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Review Article

Monocytes in HIV associated atherosclerosis: A review of pathogenesis and clinical implications

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Abstract

Atherosclerosis, a chronic inflammatory disease of arterial walls, remains a leading cause of global mortality, with ischemic heart disease (IHD) and stroke as primary contributors. In people living with HIV (PLWH), this risk is amplified due to persistent immune activation and conventional cardiovascular risk factors such as hypertension and dyslipidemia. HIV-specific mechanisms, including viral proteins, gut microbial translocation, and chronic inflammation, drive monocyte dysfunction, foam cell formation, and vascular damage, contributing to accelerated atherogenesis. Antiretroviral therapy (ART) has significantly improved the life expectancy of PLWH, transforming HIV into a chronic condition. However, ART does not fully normalize immune activation, particularly monocyte-driven inflammation, which remains central to atherosclerosis progression. Protease inhibitor (PI)-based ART regimens are associated with metabolic disturbances, exacerbating dyslipidemia and insulin resistance, further increasing cardiovascular disease (CVD) risk. Imaging techniques, such as carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) scoring, reveal subclinical atherosclerosis in this population. Adjunctive therapies like statins and anti-inflammatory agents, including interleukin (IL)-1β antagonists, show promise in mitigating inflammation and CVD risk. Targeted strategies addressing monocyte activation, chronic inflammation, and gut microbial translocation are critical. Comprehensive care for PLWH requires integrating ART optimization with lifestyle interventions, lipid-lowering therapies, and novel treatments targeting immune dysfunction. Future research should refine biomarkers for early atherosclerosis detection, tailor CVD risk assessments, and explore therapeutic innovations to reduce cardiovascular morbidity and mortality in PLWH.

Keywords: Monocytes, HIV, Atherosclerosis, Pathogenesis.

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Atherosclerosis, a persistent and evolving inflammatory condition impacting arterial walls, stands as a major global health issue, accounting for more than half of all deaths worldwide (1). This disease initiates shortly after birth, with environmental influences playing a critical role in its progression (2). The classic trio of risk factors hypertension, hyperlipidemia, and diabetes mellitus significantly drives its development (3). Atherosclerotic cardiovascular diseases(ASCVDs), including ischemic heart disease (IHD) and stroke, in order, are the first and fifth cause of death globally (3).

Most of the atherosclerosis risk factors make the vessel susceptible to reactive oxygen species production, which interferes with many important enzyme systems in atherogenesis (4). In its initial stages, arteriogenesis begins with the formation of foam cells, cholesterol-laden macrophage clusters that gather in specific, susceptible regions of arterial walls within the first decade of life (2). This process is driven by blood flow dynamics and unique arterial wall characteristics (5).

The buildup of minimally oxidized low-density lipoprotein (LDL) sparks this aggregation, prompting endothelial cells (ECs) to produce pro-inflammatory molecules, including macrophage colony-stimulating factor (M-CSF), as well as various growth factors and adhesion molecules (4). Over time, these early lesions may evolve into more complex plaques, characterized by necrotic lipid debris and the involvement of smooth muscle cells (SMCs) (2, 5). The role of the immune system in atherogenesis is well established over time. All types of CD4+ T cells found in atherosclerotic plaques have a conflicting effect in the process (5). Within atherosclerotic lesions, various immune cells exert distinct influences on disease progression. T-helper 1 (TH1) cells, for instance, secrete interferon-gamma (IFN-γ), a proatherogenic factor linked to plaque instability (6). In contrast, regulatory T cells (TREG) promote homeostasis and curb plaque development. Other subsets, such as TH2, TH17, and T follicular cells, exhibit context-dependent effects, acting as either atherogenic or atheroprotective depending on the circumstances (7). CD8+ cytotoxic T cells are also present and appear particularly significant in advanced, ruptured plaques, where they predominate. The role of B cells in atherogenesis remains complex and dual-natured: B2 cells, through a T cell-dependent germinal center response, produce IgA, IgG, and IgE antibodies that contribute to atherogenic processes, while B1 cells generate extrafollicular, marginal zone-derived IgM antibodies that offer atheroprotective benefits (5, 6). HIV, an enveloped RNA retrovirus, initiates chronic inflammation by binding to the CD4 receptor and co-receptor of its host cell, the T-helper cell, entering the cell and compelling it to produce essential proteins and glycoproteins, leading to cell death like other members of the Retroviridae family (8). Despite the initial immune system response, the virus cannot be eliminated entirely, and the infection results in inflammation. Though symptoms may emerge slowly, viruses can disrupt immune regulation, triggering serious health complications (9). In HIV-positive individuals, heightened inflammatory and coagulation markers signal increased risks, with inflammation and hypercoagulation strongly predicting morbidity and mortality. In 2022, the CDC projected 1.2 million people living with HIV, who faced double the risk of cardiovascular disease compared to uninfected individuals (10). From 1990 to 2015, among 793,635 HIV-positive individuals, the crude cardiovascular disease rate was 61.8% per 10,000 person-years, with a risk ratio of 2.16 relative to healthy peers (11). Antiretroviral therapy (ART) has extended the life expectancy of adherent HIV-positive patients to near-normal levels, shifting focus to chronic conditions like atherosclerotic cardiovascular disease (ASCVD) in later life (12). Given atherosclerosis's critical role in cardiovascular disease and its profound effect on HIV patients, understanding HIV-related chronic inflammation's impact on atherogenesis is essential. This review highlights monocytes' key contribution to atherosclerosis, as they differentiate into foam cells that drive plaque formation and vascular inflammation. These processes persist even in virologically suppressed individuals, underscoring that ART alone cannot fully mitigate the risks of HIV-driven inflammation.

Pathogenesis of atherosclerosis in HIV-positive individuals: The exact mechanisms responsible for HIV-associated ASCVD are not fully understood. However, key factors include the impact of HIV proteins on immune and vascular cells. Proteins like glycoprotein (GP) 120, trans-activator of transcription (Tat), and adverse regulatory factor (Ner) have been found to directly harm vascular cell lines (13). Some of the major known risk factors of atherosclerosis-related cardiovascular diseases are much more significant in HIV-positive patients. Prevalence of risk factors such as dyslipidemia, hyperinsulinemia, albuminuria, endothelial dysfunction, and adipose redistribution are increased among HIV-positive patients compared with general populations (14-16). Age, hypertension, metabolic syndrome, hypercholesteremia, tobacco use, and a CD4/CD8 ratio below 0.7 are also represented as subclinical atherosclerosis risk factors among HIV patients (17-19).

As we know, the process of atherosclerosis starts at the endothelium. HIV is associated with endothelial dysfunction in various mechanisms. HIV seemed to directly affect vascular cell lines through Gp 120, Tat, and Ner (20). These viral proteins stimulate endothelial cells to produce inflammatory cytokines like IL-6 and IL-8 and adhesion molecules such as intercellular adhesion molecule 1(ICAM-1) and matrix metalloproteinase (MMP) 2/9, contributing to macrophage accumulation (21). On the other hand, CD8+ T cells and CD68+ macrophage/monocyte subendothelial recruitment are increased in HIV-infected nonhuman primates. Also, endothelial nitric oxide synthase (eNOS) functions as an atheroprotective factor by producing nitric oxide (NO), which has decreased compared to non-HIV infected (20, 21). At the stage of foam cell formation, in which oxidized LDL is mentioned above as a trigger factor, HIV can also interfere by dysregulating several aspects of cholesterol metabolism. Antiviral cytokines against HIV, such as IFN-y, TNF-a, and IL-1, can cause dyslipidemia by direct or indirect roots, which contribute to decreased triglyceride clearance at the AIDS stage (22, 23), leading to

increased triglyceride levels and decreased HDL-induced hepatic fatty acid production, VLDL synthesis, and lipid metabolism dysregulation (24). Nevertheless, untreated HIV-positive patients' follow-up showed no significant difference in total cholesterol and LDL concentration after two years of follow-up (25). Several enzymatic processes, such as ROS, cause LDL oxidation. HIV upregulates inflammatory molecules such as TNF-a, macrophage inflammatory protein-1, and IL-1B, which positively modulate ROS and precipitate LDL oxidation (24). HIV can also interfere with foam cell apoptosis, causing more inflammation. HIV Nef directly interacts with the inositol triphosphate receptor and causes ionized calcium influx to the endoplasmic reticulum of foam cells, and this calcium dysregulation induces apoptosis (26, 27). In addition, the prohibitory effect of HIV on immune cell autophagy seemed to be effective in atherogenesis (27, 28). HIV Nef can also interact with cholesterol efflux regulatory receptors like ATP-binding cassette transporter A1 (ABCA1), increasing cholesterol entering foam cells, precipitating lipid accumulation, and cell death (21).

HIV impairs homeostasis as well and can be potentially relevant to coronary heart disease and peripheral atherosclerosis. Both levels of D-dimer and Von Willebrand factor (vWF) are high in HIV-positive patients; clonal hematopoiesis related to that can be a risk factor for cancers and ASCVD (29). Also, the passage of microbial products through the liver over time causes liver damage, interferes with protein synthesis, and causes coagulopathy that intermediates vascular dysfunction and proceeds with atherogenesis (9). Some imbalanced coagulation factors, such as protein C or S deficiencies and higher platelet activation, have been seen in HIV-infected persons and are similar to those seen in acute coronary syndrome (21).

The immune system is involved in the progress of atherosclerosis in many ways. The presence of HIV fortifies the share of the innate immune system in atherogenesis. HIV infection mediates the NLRP3 inflammasome activation in macrophages, causing IL-1β and IL-18 release via TLR8-mediated mechanisms. The inflammasome over-activation is known to play a role in autoimmune or chronic diseases like atherosclerosis (21, 27). On the other hand, chronicity of HIV infection means the chronicity of toll-like receptors (TLRs) on the virus itself or bacterial component passing from the damaged gastrointestinal barrier exposure to the innate immune system and causing the monocyte response through IL-1B (30). After all, it seemed to be TLR2 and four activations as an essential member of pattern recognition receptors (PRRs) of the innate immune system that play a profound role in infection-related atherosclerosis (31). Also, altered gut microbiota in HIV-positive patients has some correlations with atherosclerosis plaque microbiota. Fusobacterium and Proteus, found in both regions in those patients, secreted enzymes that interfere with lipid metabolism and increase the risk of atherosclerosis (32). Like the innate immune system, other components of the adaptive immune system are affected by the virus and responsible for atherogenesis. HIV interferes with regulating B and T cells in various ways, which will be further investigated below. Patients with HIV have elevated levels of activation in both CD4+ and CD8+ T cells, as evidenced by the co-expression of CD38 and HLA-DR, which has been linked to subclinical atherosclerosis (21). The overproduction of BAFF, a TNF family member crucial for B cell maturation due to chronic HIV infection, disrupts B cell homeostasis. Given the conflicting proatherogenic and atheroprotective nature of B cells, dysregulated homeostasis plays a pivotal role in HIV-related atherosclerosis (33).

Role of monocytes in HIV associated atherosclerosis: Monocytes are central to atherosclerosis development, from early asymptomatic lesion formation to plaque rupture (34). In HIV infection, monocyte-driven inflammatory pathways amplify atherosclerotic lesion progression. Three monocyte subsets: classical (CD14++CD16-), intermediate/inflammatory (CD14+CD16+), and non-classical/patrolling (CD14dimCD16++) are distinguished by surface receptor expression (35). HIV-positive patients exhibit elevated levels of intermediate (CD14+CD16+) and non-classical (CD14dimCD16++) monocytes, tied to disrupted immune signaling and impaired cell cycle regulation (36). Among HIV patients on antiretroviral therapy (ART), intermediate monocytes strongly correlate with atherosclerosis, evidenced by increased carotid intima-media thickness (cIMT) and elevated D-dimer levels, directly linking them to atherogenesis (37). However, an ugandan study revealed a positive association between classical monocytes and coronary artery disease (CAD), while intermediate monocytes showed a negative correlation, highlighting population-specific roles of monocyte subsets (38). Muller et al. categorized participants into four groups based on HIV and subclinical cardiovascular disease (sCVD) status (HIV-/sCVD-, HIV-/sCVD+, HIV+/sCVD-, HIV+/sCVD+), finding that CXCR4 expression on non-classical monocytes was highest in HIV-/sCVD- and lowest in HIV+/sCVD+, suggesting an atheroprotective role for CXCR4.(35). Dysregulated monocyte migration pathways, such as cAMP signaling, significantly contribute to atherosclerosis in HIV-infected individuals (39). Additionally, IL-32, a cytokine that

recruits monocytes to coronary arteries by upregulating chemokines like CCL-2 and CXCL-8, is elevated in HIV patients (40-42). This monocyte involvement implies that IL-32 may drive atherosclerotic plaque formation in HIV-positive individuals through enhanced recruitment (43).

Kearns et al. analysis revealed higher Nod-like receptor protein 3 (NLRP3) mRNA levels in the spleens of these mice, pointing to the NLRP3 inflammasome's role in driving caspase-1 activation (44). Additionally, elevated IL-1β and IL-18 levels were observed in the HIV-transcript group, suggesting that HIV infection boosts caspase-1 activation in inflammatory monocytes, elevating IL-18 and fueling vascular atherosclerosis (45). Supporting this, Caocci et al. showed that monocytes from HIV patients display enhanced foam cell formation alongside elevated NLRP3, IL-1β, IL-18, and caspase-1 levels; inhibiting NLRP3 reduced foam cell formation, underscoring its role in atherosclerosis (46). Other studies further confirm the critical involvement of caspase-1 and monocytes in atherogenesis among HIV-positive individuals (47, 48). Research also shows that monocytes from HIV-positive patients on ART are more prone to forming lipid-laden foam cells compared to those from HIV-negative individuals. Impaired cholesterol efflux in monocytes from HIV-positive patients drives this increased foam cell formation, accompanied by elevated inflammatory markers like CXCL10 and sTNF-RII, highlighting the role of immune activation and inflammation in atherosclerosis (49). El-Far et al. linked gut microbiome changes in HIV-positive patients with atherosclerosis, showing increased Rothia and Eggerthella species and reduced SCFA caproic acid, which may upregulate IL-32, IL-18, and inflammation via monocytes, driving plaque formation (41). In HIV-positive individuals, non-HDL cholesterol correlates with monocyte margination, an effect stronger in Lu-positive patients, unlike in HIV-negative counterparts (50). Monocytes in HIV patients are more ROS-sensitive due to p90RSK activation, which inhibits NRF2 via ERK5 suppression, worsened by cART, promoting atherosclerosis (51). Table 1 outlines monocytes' role in HIV-related atherosclerosis.

Table 1. Role of monocytes in HIV associated atherosclerosis

Author, year	Cytokine/Cell line/ Inflammatory Marker	Expression	Model	Pathway	Main findings	Ref
Alison C. Kearns, 2019	IL1B, IL18/ Ly6+ monocytes	Up-regulation	Mice	Caspase-1 activation	Expression of HIV increases caspase-1 activity in inflammatory monocytes and contributes to atherosclerosis	(45)
	IL-18/sCD163, MCP-1, CXCL10, LPS	Up-regulation	Human	-		
Maurizio Caocci, 2024	NLRP3, IL-1B, IL-18, caspase-1	Up-regulation	Human	Foam cell formation	HIV infection increased foam cell formation and NLRP3 and downstream cytokines including IL-1B and IL-18.	(46)
Dominic C. Chow, 2023	D-dimer	elevated	Human	Coagulation	Intermediate Monocyte transmigration in HIV patients undergoing ART had a positive correlation with D-dimer and cIMT.	(37)
Remi Bunet, 2023	IL-32/ CCL-2, CXCL-8	Up-regulated	Human	ERK1/ERK2	IL-32 triggers monocyte migration to the coronary arteries through over-expression of the chemokines CCL-2 and CXCL-8	(42)
Mukta G. Palshikar,2022	CD14+ CD16+ monocytes	Up-regulated	Human	cAMP signaling	Genes and pathways related to dysregulated trans-endothelial migration of monocytes have been identified in atherosclerotic HIV patients.	(39)

Author, year	Cytokine/Cell line/ Inflammatory Marker	Expression	Model	Pathway	Main findings	Ref
C. T. Longenecker, 2022	CD69/ CX3CR1	Down-regulated	Human	-	In patients with HIV, CAD is negatively correlated with CD69+ expression and CX3CR1 expression and positively correlated with classical monocytes.	(38)
Mohamed El-Far, 2021	IL-32, IL-18, M1 macrophage TRAIL	Up-regulated Down-regulated	Human	Cholesterol transport	Altered gut microbiome and diminished caproic acid in HIV patients cause IL-32 and IL-18 up-regulation and down-regulation of TRAIL leading to inflammation and atherosclerosis.	(41)
Emily R.Bowman, 2020	TLR4, SR-A, CD163, Tissue Factor, and CD63/ CD14+CD16+ monocytes	Up-regulated	Human	Monocyte/ macrophage activation	Over-expression of innate immune receptors and activation markers on monocytes of HIV+ patients is related to inflammation and atherosclerosis.	(36)
Angelovich, 2020	CXCL10, sTNF-RII		Human	Foam cell formation	The impaired ability of monocytes to efflux cholesterol is related to form foam cells.	(49)
Meera V. Singh, 2019	NRF2/ ERK5	Down-regulation	Human/Mice	P90RSK-NRF2 signaling	Monocytes sensitivity to ROS mediated by p90RSK phosphorylation leading to NRF2 inhibition causes plaque formation in HIV+ patients.	(51)
Karin A. L. Mueller, 2019	CXCR4 on non-classical monocytes	Down-regulated	Human		CXCR4 expression on non-classical monocytes has an atheroprotective role	(35)
Modisa S. Motswaledi, 2019	Lu	-	Human		Monocytes margination related to non-HDL cholesterols is observed in patients living with HIV who are Lu-positive.	(50)

IL1B: Interleukin-1 Beta / IL18: Interleukin-18 / sCD163: Soluble CD163 / MCP-1: Monocyte Chemoattractant Protein-1 / CXCL10: C-X-C Motif Chemokine Ligand 10 / LPS: Lipopolysaccharide / NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3 / ART: Antiretroviral Therapy / cIMT: Carotid Intima-Media Thickness / CCL-2: C-C Motif Chemokine Ligand 2 / CXCL-8: C-X-C Motif Chemokine Ligand 8 / ERK1/ERK2: Extracellular Signal-Regulated Kinase ½ / cAMP: Cyclic Adenosine Monophosphate / CD14+ CD16+ monocytes: A subset of monocytes expressing CD14 and CD16 surface markers / CD69: Cluster of Differentiation 69 / CX3CR1: C-X3-C Motif Chemokine Receptor 1 / CAD: Coronary Artery Disease / TRAIL: TNF-Related Apoptosis-Inducing Ligand / TLR4: Toll-Like Receptor 4 / SR-A: Scavenger Receptor Class A / CD163: Cluster of Differentiation 163 / CD63: Cluster of Differentiation 63 / sTNF-RII: Soluble Tumor Necrosis Factor Receptor II / NRF2: Nuclear Factor Erythroid 2-Related Factor 2 / ERK5: Extracellular Signal-Regulated Kinase 5 / P90RSK: 90 kDa Ribosomal S6 Kinase / ROS: Reactive Oxygen Species / CXCR4: C-X-C Motif Chemokine Receptor 4 / Lu: Lutheran Blood Group.

Management strategies and prevention: ART has significantly improved the life expectancy of individuals living with HIV, transforming it into a chronic condition rather than a fatal disease. However, ART does not entirely resolve the chronic immune activation and inflammation associated with HIV, particularly in monocytes. Monocyte activation persists despite viral suppression, contributing to the development of various comorbidities, including CVD (52). In this section, we focus on understanding the influence of ART on monocytes and its implications for inflammation and cardiovascular risk and investigating some novel and traditional interventions to reduce HIV-associated CVD risk:

Influence of ART on monocytes: Ongoing activation of monocytes and macrophages is characterized by elevated levels of inflammatory cytokines and macrophage/monocyte biomarkers such as soluble CD14 and soluble CD163, which have distinct roles in inflammation and immune responses (53, 54). A cross-sectional study by Temu et al. showed that despite effective

viral suppression, levels of soluble CD14 (sCD14) and soluble CD163, markers of macrophage/monocyte activation, remained elevated in HIV-infected individuals (55). Elevated sCD14 levels are associated with an increased risk of non-AIDS-defining conditions, including CVD (56). Some ART regimens, particularly those involving protease inhibitors (PIs), are associated with metabolic disturbances that can exacerbate monocyte activation (57). PIs are known to contribute to dyslipidemia and insulin resistance, both of which are linked to increased monocyte activation and inflammation (57, 58). Studies using imaging techniques such as carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) scoring have provided evidence of subclinical atherosclerosis in HIV-infected individuals on PI-based ART. Hsue et al. utilized CIMT to evaluate subclinical atherosclerosis in HIV patients, revealing that those on protease inhibitors (PIs) exhibited markedly thicker carotid artery walls compared to those on non-PI regimens. This finding indicates that PIs may hasten atherosclerosis progression, even without overt cardiovascular disease (52). This suggests that PIs may accelerate the development of atherosclerosis even in the absence of clinically evident cardiovascular disease.

Given the link between PIs and heightened CV risk, clinicians must strategically select ART regimens, especially for patients with existing CV risk factors, by employing mitigation strategies such as: (1) switching from PI-based ART to regimens with better metabolic profiles like INSTI-based options, as Dathan et al. dyslipidemia was less common with INSTIs than boosted PIs—compared to dolutegravir, dyslipidemia was more frequent with elvitegravir/cobicistat and raltegravir but less so with rilpivirine (59); (2) incorporating lipid-lowering therapies like statins for patients requiring ongoing PI use to control dyslipidemia and lower atherosclerosis risk (60); and (3) exploring therapies targeting monocyte and macrophage activity, such as CCR2 or CSF-1 receptor inhibitors, which aim to reduce monocyte recruitment to arterial walls and curb macrophage-driven inflammation, potentially slowing plaque progression and CV events (59, 60).

Therapeutic measures

Statin: Statins, by inhibiting HMG-CoA reductase, are foundational in preventing atherosclerosis in HIV-negative individuals, but their role in PLWH is gaining traction due to elevated CV risk in this group (61, 62). Recent reviews have supported statins for primary and secondary CVD prevention in HIV patients. Stein et al.'s found statins effectively lowered LDL-C and reduced inflammation markers like CRP and IL-6 in PLWH, suggesting a role in curbing atherosclerosis-related inflammation (63). Banach et al. showed moderate-intensity statins significantly reduced LDL-C, TC, and non-HDL-C while raising HDL-C, with atorvastatin outperforming others in TC reduction, though no notable differences emerged in LDL-C, HDL-C, or TG changes across statins (64). The REPRIEVE trial with over 7,500 PLWH, tests pitavastatin a statin with minimal ART interactions revealing a lower MACE rate (4.81 vs. 7.32 per 1,000 person-years, $p = 0.002$) alongside reduced LDL-C and inflammation markers, reinforcing statins' value for this high-risk group (65). Longenecker et al. found rosuvastatin slowed CIMT progression in PLWH, even with low baseline LDL-C, highlighting statins' broader CV benefits beyond lipid control (66). Future research should optimize statin regimens for PLWH, especially with newer, metabolically favorable ART, while ongoing trials like REPRIEVE will refine guidelines.

Aspirin: Given platelets' key role in atherosclerosis, aspirin, an antiplatelet agent, has been extensively studied in clinical trials and observational research. Due to bleeding risks, the ACC and AHA recommend aspirin mainly for secondary prevention of atherosclerotic diseases, emphasizing the need to pinpoint high-risk patients where benefits exceed bleeding hazards (67), as its routine use for primary prevention may lack benefit and its therapeutic efficacy remains limited (68).

Interleukin 1 beta antagonist: IL-1β, a pro-inflammatory cytokine, drives the inflammatory cascade in atherosclerosis, with elevated levels linked to heightened inflammation and plaque instability (69). The CANTOS trial showed that canakinumab, an IL-1β-targeting monoclonal antibody, significantly lowered CV events in patients with prior MI, independent of lipid reduction (70), while a smaller HIV study found it reduced inflammatory markers and aortic inflammation (71).

IL-6 antagonists: IL-6, a key cytokine in inflammation, plays a significant role in atherosclerosis progression and is often elevated in PLWH, correlating with heightened CV risk (72). It drives atherosclerosis by inducing endothelial dysfunction, upregulating adhesion molecule expression on vascular endothelium, and boosting immune cell recruitment to arterial walls (73). Tocilizumab (TCZ), an IL-6 receptor antagonist, has been used in treating autoimmune conditions like rheumatoid arthritis and has shown promise in reducing inflammatory markers associated with cardiovascular risk (73). There is growing interest in exploring tocilizumab or other IL-6 pathway inhibitors in HIV patients with atherosclerosis, particularly those who have high residual inflammatory risk despite controlled HIV infection. A study by Bowman et al. showed

that the concentrations of multiple lipid classes increase with TCZ treatment. Still, the saturated fatty acid to unsaturated fatty acid improves for some classes. IL-6 blockade may reduce some indices of inflammation in PLWH but also exacerbates lipid levels. However, similar to IL-1β inhibitors, more research is needed to understand the impact of IL-6 blockade in the context of HIV and ART.

TNF-α inhibition: TNF-α, a powerful pro-inflammatory cytokine, significantly fuels the inflammatory response in atherosclerosis by recruiting inflammatory cells to the endothelium, aiding foam cell formation, and triggering other pro-inflammatory cytokines (74). In PLWH, elevated TNF-α levels are linked to heightened CV risk (75). TNF-α inhibitors, such as infliximab, adalimumab, and etanercept, are commonly used to treat inflammatory diseases like rheumatoid arthritis and psoriasis. These agents have shown effectiveness in reducing inflammation and could theoretically benefit HIV patients by lowering their cardiovascular risk (75, 76). However, TNF-α inhibitors also carry a risk of immunosuppression, which is a significant concern in HIV-infected individuals. The balance between reducing inflammation and maintaining immune competence must be carefully considered, and further studies are necessary to explore the safety and efficacy of TNF-α inhibition in this population.

Gut microbial translocation: Gut microbial translocation, where bacterial products like lipopolysaccharides (LPS) leak from the gut into the bloodstream, is a significant driver of systemic inflammation in HIV-infected individuals (77). This process leads to the chronic activation of the immune system and contributes to the development of atherosclerosis. Therapeutic strategies aimed at reducing gut microbial translocation or its inflammatory consequences could offer a novel approach to lowering cardiovascular risk in HIV patients. These strategies may include probiotics, prebiotics, or specific antibiotics to alter the gut microbiome and agents that neutralize LPS or block its receptors, such as TLR4 antagonists (78, 79). By addressing the root cause of inflammation, these therapies could substantially impact the progression of atherosclerosis. Table 2 summarizing Cardiovascular and Inflammatory Interventions in HIV-Positive Patients.

Table 2. Cardiovascular and Inflammatory Interventions in HIV-Positive Patients

Author, year	Therapeutic intervention	Target Cytokine/Cell Line/Inflammatory Marker	Effect	Recommendation and efficacy
Grinspoon et al. 2019	statin	Inhibition of HMACoA enzyme	lowering the incidence of majorpitavastatin daily adverse cardiovascular events, significant reductions in LDL-C levels and inflammation markers(65)	Based on the REPRIEVE study, PLWH aged 40 -75 with CVD risk>5% should start moderate-intensity statin therapy (80)
Hira et al.2022 **Arnet et al. 2019**	aspirin	Inhibition of the COX-1 pathway	No reduction in markers of T-cell/monocyte activation compared with untreated controls (81)	For treatment: In PLWH with >10% 10-year CVD risk, consider if there is no history of bleeding and are willing to take it for ten years(67, 82) not recommended for primary prevention
Hsue et al. 2018	Canakinumab	Monoclonal antibody, L-1ß Antagonists	A single dose significantly reduced circulating markers of inflammation (hs CRP, IL-6, sCD163. This was paralleled by reductions in leukopoietic activity, monocyte cytokine production, and arterial inflammation. No impact on T cell activation or monocyte subsets (71)	Additional studies are underway to determine the safety and efficacy of canakinumab in HIV.
Bowman et al. 2019	Tocilizumab	A monoclonal antibody, IL-6 Antagonists	TCZ administration increases total plasma lipids across multiple lipid classes and alters the fatty acid composition of the lipidome (83).	IL-6 blockade reduces indices of inflammation in HIV+ individuals, but the consequences of TCZ-mediated alteration of the lipidome and CVD risk require further study

Author, year	Therapeutic intervention	Target Cytokine/Cell Line/Inflammatory Marker	Effect	Recommendation and efficacy
Seriolo et al. 2006	infliximab, adalimumab, etanercept	TNF-α Inhibition	increase of total and HDL cholesterol improved endothelial function (75)	No studies on PLWH were performed. Risk of immunosuppression.
d'Ettorre et al. 2015	Gut Microbial Translocation	Gut Microbial Translocation	not consistently affected biomarkers of inflammation but changes to improve biomarkers of microbial translocation (84)	Low cost, but Optimal timing of intervention, duration, and dosing present challenges

Future directions and research opportunities: Even though HIV-associated atherosclerosis has been studied extensively, there are still a lot of unanswered questions about the long-term cardiovascular risks for people living with HIV (PLWH). One important area that needs more research is the exact molecular mechanisms through which monocyte activation leads to atherosclerosis in virologically suppressed individuals. While studies have identified monocyte-driven inflammation and cholesterol metabolism impairment as critical mechanisms, the persistence of immune activation and its role in CVD requires further investigation (85). Identifying how residual viral proteins, like HIV Nef, continue to encourage foam cell formation and plaque development despite ART should be the primary goal of research (86). Additionally, the disparity in CVD outcomes between HIV-positive people demands the question of why some patients show resilience despite similar levels of monocyte activation and conventional risk factors (87). Identifying protective genetic factors or lifestyle changes could help inform personalized interventions. To create more precise risk stratification tools for clinical use, large-scale, longitudinal studies need to be conducted to monitor immune activation markers like sCD14 and IL-6 over time and correlate them with the progression of CVD (49). Furthermore, enhancing ART regimens to reduce off-target cardiovascular effects is still a top priority. Newer ART combinations show less direct cardiovascular toxicity, but how they affect inflammation and monocyte activation over time is unclear. To evaluate the efficacy of adjunct therapies in reducing cardiovascular risks, future studies should look into anti-inflammatory medications like statins or monoclonal antibodies that target interleukins (e.g., IL-6, IL-1ß) (88). Studies such as REPRIEVE (large scale clinical trial to test a strategy to prevent heart disease among people living with HIV) are critical in evaluating these therapies in combination with ART.The role of gut microbial translocation in driving systemic inflammation also requires further research (85). There is growing evidence that the dysfunction of the gut barrier is the cause of the chronic immune activation in PLWH, which raises the risk of cardiovascular disease. New approaches to lowering inflammation and atherosclerosis may be found by looking into therapeutic interventions that repair gut integrity, such as probiotics or microbial transplants. Finally, there is a necessity for the development of non-invasive biomarkers that can more precisely predict cardiovascular disease risk in HIV-positive populations. Traditional risk models fail to account for the unique inflammatory burden observed in this group. New biomarkers, such as oxidized lipoproteins (e.g. oxLDL and oxHDL) and markers of monocyte activation, may enhance risk assessment and guide early intervention methods (86). To sum up, filling in these research gaps is essential to improving the clinical management of CVD in those living with HIV. Future research should focus on improving ART regimens, finding new therapeutic targets, and enhancing cardiovascular risk prediction models to improve patient outcomes.

The complex relationship between HIV infection, chronic inflammation, and CVD risk has become known as a critical issue as people living with HIV benefit from prolonged lifespans due to effective ART. Despite viral suppression, ongoing immune activation, especially monocyte activation, persists in promoting atherosclerosis, leading to increased cardiovascular disease rates in this group of individuals. Significant research has shown that monocytes from HIV-positive individuals display impaired cholesterol efflux, increased foam cell formation, and decreased reverse transmigration, all of which are essential in the pathogenesis of atherosclerosis. HIV-specific factors, such as viral proteins like Nef and residual immune activation exacerbate these dysfunctions. They are not only linked to traditional risk factors like dyslipidemia or hypertension. Such findings underscore the need for adjunctive therapies targeting inflammation, as ART cannot wholly normalize these pathways.In addition to direct

immune mechanisms, conventional CVD risk factors (such as smoking, hypertension, and ART-induced dyslipidemia) contribute to the increased CVD risk in PLWH. Although ART regimens have been modified to reduce cardiovascular toxicity, newer therapies have not entirely removed these risks. Comprehensive CVD prevention in this population requires the combination of anti-inflammatory medications like statins and lifestyle changes like smoking cessation and diet management. The future of managing HIV-associated CVD depends on gaining a better understanding of how immune activation persists despite viral suppression, as well as developing targeted therapies that address the underlying causes of inflammation. Large-scale clinical trials, such as the REPRIEVE trial, will guide therapeutic decisions and improve patient care. Furthermore, developing non-invasive biomarkers to detect early atherosclerosis and tailoring risk assessment models specifically for PLWH could significantly improve cardiovascular outcomes. In conclusion, although ART has dramatically increased the life expectancy of PLWH, it has not entirely solved the cardiovascular challenges caused by immunological activation and chronic inflammation. Understanding the role of monocytes in driving atherosclerosis in this context provides crucial insights into the mechanisms of HIV-related CVD. It emphasizes the importance of developing integrated treatment strategies beyond viral suppression. Ongoing research should focus on novel interventions to target immune dysfunction, optimize ART, and better assess cardiovascular risk, ensuring HIV patients' long-term health and quality of life.

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