Cardiovascular Complications of HIV

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Financial Relationships With Ineligible Companies

Dr Feinstein has served as a consultant for Novartis.
(Updated 06/11/21)

Slide 2 of 42

Learning Objectives

After attending this presentation, learners will be able to:

- Describe the spectrum of clinical mechanisms of cardiovascular diseases (CVDs) in people with HIV
- Define mechanisms of HIV-associated CVDs
- Outline pragmatic approaches to CVD prevention and treatment for people with HIV

Slide 3 of 42

Outline

- **What:** Epidemiology of HIV & CVD
- **Why:** What we know, what we think, and what we don't know about
  - HIV, atherosclerosis, and thrombosis
  - HIV, cardiac dysfunction, and heart failure
- **How** can we prevent and treat CVD in HIV?
  - Risk assessment
  - Therapies: Old, New, and Future

Slide 4 of 42

Cases

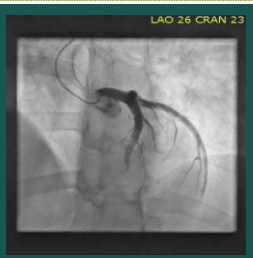
One week on a cardiology service:
3 HIV-associated CVD cases

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Case 1: Thrombosis

35 year old M with HIV (dx age 32) on ART until 1 mo. ago at which point he stopped due to perceived risk of acne, presenting with 2 days' chest pressure and pain radiating to the neck. No significant risk factors or family history of premature CAD/ASCVD

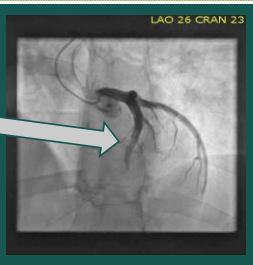
- ECG nonspecific T wave changes
- Hemodynamically stable
- Troponin 4.26 ng/mL (normal <0.05)
- HIV Viral Load 4532 copies/mL
- Low-Normal LV function on echo.



Slide 6 of 42

Case 1: Thrombosis

- Fresh & resolving spontaneous thrombus throughout LAD
- In absence of athero/plaque!
- Leading theory: viral rebound → acute/subacute inflammation & platelet activation



Slide 7 of 42

Case 2: Severe, Progressive Atherosclerosis → HF

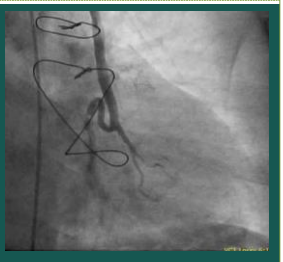
- 62y M with HIV and CAD s/p several PCIs and recent failed CABG (<6 months prior, atretic LIMA 2/2 LAD competitive flow → acutely SOB in clinic → ER
- Cath: Severe LM/LAD disease, progressively tapering vessels, much progression despite appropriate tx. Residual inflammatory risk?



Slide 8 of 42

Case 3: Traditional & Behavioral Risk Factors → CVD

- 58y M with HIV (intermittently adherent to ART) and CAD s/p 3v CABG presenting with accelerating chest pain after cocaine use.
- Highly eccentric plaque.
- Also +Smoking, hyperlipidemia, polysubstance use.



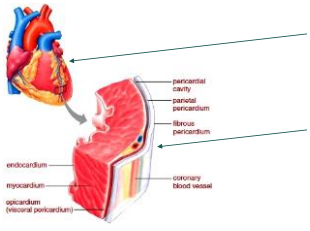
Slide 9 of 42

HIV-CVD Epidemiology

These cases reflect clinical reality!
CVD increasingly common in HIV

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But First, a Primer on CVDs

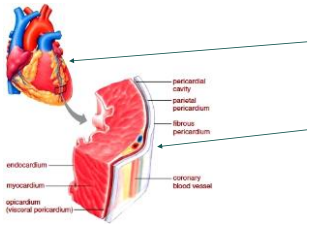


ASCVD: Vascular. Coronary arteries, aorta, peripheral vessels. Key terms: Atherosclerosis, thrombosis, MI.

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.

Slide 11 of 42

But First, a Primer on CVDs



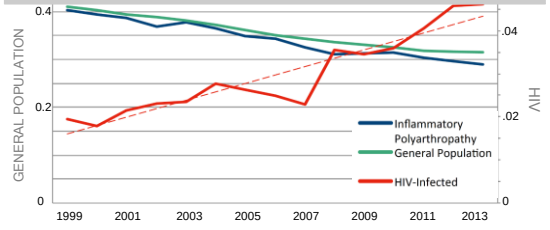
ASCVD: in HIV: Several studies, some hard outcomes studies underway, mechanistic research still needed but emphasis on trails, impl. sci too

Myocardium: 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

Slide 12 of 42

CVD Mortality (Proportion of Total), USA

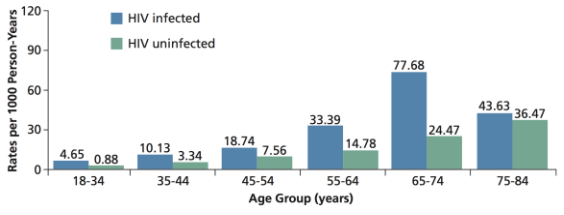
% of People with HIV dying who had CVDs as the underlying cause: 3x ↑ from 1999-2015



Slide 13 of 42

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

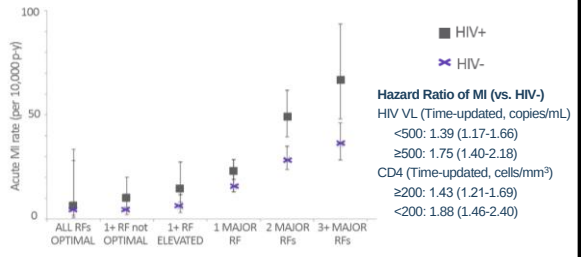
HIV and Myocardial Infarction



Slide 15 of 42

Triant V., et al. J Clin Endocrinol Metab 2007;92(7): 2506-12.
Currier, J. S. Top HIV Med 2009;17(3): 98-103.

HIV and Myocardial Infarction

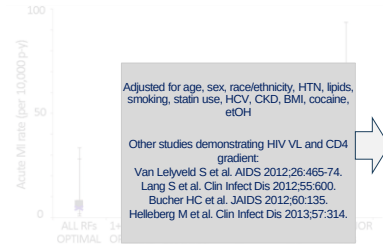


Hazard Ratio of MI (vs. HIV-)
HIV VL (Time-updated, copies/mL)
<500: 1.39 (1.17-1.66)
≥500: 1.75 (1.40-2.18)
CD4 (Time-updated, cells/mm^3)
≥200: 1.43 (1.21-1.69)
<200: 1.88 (1.46-2.40)

Slide 16 of 42

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.

HIV and Myocardial Infarction



Adjusted for age, sex, race/ethnicity, HTN, lipids, smoking, statin use, HCV, CKD, BMI, cocaine, etOH

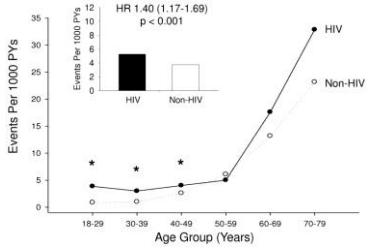
Other studies demonstrating HIV VL and CD4 gradient:
Van Lelyveld S et al. AIDS 2012;26:465-74.
Lang S et al. Clin Infect Dis 2012;55:600.
Bucher HC et al. JAIDS 2012;60:135.
Helleberg M et al. Clin Infect Dis 2013;57:314.

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

Slide 17 of 42

HIV and Ischemic Stroke

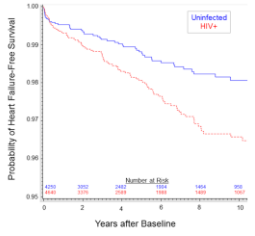


PARTNERS
- **N=4308**
- **Mean f/u: 6 yrs**
- **Adjusted for demographics and stroke risk factors**

Chow FC, et al. J Acquir Immune Defic Syndr. 2012;60(4):351-358.

Slide 18 of 42

HIV and Heart Failure: NM Cohort



Overall:
Hazard Ratio of HF **(vs. HIV-Uninfected)**:
2.10 (1.38-3.21)

Among HIV+:
HR per log_{10}higher time-updated **viral load**:
1.22 (1.11-1.33)

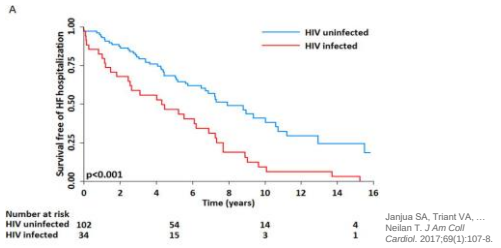
HR per 100 cells/mm^3 higher time-updated **CD 4 count**:
0.80 (0.69-0.92)

**Similar findings in VACS (97% M, admin codes; NM cohort 80% M, HF physician-adjudicated)*

Feinstein MJ, et al. *J Am Heart Assoc* 2018. 7(21):e009985. doi:10.1161/JAHA.118.009865

Slide 19 of 42

Outcomes after HF: Partners



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

Slide 20 of 42

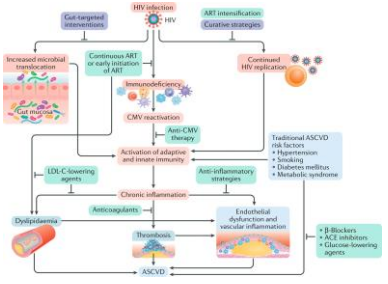
Why CVDs in HIV?

A Brief Mechanistic Detour

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HIV, Immune Dysregulation, and CVDs

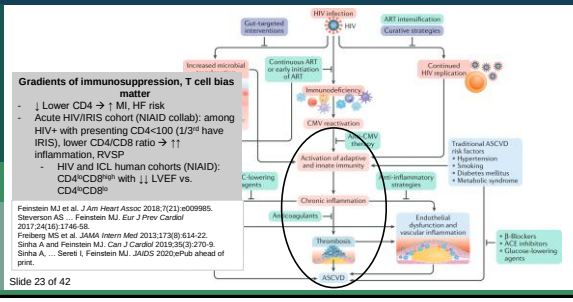
Residual immune activation despite viral suppression → ASCVD



Hsue PY et al. Nat Rev Cardiol 2019;16:745-759

Slide 22 of 42

HIV, Immune Dysregulation, and CVDs



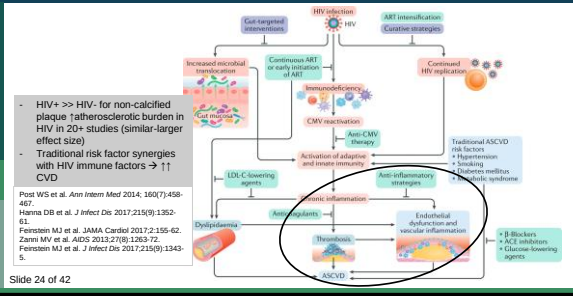
Gradients of immunosuppression, T cell bias matter

- ↓ Lower CD4 → ↑ MI, HF risk
- Acute HIV/IRIS cohort (NIAID collab): among HIV+ with presenting CD4<100 (1/3rd have IRIS), lower CD4/CD8 ratio → ↑↑ inflammation, RVSP
  - HIV and ICL human cohorts (NIAID): $CD4^{hi}CD8^{hi}$ with ↓↓ LVEF vs. $CD4^{hi}CD8^{lo}$

Feinstein MJ et al. *J Am Heart Assoc* 2018;7(21):e009985.
Steverson AS … Feinstein MJ. *Eur J Prev Cardiol* 2017;24(16):1746-58.
Freiberg MS et al. *JAMA Intern Med* 2013;173(8):614-22.
Sinha A and Feinstein MJ. *Curr J Cardiol* 2019;35(3):270-9.
Sinha A, … Sereti I, Feinstein MJ. *JAIDS* 2020;ePub ahead of print.

Slide 23 of 42

HIV, Immune Dysregulation, and CVDs

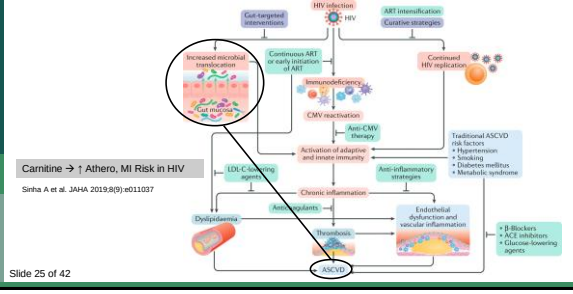


- HIV+ >> HIV- for non-calcified plaque ↑atherosclerotic burden in HIV in 20+ studies (similar-larger effect size)
- Traditional risk factor synergies with HIV immune factors → ↑↑ CVD

Post WS et al. *Ann Intern Med* 2014; 160(7):458-467.
Hanna DB et al. *J Infect Dis* 2017;215(9):1352-61.
Feinstein MJ et al. JAMA Cardiol 2017;2:155-62.
Zanni MV et al. *AIDS* 2013;27(8):1263-72.
Feinstein MJ et al. *J Infect Dis* 2017;215(9):1343-5.

Slide 24 of 42

HIV, Immune Dysregulation, and CVDs



Carnitine → ↑ Athero, MI Risk in HIV

Sinha A et al. JAHA 2019;8(9):e011037

Slide 25 of 42

What About Meds? ART >>>> No Treatment


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

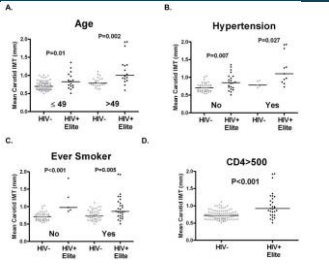
We randomly assigned persons infected with HIV who had a CD4+ cell count of more than 350 per cubic millimeter to the continuous use of antiretroviral therapy (the viral suppression group) or the episodic use of antiretroviral therapy (the drug conservation group). Episodic use involved the deferral 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

Slide 26 of 42

Insights from Elite Controllers



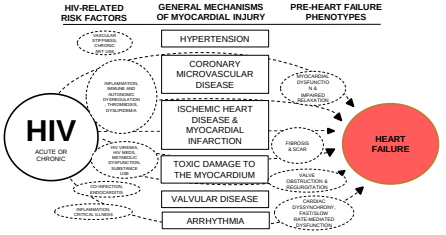
HIV+ Elite Controllers (N=33) vs. Uninfected Controls (N=92):

- Significantly greater C-IMT in general, when stratifying by CVD RFs (left), and in multivariable regression: C-IMT 0.16 mm greater for ECs (p=0.005) after adjustment for age, sex, glucose, HTN, smoking, LDL, TG, statin use, FHx CAD

Hsue PY, et al. *AIDS.* 2009; 23: 1059-1067.

Slide 27 of 42

HIV and Heart Failure: Why?



Slide 28 of 42 *Feinstein MJ et al. HIV-CVD Scientific Statement from the American Heart Association. Circulation 2019;140(2):e98-e124.*

What Can We Do About it?

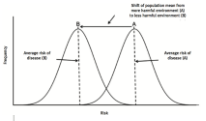
Preventing and Treating CVDs in People with HIV

IAS–USA

CVD Risk Scoring: The Basics

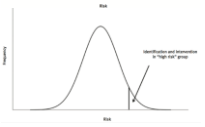
Population Strategy

Policy interventions: food supply, smoking laws



High-risk Strategy

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



Slide 31 of 42

CVD Risk Scoring: The Basics

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)

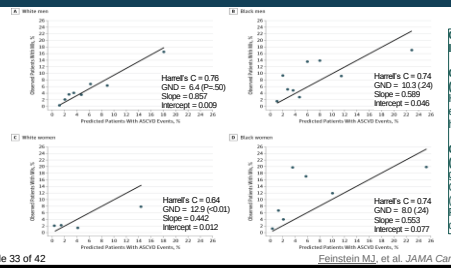
Why absolute risk matters – examples I see in clinic

- 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
- 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

Slide 32 of 42

ACC/AHA 2013 ASCVD Estimator in CNICS



Guide to Interpretation:

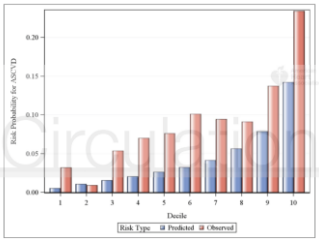
C-statistic (Discrimination): How well does the estimator rank-order higher vs. lower risk

GND or Chi-Square (Calibration): How good is the fit? Greater difference (higher number, lower P value) means worse calibration

Slide 33 of 42

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

Framingham ASCVD Estimator: PARTNERS



C-Statistic: 0.67

Calibration Chi-Square = 24.6 (p=0.0004)

Conclusion: Inadequate discrimination and calibration; consistent under-prediction of ASCVD risk. Similar findings when ACC/AHA model applied in PARTNERS

Slide 34 of 42

Triant VA, et al. *Circulation* 2018;137(19):2203-14

HIV and Statins

HIGH-QUALITY STATIN TRIAL EVIDENCE (RANDOMIZED CONTROLLED TRIALS) IN THE GENERAL POPULATION:

>220,000 PEOPLE

>1,000,000 PERSON-YEARS

STATIN TRIALS FOR HIV (ON ART):

317 PPTS

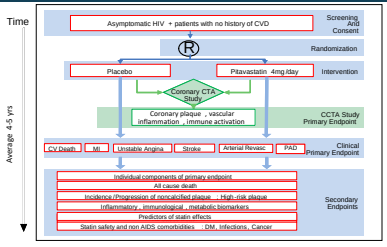
213 PERSON-YRS

NO HARD OUTCOMES

Slide 35 of 42

Feinstein MJ, et al. *Am J Cardiol* 2015;115(2):1760-6.

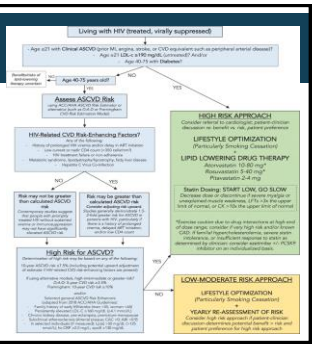
Awaiting RCT Data: REPRIEVE



Slide 36 of 42

Slide courtesy of Steven Grinspoon

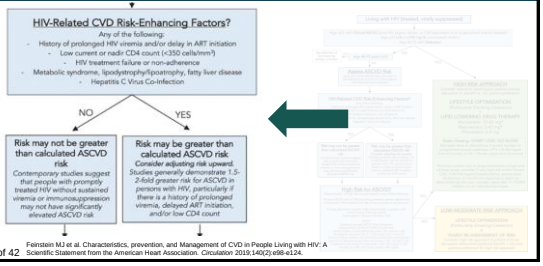
Interim Approach



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.

Slide 37 of 42

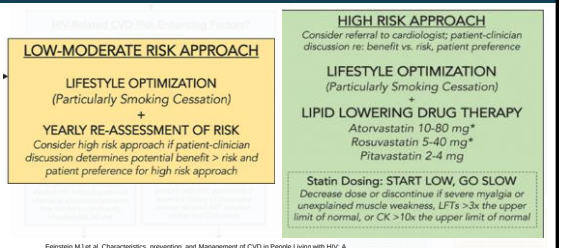
Interim Approach



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.

Slide 38 of 42

Interim Approach



Slide 39 of 42

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.

Role of Aspirin

- ASA did not impact markers of immune activation or endothelial function in HIV in a recent trial
  - Young study population (mean age 48-50), 12 week f/u, endpoint of questionable utility/reproducibility (FMD)
- Therefore, despite pro-thrombotic risk in HIV, no compelling evidence to have different approach than in the general population for CVD prevention
  - **USPSTF:** ASA for age 50-69 if 10%+ 10y ASCVD risk

Slide 40 of 42

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

Heart Failure Prevention and Treatment

- Studies ongoing to understand pathogenesis of heart failure (particularly with preserved ejection fraction) in HIV
- More investigation is needed to determine which screening tests and therapies unique to HIV-related heart failure prevention & treatment will be most useful
- In the meantime, diagnosis/treatment as in general population but with high index of suspicion

Slide 41 of 42

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
- High indices of suspicion are needed to recognize and treat these CVDs in the aging HIV population. More research is needed regarding optimal screening and treatment strategies

Slide 42 of 42

Question-and-Answer Session



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