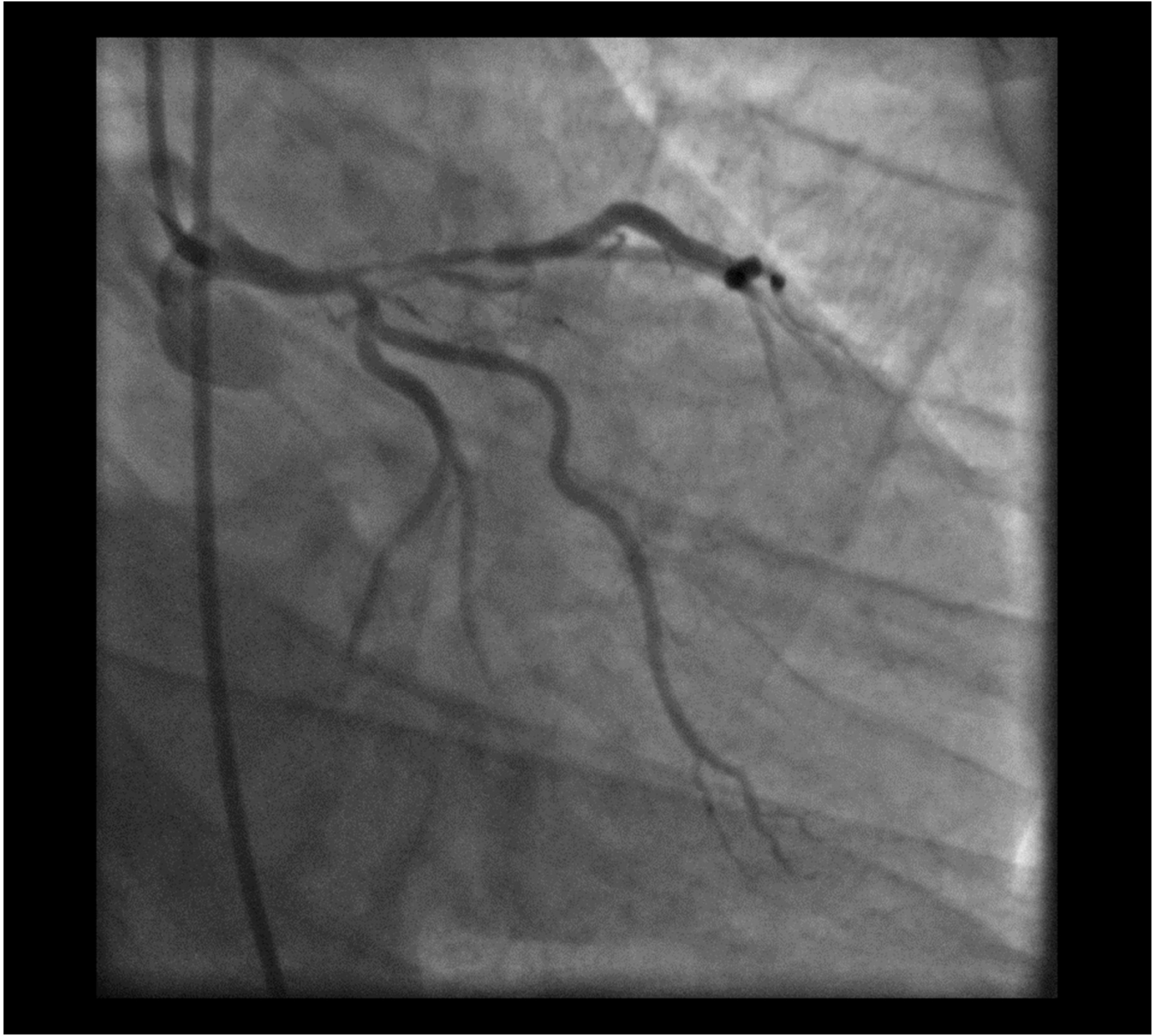


What next?

- Stress test?
- Cath?
- Cardiac CT?



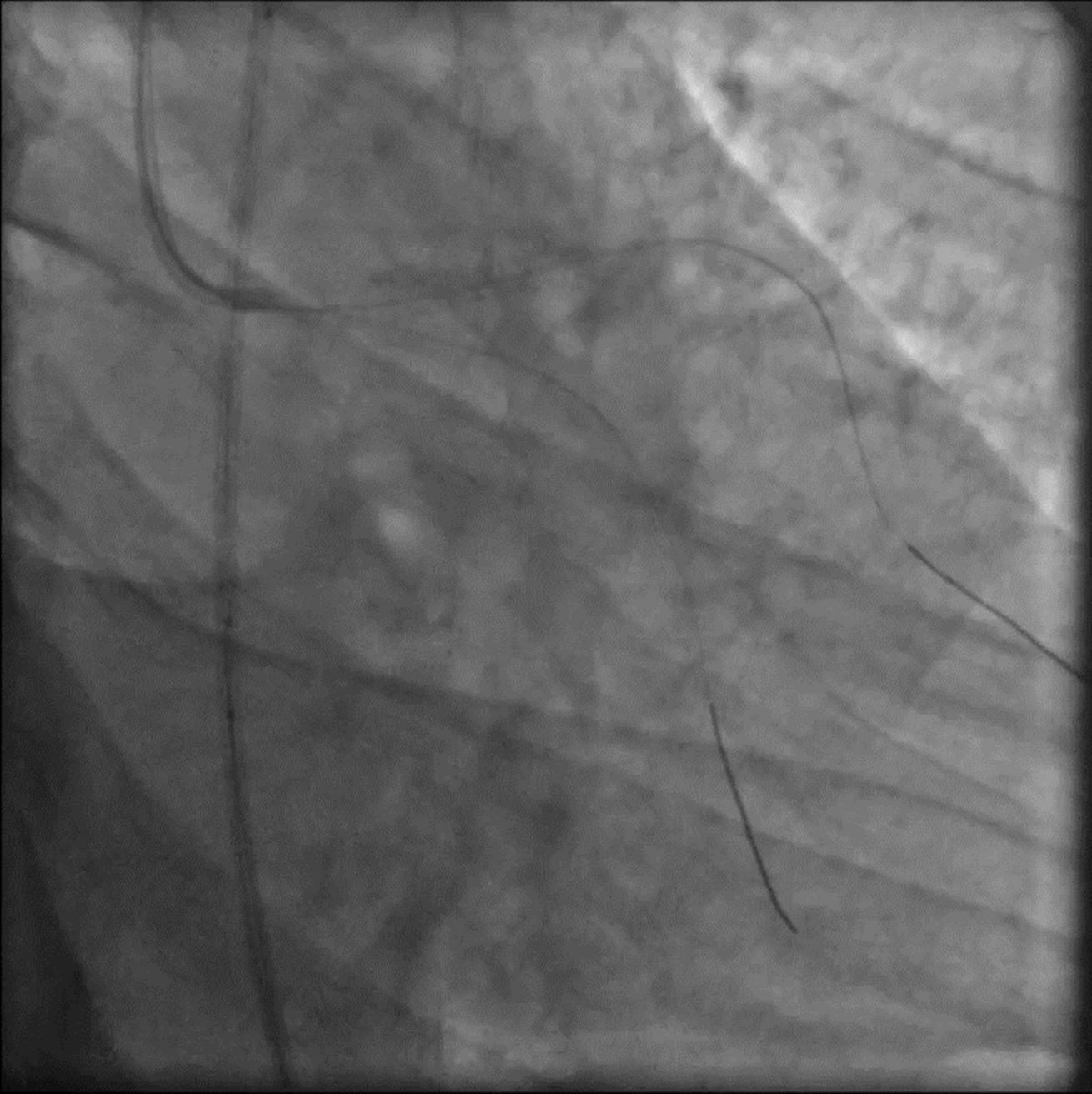




Lossy Compression - not intended for diagnosis



Lossy Compression - not intended for diagnosis



Case 1 — Follow-up

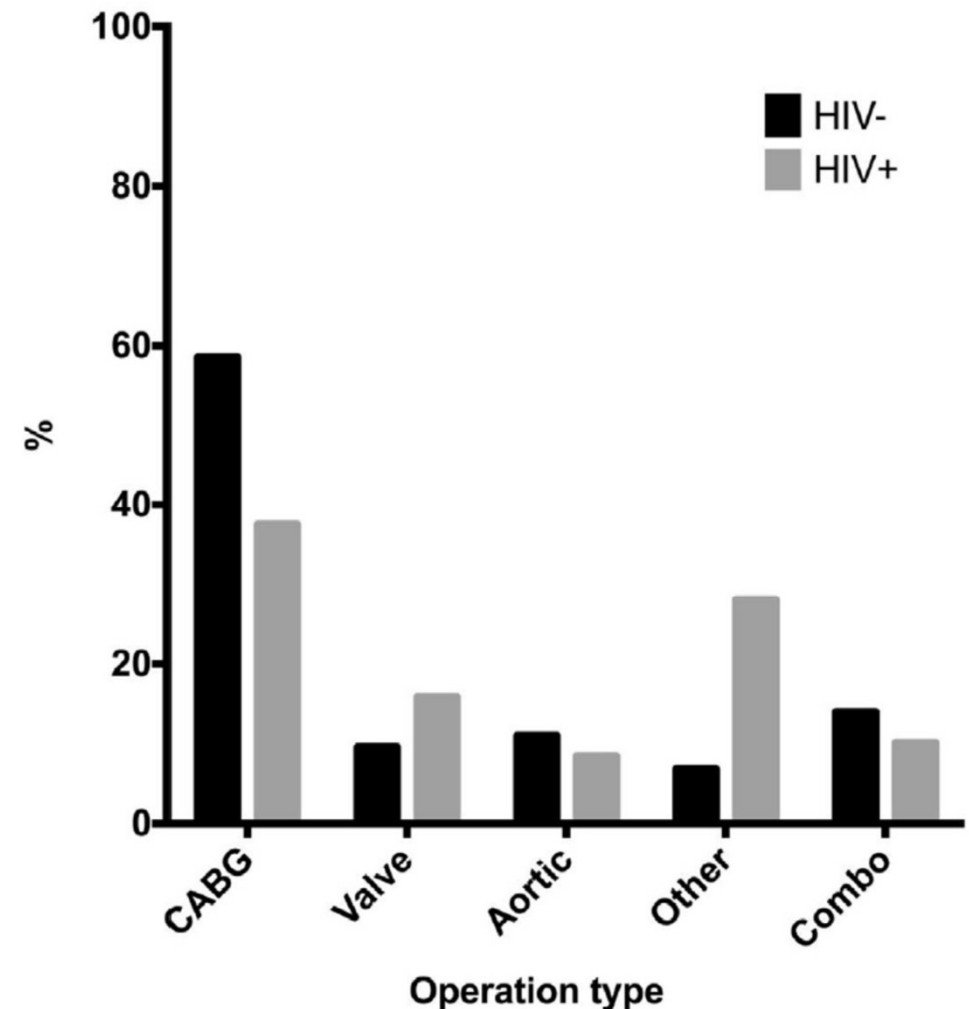
- Angina is gone and did not return in >8 years
- Stopped smoking
- No recurrent adverse cardiac events
- Now on atorvastatin 80mg

Anti-platelet therapy and boosted ART

- What antiplatelet therapy to prescribe?
 - Ticagrelor contraindicated due to CYP3A4 metabolism
 - Clopidogrel and Prasugrel are prodrugs converted to active metabolites by CYP3A4 & 2C19 in the liver
 - The AUC and Cmax of both active metabolites are reduced by ~50% in patients on cobicistat or ritonavir
 - However, prasugrel's antiplatelet effect is preserved (compared to clopidogrel, which is significantly reduced)
 - **Prasugrel is the usually the best choice for patients on a protease inhibitor or cobicistat**

PLWH can safely undergo cardiac surgery

- Nationwide Inpatient Sample
- 1998-2009
- ~10,000 HIV+ underwent surgery
- Propensity-matched analysis:
 - 1600 HIV+
 - 1600 HIV-neg



PLWH can safely undergo cardiac surgery

TABLE 5. Effect of HIV status on propensity-matched outcomes

Variable	Adjusted odds ratio (95% CI)
Total no. of patients	3266
Mortality	0.98 (0.74-1.30)
Complications	
Any complication	→ 1.16 (1.01-1.34)
Stroke	→ 0.43 (0.25-0.74)
Blood transfusion	→ 1.19 (1.01-1.40)
Wound infection	0.77 (0.45-1.32)
Renal complication	→ 0.96 (0.75-1.22)
Pneumonia	1.24 (0.97-1.58)

CI, Confidence interval.

Case 2– Genetic Misfortune

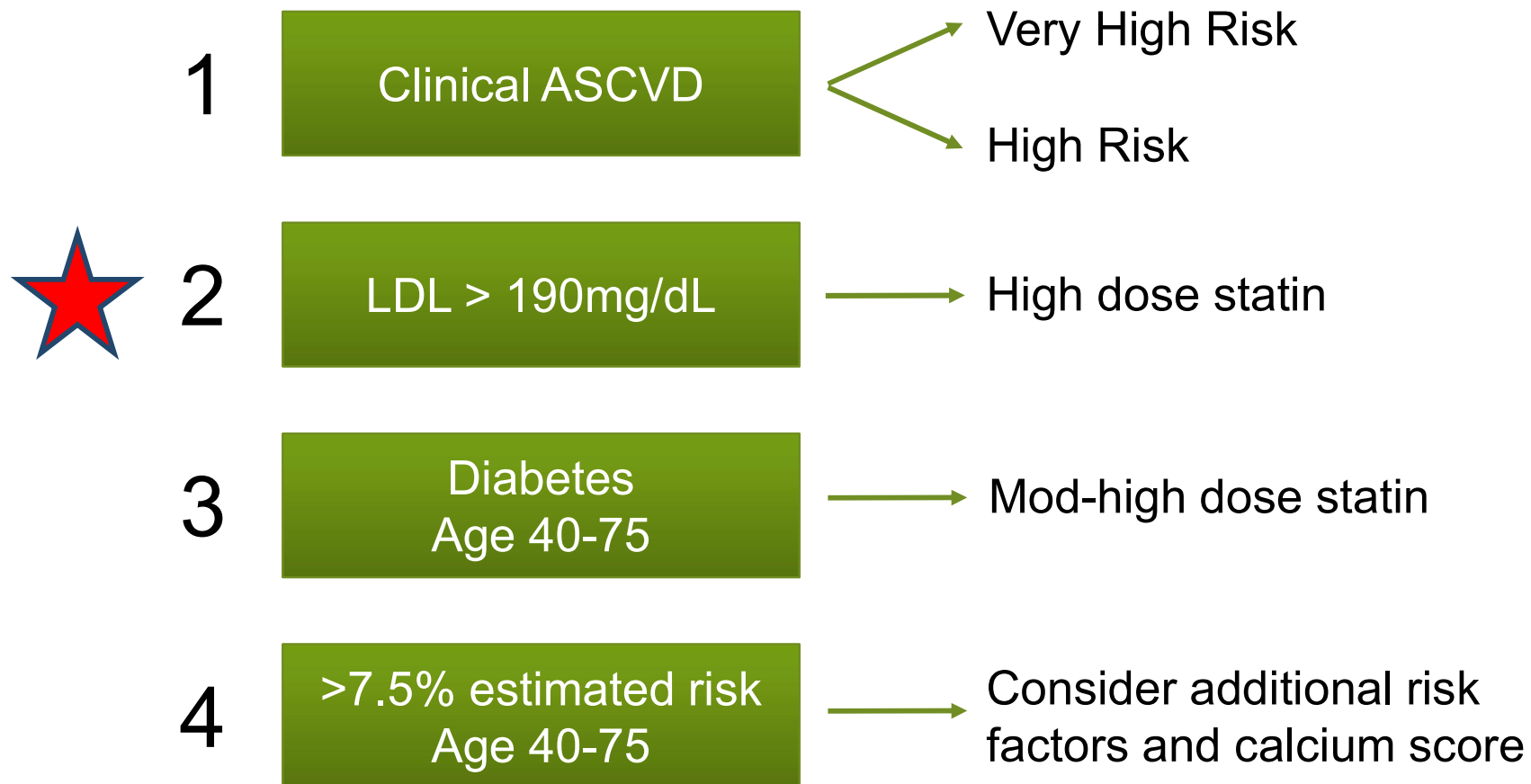
- 49 yo AA male HIV+ long-term non-progressor with near-elite control of viremia (CD4+ 907, viral load <50 with occasional blips <500), not on ART.
- Several months of an atypical intermittent stabbing chest pain lasting seconds, unrelated to exertion. Tends to be worse at night, but not related to food. No dyspnea, PND, orthopnea, or edema. No palpitations or syncope. Functional status limited by chronic low back pain.
- **Risk factors:**
 - prior smoker (15 pack-years, quit 3 years ago)
 - Hypertension
 - Dyslipidemia (LDL 240, modest TGL 167, normal HDL 56)
 - No diabetes or pertinent family history. BMI 28.
 - Lives in a neighborhood (East Cleveland) with limited access to nutritious food and safe exercise options
- **Meds:** amlodipine 10mg, atorvastatin 40mg, aspirin 81mg
- **Other labs:** Hgb A1c 5.8%; AST/ALT elevated but <3x ULN; TSH normal; CK normal

Studies

- **ECG:** normal
- **Echo:** normal EF, normal LA size, normal RV, and normal PA pressures
- **Nuclear perfusion imaging:** normal
- **CT angio in ED:** No dissection or pulmonary embolism
 - No coronary calcification
 - Hepatic steatosis

- What to make of his chest pain?
- What should I do next?

2018 ACC/AHA Statin benefit groups



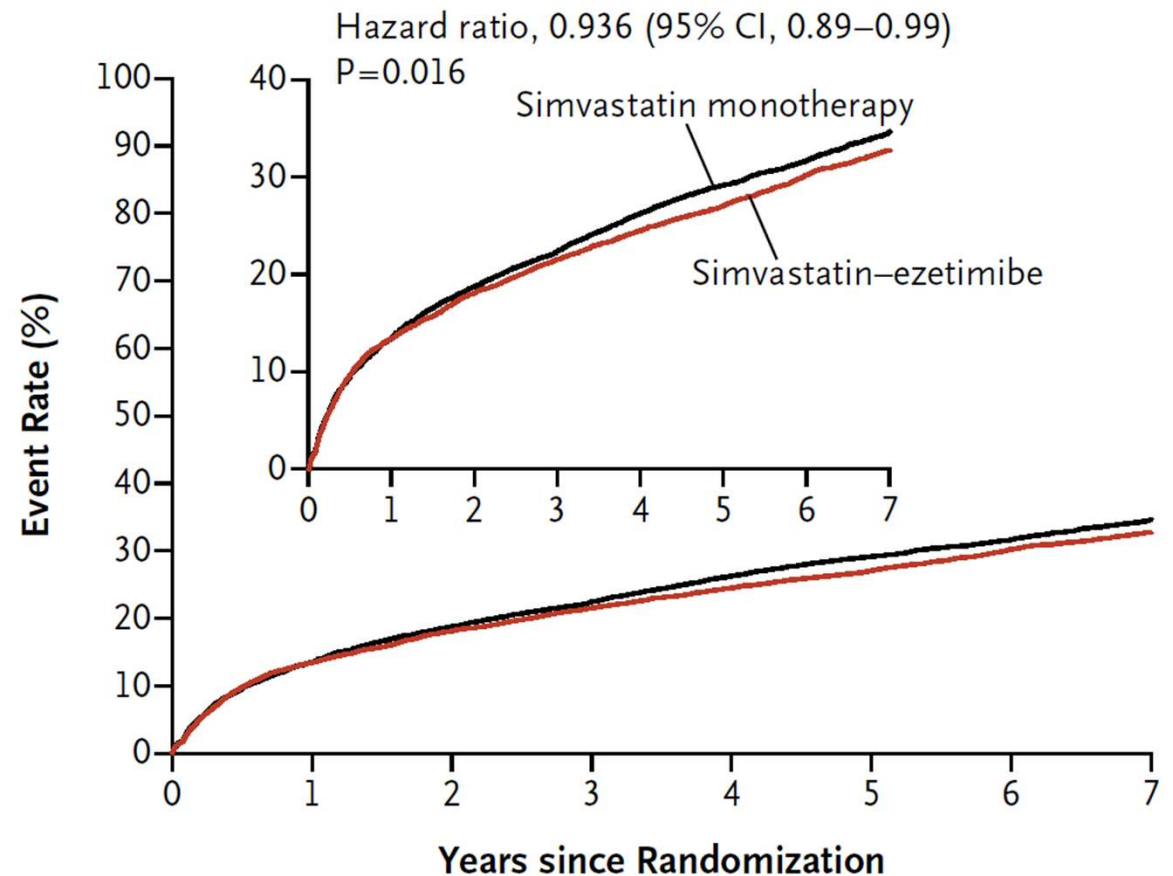
National Lipid Association– Lipid Goals

<u>Risk Category</u>	<u>Criteria</u>	<u>Consider drug therapy</u> Non-HDL-C LDL-C
Low	0-1 major risk factor	<190 mg/dl <160 mg/dl
Moderate	2 major risk factors (i.e. HIV + high BP only)	<160 mg/dl <130 mg/dl
High	≥ 3 major risk factors	<130 mg/dl <100 mg/dl
Very High	Known ASCVD OR Diabetes + ≥2 major risk factors	<100 mg/dl <70 mg/dl

Major risk factors include: HIV, Age >45 men or >55 women, family history of early CAD, smoking, hypertension, low HDL-C. **HIV added as major risk factor by NLA Expert Panel in 2015.**

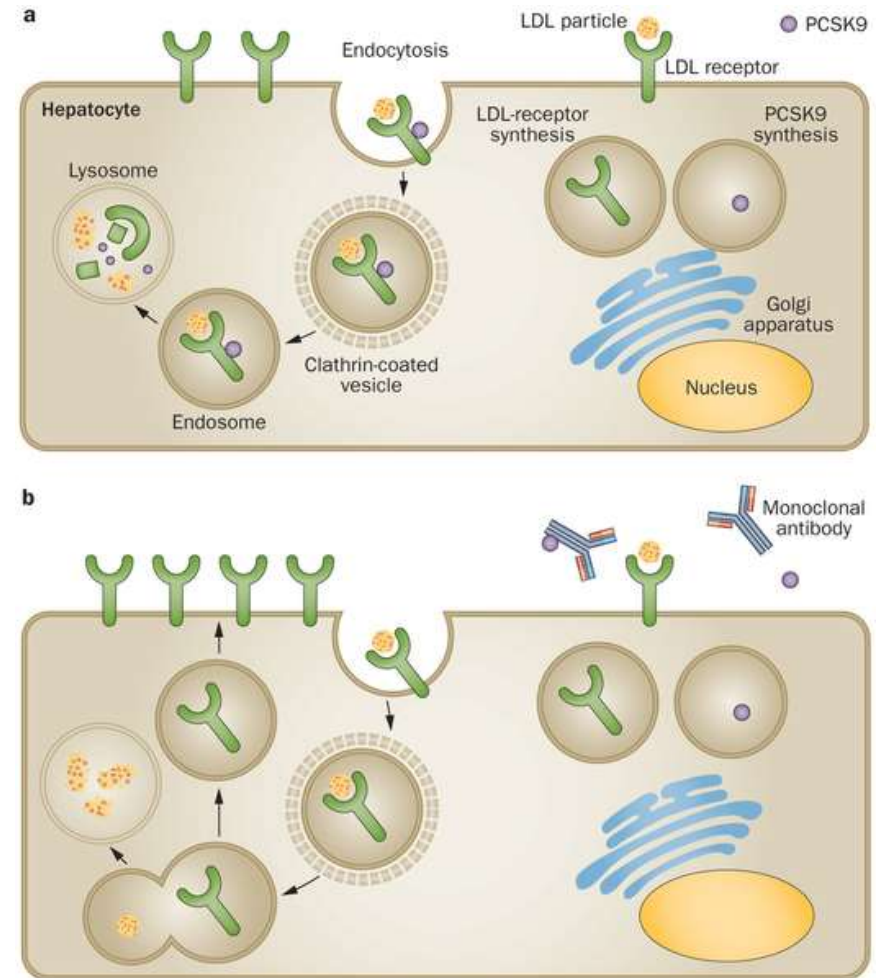
Case 2 – What would you do?

- 10yr vs. Lifetime risk
- Atorvastatin titrated to 80mg daily
- Additional agents?
 - Ezetimibe
 - PCSK9 inhibitor
 - others
- Concerned about hepatic steatosis?

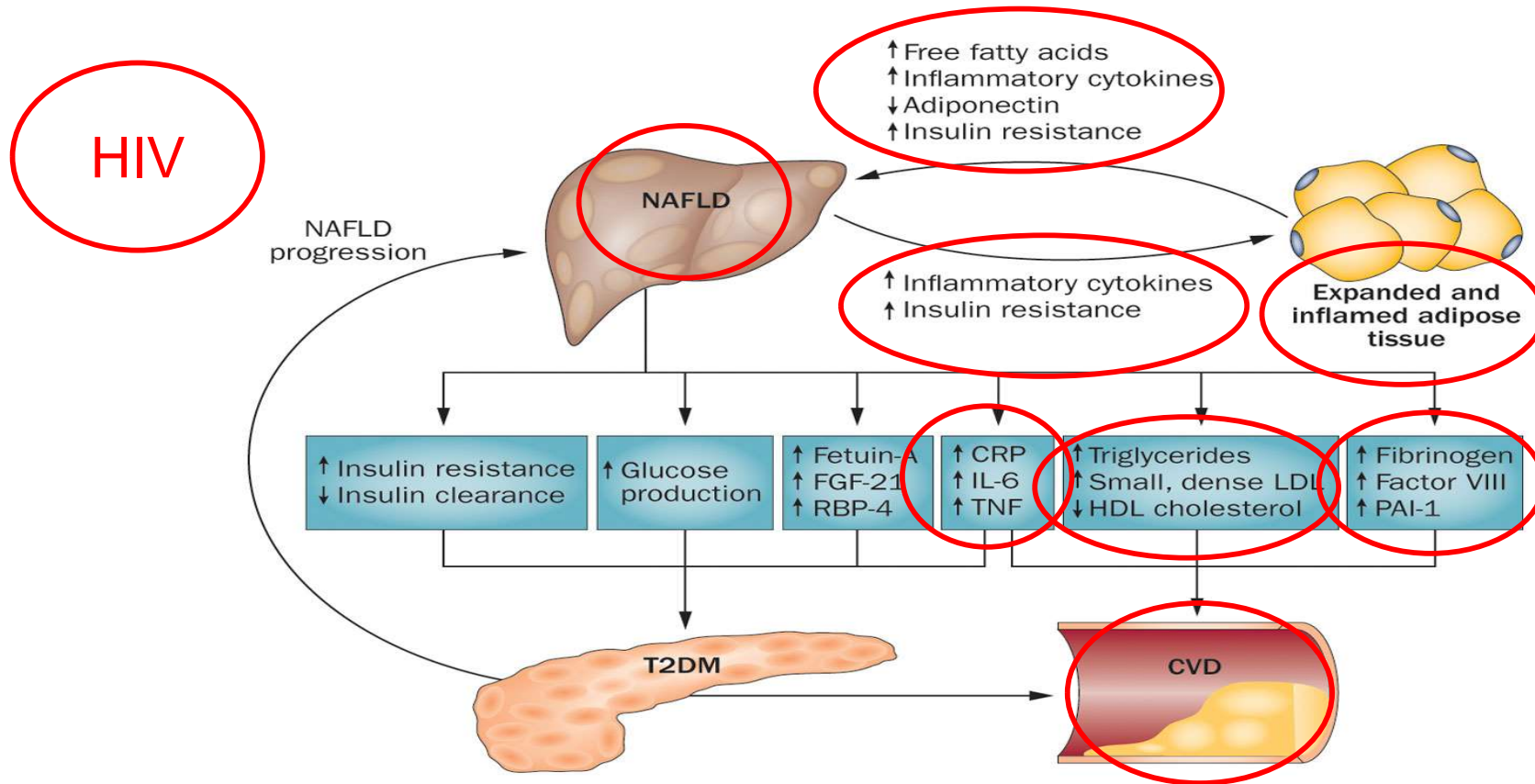


PCSK9 Inhibition in HIV

- PLWH had 10% higher levels
- N=6 in evolocumab trial → similar LDL response to HIV-uninfected (-61% ON TOP of statin)
- Significance of “very high” levels → HCV co-infection
- Switching PI-→ RTG may decrease PCSK9 (SPIRAL study)



NAFLD increases CVD risk



Management of cardiovascular risk in NAFLD

- Lifestyle changes are central to management
- Statins are safe and effective
- 2014 NLA statin safety guidelines
- Consult with liver specialist if necessary

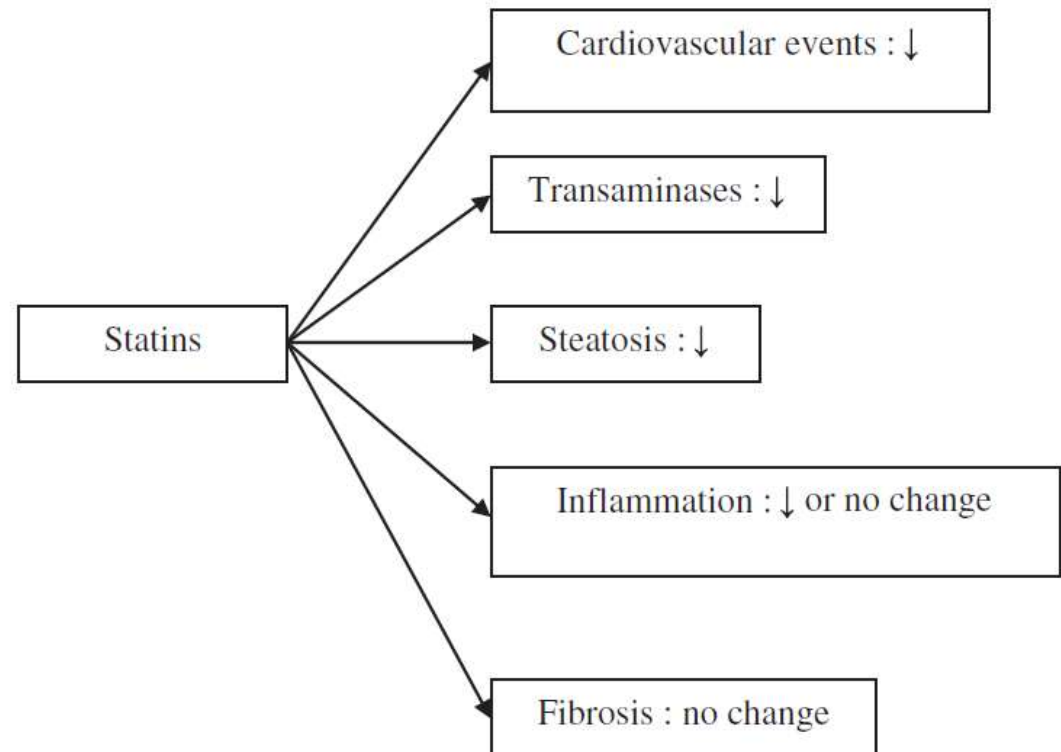
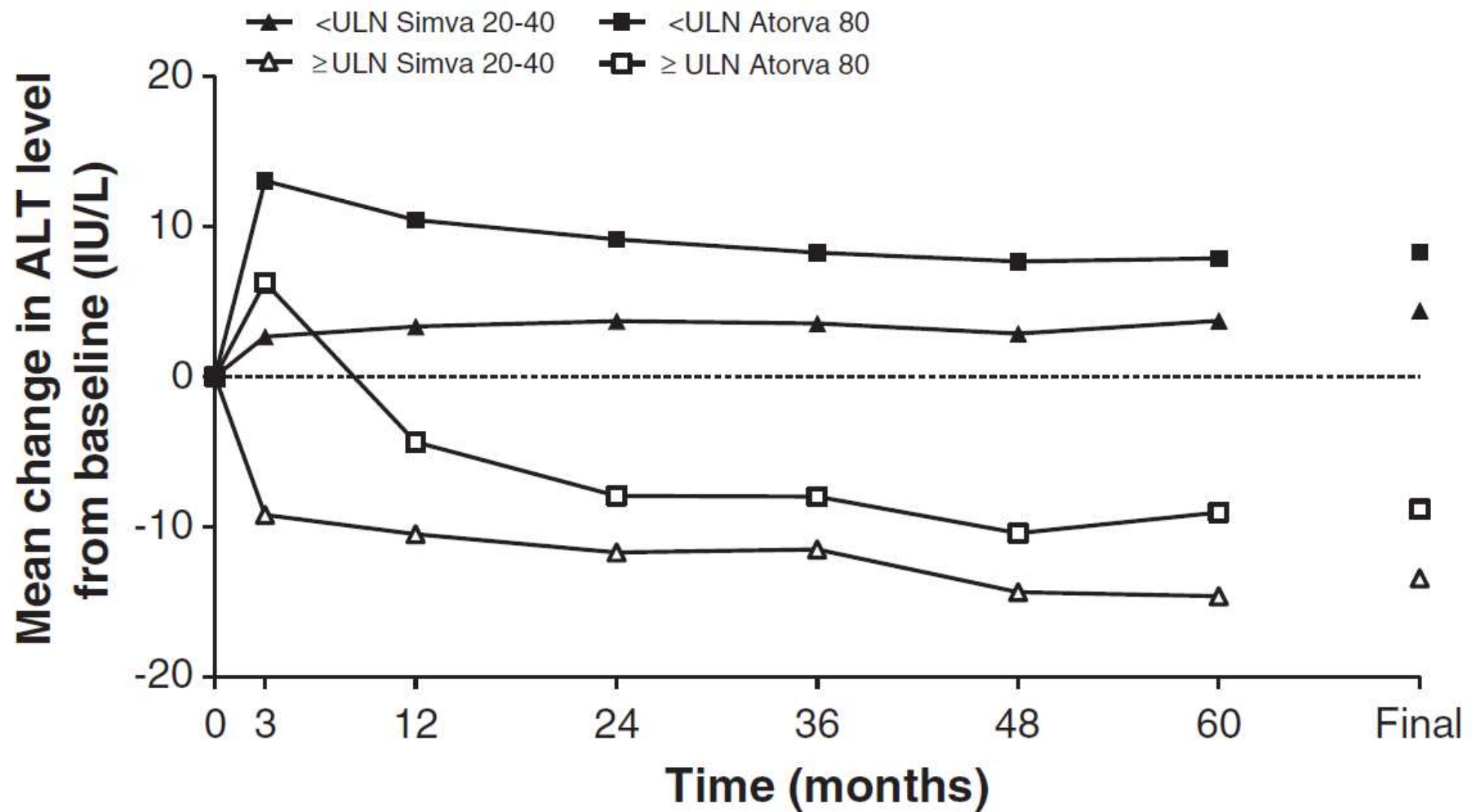


Fig. 4 – Effects of statins on cardiovascular events and on the liver in patients with nonalcoholic fatty liver disease.

Statins are safe in patients with NAFLD



Case 2 – Key Points

- This was a case of primary prevention in a patient with probable heterozygous FH and NASH
- In this 49 year old elite controller not on HIV medications, chronic inflammation/immune activation may still increase CVD risk
 - His primary HIV doc later did start ART
- LDL (non-HDL) treatment goal is <100 (130) mg/dL
- I increased atorvastatin to 80mg and added ezetimibe. LDL fell to 160's and AST/ALT modestly improved.
- Eventually started on PCSK9 inhibitor, with LDL finally falling to <100mg/dL
- HIV is a known cause of fatty liver disease, but most patients with elevated liver enzymes can safely be prescribed a statin.

American Heart Association's Life's Simple 7



Stop
Smoking



Lose Weight



Eat Better



Get Active



Control
Cholesterol



Manage
Blood
Pressure



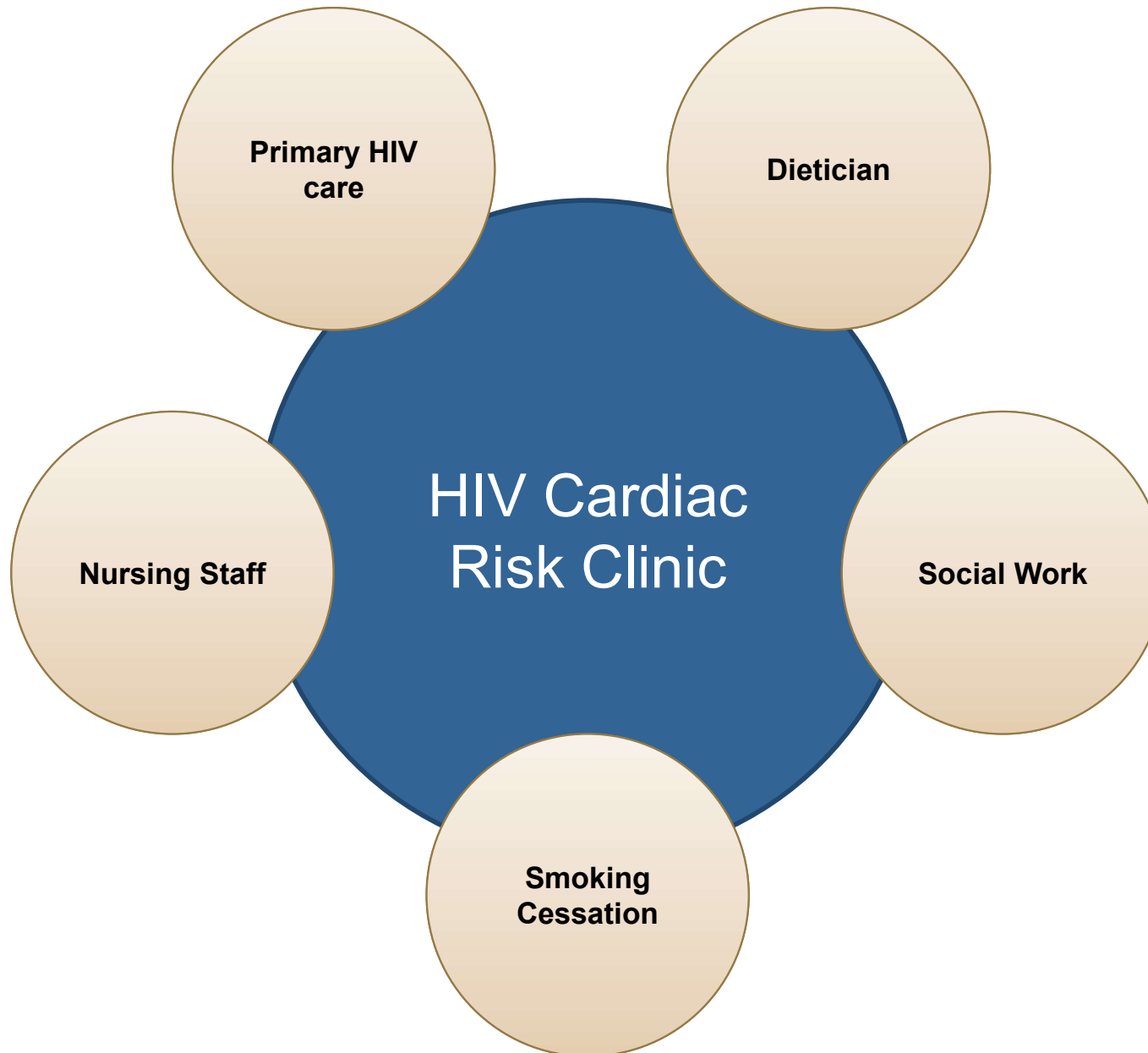
Reduce
Blood Sugar

Barriers to healthy lifestyles for some populations of people living with HIV

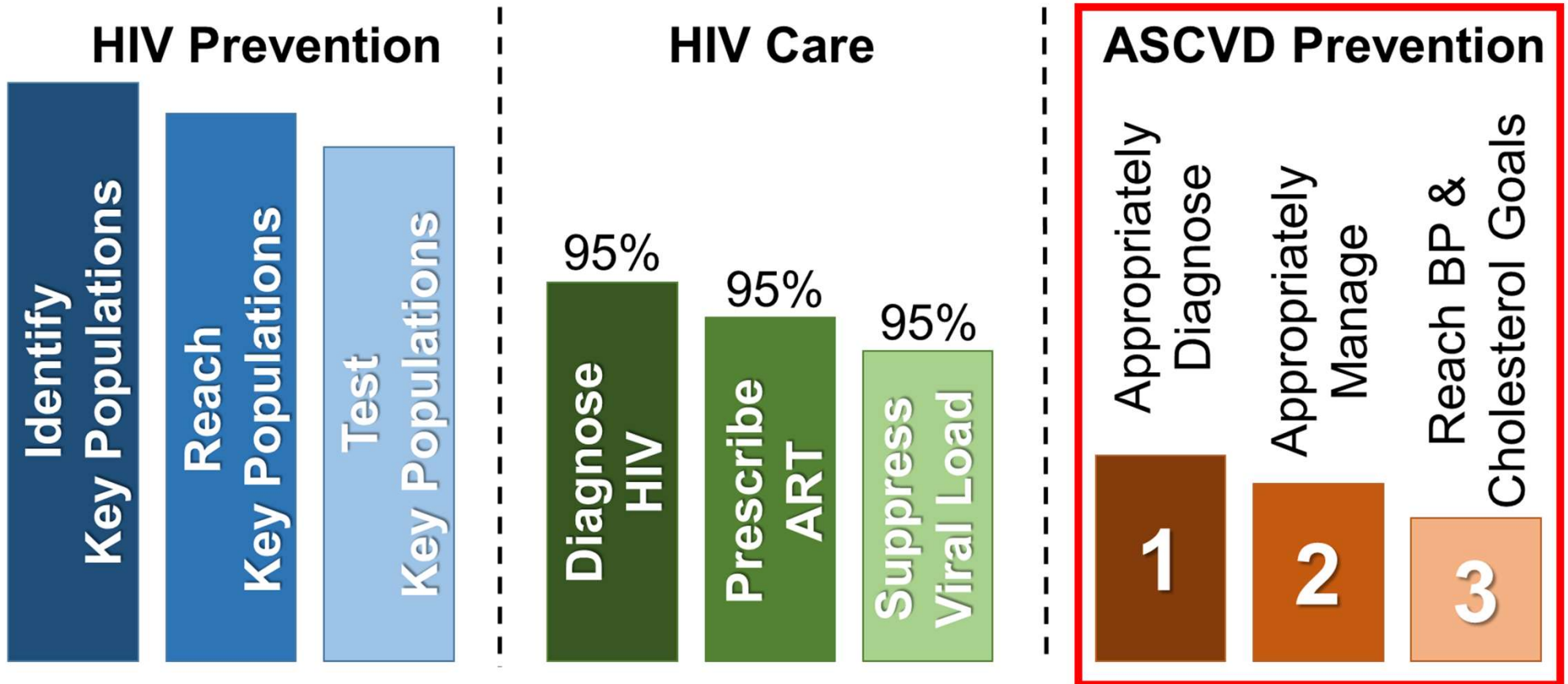
- Poverty
- Chronic stress
- Food deserts
- Safety during exercise
- Substance use



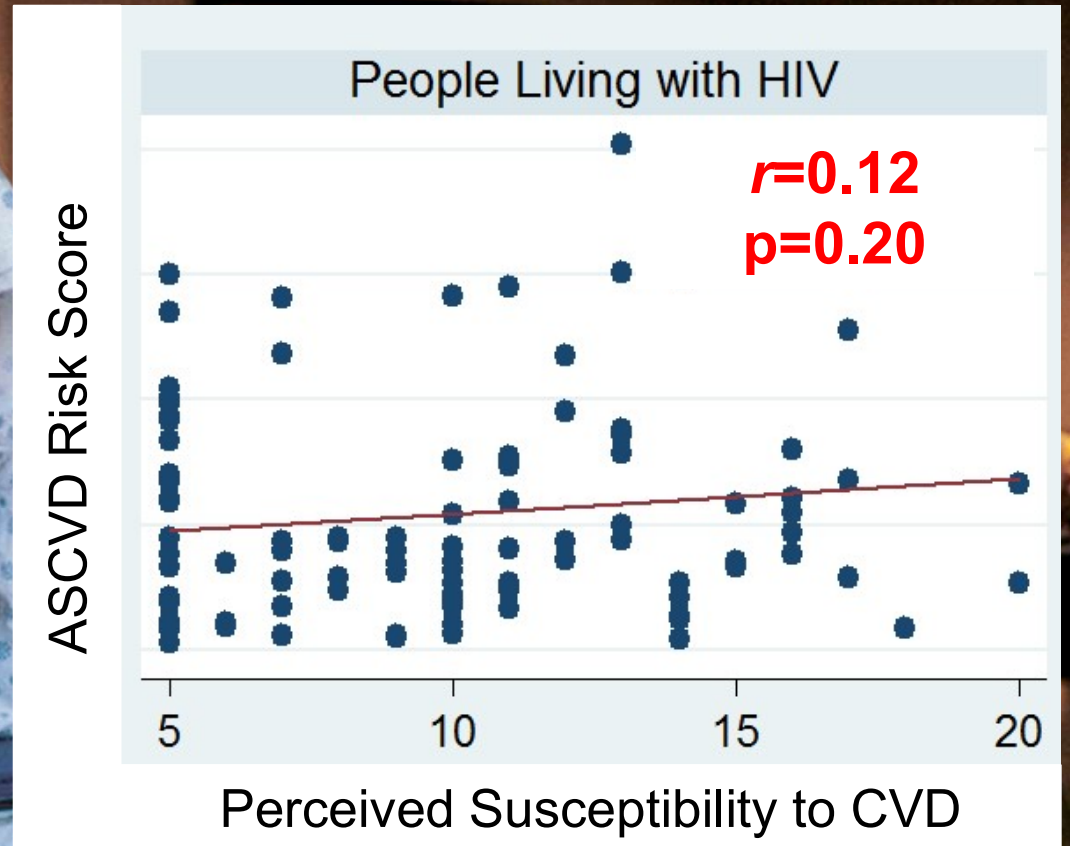
Team-based cardiovascular risk reduction



It's Time to Extend the HIV Treatment Cascade



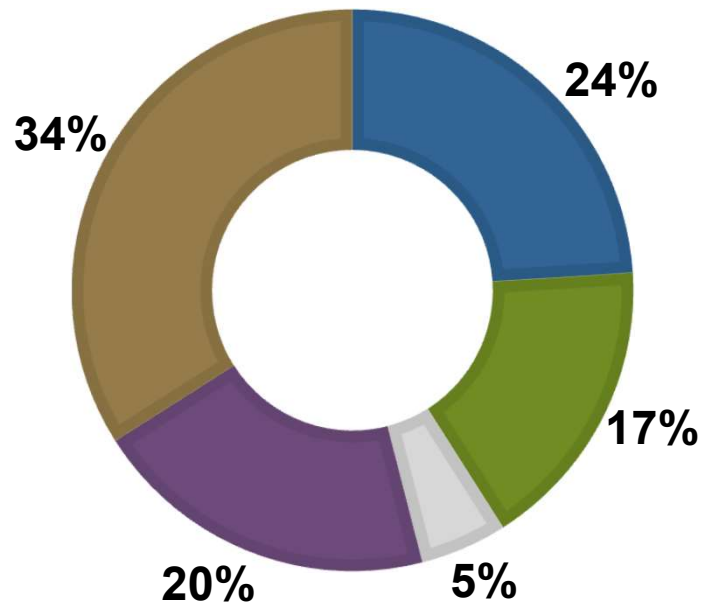
“I always thought I’d die of AIDS”



Who does primary prevention for PLWH?

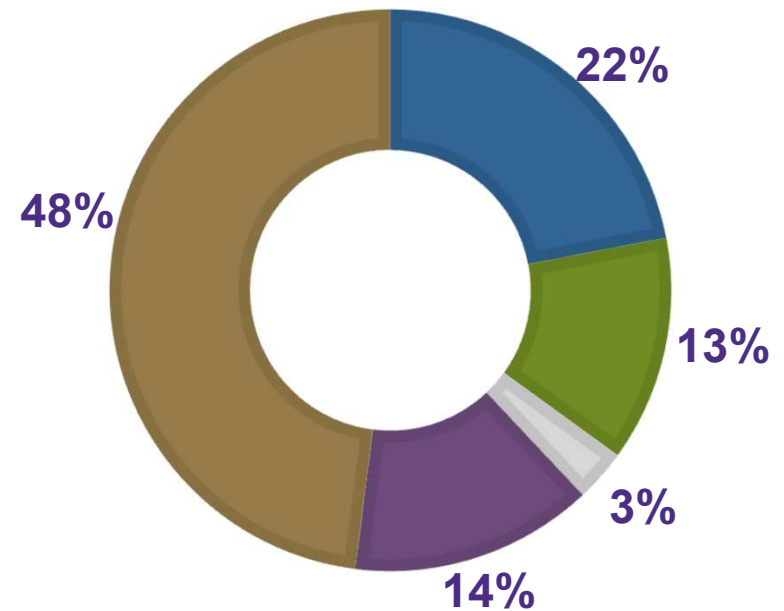
HYPERTENSION

■ ID ■ Primary Care ■ Both ■ Other ■ No meds

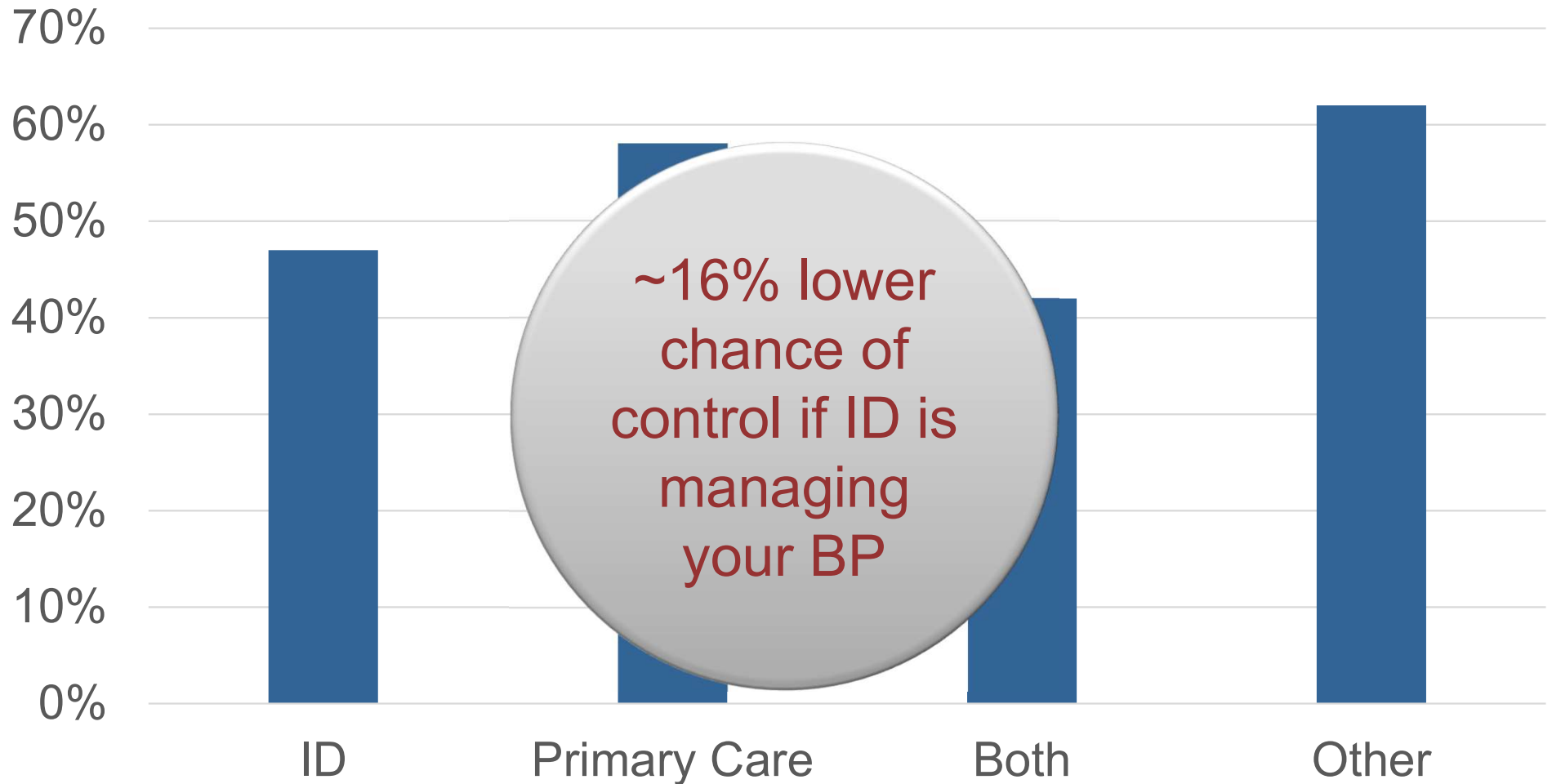


HYPERLIPIDEMIA

■ ID ■ Primary Care ■ Both ■ Other ■ No meds

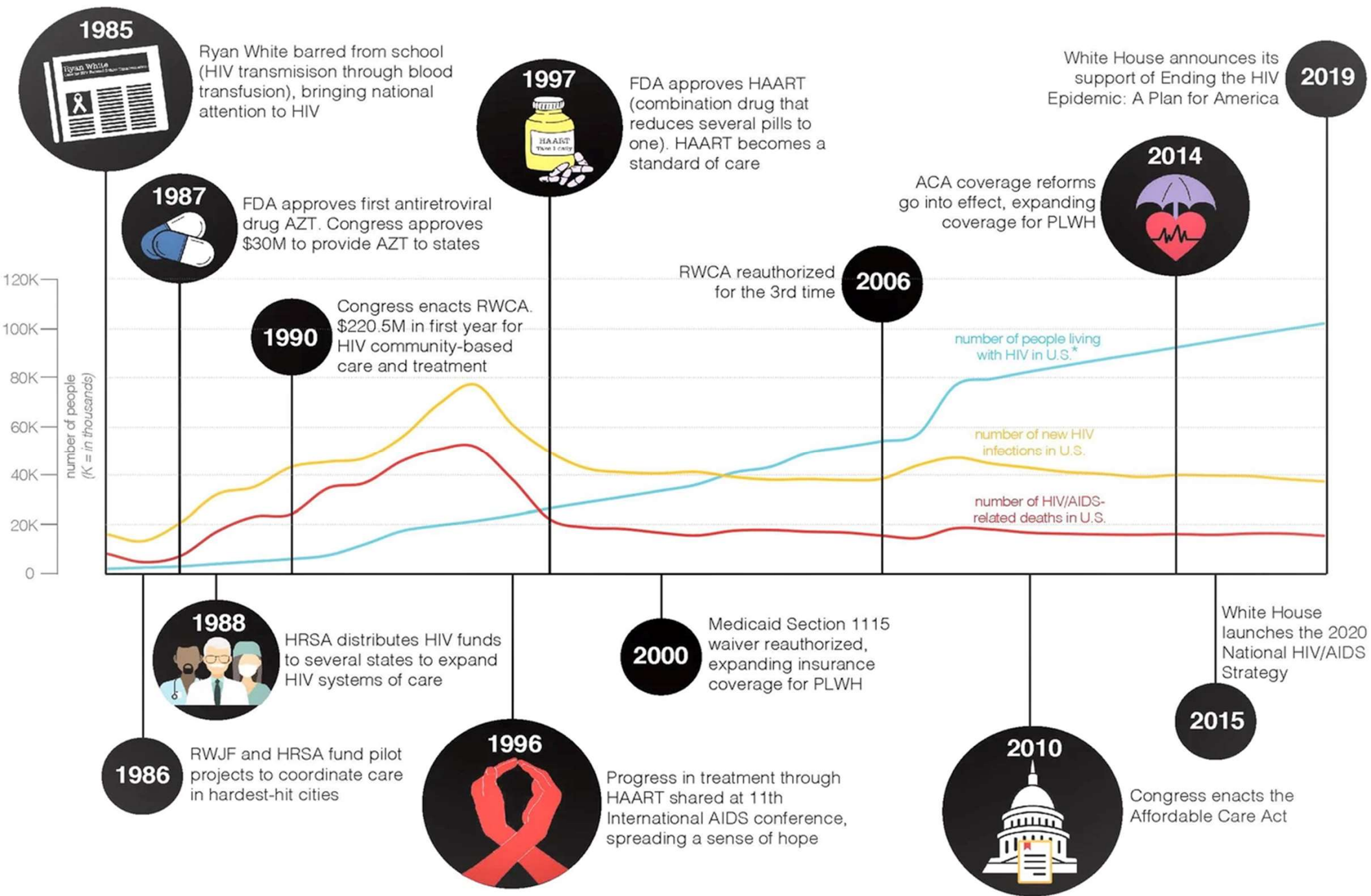


Proportion of patients with BP <140/90

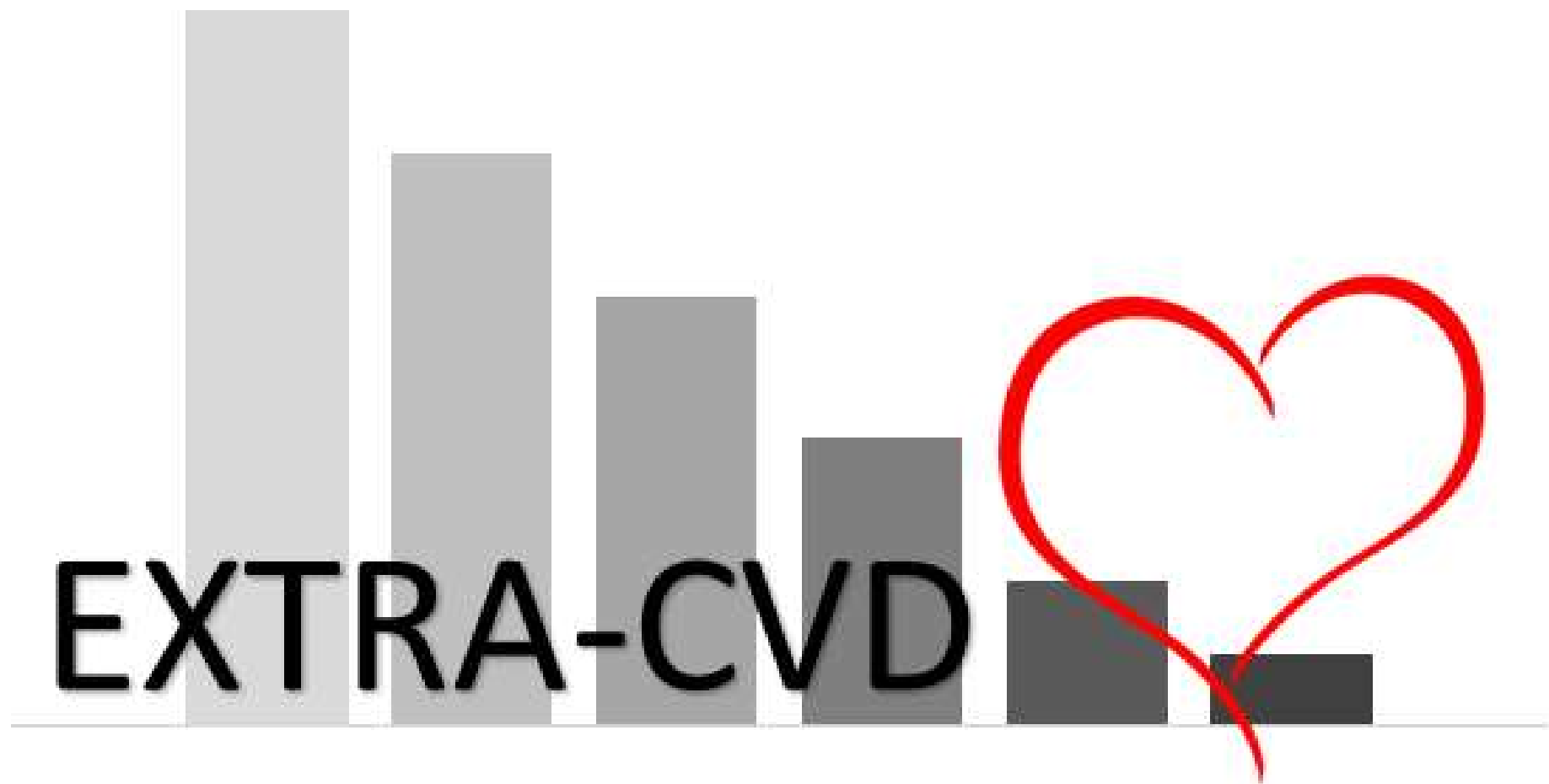


“I just have an HIV doctor, and he asked me the last time I was in if I had a primary care doctor. And I said, ‘That’s you!’ He said, ‘No, it’s not me’. And I said, ‘I just have HIV, nothing else seems to be wrong with me, so you’re my primary care doctor until such time as I feel I should see one.’”

PLWH, 25 years with HIV

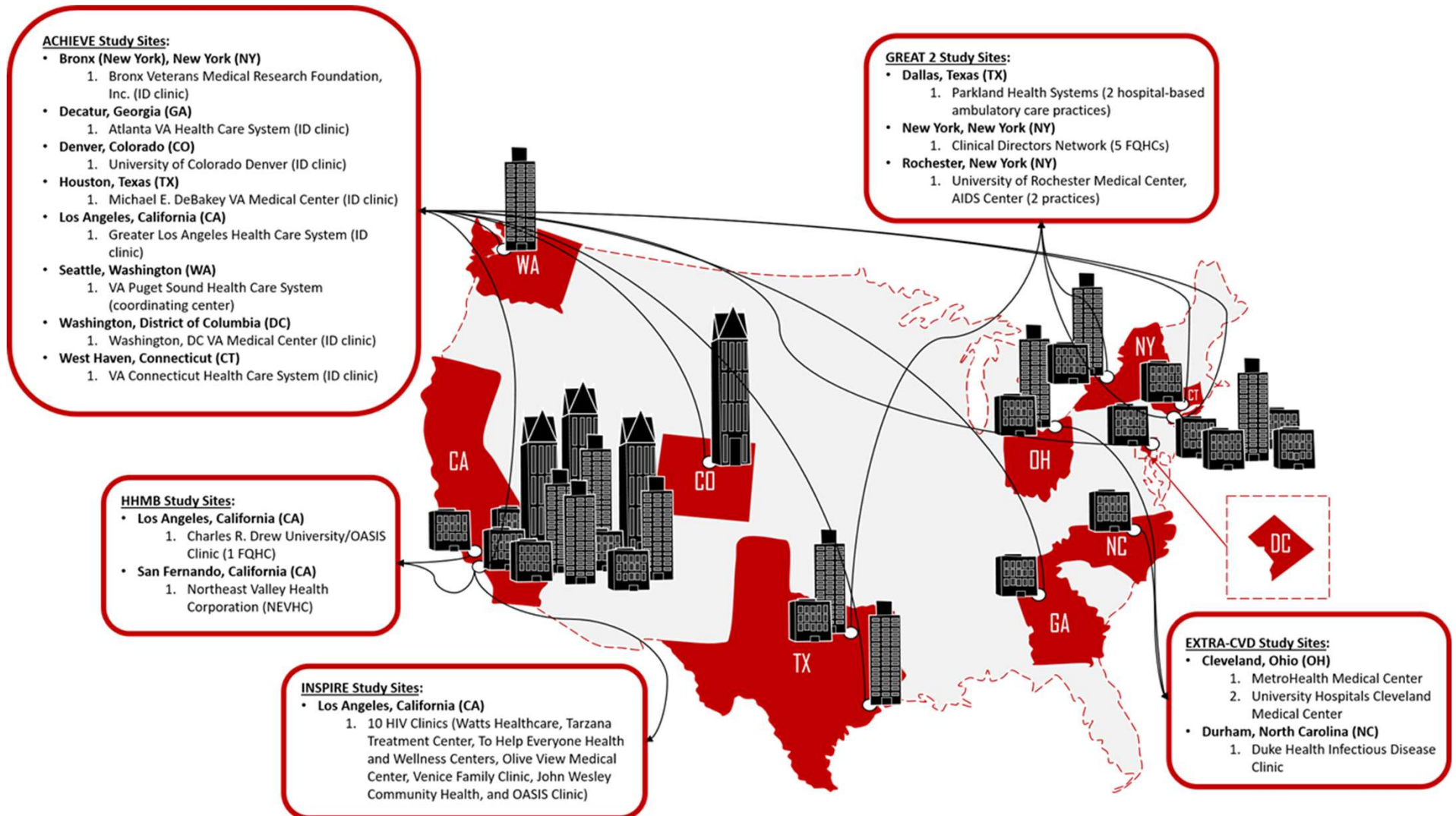


A Nurse Led Intervention to Extend the HIV Treatment Cascade for Cardiovascular Disease Prevention





PRECLUDE Consortium



Formative assessment of the current context

- 3 Academic Medical Centers
- Focus groups and semi-structured interviews
- N=51 People living with HIV
- N=34 Healthcare providers

What are the constraints on (and opportunities for) integrated CVD prevention care for PLWH?

Understanding constraints on integrated CVD prevention care for PLWH

Facilitators

- Access to resources
- Health Insurance
- Tools for CVD risk estimation
- Value of self-monitoring
- HIV providers as trusted sources of medical advice

Barriers

- Bottlenecks in clinic flow
- Transportation
- Tools to motivate lifestyle modifications
- Symptom guided self-management
- Decisions to manage CVD for PLWH
- HIV provider messaging on CVD risk



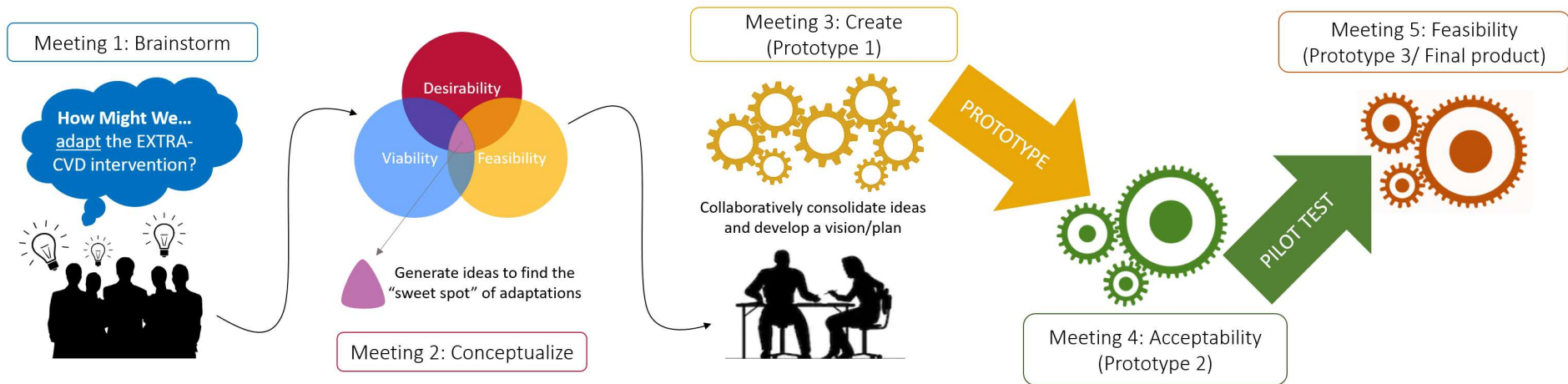
Why do our patients take their ART religiously, but not their statin or blood pressure meds?

Influence of healthcare financing?

RVUs



Human Centered Design

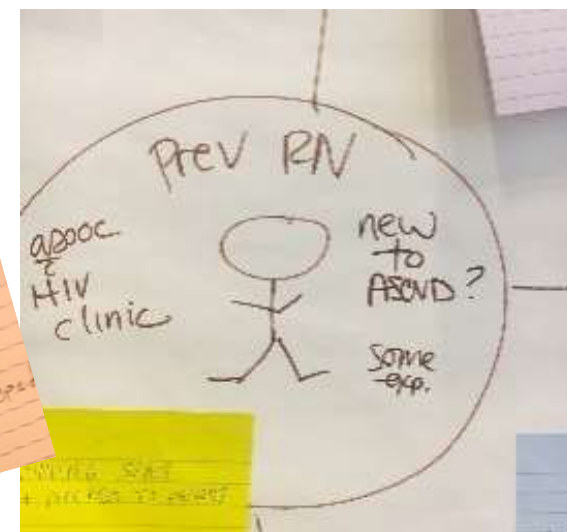


Angela Aifah, PhD
New York University School of
Medicine
EXTRA-CVD Diversity Supplement
Awardee



COMMONALITIES in THEMES

- overwhelmed (with)
- adherence (PMD)
- education + communication (by provider trust)
- risk perception (PLWIT) (P4 motivation) (that affects health)
- boundaries: research v clinical care
- interdisciplinary



Worry

Hope

① Education/Communication

PLWIT need appropriate education relative to their needs

education about PLWIT outcomes

Providers need more education to understand PLWIT needs

② Risk Perception/Mitigation

Providers need to understand PLWIT risk perception

Providers need to understand PLWIT risk mitigation

③ Research vs Clinical Care

Providers need to understand PLWIT research vs clinical care

Providers need to understand PLWIT research vs clinical care



HMW develop a diverse set of educational tools that are accessible & engaging?

↑ in clinic

Meds Too expensive

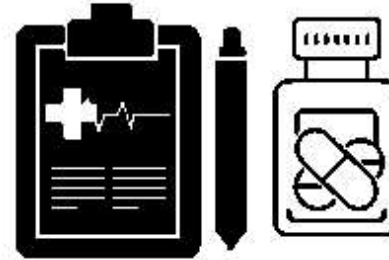
1

Nurse-led care coordination



2

Nurse-managed medication protocols and adherence support



3

Home blood pressure monitoring

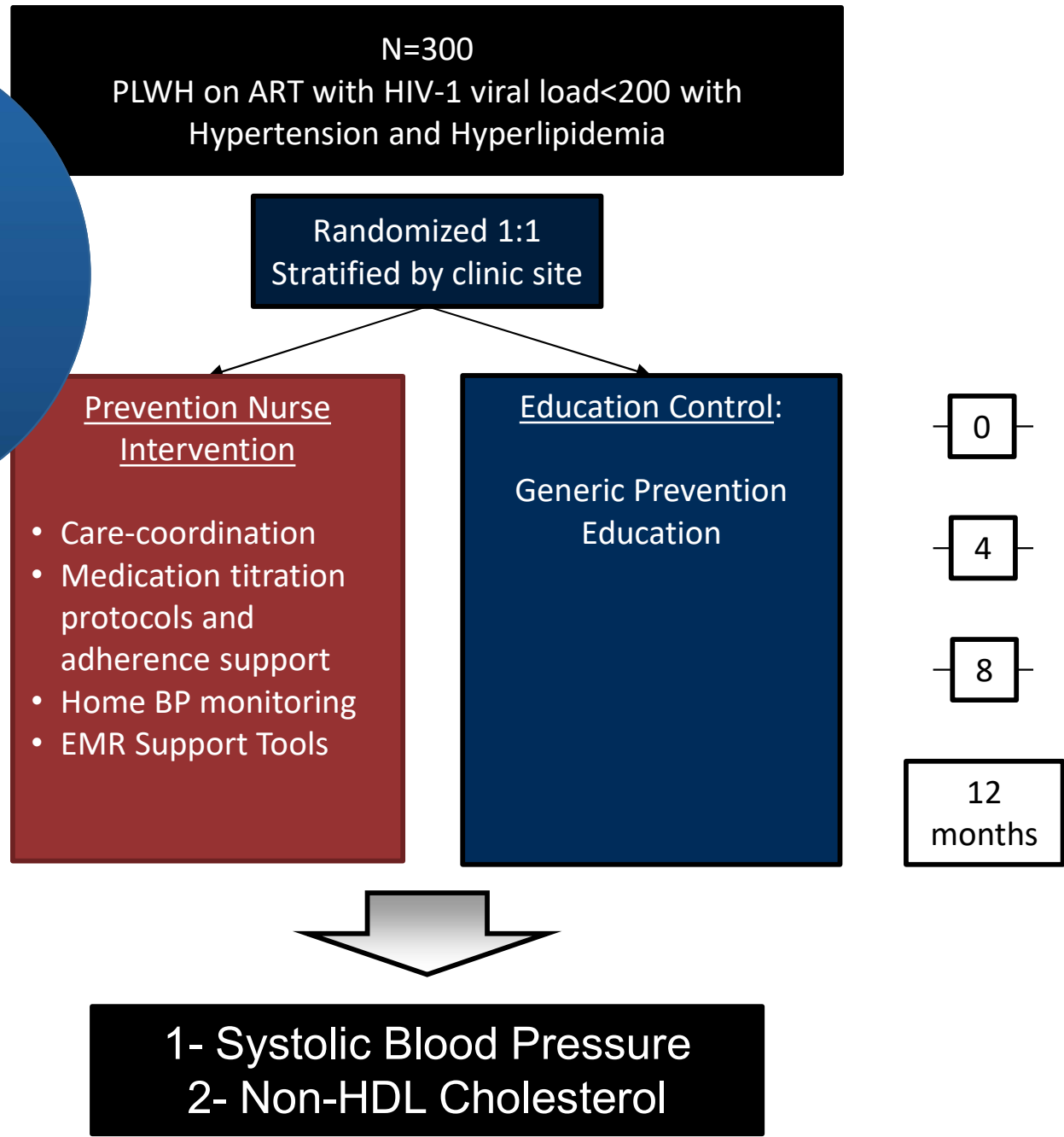


4

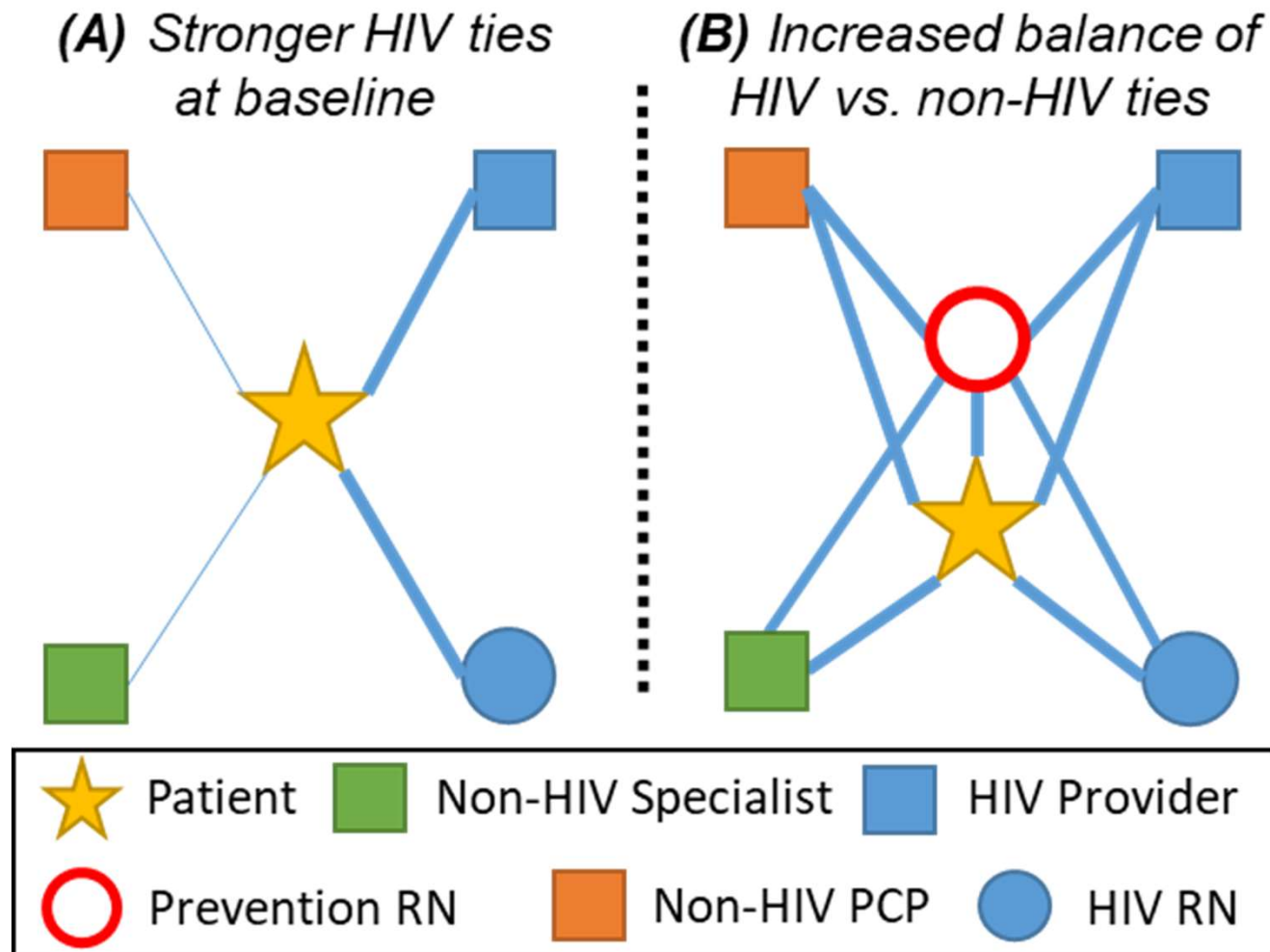
Electronic medical record support tools



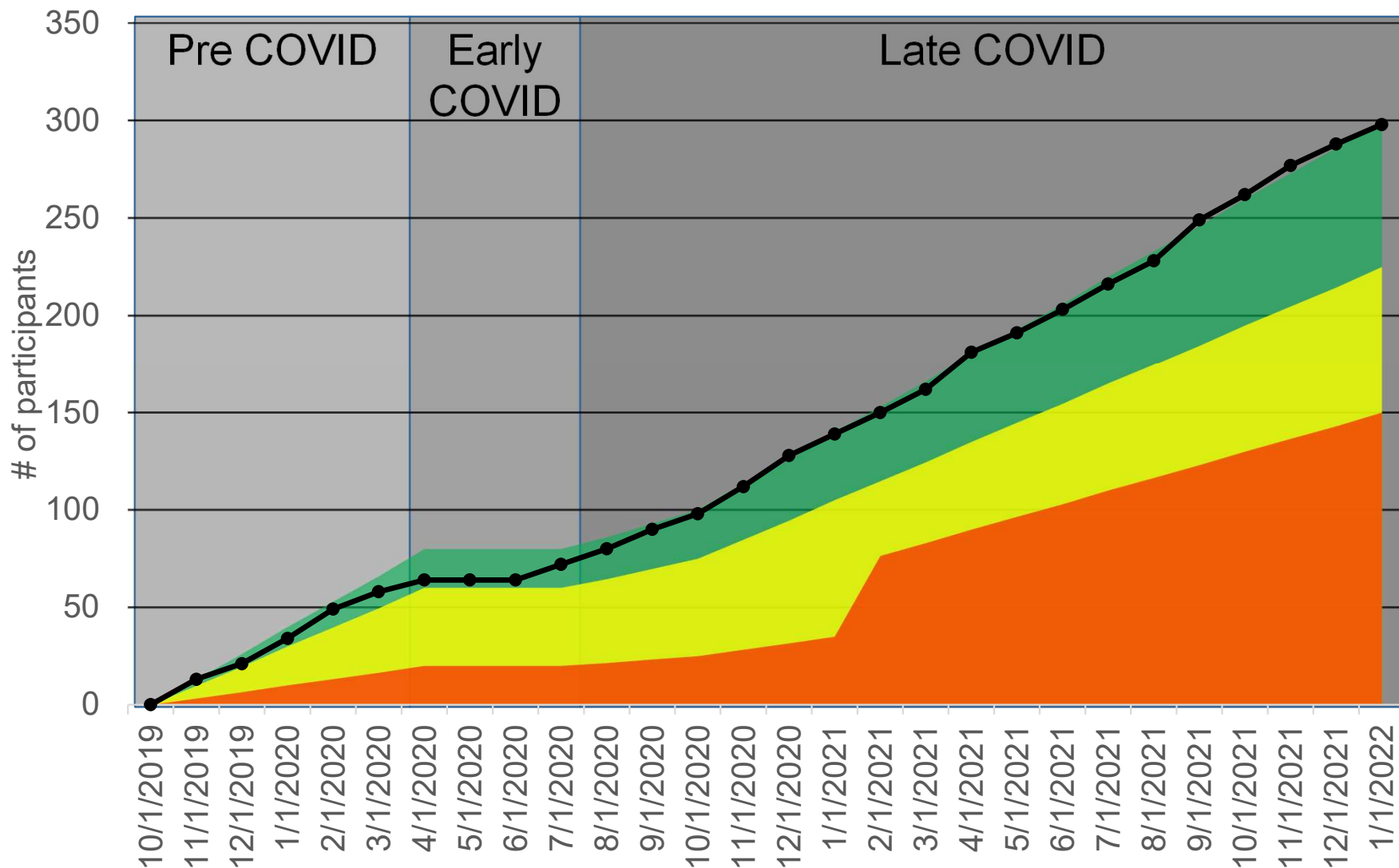
Hybrid Type I



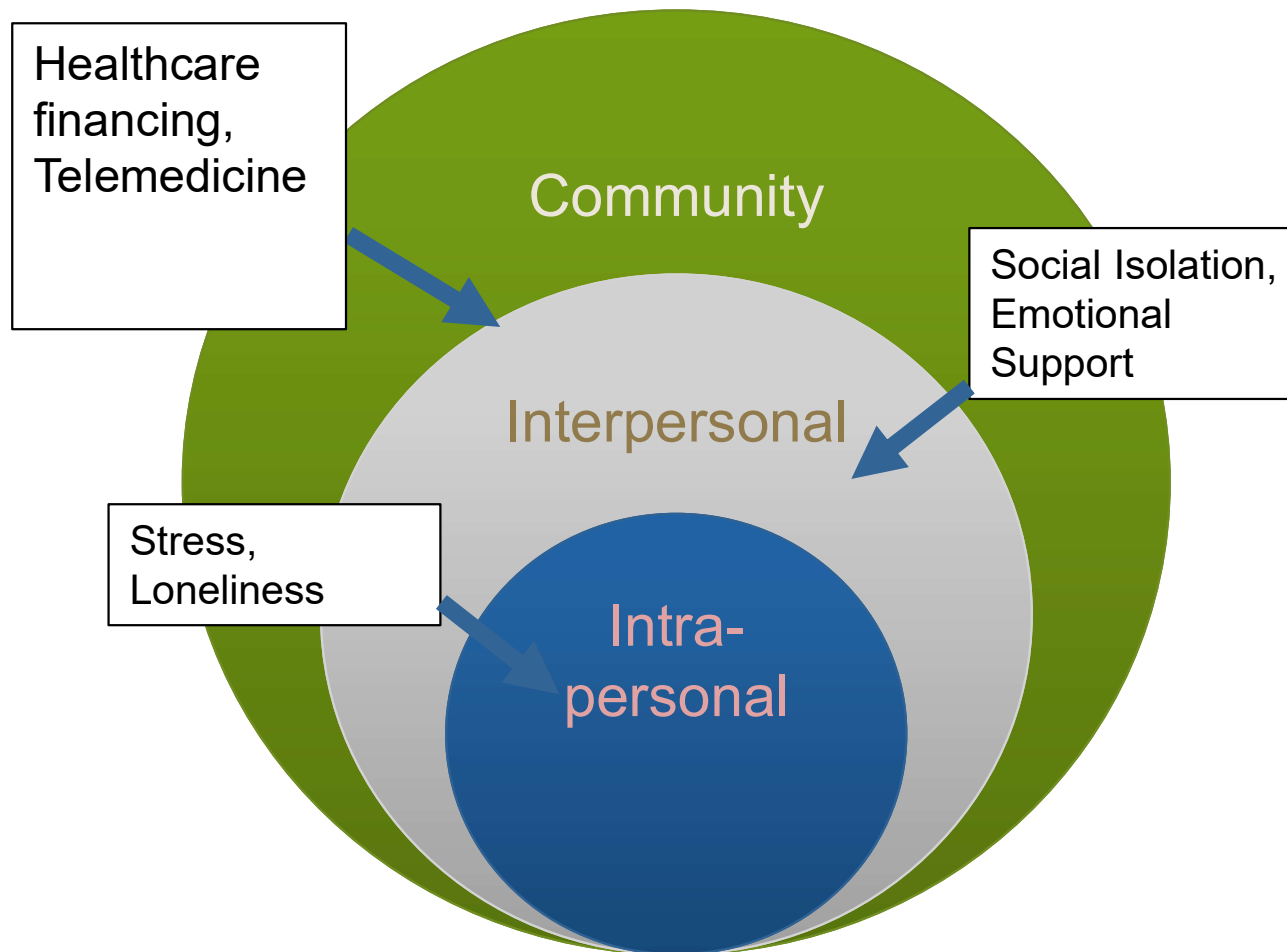
Importance of Provider Trust and Communication



Enrollment in EXTRA-CVD: Impact of COVID-19



Assess and Adapt to the Impact of COVID-19 on CVD Self-Management and Prevention Care in Adults Living with HIV (AAIM-High)





In Conclusion

- PLWH are at increased risk for a broad spectrum of cardiovascular disease including ASCVD and HF
 - Women may be particularly vulnerable
- Residual inflammation despite effective ART may be an important contributor to HIV-specific risk, but traditional risk factors are more determinative of absolute risk.
- It is time to extend the HIV cascade for cardiovascular disease prevention by focusing on the top 3 risk factors – hypertension, smoking, and cholesterol
- Close collaboration between specialists and multi-disciplinary teams has the potential to transform quality of CV prevention care for PLWH

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