REVIEW ARTICLE

Statin Therapy for Cardiovascular Disease Prevention in People Living with Human Immunodeficiency Virus: A Systematic Review of Efficacy, Safety, and Clinical Challenges

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Abstract

Background: Advances in antiretroviral therapy (ART) have prolonged survival among people living with human immunodeficiency virus (PLWH), but shifted morbidity toward non-communicable diseases, particularly cardiovascular disease (CVD), with PLWH experiencing a twofold higher myocardial infarction risk and increased heart failure and sudden death risk. This systematic review aimed to provide a comprehensive overview of the epidemiology, pathophysiology, and management of CVD in PLWH, with a particular focus on statin therapy. **Methods:** In April 2024, MEDLINE/PubMed, Scopus, Google Scholar, ClinicalTrials.gov, and CENTRAL were searched for peer-reviewed randomized clinical trials and observational studies in adults (≥18 years) comparing statins with placebo or non-statin lipid-lowering therapy and reporting cardiovascular events, lipid outcomes, adverse events, and ART interactions; two reviewers independently screened, extracted data, and narratively synthesized the findings. **Results:** Statins lower low-density lipoprotein cholesterol (approximately 15–35% in human immunodeficiency virus cohorts), increase high-density lipoprotein cholesterol, and improve surrogate vascular measures and plaque characteristics, including non-calcified/high-risk plaque features. They also exhibit immunomodulatory effects, reducing vascular inflammation and markers such as soluble cluster of differentiation 14, lipoprotein-associated phospholipase A2, interferon-gamma-inducible protein 10, and T-cell/monocyte activation, although their effects on systemic inflammation and CD4 count are inconsistent. Clinically, pitavastatin reduced serious cardiovascular events by 35% compared to placebo in a trial of >7,700 PLWH aged ≥40 years on ART, supporting its broader preventive use. **Conclusion:** Overall, statins, particularly pitavastatin, are a cornerstone for CVD risk reduction in PLWH; however, individualized prescribing, safety monitoring, and outcome research remain essential.

Key words: Antiretroviral therapy, cardiovascular disease, myocardial infarction, people living with human immunodeficiency virus, statins

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Received: 19-05-2026
Revised: 21-06-2026
Accepted: 27-06-2026

INTRODUCTION

Recent advancements in human immunodeficiency virus (HIV) treatment have extended the average lifespan of people living with HIV (PLWH). However, this has increased the risk of non-communicable diseases, particularly cardiovascular disease (CVD). Common myocardial infarction (MI) risk factors, along with HIV-specific factors, are major causes of mortality and morbidity among PLWH. These individuals are nearly twice as likely to suffer a MI and face greater risks of heart failure (HF) and sudden death than those without infection.[1]

The link between HIV infection and cardiovascular health involves several factors. PLWH encounter traditional risk factors such as dyslipidemia, hypertension, and smoking, as well as HIV-specific factors, including chronic inflammation, immune activation, and direct viral effects on endothelial function and atherosclerosis.[2] In addition, certain antiretroviral drugs, especially protease inhibitors (PIs), are associated with metabolic disturbances, further increasing the cardiovascular risk in PLWH [Figure 1].[3]

To address these issues, statins have been identified as a promising strategy for reducing the cardiovascular risk in PLWH. By inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, statins lower cholesterol levels, decrease low-density lipoprotein cholesterol (LDL-C), and reduce the risk of atherosclerotic cardiovascular events.[4] In addition to lipid-lowering effects, statins also have anti-inflammatory, antioxidant, and endothelial function-enhancing effects, which help lower cardiovascular-related morbidity and mortality.[5]

However, statin use in PLWH presents challenges. Drug interactions between statins and antiretroviral medications can affect statin metabolism and increase the risk of adverse effects.[6] Genetic polymorphisms affecting drug-metabolizing enzymes and transporters may also influence statin pharmacokinetics and pharmacodynamics, underscoring the importance of pharmacogenetic factors when prescribing statins to this group.[7] Growing evidence indicates substantial benefits for PLWH in routine clinical practice: Meta-analyses of randomized controlled trials (RCTs) show reduced LDL-C and improved surrogate cardiovascular risk markers,[8] observational studies link statin use to lower cardiovascular event rates,[9] and a study of over 7,700 PLWH aged 40 years or older receiving antiretroviral therapy (ART) showed that pitavastatin significantly reduced serious cardiovascular event risk by 35% compared to placebo.[10]

In light of these findings, it is necessary to integrate statin therapy into the cardiovascular management plans for PLWH. This systematic review aimed to provide a comprehensive overview of the epidemiology, pathophysiology, and management of CVD in PLWH, with a particular focus on statin therapy.

MATERIALS AND METHODS

This systematic review adhered to the preferred reporting items for systematic reviews and meta-analyses guidelines.[11,12] Figure 2 illustrates the prisma flow diagram. Studies were selected based on the following criteria: Population (Individuals aged 18 years or older PLWH); Intervention (Aimed at preventing or treating CVD); Comparison (Non-statin lipid-lowering therapy or placebo);

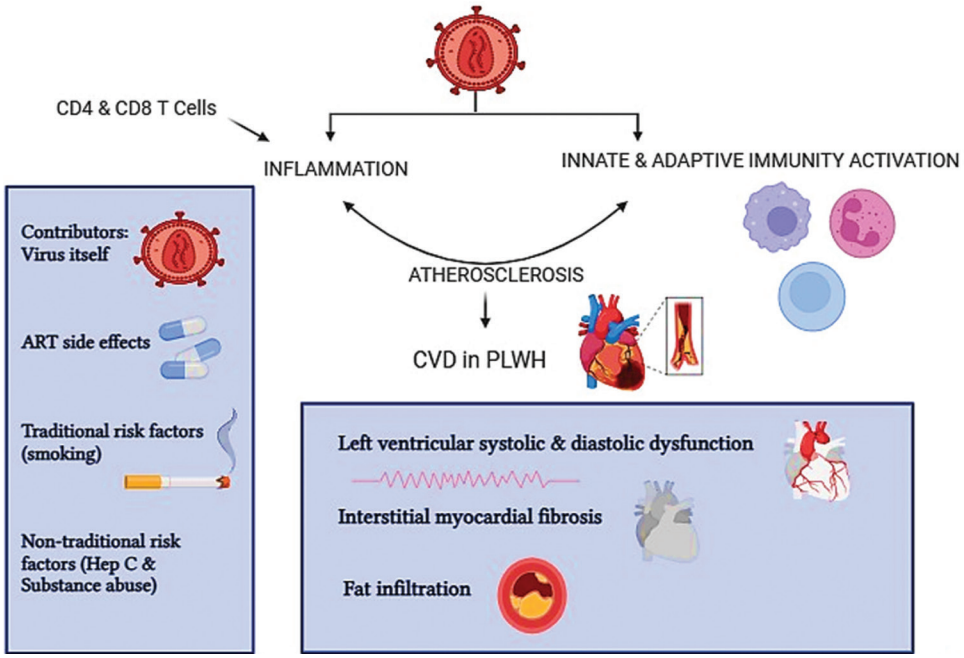

Figure 1: The relationship between human immunodeficiency virus infection and cardiovascular health

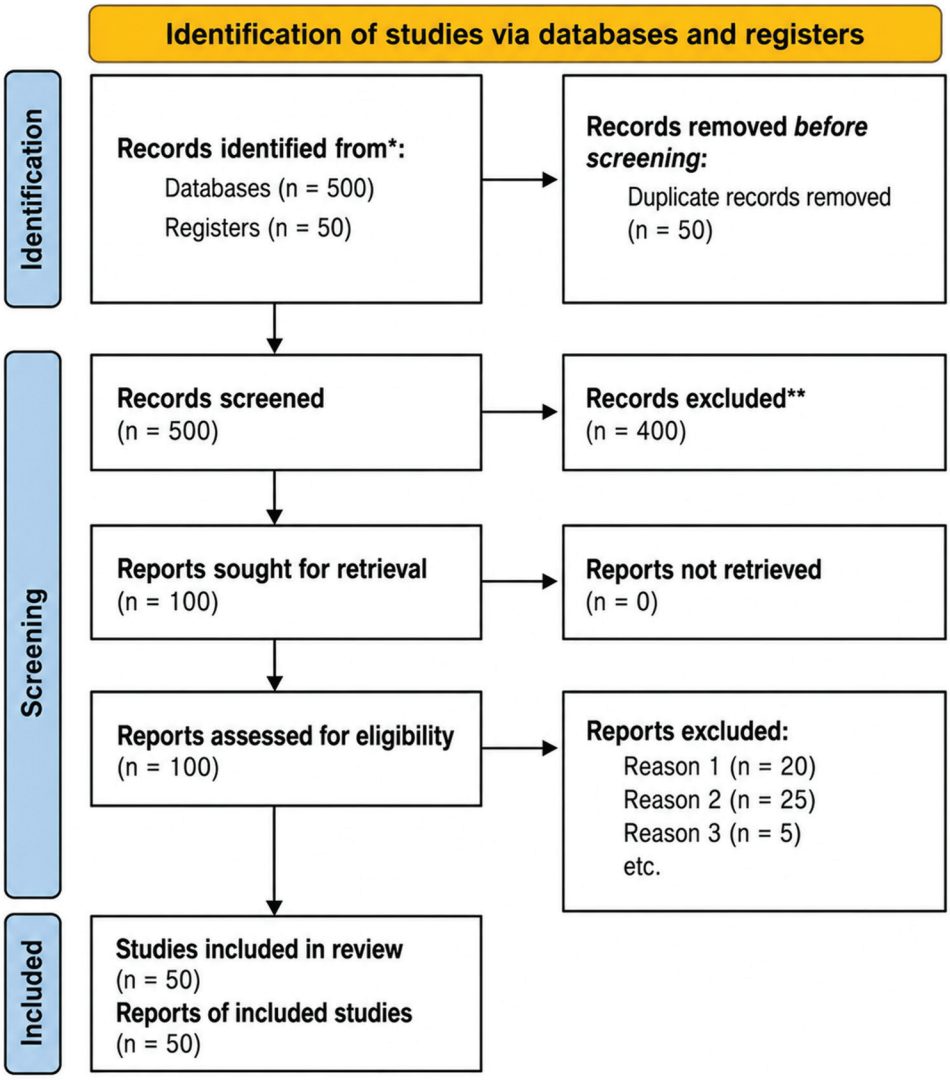

Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart of study selection

Outcomes (Research focusing on cardiovascular events, lipid profile changes (LDL-C, High-density lipoprotein cholesterol [HDL-C], total cholesterol), adverse events related to statins (drug, metabolic), and any negative outcomes); Study Design (Published in peer-reviewed journals, including RCTs, cohort studies, and observational studies).

In April 2024, an extensive literature search was conducted using the MEDLINE/PubMed, Scopus, Google Scholar, and ClinicalTrials. gov, and the Cochrane Central Register of Controlled Trials databases. The search terms used were "HIV," "cardiovascular disease," "CVD," "statins," "lipid-lowering therapy," "drug interaction," and "antiretroviral therapy (ART)," combined with Boolean operators to capture all pertinent studies.

Two reviewers independently screened the titles, abstracts, and full texts for eligibility. Disagreements between the reviewers were resolved through discussion or by consulting a third reviewer. Studies were excluded if they focused solely on pediatric populations, non-HIV-related CVD, or if statins were used for purposes other than CVD prevention in PLWH.

Data extraction was performed independently by two reviewers, who gathered the following details: Study characteristics (Design, location, sample size, duration, year, and author); Population details (ART regimen, HIV status, and baseline cardiovascular risk); Intervention specifics (Type and dose of statins); Outcomes (Changes in lipid profiles, adverse effects, cardiovascular events, and ART interactions were assessed); Adherence and follow-up duration were also assessed.

A narrative synthesis was employed due to the diversity in study designs, populations, and outcomes. The study results are presented narratively, highlighting key trends and findings without a quantitative analysis.

RESULTS AND DISCUSSION

Epidemiology and pathophysiology of CVD in HIV

Epidemiology and etiology

The risk of CVD in PLWH arises from the interplay between the virus, effects of ART, and conventional (e.g., smoking) and unconventional (e.g., hepatitis C, substance abuse) heart disease risk factors [Figure 3].

Coronary heart disease results from atherosclerosis, which is linked to lipid metabolism and immune activation. HIV infection and ART elevate this risk by promoting atherosclerosis.[13] PLWH may receive less intervention for CVD risk factors and medical procedures than those without HIV infection, increasing CVD morbidity and mortality.[14] Research has identified ART as a CVD risk factor, prompting the Strategies for Management of ART trial.[13]

Pathophysiology of CVD in HIV

Inflammation and activation of innate and adaptive immune responses play crucial roles in CVD. In atherosclerosis, T cells trigger immune-mediated damage, whereas proinflammatory and prothrombotic cytokines and chemokines recruit monocytes.[15] CD4+ and CD8+ T cells contribute to tissue inflammation,[16] and activated macrophages engulf oxidized low-density lipoproteins and other proatherogenic lipids, promoting the formation of foam cells and stable and unstable plaques [Figure 4]. Chronic HIV infection may exacerbate coronary artery disease by affecting both adaptive and innate immune pathways.

However, ART does not fully restore adaptive immunity. CD4+ T-cell recovery remains insufficient, and CD8+ T-cell activation persists despite ART due to ongoing anti-HIV responses and stimulation by co-pathogens such as cytomegalovirus.[17,18] Even with effective viral suppression through ART, PLWH experience persistent inflammation due to continued HIV infection in lymphatic tissues, microbial translocation, and co-infections.[19] PLWH with elevated inflammatory biomarkers, monocyte activation, and increased coagulation activity are at a higher risk of CVD events and atherosclerosis.[20]

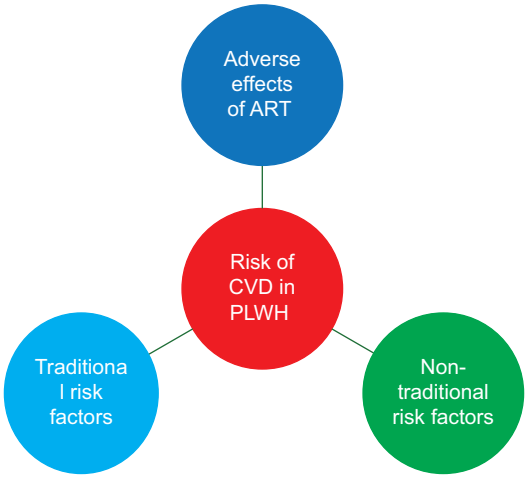

Figure 3: Risk factors of cardiovascular disease in people living with human immunodeficiency virus

Role of statins in CVD management

Statins are central to preventive cardiology because they lower lipid levels and stabilize atherosclerotic plaques, thereby reducing atherothrombotic events. The benefit of therapy depends on the extent of the atherosclerotic plaque burden.[21] Randomized clinical trial findings have driven cholesterol-lowering initiatives and a global decline in Atherosclerotic CVD (ASCVD) incidence over time.[22] In primary prevention, statins can reduce lifetime cardiovascular risk by treating hypercholesterolemia early and applying the concept of cholesterol exposure years.[21] A meta-analysis of RCTs in children with familial hypercholesterolemia showed a 30% reduction in LDL-cholesterol without notable differences in adverse effects, including muscle or liver toxicity or Tanner staging, compared to placebo.[23]

Mechanism of statins and pleiotropic effects

Statins inhibit HMG-CoA reductase in liver cells, decreasing intracellular cholesterol levels, increasing hepatic LDL receptor activity, and lowering circulating LDL levels. This reduces oxidized LDL accumulation in the arterial intima and interrupts inflammation, promoting monocyte recruitment and foam cell formation, which are key early steps in atherosclerosis. Research on these mechanisms and pharmacology has shaped the current CVD treatment guidelines.[24] Statins also have cardioprotective effects that are independent of LDL cholesterol reduction. They affect innate and adaptive immune responses by decreasing inflammatory cytokines, cellular adhesion molecules, and reactive oxygen species (ROS), modifying endothelial nitric oxide synthase expression, and reducing platelet reactivity, thereby stabilizing the atherosclerotic plaques.[25] These effects may be related to C-reactive protein (CRP). The JUPITER trial comparing rosuvastatin with placebo showed a 50% reduction in LDL-C, a 37% decrease in CRP level, and a 44% reduction in the primary outcome.[26] Statins also lower CRP levels and inhibit inflammatory mediators, such as tumor necrosis factor-alpha and interleukin (IL) 1b.[24]

Pleiotropic effects of statins in atherosclerosis

Atherothrombosis results from interactions between plaques, damaged endothelium, oxidized lipoproteins, inflammation, and platelets.[27] Statins influence atherogenic plaques by eliminating lipid and necrotic cores, restoring endothelial function, and suppressing smooth muscle cell proliferation.[28] Meta-analyses using virtual-histology intravascular ultrasound showed that statins modify plaque composition by decreasing fibrous volume.[29]

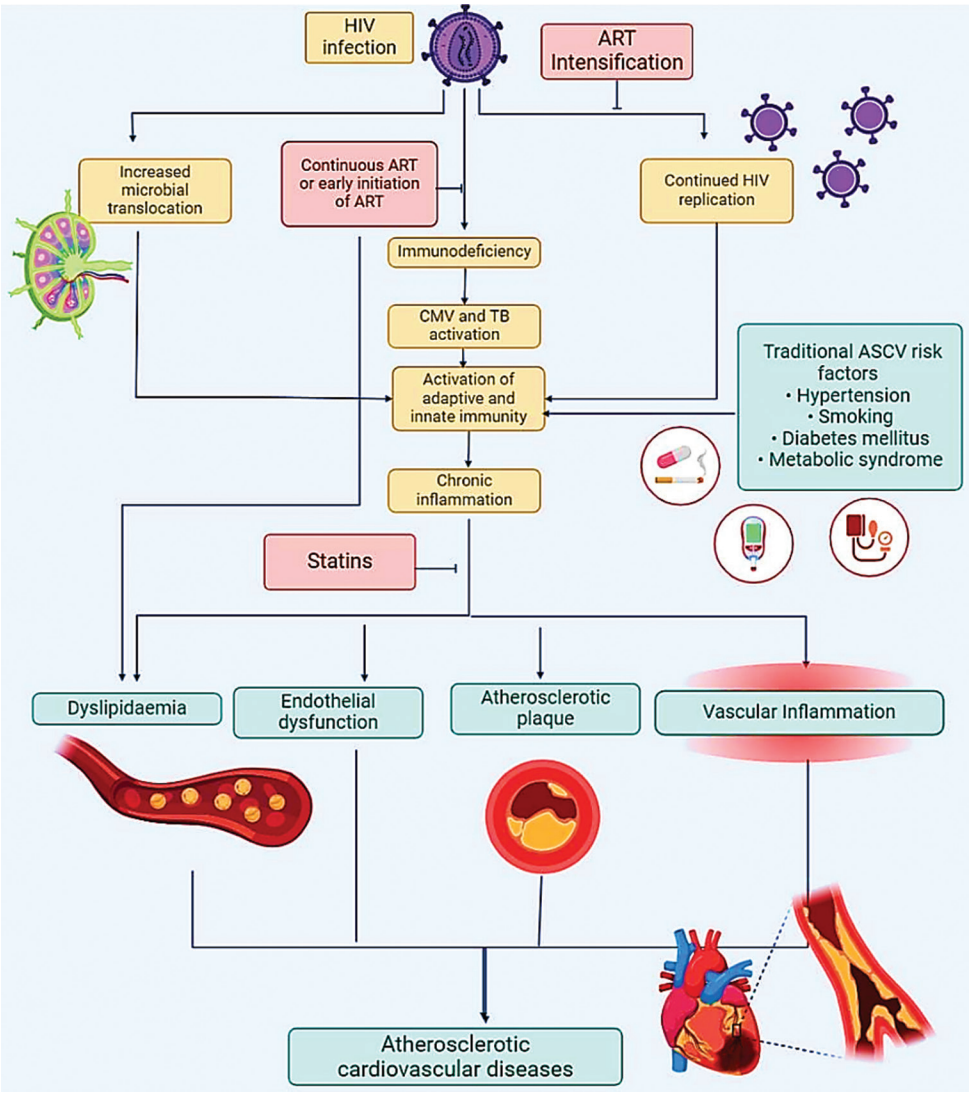

Figure 4: Pathophysiology of cardiovascular disease in human immunodeficiency virus

Statins stabilize plaques by reducing non-calcified volumes and increasing dense calcification. Macrophage phenotypes regulate this process: proinflammatory M1 macrophages promote microcalcification via smooth muscle cell conversion,[30] whereas anti-inflammatory M2 macrophages promote macroscopic calcium deposition, aiding stability.[24] The effect of atorvastatin therapy on fibrous cap thickness trial, using optical coherence tomography, showed that atorvastatin (20 mg/day) increases fibrous cap thickness while lowering LDL and high-sensitivity CRP levels,[31] a finding supported by meta-analyse.[32] Statins further enhance stability by reducing ROS and proinflammatory cytokine levels, preventing monocyte recruitment, and slowing disease progression.[33]

Statins possess anti-inflammatory properties, altering T-cell phenotypes by inhibiting proinflammatory IL-17 helper T-cells and promoting FoxP3 regulatory T-cells to enhance tolerance.[34] They decrease T-cell activation by reducing major histocompatibility complex II expression on antigen-presenting cells.[35] In addition, statins bind to the β2-integrin function-associated antigen-1 protein, inhibiting lymphocyte adherence and T-cell co-stimulation.[36]

Latest evidence on statin therapy in HIV

Research involving more than 7,700 HIV-positive individuals aged 40 and above on ART showed that pitavastatin reduced the risk of cardiovascular events by 35% compared to placebo, prompting early trial termination. Consequently, statin therapy is advised for individuals aged ≥40 years with an ASCVD score of ≥5 %. Statin use is considered for lower risk, although the absolute benefit may be limited. For those under 40 or over 75 years of age, management follows guidelines for individuals without HIV.[10]

CVD increasingly causes mortality in PLWH as life expectancy rises, with a relative risk of 1.61–2.00 and a doubled likelihood versus those without HIV.[37-39] Over the past 20 years, the global burden of HIV-related CVD has tripled, causing 2.6 million disability-adjusted life years.[37]

Although ART may improve CVD outcomes in PLWH,[40] it is insufficient alone because residual immune and arterial inflammation persists despite adequate treatment.[41,42] Therefore, an effective CVD prevention strategy for PLWH is needed to minimize the risk, reduce the medication burden, and target the factors driving CVD progression.[43] Table 1 summarizes the trials assessing the use of statins for primary CVD prevention in PLWH.

Lipid-lowering effects

Pitavastatin, a potent HMG-CoA reductase inhibitor, consistently lowers lipid levels in a wide range of clinical studies. In eleven trials, pitavastatin reliably increased HDL-C and decreased non-HDL-C in various patient groups.[44] Research in hypercholesterolemic patients with HIV underscored the effectiveness of statins, including pitavastatin, in lowering LDL-C by 15–35% compared to placebo.[45] Ezetimibe combined with pravastatin showed similar LDL-C reductions and improved endothelial function.[46] Fenofibrate combined with pravastatin improved lipid profiles with acceptable safety, especially in patients with HIV-related dyslipidemia.[47] Studies have indicated that statins and fibrates offer comparable efficacy and tolerability, making them viable options for diet-resistant hyperlipidemia.[48] Table 2 summarizes the trials examining the effects of statins.

Statin safety

Pitavastatin was well-received, with low discontinuation from adverse effects.[49] A review of 18 randomized controlled statin trials in PLWH on ART indicated that atorvastatin is safe at less than maximum doses when monitored.[45] Evidence suggests that ciprofibrate and rosuvastatin are effective, safe, and well-tolerated for dyslipidemia in this patient group.[50] A review of trials showed that statins, particularly rosuvastatin, can slightly increase blood sugar levels, with more patients on statins diagnosed with diabetes mellitus than those not using statins.[51,52] Conversely, simvastatin and lovastatin are linked to rhabdomyolysis and toxicity and should be avoided with PIs.[53] The long-term effectiveness and safety of primary CVD prevention in PLWH remain under-researched.[54] Statin-antiretroviral interactions complicate treatment and management.[55]

Table 1: Clinical trials evaluating the efficacy and safety of statins for primary CVD prevention in PLWH

Title	Clinicaltrials.Gov ID	Country	Outcomes
The effects of statin therapy on coronary flow reserve and inflammatory markers in HIV-positive patients.[66]	NCT02234492	Canada	Primary outcome measure: Correlation between CFR and TBR_{max} Secondary outcome measures: CFR, TBR_{max}, and neurocognitive function
Use of rosuvastatin in HIV-infected subjects to modulate cardiovascular risks.[67]	NCT01218802	United States	Primary outcome measures: BMD and carotid IMT
Does rosuvastatin delay progression of atherosclerosis in HIV.[68,69]	NCT01813357	New Zealand	Primary outcome measures: Progression of carotid IMT Secondary outcome measures: Adverse events
Statin therapy to improve atherosclerosis in HIV patients.[69]	NCT00965185	United States	Primary outcome measures: Coronary and aortic plaque inflammation Secondary outcome measures: Plaque progression, endothelial function, immune function, lipid profile, CRP, adipocytokines, LFTs
Pravastatin for hyperlipidemia in HIV.[70]	NCT00227500	Australia	Primary outcome measures: Variation in the time-adjusted shift from baseline in fasting serum total cholesterol levels. Secondary outcome measures: Alteration from week 4 in fasting serum total cholesterol, HDL-C, triglycerides, overall and regional body fat distribution, and endothelial function.
Effect of atorvastatin on subclinical atherosclerosis.[71]	NCT04101136	Indonesia	Primary outcome measures: Carotid IMT change. Secondary outcome measures: Flow-mediated vasodilatation change, Liver fibrosis change, Liver steatosis change, Fasting lipid change, Neurocognitive function change, CPI, B2M, Soluble CD14, ICAM-1, hs-CRP, and VCAM-1 changes

CFR: Coronary flow reserve, TBR_{max}: Maximum tumor-to-background ratio, HIV: Human immunodeficiency virus, BMD: Bone mineral density, CRP: C-reactive protein, LFTs: Liver function tests, HDL-C: High-density lipoprotein cholesterol, IMT: Intima media thickness, CPI: Community periodontal index, B2M: Beta 2-microglobulin, Soluble CD14 change, ICAM-1 change, ICAM-1: Intercellular Adhesion Molecule-1, hs-CRP: High sensitivity C-reactive protein, VCAM-1: Vascular cell adhesion molecule-1, CVD: Cardiovascular disease, PLWH: People living with human immunodeficiency virus

Table 2: Clinical trials evaluating lipid-lowering effects of statins for primary CVD prevention in PLWH

Trial	Comparison	Type of Study	Population	Time frame	Main finding
Wangpatharawanit *et al.*[73]	Switching lopinavir/ Ritonavir to atazanavir/Ritonavir versus adding atorvastatin in HIV-infected	A randomized controlled trial	50 PLWH Male - 58% Mean age - 46.5	48 weeks	Atorvastatin added group: ↓LDL - 28.7 mg/dL ↓TC - 51.8 mg/dL Switching group↓TC - 16.7 mg/dL
Nixon *et al.*[72]	Atorvastatin	A multicenter, prospective, randomized, double-blind, placebo- controlled, crossover pilot study	97 PLWH on PIs	20 weeks	↓LDL - 38% ↓Oxidized LDL - 33% ↓Lp-PLA2-31%
Lu *et al.*[74]	Pitavastatin	Double-blind, placebo-controlled randomized clinical trial	611 PLWH Male - 84.0% Mean (SD) age - 51	24 months	↓LDL - 28.5 mg/dL ↓Oxidized LDL - 29% ↓Lp-PLA2-7%
Stein *et al.*[75]	Placebo versus Pravastatin	Placebo-controlled, double-blind, crossover study	20 PLWH on PIs	12 weeks	↓Small VLDL - 44.9% ↓LDL - 20.8%
Aslangul *et al.*[76]	Rosuvastatin versus Pravastatin	A randomized controlled trial	88 PLWH	45 days	Rosuvastatin group: ↓LDL-C - 37% ↓TC - 19% Pravastatin group: ↓LDL-C - 19% ↓TC - 7%
Aberg *et al.*[77]	Pitavastatin versus Pravastatin	Multicenter, randomized, double-blind, superiority trial	252 PLWH Male - 86% Mean age - 50	12 weeks; 40-week safety extension	Pitavastatin group: ↓LDL-C - 31.1% Pravastatin group: ↓LDL-C 20.9%

LDL-C: Low-density lipoprotein cholesterol, TC: Total cholesterol, Lp-PLA2: Lipoprotein-associated phospholipase A2, PLWH: People living with HIV, PIs: Protease inhibitors, SD: Standard deviation, HIV: Human immunodeficiency virus. ↓: Decreased levels

Statins lower the risk of acute MI, cardiovascular revascularization, cerebrovascular events, vascular and overall mortality, and LDL-C levels.[56,57] These findings align with the cholesterol treatment trialists meta-analysis, which reported reduced 5-year serious cardiovascular events, all-cause mortality, and coronary mortality.[58] The PROVE-IT TIMI 22 and IMPROVE-IT trials showed statin effectiveness in acute coronary syndrome and lower HF hospitalizations.[59,60] Statin treatment stabilizes and reduces atheroma plaques and may influence their composition.[61]

Combining Pitavastatin with ART may benefit patients with chronic HIV through decreased immune activation and a favorable pharmacokinetic profile.[62] Recommendations support the use of statins to lower CVD risk in PLHW, following guidelines. Pitavastatin does not adversely interact with ART or affect glucose metabolism, making it an optimal choice for adults with PLWH.[63] PLWH face the risk of atherosclerosis and heart disease, although plaque progression can differ. Statins stabilize plaques by reducing fatty and fibrotic components without affecting the calcified portions.[64] In HIV+ patients with subclinical atherosclerosis, statins reduced non-calcified and high-risk plaque features compared to placebo.[65]

CONCLUSION

Statins reduce atherosclerotic plaques and lower the risk of cardiac arrest. They do this by stabilizing plaques, encouraging protective film formation around them, and decreasing proinflammatory cytokines. Although statins positively affect CVD rates in PLWH, complications can arise. ART is the standard treatment for HIV, and these medications can interact with statins, leading to side effects such as insulin resistance, statin-induced myopathy, and liver toxicity. Recent research and clinical trials indicate that not all HIV patients can receive the same treatment due to potential interactions with standard HIV therapies. At present, Pitavastatin has demonstrated improvements in PLWH with minimal side effects.

Although statins have shown effectiveness, more data are needed on the interactions between statins and HIV medications. Presently, discrepancies between the guidelines of the American Heart Association and the European Atherosclerosis Society have resulted in clinicians hesitating to prescribe statins. Additional clinical trials are necessary to gather substantial data to enable the development of suitable treatment options tailored to individual patients.

Informed consent statement

Not applicable.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the Clinical Research Unit at Rafha General Hospital for its valuable technical support and assistance in the preparation of this manuscript.

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Source of Support: Nil. **Conflicts of Interest:** None declared.