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Feinberg School of Medicine

HIV and Heart Health

Promoting Health and Preventing Disease

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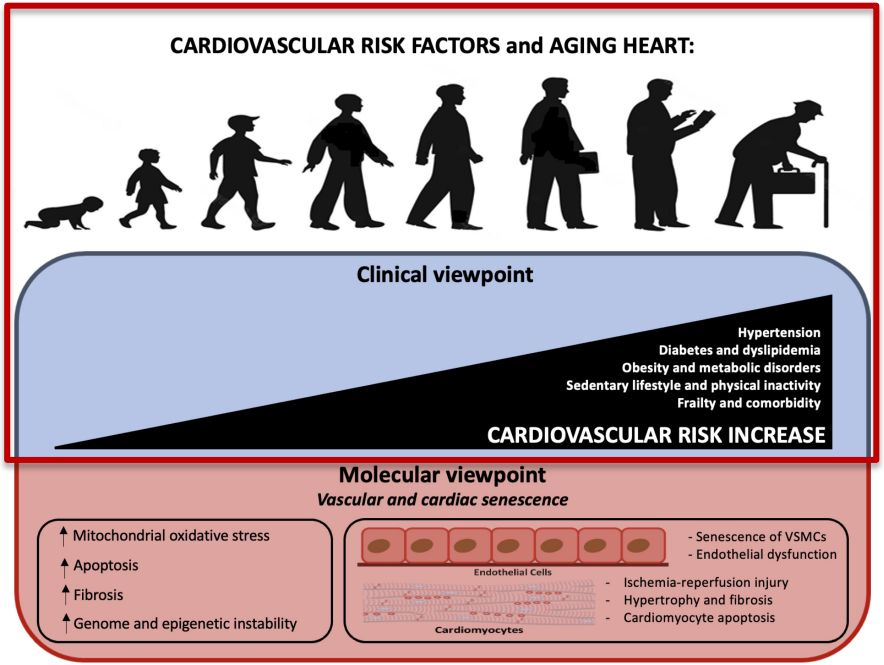
Disclosures

- National Institutes of Health (grant funding), American Heart Association (grant funding), Novo Nordisk (Consultant / advisory board), NewAmsterdam Pharma (Consultant / advisory board), Gilead (Consultant / advisory board)

Outline

- **How does cardiovascular disease manifest in HIV?**
- **What are the upstream factors that dictate cardiovascular health and disease in general, and in HIV?**
  - Framework of HIV, inflammation, and CVDs
  - Contribution of traditional CVD risk factors (e.g., smoking) & ARVs
- **How do we best promote cardiovascular health and prevent disease in general, and in people with HIV?**



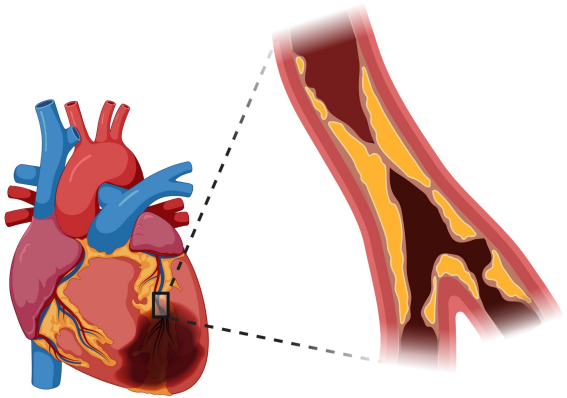
https://doi.org/10.3390/ijms232416033

What do we mean by Cardiovascular Disease?

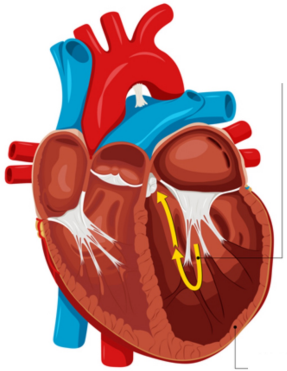
And what are its presentations in HIV?

CVDs: Overview

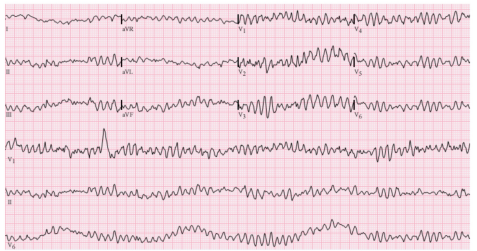
Common, Highly Morbid CVD Outcomes ↑ in HIV



Coronary Artery Disease and Myocardial Infarction (MI)



Heart Failure

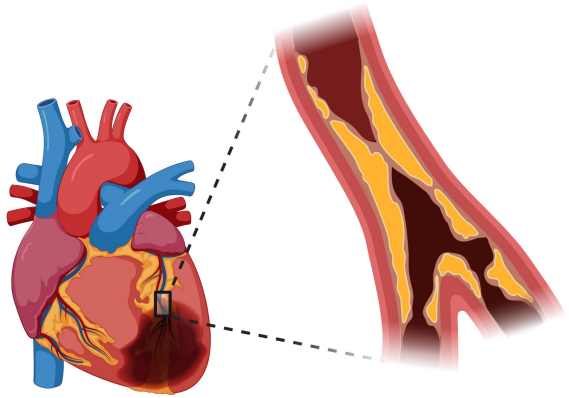


Arrhythmia and Sudden Cardiac Death

(1) Triant V., et al. J Clin Endocrinol Metab 2007;92(7): 2506-12. (2) Freiberg MS, et al. JAMA Intern Med 2013;173:614-622. (3) Paisible AL, et al. J Acquir Immune Defic Syndr 2015;68:209-215

HIV and Athero-Thrombosis

Athero = plaque; thrombosis = clot



Coronary Artery Disease and Myocardial Infarction (MI)

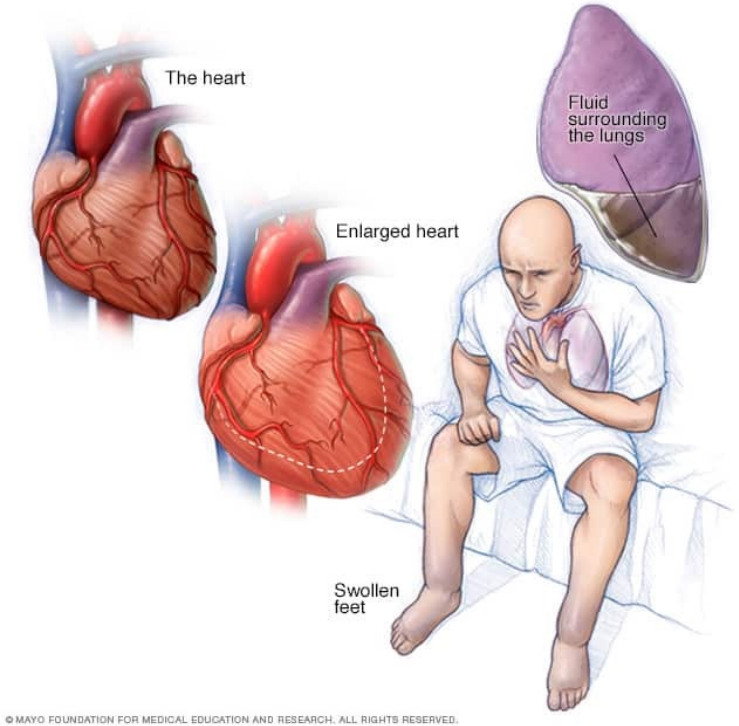
Athero-Thrombosis

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

Key Features include:

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

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

What causes CVDs?

And makes people with HIV at higher risk?

Combination of Traditional Risk Factors and HIV-Specific Ones

Cardiovascular Risk Factors

Modifiable & Non-modifiable

Things you can change

- Blood pressure
- Blood sugar/diabetes
- BMI
- Chronic inflammation
- Diet
- Exercise
- HDL cholesterol
- Smoking
- Stress
- Total cholesterol

Things you can't change

- Age
- Family history of cardiovascular disease
- Previous history of cardiovascular disease

Social factors

- Environment
- Income
- Social isolation

https://my.clevelandclinic.org/health/articles/17085-heart-risk-factor-calculators

HIV and Cardiovascular Risk Factors

"Traditional" Cardiovascular Risk Factors

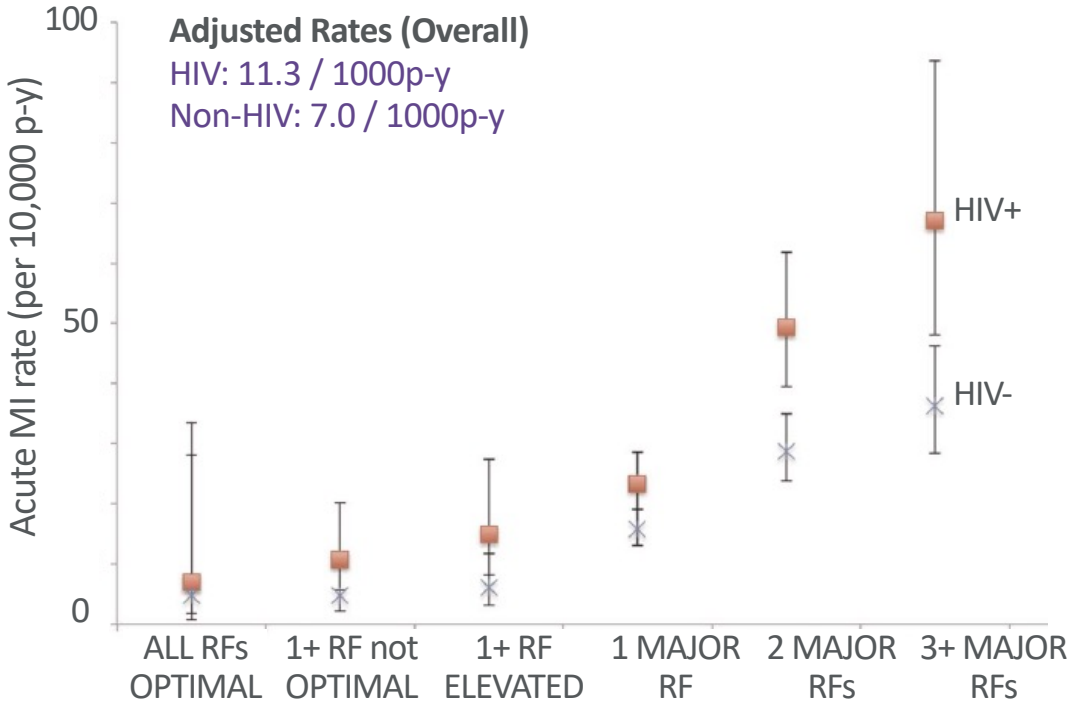
- Smoking: Highly Prevalent
- **Problematic Cholesterol Levels / Dyslipidemia**
  - Due to virus/inflammation: ↑HIV RNA: ↓HDL, stable/↓LDL-c(but some ApoB discordance), ↑TG, ↑TC/HDL ratio
  - ART-related (some)
    - PIs: ↑ TC, LDL, and TG levels
    - NNRTIs: Variable, may ↑ TC, LDL, and TG levels
    - NRTIs: Variable, may ↑ TC and TG levels
    - Fusion inhibitors, CCR5 antagonists, INSTIs: limited data
- Diabetes
- Fat distribution: lipodystrophy / atrophy / hypertrophy

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.

HIV and Cardiovascular Risk Factors

HIV-specific

- Lower CD4, Higher VL → increased risk for MI, HF



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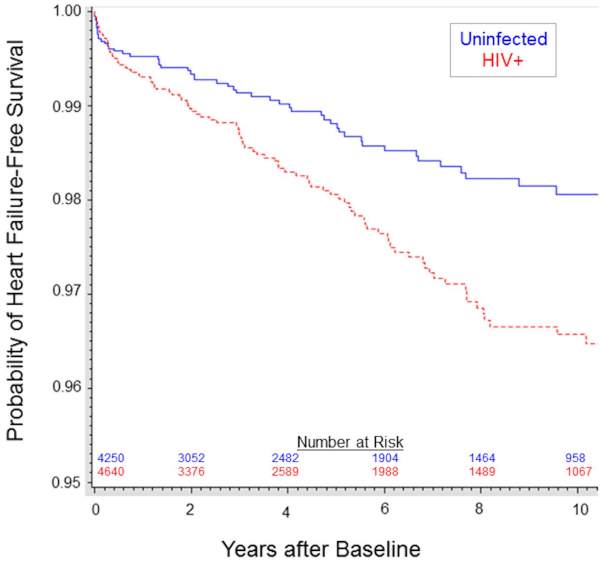

Overall:

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)**

Similar findings, gradients in large VA cohort (VACS)

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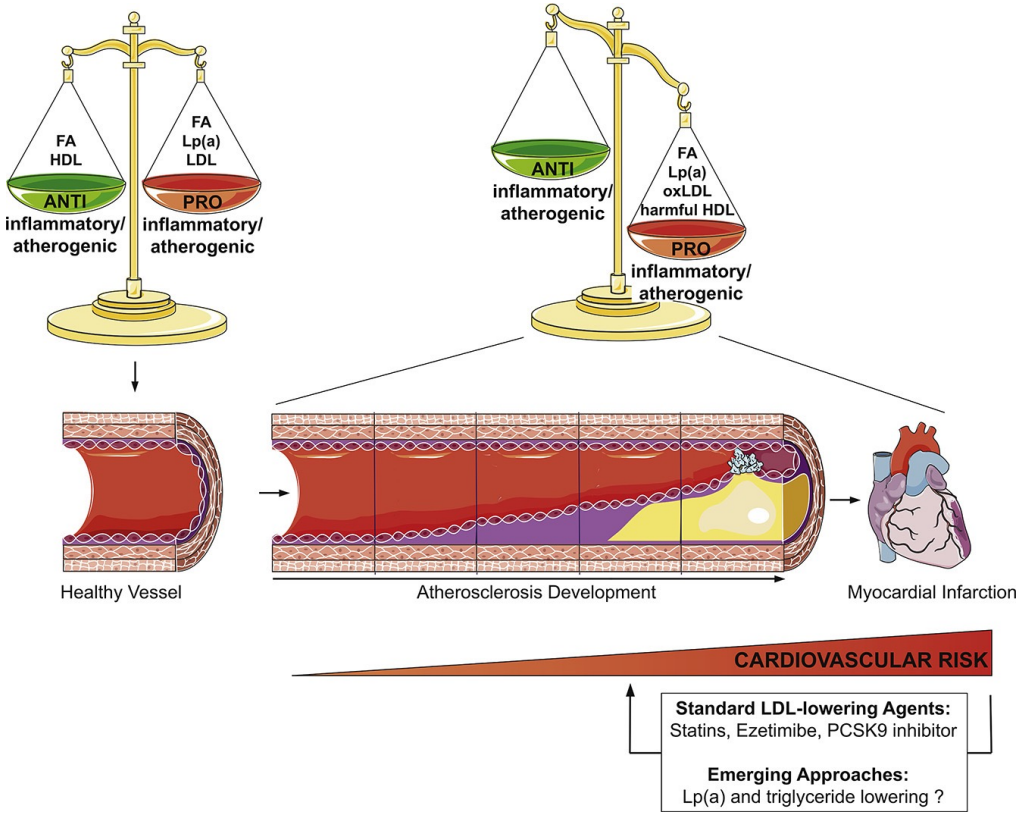
HIV and Cardiovascular Risk Factors

Deeper dive into cholesterol & LDL



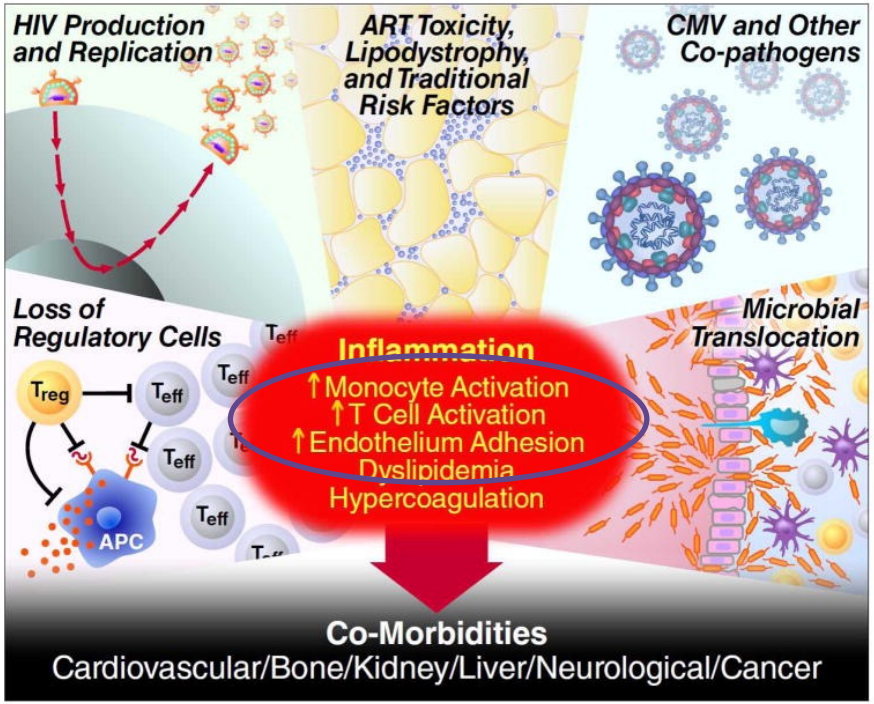
https://doi.org/10.1016/j.addr.2020.07.019

HIV and 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.

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

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

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

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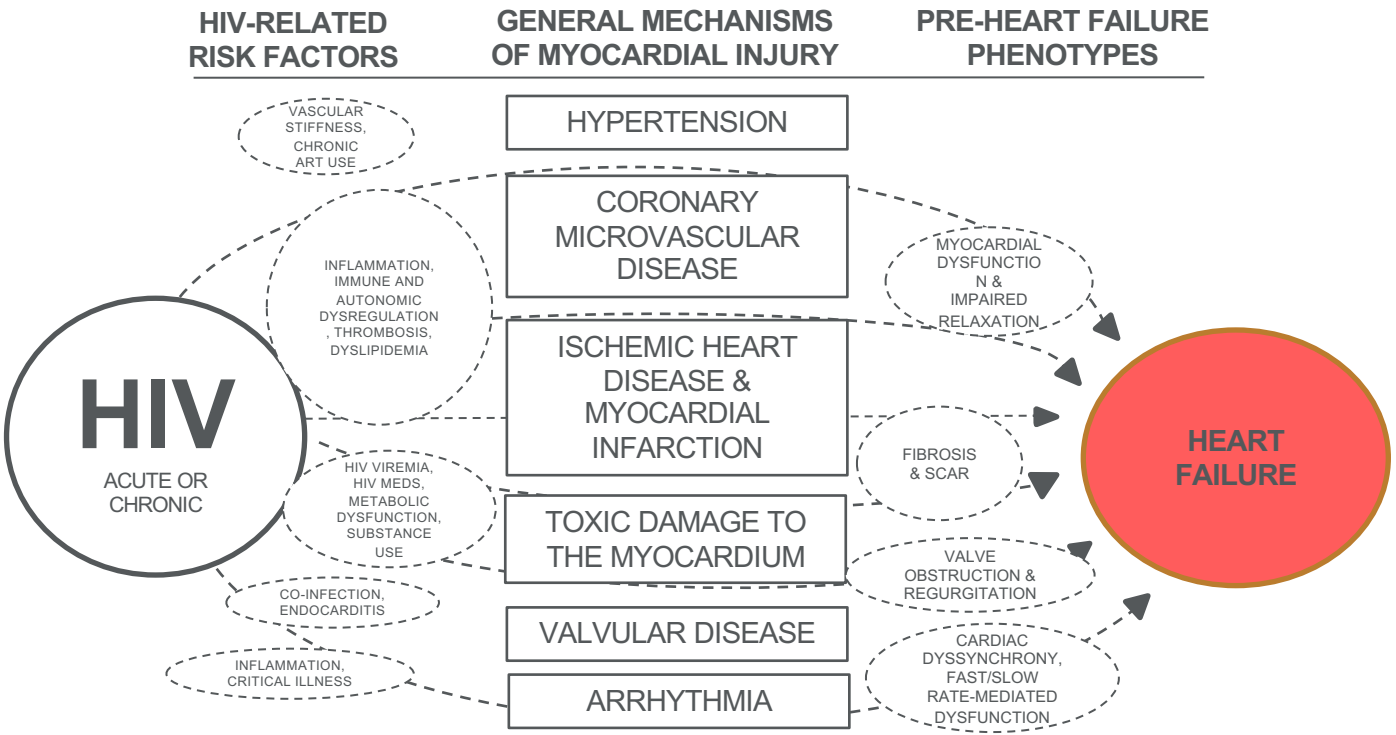
HIV and Heart Failure: Why?

Traditional and non-traditional risk factors



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How do we best promote cardiovascular health and prevent disease in general, and in people with HIV?

ASCVD Prevention: Key Definitions

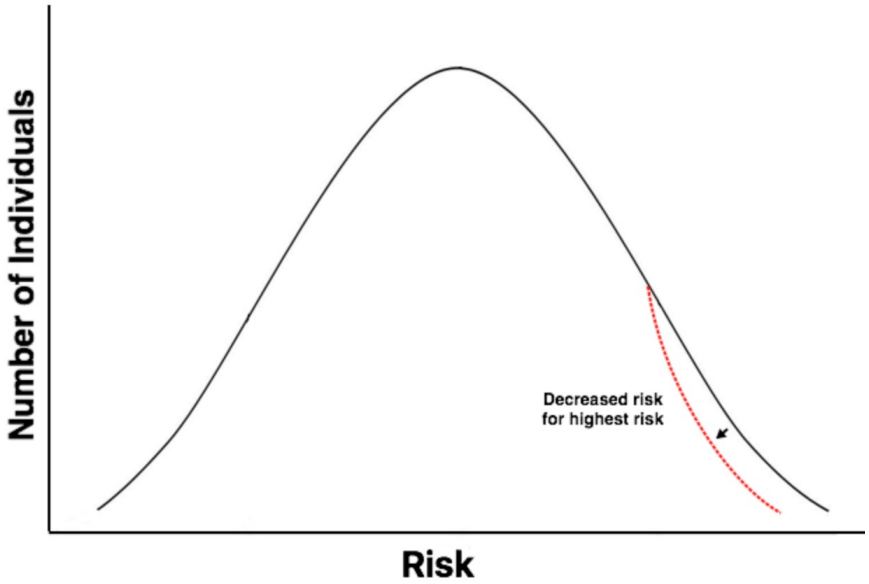
	Definition	Benefit to Individual (ARR)	Benefit to Population (Incidence Rates)
Primordial Prevention	Prevention of the development of RF (Maintenance of CV Health)	++++	++++
Primary Prevention	Treatment of Risk Factors in individuals	+	++
Secondary Prevention	Treatment of Individuals with Disease to Prevent Future Events	++	+

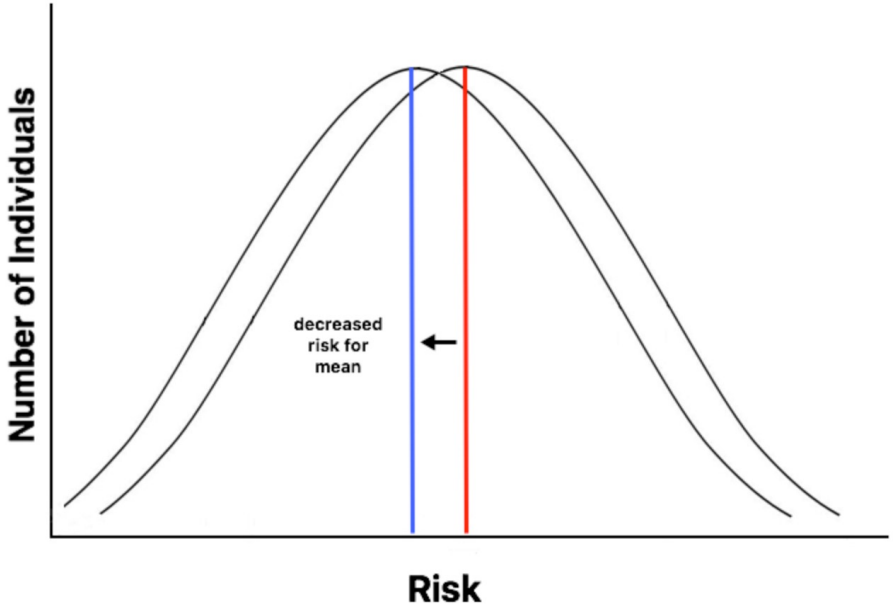
ASCVD Prevention: Approaches

Reduction in SBP mmHg	% Reduction in Mortality Stroke	CHD	Total
2	-6	-4	-3
3	-8	-5	-4
5	-14	-9	-7

Stamler 1991; Whelton 2002

ASCVD Prevention: Approaches





Stamler 1991; Whelton 2002

CVD Risk Assessments – Primary Prevention

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 in HIV

CVD Risk Scores:

Under-predict risk for ASCVD among people with HIV (in most cohorts and with most equations)

Especially women & black individuals

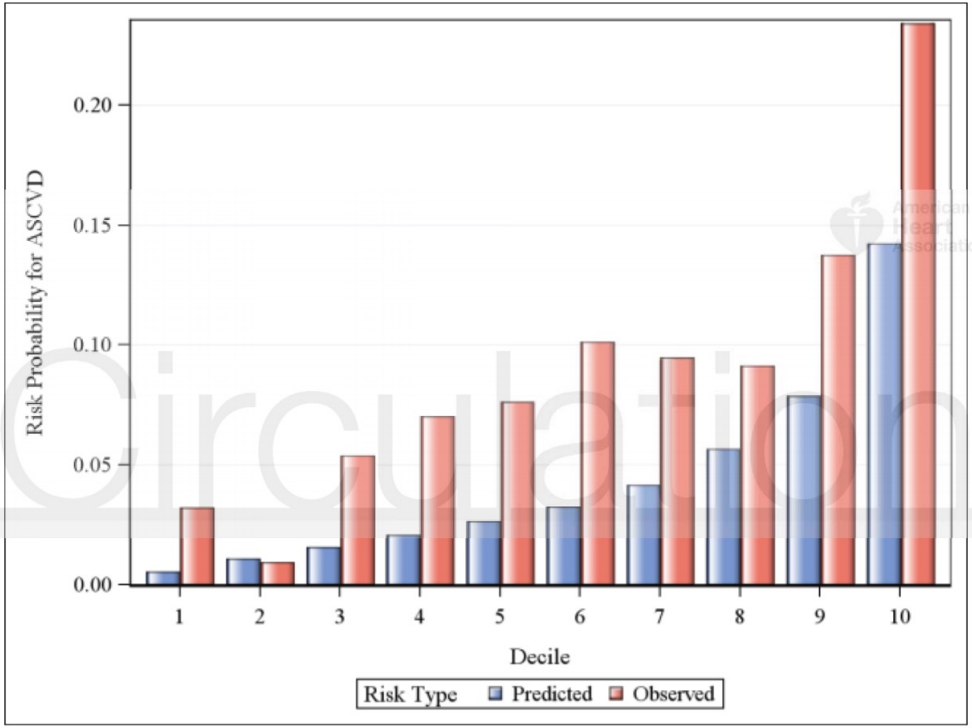


Figure from Triant VA, et al. *Circulation* 2018;137:2203-14

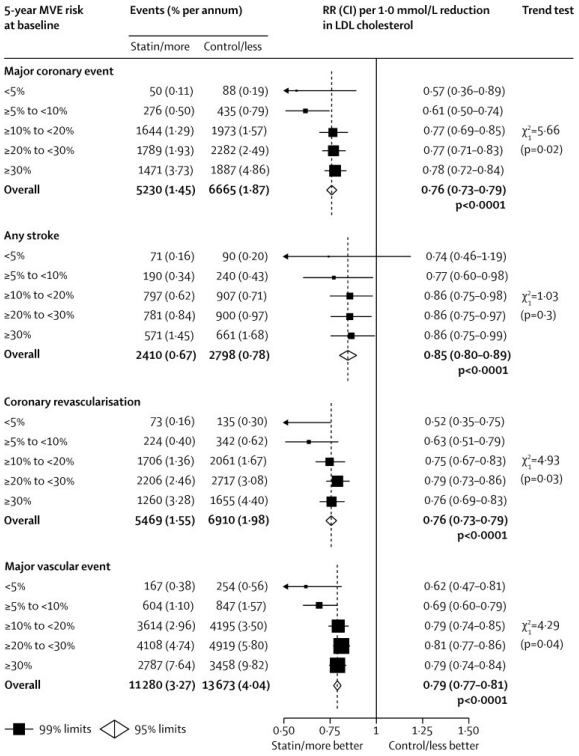
Triant VA, et al. *Circulation* 2018;137:2203-14.
Feinstein MJ, et al. *JAMA Cardiology*. 2017;2:155-162.
Achhra AC, et al. *Curr HIV/AIDS Rep*. 2021;18(4):271-9.

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)



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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 24, 2023 VOL. 389 NO. 8

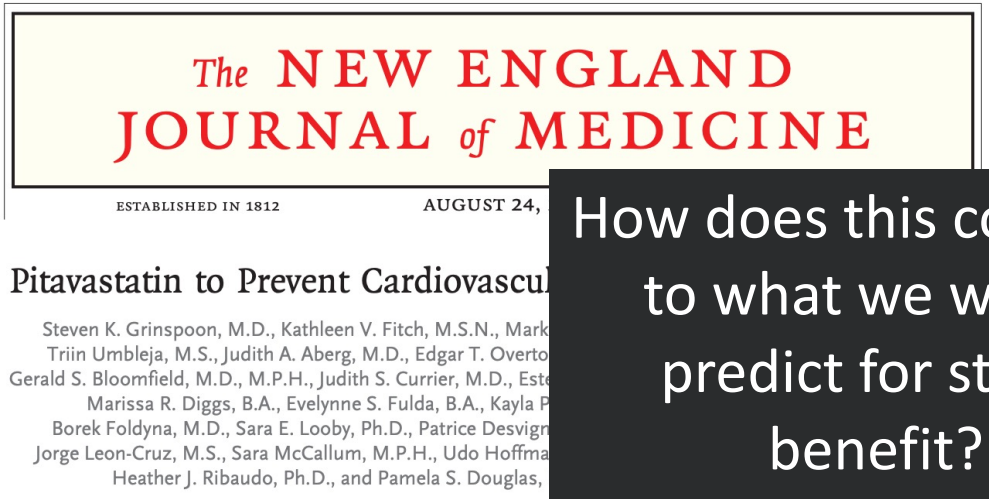
Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaudo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*

N=7769 PWH globally

- 3888 pitavastatin 4 mg vs. 3881 placebo
- Low-moderate predicted ASCVD risk (4.5% 10y risk, IQR 2.1-7.0%)
- LDL-c lowering average 0.86 mmol/L in pitavastatin group
- Median f/u 5.1 years
- MACE: 4.81/1000 person-years (pitavastatin) vs. 7.32/1000 person-years (placebo), HR 0.65

REPRIEVE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ESTABLISHED IN 1812 AUGUST 24,

Pitavastatin to Prevent Cardiovascul

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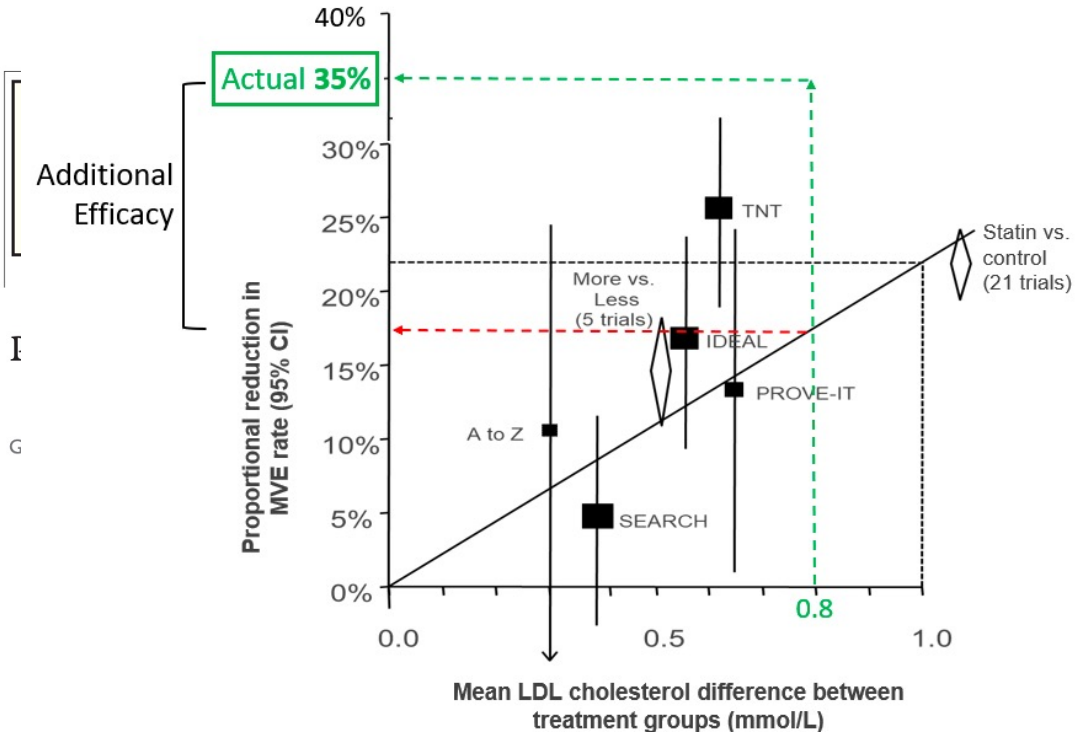
How does this compare to what we would predict for statin benefit?

N=7769 PWH globally
- 3888 pitavastatin 4 mg vs. 3881 placebo
- Low-moderate predicted ASCVD
  5% 10y risk, IQR 2.1-7.0%)
  owering average 0.86
  in pitavastatin group
  f/u 5.1 years
  4.81/1000 person-years
  statin) vs. 7.32/1000 person-years (placebo), HR 0.65

REPRIEVE

How does this compare to what we would predict for statins?



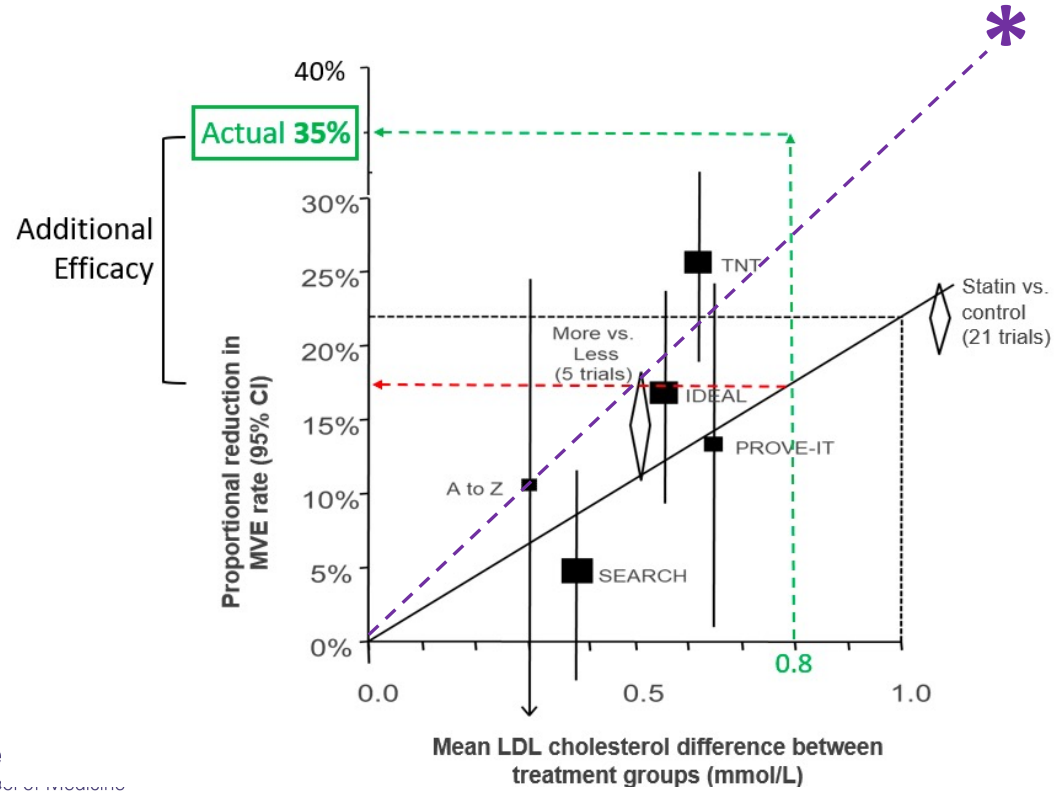
Slide courtesy: Steve Grinspoon

Presented at: CROI 2024

Figure Adapted From: Lancet 2010; 376: 1670-81

REPRIEVE

How does this compare to what we would predict for statins?



Note: Trials included in graph are secondary prevention; many compare high vs. low dose statin

**Jupiter (high CRP, primary prevention): 1.2 mmol/L dec; 44% RRR*

REPRIEVE

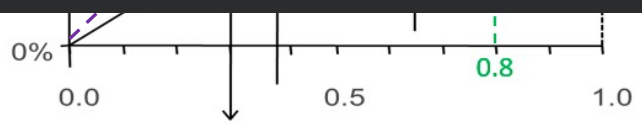
How does this compare to what we would predict for statins?

* Note: Trials included

How might the 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!)

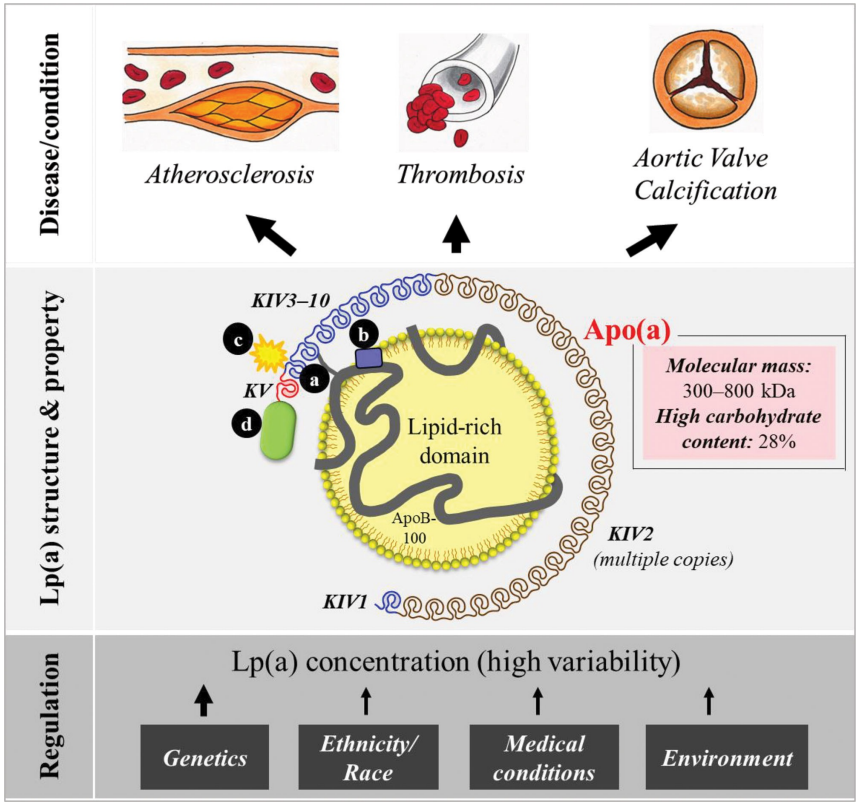
- Somewhat more than anticipated benefit for statins in HIV
- Side effect profile similar as in gen pop
- Lower threshold to initiate / converse with patients re: statins & shared decision-making



What about other lipid mediators of ASCVD?

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

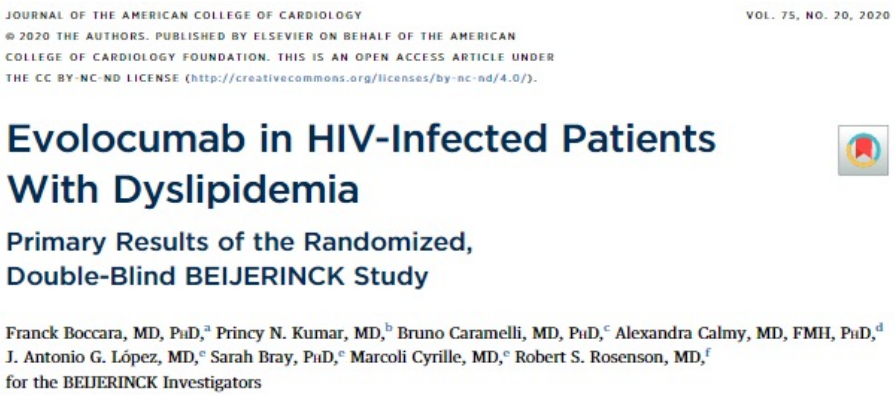
Reyes-Soffer G, et al. Arterioscler Thromb Vasc Bio 2021;42:e48-60.

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, +side effects

- Under investigation: IL-6 antagonism

- General inflammation reduction in HIV: TBD whether benefit>risk with respect to CVDs but also immune function

What do the guidelines say about lipid-lowering therapy?

DHHS 2024 Guidelines – HIV and CVD prevention

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/statin-therapy-people-hiv

Panel's Recommendations

For people with HIV who have low-to-intermediate (<20%) 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimates

- Age 40–75 years
  - When 10-year ASCVD risk estimates are 5% to <20%, the Panel for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (the Panel) recommends initiating at least moderate-intensity statin therapy **(AI).**
    - Recommended options for moderate-intensity statin therapy include the following:
      - Pitavastatin 4 mg once daily **(AI)**
      - Atorvastatin 20 mg once daily **(AII)**
      - Rosuvastatin 10 mg once daily **(AII)**
  - When 10-year ASCVD risk estimates are <5%, the Panel favors initiating at least moderate-intensity statin therapy **(CI).** The absolute benefit from statin therapy is modest in this population; therefore, the decision to initiate a statin should take into account the presence or absence of HIV-related factors that can increase ASCVD risk.[a]
    - Same options for moderate-intensity statin therapy as recommended for 10-year ASCVD risk estimates of 5% to <20% (see above)
- Age <40 years
  - Data are insufficient to recommend for or against statin therapy as primary prevention of ASCVD in people with HIV. In the general population, lifestyle modifications are recommended for people age <40 years, with statin therapy considered only in select populations (see American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Guidelines).

ESC Guidelines 2021

Recommendations	Class
Risk factors and interventions at the individual level	
It is recommended to reduce sedentary time to engage in at least light activity throughout the day to reduce all-cause and CV mortality and morbidity.	I
It is recommended to adopt a Mediterranean or similar diet to lower risk of CVD.	I
It is recommended to restrict alcohol consumption to a maximum of 100 g per week.	I
It is recommended to eat fish, preferably fatty, at least once a week and restrict (processed) meat.	I
Patients with mental disorders need intensified attention and support to improve adherence to lifestyle changes and drug treatment.	I
Smoking cessation is recommended regardless of weight gain, as weight gain does not lessen the ASCVD benefits of cessation.	I

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

ESC Guidelines 2021

Recommendations	Class
Risk factors and interventions at the individual level (continued)	
In patients with established ASCVD, lipid-lowering treatment with an ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction of LDL-C vs. baseline is recommended.	I
For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended.	I
In patients with type 2 DM at very high risk (e.g. with established ASCVD and/or severe TOD), intensive lipid-lowering therapy, ultimately aiming at ≥50% LDL-C reduction and an LDL-C of <1.4 mmol/L (<55 mg/dL) is recommended.	I
In patients with type 2 DM >40 years of age at high risk, lipid-lowering treatment with an ultimate LDL-C goal of ≥50% LDL-C reduction and an LDL-C of <1.8 mmol/L (70 mg/dL) is recommended.	I

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ESC Guidelines 2021

New recommendations (10)

Recommendations	Class
Risk factors and interventions at the individual level (continued)	
An ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and LDL-C reduction of ≥50% from baseline should be considered in apparently healthy persons <70 years at very high risk.	**IIa**
An ultimate LDL-C goal of <1.8 mmol/L (70 mg/dL) and LDL-C reduction of ≥50% from baseline should be considered in apparently healthy persons <70 years at high risk.	**IIa**
For those motivated to try, considerable weight loss with use of low-calorie diets followed by food reintroduction and weight-maintenance phases early after diagnosis can lead to DM remission and should be considered.	**IIa**

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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*?

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?

- What do we *know*?

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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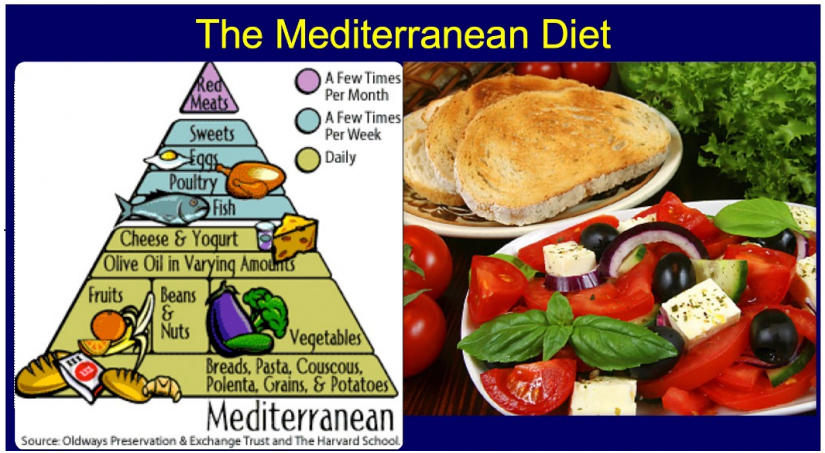
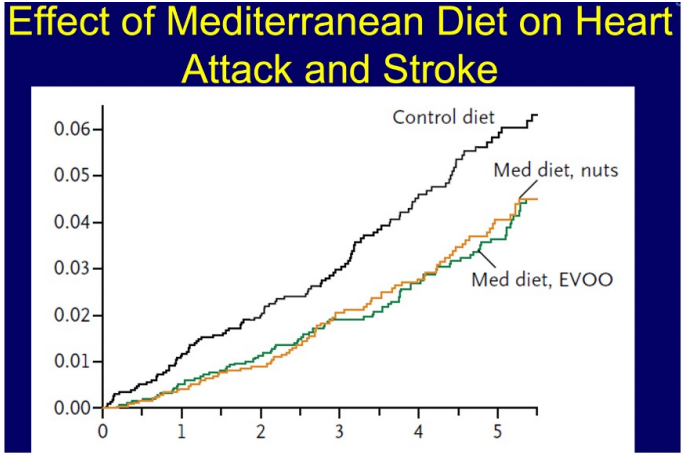
Practical Guidance to CVD Risk Assessment

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

- What do we *know*? A brief Diet interlude





https://www.nature.com/articles/s41387-018-0025-1

Practical Guidance to CVD Risk Assessment

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

- What do we *know*?

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)
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

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

- What do we *know*?
- 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 more in favor of net benefit>risk of statins. In the short-term, limited absolute benefit at low risk / younger individuals, but worth a conversation / shared decision-making)

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
- Relatively recent data demonstrate statins are particularly effective in CVD risk reduction in HIV → Lower threshold to consider ASCVD-preventive statin Rx in HIV
- 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)

Thank You and Discussion

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