

**PRIORITY UPDATES FROM THE RESEARCH LITERATURE (PURLs)**

# Pitavastatin Reduces Major Atherosclerotic Cardiovascular Events in Adults with HIV

*Kathryn K. Garner, MD, FAAFP, Chris Colvin, DO, CAQSM, and Brock Cardon, MD, FAAFP*

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**Initiation of pitavastatin in adults aged 40 to 75 living with HIV treated with highly active antiretroviral therapy (HAART) with low-to-moderate 10-year atherosclerotic cardiovascular disease (ASCVD) risk decreases the incidence of major cardiovascular events (MACE). (J Am Board Fam Med 2025;38:586–588.)**

**Keywords:** HIV, Hyperlipidemia, Statin

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## Strength of Recommendation B:

Based on randomized controlled trial with patient-oriented outcomes.<sup>1</sup>

## Illustrative Case

A 48-year-old White male with history of hypertension and HIV presents for his annual visit. He has been on a stable dose of Highly Active Antiretroviral Therapy (HAART) medications for the last year. His current CD4 count is 650 cells/mm<sup>3</sup> and a recent lipid panel revealed a total cholesterol of 195 mg/dL, HDL 39 mg/dL, and LDL 109 mg/dL. His blood pressure today is 130/81 mmHg. The rest of his labs were found to be unremarkable. His atherosclerotic cardiovascular disease (ASCVD) 10-year risk is calculated to be 4.3%. He has been compliant with his HAART therapy and will be continuing these

medications. Though his calculated ASCVD risk is low, should you also consider starting a statin?

## Clinical Context

With the advent of effective treatment for HIV and subsequent decrease in mortality related to infectious complications, new concerns have arisen regarding the effects of long-term HIV infection and HAART therapy on traditional cardiovascular risk factors. It is estimated that up to 1 in 5 patients living with HIV today is at moderate to high risk of ASCVD and are twice as likely as patients without HIV to suffer a cardiovascular event.<sup>2</sup> HAART itself seems to be an independent risk factor for dyslipidemia and myocardial infarction, with evidence suggesting a dose dependent relationship between HAART and cardiovascular events.<sup>3,4</sup> Typically, HAART includes 3 to 4 antiretroviral medications, all which carry hepatic and metabolic risks, including hypercholesterolemia.<sup>5</sup> Protease inhibitors within these combination therapies can lead to a metabolic syndrome characterized by changes in body fat distribution, hyperlipidemia, and insulin resistance.<sup>6</sup> Most notably, within the lipid profile, the very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL) are affected and can lead to serious cardiovascular outcomes.<sup>6</sup>

In the 2018 American Heart Association/American College of Cardiology (AHA/ACC) Guideline on the Management of Blood Cholesterol, it is a Level IIa

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From the Nellis Air Force Base Family Medicine Residency, Nellis AFB, NV (KKG, CC, BC).

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Editor: Brown Carina, MD Cone Health Family Medicine Residency, Greensboro, NC, [carina.brown@conehealth.com](mailto:carina.brown@conehealth.com).

Corresponding author: Brock Cardon, MD, FAAFP, Nellis Air Force Base Family Medicine Residency, Nellis AFB, NV, 1400 S Potomac Street, Aurora, CO 80012 (E-mail: [bcardon@cornerstone-fp.com](mailto:bcardon@cornerstone-fp.com)).

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recommendation to start moderate to high intensity statins for patients 40 to 75 years of age with HIV who have a 10-year ASCVD risk of 7.5% or higher, and LDL-C 70 to 189 mg/dL.<sup>7</sup> The 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular disease states that clinicians use risk-enhancing factors, of which HIV is one, to guide decisions about preventive interventions (like statins) for adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (>7.5% to <20% 10-year ASCVD).<sup>8</sup> Additional risk-enhancing factors include family history of premature ASCVD, chronic inflammatory disease, south Asian ancestry, chronic kidney disease, and metabolic syndrome.<sup>8</sup>

Given the increased risk of cardiovascular events in patients living with HIV on HAART, this trial aimed to determine if starting a statin in patients aged 40 to 75 living with HIV on HAART was beneficial in lowering the risk of adverse cardiovascular events.

## Methods

This article was identified as a potential PURL through the standard systematic methodology. An additional literature search was conducted by searching Up To Date and DynaMed with the terms “HIV,” “statin,” and “dyslipidemia” to find additional literature to place this research into the context of current clinical practice.

## Study Summary

This phase III randomized controlled trial sought to determine if 4 mg of pitavastatin once daily ( $n = 3888$ ) reduced MACE in patients living with well-controlled HIV and low-to-moderate ASCVD risk compared with placebo ( $n = 3881$ ). Participants were 40 to 75 years old living with HIV treated with a stable anti-retroviral regimen. Researchers only included patients with CD4+ cell counts greater than 100 cells/mm<sup>3</sup>, hemoglobin greater than 8 g/dL (women) or 9 g/dL (men), fasting triglycerides less than 500 mg/dL and no significant renal or hepatic disease. Patients were excluded with a history of statin use within the previous 90 days or known atherosclerotic disease.

Participants had a mean age of 50, 65% identified as non-White, and 31% identified as women. The median starting was LDL of 108 mg/dL, CD4+ cell count of 621 cells/mm<sup>3</sup>, and 10-year ASCVD risk of 4.5% (interquartile 2.1 to 7.0%),

with all included participants carrying a 10-year risk of less than 10%. Ten-year ASCVD risk was categorized according to the AHA/ACC 2013 Pooled Cohort risk calculator as low (<5%), borderline (5 to <7.5%), intermediate (7.5 to <20%) or high (>20%). The primary outcome of the study was time to first MACE which included death from a cardiovascular cause, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization of a coronary, carotid, or peripheral artery, or death from an undetermined cause. Secondary outcomes included a composite of MACE or death from any cause, changes in LDL or HDL levels, development of diabetes, grade 3 or 4 liver injury, and incidence of myalgias and myopathy. The median duration of follow-up was 5.1 years. Most participants remained until completion of the study (83%), and each year greater than 80% of participants in both arms said they had very good or excellent adherence to daily treatment.

The rate of the primary outcome was 4.81/1,000 person-years in the pitavastatin group as compared with 7.32/1,000 person-years in the placebo arm (hazard ratio [HR] 0.65; 95% CI, 0.48 to 0.90;  $P = .002$ ; 5-year number needed to treat [NNT] 106). Due to a sizable reduction in the risk of MACE in the pitavastatin group, this study was discontinued early. The incidence of the composite of major cardiovascular events or death from any cause was 9.18/1000 person years in the pitavastatin arm and 11.63/1000 person years in the placebo arm (HR 0.79; 95% CI, 0.65 to 0.96). Median fasting LDL levels after 12 months were 77 mg/dL (95% CI, 76 to 78) in the pitavastatin group and 106 mg/dL (95% CI, 105 to 107) in the placebo group.

As for adverse effects of pitavastatin, the incident rate ratio for development of diabetes while taking pitavastatin was 1.35 (95% CI, 1.09 to 1.66). Pitavastatin receiving participants also reported a higher frequency of myalgias and myopathy compared with placebo (incident rate ratio 1.74; 95% CI, 1.24 to 2.45), but few participants left the study as a result (1.1% vs 0.5%, respectively).

## What Is New

In middle-aged patients living with well-controlled HIV, starting pitavastatin 4 mg daily for low-to-moderate ASCVD risk results in a significant reduction in MACE with a 5-year NNT of 106.

## Caveats

Like the general population, clinicians should weigh the slightly increased risk of diabetes when discussing statin initiation in patients living with HIV. Though reductions in ASCVD risk with other statins are hypothesized, this trial is only specific to pitavastatin and head-to-head trials of statin use in patients living with HIV are lacking. Lastly, the early discontinuation of this trial limits assessment of adverse effects.

## Challenges to Implementation

As current guidelines do not stress HIV infection or HAART therapy as independent risk factors for ASCVD, many physicians may be unaware of the cardiovascular risks of HIV infection and the potential benefits of earlier statin initiation in infected patients. Outside of increasing clinician knowledge, the wide availability and affordability of statins provide few barriers to broader use in patients living with HIV.

To see this article online, please go to: <http://jabfm.org/content/38/3/586.full>.

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