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Cardiovascular Diseases in HIV in the Current Era: Bridging the Gap from Research to the Clinic

NATAP Webinar March 2022

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Disclosures

- No relationships with industry or financial conflicts of interest

- Funding Sources
  - American Heart Association
    - Fellow-to-Faculty Award: AHA FTF31200010 (PI: Feinstein)
  - National Institutes of Health
    - R01HL154862
    - R01HL156792
    - Center for AIDS Research Administrative Supplement: P30AI117943 (PI: Feinstein; Parent Grant PI: D'Aquila)

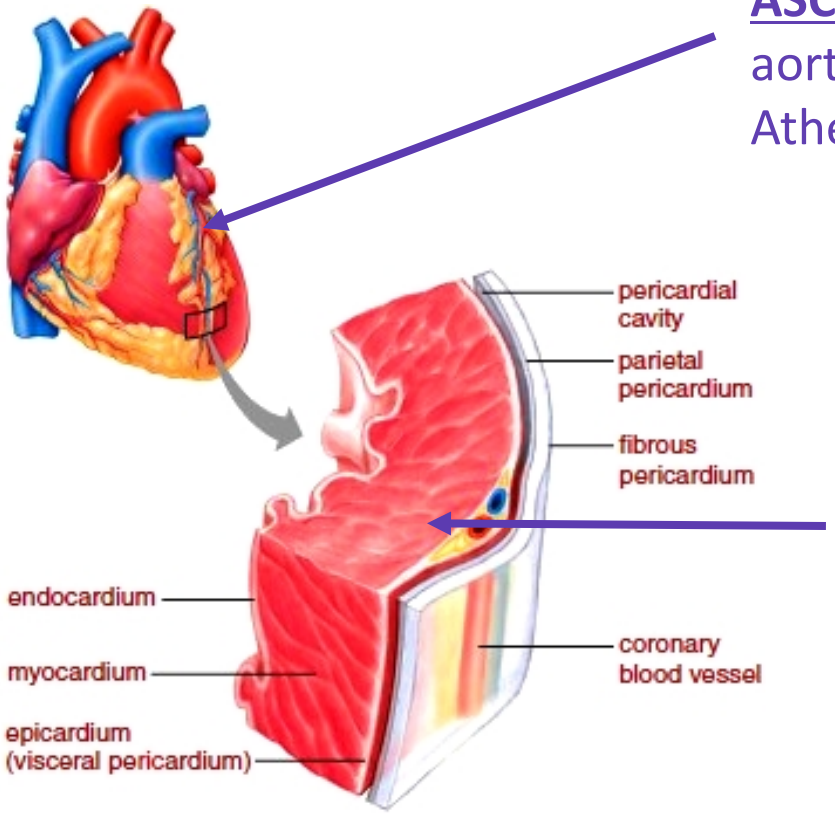
Outline

1. What do we see? Clinical Scope of Cardiovascular Diseases (CVDs) in People with HIV in the Modern ART Era
   - Atherosclerosis and Thrombosis (ASCVD: Atherosclerotic CVD)
   - Heart Failure
   - Heart Rhythm Issues

2. Why do we see it?
   - Immunologic changes → inflammation
   - Behavioral factors
   - ART: Helpful but complicated

3. How do we address it?
   - Prevention and Risk Assessment
   - Treatment

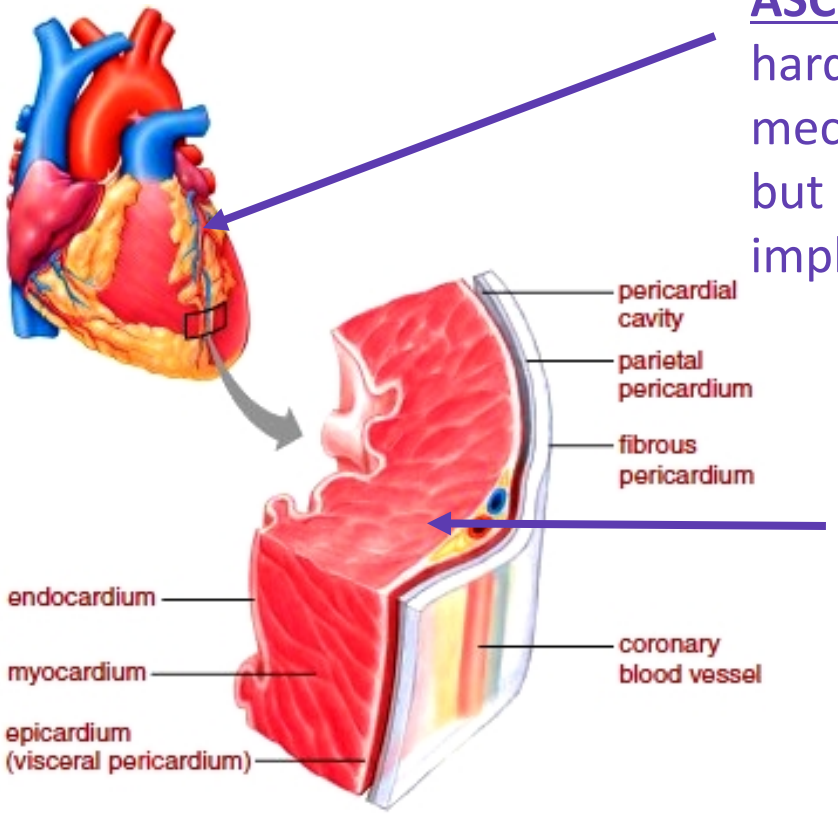
Review: Myocardial Disease vs. ASCVD



ASCVD: Vascular. Coronary arteries, aorta, peripheral vessels. Key terms: Atherosclerosis, thrombosis, MI.

Myocardium: The Heart Muscle. Factors influencing the size, function, and composition of the heart muscle may be vascular (e.g., MI leading to cell death), toxic, infectious (e.g., myocarditis), inflammatory, or other systemic (e.g. fibrosis). Key terms: fibrosis, myocarditis, hypertrophy, systolic dysfunction, diastolic dysfunction, heart failure.

Review: Myocardial Disease vs. ASCVD



ASCVD in HIV: Several studies, some hard outcomes studies underway, mechanistic research still needed but emphasis on trials, implementation science too

Myocardial Dysfunction and Heart failure in HIV: Limited data, particularly in the modern ART era, regarding role of HIV in myocardial dysfunction. Some epidemiological studies, few mechanistic ones. No difference in current clinical guidance for HIV vs. gen pop

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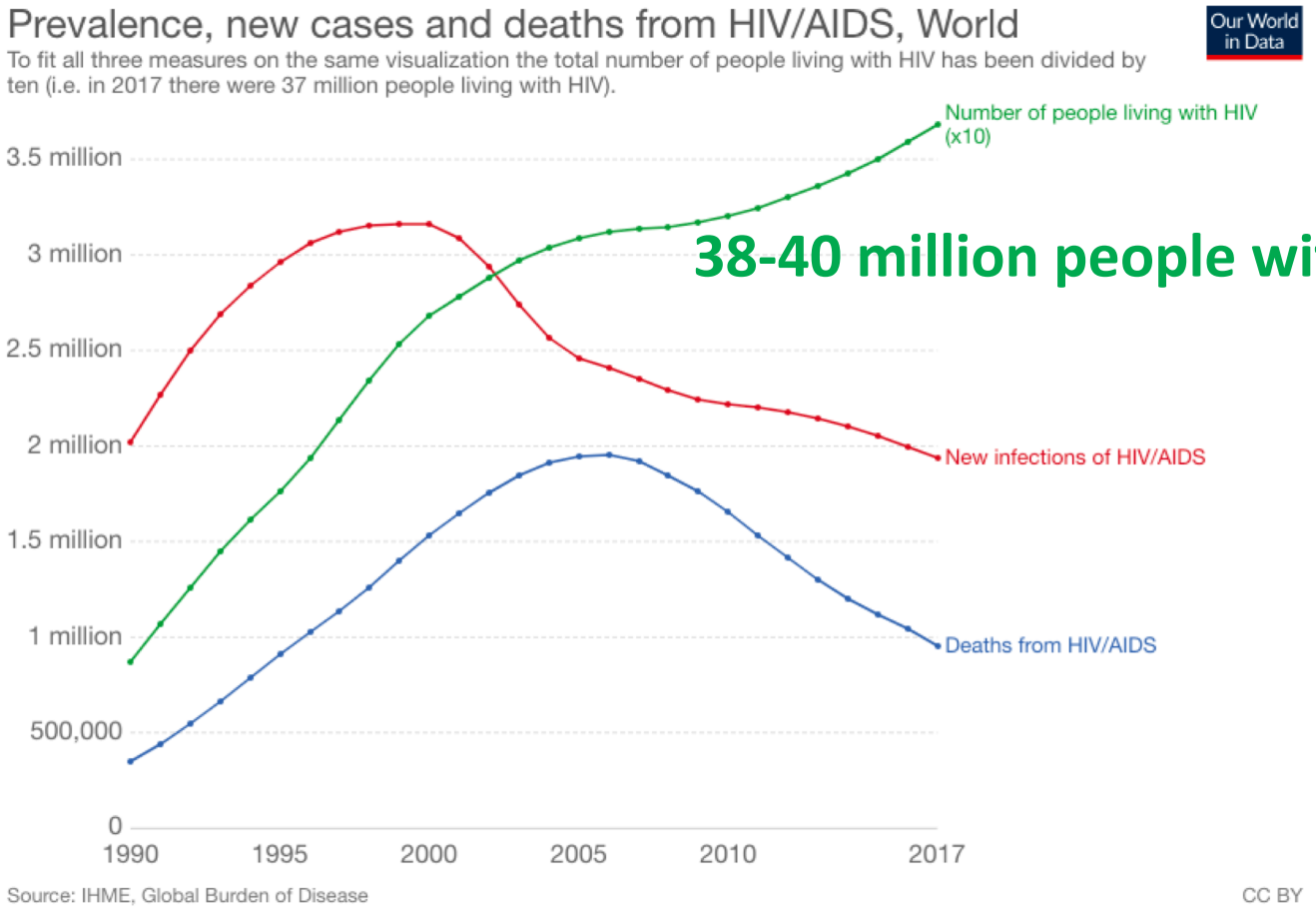
Epidemiology/Scope of HIV and CVDs

HIV as a Chronic Inflammatory Disease

Epidemiology: Changes over time



38-40 million people with HIV

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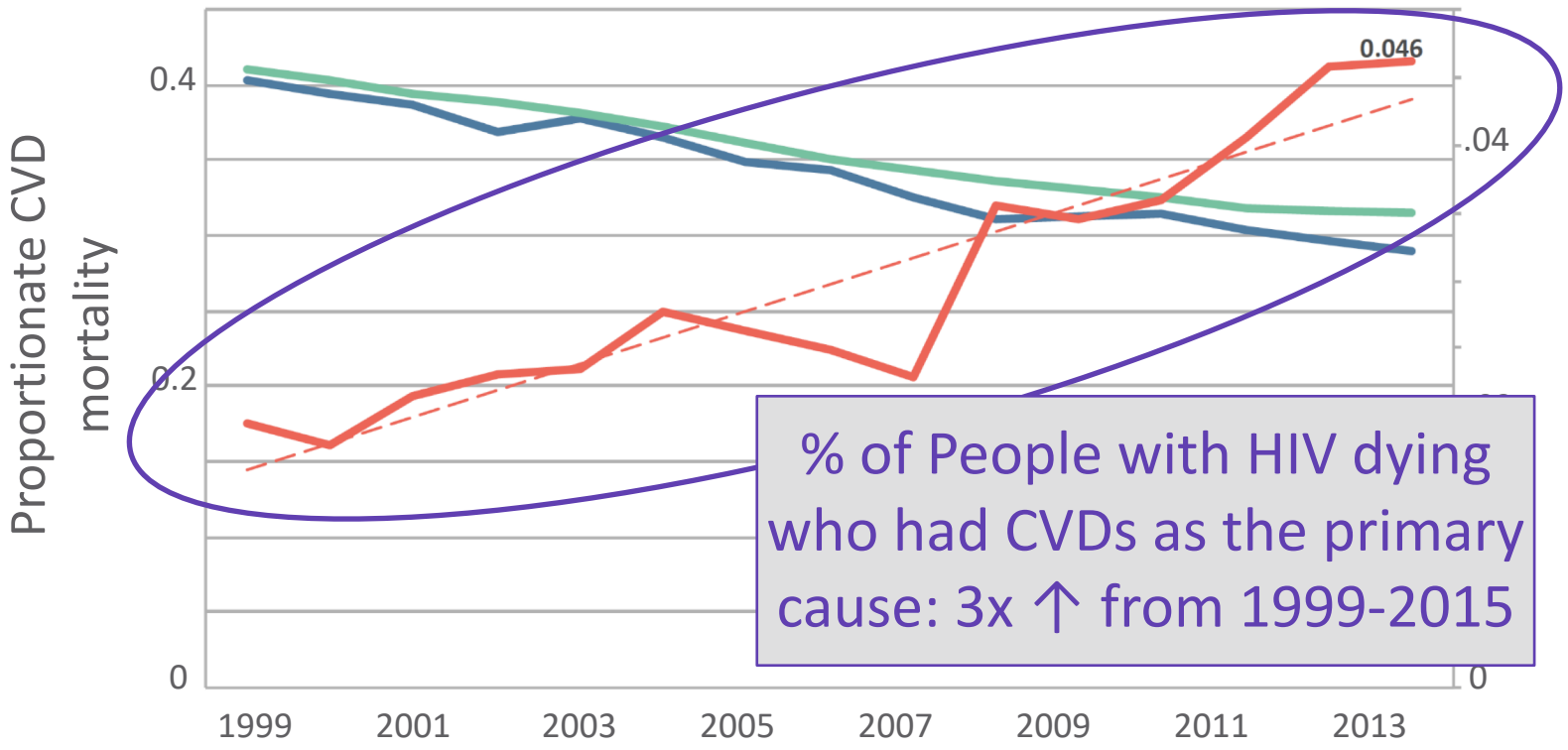
https://ourworldindata.org/hiv-aids from Oxford University

HIV and Cardiovascular Risk

Epidemiology: Changes over time…and implications for CVDs



% of People with HIV dying who had CVDs as the primary cause: 3x ↑ from 1999-2015

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Feinstein MJ, et al. *Am J Cardiol*. 2016;115(12):1760-6.

Heart Attack Risk 1.5 – 2x Greater in HIV

Myocardial Infarction (MI) = Heart Attack

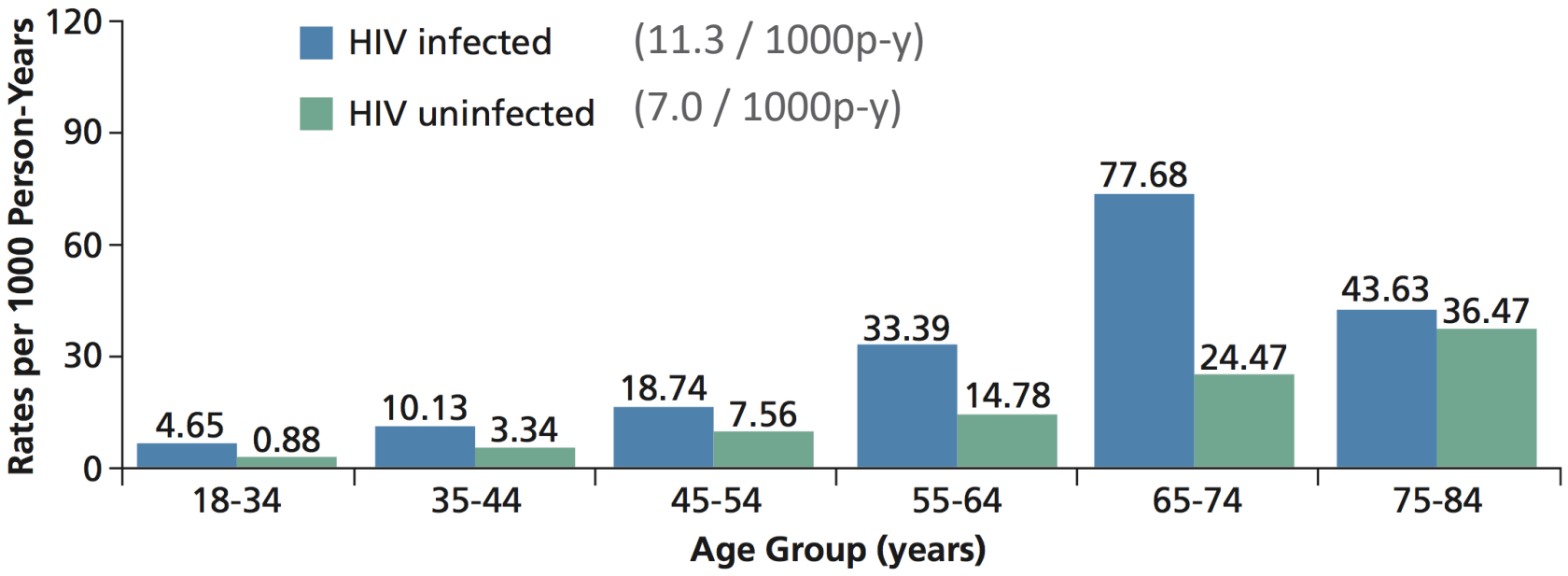

Figure **1.** Myocardial infarction rates in HIV-infected (n = 3851) versus HIV-uninfected (n = 1,044,589) patients in a Massachusetts administrative hospital database, for 1996-2004. Adapted from Triant et al, *J Clin Endocrinol Metab*, 2007.

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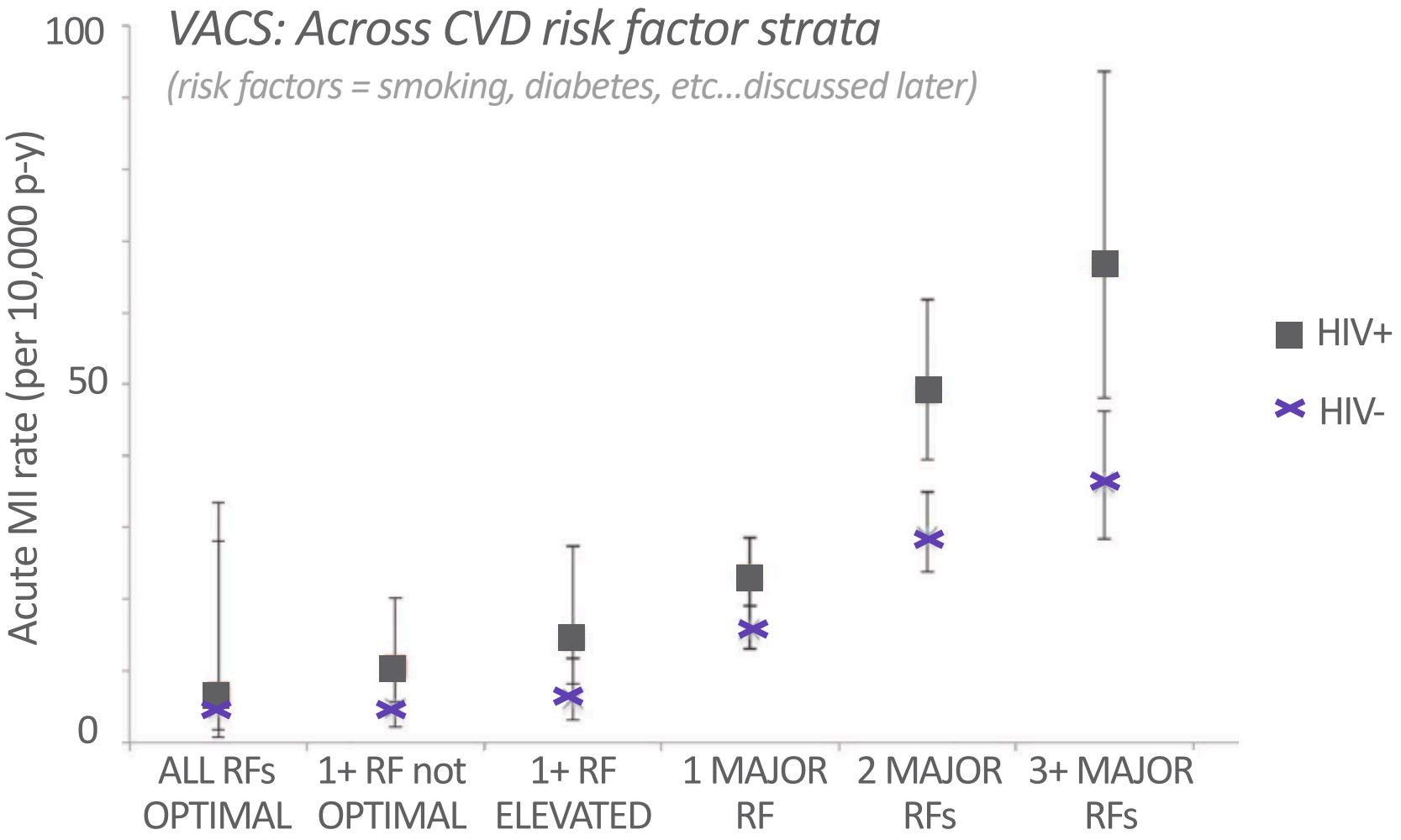
Currier, J. S. "Update on cardiovascular complications in HIV infection." Top HIV Med 2009;17(3): 98-103.

MI Risk 1.5 – 2x Greater in HIV



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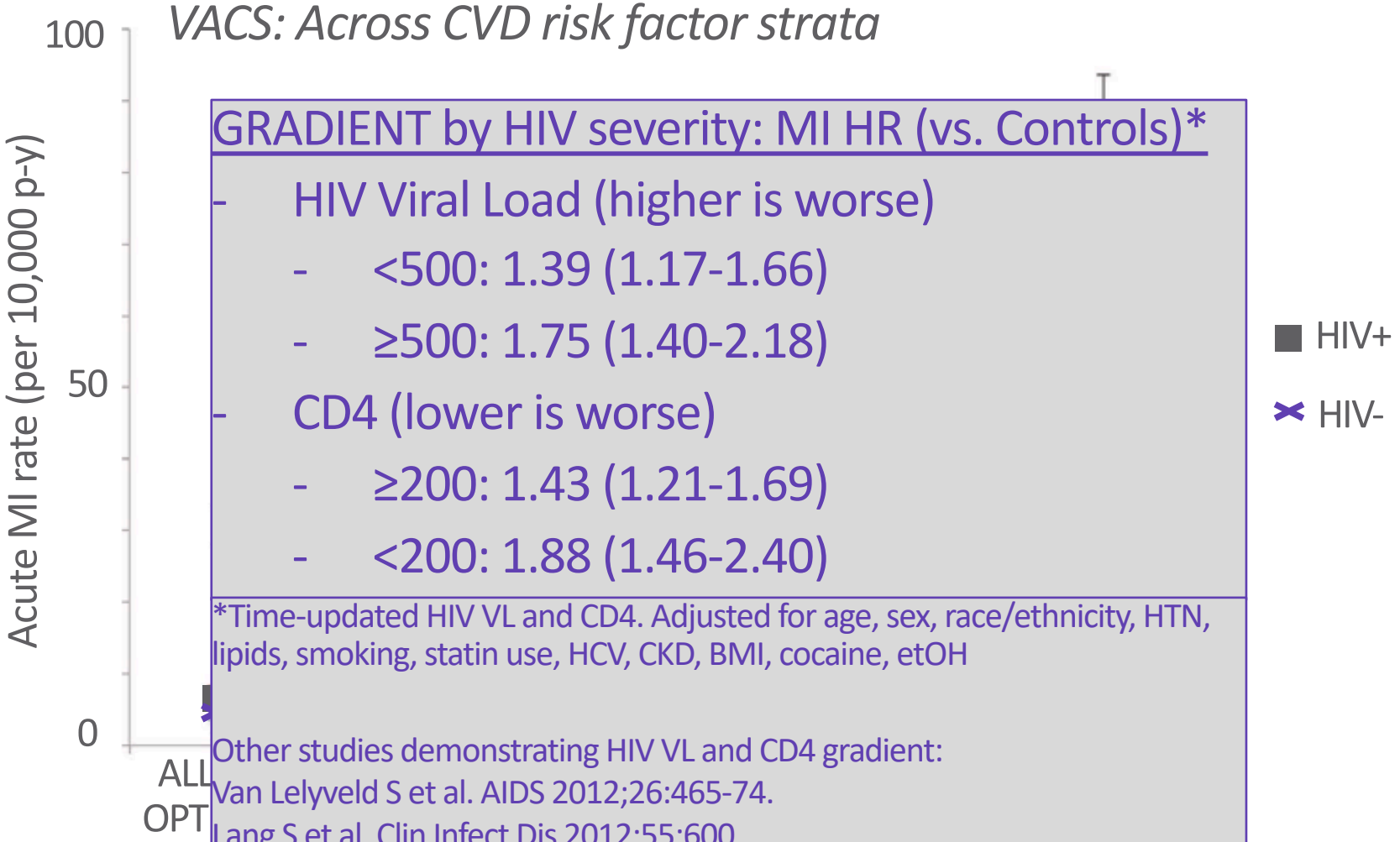
Freiberg MS, et al. *JAMA Intern Med* 2013;173:614-622.\
Figure from: Paisible AL, et al. *J Acquir Immune Defic Syndr* 2015;68:209-215

MI Risk 1.5 – 2x Greater in HIV

VACS: Across CVD risk factor strata



GRADIENT by HIV severity: MI HR (vs. Controls)*

- HIV Viral Load (higher is worse)
  - <500: 1.39 (1.17-1.66)
  - ≥500: 1.75 (1.40-2.18)
- CD4 (lower is worse)
  - ≥200: 1.43 (1.21-1.69)
  - <200: 1.88 (1.46-2.40)

*Time-updated HIV VL and CD4. Adjusted for age, sex, race/ethnicity, HTN, lipids, smoking, statin use, HCV, CKD, BMI, cocaine, etOH

Other studies demonstrating HIV VL and CD4 gradient:
Van Lelyveld S et al. AIDS 2012;26:465-74.
Lang S et al. Clin Infect Dis 2012;55:600.
Bucher HC et al. JAIDS 2012;60:135.
Helleberg M et al. Clin Infect Dis 2013;57:314.

Figure from: Paisible AL, et al. *J Acquir Immune Defic Syndr* 2015;68:209-215

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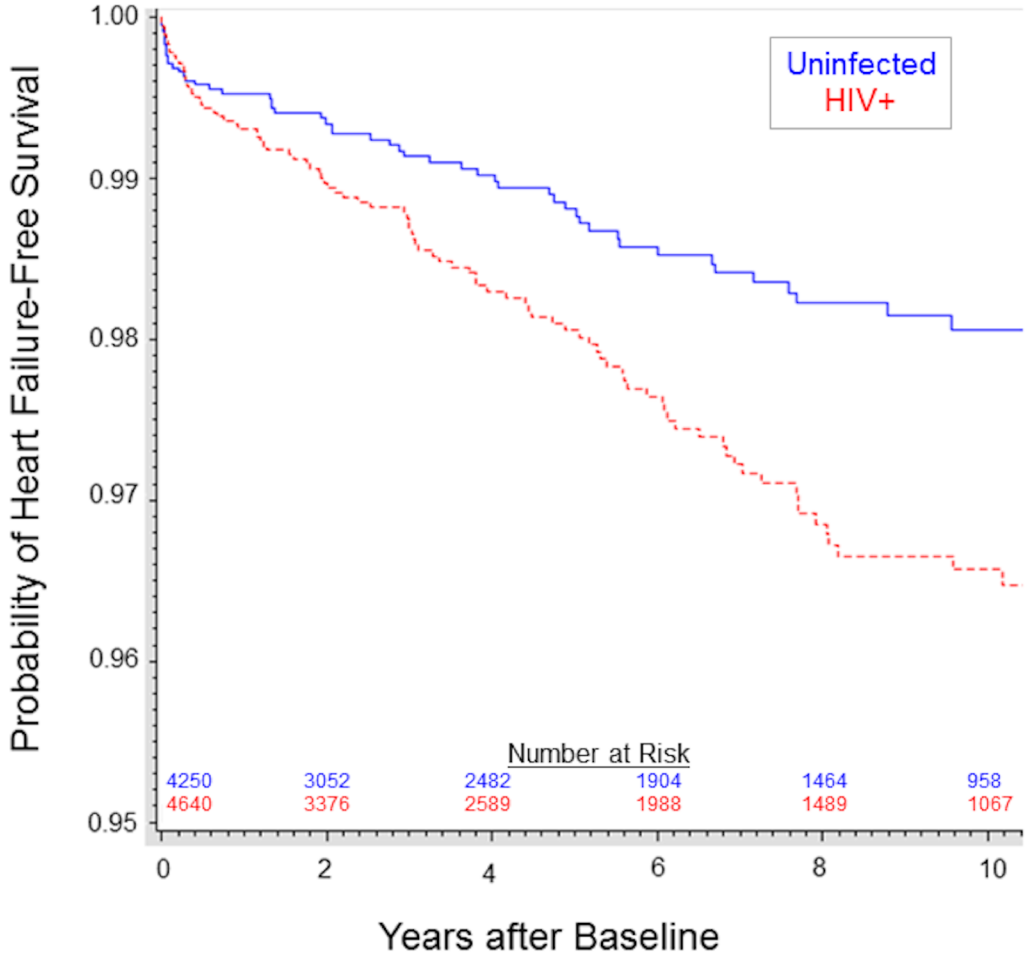
Heart Failure in HIV

Northwestern Medicine Cohort (20% female, physician-adjudicted HF)



Overall:

Hazard Ratio of HF **(HIV+ vs. Uninfected)**:

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

Heart Failure in HIV

Veterans Aging Cohort Study (large, 3% female, admin code-based HF)

Table 4. Human Immunodeficiency Virus (HIV) Infection and the Risk of Total Heart Failure (HF) and HF Type by HIV-1 RNA Viral Load and CD4 Cell Count

	HR (95% CI)[a]				
Variable	Total HF	HFpEF≥50%	Borderline HFpEF 40%-49%	HFrEF	EF Missing
HIV-1 RNA viral load model[a]					
HIV⁻	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
HIV⁺ and RNA<500	1.30 (1.16-1.46)	1.20 (0.98-1.46)	1.32 (0.98-1.79)	1.41 (1.17-1.70)	1.27 (0.91-1.78)
HIV⁺ and RNA≥500	1.52 (1.36-1.70)	1.22 (0.99-1.50)	1.42 (1.06-1.91)	1.82 (1.54-2.16)	1.60 (1.17-2.19)
CD4 cell count model[a]					
HIV⁻	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
HIV⁺ and CD4 ≥ 500	1.25 (1.08-1.43)	1.03 (0.82-1.31)	1.32 (0.93-1.86)	1.53 (1.24-1.88)	0.98 (0.64-1.49)
HIV⁺ and CD4 200-499	1.41 (1.25-1.59)	1.29 (1.05-1.59)	1.28 (0.92-1.80)	1.51 (1.24-1.83)	1.61 (1.18-2.20)
HIV⁺ and CD4 < 200	1.72 (1.49-1.99)	1.38 (1.05-1.81)	1.66 (1.10-2.49)	2.03 (1.61-2.55)	1.88 (1.28-2.77)
P values					
RNA<500 vs ≥500	.04	.88	.70	.02	.29
CD4 200-499 vs ≥500	.15	.13	.91	.92	.045
CD4 < 200 vs ≥500	.001	.08	.38	.048	.01
CD4 200-499 vs <200	.02	.67	.31	.03	.47

Abbreviations: CD4, CD4 cell count (in cells per cubic millimeter); EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIV⁺, HIV positive; HIV⁻, HIV negative; HR, hazard ratio; RNA, HIV-1 RNA viral load (in copies per milliliter).

[a] Models are adjusted for age, race/ethnicity, hypertension, lipid levels, low-density lipoprotein and high-density lipoprotein cholesterol levels, triglyceride levels, smoking status, hydroxymethylglutaryl coenzyme A reductase inhibitor use, hepatitis C virus infection, renal disease, body mass index, substance use, atrial fibrillation, and major depression.

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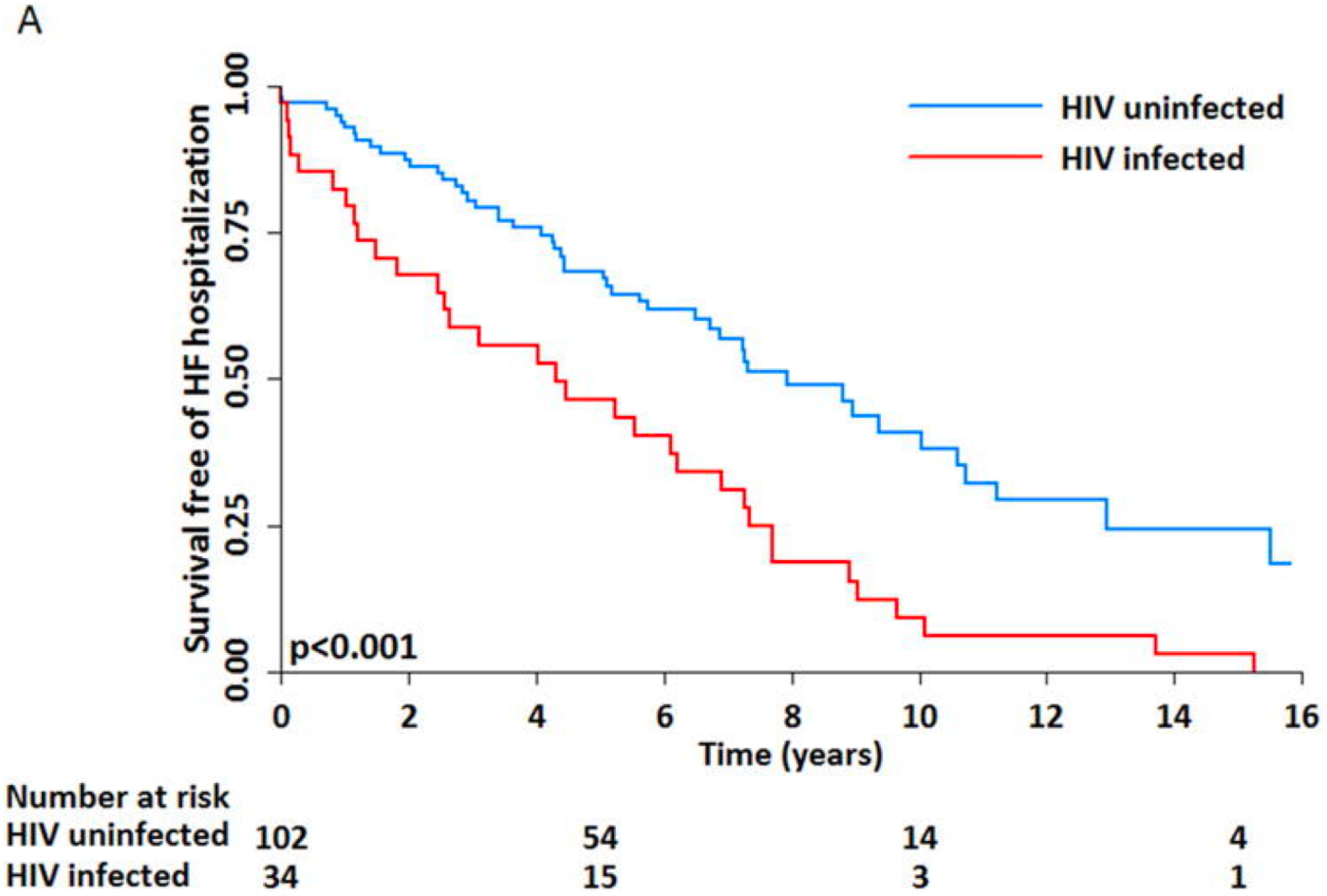
Freiberg MS, et al. *JAMA Cardiology*. 2017;2:536-546.

Heart Failure in HIV

Outcomes following HF diagnosis: Partners system



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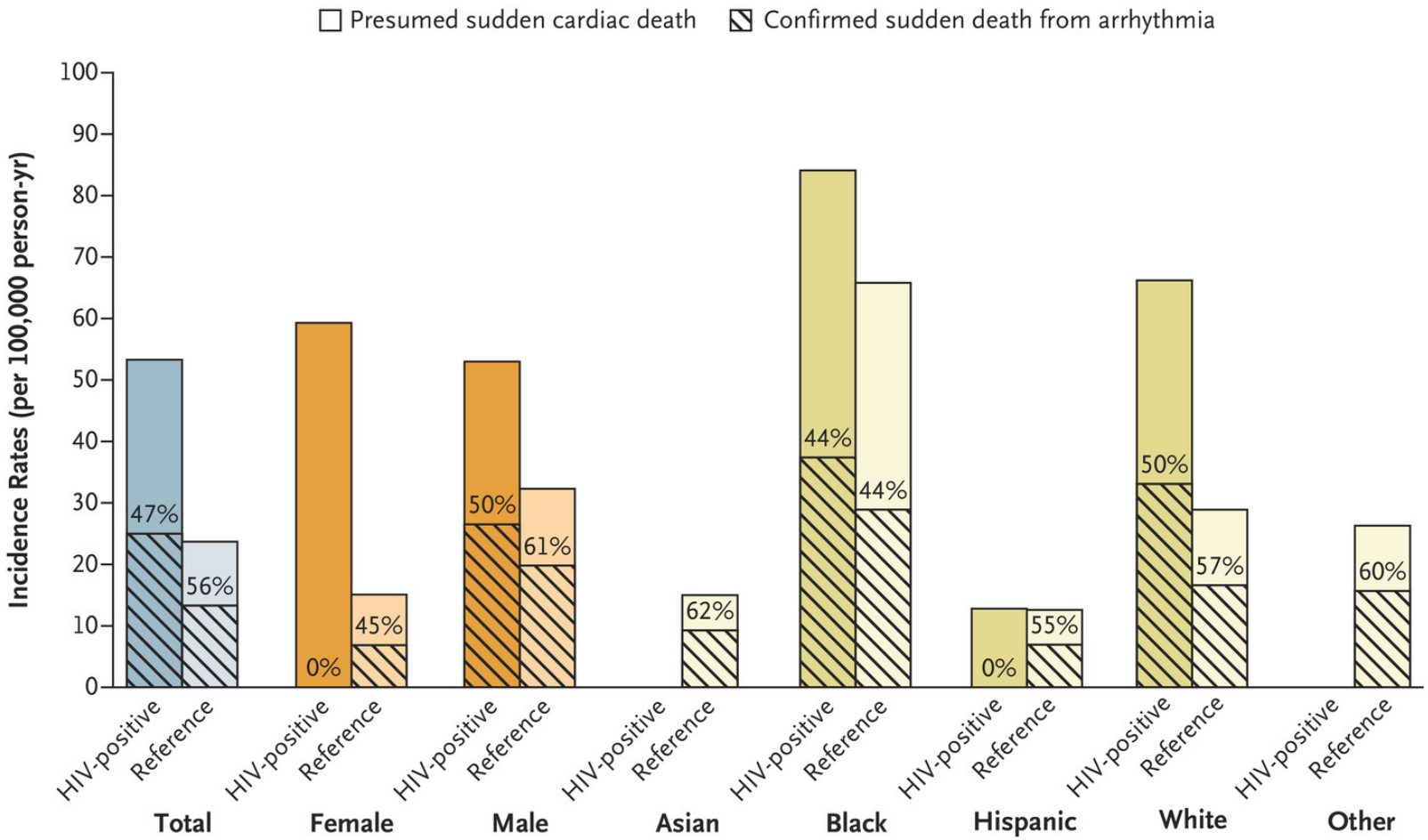
Janjua SA, Triant VA, … Neilan T. *J Am Coll Cardiol*. 2017;69(1):107-8.

Arrhythmias / Sudden Cardiac Death

San Francisco Medical Examiner



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

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HIV-related athero-thrombosis

Overview of pathophysiology and inflammation

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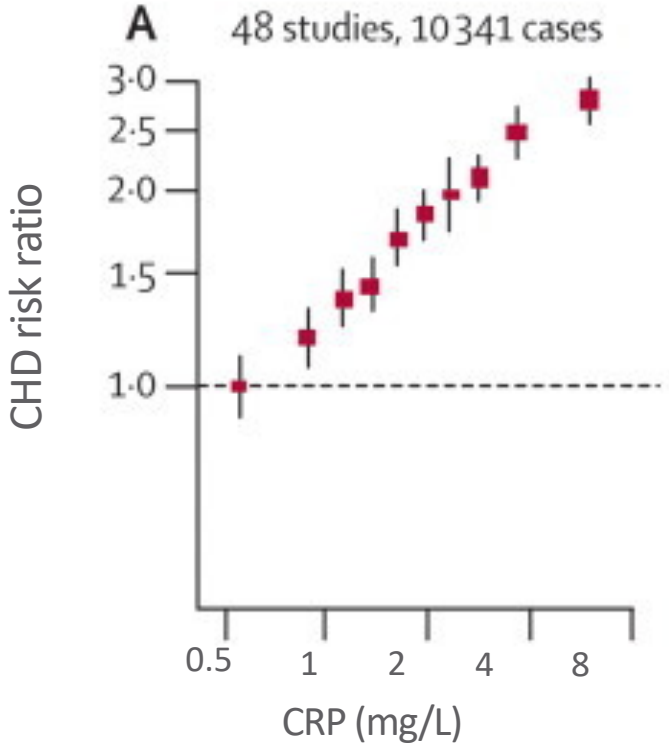
But first, a quick sidebar into inflammation and CVD

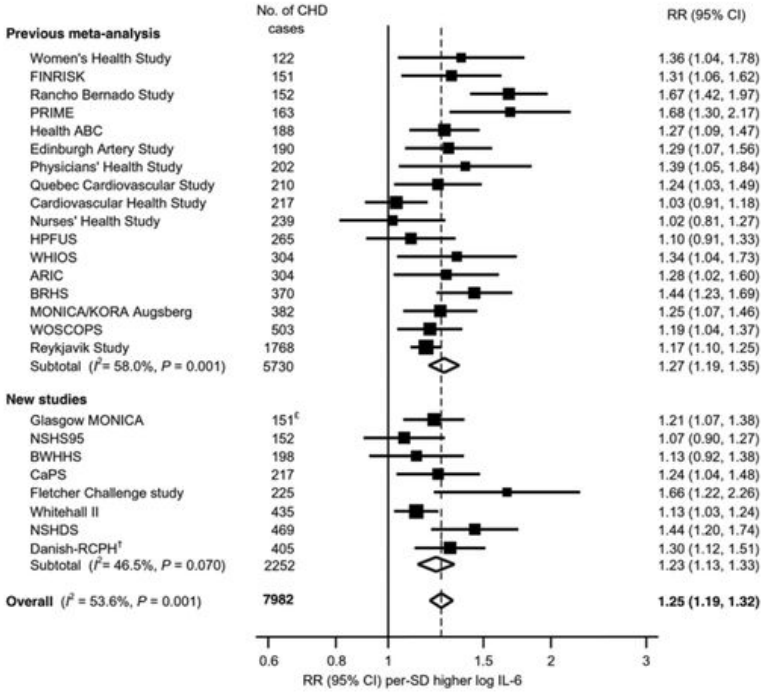
Clinical Evidence: Inflammation and CHD/MI

Residual ↑ CHD risk after adjustment for traditional risk factors

C-reactive protein (CRP)



Interleukin 6 (IL-6)



1.25 ↑ CHD risk per SD ↑ log-IL-6

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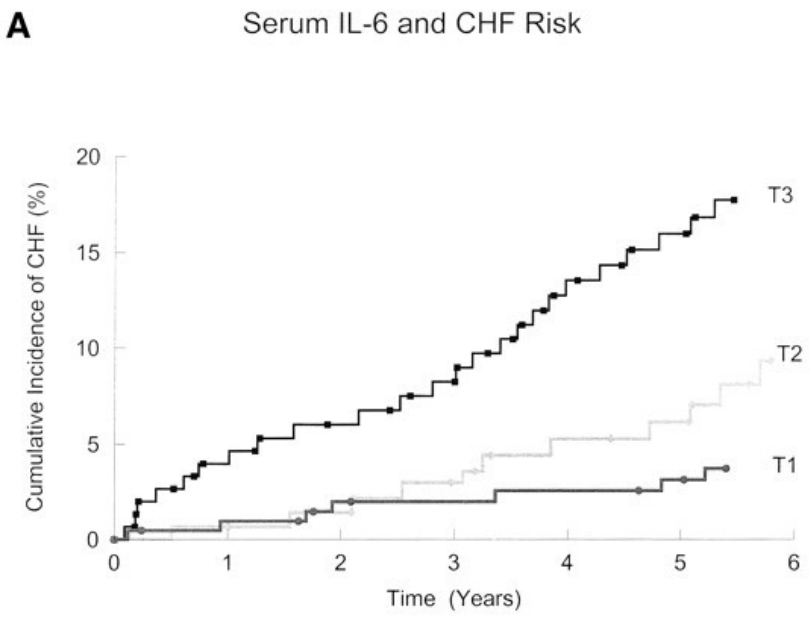
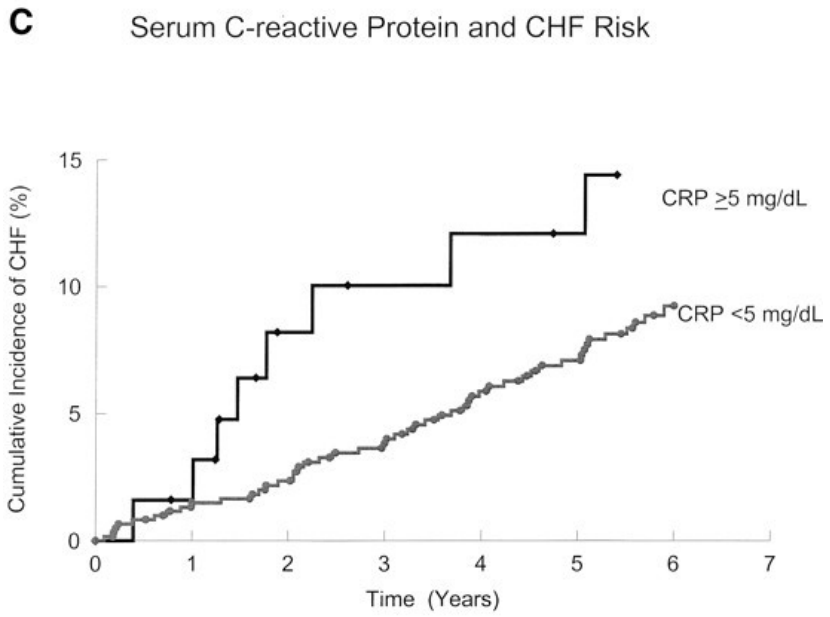
Kaptoge et al for the Emerging Risk Factors Collaboration. *Lancet* 2010;375(9709):132-40.
Kaptoge et al. *Eur Heart J* 2014;35(9):578-89.

Clinical Evidence: Inflammation and HF

Residual ↑ HF risk after adjustment for traditional risk factors (Framingham)





Multivariable-adjusted HR for incident HF (highest vs. lowest IL-6 tertile): 3.07 (1.26-7.47)

Multivariable-adjusted HR for incident HF (CRP ≥5 vs. <5): 2.81 (1.22-6.50)

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Vasan RS et al. *Circulation* 2003;107:1486-91.

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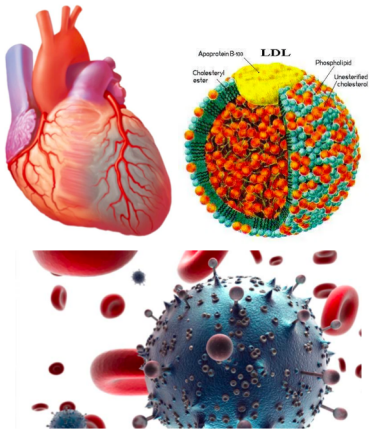
But what CAUSES inflammation?

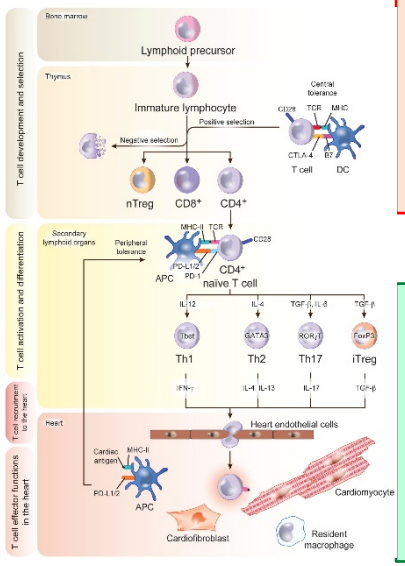
And why is it relevant here?

Inflammation Complexity: Causes, Timing, Sequelae

Inflammation = Immune response to something (antigen)

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

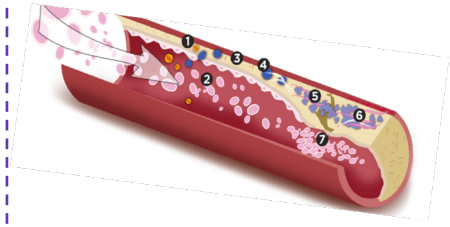


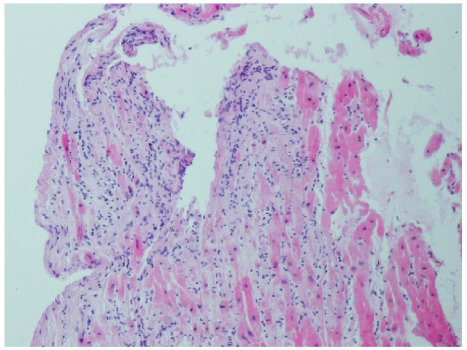


Inflammation
Key effectors: monocyte-derived (CCR2+) macrophages, CD4+ Th1/Th17

vs.

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





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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 Complexity: Causes, Timing, Sequelae

Inflammation = Immune response to something (antigen)

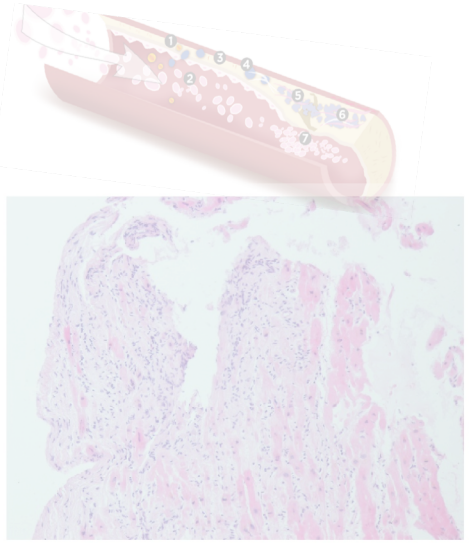
Antigens & Antigen-like triggers → Immune Response: *Immune cell activation/biasing; phenotype switching: Self-tolerance vs. autoimmunity* → Cardiac & Vascular Inflammation, Overt CVDs

Balance & Timing is Critical:
"appropriate" inflammation (pathogen/debris clearance) vs. sustained inflammation, loss of self-tolerance, amplified auto-reactivity

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

vs.

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



Blanton RM, Alcaide P, et al. Am J Physiol 2019;317(1):H324-H340.
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Simons KH et al. *Nature Rev Cardiol* 2019;16(6):325-343.
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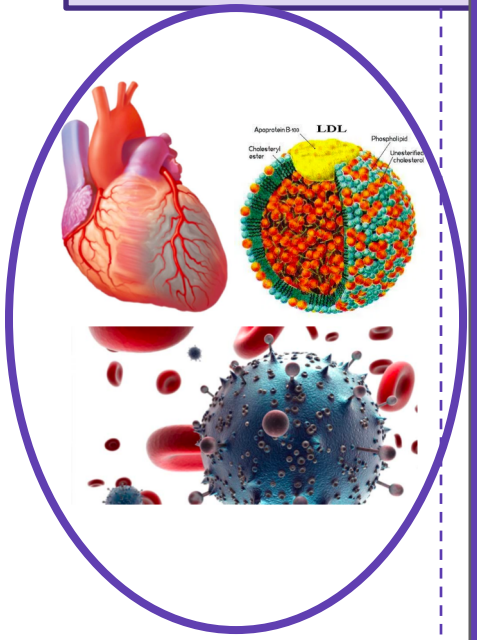
Inflammation Complexity: Causes, Timing, Sequelae

Inflammation = Immune response to something (antigen)

Antigens & Antigen-like triggers

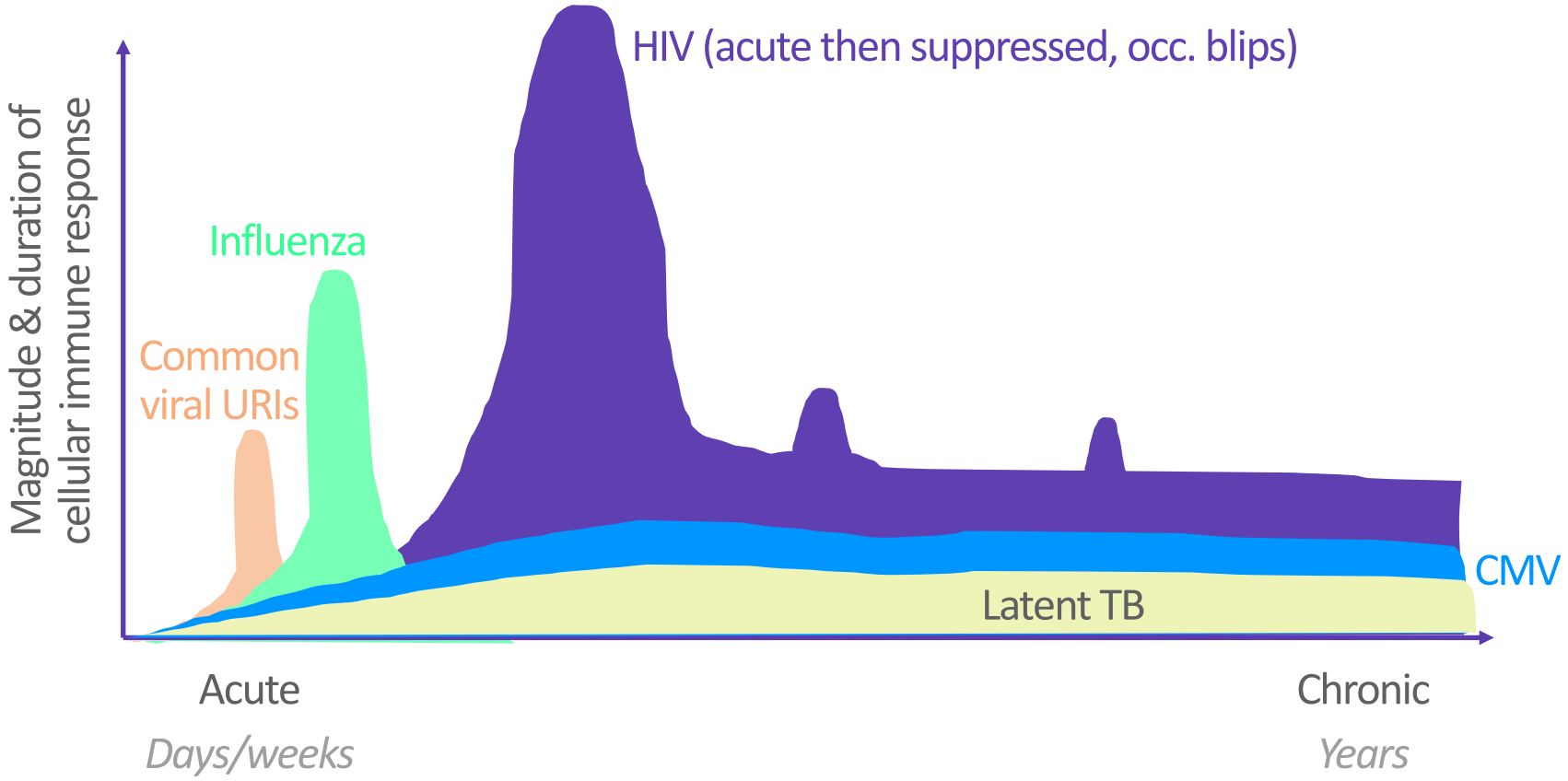


Antigens & Immuno-Cardiology: Logic & Hypotheses

1. Antigens & underlying factors (comorbidities, immune senescence, genetic) drive immune cell biasing & phenotype-switching
2. This dictates inflammatory balance (++ vs. resolving), with clear implications for CVD
3. Elucidating these antigens and variable immune responses to them will provide upstream, targetable insights into inflammation-driven CVD

Antigens of interest

Infections and immune biasing: insights from model populations



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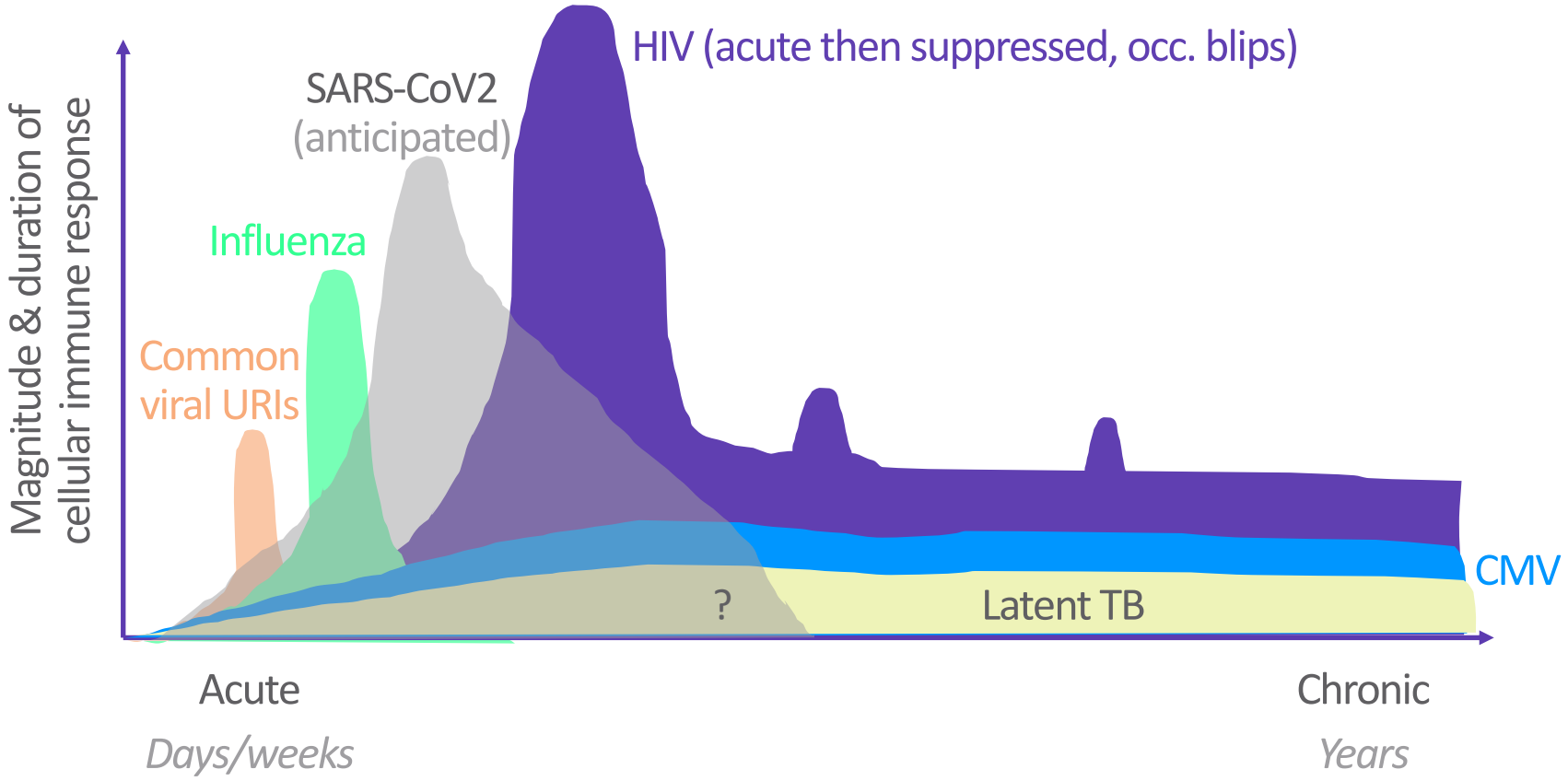
Antigens of interest

Infections and immune biasing: insights from model populations



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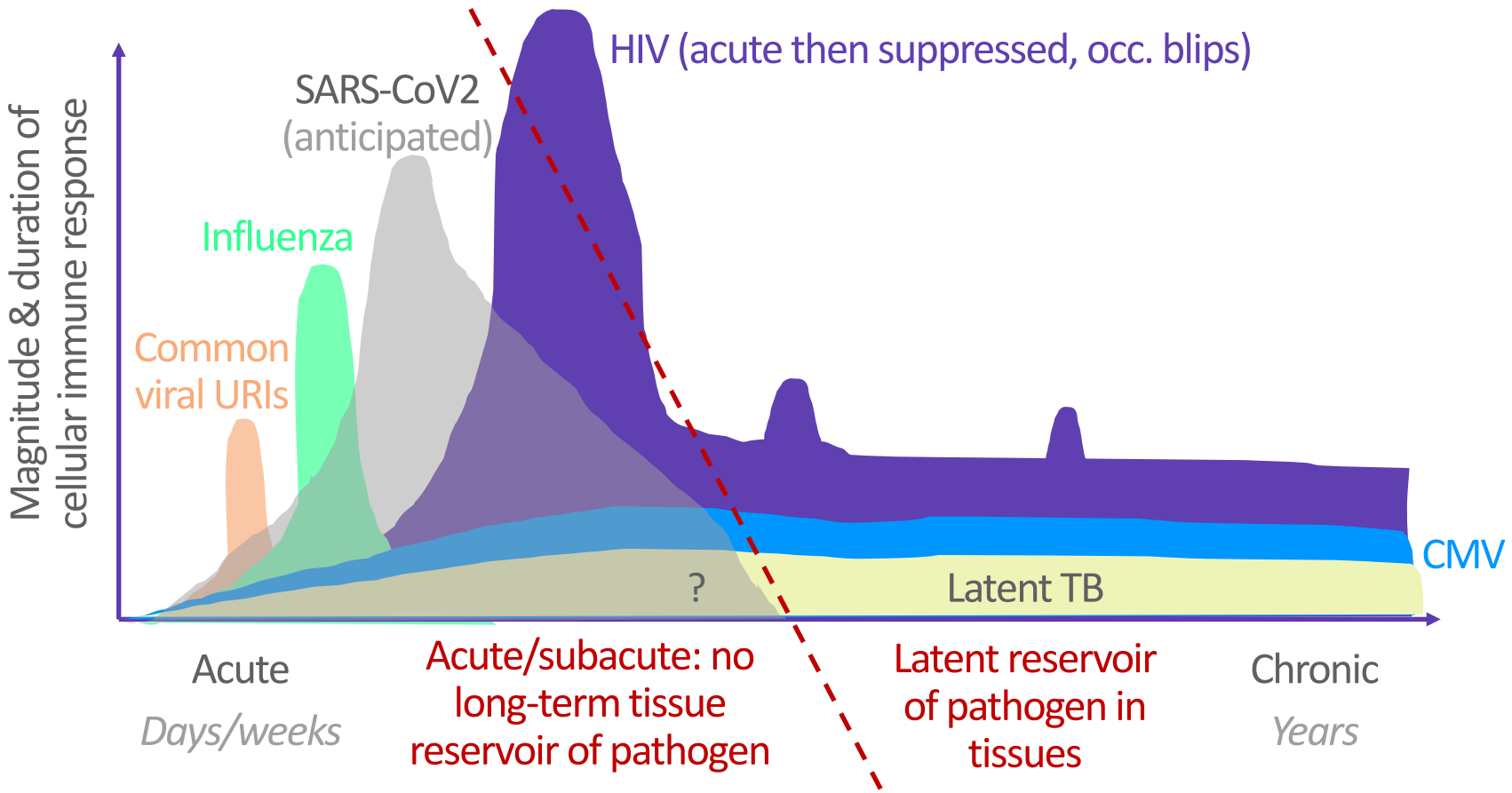
Antigens of interest

Infections and immune biasing: insights from model populations



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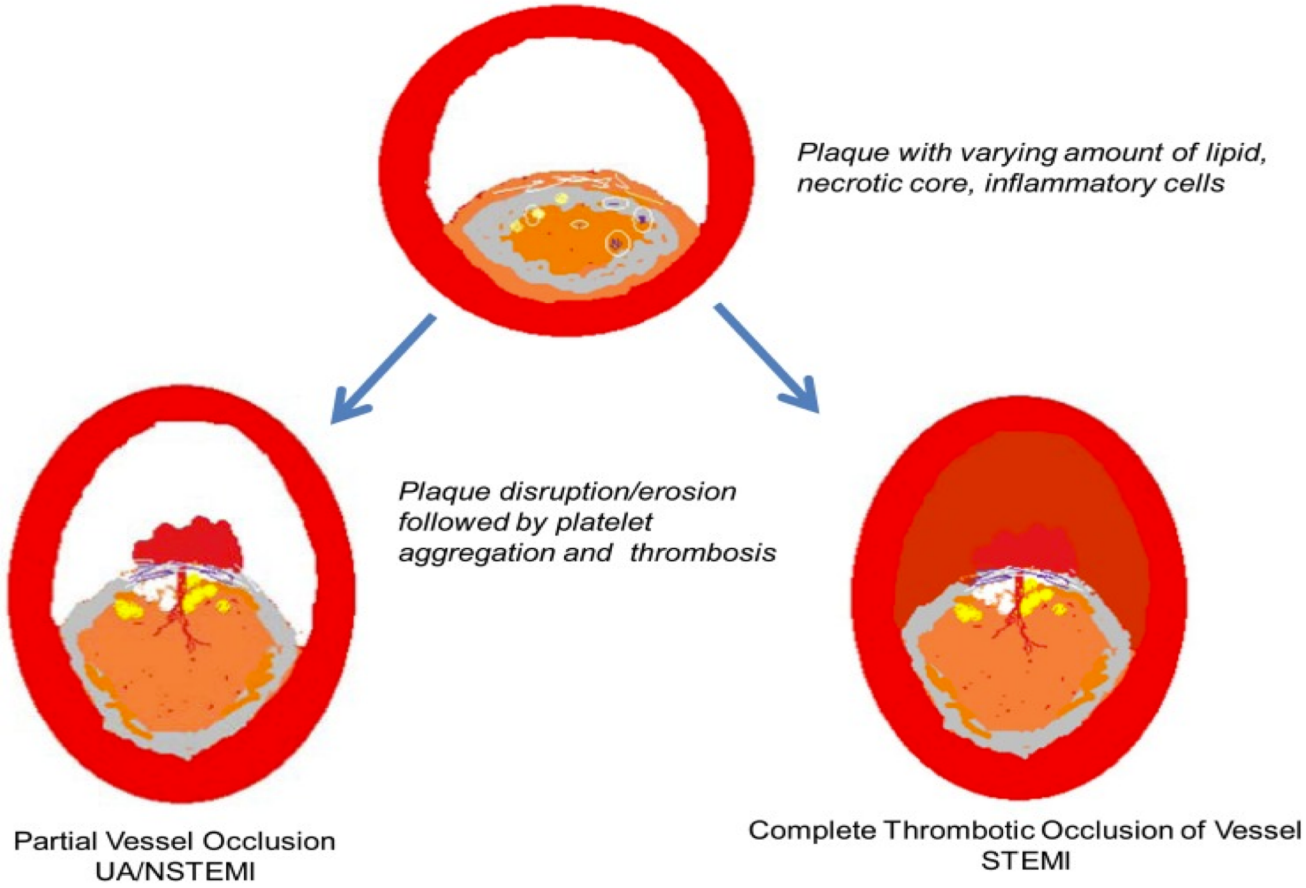
Now, back to HIV and Athero-Thrombosis

With new knowledge on inflammation

Myocardial Infarction: *(Athero-) + (-Thrombosis)*

A dynamic situation, driven by inflammation



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Srikanth S et al. Curr Cardiol Rev 2012;8(3):168-176.

Cardiovascular Risk Factors in General Population

Still Important in HIV! Increase risk for heart disease

- Traditional Risk factors
  - Smoking (!!)
  - Dyslipidemia: High “bad” cholesterol (LDL, total cholesterol, triglycerides), low “good cholesterol (HDL)
  - Diabetes
  - High blood pressure
  - Obesity
- Additional Risk-enhancing factors
  - Chronic kidney disease
  - Family history of early heart attack or stroke (M<55 yrs, F<65)
  - Chronic inflammatory conditions (including HIV; RA, lupus, Pso)
  - Imaging evidence of subclinical disease

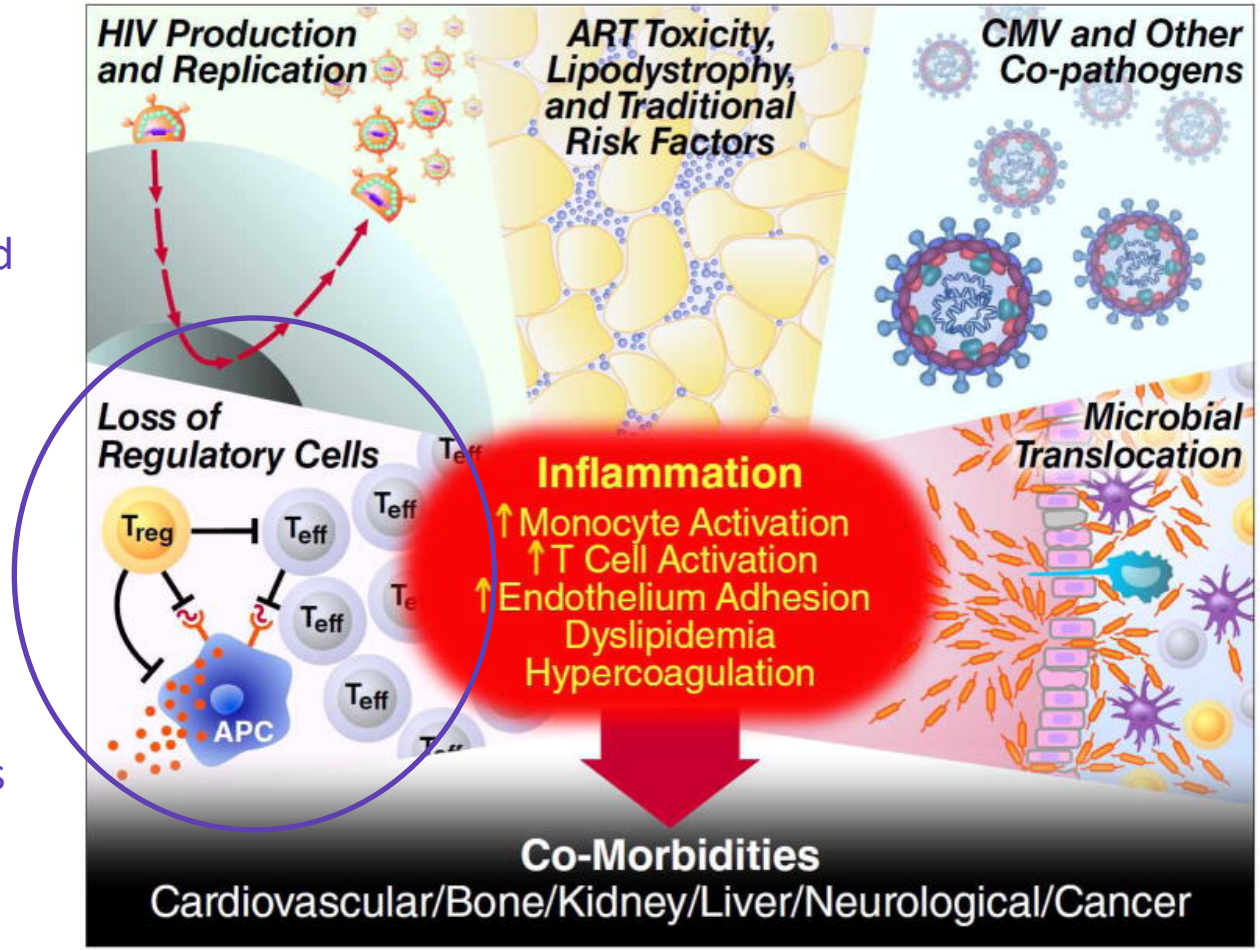
Arnett DK et al. Circulation 2019;140:e596-e646.

HIV as a Model

Immune Activation, Impaired Resolution of Inflammation → CVDs

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.

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HIV-Related Vascular Inflammation

Other HIV-Associated Factors:

- Traditional CV risk factors (e.g. smoking)
- Older HIV therapies (certain PIs, AZT, d4T)

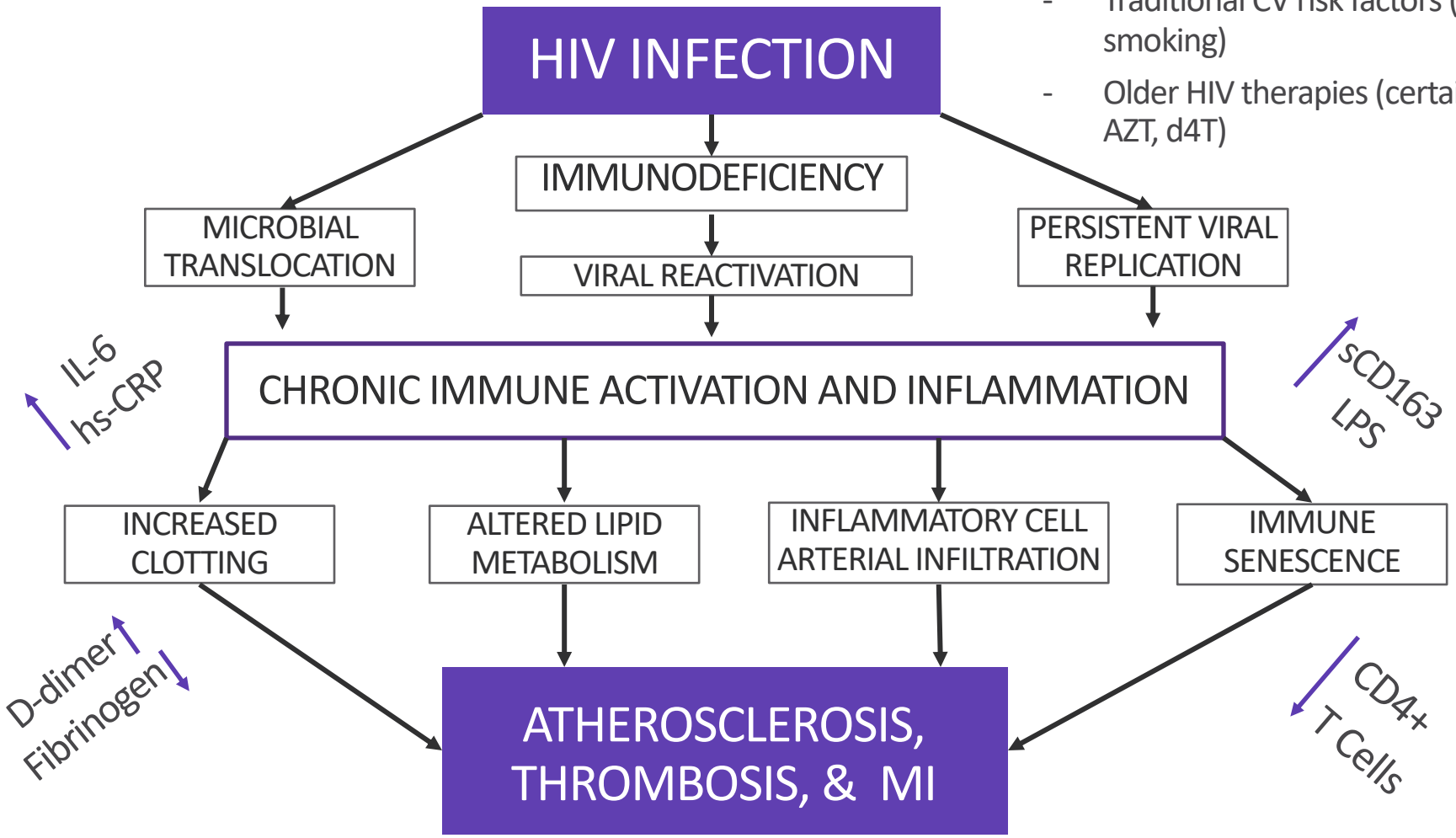

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Figure adapted from: Hsue PY, et al. *J infect dis*. 2012;205 Suppl 3:S375-382
Currier JS. *Top HIV Med* 2009;17(3): 98-103.
Post WS, et al. *Ann Intern Med*. 2014;160:458-467.

"Is it all just the meds?" → No

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 (2700 person-yrs f/u):

- **ART Interruption: 1.3/100 person/years**
- **ART Uninterrupted: 0.8/100 person/years**

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But does the specific ARV drug matter?

Maybe

ART and CVD

- Context: ART still >>>> no ART!
- But not all ART created equal re: CVD risk!
- Includes protease inhibitors: not a class effect
  - 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; 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

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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So what do we do about it?

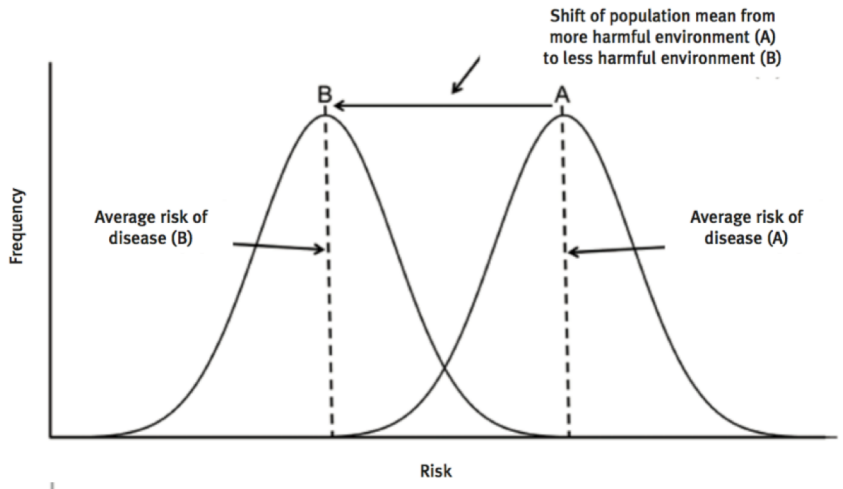
ASCVD risk stratification, prevention, and treatment in HIV

Assessing Athero-Thrombotic Risk in HIV

CVD Risk Scoring in General: Why, What, and How

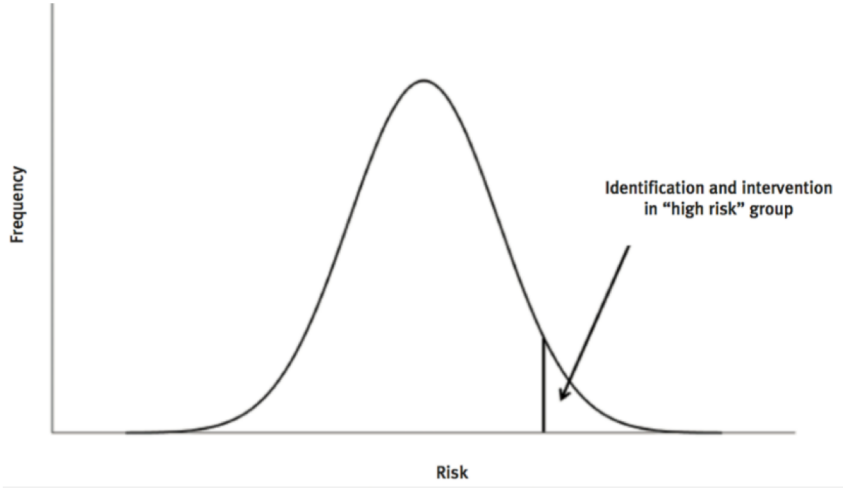
Population Strategy

Policy interventions: food supply, smoking laws



High-risk Strategy

Individual-level risk stratification to match intensity of therapy to risk



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Assessing Athero-Thrombotic Risk in HIV

CVD Risk Scoring in General: Why, What, and How

- What a risk score is: A prognostic model that converts a combination of predictor variables into a risk estimate of experiencing a specific endpoint within a specific period of time.

- Key requirements:
  - Cohort of individuals (prospective)
    - Defined predictor variables (risk factors)
    - Clinically relevant endpoints
    - Followed for a period of time
  - Mathematical model
  - Risk estimate (preferably absolute risk)

Assessing Athero-Thrombotic Risk in HIV

CVD Risk Scoring in General: Why, What, and How

- Primer on absolute risk vs. relative risk – why absolute risk matters in risk scoring

- Statin therapy reduces ASCVD risk (*relative* risk reduction) by 1/3rd across most groups studied (…still awaiting large HIV data)

- Why absolute risk matters – examples I see in clinic
  - 55 year old with 3% risk for ASCVD in next 10y → statin reduces to 2%. So adding statin gives 1/100 chance of preventing ASCVD over next 10y
  - vs. 55 year old with 30% risk for ASCVD in next 10y → statin reduces to 20%. So adding statin gives 1/10 chance of preventing ASCVD over next 10y
  - With ~5% chance of side effects, easier to justify absolute risk reduction of 10% (net clinical benefit of 10-5=5%) than 1% → starting for higher risk ppl

Assessing Athero-Thrombotic Risk in HIV

CVD Risk Scoring in General: Why, What, and How

- Primer on absolute risk vs. relative risk – why absolute risk matters in risk scoring

Q: So how do these risk prediction models perform in HIV?

A: Not very well!

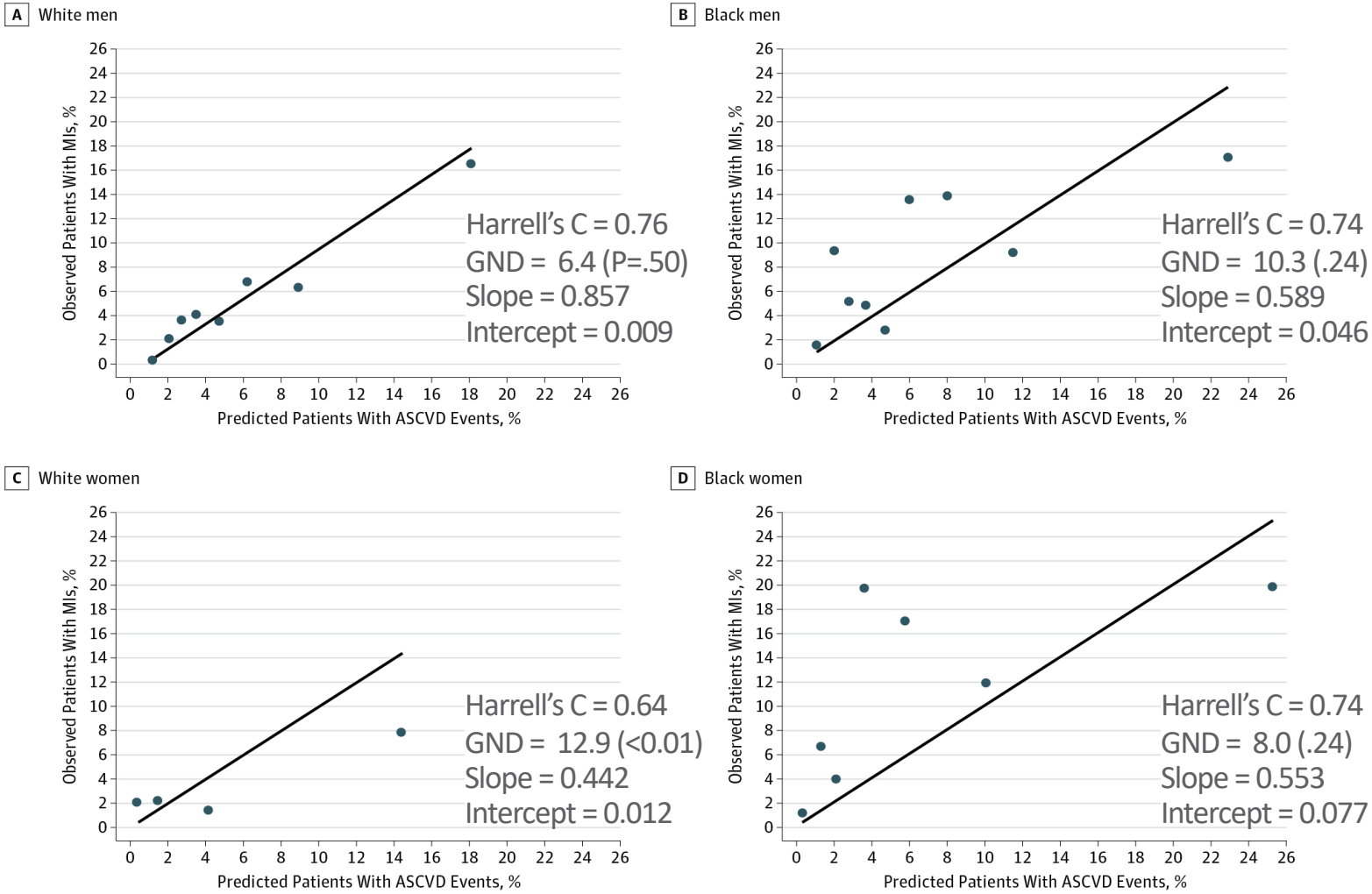
%.

So adding statin gives 1/10 chance of preventing ASCVD over next 10y

  - With ~5% chance of side effects, easier to justify absolute risk reduction of 10% (net clinical benefit of 10-5=5%) than 1% → starting for higher risk ppl

Assessing Athero-Thrombotic Risk in HIV

CNICS: Under-prediction (especially for Black men & women)



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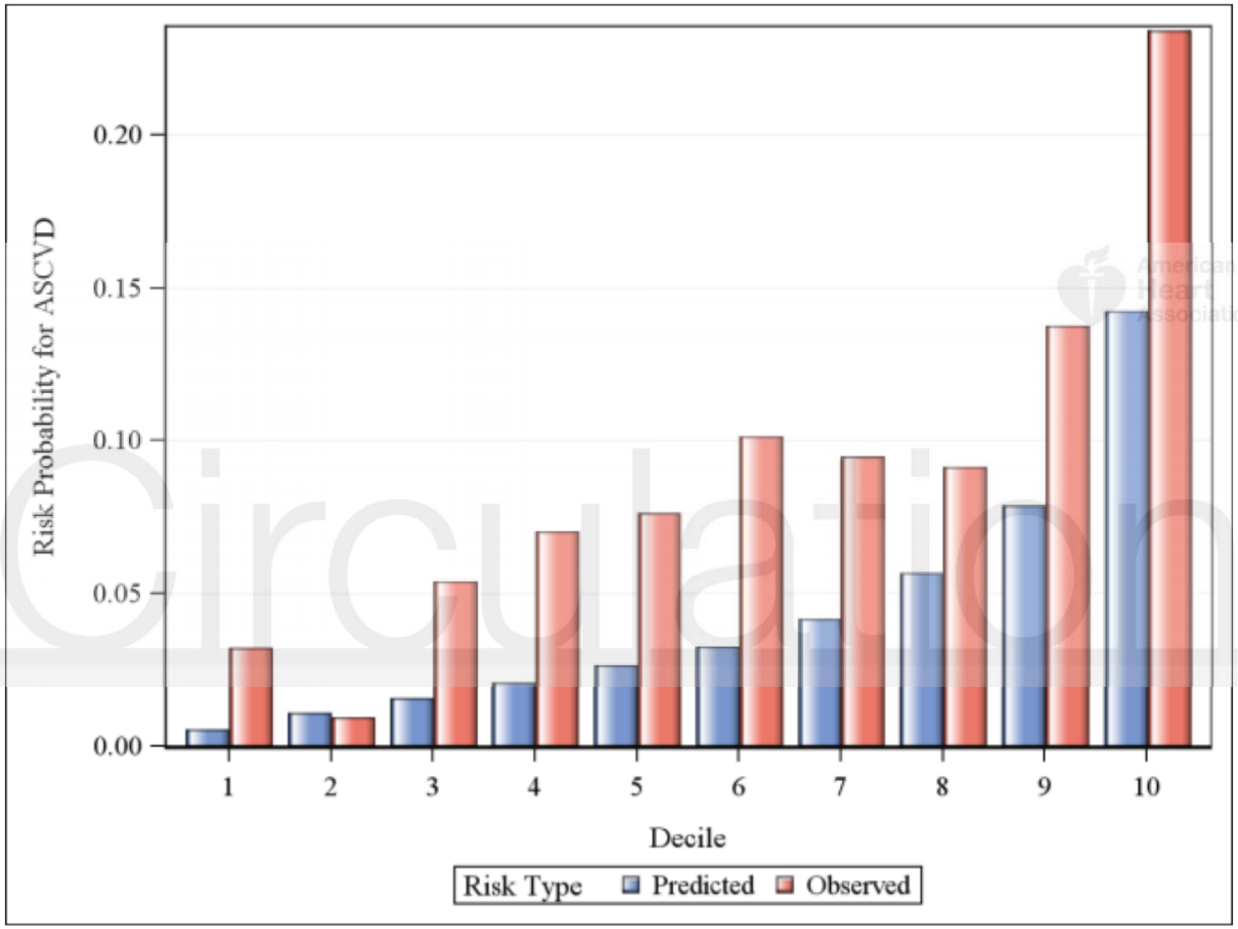
Feinstein MJ, et al. *JAMA Cardiology*. 2017;2:155-162.

Assessing Athero-Thrombotic Risk in HIV

Partners: Consistent under-prediction



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Triant VA et al. *Circulation* 2018;137(19):2203-2214.

Athero-thrombosis in HIV: State of the science

Review of pathophysiology and risk stratification

1. Myocardial infarctions result from *athero-* and *–thrombosis*

2. HIV on ART: ↑ athero and ↑ thrombosis

3. Mechanisms are reasonably well understood. Important remaining questions relate to which interventions on HIV-associated immune activation, atherogenic dyslipidemia, and thrombosis will have the optimal net benefit (benefit >> harm) and in which specific risk strata/populations these benefits will be greatest

Intervening on Athero-Thrombosis in HIV

Endpoint-driven trials of lipid-lowering therapy in HIV

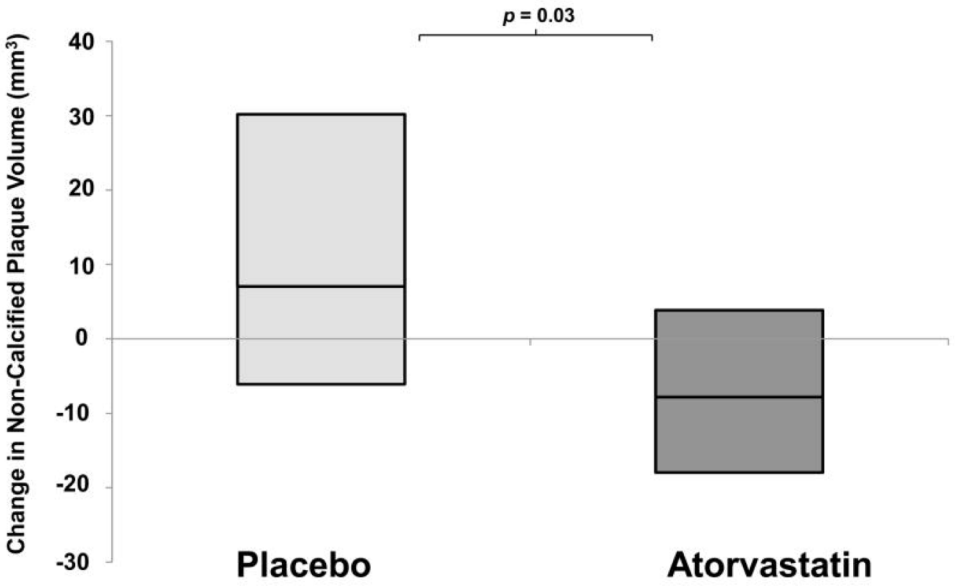
P: 40 HIV+ with subclinical atherosclerosis and arterial (aortic) inflammation on FDG-PET

I/C: Atorvastatin 20→40 mg vs. placebo

O: Arterial inflammation (FDG-PET) and coronary plaque (CT)

T: 12 months

12m change in noncalcified plaque volume for atorvastatin (n=19) vs. placebo (n=21)



+ lower LDL-c, Lp-PLA2
+ few SAEs (2 in atorva, 1 placebo), none leading to study d/c (6 muscle sx atorva, 5 placebo)
- no significant difference in Ao inflammation

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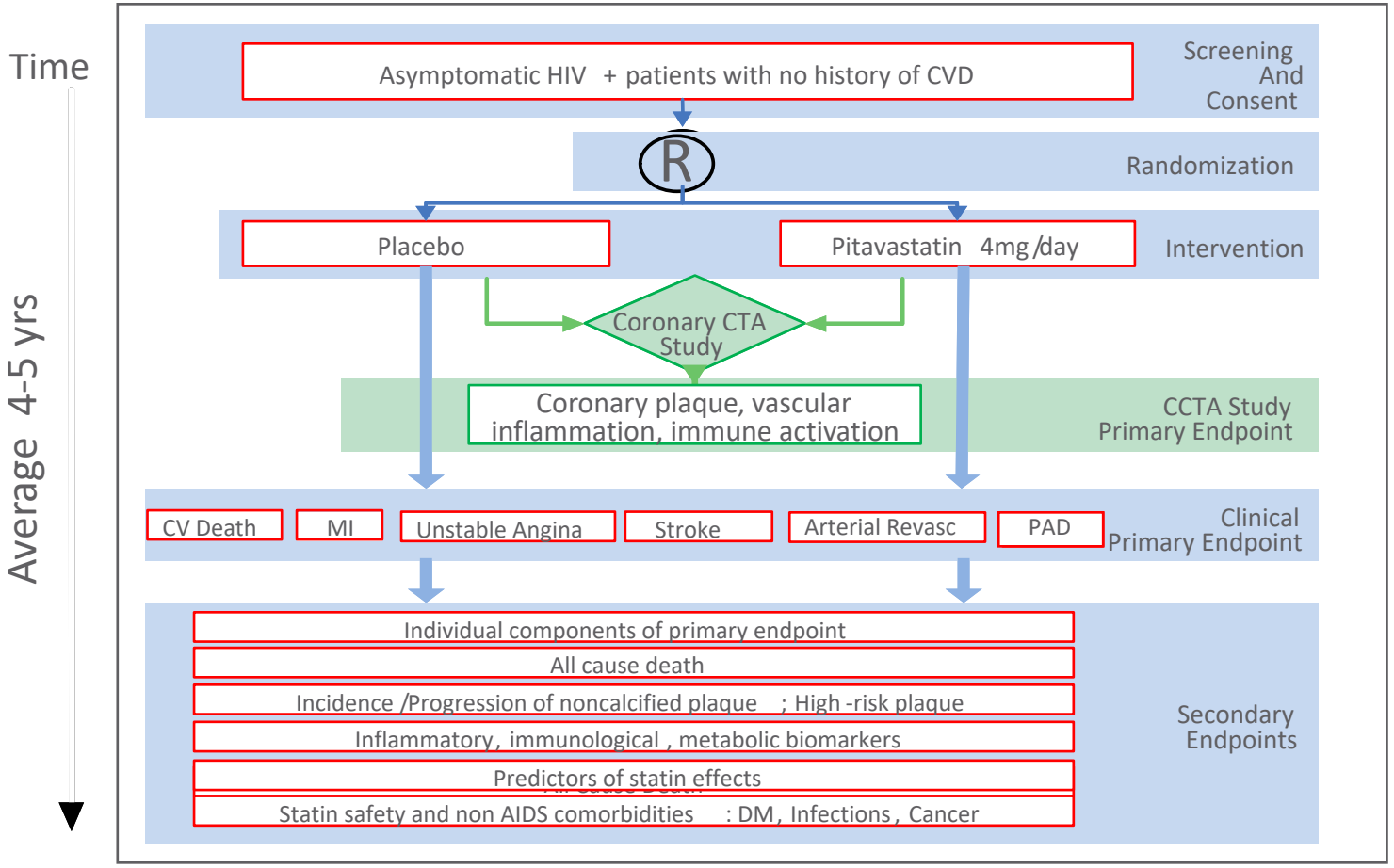
Lo J et al. Lancet HIV. 2015;2(2):e52-e63.

Intervening on Athero-Thrombosis in HIV

Endpoint-driven trials of lipid-lowering therapy in HIV: REPRIEVE



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Slide courtesy of Steven Grinspoon

Intervening on Athero-Thrombosis in HIV

Endpoint-driven trials of lipid-lowering therapy in HIV: 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)

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

Intervening on Athero-Thrombosis in HIV

Endpoint-driven trials of lipid-lowering therapy in HIV: REPRIEVE

Cardiovascular and Metabolic						
BMI[9]						
<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)
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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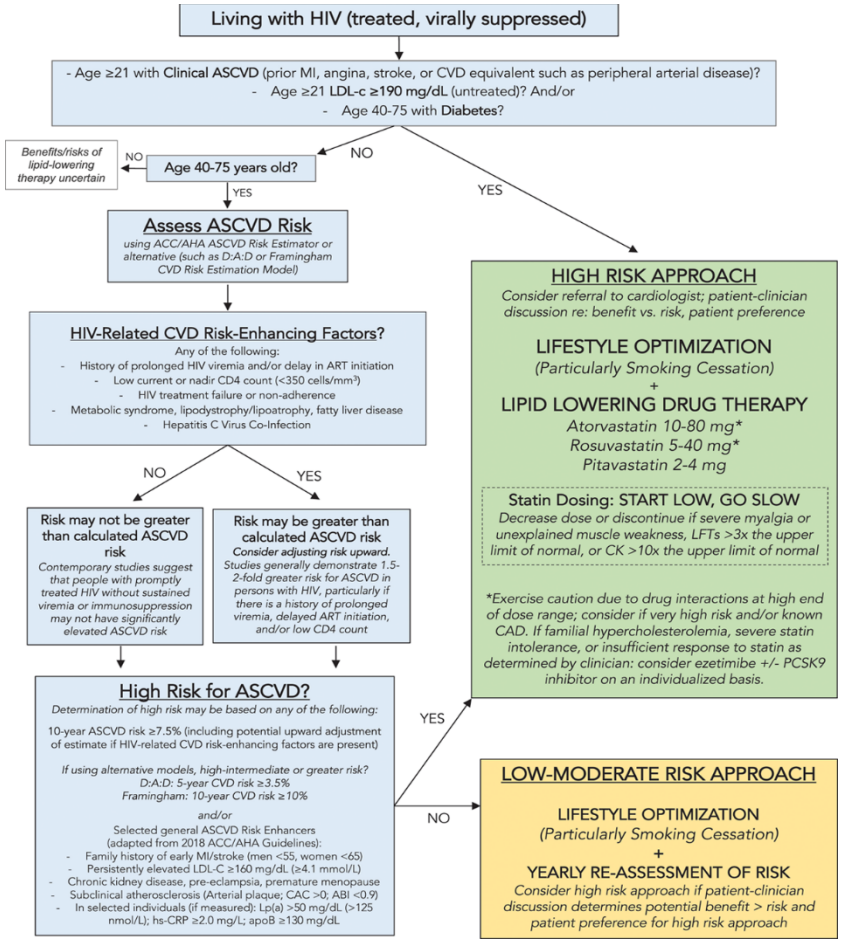
Intervening on Athero-Thrombosis in HIV

Interim clinical approach, in absence of robust RCT data



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Feinstein MJ et al. Characteristics, prevention, and Management of CVD in People Living with HIV: A Scientific Statement from the American Heart Association. *Circulation* 2019;140(2):e98-e124.

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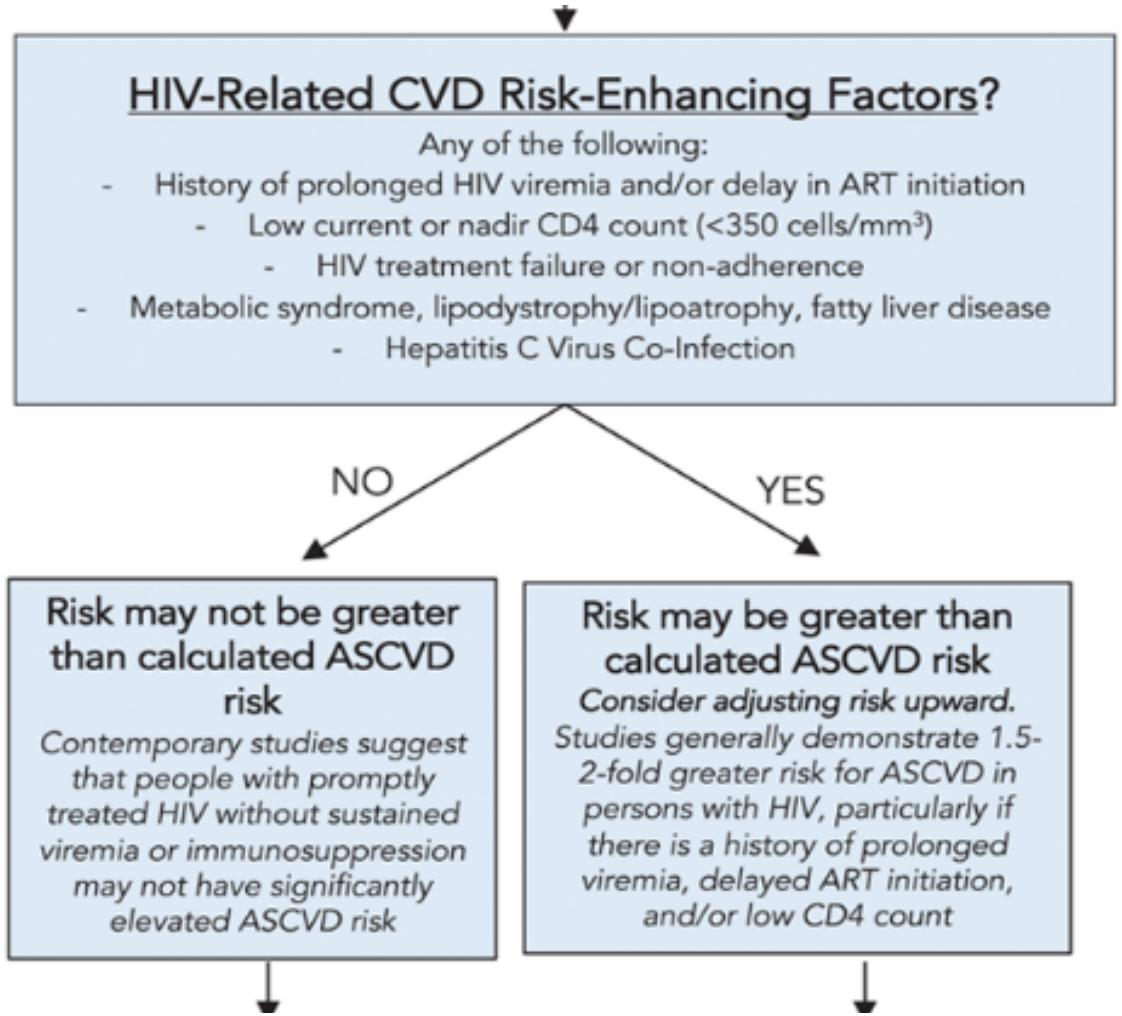

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Intervening on Athero-Thrombosis in HIV

Interim clinical approach, in absence of robust RCT data

LOW-MODERATE RISK APPROACH

LIFESTYLE OPTIMIZATION
(Particularly Smoking Cessation)
+
YEARLY RE-ASSESSMENT OF RISK
Consider high risk approach if patient-clinician discussion determines potential benefit > risk and patient preference for high risk approach

HIGH RISK APPROACH

Consider referral to cardiologist; patient-clinician discussion re: benefit vs. risk, patient preference

LIFESTYLE OPTIMIZATION
(Particularly Smoking Cessation)
+
LIPID LOWERING DRUG THERAPY
*Atorvastatin 10-80 mg**
*Rosuvastatin 5-40 mg**
Pitavastatin 2-4 mg

Statin Dosing: START LOW, GO SLOW
Decrease dose or discontinue if severe myalgia or unexplained muscle weakness, LFTs >3x the upper limit of normal, or CK >10x the upper limit of normal

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Feinstein MJ et al. Characteristics, prevention, and Management of CVD in People Living with HIV: A Scientific Statement from the American Heart Association. *Circulation* 2019;140(2):e98-e124.

What about thrombosis?

- Limited data on antiplatelet meds in HIV; some trials (ACTG A5331) suggest less antiplatelet effect than would expect from the general population, no anti-inflammatory effect

- Aspirin for primary prevention remains a moving target in the general population

- My interim approach: risk/benefit in context of likely absolute risk for clot (MI/stroke) vs. bleed. Transparent discussion with patients

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

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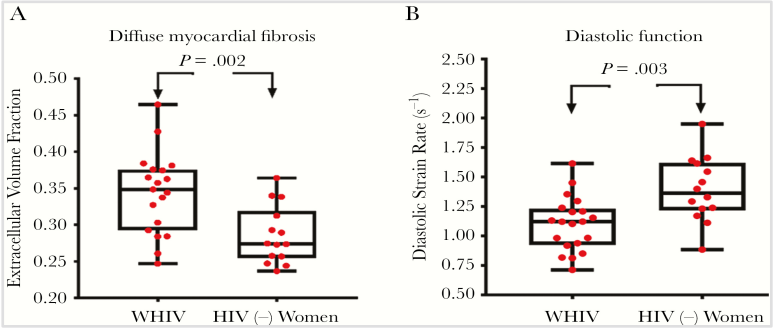
HIV and heart failure

Overview of proposed pathophysiology, future directions

Myocardial Dysfunction & HF in HIV

Intermediate/subclinical manifestations underlying 1.5-2x inc. HF risk in HIV



- Women with HIV (n=19) vs. HIV- control women (n=14): more fibrosis and diastolic dysfunction on cardiac MRI (CMR).
- Monocyte activation markers a/w fibrosis and worse diastolic function

  Zanni MV et al. J Infect Dis 2020;8:1315-1320

- Myocardial fibrosis (on CMR) more common for HIV+ vs. HIV- healthy subjects

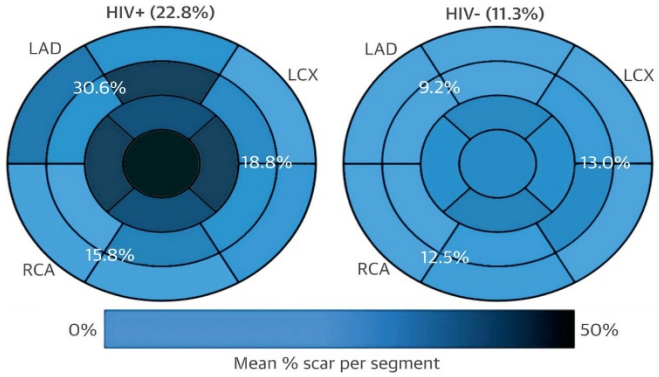
  Holloway CJ et al. Circulation 2013;128:814-822
- Myocardial lipid/steatosis and fibrosis on CMR → dysfunction in HIV

  Thiara DK et al. J Infect Dis 2015;212:1544-1551
- HIV+ have higher prevalence of diastolic dysfunction and LV mass index vs. controls

  Hsue PY et al. Circ Heart Fail 2010;3(1):312-319.

- HIV+ with CAD/MI have 2x extent of ischemia/MI-related scar, lower LVEF (36% vs. 49%) post-MI compared with HIV-

  Feinstein MJ et al. J Am Coll Cardiol 2016; 68:2026-7



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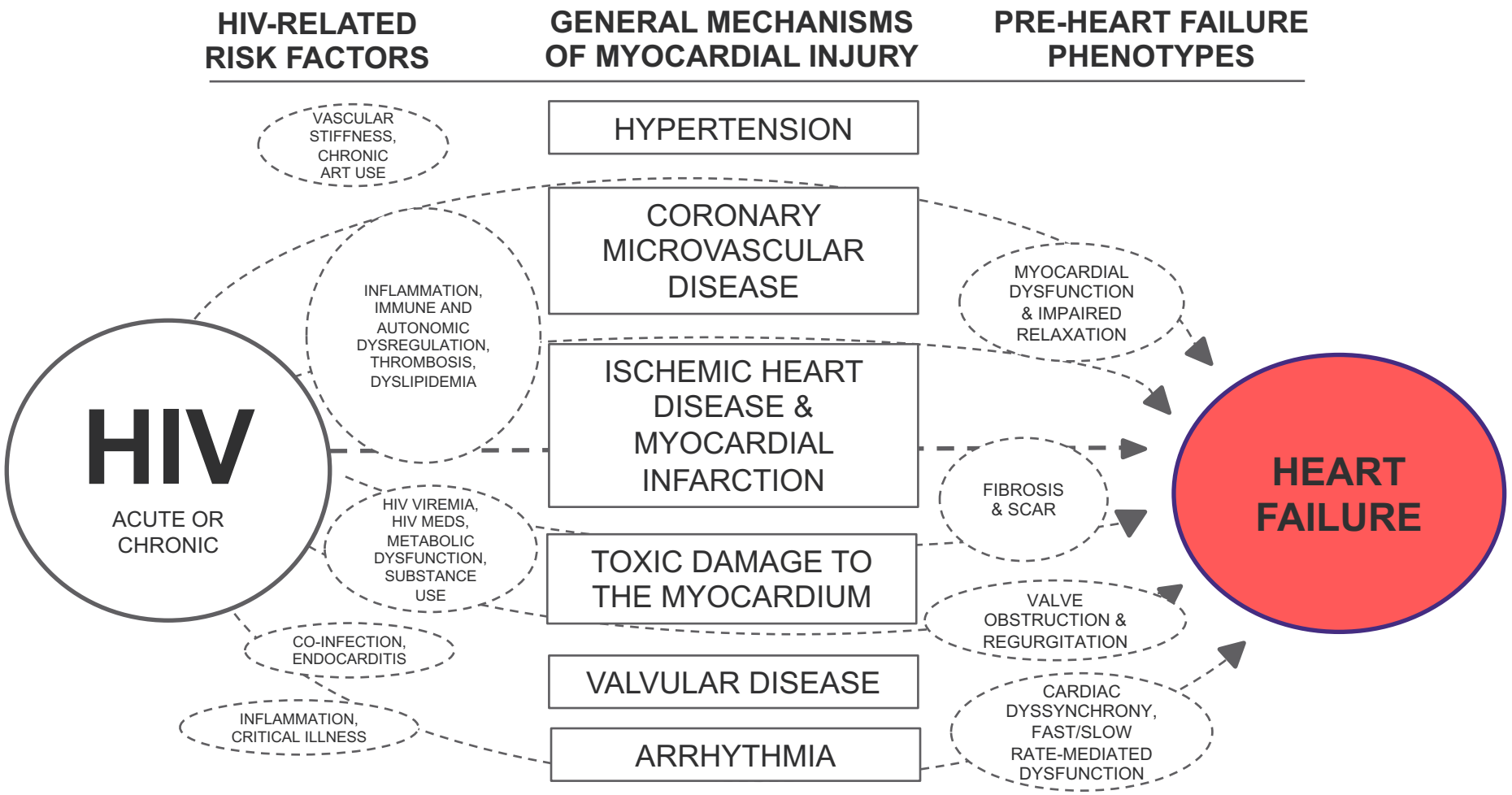
Myocardial Dysfunction & HF in HIV

Proposed mechanisms – in need of investigation!



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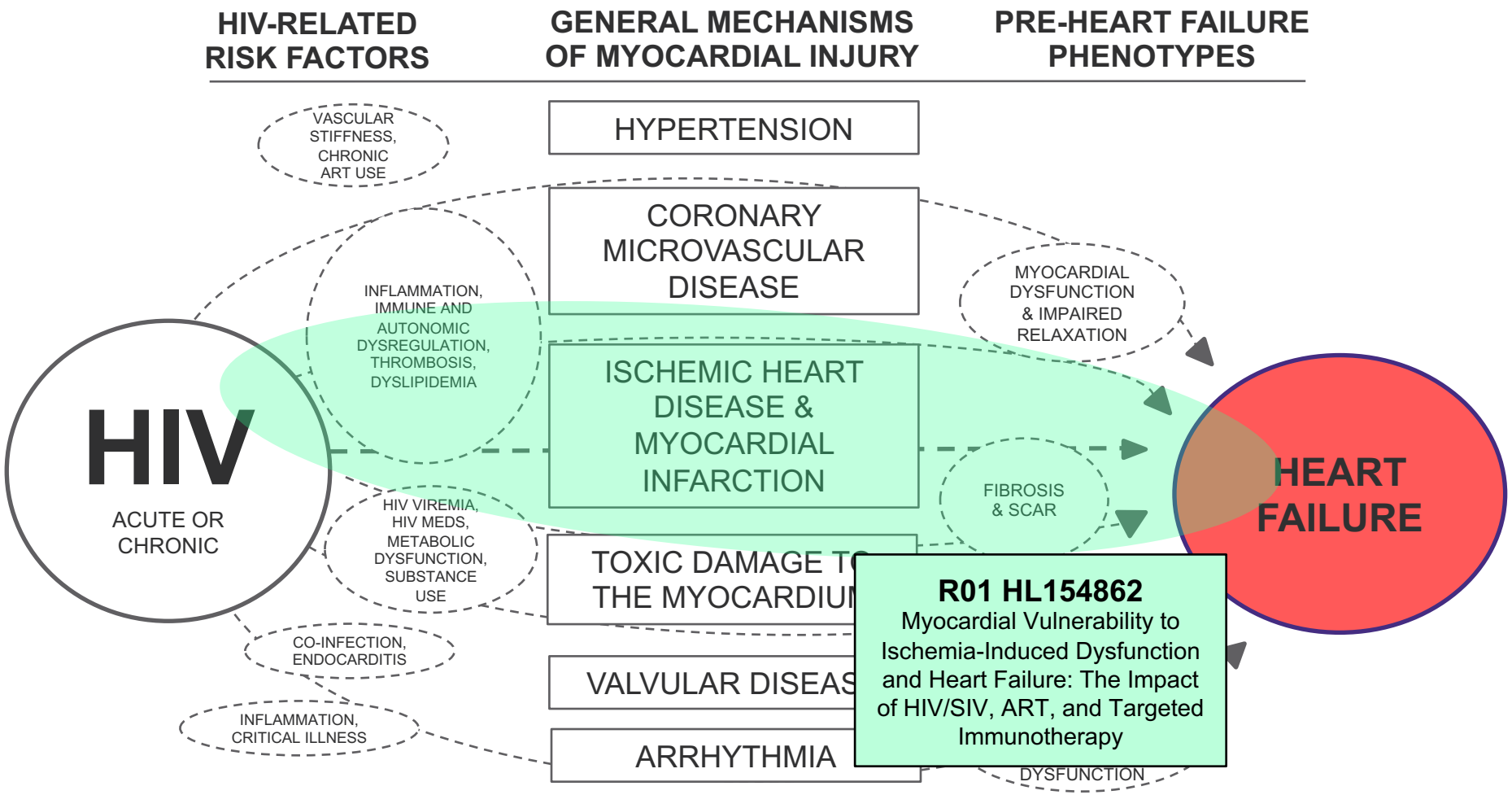

R01 HL154862
Myocardial Vulnerability to Ischemia-Induced Dysfunction and Heart Failure: The Impact of HIV/SIV, ART, and Targeted Immunotherapy

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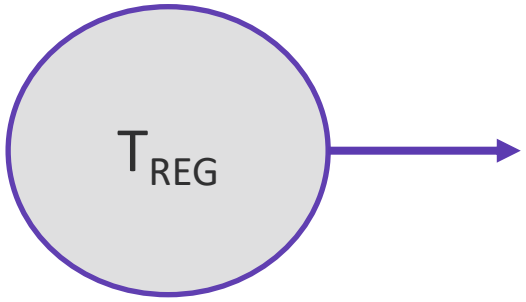
HIV, Myocardial Dysfunction, and HF

Myocardial Vulnerability to Ischemia: Role of T_{regs}

1. **Imbalance between immune activation/inflammation and resolution thereof drives adverse cardiac remodeling and HF after MI in general**
2. Guiding hypothesis: Abnormal immune responses/impaired inflammation resolution drive harmful, tissue-damaging responses to ischemia and MI in HIV
3. People with HIV have more cardiac damage and dysfunction after MI than non-HIV

- T_{regs}:
  - Reduce infarct size, attenuate adverse remodeling by:



↑ Peri-infarct neovascularization

↓ Pro-inflammatory cytokine expression

↓ Pro-inflammatory immune cell infiltration

↓ Excessive matrix degradation

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Tang TT, et al. *Bas Res Cardiol*. 2012;107:332.
Meng X, et al. Nat Rev Cardiol. 2016;13:167-179.
Hofmann U, et al. *Circulation Research*. 2015;116:354-367.

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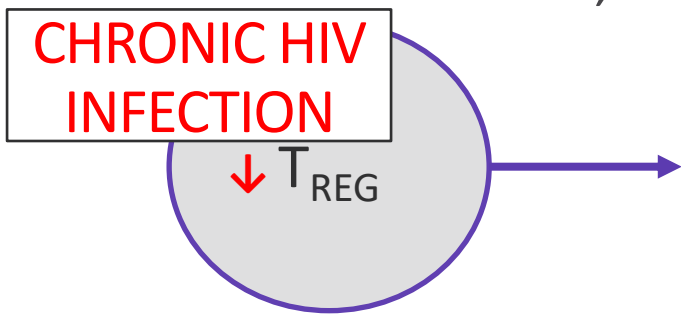

- ↓ Peri-infarct neovascularization
- ↑ Pro-inflammatory cytokine expression
- ↑ Pro-inflammatory immune cell infiltration
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NMEDW: Compare Infarct-associated LGE on CMRI for HIV+ vs. HIV- controls (matched on risk, CAD)

	HIV+ (N=12)	HIV- (N=22)	*P* value
Arteries with ≥50% Stenosis	2.25±0.30	2.27±0.20	0.95
Number (%) of participants with angiographic characteristics			
LAD			
Stenosis ≥50%	92%	91%	0.94
LCx			
Stenosis ≥50%	58%	68%	0.57
RCA			
Stenosis ≥50%	58%	59%	0.97

Feinstein MJ et al. *J Am Coll Cardiol*. 2016;68(18):2026-7.

HIV, Myocardial Dysfunction, and HF

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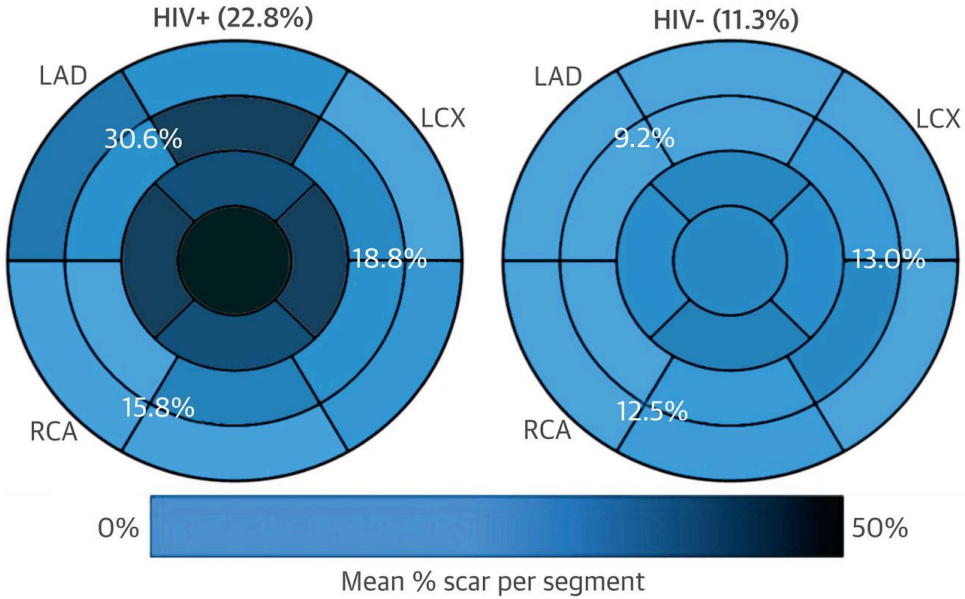
NMEDW: Compare Infarct-associated LGE on CMRI for HIV+ vs. HIV- controls (matched on risk, CAD)

HIV+: 2x infarct-associated scar vs. HIV-!



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HIV, Myocardial Dysfunction, and HF

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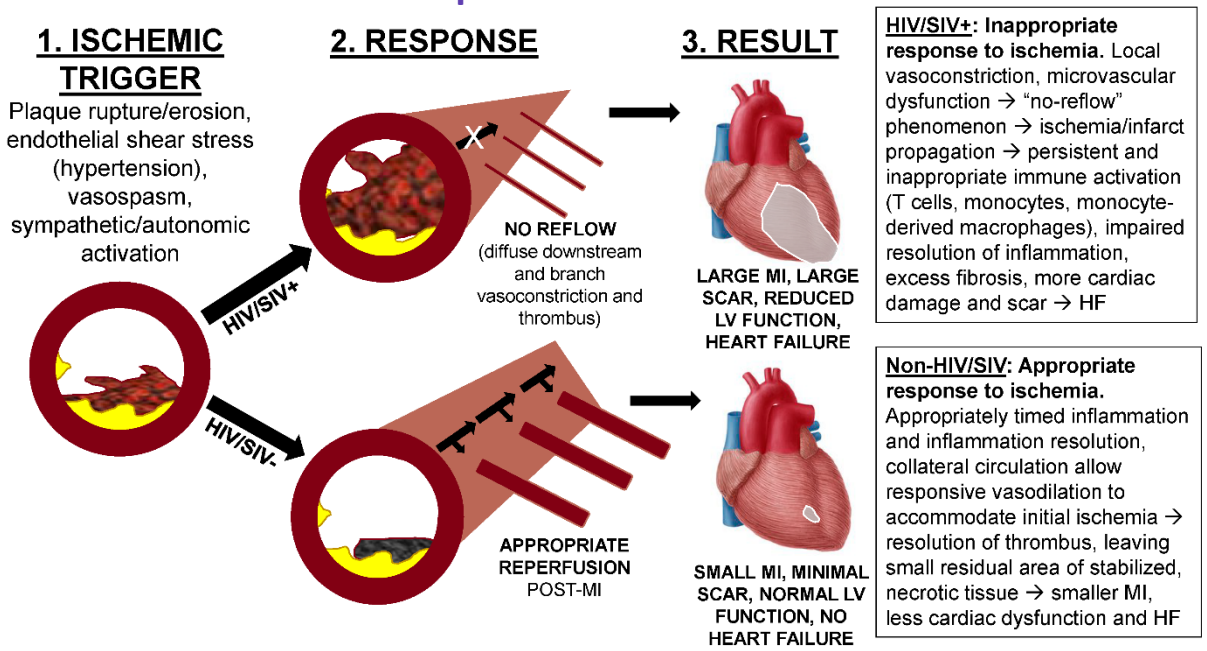
Proposed Model



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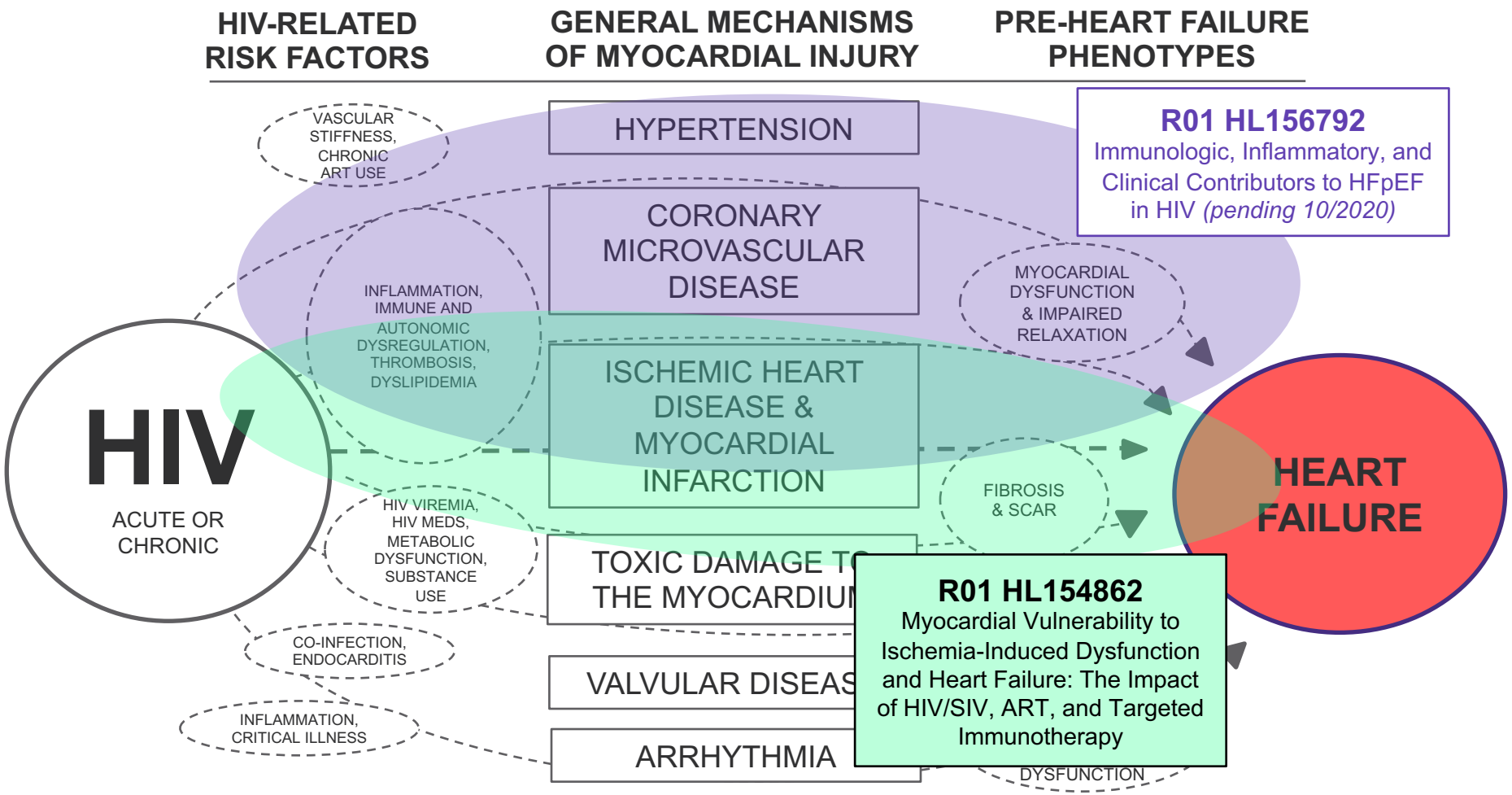
Sinha A and Feinstein MJ. *Prog Cardiovasc Dis* 2020;63(2):134-141.

Myocardial Dysfunction & HF in HIV

Proposed mechanisms needing investigation (and discussion at later date!)



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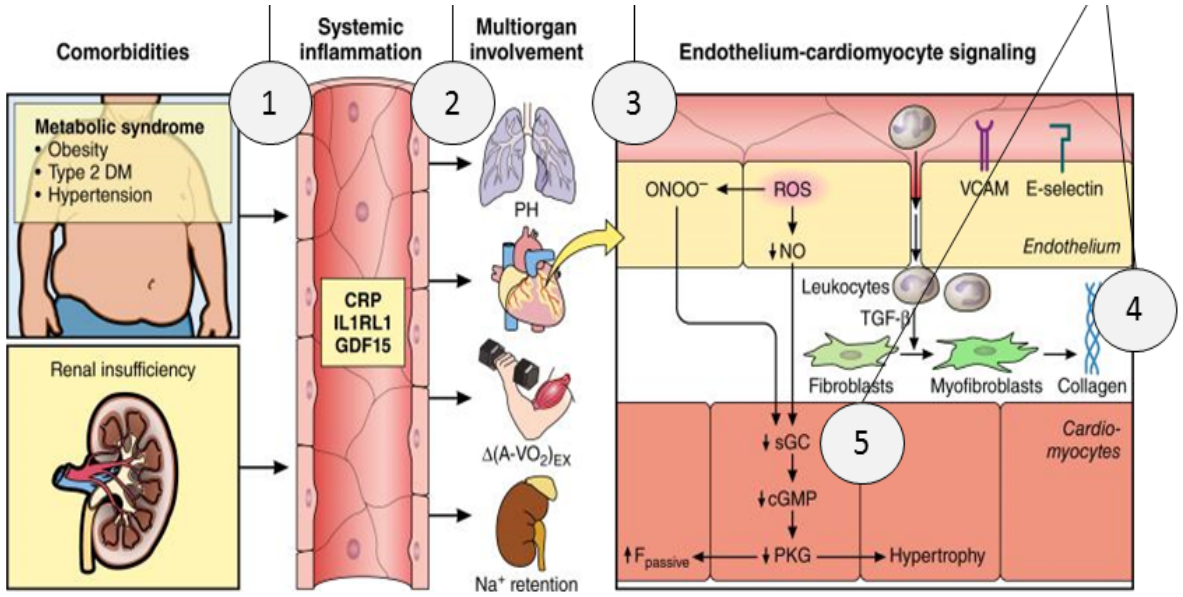
Immune Dysregulation & HFpEF: HIV as Model

R01 HL156792: Immunologic, Inflammatory, Clinical Contributors to HIV-HFpEF

Premise: HFpEF as a multi-hit phenomenon marked by adverse immune responses to local and systemic stressors

(supporting data: observational studies in humans & animal immune cell KO/adoptive transfer models)



In general, immune effector functions contribute to HFpEF via:

1. Inflammatory response to comorbid dx's
2. Cellular infiltration of heart & tissues
3. Endothelial permeability
4. Fibrosis/collagen dep.
5. Cardiomyocyte hypertrophy

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Laroumanie F et al *Circulation* 2014; 129(21):2111-24; Winterberg PD et al *J Am Soc Nephrol* 2019; Anzai et al *J Exp Med* 2019;216(2):369-83; Tang TT et al Basic Res Cardiol 2012;107(1):232; Vdovenko D et al J Immunol Res 2018:4396351; Shah SJ et al *Circulation* 2015;131(3):269-79.

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Premise: HFpEF as a multi-hit phenomenon marked by adverse immune

Central Hypothesis of HFpEF in HIV:

Chronic, persistent immune activation in ART-treated people with HIV interacts with "second hit" clinical comorbidities to drive HFpEF pathogenesis

Plan: Leverage large, diverse US HIV cohort (N>35,000) with linked bio-samples to determine clinical, immunologic, & inflammatory contributors to HIV-HFpEF → dx/tx targets

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Laroumanie F et al *Circulation* 2014; 129(21):2111-24; Winterberg PD et al *J Am Soc Nephrol* 2019; Anzai et al *J Exp Med* 2019;216(2):369-83; Tang TT et al Basic Res Cardiol 2012;107(1):232; Vdovenko D et al J Immunol Res 2018:4396351; Shah SJ et al *Circulation* 2015;131(3):269-79.

Immune Dysregulation & HFpEF: HIV as Model

R01 HL156792: Immunologic, Inflammatory, Clinical Contributors to HIV-HFpEF

N=35,727 HIV+ (+plasma/PBMCs)

- **Aim 1 (Clinical/Epi)**
  - ***H1:*** *HIV+ with time-updated CD4 count <500 cells/mm^3 and/or CD4/CD8 ratio <0.8 (impaired immune recovery) + 2nd traditional comorbidity "hits" → ↑↑ HFpEF*
- **Aim 2 (Inflammatory biomarkers →HFpEF)**
  - ***H2:*** *HIV+ with incident HFpEF (vs. HFpEF-): ↑↑ mono. trafficking, endothelial transmigration, and fibroblast senescence, as well as impaired regulatory T cell activity.*
- **Aim 3 (Immune response/gene expression)**
  - ***H3:*** *Circulating immune cells of HIV+ with incident HFpEF highly express genes encoding for pro-inflammatory proteins before HFpEF onset*
- **Aim 4 (Myocardial tissue validation)**
  - *Explore single-cell immune landscapes of peripheral blood and fresh frozen postmortem myocardial tissue from HIV+ with vs. without HFpEF*

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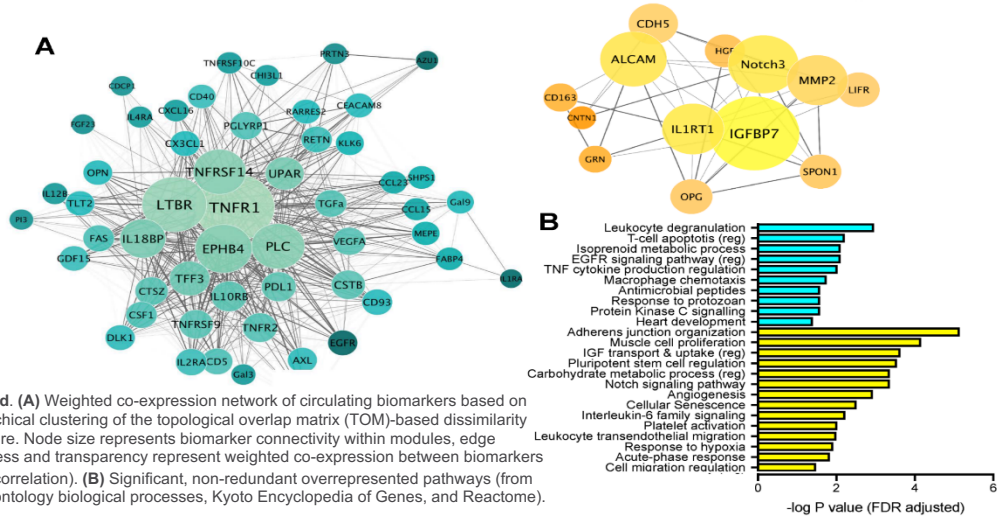
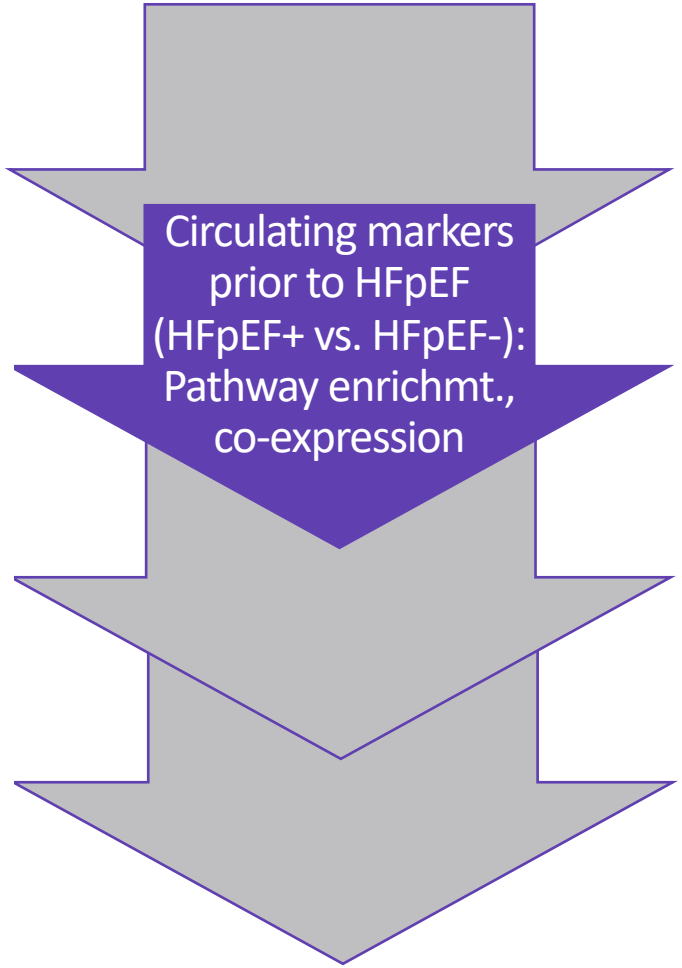


Legend. **(A)** Weighted co-expression network of circulating biomarkers based on hierarchical clustering of the topological overlap matrix (TOM)-based dissimilarity measure. Node size represents biomarker connectivity within modules, edge thickness and transparency represent weighted co-expression between biomarkers (e.g., correlation). **(B)** Significant, non-redundant overrepresented pathways (from gene ontology biological processes, Kyoto Encyclopedia of Genes, and Reactome).



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CNICS CFAR Network Of Integrated Clinical Systems

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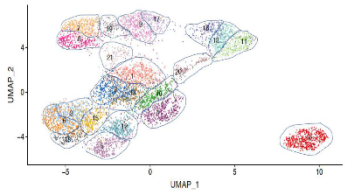
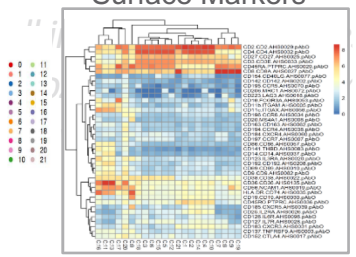
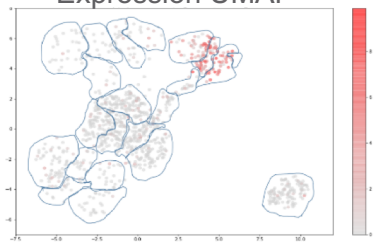
1. Rhapsody-derived cell subtypes



2. Heatmap of Surface Markers



3. Monocyte CCR3 Expression UMAP



Cellular-level drivers prior to HFpEF: Immune cell gene exp. (scRNA-seq) & proteins encoded

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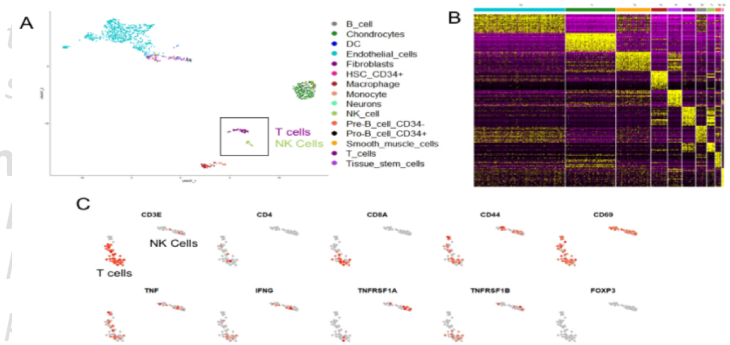

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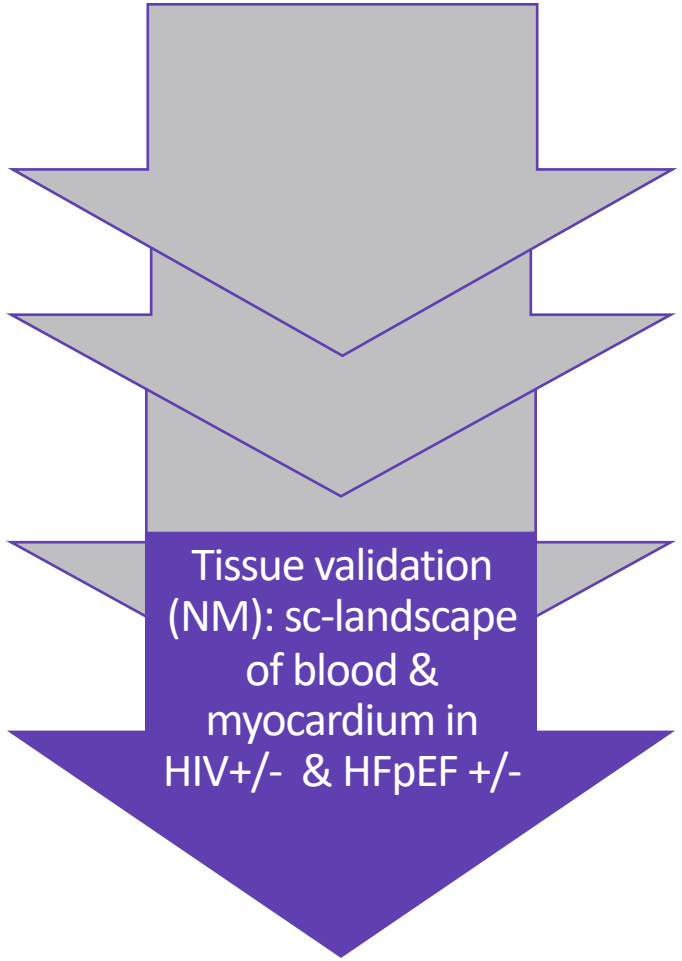

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State of the science and practical points

HIV and CVD: What we know and need to know

Conceptual Model: HIV, Inflammation, and CVD

- Who: the host (susceptibility, comorbidity)
  - Comorbidities, traditional risk factors in HIV (smoking) → CVD
  - Aging of HIV population
- What/how: immune landscape/effectors driving inflammatory response and resolution
  - HIV: CD4 lymphopenia as major predictor of CVD; relative risk not all that elevated for people without sustained viremia or immune prog.
    - Informative for CVD risk stratification: HIV-related risk enhancers
  - Potential relevance to other conditions: T cell regulatory balance in CVD pathogenesis. Myocardial dysfunction (incl. ICI myocarditis)
- Where: Systemic and tissue-level responses
  - HIV and Athero-thrombosis: at the vascular endothelium, dynamic interplay determining plaque stability/rupture and thrombosis/thrombo-resolution
  - HIV and HF: vascular and non-vascular (direct myocardial damage)

Conceptual Model: HIV, Inflammation, and CVD

- When: Early/innate/acute vs. later/adaptive/subacute
  - HIV: viremia and lymphopenia (often in early, uncontrolled HIV) → CVD
  - Different approaches during different "vulnerable periods"? Role for immuno-regulation/suppressive tx post-MI and/or during periods of extensive myocardial immune cell infiltration?

- Why: Antigens or antigen-like triggers
  - HIV: Co-infections and re-activation (e.g. CMV) as potential drivers of immune exhaustion, biasing toward less regulatory phenotypes
  - Non-infectious "antigens" and immune response to these highlight importance of immunity in many aspects of CVD (ASCVD, cardiomyopathy)

Where are we now

HIV and CVD: Final practical points

- ↑ CVD (MI, HF) after adj. for traditional risk factors
- T cell imbalance/phenotypic shift → ↑ Risk
- Gaps for HIV-ASCVD: RCTs, implementation (mechanisms reasonably well understood)
- Gaps for HIV-HF: More; need mechanistic understanding
  - *HIV-HF ongoing & future studies: May be valuable model for interaction of immune dysreg. with traditional risk factors, ischemia in multi-hit model of HF and HFpEF*

Acknowledgments

Key Lab Personnel

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Arjun Sinha
Adovich Rivera
Shalini Singh
Ricardo Tellez
Kris Glinton

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UH-Case: Chris Longenecker
U. Manitoba: J.A. Chris Delaney
U. Sao Paulo / InCor: Jorge Kalil, Edecio Cunha-Neto
UVM: Russ Tracy
UW: Heidi Crane, Robin Nance, Bruce Psaty
Vanderbilt: Matt Freiberg

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Thank You

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