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Feinberg School of Medicine

HIV and Cardio-Metabolic Risks

Research, Practice, and Questions

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Disclosures / conflicts

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  - National Institutes of Health (R01HL156792, R01HL154862, as PI)
  - American Heart Association

Outline

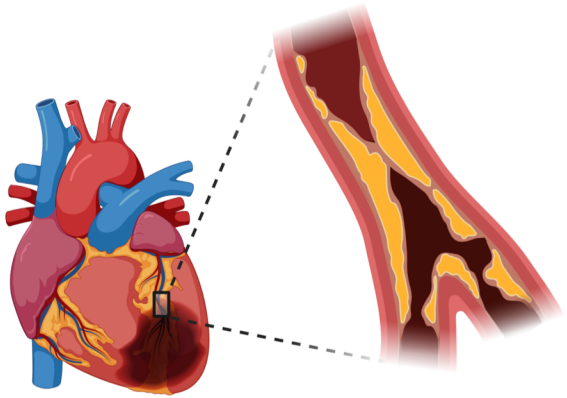
- **What:** Scope & Clinical Manifestations of CVD in HIV
  - Discussion of CLINICAL presentations / manifestations
- **Why:** CVD Mechanisms and Risk Factors in HIV
  - Framework of HIV, inflammation, and CVDs
  - Contribution of traditional CVD risk factors (e.g., smoking) & ARVs
- **How, When** and in **Whom**: CVD Prevention & Treatment
  - Risk assessment
  - Therapies: old, new, and future

HIV and Cardiovascular Diseases

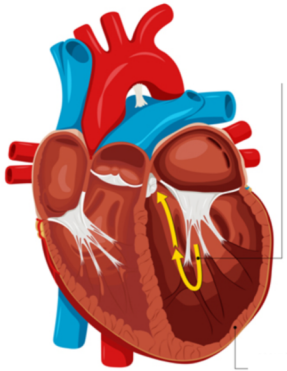
Scope and Manifestations

But First, a Primer on CVDs

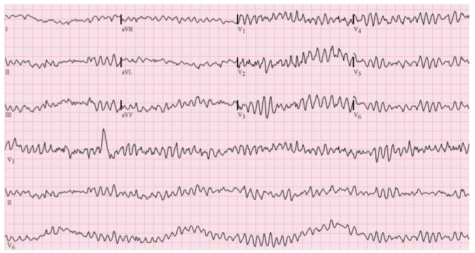
Common, Highly Morbid CVD Outcomes ↑ in HIV



Coronary Artery Disease and Myocardial Infarction (MI)



Heart Failure



Arrhythmia and Sudden Cardiac Death

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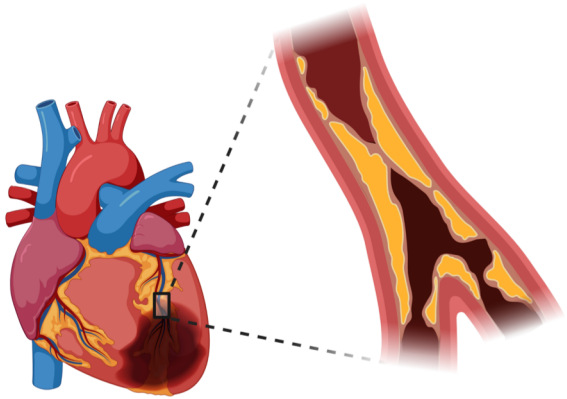
HIV and Athero-Thrombosis

Athero = plaque; thrombosis = clot



Coronary Artery Disease and Myocardial Infarction (MI)

Athero-Thrombosis

Arterial Plaque due to cholesterol and inflammatory material getting under the artery lining

Key Features include:

- **Lipid/cholesterol** (inflammatory response to retention in artery lining)
- **Activated/inflamed artery lining**

HIV and Athero-Thrombosis

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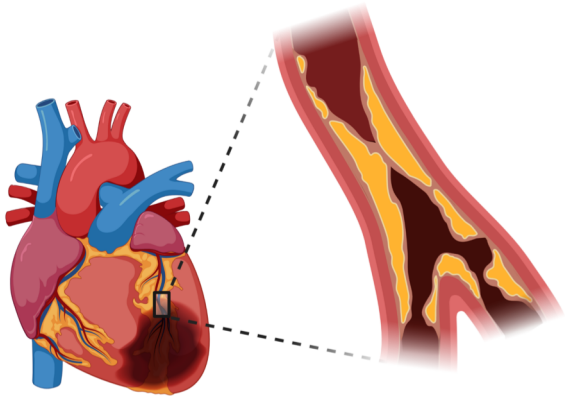
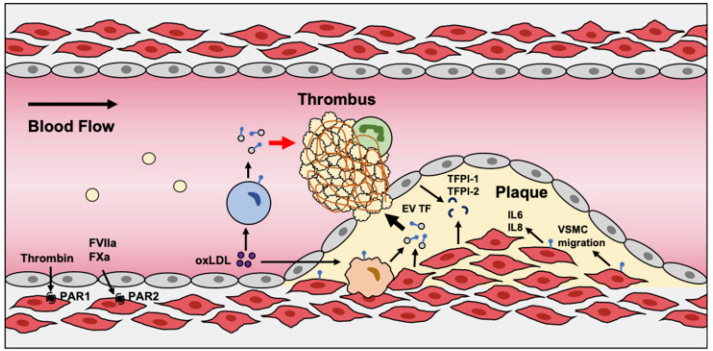


Coronary Artery Disease and Myocardial Infarction (MI)

Athero-Thrombosis

Clot forming (generally) in response to plaque rupture or erosion



Grover SP and Mackman N. *Atherosclerosis* 2020;307:80-86.

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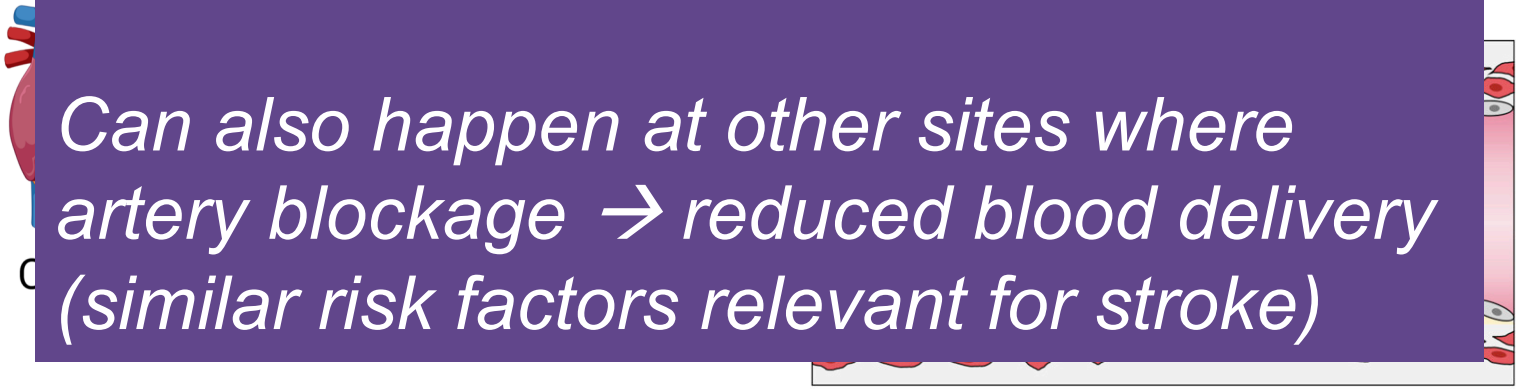
HIV and Athero-Thrombosis

End Result: Flow-Limiting Blockage resulting in reduced blood/oxygen delivery to the heart → angina, heart attack (MI)

Can also happen at other sites where artery blockage → reduced blood delivery (similar risk factors relevant for stroke)



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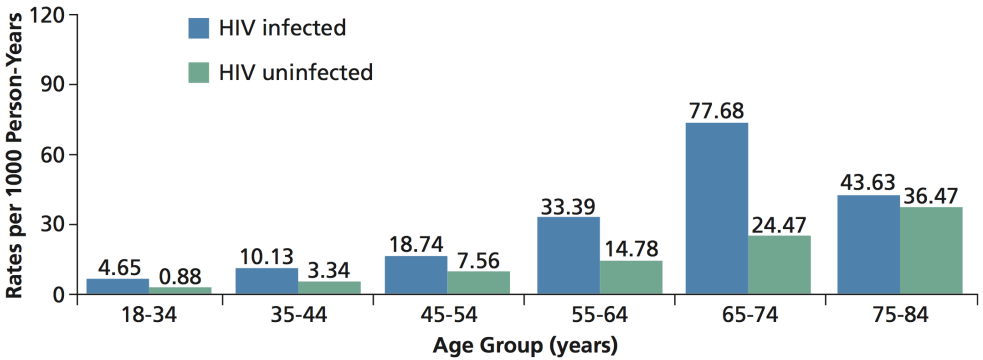
HIV and Athero-Thrombosis

Epidemiology: 1.5-2x HIV-associated MI (heart attack) risk

Increased MI risk across age ranges (early/pre-ART: Partners)



adapted from Triant V., et al. J Clin Endocrinol Metab 2007;92(7): 2506-12.

VACS: Increased MI Risk Across Risk Factor Strata

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HIV and Athero-Thrombosis

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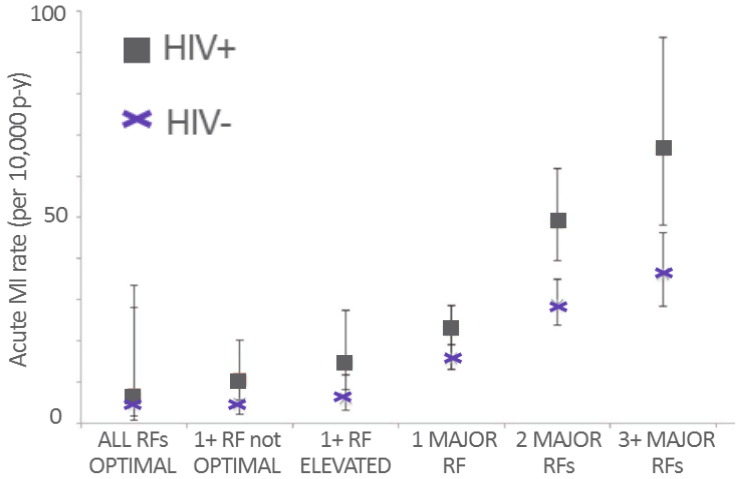
Increased MI Risk Across Risk Factor Strata (2003-2009; VACS)



Freiberg MS, et al. *JAMA Intern Med* 2013;173:614-622.
Figure Adapted from: Paisible AL, et al. *J Acquir Immune Defic Syndr* 2015;68:209-215

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HIV and Athero-Thrombosis

Epidemiology: 1.5-2x HIV-associated MI (heart attack) risk

Biologic Gradient: Viremia and Immune Progression Matter

Hazard Ratio of MI (vs. HIV-)

HIV VL (Time-updated, copies/mL)

<500: 1.39 (1.17-1.66)

≥500: 1.75 (1.40-2.18)

CD4 (Time-updated, cells/mm^3)

≥200: 1.43 (1.21-1.69)

<200: 1.88 (1.46-2.40)

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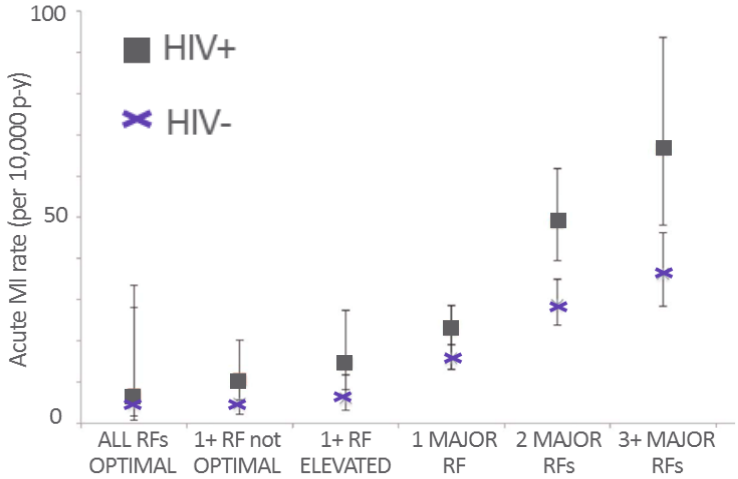
Increased MI Risk Across Risk Factor Strata (2003-2009; VACS)



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HIV and Athero-Thrombosis

Epidemiology: 1.5-2x HIV-associated MI risk – Still in the Contemporary Era

Kaiser Permanente Northern California & Partners (Boston)

2005-2017 (baseline) followed up for up to 5 years, through 2020

- 9401 PWH, 29,408 propensity-matched PWoH
  Matched on: demographics & cardiovascular risk factors

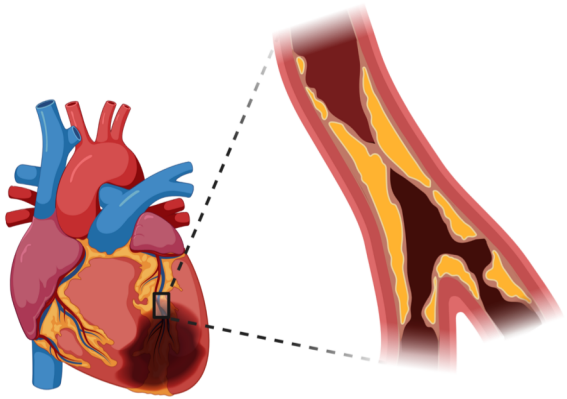
- Difference in cumulative incidence of MI for PWH vs. PWoH actually *increased* from 2005-9 to 2010-17 baseline periods: HR for MI 1.6 for PWH vs. PWoH

Silverberg MJ, Triant VA, et al. Conference on Retroviruses and Opportunistic Infections 2022.

Defic Syndr 2015;68:209-215

HIV and Heart Failure

Common, Highly Morbid CVD Outcomes ↑ in HIV



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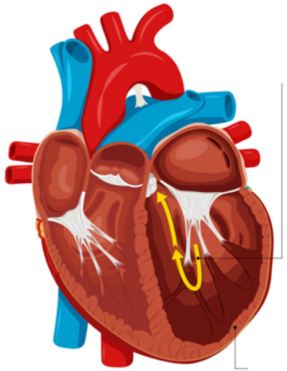

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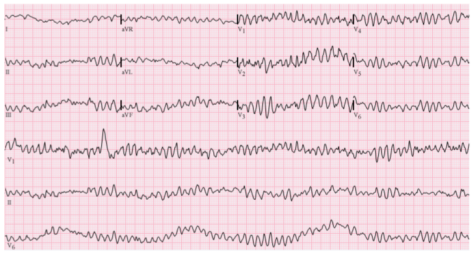

Arrhythmia and Sudden Cardiac Death

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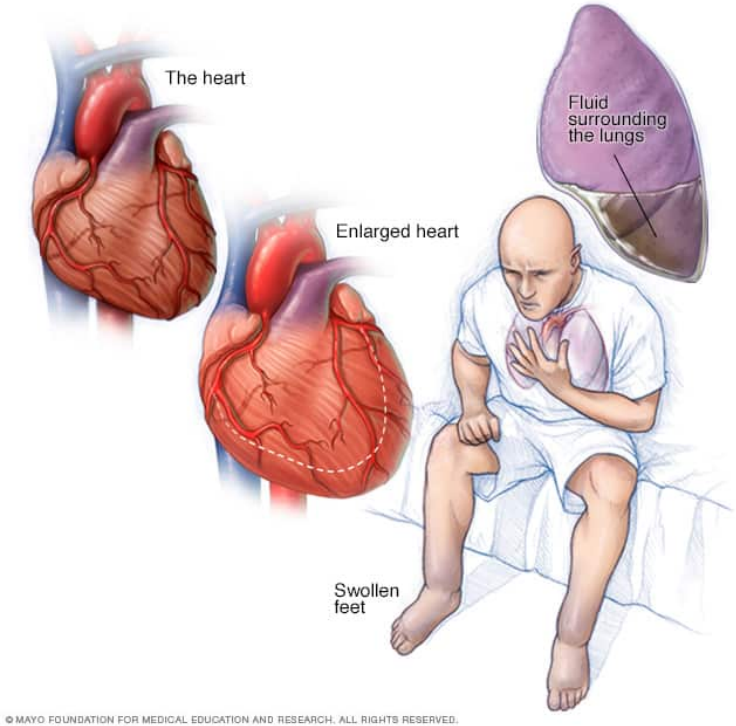
HIV and Heart Failure



Clinical Syndrome arising from

- *Impaired heart pump function and/or*
- *Inadequate relaxation of the heart*

Resulting in clinical congestion

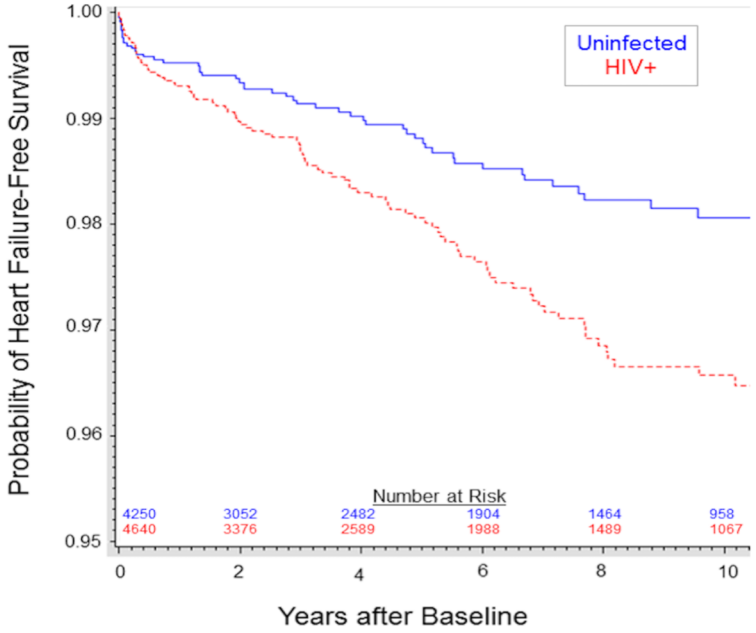
- *Shortness of breath, leg swelling*

*Highly heterogeneous – many potential causes (including MI, pulmonary HTN) & presentations

HIV and Heart Failure

Epidemiology: ~1.5-2x HIV-associated HF risk

Northwestern Cohort (N=8890): 2000-2016



Overall:

Hazard Ratio of HF **(vs. PWoH)**:

2.10 (1.38-3.21)

Among HIV+:

HR per $\log_{10}$higher time-updated **viral load**: **1.22 (1.11-1.33)**

HR per 100 cells/mm^3 higher time-updated **CD 4 count**: **0.80 (0.69-0.92)**

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Feinstein MJ, et al. *J Am Heart Assoc* 2018. 7(21):e009985. doi:10.1161/JAHA.118.0099865

HIV and Heart Failure

Epidemiology: ~1.5-2x HIV-associated HF risk

Veterans Aging Cohort Study (2003-2012)

Table 3. Human Immunodeficiency Virus (HIV) Infection and the Risk of Total Heart Failure (HF) and HF Type by Subgroup

Variable	No.	Total HF		HFpEF≥50%		Borderline HFpEF 40%-49%		HFrEF		EF Missing	
		No. of Events	HR (95% CI)[a]	No. of Events	HR (95% CI)[a]	No. of Events	HR (95% CI)[a]	No. of Events	HR (95% CI)[a]	No. of Events	HR (95% CI)
Total[a]											
HIV⁻	66 492	1695	1 [Reference]	629	1 [Reference]	267	1 [Reference]	597	1 [Reference]	202	1 [Reference]
HIV⁺	31 523	941	1.41 (1.29-1.54)	284	1.21 (1.03-1.41)	142	1.37 (1.09-1.72)	380	1.61 (1.40-1.86)	135	1.43 (1.12-1.82)
White race/ethnicity[b]											
HIV⁻	25 382	583	1 [Reference]	227	1 [Reference]	93	1 [Reference]	173	1 [Reference]	90	1 [Reference]
HIV⁺	12 254	303	1.31 (1.12-1.52)	94	1.13 (0.86-1.47)	52	1.44 (0.99-2.11)	104	1.54 (1.18-2.02)	53	1.15 (0.79-1.67)
Black race/ethnicity[c]											
HIV⁻	32 067	982	1 [Reference]	368	1 [Reference]	148	1 [Reference]	377	1 [Reference]	89	1 [Reference]
HIV⁺	15 246	549	1.41 (1.26-1.59)	161	1.16 (0.94-1.42)	77	1.31 (0.96-1.79)	243	1.61 (1.35-1.93)	68	1.76 (1.23-2.52)
Age <40 y[d]											
HIV⁻	10 896	55	1 [Reference]	18	1 [Reference]	7	1 [Reference]	21	1 [Reference]	9	1 [Reference]
HIV⁺	5888	62	2.41 (1.60-3.63)	12	1.16 (0.48-2.83)	7	2.12 (0.64-7.04)	34	3.59 (1.95-6.58)	9	1.84 (0.65 to 5.22)

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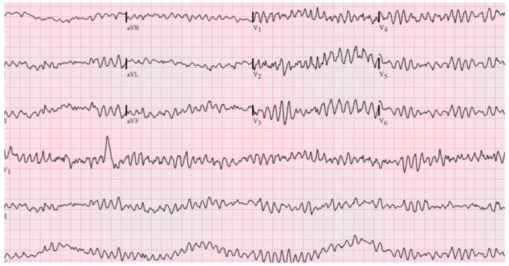
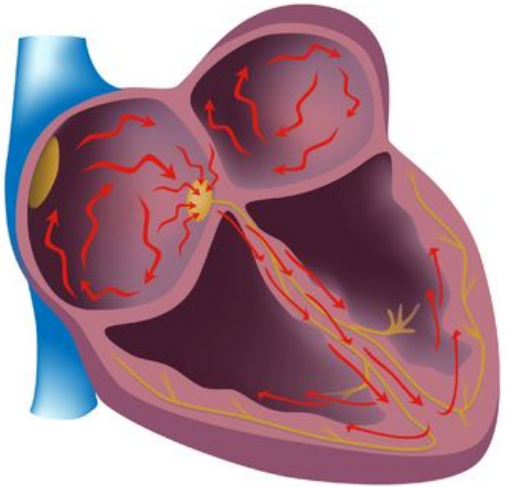
Freiberg MS, et al. *JAMA Cardiology* 2017;2(5):536-46

HIV and Arrhythmias

Irregular, often fast, heartbeats



- General Principles
  - Tachycardia means fast, chamber of origin precedes (e.g. ventricular tachycardia vs. atrial)
- Upper chambers of the heart (atria)
  - More “benign” (less deadly) rhythms
  - Atrial fibrillation, atrial flutter
- Lower chambers of the heart (ventricles)
  - Ventricular tachycardia, ventricular fibrillation



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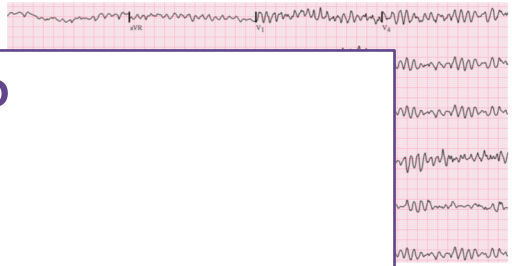
HIV and A



- Genera
  - Tachy
    (e.g. v
- Upper
  - More
  - Atrial
- Lower
  - Ventr

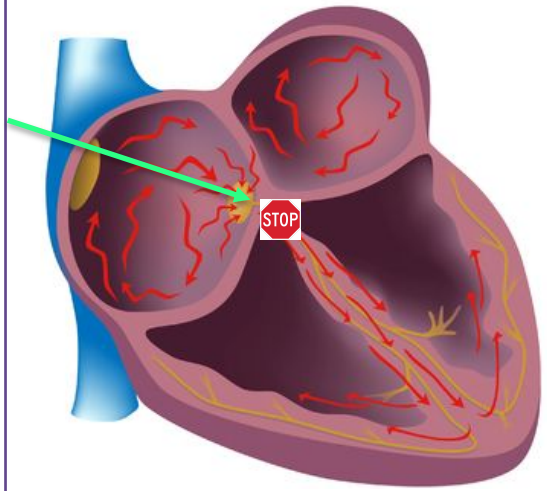
es

WHY?

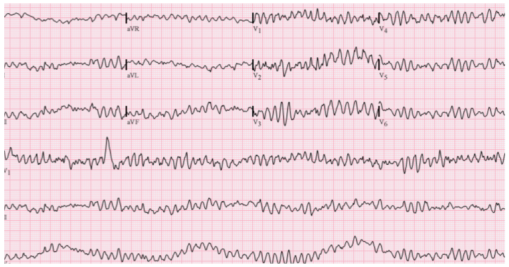
AV Node:
"Stop sign"

50 to ~125 ventricular beats per minute should be tolerable (higher fine for limited periods, e.g. exercise)

200+ ventricular beats per minute is not → inadequate filling time, less blood pumping forward, loss of pulse / death



HIV and Arrhythmias



- **What do we know about HIV and arrhythmias?**

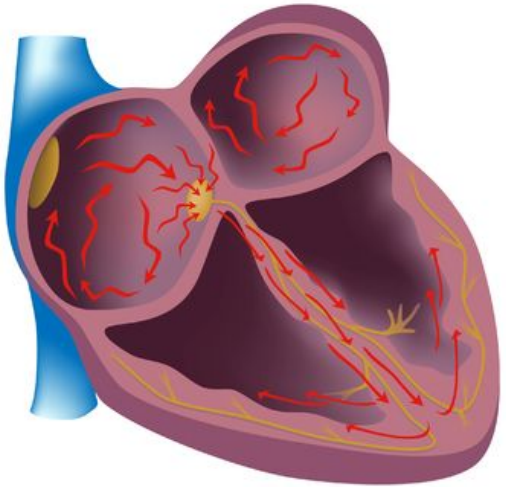
- HIV and Atrial Fibrillation Risk: Uncertain

No Difference: MACS, NM Cohorts

Osuji N, Post WS et al. Medicine 2021;100(29):e26663
Sanders JM, Feinstein MJ, et al. PLoS One 2018;13(3):e0194754

Increased Risk: UCSF Cohort

Sardana M, Hsue PY, et al. JACC 2019;74(11):1512-4.



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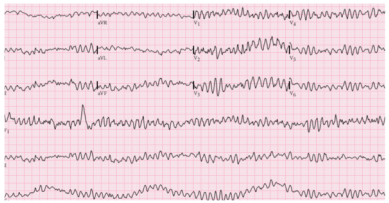
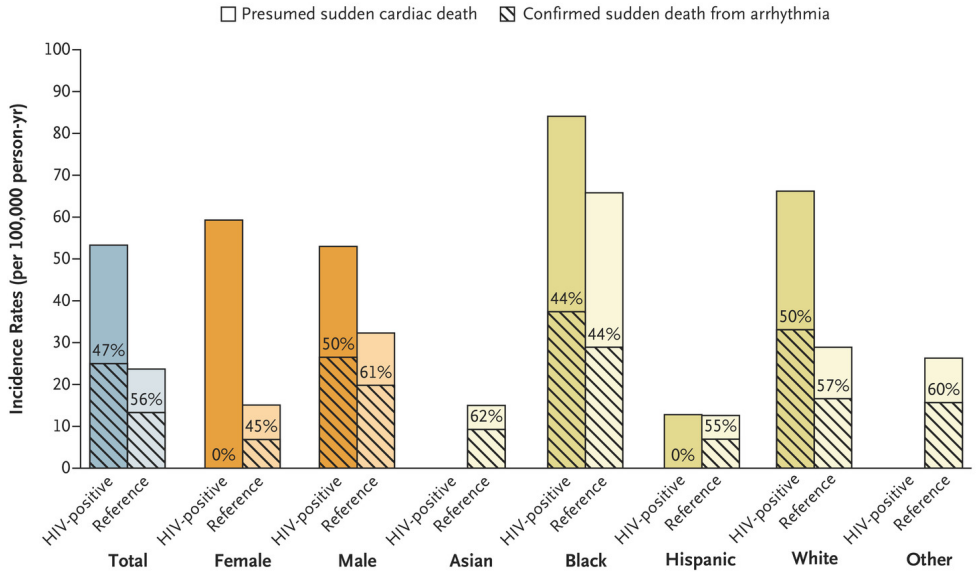
HIV and Arrhythmias



- **HIV and Sudden Cardiac Death: ↑ Risk**



Sudden Cardiac Death Incidence Rates (SF Medical Examiner)

HIV: 53.3 deaths/100k p-y

- Mean CD4 475; 79% ART

PWoH: 23.7 deaths/100k p-y

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Tseng ZH … Hsue PY. *N Engl J Med* 2021;384:2306-2316.

Why CVDs in HIV?

A Mechanistic Detour:

- *1. Inflammation and Cardiovascular Disease*

2. Why this is relevant for HIV

Inflammation and CVDs

What we know

1. ***Myeloid & lymphoid inflammation are clinically/epidemiologically and causally/experimentally implicated in CVDs***

   - **CAD:** plaque rupture, erosion, and vasculopathy
   - **HF:** Maladaptive response to injury, microvascular dysfunction, direct myocardial inflammatory infiltrates → systolic +/- diastolic dysfunction, ,HF
   - **Arrhythmia:** implicated in both electrical and structural remodeling

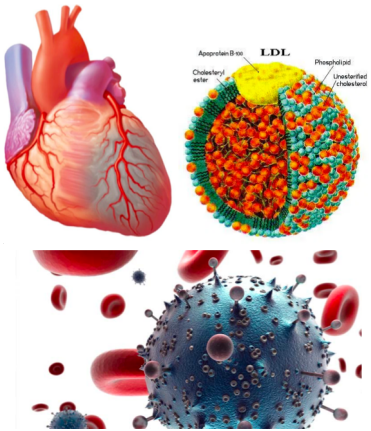
2. ***A complex interplay between comorbidities and underlying immunologic abnormalities/inflammatory bias can accelerate inflammation-CVD***

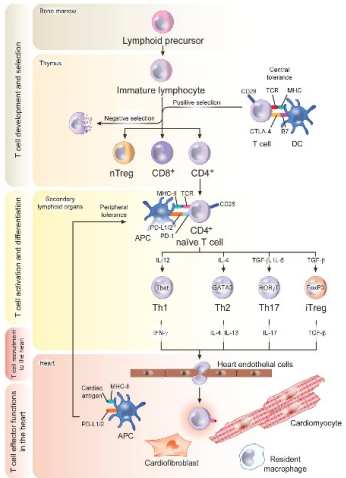
Blanton RM, Alcaide P, et al. Am J Physiol 2019;317(1):H324-H340.
Libby P et al. *J Am Coll Cardiol* 2018;72(17):2071-2081.
Simons KH et al. *Nature Rev Cardiol* 2019;16(6):325-343.
Tracy RP et al. *J Am Heart Assoc* 2013;2(3):e000117

Inflammation and CVDs

Antigens ("the thing" – e.g., piece of virus ("epitope") or even cholesterol!) → immune response recognizing these

Antigens & Antigen-like triggers	→	Immune Response: *Immune cell activation/biasing; phenotype switching: Self-tolerance vs. autoimmunity*	→	Cardiac & Vascular Inflammation, Overt CVDs





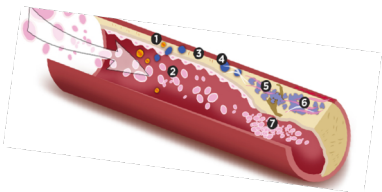
Inflammation

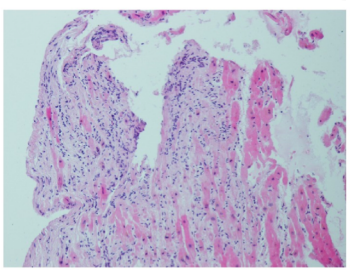
Key effectors: monocyte-derived (CCR2+) macrophages, CD4+ Th1/Th17

VS.

Inflammation Resolution

Key effectors: T_{regs} (when functional), cardiac resident (CCR2-) macrophages





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Adapted from Feinstein MJ, *Arterioscler Thromb Vasc Biol* 2021;41:523-5

Inflammation and CVDs

Antigens ("the thing" – e.g., piece of virus ("epitope") or even cholesterol!) → immune response recognizing these

Antigens & Antigen-like triggers → Immune Response: *Immune cell activation/biasing; phenotype switching: Self-tolerance vs. autoimmunity* → Cardiac & Vascular Inflammation, Overt CVDs

Balance & Timing is Critical:

"appropriate" inflammation (pathogen/debris clearance) vs. sustained inflammation, loss of self-tolerance, amplified auto-reactivity

Inflammation

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VS.

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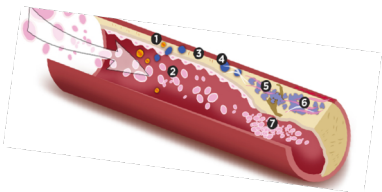

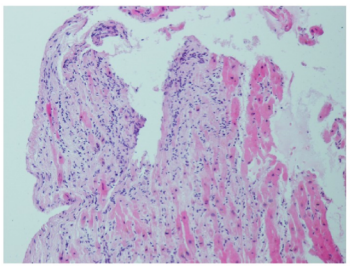

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Antigens & Antigen-like

Immune Response:
activation/biasing; phenotype
vs. autoimmunity

Cardiac & Vascular Inflammation, Overt CVDs

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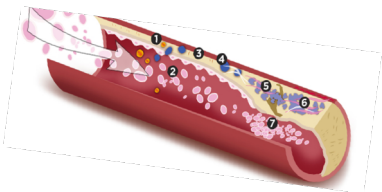
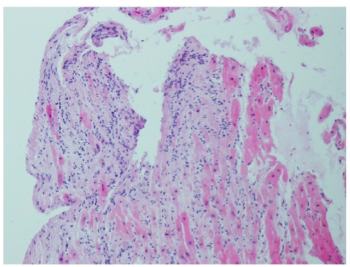
(CCR2-) macrophages





How does HIV-related immune progression affect this bias between persistent inflammation and resolution thereof?

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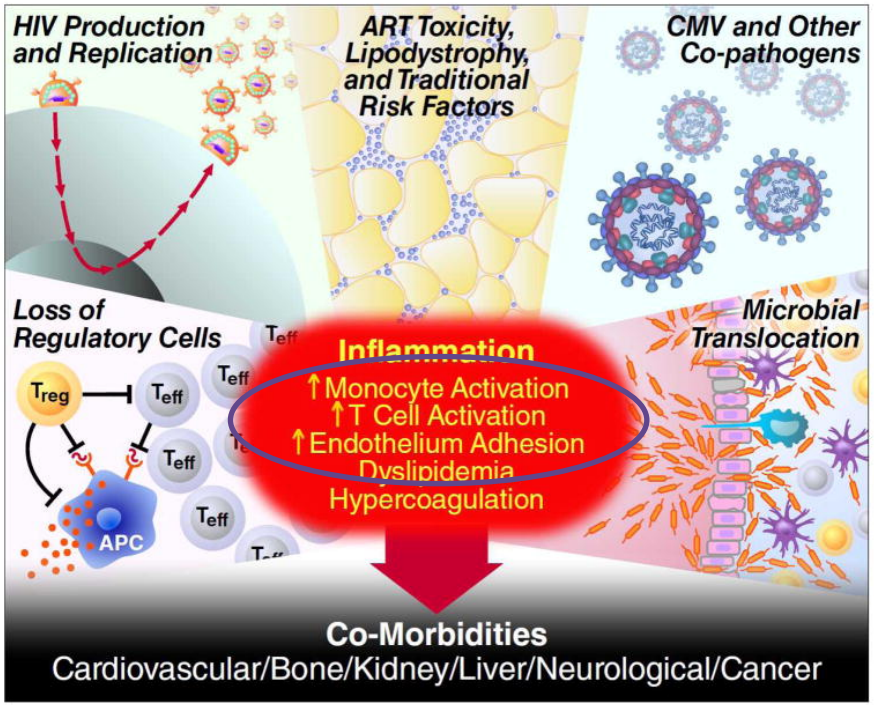
Adapted from Feinstein MJ, *Arterioscler Thromb Vasc Biol* 2021;41:523-5

HIV and Persistent Inflammation

Core mechanisms

Bias away from regulation, toward persistent inflammatory/ effector response

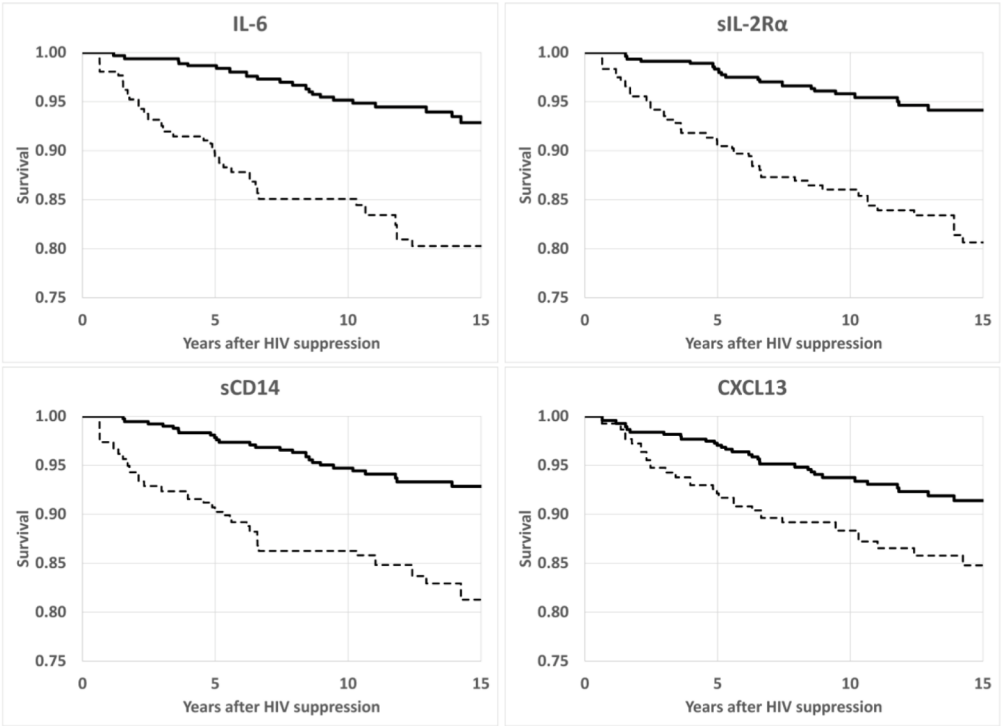
**Even when suppressed peripheral viral load, reservoir in tissues remains as antigenic trigger



Deeks SG, et al. *Lancet* 2013;382:1525-33.

HIV and Persistent Inflammation

Observational evidence…and evidence that it matters (mortality)



Wada N et al. Clin Infect Dis 2016;63(7):984-990.

HIV and Persistent Inflammation

Concomitant "Traditional" Cardiovascular Risk Factors

- Smoking: Highly Prevalent
- Dyslipidemia
  - Due to virus/inflammation: ↑HIV RNA: ↓HDL, stable/↓LDL-c(but some ApoB discordance), ↑TG, ↑TC/HDL ratio
  - ART-related (some)
    - PIs: ↑ TC, LDL, and TG levels
    - NNRTIs: Variable, may ↑ TC, LDL, and TG levels
    - NRTIs: Variable, may ↑ TC and TG levels
    - Fusion inhibitors, CCR5 antagonists, INSTIs: limited data
- Metabolic dysregulation & more

El-Sadr WM et al. *HIV Med* 2005;6(2):114-21.
Feinstein MJ et al. Circulation 2019;140(2):e98-e124
Feinstein MJ et al *Am J Cardiol* 2016
Oka F et al. *J Infect Chemother* 2012;18(1):17-21.

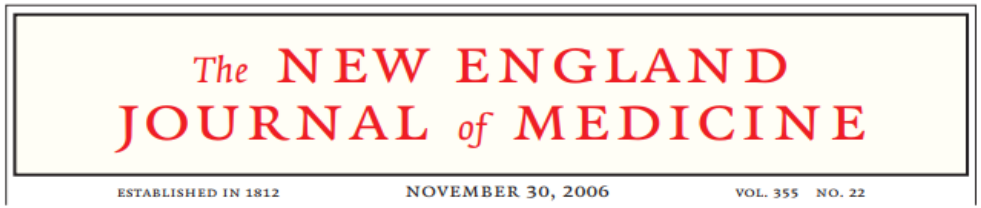
What is the Role of ART?

1. ART is clearly better than no ART (CVD and overall)

2. But there is drug- and class-specific nuance re: CVD risk

Effective ART better than none re: MI

(and, of course, HIV control in general)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 30, 2006 VOL. 355 NO. 22

CD4+ Count–Guided Interruption of Antiretroviral Treatment

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group*

METHODS

We randomly assigned persons infected with HIV who had a CD4+ cell count of more than 350 per cubic millimeter to the continuous use of antiretroviral therapy (the viral suppression group) or the episodic use of antiretroviral therapy (the drug conservation group). Episodic use involved the deferral of therapy until the CD4+ count decreased to less than 250 per cubic millimeter and then the use of therapy until the CD4+ count increased to more than 350 per cubic millimeter. The primary end point was the development of an opportunistic disease or death from any cause. An important secondary end point was major cardiovascular, renal, or hepatic disease.

MI Rate (over 2700 person-years' follow-up):

- **Interrupted** ART: **1.3 per 100** person-years
- **Uninterrupted** ART: **0.8 per 100** person/years

ARV-specific implications re: CVDs

Some signals, some spotty data

- **Not all ARVs are created equal re: CVD risk!**
- Protease inhibitors; initial concern re: class effect (NEJM 2007) for MI risk, but more drug-specific nuance now apparent
  - Ritonavir-boosted darunavir: ↑ CVD risk
  - Ritonavir-boosted Atazanavir: Neutral to ↓ CVD risk
- NRTIs
  - Older: ↑↑ Mitochondrial toxicity → myopathy, neuropathy, etc
  - TDF – nephrotoxicity; ABC – cardiomyopathy; 3TC – neuropathy
  - TAF vs. TDF: increased cholesterol, LDL; TDF→TAF weight gain; less clear actual CVD effect
- More on abacavir
  - Longer term follow-up cohorts: ↑ CVD risk vs. non-abacavir ART
    - ?mechanisms: Endothelial dysfunction, vascular inflammation, platelet reactivity
  - Shorter term clinical trials: No significant effect on CVD risk
- INSTIs: Weight gain but =/↓ CVD risk

References for ART-CVD Slides :

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Feinstein MJ et al. Circulation 2019;140:e98-e124

Monforte Ad et al. AIDS 2013;27:407-15

Ryom L et al. Lancet HIV 2018;5:e291-300.

Marconi VC et al. JAHA 2018;7:e007792.

Marcus JL et al. JAIDS 2016;71:413-419

Elion RA et al. JAIDS 2018;78:62-72.

Hsue PY et al. AIDS 2009;23:2021-7

Alvarez A et al. AIDS 2017;31:1781-95

Cid-Silva P et al. Basic Clin Phamarcol Toxicol 2019;124(4):479-90

Huhn G et al. OFID 2019;7(1):ofz472 –

O'Halloran JA et al. JAIDS 2020;84(4):396-9.

Kileel EM et al. OFID 2021;8(12):ofab537

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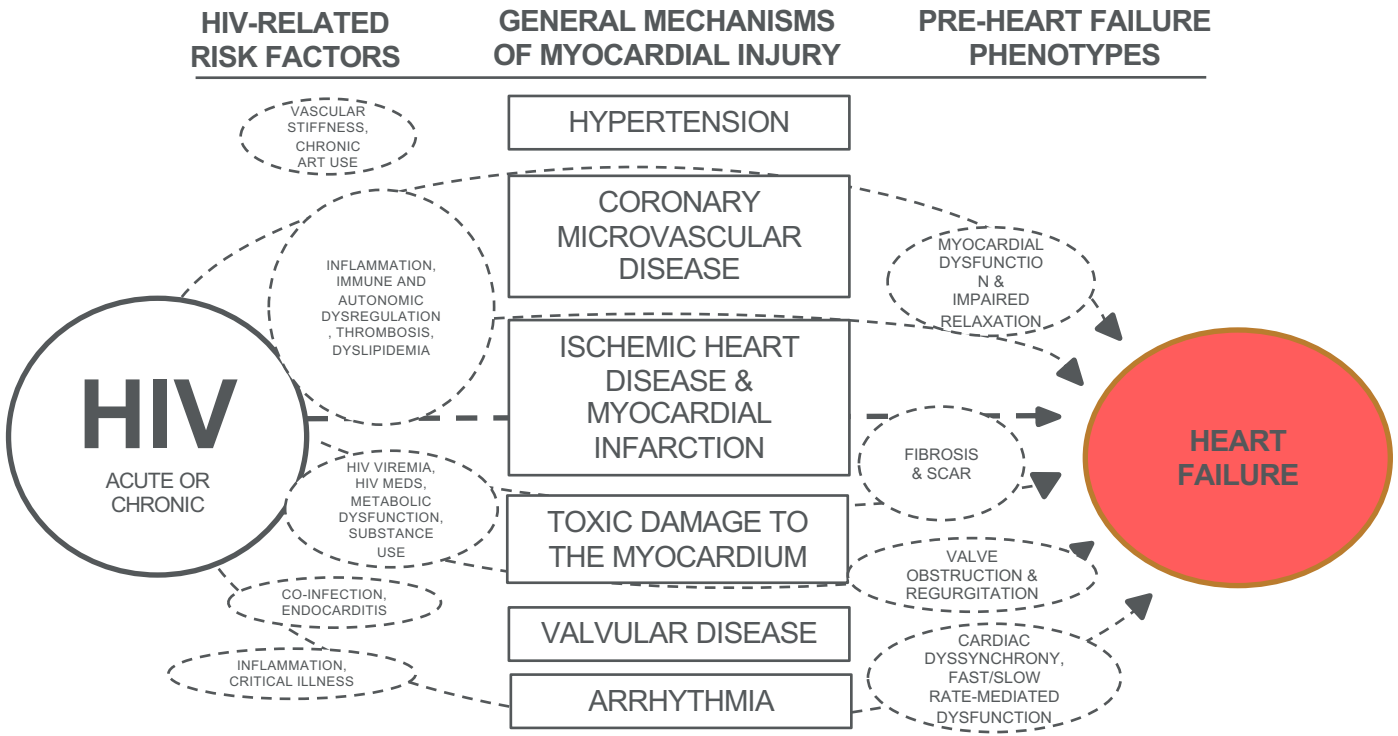
HIV and Heart Failure: Why?

Heart Failure as "Final Common Pathway"…which means many potential causes…address underlying causes!



@MattFeinsteinMD

Feinstein MJ et al. *Circulation* 2019;140(2):e98-e124.

What Can We Do About it?

Preventing and Treating CVDs in People with HIV

CVD Risk Assessments

Why Assess Risk?

General Principle:

Higher Absolute Risk → Higher Absolute Benefit from CVD-Reducing Rx

A (not very) theoretical example:

- 55 y/o person A with 3% risk for ASCVD in next 10y → Theoretical Med X reduces to 2%. So ***adding Med X gives 1/100 chance of preventing ASCVD over next 10y***
- 55 y/o person B with 30% risk for ASCVD in next 10y → Theoretical Med X reduces to 20%. So ***adding Med X gives 1/10 chance of preventing ASCVD over next 10y***

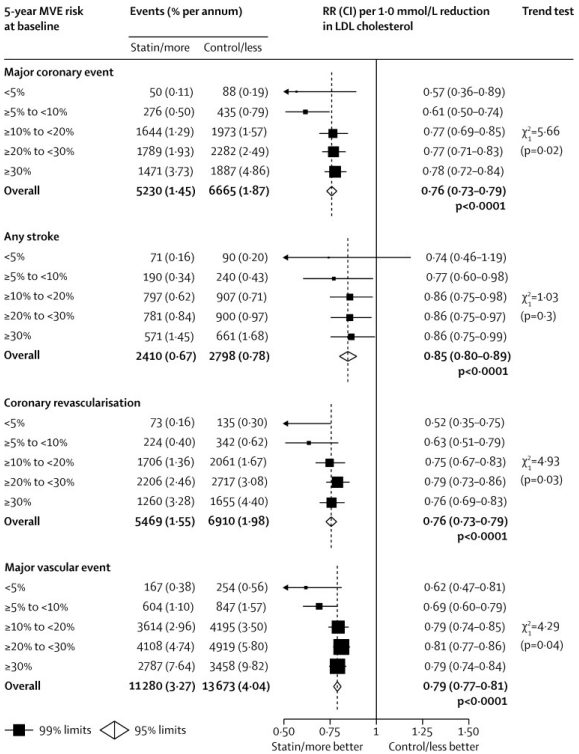
How does this absolute risk reduction balance against side effects risk? If 5% getting significant adverse/side effects, Med X justifiable in person B >>> A

CVD Risk Assessments

Why Assess Risk?

Statin therapy reduces ASCVD risk (*relative* risk reduction) by ~20-25% across most groups studied

…and now we have data in HIV (maybe stronger effect)



5-year MVE risk at baseline	Events (% per annum) Statin/more	Control/less	RR (CI) per 1·0 mmol/L reduction in LDL cholesterol	Trend test
Major coronary event				
<5%	50 (0·11)	88 (0·19)	0·57 (0·36–0·89)	
≥5% to <10%	276 (0·50)	435 (0·79)	0·61 (0·50–0·74)	
≥10% to <20%	1644 (1·29)	1973 (1·57)	0·77 (0·69–0·85)	χ^2_1=5·66
≥20% to <30%	1789 (1·93)	2282 (2·49)	0·77 (0·71–0·83)	(p=0·02)
≥30%	1471 (3·73)	1887 (4·86)	0·78 (0·72–0·84)	
Overall	**5230 (1·45)**	**6665 (1·87)**	**0·76 (0·73–0·79) p<0·0001**	
Any stroke				
<5%	71 (0·16)	90 (0·20)	0·74 (0·46–1·19)	
≥5% to <10%	190 (0·34)	240 (0·43)	0·77 (0·60–0·98)	
≥10% to <20%	797 (0·62)	907 (0·71)	0·86 (0·75–0·98)	χ^2_1=1·03
≥20% to <30%	781 (0·84)	900 (0·97)	0·86 (0·75–0·97)	(p=0·3)
≥30%	571 (1·45)	661 (1·68)	0·86 (0·75–0·99)	
Overall	**2410 (0·67)**	**2798 (0·78)**	**0·85 (0·80–0·89) p<0·0001**	
Coronary revascularisation				
<5%	73 (0·16)	135 (0·30)	0·52 (0·35–0·75)	
≥5% to <10%	224 (0·40)	342 (0·62)	0·63 (0·51–0·79)	
≥10% to <20%	1706 (1·36)	2061 (1·67)	0·75 (0·67–0·83)	χ^2_1=4·93
≥20% to <30%	2206 (2·46)	2717 (3·08)	0·79 (0·73–0·86)	(p=0·03)
≥30%	1260 (3·28)	1655 (4·40)	0·76 (0·69–0·83)	
Overall	**5469 (1·55)**	**6910 (1·98)**	**0·76 (0·73–0·79) p<0·0001**	
Major vascular event				
<5%	167 (0·38)	254 (0·56)	0·62 (0·47–0·81)	
≥5% to <10%	604 (1·10)	847 (1·57)	0·69 (0·60–0·79)	
≥10% to <20%	3614 (2·96)	4195 (3·50)	0·79 (0·74–0·85)	χ^2_1=4·29
≥20% to <30%	4108 (4·74)	4919 (5·80)	0·81 (0·77–0·86)	(p=0·04)
≥30%	2787 (7·64)	3458 (9·82)	0·79 (0·74–0·84)	
Overall	**11 280 (3·27)**	**13 673 (4·04)**	**0·79 (0·77–0·81) p<0·0001**	

99% limits 95% limits

0·50 0·75 1 1·25 1·50

Statin/more better Control/less better

Cholesterol Treatment Trialists Collaboration. *Lancet* 2012;380(9841):581-90

CVD Risk Assessments

Why Assess Risk?

Statin therapy reduces ASCVD risk (*relative* risk reduction) by ~20-25% across most groups studied

…and now we have data in HIV (maybe stronger effect..35%)

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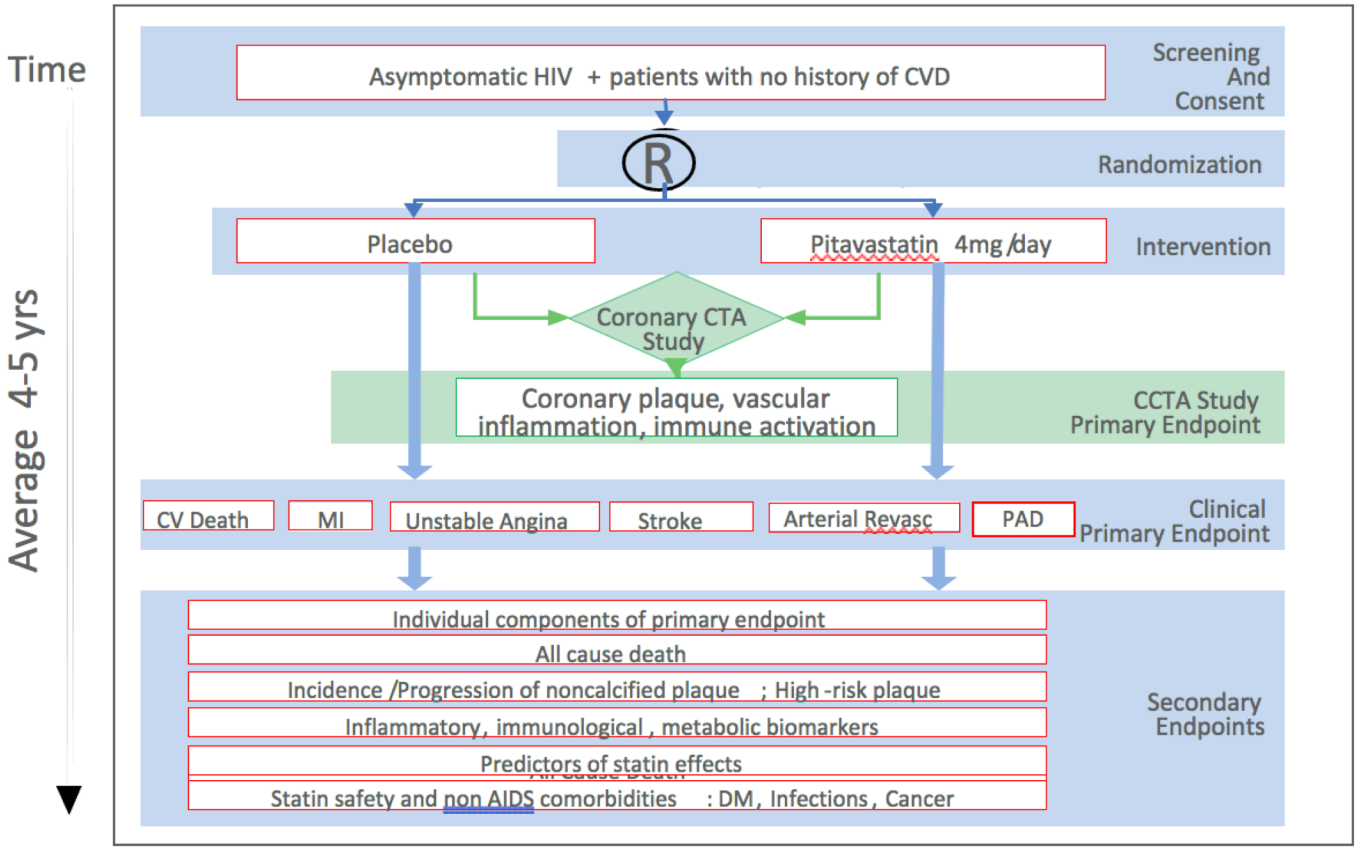
NEWS RELEASES

Tuesday, April 11, 2023

Daily statin reduces the risk of cardiovascular disease in people living with HIV, large NIH study finds

A National Institutes of Health (NIH) clinical trial was stopped early because a daily statin medication was found to reduce the increased risk of cardiovascular disease among people living with HIV in the first large-scale clinical study to test a primary cardiovascular prevention strategy in this population. A planned interim analysis of data from the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study found that participants who took pitavastatin calcium, a daily statin, lowered their risk of major adverse cardiovascular events by 35% compared with those receiving a placebo. Adverse drug events observed in the study were like those in the general population taking statin therapy. The interim analysis was sufficiently compelling that the study's independent Data Safety and Monitoring Board (DSMB) recommended it be stopped early given adequate evidence of efficacy. The NIH accepted the DSMB recommendations.

REPRIEVE – review of design/inclusions



@MattFeinsteinMD

Slide courtesy of Steve Grinspoon

REPRIEVE

Table 1. Demographic and Cardiovascular Characteristics by Entry Antiretroviral Therapy[a]

Characteristic	Participants, No. (%)[b]					
	Total (N = 7770)	NRTI + INSTI (n = 1978)	NRTI + NNRTI (n = 3676)	NRTI + PI (n = 1439)	NRTI Sparing (n = 199)	Other NRTI Containing (n = 476)
Demographic and Behavioral						
Age, median (IQR), y	50 (45–55)	51 (46–55)	49 (44–54)	50 (46–55)	51 (47–56)	51 (47–55)
Natal sex						
Male	5352 (69)	1563 (79)	2293 (62)	974 (68)	150 (75)	370 (78)
Female	2418 (31)	415 (21)	1383 (38)	465 (32)	49 (25)	106 (22)
Race[c]						
Black or African American	3378 (43)	786 (40)	1679 (46)	630 (44)	65 (33)	218 (46)
White	2701 (35)	1064 (54)	829 (23)	487 (34)	101 (51)	218 (46)
Asian	1139 (15)	24 (1)	893 (24)	193 (13)	20 (10)	9 (2)
Other	552 (7)	104 (5)	275 (7)	129 (9)	13 (7)	31 (7)
Ethnicity[d]						
Hispanic or Latino	698 (18)	302 (17)	188 (20)	117 (18)	23 (16)	68 (17)
Not Hispanic or Latino	3187 (81)	1472 (82)	743 (79)	532 (81)	115 (82)	324 (83)
Unknown	34 (1)	13 (1)	14 (1)	4 (1)	3 (2)	0 (0)
Smoking status						
Current	1933 (25)	586 (30)	764 (21)	378 (26)	52 (26)	153 (32)
Former	1906 (25)	606 (31)	752 (20)	352 (24)	54 (27)	140 (30)
Never	3923 (51)	784 (40)	2158 (59)	708 (49)	93 (47)	180 (38)
Substance use						
Current	152 (2)	52 (3)	52 (1)	34 (2)	6 (3)	8 (2)
Former	2277 (29)	958 (48)	592 (16)	431 (30)	83 (42)	213 (45)
Never	5333 (69)	967 (49)	3030 (82)	972 (68)	110 (55)	252 (53)
Cardiovascular and Metabolic						
BMI[e]						
<18.5	288 (4)	19 (1)	226 (6)	34 (2)	3 (2)	6 (1)
18.5–24.9	3115 (40)	613 (31)	1656 (45)	585 (41)	77 (39)	184 (39)
25–29.9	2664 (34)	755 (38)	1190 (32)	490 (34)	79 (40)	148 (31)
≥30	1696 (22)	586 (30)	603 (16)	329 (23)	40 (20)	138 (29)

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Fichtenbaum CJ, … Grinspoon SK on behalf of the REPRIEVE Investigators. J Infect Dis. 2020;222(S1):S8-19.

REPRIEVE

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HIV-Related Health Status						
Nadir CD4 T-cell count						
<50/ μ L	1406 (18)	352 (18)	513 (14)	307 (21)	57 (29)	176 (37)
50–199/ μ L	2386 (31)	490 (25)	1193 (32)	473 (33)	69 (35)	160 (34)
200–349/ μ L	2039 (26)	501 (25)	1031 (28)	397 (28)	33 (17)	77 (16)
≥350/ μ L	1677 (22)	541 (27)	834 (23)	224 (16)	33 (17)	45 (9)
Unknown	262 (3)	94 (5)	105 (3)	38 (3)	7 (4)	18 (4)
History of AIDS-defining event	1849 (24)	328 (17)	874 (24)	432 (30)	65 (33)	150 (32)
CD4 T-cell count, median (IQR), cells/ μ L	620 (447–826)	628 (456–845)	633 (468–832)	612 (422–820)	605 (447–834)	521 (348–720)
CD8 T-cell count median (IQR), cells/ μ L	779 (564–1032)	775 (555–1006)	750 (547–992)	838 (600–1129)	840 (601–1083)	886 (664–1112)
HIV-1 RNA level below LLQ						
<20 copies/mL	2819 (47)	1207 (64)	849 (37)	442 (38)	96 (51)	223 (50)
<40 copies/mL	2243 (37)	407 (22)	1131 (49)	528 (45)	56 (30)	121 (27)
<400 copies/mL	187 (3)	31 (2)	129 (6)	21 (2)	4 (2)	2 (<0.5)
≥LLQ	750 (13)	240 (13)	202 (9)	179 (15)	31 (17)	98 (22)
ART History						
Total ART use median (IQR)	9.6 (5.3–14.8)	9.0 (4.8–15.6)	8.3 (4.7–12.3)	11.0 (6.5–16.0)	17 (11–21)	16.0 (10.4–20.3)
Total ART use						
<5 y	1709 (22)	503 (25)	968 (26)	209 (15)	6 (3)	23 (5)
5–10 y	2305 (30)	556 (28)	1230 (33)	406 (28)	35 (18)	78 (16)
≥10 y	3754 (48)	918 (46)	1478 (40)	823 (57)	158 (79)	375 (79)
Unknown	2 (<0.5)	1 (<0.5)	0 (0)	1 (<0.5)	0 (0)	0 (0)
Protease exposure	3624 (47)	985 (50)	615 (17)	1400 (97)	192 (96)	430 (90)
Thymidine exposure	3799 (49)	601 (30)	1870 (51)	867 (60)	137 (69)	323 (68)
Abacavir exposure	1618 (21)	775 (39)	297 (8)	262 (18)	74 (37)	209 (44)
Tenofovir exposure	6572 (85)	1707 (86)	3035 (83)	1241 (86)	151 (76)	437 (92)
Duration of entry ART regimen, median (IQR), y	2.3 (0.8–5.2)	1.0 (0.5–1.9)	3.6 (1.7–6.8)	2.9 (0.9–6.2)	1.8 (0.7–4.6)	1.4 (0.6–3.8)

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Fichtenbaum CJ, … Grinspoon SK on behalf of the REPRIEVE Investigators. J Infect Dis. 2020;222(S1):S8-19.

CVD Risk Assessments

But how do our risk scores work?

CVD Risk Scores: *Under-predict risk for ASCVD among people with HIV (in most cohorts and with most equations)*

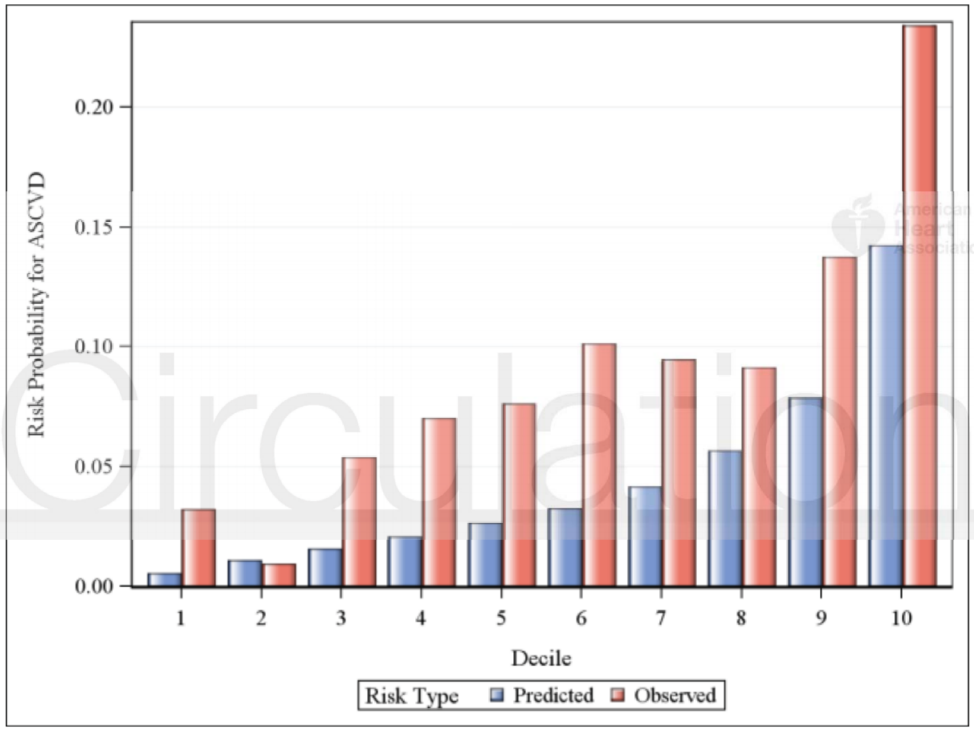

Figure from Triant VA, et al. *Circulation* 2018;137:2203-14

Triant VA, et al. *Circulation* 2018;137:2203-14.
Feinstein MJ, et al. *JAMA Cardiology*. 2017;2:155-162.
Achhra AC, et al. *Curr HIV/AIDS Rep*. 2021;18(4):271-9.

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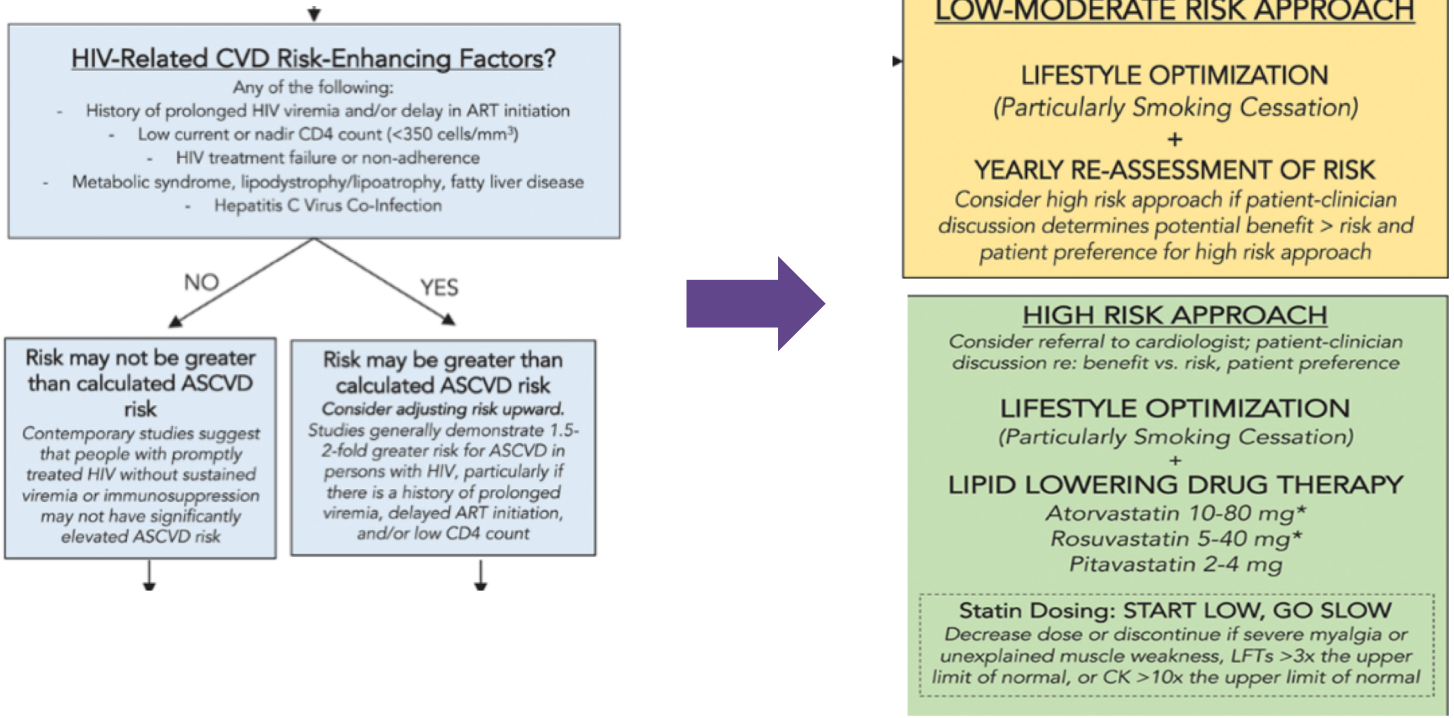
Interim Approach

To CVD-preventive statin Rx



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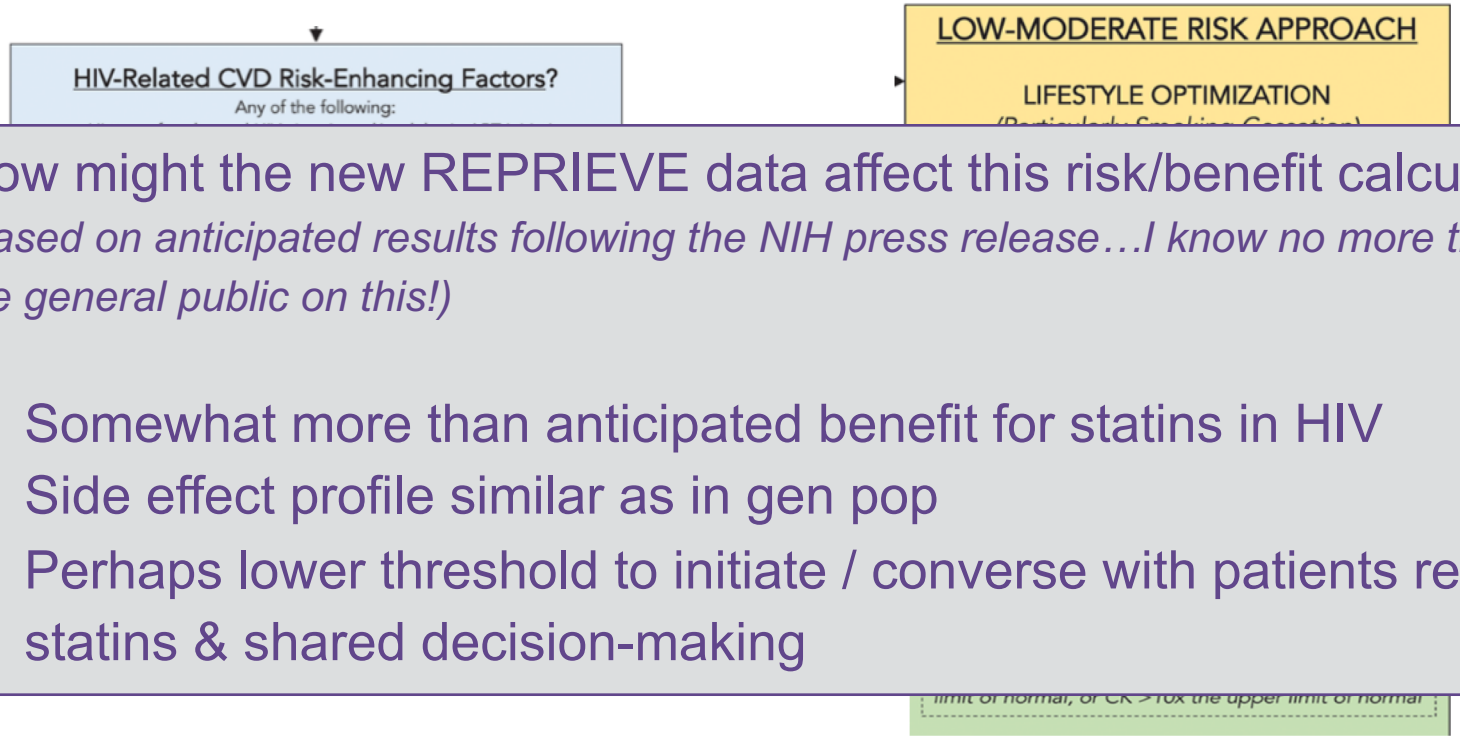
Feinstein MJ et al. *Circulation* 2019;140(2):e98-e124.

Interim Approach

To CVD-preventive statin Rx



How might the new REPRIEVE data affect this risk/benefit calculus?

(based on anticipated results following the NIH press release…I know no more than the general public on this!)

- Somewhat more than anticipated benefit for statins in HIV
- Side effect profile similar as in gen pop
- Perhaps lower threshold to initiate / converse with patients re: statins & shared decision-making

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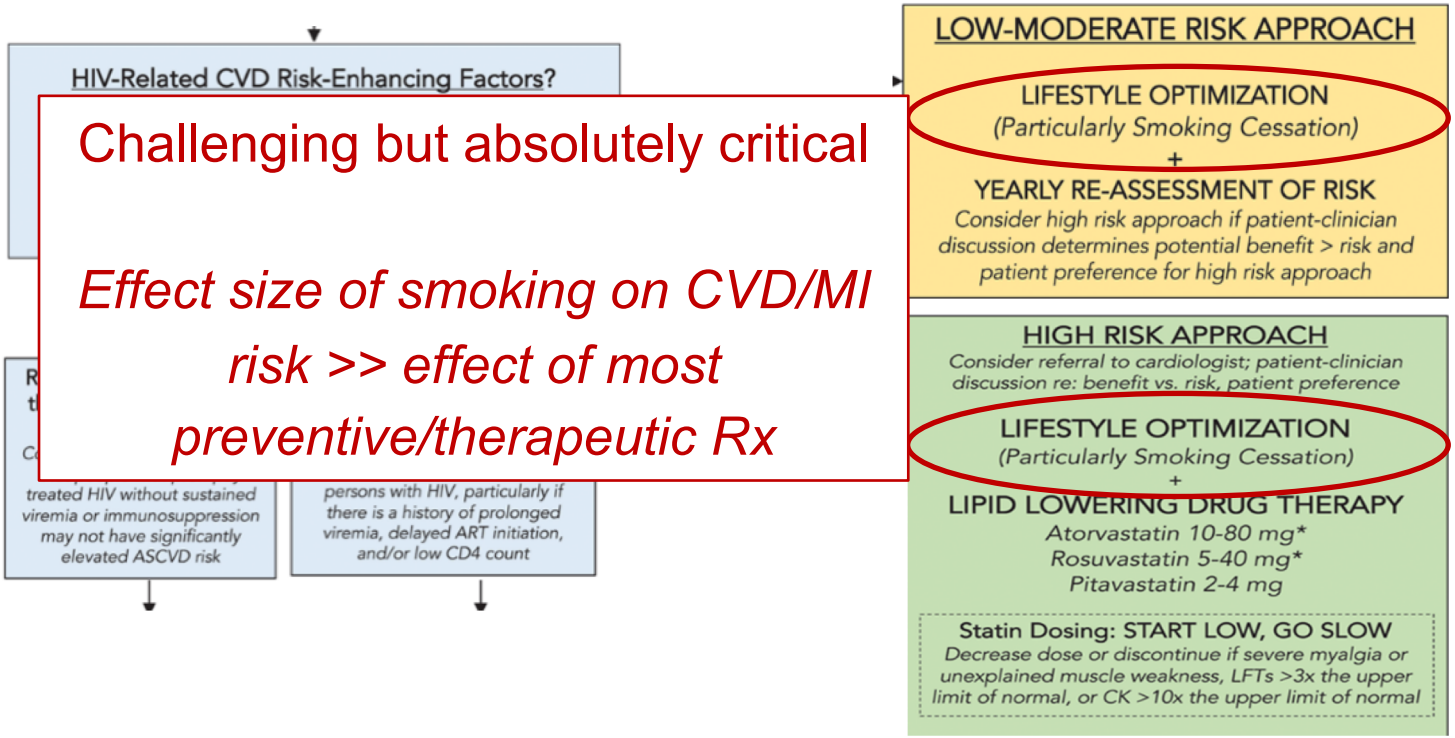
Feinstein MJ et al. *Circulation* 2019;140(2):e98-e124.

Interim Approach

To CVD-preventive statin Rx



Challenging but absolutely critical

Effect size of smoking on CVD/MI risk >> effect of most preventive/therapeutic Rx

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Feinstein MJ et al. *Circulation* 2019;140(2):e98-e124.

What about Antiplatelet Therapy?

Aspirin, clopidogrel, others?

- Aspirin (ASA) did not impact markers of immune activation or endothelial function in HIV in RCT
  - Young study population (mean age 48-50), 12 week f/u, FMD endpoint

O'Brien MP, et al. *Open Forum Infect Dis* 2017;4(1):ofw278.

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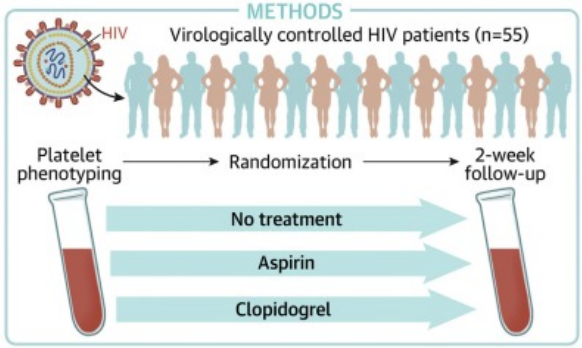
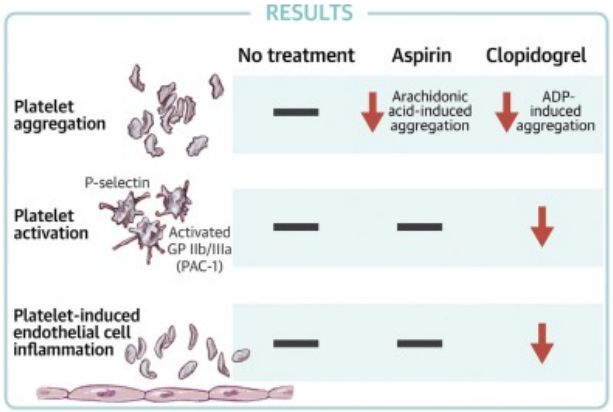
- What about clopidogrel? Recent RCT: Reduced platelet activation and platelet-induced endothelial inflammation whereas ASA did not





Marcantoni E, et al. J Am Coll Cardiol Basic Trans Science. 2022;7(11):1086-97.

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What about Antiplatelet Therapy?

Aspirin, clopidogrel, others?

- What does this mean for antiplatelet Rx for primary prevention of ASCVD in HIV? Despite pro-thrombotic milieu in HIV, need clinical data to inform risks/benefits of antiplatelet Rx for primary prevention

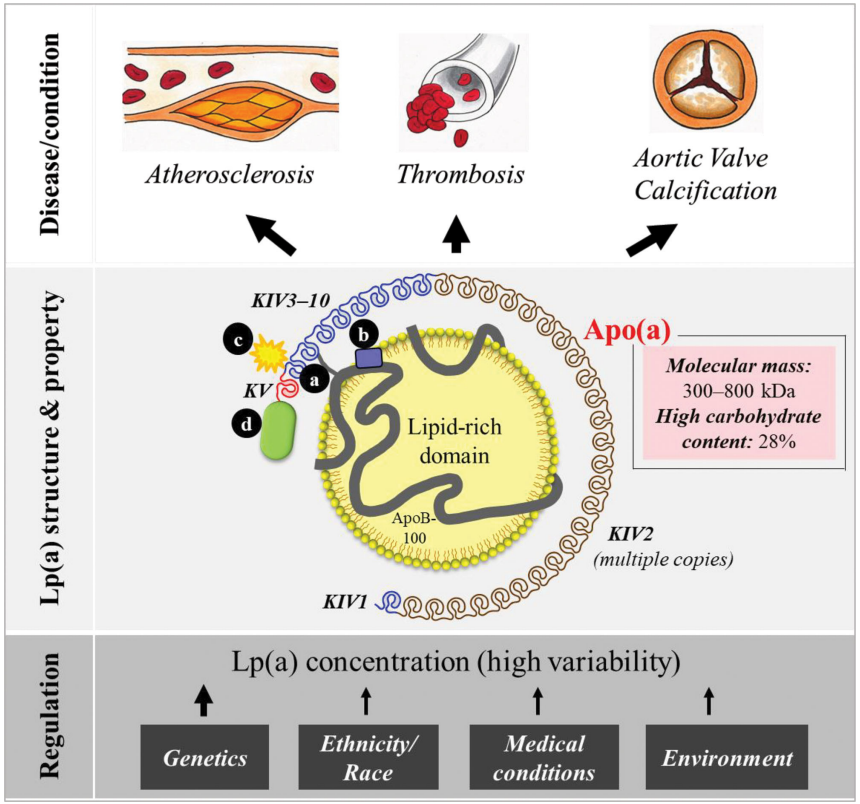
- For secondary prevention (e.g., after MI or coronary intervention), if single antiplatelet Rx long term may preference clopidogrel > aspirin

What about other ASCVD Risk Enhancers?

Lipoprotein (a)

- Lipoprotein (a), or Lp(a)
- Increases risk for cardiovascular diseases (remember *athero* + *thrombosis*).
- Strong genetic basis and conflicting data in HIV (lower along with other lipids in viremia, increases with ART)
- In general: When elevated, marker of increased risk, so treat with known CVD risk-reducing meds (statins, less clear role of aspirin but often used)
- Statins do not reduce Lp(a); PCSK9i's do. Novel Lp(a)-targeted RNA silencing under investigation

Enkhmaa B et al. J Lipid Res 2018;59(10):1967-76



Reyes-Soffer G, et al. Arterioscler Thromb Vasc Bio 2021;42:e48-60.

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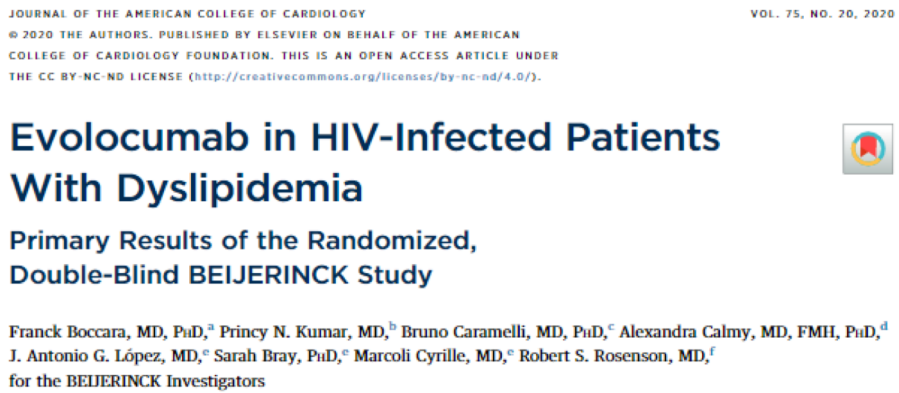
Newer Cholesterol-reducing therapies: relevance in HIV?

Limited data

- PCSK9 inhibition – direct, substantial reduction in LDL cholesterol and ASCVD events in general population. Via monoclonal antibody or (investigational) RNA silencing. Limited data in HIV show LDL-c reduction of 56.9%, as well as reduction in Lp(a), ApoB

- Bempedoic acid: statin alternative (less potent), TBD in HIV and need outcome data in gen. pop



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Evolocumab in HIV-Infected Patients With Dyslipidemia

Primary Results of the Randomized, Double-Blind BEIJERINCK Study

Franck Boccara, MD, PhD,[a] Princy N. Kumar, MD,[b] Bruno Caramelli, MD, PhD,[c] Alexandra Calmy, MD, FMH, PhD,[d] J. Antonio G. López, MD,[e] Sarah Bray, PhD,[e] Marcoli Cyrille, MD,[e] Robert S. Rosenson, MD,[f] for the BEIJERINCK Investigators

What about Inflammation Reduction?

We know even less about this

- Gen Pop: IL-1β antagonism modest effect size but fatal infection risk; colchicine modest effect size
- General inflammation reduction in HIV: TBD whether benefit>risk with respect to CVDs but also immune function

Heart Failure and Sudden Cardiac Death

Limited data. Prevent/treat contributors in the meantime

- Studies ongoing to understand the *why's* (mechanisms, manifestations)

- More investigation is needed to determine which screening tests and therapies unique to HIV-related heart failure prevention & treatment will be most useful. These have implications for sudden cardiac death & its substrate

- In the meantime, diagnosis/treatment as in general population but with high index of suspicion. And with focus on treating underlying causes (e.g., CAD/MI prevention, hypertension, metabolic dysregulation)

So, What Can *I* Do About HIV and CVD?

Guidance for self-advocacy and patient-provider discussions

(a.k.a, doing the most with what we know to maximize benefit but avoid unanticipated harm)

Practical Guidance to CVD Risk Assessment

How can we inform our patient-provider discussions? Our advocacy work?

- What do we *know*?
- What do we *think*?
- What do we *have no idea about*?

Practical Guidance to CVD Risk Assessment

How can we inform our patient-provider discussions? Our advocacy work?

- What do we *know*?
  - Can be most assertive about this
- What do we *think*?
- What do we *have no idea about*?

Practical Guidance to CVD Risk Assessment

How can we inform our patient-provider discussions? Our advocacy work?

- What do we *know*?
  - Can be most assertive about this

1. **People with HIV have elevated cardiovascular disease risk.**

   This is true in particular for atherosclerotic/thrombotic cardiovascular diseases (including coronary artery disease and myocardial infarction) and heart failure.

   Treating HIV effectively with ART helps reduce this risk but does not get rid of it.

Practical Guidance to CVD Risk Assessment

How can we inform our patient-provider discussions? Our advocacy work?

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1. People with HIV have elevated cardiovascular disease risk.
2. **Given this elevated CVD risk, anyone with HIV can and should consider the following in their discussion with providers (as should HIV providers)**
   - What are my cardiovascular risk factors / risk enhancing factors? How might this impact my risk? Can consider risk calculator (ASCVD, FRS) to quantify, but imperfect
   - Examples (general): Smoking (cessation is key CVD risk-reducing behavioral change), drugs (meth!), hypertension, hyperlipidemia, diabetes. Treat w lifestyle +/- meds
   - HIV-specific: History of viremia? CD4 progression (<500 or <200 nadir or current)?
   - AGE. CVD risk up with age. Absolute risk up → lower threshold for CVD-preventive Rx

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2. Given this elevated CVD risk, anyone with HIV can and should consider the following in their discussion with providers (as should HIV providers)
3. **Limited data exist on ARV-specific CVD risks**
   - How might my antiretroviral regimen be affecting my risk?
   - Strongest data on abacavir with respect to cardiovascular risk increase. Otherwise re: most modern regimens the data are limited. Most important is being on something that effectively suppresses HIV viremia

Practical Guidance to CVD Risk Assessment

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- What do we *think*?

  1. Cardiovascular risk stratification may help inform potential benefit of CVD risk-reducing therapy

  - But what type of risk stratification to consider? Risk calculator to start (probably)
  - Beyond risk factor counting, would risk-stratification via imaging (CAC, carotid plaque ultrasound) help meaningfully stratify?
  - What does REPRIEVE mean for me? (probably tilts balance slightly more in favor of net benefit>risk of statins, but limited absolute benefit at low risk / younger individuals)

Practical Guidance to CVD Risk Assessment

How can we inform our patient-provider discussions? Our advocacy work?

- What do we *know*?
- What do we *think*?
- **What do we *have no idea about*?**
  - What is the role for cardiovascular screening for *existing* disease (e.g., ECG, echocardiogram. Different than CAC for subclinical disease for risk stratification)? Symptom-/risk-triggered
  - ECG/echo broad disease screening not routine in general population, and pretest probability informs this (when too low, risk of false positives is high → subsequent testing, over-Rx, harm)
    - Appropriate, potentially helpful: symptom-triggered (e.g., palpitations + lightheadedness potentially due to arrhythmia → ECG/monitor; exertional chest pressure → ischemic eval)
    - Less appropriate or likely to be helpful: no symptoms, good exertional tolerance → "routine" ECG or monitor (finding something doesn't mean it matters or is actionable)

Conclusions

- People living with HIV have elevated risks for atherosclerotic disease, thrombosis, and cardiac dysfunction / heart failure

- Chronic inflammation and immune activation persist despite effective ART and appear to play a role in CVD pathogenesis

- New data suggest statins may be particularly effective in CVD risk reduction in HIV (await full REPRIEVE results) → Lower threshold to consider ASCVD-preventive statin Rx in HIV may be reasonable.

- We still don't know how to best prevent/treat HF in HIV. Need mechanistic and clinical data to inform this. Reducing burden of common risk factors with lifestyle, then meds as necessary is a good start to preventing HIV-associated CVDs (and CVDs in general)

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Thank You and Discussion

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