

Review Article

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The effect of statin use on vascular inflammatory biomarkers in people living with HIV: A living systematic review of randomized controlled trials

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ABSTRACT

Objective: To evaluate the effect of statin therapy on biomarkers of vascular inflammation in people living with HIV (PLWH).

Methods: We conducted a living systematic review of randomized controlled trials (RCTs). We searched Scopus, PubMed, Cochrane Library, and Scilit up to April 4, 2025, with a predefined plan for ongoing evidence surveillance and updating. Nine RCTs involving 1721 participants were included. Data were extracted on changes in key biomarkers, including interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), soluble CD14 (sCD14), soluble CD163 (sCD163), oxidized LDL (oxLDL), and lipoprotein-associated phospholipase A_2 (Lp-PLA_2). The Cochrane Risk of Bias (RoB 2) tool was used for quality assessment. This review is not intended to be retired from the living mode at this stage.

Results: Statin therapy significantly reduced key biomarkers of monocyte activation and vascular inflammation, particularly IL-6 and sCD14, with effects being most consistent and pronounced with pitavastatin. Pitavastatin also demonstrated greater efficacy in reducing oxLDL and Lp-PLA_2 compared to other statins. Reductions in hs-CRP were inconsistent across studies. A critical finding was that treatment duration was a major modifier of effect, with interventions lasting ≥12 months yielding substantially greater anti-inflammatory benefits. The mechanistic profile suggests statins specifically target the LPS-sCD14 pathway of innate immune activation, which is highly relevant to HIV pathogenesis.

Conclusions: Pitavastatin emerges as the most effective statin for reducing vascular inflammation in PLWH, offering a targeted strategy to mitigate cardiovascular disease risk in this population. These findings, derived from the current iteration of a living systematic review, support the use of long-term pitavastatin therapy for PLWH with evidence of residual inflammation and highlight the need for its inclusion in future clinical guidelines as new evidence continues to emerge.

KEYWORDS: Living systematic review; Human immunodeficiency virus; Cardiovascular disease; Statin; Inflammatory biomarkers

1. Introduction

The advent of antiretroviral therapy (ART) has significantly improved life expectancy among people living with HIV (PLWH), transforming HIV infection into a manageable chronic condition[1]. However, as this population ages, the burden of non-AIDS comorbidities has emerged as a major concern, particularly cardiovascular disease (CVD), which is now a leading cause of

Summary

Question: What is the effect of statin therapy on vascular inflammatory biomarkers in people living with HIV?

Findings: In this living systematic review of 9 randomized controlled trials involving 1721 participants, statin therapy, particularly pitavastatin, consistently reduced biomarkers of vascular inflammation and monocyte activation, including IL-6, sCD14, oxLDL, and Lp-PLA_2. Longer treatment duration was associated with greater anti-inflammatory effects.

Meaning: Pitavastatin may represent the preferred statin strategy to reduce residual vascular inflammation and cardiovascular risk in people living with HIV.

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morbidity and mortality in PLWH[2]. Chronic immune activation and systemic inflammation, even under effective ART, are believed to contribute to the accelerated development of vascular complications[3]. This residual inflammatory state is thought to be driven by factors such as persistent viral reservoirs, microbial translocation from a compromised gut barrier, and co-infections[4].

Among the key contributors to this heightened cardiovascular risk are elevated levels of vascular inflammation biomarkers, such as interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), *D*-dimer, soluble CD14 (sCD14), and soluble CD163 (sCD163)[5,6]. These biomarkers reflect persistent immune dysregulation and endothelial dysfunction, a state that often persists despite effective ART[3,7]. For instance, IL-6 and hs-CRP have been independently associated with an increased incidence of cardiovascular events in PLWH, while biomarkers of microbial translocation and macrophage activation have been linked to the progression of subclinical atherosclerosis in this population[5,7,8]. Thus, adjunctive therapies aimed at modulating inflammation are increasingly being explored to improve cardiovascular outcomes in this population[9].

Statins, widely used lipid-lowering agents, have shown pleiotropic effects beyond cholesterol reduction, including anti-inflammatory and immunomodulatory properties, with significant reductions in cardiovascular events observed among individuals with elevated hs-CRP levels[10,11]. In the general population, statin therapy significantly reduces cardiovascular events in individuals with elevated hs-CRP but normal low-density lipoprotein (LDL) levels, highlighting the importance of their anti-inflammatory mechanism[11]. Several studies have investigated the role of statin therapy in reducing systemic inflammation and vascular risk in PLWH, leading to the development of large-scale clinical trials such as REPRIEVE to further evaluate the cardiovascular benefits of statins in this population[12]. However, their efficacy in PLWH remains less clear due to heterogeneity in study designs, statin types, and biomarker responses[12–14]. Notably, significant reductions in IL-6 and sCD14 have been reported with pitavastatin[13]; whereas rosuvastatin has demonstrated minimal effects in other trials[14].

Given the clinical relevance of vascular inflammation in PLWH and the potential of statins to modify this risk, a comprehensive synthesis of the evidence is needed. This systematic review aims to evaluate the effect of statin therapy on biomarkers of vascular inflammation in PLWH, thereby informing future clinical strategies to mitigate cardiovascular risk in this vulnerable population.

2. Methods

2.1. Study design and living systematic review framework

This study was conducted as a living systematic review of randomized controlled trials (RCTs) to evaluate the effect of statin therapy on biomarkers of vascular inflammation in PLWH. The review was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and incorporates a predefined plan for regular evidence surveillance and updating. Given the rapidly evolving evidence base related to statin therapy, immune activation, and cardiovascular risk modification in PLWH, a living systematic review approach was adopted to ensure that emerging high-quality randomized evidence can be incorporated in a timely manner. This article represents version 1.0 of the living systematic review. Future updates will incorporate newly identified randomized evidence and will be reported as subsequent versions, ensuring that the review remains current and clinically relevant.

A formal protocol for this living systematic review was not prospectively registered in PROSPERO prior to initiation. This decision was based on the evolving scope of evidence synthesis required for a living systematic review framework and the absence of established registration pathways tailored specifically for continuously updated reviews at the time of study conception. Nevertheless, the review methods, eligibility criteria, and outcome definitions were predefined and consistently applied throughout the review process, in accordance with PRISMA 2020 recommendations.

2.2. Research question

The review addressed the following research question: What is the current and evolving evidence on the effect of statin therapy on biomarkers of vascular inflammation in PLWH? The question was formulated to capture both established findings and emerging evidence relevant to cardiovascular risk stratification and immunoinflammatory mechanisms in PLWH.

2.3. Inclusion and exclusion criteria

To determine the eligibility criteria, the PICO framework (Population, Intervention, Comparator, and Outcome) was utilized. The population of interest included adults aged 18 years and older living with HIV, regardless of sex, antiretroviral therapy (ART) status, or stage of disease. The intervention was statin therapy, including commonly used agents such as atorvastatin, rosuvastatin, pravastatin, and simvastatin. The comparator groups consisted of PLWH who did not receive statins, were given a placebo, or were evaluated based on baseline inflammatory biomarker levels. The primary outcomes were changes in biomarkers of vascular inflammation, specifically hs-CRP, IL-6, monocyte chemoattractant protein-1 (MCP-1/CCL2), interferon gamma-induced protein 10 (IP-10/CXCL10), sCD14, sCD163, oxidized low-density lipoprotein (oxLDL), lipoprotein-associated phospholipase A_2 (Lp-PLA_2), and markers of endothelial

activation such as soluble vascular cell adhesion molecule-1 (sVCAM-1), CD40 ligand (CD40L), and P-selectin. Additional cytokines and chemokines considered included interleukin-1β (IL-1β), interleukin-12 (IL-12), interleukin-17 (IL-17), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), macrophage inflammatory protein-1α (MIP-1α), macrophage inflammatory protein-1β (MIP-1β), regulated on activation, normal T cell expressed and secreted (RANTES/CCL5), and vascular endothelial growth factor (VEGF). Studies were included if they examined the effect of statins on any of these biomarkers in PLWH. Exclusion criteria encompassed studies involving participants with co-infections (*e.g.*, hepatitis C) or those receiving other immunomodulatory or anti-inflammatory treatments that could confound the results. Conference abstracts, commentaries, case reports, and retracted articles were excluded from the review. Articles written in languages other than English were translated using Google Translate to assess eligibility.

2.4. Living evidence surveillance and update plan

Updates to this living systematic review will be conducted on a scheduled six-monthly basis, with comprehensive literature searches repeated across all databases using the original search strategy. Newly identified records will undergo incremental screening, whereby titles and abstracts published since the last search date will be screened, followed by full-text assessment using the same predefined eligibility criteria. A major update will be triggered when newly published randomized controlled trials are identified that are likely to meaningfully influence the direction, certainty, or clinical interpretation of the evidence. These include trials with extended statin exposure (≥12 months), substantially larger sample sizes, head-to-head statin comparisons, or the evaluation of novel or clinically relevant inflammatory biomarkers not previously synthesized. Minor updates, such as the inclusion of small pilot studies without impact on overall conclusions, will be documented without altering the primary conclusions. Each update will be reported as a subsequent version of the review, with clear documentation of the search date, newly included studies, and any changes to the evidence synthesis, ensuring transparency and continuity of the living systematic review process. At present, no predefined criteria for retirement from the living mode have been established, and the review will continue to be updated as long as relevant randomized evidence continues to emerge.

2.5. Information sources and search strategy

A comprehensive literature search was conducted in PubMed, Cochrane Library, Scopus, and Scilit, with the initial search performed on 4 April 2025. The search strategy was developed to identify randomized controlled trials evaluating the effects of statin therapy on biomarkers of vascular inflammation in PLWH. The following combination of keywords and Boolean operators was used: (HIV OR "human immunodeficiency virus" OR PLWH) AND (statin OR statins OR atorvastatin OR rosuvastatin OR pravastatin OR simvastatin) AND ("vascular inflammation" OR "endothelial activation" OR "inflammatory biomarkers"). Controlled vocabulary terms, where applicable, were combined with free-text keywords to maximize sensitivity. The complete search strategies for all databases are provided in Supplementary Table 1. As part of the living systematic review framework, database searches will be updated at regular intervals, and automated alerts have been established to identify newly published randomized controlled trials relevant to the research question.

2.6. Screening and selection of the records

We used PRISMA guideline to guide our screening and selection process which were carried out by two independent reviewers (M.H. and K.F.J.)[15]. Duplicates were immediately removed once the identified records were imported to Mendeley Desktop v1.19.8. The screening process was then conducted based on the 'Title' and 'Abstract', and selectively reduced by full-text screening according to the predetermined inclusion/exclusion criteria. Discrepancies in the final results were resolved by re-evaluating the articles and discussing them until a consensus was reached. Consultation with the third reviewer (M.S.) was done when the discrepancies persisted.

2.7. Data extraction

Data extraction was performed to collect both study characteristics and outcome measures relevant to the objectives of this review. Information extracted from each study included: author and year of publication, study design, country of origin, and sample size (intervention and placebo groups). Subject-level data such as mean age and population status, including HIV-related characteristics (*e.g.*, CD4 count, viral load, and ART status), were also collected. Intervention-related data comprised the type of statin administered, dosage, and duration of therapy, as well as comparator conditions (*e.g.*, placebo or no statin therapy). Outcome data focused on changes in vascular inflammation biomarkers, specifically hs-CRP, IL-6, sCD14, sCD163, oxLDL, Lp-PLA_2, MCP-1, IP-10, sVCAM-1, CD40L, P-selectin, IL-1β, IL-12, IL-17, TNF-α, IFN-γ, MIP-1α, MIP-1β, RANTES, and VEGF. Biomarker levels were extracted both at baseline and after statin intervention. Data extraction was conducted independently by two reviewers, and discrepancies were resolved through discussion or by involving a third reviewer if necessary.

2.8. Quality assessment

To determine the methodological quality of the included randomized controlled trials, we used the Cochrane Risk of Bias 2 (RoB 2) tool. This tool evaluates five domains of potential bias: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. Each domain was judged as low risk of bias, some concerns, or high risk of bias. An overall judgment was then derived for each study based on the domain level assessments. Detailed domain-level risk of bias assessments for each included study are provided in Supplementary Table 2.

2.9. Data synthesis

Given the heterogeneity of statin types, treatment durations, biomarker panels, and laboratory measurement methods across studies, a quantitative meta-analysis was not performed. Instead, results were synthesized using a structured narrative approach. Findings were organized according to statin class, duration of therapy, and category of inflammatory biomarker to identify consistent patterns of effect, potential effect modifiers, and areas of uncertainty. This synthesis framework was selected to facilitate future updates of the living systematic review as new evidence becomes available. No standardized effect measures were calculated due to heterogeneity in biomarker reporting and study designs; results were therefore synthesized narratively.

3. Results

3.1. Characteristics of the included studies

This systematic review included nine RCTs comprising a total of 1 721 participants (Table 1 and Figure 1)[13,14,16-22]. The majority of trials were conducted in the United States, while additional studies were performed in Australia, Switzerland, Puerto Rico, and Thailand, ensuring a relatively broad geographical representation. All included studies applied double-blind randomized designs, with most being placebo-controlled, thereby strengthening the internal validity of findings. Study populations consisted of PLWH who were generally on stable ART with suppressed viral load. Participants were typically at low-to-moderate CVD risk, and several trials restricted inclusion to individuals with low-density lipoprotein cholesterol (LDL-C) ≤130 mg/dL to minimize confounding by baseline lipid levels. The interventions assessed included pitavastatin (2-4 mg/day), rosuvastatin (10-20 mg/day), and atorvastatin (10-20 mg/day). Two studies also compared pitavastatin 4 mg/day with pravastatin 40 mg/day. Treatment duration varied considerably, ranging from 12 weeks[22] to 24 months[13], allowing assessment of both short- and long-term effects. Across studies, a broad spectrum of vascular inflammatory biomarkers was evaluated. These included hs-CRP, IL-6, sCD14, sCD163, oxLDL, Lp-PLA$_2$, MCP-1/CCL2, IP-10/ CXCL10, sVCAM-1, CD40 ligand, and P-selectin. Additional proinflammatory cytokines, including IL-1β, IL-12, IL-17, TNF-α, IFN-γ, and chemokines such as MIP-1α, MIP-1β, and RANTES, were explored in smaller studies. Sample sizes ranged widely, from 24 participants in the pilot trial by Srichatrapimuk *et al.* (2023) to over 600 participants in the randomized trial to prevent vascular events (REPRIEVE) substudy[13,22]. The mean age of participants was consistently in the mid 40 years to early 50 years, reflecting the demographic shift of aging PLWH. Overall, the included trials provided a comprehensive evaluation of statins' anti-inflammatory effects in diverse HIV-positive populations, with variability in sample size, statin type, treatment duration, and biomarker endpoints (Table 1).

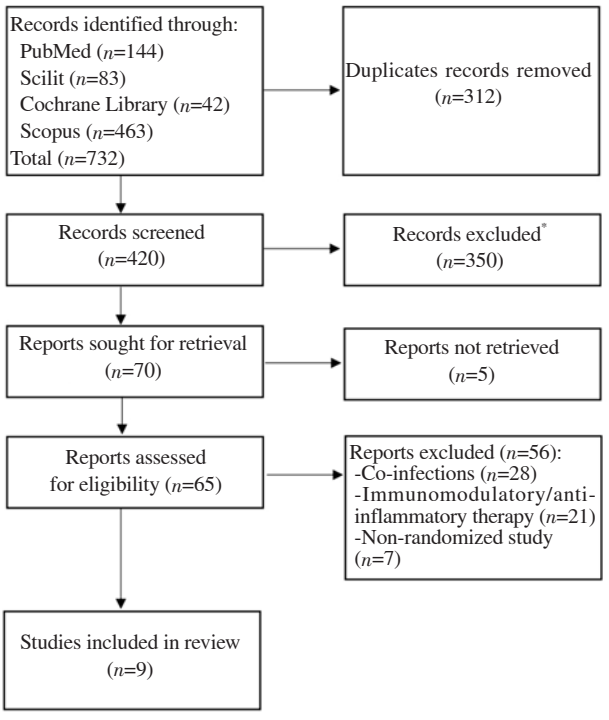


Figure 1. PRISMA diagram for the screening and selection process. *Records excluded during title and abstract screening due to irrelevance to the study objective.

3.2. Effect of statins on vascular inflammation in PLWH

Across the nine included trials, the impact of statins varied significantly by statin type, treatment duration, and the specific

Table 1. Characteristics of the included studies (current iteration).

Author (year)	Study design	Country	Sample size (intervention/ placebo)	Age (years)	Population status	Statin type (dose)	Duration	Key biomarkers
Lu *et al.*[13] (2024)	Double-blind RCT	United States	302/309 (*n*=611)	51 ± 6	Adults with HIV, on ART, low-to-moderate CVD risk, unknown CVD	Pitavastatin 4 mg daily	24 months	oxLDL, Lp-PLA$_2$, hs-CRP, IL-6, MCP-1, sCD14, sCD163
Eckard *et al.*[16] (2014)	Double-blind RCT	United States	72/75 (*n*=147)	Intervention: 45.6 (41.1-51.4), Placebo: 46.9 (39.2-53.6)	PLWH on stable ART, LDL ≤130 mg/dL, elevated inflammation	Rosuvastatin 10 mg daily	24 weeks	Lp-PLA$_2$, hs-CRP, IL-6, IP-10
Funderburg *et al.*[17] (2015)	Double-blind RCT	United States	72/75 (*n*=147)	47	ART-treated PLWH, suppressed HIV, LDL ≤130 mg/dL	Rosuvastatin 10 mg daily	48 weeks	sCD14, Lp-PLA$_2$, IP-10
Hearps *et al.*[18] (2021)	Double-blind RCT	Australia and Switzerland	33/36 (*n*=69)	Intervention: 54.7 ± 18.5, Placebo: 54.7 ± 19.3	PLWH, moderate CVD risk, suppressed HIV, normal lipids	Rosuvastatin 20 mg daily	48 weeks	IL-6, CXCL10, sCD14, sVCAM-1
DeFilippi *et al.*[19] (2020)	Randomized, double-blind, active-controlled trial (INTREPID)	Multicenter (USA & Puerto Rico)	126/126 (*n*=252)	50.4 ± 8.2	Adults living with HIV and dyslipidemia, on stable ART, no CVD history	Pitavastatin (4 mg/day) *vs.* Pravastatin (40 mg/day)	52 weeks	TFPI, Lp-PLA$_2$, hs-CRP, oxLDL
Hileman *et al.*[14] (2016)	Randomized, double-blind, placebo-controlled trial (SATURN-HIV)	United States	72/75 (*n*=147)	45.4 ± 9.1 (statin), 45.4 ± 10.7 (placebo)	HIV-infected adults on stable ART, LDL <130 mg/dL, heightened inflammation or T-cell activation	Rosuvastatin 10 mg daily	48 weeks	Lp-PLA$_2$, oxLDL, hs-CRP, sCD14, sCD163, IL-6
Toribio *et al.*[20] (2017)	RCT	United States and Puerto Rico	113/117 (*n*=230)	50.3 ± 8.2	HIV-infected adults on stable ART with dyslipidemia, no CVD history	Pitavastatin 4 mg/day *vs.* Pravastatin 40 mg/day	52 weeks	sCD14, oxLDL, Lp-PLA$_2$
Nixon *et al.*[21] (2017)	Multicenter, randomized, double-blind, placebo-controlled, cross-over pilot study (ACTG A5275)	United States	46/48 (*n*=94)	Intervention: 47.0 ± 11.9, Placebo: 49.0 ± 9.6	HIV-infected adults ≥18 years, on boosted protease inhibitor-based ART 6 months, HIV-1 RNA <40 copies/mL ≥180 days, LDL-C 70-<130 mg/dL, without CVD, diabetes, or active hepatitis	Atorvastatin 10 mg/day for 4 weeks, followed by 20 mg/day for 16 weeks	20 weeks	IL-6, MCP-1, IP-10, hs-CRP, sCD14, sCD163, CD40L, P-selectin, oxLDL, Lp-PLA$_2$
Srichatrapimuk *et al.*[22] (2023)	Double-blind RCT	Thailand	12/12 (*n*=24)	46.8 ± 9.6	PLWH with dyslipidemia on ritonavir-boosted atazanavir (ATV/r), virologically suppressed	Pitavastatin 2 mg/day *vs.* placebo	12 weeks	hs-CRP, IL-1β, IL-6, IL-12, IL-17, TNF-α, IFN-γ, IP-10 (CXCL10), MCP-1 (CCL2), MIP-1α, MIP-1β, RANTES (CCL5), VEGF

ART: antiretroviral therapy; ATV/r: ritonavir-boosted atazanavir; CD4: cluster of differentiation 4; CVD: cardiovascular disease; HIV: human immunodeficiency virus; LDL: low-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; PLWH: people living with HIV; RNA: ribonucleic acid; oxLDL: oxidized low-density lipoprotein; Lp-PLA$_2$: lipoprotein-associated phospholipase A$_2$; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; IL-1β: interleukin-1 beta; IL-1ra: interleukin-1 receptor antagonist; IL-2: interleukin-2; IL-4: interleukin-4; IL-6: interleukin-6; IL-7: interleukin-7; IL-8: interleukin-8; IL-9: interleukin-9; IL-10: interleukin-10; IL-12: interleukin-12; IL-13: interleukin-13; IL-15: interleukin-15; IL-17: interleukin-17; TNF-α: tumor necrosis factor alpha; IFN-γ: interferon gamma; MCP-1 (CCL2): monocyte chemoattractant protein-1; IP-10 (CXCL10): interferon gamma-induced protein-10; MIP-1α (CCL3): macrophage inflammatory protein-1 alpha; MIP-1β (CCL4): macrophage inflammatory protein-1 beta; RANTES (CCL5): regulated upon activation, normal T-cell expressed and secreted; VEGF: vascular endothelial growth factor; sCD14: soluble cluster of differentiation 14; sCD163: soluble cluster of differentiation 163; sVCAM-1: soluble vascular cell adhesion molecule-1; CD40L: CD40 ligand (CD154); P-selectin: platelet selectin (CD62P); TFPI: tissue factor pathway inhibitor; PON3: paraoxonase 3; LDLR: low-density lipoprotein receptor; Galectin-4: galectin-4 protein; IGFBP-2: insulin-like growth factor binding protein-2; sTNFR2: soluble tumor necrosis factor receptor-2; basic FGF: basic fibroblast growth factor; PDGF-BB: platelet-derived growth factor-BB; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; eotaxin (CCL11): chemokine C-C motif ligand 11.

biomarker assessed. Reduction in vascular inflammatory biomarkers was consistently observed in several trials. In the large REPRIEVE mechanistic substudy, pitavastatin (4 mg daily for 24 months) significantly reduced oxLDL, Lp-PLA_2, and soluble markers of monocyte activation such as sCD14 and sCD163 compared with placebo[13]. Similarly, Funderburg *et al*. reported that 48 weeks of rosuvastatin (10 mg daily) significantly decreased sCD14, Lp-PLA_2, IP-10, and tissue factor-positive patrolling monocytes, alongside reductions in T-cell activation[17]. Toribio *et al*. also demonstrated that pitavastatin induced greater reductions in oxLDL and Lp-PLA_2 than pravastatin[20].

By contrast, neutral effects were seen in some studies. Hearps *et al*. found that high-dose rosuvastatin (20 mg daily for 48 weeks) did not significantly change plasma IL-6, soluble TNF-R][, CXCL10, sCD14, or sVCAM-1 among PLWH at intermediate cardiovascular risk, though it altered monocyte subset distribution[18]. Similarly, Srichatrapimuk *et al*. reported no significant change in hs-CRP or most cytokines with pitavastatin (2 mg daily), although basic fibroblast growth factor increased and activation markers on $CD4^+$ T-cells was decreased[22]. In a 52-week trial specifically designed to compare pitavastatin with pravastatin for treating dyslipidemia in people with HIV, Defilippi *et al*. demonstrated differential effects on novel biomarkers including TFPI, paraoxonase 3, low-density lipoprotein receptor, and galectin-4, supporting broader anti-inflammatory effects of statins beyond conventional markers[19]. Shorter term studies showed more modest results. Nixon *et al*. using atorvastatin up to 20 mg daily in a crossover design, reported no consistent reductions in hs-CRP, IL-6, or *D*-dimer, though modest declines in oxLDL and Lp-PLA_2 were noted[21]. Eckard *et al*. observed significant reductions in Lp-PLA_2 after 24 weeks of rosuvastatin but no effect on hs-CRP or IL-6[16]. Hileman *et al*. further confirmed in a study of rosuvastatin in HIV that 48 weeks of treatment reduced oxLDL and some immune activation markers, though changes in hs-CRP and IL-6 were less consistent[14]. Overall, statin therapy in PLWH appears to reduce specific vascular inflammatory biomarkers particularly oxLDL, Lp-PLA_2, and monocyte activation markers (sCD14, sCD163) with less consistent effects on systemic cytokines such as hs-CRP and IL-6. Differences in findings may relate to the choice of statin (pitavastatin *vs*. rosuvastatin *vs*. atorvastatin), study duration, baseline risk, and the spectrum of biomarkers analyzed.

3.3. Results from the quality appraisal

The risk of bias assessment for the nine included randomized controlled trials was conducted using the Cochrane RoB 2 tool. The results are summarized in Figure 2, which presents the proportion of studies judged as low risk or some concerns across the five domains and the overall assessment. In general, the included trials demonstrated acceptable methodological quality, with most domains rated as low risk and none categorized as high risk of bias. For the randomization process, the majority of studies were at low risk[13,14,16,17,20,21], while three studies provided insufficient methodological detail, resulting in some concerns[18,19,22]. All studies were judged at low risk for deviations from intended interventions, as they were double-blind, placebo-controlled, and implemented regular adherence monitoring. For missing outcome data, four trials provided nearly complete follow-up and were rated low risk[20–22]; while others reported partial attrition in biomarker subgroups or incomplete explanations for missing data, leading to some concerns[13,14,17–19]. The measurement of outcomes was consistently judged low risk, as biomarkers were assessed using validated assays in central laboratories, with blinded outcome assessors. In the domain of selection of the reported result, most studies were judged as low risk because the reported outcomes were generally consistent with the study objectives and prespecified biomarkers[19–21]. However, several studies raised some concerns due to limited information regarding prespecification of exploratory biomarker analyses or multiplicity adjustment for multiple outcomes[13,14,17,18,22]. In summary, most included RCTs were rated as low risk of bias in key domains such as randomization, blinding, and outcome measurement, while the main methodological limitations were related to incomplete reporting of missing biomarker data and the prespecification of exploratory endpoints. The graphical distribution of domain-level risk of bias judgments is shown in Figure 2.

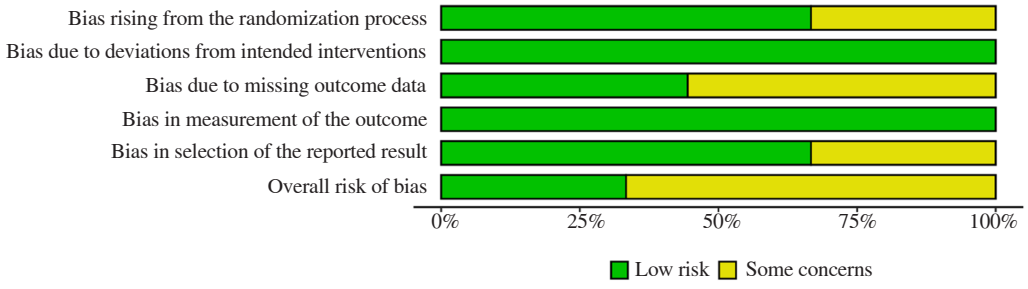


Figure 2. Summarized results of the quality appraisal based on the Cochrane Risk of Bias 2 (RoB 2) tool.

3.4. Stability and evolution of evidence in the living systematic review

Within the context of this living systematic review, the available evidence can be broadly categorized according to its stability and likelihood of change with future updates. Evidence supporting the anti-inflammatory effects of statin therapy on specific vascular biomarkers, particularly oxLDL, Lp-PLA_2, and markers of monocyte activation such as sCD14, appears relatively stable, as these findings have been consistently demonstrated across multiple randomized controlled trials with moderate to long treatment durations.

In contrast, evidence regarding the effects of statins on systemic inflammatory biomarkers, including high-sensitivity hs-CRP and IL-6, remains evolving. While reductions in these markers were observed in selected trials, particularly with pitavastatin and longer treatment durations, results across studies were heterogeneous and influenced by differences in statin class, baseline inflammatory status, and duration of therapy. Consequently, conclusions related to these biomarkers should be interpreted as provisional and may be refined as additional long-term randomized evidence becomes available.

Evidence derived from smaller trials, short-duration interventions, or exploratory biomarker panels is considered most likely to change with future updates of this living systematic review. Ongoing and future randomized studies with extended follow-up, larger sample sizes, or novel biomarker assessments are expected to further clarify the magnitude and consistency of statin-associated anti-inflammatory effects in PLWH. As this represents version 1.0 of the living systematic review, no changes from previous versions are reported.

4. Discussion

This living systematic review demonstrates that statin therapy, particularly pitavastatin, produces significant reductions in key inflammatory biomarkers among PLWH, providing important insights for cardiovascular risk management in this population. Our findings substantially extend previous research by elucidating specific patterns of statin effects within the context of HIV-associated inflammation.

The robust reduction in IL-6 levels observed with pitavastatin corroborates and expands upon earlier findings from the clinical trials investigating rosuvastatin[14]. Greater performance of pitavastatin may be related to its favorable pharmacokinetic profile and minimal drug-drug interactions with antiretroviral therapy, as demonstrated in recent clinical studies[13]. This finding is particularly significant given that elevated IL-6 levels have been independently associated with increased risk of cardiovascular events in PLWH[5,7].

Statins demonstrate a distinct pattern of monocyte modulation in HIV, characterized by a marked reduction in sCD14 alongside unchanged sCD163 levels, offering novel insights into their mechanism of action. These findings suggest that statins may preferentially influence pathways related to monocyte activation and microbial translocation, particularly those involving sCD14[17]. This specificity provides mechanistic insight into why statins demonstrate particular efficacy in HIV-related inflammation, where microbial translocation represents a key driver of immune activation[4]. Our findings thereby bridge an important knowledge gap between previous clinical trials by clarifying potential mechanisms for cardiovascular protection[13,14].

Our duration response findings provide crucial guidance for clinical practice, indicating that treatment periods exceeding twelve months yield substantially greater anti-inflammatory effects. This temporal pattern is consistent with the rationale underlying long-term statin therapy in HIV-focused cardiovascular prevention trials such as REPRIEVE[12]. The absence of a clear dose-response relationship, which contrasts with observations in the general population[11], may reflect pharmacokinetic interactions between statins and antiretroviral medications[22].

The clinical importance of optimizing cardiovascular prevention strategies in PLWH is further underscored by persistent inflammation and immune activation despite effective antiretroviral therapy[23], as well as the increased burden of heart failure and other cardiovascular complications observed in the ART era[24].

Several promising research directions emerge from our analysis. The substantial effect on sCD14 suggests that combining statins with gut-barrier strengthening agents might provide additive anti-inflammatory benefits[4]. The heterogeneous biomarker responses highlight the potential for precision medicine approaches utilizing baseline IL-6 or sCD14 levels to identify individuals most likely to benefit from statin therapy[3]. Future research should incorporate vascular imaging endpoints to correlate biomarker changes with anatomical outcomes, as successfully implemented in recent clinical trials[13]. On the other hand, the important limitations require consideration. Variability in biomarker assessment methodologies across studies, particularly for hs-CRP, underscores the need for standardized measurement protocols in HIV research. The underrepresentation of women and non-North American populations in included trials limits the generalizability of our findings and highlights important equity considerations. Furthermore, heterogeneity in patient populations across the included trials represents an additional limitation. Differences in baseline cardiovascular risk, lipid profiles, antiretroviral therapy regimens,

inflammatory status, and eligibility criteria may have influenced treatment responses and biomarker outcomes, making interpretation of the overall findings more challenging. Therefore, caution is warranted when generalizing these results to all populations of PLWH. Additionally, the limited data on emerging inflammatory markers suggest that future studies should incorporate broader biomarker panels to fully characterize the anti-inflammatory effects of statins in HIV.

In conclusion, our findings significantly advance understanding of statin therapy in HIV by identifying pitavastatin as the most effective statin class, clarifying specific inflammatory pathways affected, and providing evidence-based guidance regarding treatment duration. These results support the evolving paradigm of targeted anti-inflammatory therapy in HIV while highlighting critical areas for future investigation to optimize cardiovascular prevention in this vulnerable population.

Based on the current iteration of this living systematic review, statin therapy, particularly with pitavastatin, confers significant anti-inflammatory benefits in PLWH by effectively reducing key biomarkers of vascular inflammation and immune activation, such as IL-6 and soluble sCD14. These effects are most pronounced with longer treatment durations, highlighting the importance of sustained therapy to mitigate the chronic inflammatory state that persists despite effective antiretroviral therapy.

The greater efficacy of pitavastatin, attributed to its favorable pharmacokinetic profile and minimal drug-drug interactions with antiretroviral regimens, positions it as the preferred statin choice for addressing residual cardiovascular risk in this population. These findings address a critical gap in current clinical guidelines by providing evidence-based support for the selection of pitavastatin and underscoring the importance of long-term statin therapy in PLWH with evidence of persistent inflammation.

Future research should prioritize standardized biomarker assessment protocols, include more diverse demographic populations to enhance generalizability, and explore combination therapies targeting gut barrier integrity to provide additive anti-inflammatory effects. As this living systematic review continues to be updated, these findings support the integration of targeted anti-inflammatory strategies, with pitavastatin as a cornerstone, into comprehensive cardiovascular risk management for PLWH.

Conflict of interest statement

The authors declare that there is no conflict of interests.

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Authors' contributions

M.H. conceptualized the study, performed the literature search, extracted the data, and drafted the manuscript. M.A.N. contributed to data collection, literature screening, and manuscript editing. K.F.J. supervised the study design and critically revised the manuscript. D.D. contributed to data interpretation and methodological evaluation. M.S. contributed to quality assessment and final manuscript revision. All authors reviewed and approved the final version of the manuscript.

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Supplementary Table 1. Search strategy.

Database	Keyword combination
PubMed	(("statins"[tiab] OR "atorvastatin"[tiab] OR "rosuvastatin"[tiab] OR "pitavastatin"[tiab] OR "simvastatin"[tiab] OR "pravastatin"[tiab] OR "fluvastatin"[tiab] OR "lovastatin"[tiab]) AND ("HIV"[Mesh] OR "HIV Infections"[Mesh] OR "HIV"[tiab] OR "PLWH"[tiab] OR "people living with HIV"[tiab]) AND ("Biomarkers"[Mesh] OR "inflammation"[tiab] OR "vascular inflammation"[tiab] OR "immune activation"[tiab]))
Scopus	TITLE-ABS-KEY(("statin*" OR "atorvastatin" OR "rosuvastatin" OR "pitavastatin" OR "simvastatin" OR "pravastatin" OR "fluvastatin" OR "lovastatin") AND ("HIV" OR "PLWH" OR "people living with HIV") AND ("biomarker*" OR "inflammation" OR "vascular inflammation" OR "immune activation"))
Scilit	("statin therapy" OR "HMG-CoA reductase inhibitor*" OR statin* OR atorvastatin OR rosuvastatin OR pitavastatin)[Title, Abstract, Keyword] AND ("HIV" OR "people living with HIV" OR "PLWH" OR "AIDS" OR "acquired immunodeficiency syndrome")[Title] AND ("vascular inflammation" OR "inflammatory biomarker*")[Title, Abstract, Keyword]
Cochrane Library	Statins on inflammatory markers in HIV in Title Abstract Keyword

Supplementary Table 2. Risk of bias assessment using the Cochrane RoB 2 tool.

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result (reporting bias)	Overall
Lu *et al*.[13] (2024)	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Eckard *et al*.[16] (2014)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Funderburg *et al*.[17] (2015)	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Hearps *et al*.[18] (2021)	Some concerns	Low risk	Some concerns	Low risk	Some concerns	Some concerns
DeFilippi *et al*.[19] (2020)	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns
Hileman *et al*.[14] (2016)	Low risk	Low risk	Some concerns	Low risk	Some concerns	Some concerns
Toribio *et al*.[20] (2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nixon *et al*.[21] (2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Srichatrapimuk *et al*.[22] (2023)	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns