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Data from the REPRIEVE trial: implementation in clinical practice

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REPRIEVE

Randomized Trial to Prevent Vascular Events in HIV

Number of Participants	Percentage of Women	Mean Age	Mean Years Living with HIV	Manuscripts Published
7769	32%	50	13	45

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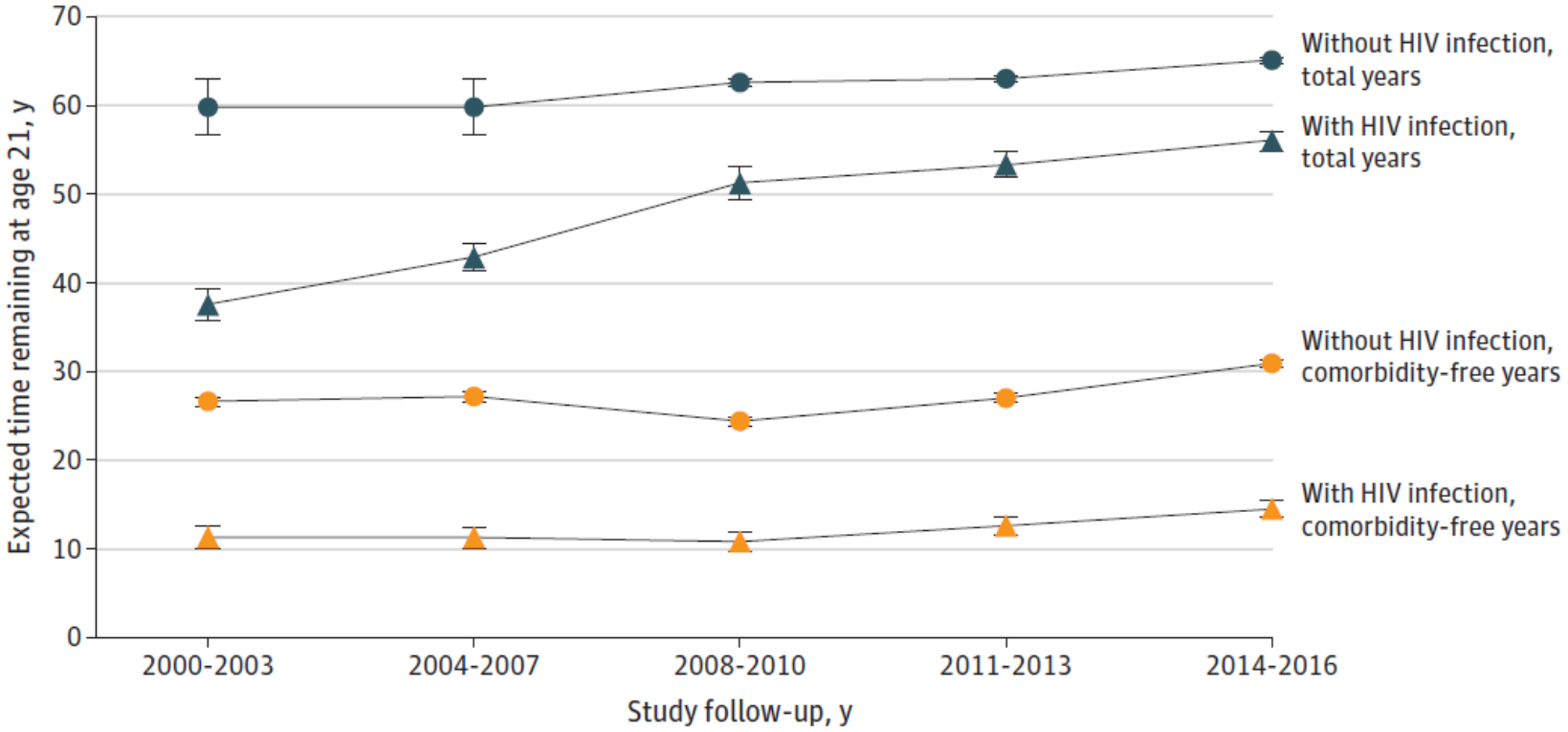
Rationale

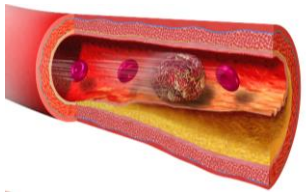


Feinstein et al. Am J Card. 2016

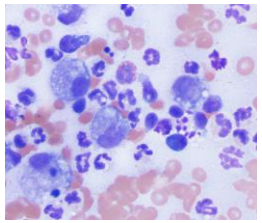
Beyond LDL: Pleiotropic Effects of Statins

- Statins primary effect is to inhibit HMG-CoA reductase to lower LDL cholesterol
- Statins have many other beneficial effects to reduce vascular disease

Anti-inflammatory



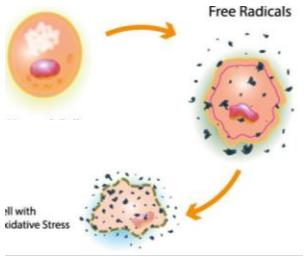
Anti-thrombotic



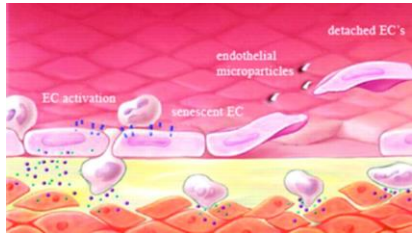
Immunomodulation

STATINS

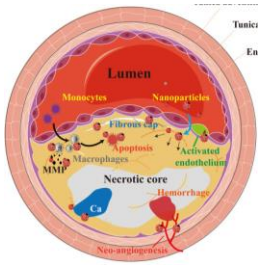
Reduced Oxidative Stress



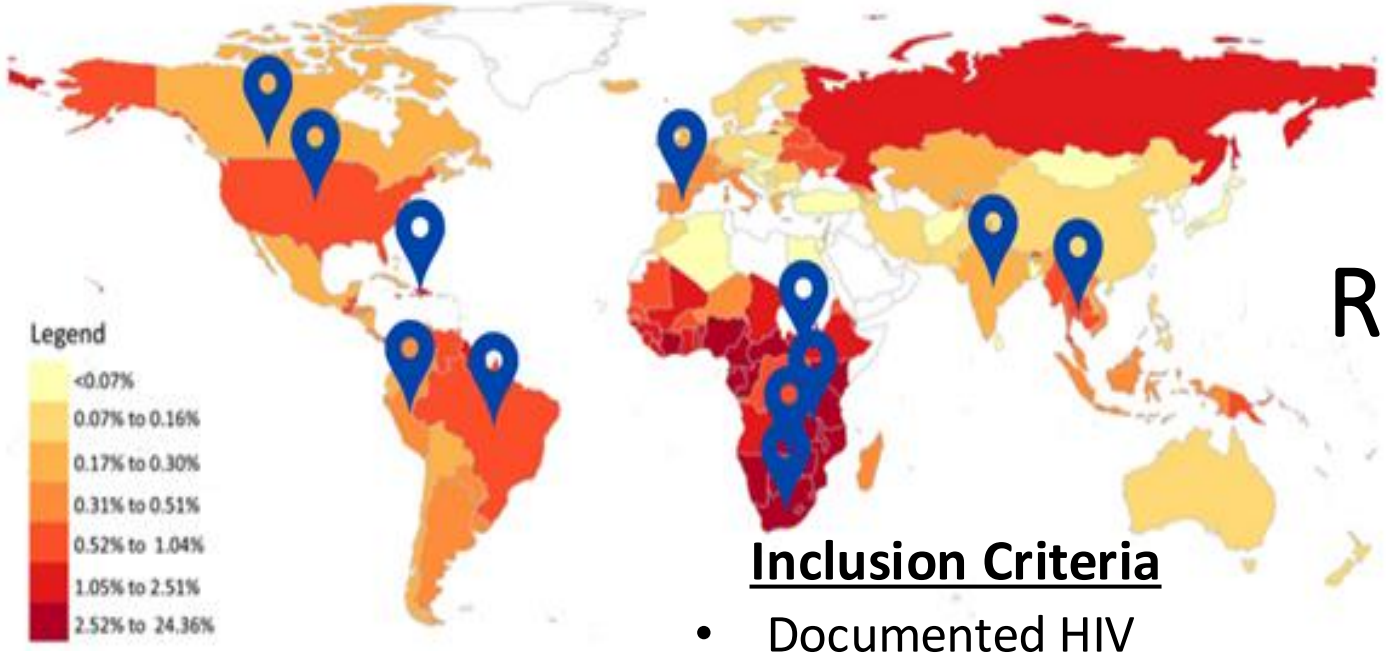
Improved Endothelial Function/Vascular Tone



Plaque Stabilization



German et al. Arch Toxicol. 2023



REPRIEVE Study Population

Inclusion Criteria

- Documented HIV
- Receiving stable ART
- CD4+ > 100 cells/mm3
- Age ≥ 40 years, ≤ 75 years
- No known atherosclerotic cardiovascular disease (ASCVD)
- 10-yr ASCVD risk score
  - <7.5% LDL < 190 mg/dL
  - ≥7.5% and ≤ 10% LDL, < 160 mg/dL
  - >10% and ≤15%, LDL < 130 mg/dL
- Certain laboratory parameters

Exclusion Criteria

- Current use of statins, gemfibrozil, or PCSK9 inhibitors
- Known decompensated cirrhosis

Grinspoon et al. N Engl J Med 2023

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Age This calculator only applies to individuals 40-75 years of age.	Norm: 20 - 79	years
Diabetes	**No**	Yes
Sex	Female	Male
Smoker	**No**	Yes
Total cholesterol	Norm: 150 - 200	mg/dL ⇆
HDL cholesterol	Norm: 0 - 60	mg/dL ⇆
Systolic blood pressure	Norm: 100 - 120	mm Hg
Treatment for hypertension	**No**	Yes
Race Race may/may not provide better estimates of CV risk; optional	White	
	African American	
	Other	

Spectrum of Statin Intensity

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL on average by ≥50%	Daily dose lowers LDL on average by approximately 30-49%	Daily dose lowers LDL on average by <30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

Baseline Characteristics

		Total (N=7769)	Pitavastatin (N=3888)	Placebo (N=3881)
Age (years)	Median (Q1 – Q3)	50 (45-55)	50 (45-55)	50 (45-55)
Natal sex	Male	5350 (69%)	2677 (69%)	2673 (69%)
	Female	2419 (31%)	1211 (31%)	1208 (31%)
Gender identity	Cisgender	7367 (95%)	3687 (95%)	3680 (95%)
	Transgender spectrum	127 (2%)	63 (2%)	64 (2%)
	Not reported	275 (4%)	138 (4%)	137 (4%)
Race	White	2704 (35%)	1634 (35%)	1340 (35%)
	Black/African American	3208 (41%)	1569 (40%)	1639 (42%)
	Asian	1138 (15%)	571 (15%)	567 (15%)
CD4 count (cells/mm3)	Median (Q1 – Q3)	621 (448-827)	620 (449-832)	622 (445-824)
Nadir CD4 count (cells/mm3)	< 50	1409 (18%)	688 (18%)	721 (19%)
	50-199	2392 (31%)	1202 (31%)	1190 (31%)
	≥ 200	3706 (48%)	1859 (49%)	1847 (47%)
HIV RNA (Copies/mL)	< LLQ	5250 (88%)	2641 (88%)	2609 (87%)
	LLQ - < 400	617 (10%)	305 (10%)	312 (10%)
	400+	130 (2%)	63 (2%)	67 (2%)
	Missing	1772	879	893
ASCVD risk score, (%)	Median (Q1 – Q3)	4.5 (2.1-7.0)	4.5 (2.1-7.0)	4.5 (2.2-7.0)
LDL-C (mg/dL)	Median (Q1 – Q3)	108 (87-128)	109 (87-128)	108 (87-127)

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A Estimated Treatment Effect

Subgroup	Pitavastatin (N=3888)	Placebo (N=3881)	Hazard Ratio (95% CI)
	no./1000 person-yr (no. of events)		
Primary outcome and supporting analyses			
First MACE	4.81 (89)	7.32 (136)	0.65 (0.48 to 0.90)
First MACE including vital status follow-up	4.75 (90)	7.22 (137)	0.66 (0.50 to 0.86)
First confirmed MACE	3.83 (71)	5.92 (110)	0.65 (0.48 to 0.87)
First MACE (as-treated analysis)	4.44 (77)	6.25 (107)	0.71 (0.53 to 0.95)
First MACE (per-protocol analysis)	4.54 (80)	6.77 (120)	0.67 (0.50 to 0.89)
Individual components of MACE			
First cardiac ischemia or myocardial infarction	1.40 (26)	2.51 (47)	0.56 (0.34 to 0.90)
First cerebrovascular event (stroke or TIA)	1.56 (29)	2.36 (44)	0.66 (0.41 to 1.05)
First peripheral arterial ischemia	0.11 (2)	0.16 (3)	0.67 (0.11 to 4.02)
Death from cardiovascular causes	0.64 (12)	0.85 (16)	0.75 (0.36 to 1.59)
Death from cardiovascular or undetermined causes	1.60 (30)	2.24 (42)	0.71 (0.45 to 1.14)
First cardiac catheterization or revascularization	0.97 (18)	1.66 (31)	0.59 (0.33 to 1.05)
First carotid or cerebrovascular revascularization	0.00 (0)	0.00 (0)	—
First peripheral arterial revascularization	0.00 (0)	0.32 (6)	0.00 (0.00 to 0.66)

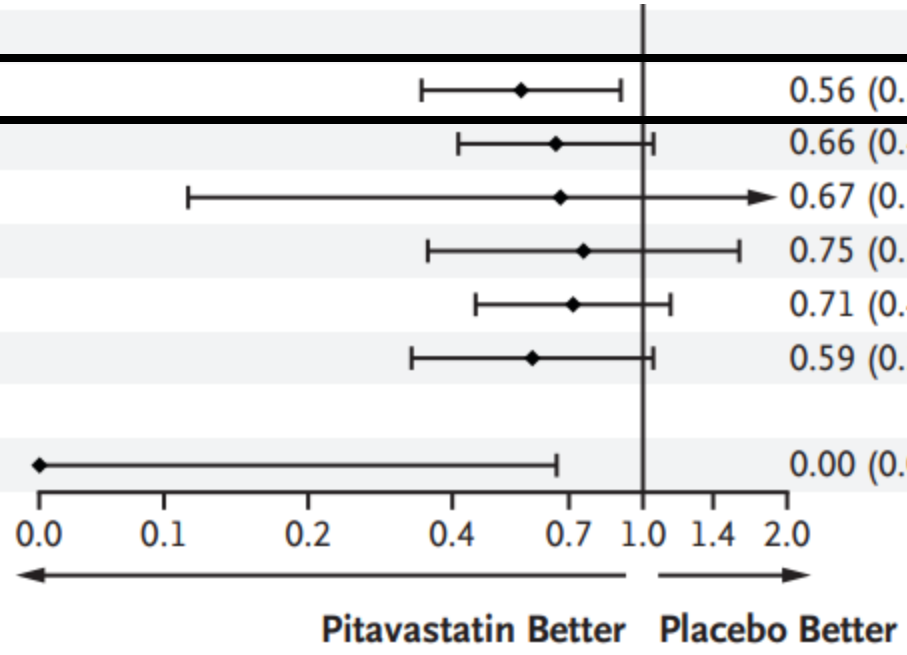

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Table 2. Adverse Events.

Event	Pitavastatin (N = 3888)		Placebo (N = 3881)		Incidence Rate Ratio (95% CI)*
	No. with Event	Incidence Rate (95% CI) *no./100 person-yr*	No. with Event	Incidence Rate (95% CI) *no./100 person-yr*	
Nonfatal serious adverse event	695	4.16 (3.86–4.48)	694	4.13 (3.84–4.45)	1.01 (0.91–1.12)
Diabetes mellitus†	206	1.13 (0.99–1.30)	155	0.84 (0.72–0.99)	1.35 (1.09–1.66)
Myalgia, muscle weakness, or myopathy of grade ≥3 or treatment-limiting‡	91	0.49 (0.40–0.61)	53	0.28 (0.22–0.37)	1.74 (1.24–2.45)
Rhabdomyolysis of grade ≥3 or treatment-limiting	3	0.02 (0.01–0.05)	4	0.02 (0.01–0.06)	0.75 (0.17–3.37)§
Alanine aminotransferase elevation of grade ≥3	11	0.06 (0.03–0.11)	8	0.04 (0.02–0.08)	1.38 (0.56–3.43)§
Any adverse event¶	1304	8.88 (8.41–9.38)	1256	8.37 (7.92–8.84)	1.06 (0.98–1.15)

Grinspoon et al. N Engl J Med 2023

Statin Therapy in People With HIV

Updated: September 12, 2024
Reviewed: September 12, 2024

Recommendations for the Use of Statin Therapy as Primary Prevention of Atherosclerotic Cardiovascular Disease in People With HIV

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).

BHIVA rapid guidance on the use of statins for primary prevention of cardiovascular disease in people living with HIV

- We recommend optimising antiretroviral therapy in people at high risk of CVD in line with BHIVA treatment guidelines (Grade 1C).
- We recommend that all people living with HIV aged 40 years or older should be offered a statin for primary prevention of CVD irrespective of lipid profile or estimated CVD risk (Grade 1B).
- We suggest that people living with HIV aged 40 years or older with an estimated 10-year CVD risk of 5% or greater are prioritised for primary prevention with a statin (GPP).
- We recommend pitavastatin 4 mg daily as the first-line choice for primary prevention when it becomes available in the UK (Grade 2A).
- We suggest that atorvastatin 20 mg daily can be used as an alternative statin (Grade 2B).
- We suggest that people on a low-intensity statin should switch to one of moderate intensity if clinically appropriate and tolerated (GPP).
- For people unable to tolerate a statin, we advise offering an alternative lipid-lowering agent in line with national guidelines (GPP).
- It is best practice for statins for primary prevention to be prescribed and monitored in primary care (GPP).

British HIV Association. March 2024

European AIDS Clinical Society (EACS) Interim Guidance on the Use of Statin Therapy for the Primary Prevention of Cardiovascular Disease in People with HIV

Key Recommendations:

The recommendations below should be combined with discussions on healthy lifestyle measures such as smoking cessation, nutrition, physical activity, weight management and alcohol intake for the prevention of cardiovascular disease (CVD) and other comorbidities [1,2].

We recommend that 10-year CVD risk is estimated annually in people with HIV aged ≥40 years, using the SCORE2 (for people aged 40 – 69 years) or SCORE2-OP (for people aged ≥70 years) tools [2–4].

- When CVD risk estimate is ≥10%:
  - **Statin therapy is indicated** as per the current EACS guidelines [2].
  - Treatment goals for LDL-cholesterol (LDL-c) to reduce CVD risk depend on CVD risk estimation (see page 77, https://www.eacsociety.org/media/guidelines-12.0.pdf) [1,2].
- When CVD risk estimate is 5 to <10%:
  - **We recommend** moderate-intensity statin therapy, options include:
    - Pitavastatin 4mg once daily, where available
    - Atorvastatin 20mg once daily
    - Rosuvastatin 10mg once daily
- When CVD risk estimate is <5%:
  - **Consider** moderate-intensity statin therapy (see options above) if following an evaluation of the risks and benefits, the individual makes an informed decision to proceed.

OBJECTIVE To investigate the effects of pitavastatin on noncalcified coronary artery plaque by coronary computed tomography angiography (CTA) and on inflammatory biomarkers as potential mechanisms for MACE prevention.

DESIGN, SETTING, AND PARTICIPANTS This double-blind, placebo-controlled randomized clinical trial enrolled participants from April 2015 to February 2018 at 31 US clinical research sites. PWH without known CVD who were taking antiretroviral therapy and had low to moderate 10-year CVD risk were included. Data were analyzed from April to November 2023.

INTERVENTION Oral pitavastatin calcium, 4 mg per day.

MAIN OUTCOMES AND MEASURES Coronary CTA and inflammatory biomarkers at baseline and 24 months. The primary outcomes were change in noncalcified coronary plaque volume and progression of noncalcified plaque.

RESULTS Of 804 enrolled persons, 774 had at least 1 evaluable CTA. Plaque changes were assessed in 611 who completed both CT scans. Of 611 analyzed participants, 513 (84.0%) were male, the mean (SD) age was 51 (6) years, and the median (IQR) 10-year CVD risk was 4.5% (2.6-7.0). A total of 302 were included in the pitavastatin arm and 309 in the placebo arm. The mean noncalcified plaque volume decreased with pitavastatin compared with placebo (mean [SD] change, −1.7 [25.2] mm^3 vs 2.6 [27.1] mm^3; baseline adjusted difference, −4.3 mm^3; 95% CI, −8.6 to −0.1; $P = .04$; 7% [95% CI, 1-12] greater reduction relative to placebo). A larger effect size was seen among the subgroup with plaque at baseline (−8.8 mm^3 [95% CI, −17.9 to 0.4]). Progression of noncalcified plaque was 33% less likely with pitavastatin compared with placebo (relative risk, 0.67; 95% CI, 0.52-0.88; $P = .003$). Compared with placebo, the mean low-density lipoprotein cholesterol decreased with pitavastatin (mean change: pitavastatin, −28.5 mg/dL; 95% CI, −31.9 to −25.1; placebo, −0.8; 95% CI, −3.8 to 2.2). The pitavastatin arm had a reduction in both oxidized low-density lipoprotein (−29% [95% CI, −32 to −26] vs −13% [95% CI, −17 to −9]; $P < .001$) and lipoprotein-associated phospholipase A2 (−7% [95% CI, −11 to −4] vs 14% [95% CI, 10-18]; $P < .001$) compared with placebo at 24 months.

CONCLUSIONS AND RELEVANCE In PWH at low to moderate CVD risk, 24 months of pitavastatin reduced noncalcified plaque volume and progression as well as markers of lipid oxidation and arterial inflammation. These changes may contribute to the observed MACE reduction in REPRIEVE.

JAMA Cardiology | Original Investigation

Effects of Pitavastatin on Coronary Artery Disease and Inflammatory Biomarkers in HIV

Mechanistic Substudy of the REPRIEVE Randomized Clinical Trial

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Effects of Pitavastatin on COVID-19 Incidence and Seriousness Among a Global Cohort of People With HIV

Background. Among people with HIV (PWH), COVID-19 is common and potentially severe. We leveraged REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) to assess the effects of statin therapy for cardiovascular disease prevention on COVID-19 outcomes (incidence and serious cases) among a global cohort of PWH.

Methods. COVID-19 data collection was implemented April 2020 to capture events from January 2020. COVID-19 was defined by positive test result or clinical diagnosis and serious COVID-19 according to the International Conference on Harmonisation definition. Among participants in follow-up on 1 January 2020, Cox proportional hazards modeling was used to estimate the hazard ratio (HR) of COVID-19 (pitavastatin/placebo), stratified by Global Burden of Disease region. Modification of statin effect following COVID-19 vaccination was evaluated via interaction with time-updated vaccination status.

Results. Among 6905 PWH, 32% were natal female and 41% were Black or African American. The median age was 53 years and the 10-year atherosclerotic cardiovascular disease risk score 4.5%. Statin therapy did not reduce COVID-19 incidence (HR, 1.05; 95% CI, .95–1.15) but appeared to reduce incidence of serious COVID-19 (HR, 0.75; 95% CI, .52–1.09). Among 1701 PWH with COVID-19, the relative risk (pitavastatin/placebo) for serious COVID-19 was 0.73 (95% CI, .52–1.03). The treatment effect size for serious COVID-19 fell within the hypothesized range, but the 95% CI crossed 1 given fewer-than-anticipated cases (117 vs 200). Furthermore, 83% reported COVID-19 vaccination by end of study, with a strong protective effect on serious COVID-19 (HR, 0.27; 95% CI, .14–.53; $P < .0001$). A protective statin effect was observed prior to vaccination.

Conclusions. Among PWH, statin therapy had no effect on COVID-19 incidence but showed potential to reduce risk of serious COVID-19 prior to COVID-19 vaccination.

Zanni et al. Open Forum Infect Dis. 2024

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Association of Cardiac Troponin T With Coronary Atherosclerosis in Asymptomatic Primary Prevention People With HIV

ABSTRACT

BACKGROUND Coronary plaque is common among people with HIV (PWH) with low-to-moderate traditional atherosclerotic cardiovascular disease (ASCVD) risk.

OBJECTIVES The purpose of this study was to determine the association of high-sensitivity cardiac troponin T (hs-cTnT) levels with coronary plaque characteristics and evaluate if hs-cTnT improves identification of these features beyond traditional ASCVD risk factors among PWH.

METHODS Among PWH receiving stable antiretroviral therapy with low-to-moderate ASCVD risk and no known history of ASCVD, hs-cTnT levels and measures of plaque by coronary computed tomography angiography were assessed. Primary outcomes included the association of hs-cTnT level with the presence of any plaque, vulnerable plaque, coronary artery calcium (CAC) score, and Leaman score. Assessment of model discrimination of hs-cTnT for plaque characteristics was also performed.

RESULTS The cohort included 708 U.S. participants with a mean age of 51 ± 6 years, 119 (17%) females, a median ASCVD risk score of 4.4% (Q1-Q3: 2.5%-6.6%), and a median hs-cTnT level of 6.7 ng/L (detectable level ≥6 ng/L in 61%). Any plaque was present in 341 (48%), vulnerable plaque in 155 (22%), CAC>100 in 68 (10%), and a Leaman score >5 in 105 (15%). After adjustment for ASCVD risk score, participants with hs-cTnT >9.6 ng/L (highest category) versus an undetectable level (<6 ng/L) had a greater relative risk for any plaque (1.37, 95% CI: 1.12-1.67), vulnerable plaque (1.47, 95% CI: 1.16-1.87), CAC>100 (2.58, 95% CI: 1.37-4.83), and Leaman score >5 (2.13, 95% CI: 1.32-3.46). The addition of hs-cTnT level modestly improved the discrimination of ASCVD risk score to identify critical plaque features.

CONCLUSIONS In PWH without known ASCVD, hs-cTnT levels were strongly associated with and improved prediction of subclinical coronary plaque. (Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults [REPRIEVE]; NCT02344290) (JACC Adv. 2024;3:101206)

deFilippi et al. JACC Adv. 2024

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Cytomegalovirus IgG is Associated With Physical Function But Not Muscle Density in People With HIV

Abstract

Background: Cytomegalovirus (CMV) seropositivity is associated with poor outcomes, including physical function impairment, in people without HIV. We examined associations between CMV IgG titer and physical function in virologically suppressed people with HIV (PWH).

Methods: REPRIEVE is a double-blind randomized trial evaluating pitavastatin for primary prevention of atherosclerotic cardiovascular disease in PWH. This analysis focused on participants enrolled in a substudy with additional biomarker testing, imaging [coronary CT angiography], and physical function measures at entry. CMV IgG was measured using quantitative enzyme immunoassay, physical function by Short Physical Performance Battery, and muscle density and area by CT. Associations between CMV IgG (risk factor) and outcomes were evaluated using the partial Spearman correlation and linear and log-binomial regression.

Results: Among 717 participants, 82% male, the median CMV IgG was 2716 (Q1, Q3: 807, 6672) IU/mL, all above the limit of quantification. Among 631 participants with imaging, there was no association between CMV IgG and CT-based muscle density or area, controlling for age ($r = -0.03$ and $r = -0.01$, respectively; $P \geq 0.38$). Among 161 participants with physical function data, higher CMV IgG was associated with poorer overall modified Short Physical Performance Battery score ($P = 0.02$), adjusted for age, nadir CD4, and high-sensitivity C-reactive protein.

Conclusions: Higher CMV IgG titer was associated with poorer physical function, not explained by previous immune compromise, inflammation, or muscle density or area. Further mechanistic studies are needed to understand this association and whether CMV-specific therapy can affect physical function in PWH.

Abidi et al. J Acquir Immune Defic Syndr. 2024

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Ideal cardiovascular health, biomarkers, and coronary artery disease in persons with HIV

Objective: To investigate relationships between Life's Simple 7 (LS7), an assessment of cardiovascular health (CVH), and coronary plaque among people with HIV (PWH).

Design: Cross-sectional.

Methods: Coronary computed tomography angiography, immune/inflammatory biomarkers, and characterization of LS7 were collected among a subset of ART-treated PWH enrolled in REPRIEVE, a primary prevention trial. Analyses adjusted for cardiovascular disease risk (ASCVD score).

Results: Median age of the 735 participants was 51(±6) years, 16% female, and median (Q1–Q3) CVD risk was 4.5% (2.6–6.9). Forty percent had poor (≤2 ideal components), 51% had intermediate (three or four ideal components), and only 9% had ideal CVH (≥5). Coronary plaque was present in 357 (49%); 167 (23%) had one or more vulnerable plaque features, 293 (40%) had noncalcified plaque, and 242 (35%) had a coronary artery calcium score >0. All three phenotypes were increasingly more prevalent with poorer CVH and these relationships remained after adjusting for ASCVD risk. Poor CVH was associated with higher high-sensitivity C-reactive protein, oxidized low-density cholesterol, and interleukin-6. The relationship of LS7 to plaque remained after adjusting for these biomarkers.

Conclusions: Among PWH, poor CVH as measured by LS7 was associated with coronary plaque presence, vulnerable features, and calcification. LS7 was also associated with selected biomarkers; adjustment for these and ASCVD score reduced but did not eliminate LS7's association with plaque, suggesting the possibility of additional protective mechanisms against atherogenesis and plaque remodeling.

Douglas et al. AIDS. 2023

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Thank you for your attention!