

The Emerging Role of Interleukin-32 in HIV-Associated Cardiovascular Comorbidities: A Mini Review

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Abstract: With the widespread use of antiretroviral therapy (ART), the life expectancy of people living with HIV (PLWH) has significantly improved. However, the incidence of cardiovascular disease (CVD) in this population has progressively increased. PLWH exhibit a significantly higher risk of cardiovascular diseases compared to the general population. Consequently, CVD has become one of the leading contributors to mortality not related to AIDS. The pathogenesis may involve several factors: HIV-related proteins exacerbating endothelial injury and inflammation; immune activation and chronic inflammation; adverse effects of ART; and traditional cardiovascular risk factors. Although multiple inflammatory cytokines are implicated in HIV-associated CVD, interleukin-32 (IL-32) stands out due to its distinctive multifunctional properties. Compared with other cytokines, Interleukin-32 (IL-32), a multifunctional pro-inflammatory cytokine, plays key roles in inducing the release of inflammatory cytokines, promoting endothelial dysfunction, and driving monocyte migration. IL-32 is closely associated with the development of HIV-associated CVD and shows potential as a novel biomarker and therapeutic target. This review aims to summarize recent advances in understanding the role of IL-32 in HIV-associated CVD. It also provides new insights for the diagnosis and treatment of CVD in PLWH.

Keywords: IL-32, HIV, cardiovascular disease, chronic inflammation, biomarker

Introduction

Recent reports indicate that there are approximately 39.9 million people living with the human immunodeficiency virus (HIV) globally, with 1.3 million new HIV infections.¹ In recent years, the widespread use of antiretroviral therapy (ART) has significantly reduced AIDS-related mortality and markedly increased the life expectancy of people living with HIV (PLWH).² However, even with long-term effective ART, chronic inflammation and systemic immune activation markers do not return to normal levels in PLWH. This persistent chronic inflammation increases the risk of various comorbidities.^{3,4} Studies have shown that PLWH have a significantly higher risk of cardiovascular disease (CVD) comorbidities compared to the general population. Specifically, PLWH are more susceptible to atherosclerosis, myocardial infarction, ischemic cardiomyopathy, atrial fibrillation, heart failure, and stroke, with a CVD risk 1.5 to 2 times higher than that of the general population.⁵ This increased risk may be associated with chronic inflammation, immune activation, traditional cardiovascular risk factors, and the side effects of ART drugs. CVD has become one of the leading causes of non-AIDS-related morbidity and mortality.⁶ In recent years, the role of interleukin-32 (IL-32), a pleiotropic pro-inflammatory cytokine, in HIV-related CVD has gained increasing attention.

Research indicates that IL-32 expression is upregulated early in HIV infection and remains elevated even after ART, suggesting its involvement in HIV-associated chronic inflammation and immune activation. IL-32 affects cardiovascular health through multiple mechanisms, including promoting the release of pro-inflammatory factors, inducing endothelial dysfunction, driving monocyte migration, and exacerbating oxidative stress and cardiomyocyte apoptosis via signaling

pathways such as NOD2/NOX2/MAPK. Furthermore, different isoforms of IL-32 may have isoform-specific functions in HIV-related CVD.

This review aims to outline the biological characteristics of IL-32 and to elucidate its potential mechanisms and recent research advances in HIV-associated chronic inflammation and CVD pathogenesis. Additionally, it provides perspectives on future translational research directions.

Risk Factors and Mechanisms of HIV-Associated CVD

The precise mechanisms by which HIV affects vascular function are not fully elucidated, but several factors are considered to play key roles in this damage.

Traditional Cardiovascular Risk Factors

The prevalence of traditional CVD risk factors varies across regions, populations, living environments, and diets. However, dyslipidemia, smoking, and hypertension consistently have significant impacts on CVD risk in PLWH. A European study revealed higher rates of smoking, dyslipidemia, hypertension, overweight, and obesity among HIV-positive individuals compared to their HIV-negative counterparts.⁷ A retrospective study in China identified dyslipidemia, smoking, hypertension, diabetes, and obesity as common traditional CVD risk factors in PLWH, with 67.7% of patients having at least one CVD risk factor.⁸

A study on CVD risk in PLWH indicated that the risk was relatively low for individuals under 50 years old, regardless of gender, but increased substantially beyond this age. Moreover, obesity and related CVD risk factors, such as type 2 diabetes, chronic kidney disease (CKD), hypertension, and hypertriglyceridemia, were highly prevalent in this cohort.⁹ Furthermore, studies have indicated that women living with HIV face a cardiovascular disease risk that is 1.5 to 2 times higher than that of men with HIV. The mechanisms underlying this elevated risk are multifactorial, involving metabolic dysregulation, accelerated reproductive aging, and amplified pathways of traditional risk factors. Simultaneously, adolescent girls exhibit a heightened biological susceptibility to HIV acquisition due to distinct physiological factors, such as mucosal barrier vulnerability and hormonal influences.^{10,11}

A systematic review estimated the prevalence of hypertension in the HIV population to be as high as 35%, potentially linked to chronic immune activation and activation of the renin-angiotensin-aldosterone system.¹² The incidence of insulin resistance and diabetes is significantly higher in people with HIV than in the general population, likely caused by chronic inflammation, certain ARV drugs affecting glucose transport, and HIV proteins.¹³ Compared to the general population, traditional CVD risk factors are more prominent and prevalent among PLWH.

Inflammatory Response and Immune Activation

Chronic HIV infection leads to persistent inflammation. Studies have confirmed that people living with HIV (PLWH) exhibit abnormal inflammatory responses and immune activation. These aberrant markers strongly predict mortality, non-AIDS events, and the occurrence of cardiovascular disease (CVD). Compared to HIV-negative individuals, people living with HIV (PLWH) show more severe inflammatory responses that correlate with elevated circulating inflammatory markers. Defective viral particles and alterations in viral proteins may be key factors. HIV infection directly damages vascular endothelial cells, leading to increased permeability. In addition, HIV-associated proteins—primarily gp120, Tat, and Nef—promote vascular endothelial dysfunction. They do so by mediating endothelial cell activation and enhancing immune activation and inflammation.¹⁴ The gp120 protein disrupts endothelial cell function and cellular junctions, increasing vascular permeability and triggering pathological changes such as vascular degeneration and necrosis, ultimately leading to cardiovascular disease.¹⁵ The Nef protein enhances the adhesion of T lymphocytes to endothelial cells, alters cholesterol homeostasis within endothelial cells, impairs cholesterol efflux, and promotes foam cell formation.¹⁶ Research indicates that the HIV transactivator of transcription (Tat) protein acts as a trans-activator activating Nuclear Factor-kappa B (NF- κ B) signaling. This induces the expression of inflammatory mediators in monocytes and macrophages and promotes the secretion of inflammatory cytokines IL-6 and TNF- α .^{17,18} Both IL-6 and TNF- α play significant roles in the development and progression of CVD. IL-6 can induce the expression of adhesion molecules and chemokines in vascular endothelial cells, promoting the migration of inflammatory cells into the vascular

wall,¹⁹ It also stimulates the liver to produce more cholesterol, thereby exacerbating atherosclerotic lesions.²⁰ TNF- α is a cytokine with both pro-inflammatory and anti-inflammatory properties that also influences lipid metabolism by reducing HDL levels and increasing LDL levels. Elevated TNF- α levels in patients with coronary heart disease may exacerbate the inflammatory response.²¹

Furthermore, early damage to CCR5+ CD4+ T lymphocytes in the gut mucosa of PLWH causes microbial translocation. Microbes and their metabolites enter the systemic circulation through the compromised intestinal barrier, triggering immune activation and inflammatory responses.²² Reportedly, markers of microbial translocation are associated with inflammation and mortality markers in PLWH. Individuals with higher levels of microbial translocation markers exhibit increased levels of inflammatory cytokines IL-6 and TNF, potentially contributing to the pathogenesis of CVD.²³

A compromised immune system, indicated by a CD4 count <200 cells/ μ L or a CD8/CD4 ratio <1, increases the risk of subclinical CVD. A cross-sectional study in Thailand reported an association between low CD4 count and carotid artery stenosis or plaque formation,²⁴ and similar findings have been reported in other countries.²⁵ A cohort study also reported an association between the duration of ART exposure and abnormal carotid intima-media thickness (cIMT).²⁶ In AIDS patients under 50 years of age, a low CD4/CD8 ratio is an independent risk factor for increased CVD risk.²⁷ Moreover, the onset of subclinical CVD (such as abnormal cIMT and carotid plaques) in PLWH occurs earlier than in non-HIV individuals.^{28,29}

Impact of Antiretroviral Therapy

ART effectively suppresses viral replication, controls disease progression, and reverses the clinical course in PLWH. However, some ARV drugs may increase the risk of CVD. Numerous studies suggest that some ART regimens may contribute to endothelial dysfunction and promote atherosclerosis. Additionally, the use of antiretroviral drugs in PLWH is frequently associated with lipid metabolism disorders, which may be linked to enhanced innate immune activation. Protease inhibitors, particularly ritonavir, have been shown to significantly elevate levels of triglycerides, total cholesterol, and LDL cholesterol.^{30–32} Research by Msoka et al confirmed that combination therapies comprising different regimens of nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) exacerbate inflammatory responses in arterial endothelial cells; thereby, accelerating the development of cardiovascular disease.³³ Additionally, ART may induce mitochondrial dysfunction, leading to the activation of inflammatory and immune cells.³⁴

Biological Functions of IL-32

Interleukin-32 (IL-32) is a relatively novel cytokine, also known as tumor necrosis factor (TNF)- α -inducing factor and natural killer cell transcript 4 (NK4). Identified as a pro-inflammatory cytokine, it was first discovered and named in 2005.³⁵ The IL-32 gene is located on human chromosome 16p13.3. It encodes multiple isoforms at the mRNA level through alternative splicing, such as IL-32 α , IL-32 β , IL-32 γ , IL-32 δ , IL-32 ϵ , IL-32 ζ , IL-32 η , IL-32 θ , and a small IL-32 isoform. The expression patterns and functions of different IL-32 isoforms may vary across tissues and cell types. IL-32 α is the most common isoform and has been shown to induce inflammation by upregulating IL-8, TNF, and CCL2. In contrast, IL-32 θ has demonstrated anti-inflammatory effects that may function as a tumor suppressor, while IL-32 γ is considered the most biologically active isoform.^{36,37}

Previous studies have reported IL-32 expression in various immune and non-immune cells, including T cells, natural killer (NK) cells, monocytes, macrophages, and epithelial cells. Human monocytes can produce endogenous IL-32, and its levels increase upon stimulation with IL-1 β and TNF- α . IL-32 can induce the release of multiple cytokines and chemokines, including tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and interleukin-8 (IL-8), leading to increased cytokine expression in the extracellular matrix. It is associated with a growing number of diseases such as arthritis, inflammatory bowel disease, and skin disorders, and plays important roles in numerous biological processes. These include antimicrobial responses, inflammation, immune activation, immune suppression, mitogenic signaling, migration, adhesion, angiogenesis, metabolism, oxidative stress, cell death, and bone homeostasis. Additionally, IL-32 can enhance antiviral immune responses and promote the clearance of virus-infected cells.^{38,39}

Research indicates that IL-32 is involved in various cancers and may serve as a biomarker for cancer immune infiltration and poor prognosis. For example, exosomal IL-32 promotes M2 macrophage polarization and metastasis in esophageal squamous cell carcinoma via the FAK/STAT3 pathway.⁴⁰ Activation of Toll-like receptors (TLRs) in multiple myeloma (MM) cells promotes IL-32 expression via NF- κ B activation. This increase enhances MM cell proliferation and survival and may be associated with tumor recurrence.⁴¹ Patients with active chronic hepatitis B show an increased frequency of the IL-32 T allele and elevated serum IL-32 levels. Moreover, the IL-32 T/T polymorphism may be associated with liver flares in chronic HBV infection.⁴² Chang et al detected IL-32 expression in tissue and blood samples from patients with atopic dermatitis. IL-32 upregulates JAK1 expression and phosphorylation of downstream genes, promotes miR-155 expression, thereby activating the JAK signaling pathway and contributing to the development of atopic dermatitis.⁴³ IL-32 polarizes inflammatory reactive astrocytes and is upregulated in astrocytes within multiple sclerosis lesions, where it activates mTOR. Additionally, IL-32 influences metabolic disorders in human nucleus pulposus cells by activating FAT4-mediated Hippo/YAP signaling, thereby exacerbating intervertebral disc degeneration.⁴⁴ Downregulation of IL-32 reduces triglyceride and type I collagen levels in primary hepatocytes, implicating it in non-alcoholic fatty liver disease and insulin resistance.³⁹

Based on the persistent upregulation of IL-32 in HIV infection and its independent pathogenic role in CVD, we propose it as a key bridging molecule connecting the two disease processes for further investigation.

Potential Significance of IL-32 in HIV and Cardiovascular Disease

IL-32 and HIV Infection

IL-32 is induced early following HIV infection and remains elevated in long-term treated HIV-1 patients, with IL-32 mRNA expression levels increasing with age. Plasma levels of total IL-32 predict inflammation, reflected by CD4⁺ T cell decline and increased viral load, in HIV-infected slow progressors. In HIV-1-infected individuals, increased IL-32 expression correlates with IFN- γ , Th1, and Tc1 responses, while showing a negative correlation with the frequency of intestinal T cell subsets producing interferon-gamma.^{45,46}

Early studies found that elevated IL-32 levels in HIV infection could suppress HIV replication.⁴⁷ However, recent research reveals a dual role for IL-32 in HIV-1 infection. IL-32 γ is considered the most active isoform. In contrast, IL-32 β typically acts as a safety switch by reducing chronic inflammation and modulating IL-32 γ effects.

In ART-treated HIV-1 patients, different IL-32 isoforms demonstrate distinct expression patterns and immune functions. All IL-32 isoforms are significantly upregulated, with IL-32 β being the dominant isoform in T cells and NK cells. Functionally, the isoforms play diverse roles in immune regulation: IL-32 γ exerts typical pro-inflammatory effects; IL-32 α exhibits anti-inflammatory properties; and IL-32 β demonstrates both pro- and anti-inflammatory functions, representing a unique dual-functional phenotype. Importantly, the strongly pro-inflammatory IL-32 γ isoform has been shown to specifically activate latently infected CD4⁺ T cells, leading to HIV-1 production.⁴⁸ IL-32 β and γ isoforms impair both the proliferation and effector functions of HIV-specific cytotoxic T lymphocytes (CTLs) by downregulating CD96 expression, thereby contributing to disease progression.⁴⁹ This suggests IL-32 γ may be a key factor in reactivating viral reservoirs and influencing disease progression.

Research has found that in monocyte-derived macrophages (MDMs), IL-32 inhibits HIV-1 production dependent on SAM domain and HD domain-containing protein 1 (SAMHD1), a deoxynucleoside triphosphate triphosphohydrolase that inhibits viral reverse transcription. IL-32 increases the non-phosphorylated, active form of SAMHD1, thereby suppressing viral reverse transcription. Concurrently, IL-32 upregulates immunosuppressive molecules in MDMs, including IDO1, IDO2, TDO, and PD-L1, which may support HIV-1 replication by suppressing T cell immune responses. IL-32 also indirectly promotes MDM motility, which may facilitate cell-to-cell HIV-1 transmission.⁵⁰

In HIV-associated Kaposi's sarcoma (KS) tissues, mRNA expression of IL-32 β and IL-32 γ isoforms is significantly higher than in non-HIV-associated KS and normal skin tissues, with a reduced splicing ratio of IL-32 γ to IL-32 β . Altered splicing from IL-32 γ to IL-32 β , along with IL-6, IL-8, and CXCR1 signaling, may counteract the pro-apoptotic effects of the IL-32 γ isoform, thereby favoring the progression of HIV-associated KS.⁵¹

These findings collectively indicate that the pro-inflammatory cytokine IL-32 is highly expressed in the serum and tissues of PLWH and may participate in HIV-associated chronic inflammation and immune activation.

Role of IL-32 in Cardiovascular Disease

The role of IL-32 in cardiovascular disease is increasingly recognized. Specifically, studies have identified elevated IL-32 expression in atherosclerotic plaques, where it promotes inflammatory responses in vascular endothelial cells and smooth muscle cells, thereby accelerating atherosclerosis progression and correlating with unstable plaque phenotypes.⁵² Compared to coronary arteries from healthy donors, atherosclerotic plaques from patients with coronary artery disease (CAD) demonstrate significantly increased IL-32 expression in macrophages. Furthermore, plasma levels of IL-32, interferon-gamma (IFN- γ), and interleukin-17 (IL-17) are substantially higher in CAD patients—including those with stable angina, unstable angina, and acute myocardial infarction—compared to non-CAD controls, increasing progressively with CAD severity. Plasma IL-32 levels may correlate with both the Gensini score (an indicator of coronary stenosis severity) and the efficacy of percutaneous coronary intervention (PCI) in CAD patients.^{53,54}

IL-32 is believed to regulate endothelial cell function and serum high-density lipoprotein (HDL) concentration, and it also modulates key inflammatory pathways implicated in inflammatory diseases and atherogenesis—including TNF- α , IL-6, and IL-1 β .⁵⁵ Specific IL-32 isoforms (IL-32 β and γ) selectively influence the production of the pro-inflammatory cytokine IL-6 in coronary artery endothelial cells. These isoforms drive monocyte migration and induce endothelial dysfunction by upregulating adhesion molecules ICAM-1 and VCAM-1, as well as the chemoattractants CCL2, CXCL8, and CXCL1.⁵⁶

Moreover, IL-32 can induce cardiomyocyte apoptosis, potentially contributing to myocardial infarction and heart failure. A study modeled myocardial ischemia-reperfusion injury by subjecting cardiomyocytes to hypoxia/reoxygenation (H/R). IL-32 was shown to induce oxidative stress, inflammation, and apoptosis via the NOD2/NOX2/MAPK signaling pathway. Downregulation of IL-32 expression attenuated H/R-induced impairments in cell viability, LDH release, oxidative stress, inflammation, and apoptosis.⁵⁷ IL-32 can induce nitric oxide, pro-angiogenic molecule and IL-8 production by IFN- γ -stimulated endothelial cells by triggering the integrin α V β 3 signaling pathway, which implies that it has a critical role in angiogenesis.⁵⁸

Emerging evidence indicates that IL-32 is highly expressed in human placental villi and enhances the invasive capacity of trophoblast cell lines (HTR8/SVneo cells). Through miR-205-mediated regulation of the NF- κ B pathway, IL-32 increases the expression of MMP2 and MMP9 in these cells, suggesting a potential role in pregnancy-induced hypertension.⁵⁹

Role of IL-32 in HIV-Associated CVD

Persistent inflammation during HIV infection is associated with increased cardiovascular disease (CVD) risk. A cross-sectional study compared peripheral blood IL-32 levels and carotid plaque presence between HIV-positive women (WLWH) and HIV-negative women. This study identified IL-32 as a potential biomarker for subclinical carotid atherosclerosis in WLWH.⁶⁰ Compared to HIV-negative controls, ART-treated PLWH show significantly elevated expression of all tested peripheral blood IL-32 isoforms (α , β , γ , δ , ϵ , and θ). Among these, IL-32 δ and IL-32 θ isoforms are further upregulated in individuals with coronary atherosclerosis. In vitro experiments suggest that IL-32 is associated with macrophage activation, IL-18 production, and downregulation of the atheroprotective protein TRAIL. These factors collectively constitute a distinct pro-atherogenic inflammatory signature in PLWH. Concurrently, increased IL-32 isoform expression in PLWH correlates with gut microbiota alterations and reduced levels of the gut microbiota-derived short-chain fatty acid (SCFA) caproic acid. Caproic acid can attenuate IL-32, IL-18, and IL-1 β production by human PBMCs stimulated with bacterial LPS, thereby potentially counteracting atherosclerosis development.⁶¹ IL-32 β and IL-32 γ upregulate the production of the inflammatory cytokine IL-6 while downregulating the anti-inflammatory cytokine IL-10 in primary coronary artery endothelial cells (CAECs). They also significantly increase the expression of endothelial dysfunction markers ICAM-1 and VCAM-1. An association between IL-32 expression and arterial stiffness was observed in relatively young PLWH but not in older PLWH, suggesting that IL-32 may accelerate vascular disease at earlier ages in PLWH.⁵⁶

Research has found that IL-32 β and γ isoforms can induce a specific phenotype of CD4⁺ T cells expressing the c-Met receptor, conferring cardiac-homing properties. In vitro, IL-32 β and γ upregulate CCL22 and CCL24 expression—chemokines that may promote the migration of T cells expressing corresponding receptors to inflammatory sites. In PLWH, CCR4⁺CXCR3⁺ double-positive (DP) memory CD4⁺ T cell subsets with cardiac-homing potential are associated with subclinical

atherosclerosis, suggesting that IL-32 isoforms may exacerbate cardiac inflammation and CVD progression by promoting the homing of HIV-infected CD4⁺ T cells to the heart.⁶² In PLWH, different IL-32 isoforms exert opposing effects on the skeletal and vascular systems. The IL-32 α isoform promotes monocyte differentiation into osteoblasts and may inhibit pathological vascular calcification. In contrast, IL-32 β and IL-32 γ suppress this function by inhibiting TGF- β , instead inducing monocyte differentiation into osteocalcin-producing osteoblasts and exacerbating vascular calcification.⁶³

Collectively, these studies indicate that IL-32, particularly its pro-inflammatory isoforms, constitutes a central mechanism driving accelerated atherosclerosis in PLWH through chronic inflammation, endothelial dysfunction, and aberrant immune cell homing.

Conclusion

Although antiretroviral therapy has substantially improved clinical outcomes in PLWH, their risk of cardiovascular disease (CVD) remains persistently elevated compared with the general population. This excess risk is largely attributable to chronic inflammation that persists despite effective viral suppression. Established CVD risk prediction tools often underestimate the risk in this population.⁶⁴ Identifying novel inflammatory mediators with intrinsic potential as CVD biomarkers and therapeutic targets is therefore crucial for improved risk stratification and disease management in PLWH.

This review systematically delineates the emerging role of the pro-inflammatory cytokine IL-32 in the pathogenesis of CVD among PLWH. Current evidence indicates that the sustained high expression of IL-32—particularly the IL-32 β and IL-32 γ isoforms—following effective ART is a key driver of chronic inflammation and immune activation. It promotes the progression of atherosclerosis through multiple mechanisms, including inducing endothelial dysfunction, activating monocytes/macrophages, modulating cardiac homing in specific T-cell subsets, and exacerbating vascular calcification. The functional heterogeneity across IL-32 isoforms—exemplified by the potent pro-inflammatory and latent virus-reservoir activating effects of IL-32 γ versus the potentially anti-inflammatory and protective roles of IL-32 α —further amplifies the complexity of IL-32 within the linking HIV and cardiovascular disease pathological network.

However, research on the specific functions of individual IL-32 isoforms in HIV-associated CVD remains limited, and numerous questions require exploration. Current research in this field remains largely reliant on cross-sectional association analyses, with numerous critical questions still unresolved. Prospective cohort studies are urgently needed to establish whether IL-32 and its specific isoforms can serve as independent predictors of cardiovascular disease risk in PLWH and to determine their diagnostic thresholds as clinical biomarkers. From a therapeutic perspective, further preclinical and translational clinical studies are warranted to evaluate whether targeting IL-32 with monoclonal antibodies, siRNA, or small-molecule inhibitors can attenuate HIV-associated cardiovascular inflammation. Moreover, immunomodulatory strategies should extend beyond single-target approaches. Given the complexity of inflammatory networks, single-target interventions may be insufficient to fully control disease progression. For example, research in autoimmune diseases has demonstrated that certain natural compounds can modulate the Th17/Treg balance and reduce levels of inflammatory cytokines such as IL-6,⁶⁵ suggesting that multi-targeted modulation of inflammatory networks may offer promising adjunctive therapeutic avenues for HIV-related CVD.

Based on the current preliminary understanding of the role of IL-32 in HIV-associated cardiovascular disease (CVD), we propose that future research should advance in the following directions.

At the mechanistic level, knowledge regarding the precise signaling networks of different IL-32 isoforms in specific cell types—such as endothelial cells, smooth muscle cells, and tissue-resident macrophages—remains limited. Future basic research should employ novel technologies including single-cell sequencing and spatial transcriptomics to systematically map the intracellular signaling profiles specific to each IL-32 isoform. Particular attention should be paid to differences between IL-32 γ and IL-32 β in activating NF- κ B and MAPK pathways, and to how these differences influence downstream inflammatory cytokine cascades. Furthermore, the crosstalk between IL-32 and classical inflammatory pathways, such as the NLRP3 inflammasome and type I interferon signaling, may constitute a complex regulatory network. Deciphering this network could reveal novel targets for intervention.

In translational research, there is a need to establish preclinical animal models that recapitulate HIV-associated atherosclerosis to evaluate the efficacy of IL-32-targeted interventions. However, a major challenge is the absence of the IL-32 gene in conventional HIV-susceptible animal models, such as mice and non-human primates. Efforts should

therefore be directed toward developing IL-32-specific inhibitors—including monoclonal antibodies and small-molecule compounds—and designing rational early-phase clinical trial protocols. Notably, given the functional heterogeneity among IL-32 isoforms, future studies may require the development of isoform-selective inhibitors. For instance, selectively inhibiting the pro-inflammatory IL-32 γ isoform while preserving the potentially protective functions of IL-32 α could represent a more refined therapeutic strategy.

At the clinical research level, the scarcity of prospective cohort studies remains a key bottleneck in the field. Future investigations should focus on designing large-scale, multicenter longitudinal studies to systematically collect dynamic IL-32 expression profiles, cardiovascular imaging parameters, and clinical outcomes in PLWH. These studies should not only examine total IL-32 levels but also perform in-depth analyses of the correlation between shifts in isoform proportions and disease progression. Integrating such multidimensional data through approaches like machine learning may enable the construction of more accurate HIV-specific cardiovascular risk prediction models.

In summary, the role of IL-32 in HIV-associated CVD offers important insights into disease pathogenesis and the development of novel interventions. Continued efforts in these research directions will help to delineate a more comprehensive pathogenic network and may provide new biomarkers and therapeutic targets for the early diagnosis, risk stratification, and precision management of cardiovascular disease in PLWH, ultimately improving their long-term quality of life and cardiovascular health outcomes.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

References

1. World Health Statistics. Data on the size of the HIV/AIDS epidemic [Internet]. 2024 [cited October 20, 2025]. Available from: <https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/data-on-the-size-of-the-hiv-aids-epidemic?lang=en>. Accessed February 4, 2026.
2. McMyn NF, Variale J, Fray EJ, et al. The latent reservoir of inducible, infectious HIV-1 does not decrease despite decades of antiretroviral therapy. *J Clin Invest*. 2023;133(17):e171554. doi:10.1172/JCI171554
3. Mazzuti L, Turriziani O, Mezzaroma I. The many faces of immune activation in HIV-1 infection: a multifactorial interconnection. *Biomedicines*. 2023;11(1):159. doi:10.3390/biomedicines11010159
4. Bares SH, Wu X, Tassiopoulos K, et al. Weight Gain After Antiretroviral Therapy Initiation and Subsequent Risk of Metabolic and Cardiovascular Disease. *Clin Infect Dis*. 2024;78(2):395–401. doi:10.1093/cid/ciad545
5. Shah ASV, Stelzle D, Lee KK, et al. Global burden of atherosclerotic cardiovascular disease in people living with HIV: systematic review and meta-analysis. *Circulation*. 2018;138(11):1100–1112. doi:10.1161/CIRCULATIONAHA.117.033369
6. Du M, Zhang S, Liu M, Liu J. Cardiovascular disease and its risk factors among people living with HIV: a systematic review and meta-analysis. *J Infect Public Health*. 2025;18(2):102654. doi:10.1016/j.jiph.2025.102654
7. Dobe I, Manafe N, Majid N, Zimba I, Manuel B, Mocumbi A. Patterns of cardiovascular risk and disease in HIV-positive adults on anti-retroviral therapy in Mozambique. *Cardiovasc J Afr*. 2020;31(4):190–195. doi:10.5830/CVJA-2020-007
8. Guo F, Hsieh E, Lv W, et al. Cardiovascular disease risk among Chinese antiretroviral-naïve adults with advanced HIV disease. *BMC Infect Dis*. 2017;17(1):287. doi:10.1186/s12879-017-2358-0
9. Ko S, Dominguez-Dominguez L, Ottaway Z, et al. Cardiovascular disease risk in people of African ancestry with HIV in the United Kingdom. *HIV Med*. 2024;25(12):1289–1297. doi:10.1111/hiv.13706

10. Kentoffio K, Temu TM, Shakil SS, Zanni MV, Longenecker CT. Cardiovascular disease risk in women living with HIV. *Curr Opin HIV AIDS*. 2022;17(5):270. doi:10.1097/COH.0000000000000756
11. Musa SS, Othman ZK, Fadele KP, et al. Gender disparities in HIV infections: a narrative review of the persistent vulnerability of adolescent girls in Sub-Saharan Africa. *Narra X*. 2025;3(2):e211. doi:10.52225/narrax.v3i2.211
12. Rethy LB, Feinstein MJ, Achenbach CJ, et al. Antihypertensive class and cardiovascular outcomes in patients with HIV and hypertension. *Hypertension*. 2021;77(6):2023–2033. doi:10.1161/HYPERTENSIONAHA.120.16263
13. Spieler G, Westfall AO, Long DM, et al. Trends in diabetes incidence and associated risk factors among people with HIV in the current treatment era. *AIDS*. 2022;36(13):1811–1818. doi:10.1097/QAD.0000000000003348
14. Kovacs L, Kress TC, Belin de Chantemèle EJ. HIV, combination antiretroviral therapy, and vascular diseases in men and women. *JACC Basic Transl Sci*. 2022;7(4):410–421. doi:10.1016/j.jacbs.2021.10.017
15. Avagimyan A, Pogossova N, Kakturskiy L, et al. HIV-related atherosclerosis: state-of-the-art-review. *Curr Prob Cardiol*. 2023;48(9):101783. doi:10.1016/j.cpcardiol.2023.101783
16. Paternò Raddusa MS, Marino A, Ceslia BM, et al. Atherosclerosis and Cardiovascular Complications in People Living with HIV: a Focused Review. *Infect Dis Rep*. 2024;16(5):846–863. doi:10.3390/idr16050066
17. Meng Z, Hernandez R, Liu J, et al. HIV protein tat induces macrophage dysfunction and atherosclerosis development in low-density lipoprotein receptor-deficient mice. *Cardiovasc Drugs Ther*. 2022;36(2):201–215. doi:10.1007/s10557-021-07141-x
18. Perkins MV, Joseph SB, Dittmer DP, Mackman N. Cardiovascular Disease and Thrombosis in HIV Infection. *Arterioscler Thromb Vasc Biol*. 2023;43(2):175–191. doi:10.1161/ATVBAHA.122.318232
19. Dirajlal-Fargo S, Funderburg N. HIV and cardiovascular disease: the role of inflammation. *Curr Opin HIV AIDS*. 2022;17(5):286–292. doi:10.1097/COH.0000000000000755
20. Hsue PY, Waters DD. HIV infection and coronary heart disease: mechanisms and management. *Nat Rev Cardiol*. 2019;16(12):745–759. doi:10.1038/s41569-019-0219-9
21. Zegeye MM, Nakka SS, Andersson JSO, et al. Soluble LDL-receptor is induced by TNF- α and inhibits hepatocytic clearance of LDL-cholesterol. *J Mol Med*. 2023;101(12):1615–1626. doi:10.1007/s00109-023-02379-4
22. Ouyang J, Yan J, Zhou X, et al. Relevance of biomarkers indicating gut damage and microbial translocation in people living with HIV. *Front Immunol*. 2023;14:1173956. doi:10.3389/fimmu.2023.1173956
23. Tincati C, Bono V, Cannizzo ES, et al. Primary HIV infection features colonic damage and neutrophil inflammation yet containment of microbial translocation. *AIDS*. 2024;38(5):623–632. doi:10.1097/QAD.0000000000003799
24. Siwamogsatham S, Chutinet A, Vongsayan P, et al. Low CD4 cell counts are associated with carotid plaque and intima-media thickness in virologically suppressed HIV-infected Asians older than 50 years. *AIDS Res Hum Retroviruses*. 2019;35(11–12):1160–1169. doi:10.1089/aid.2019.0126
25. Utama S, Patriawan P, Dewi A. Correlation of CD4/CD8 Ratio with Carotid Intima-Media Layer Thickness in HIV/AIDS Patients at Sanglah General Hospital, Bali, Indonesia. *Open Access Maced J Med Sci*. 2019;7(11):1803–1807. doi:10.3889/oamjms.2019.479
26. Karim B, Wijaya IP, Rahmanyah R, et al. Factors affecting affect cardiovascular health in Indonesian HIV patients beginning ART. *AIDS Res Ther*. 2017;14(1):52. doi:10.1186/s12981-017-0180-9
27. Castilho JL, Shepherd BE, Koethe J, et al. CD4+/CD8+ ratio, age, and risk of serious noncommunicable diseases in HIV-infected adults on antiretroviral therapy. *AIDS*. 2016;30(6):899–908. doi:10.1097/QAD.0000000000001005
28. Aurpibul L, Srihanaviboonchai K, Kerkasem K, Tangmunkongvorakul A, Sitthi W, Musumari PM. Prevalence of subclinical atherosclerosis and risk of atherosclerotic cardiovascular disease in older adults living with HIV. *AIDS Res Hum Retroviruses*. 2019;35(11–12):1136–1142. doi:10.1089/aid.2019.0023
29. Putcharoen O, Pleumkanitkul S, Chutinet A, et al. Comparable carotid intima-media thickness among long-term virologically suppressed individuals with HIV and those without HIV in Thailand. *J Virus Erad*. 2019;5(1):23–27.
30. Alvi RM, Neilan AM, Tariq N, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV and heart failure. *J Am Coll Cardiol*. 2018;72(5):518–530. doi:10.1016/j.jacc.2018.04.083
31. Jia H. 基于CiteSpace的HIV/AIDS患者血脂异常研究热点可视化分析 - 中国知网 [Internet]. 2022 [cited October 19, 2025]. doi: 10.13419/j.cnki.aids.2024.04.06.
32. Xu J. 中老年人免疫缺陷病毒和获得性免疫缺陷综合征患者血脂异常的相关危险因素分析 - 中国知网 [Internet]. 2024 [cited October 19, 2025]. Available from: https://kns.cnki.net/kcms2/article/abstract?v=uFh1Y7sXU0KtwxtQIIHzBD0XNy429N7E7rdJZHK5MCV_sjhlY4sgdYJ0n2oKjy4wwTccAeC31hbUt4vTc56PUZ1NNR50_HVOy7GN-NABNkfCIRnWJq7PWYpX0Qr7xRXB_dghmL9TGUnade7EP2IN9o6UdnKwqgTBCItsOrTWZWRZQbe41xqdEg=&uniplatform=NZKPT&language=CHS. Accessed February 4, 2026.
33. Msoka TF, Van Guilder GP, Smulders YM, van Furth M, Bartlett JA, van Agtmael MA. Association of HIV-infection, antiretroviral treatment and metabolic syndrome with large artery stiffness: a cross-sectional study. *BMC Infect Dis*. 2018;18(1):708. doi:10.1186/s12879-018-3637-0
34. Santinelli L, Rossi G, Gioacchini G, et al. The crosstalk between gut barrier impairment, mitochondrial dysfunction, and microbiota alterations in people living with HIV. *J Med Virol*. 2023;95(1):e28402. doi:10.1002/jmv.28402
35. Kim SH, Han SY, Azam T, Yoon DY, Dinarello CA. Interleukin-32: a cytokine and inducer of TNF α . *Immunity*. 2005;22(1):131–142. doi:10.1016/j.immuni.2004.12.003
36. Dinarello CA, Kim SH. IL-32, a novel cytokine with a possible role in disease. *Ann Rheum Dis*. 2006;65(Suppl 3):iii61–64. doi:10.1136/ard.2006.058511
37. Hough JT, Zhao L, Lequio M, et al. IL-32 and its paradoxical role in neoplasia. *Crit Rev Oncol Hematol*. 2023;186:104011. doi:10.1016/j.critrevonc.2023.104011
38. Aass KR, Kastnes MH, Standal T. Molecular interactions and functions of IL-32. *J Leukoc Biol*. 2021;109(1):143–159. doi:10.1002/JLB.3MR0620-550R
39. Sasidharan K, Caddeo A, Jamialahmadi O, et al. IL32 downregulation lowers triglycerides and type I collagen in di-lineage human primary liver organoids. *Cell Rep Med*. 2024;5(1):101352. doi:10.1016/j.xcrm.2023.101352
40. Sun Y, Qian Y, Chen C, et al. Extracellular vesicle IL-32 promotes the M2 macrophage polarization and metastasis of esophageal squamous cell carcinoma via FAK/STAT3 pathway. *J Exp Clin Cancer Res*. 2022;41(1):145. doi:10.1186/s13046-022-02348-8

41. Aass KR, Tryggestad SS, Mjelle R, et al. IL-32 is induced by activation of toll-like receptors in multiple myeloma cells. *Front Immunol.* **2023**;14. doi:10.3389/fimmu.2023.1107844
42. Zheng S, Li M, Pan X, Huang X. Association of IL-32 rs28372698 polymorphism with active chronic HBV infection. *J Med Virol.* **2021**;93(11):6236–6240. doi:10.1002/jmv.27140
43. Chang J, Zhou B, Wei Z, Luo Y. IL-32 promotes the occurrence of atopic dermatitis by activating the JAK1/microRNA-155 axis. *J Transl Med.* **2022**;20(1):207. doi:10.1186/s12967-022-03375-x
44. Li P, Que Y, Wong C, et al. IL-32 aggravates metabolic disturbance in human nucleus pulposus cells by activating FAT4-mediated Hippo/YAP signaling. *Int Immunopharmacol.* **2024**;141:112966. doi:10.1016/j.intimp.2024.112966
45. El-Far M, Kouassi P, Sylla M, et al. Proinflammatory isoforms of IL-32 as novel and robust biomarkers for control failure in HIV-infected slow progressors. *Sci Rep.* **2016**;6:22902. doi:10.1038/srep22902
46. Santinelli L, Statzu M, Pierangeli A, et al. Increased expression of IL-32 correlates with IFN- γ , Th1 and Tc1 in virologically suppressed HIV-1-infected patients. *Cytokine.* **2019**;120:273–281. doi:10.1016/j.cyto.2019.01.012
47. Rasool ST, Tang H, Wu J, et al. Increased level of IL-32 during human immunodeficiency virus infection suppresses HIV replication. *Immunol Lett.* **2008**;117(2):161–167. doi:10.1016/j.imlet.2008.01.007
48. Zaidan SM, Leyre L, Bunet R, et al. Upregulation of IL-32 Isoforms in Virologically Suppressed HIV-Infected Individuals: potential Role in Persistent Inflammation and Transcription From Stable HIV-1 Reservoirs. *J Acquir Immune Defic Syndr.* **2019**;82(5):503–513. doi:10.1097/QAI.0000000000002185
49. Bunet R, Nayrac M, Ramani H, et al. Loss of CD96 expression as a marker of HIV-specific CD8⁺ T-cell differentiation and dysfunction. *Front Immunol.* **2021**;12:673061. doi:10.3389/fimmu.2021.673061
50. Nasser H, Takahashi N, Eltalkhaw Y, et al. Inhibitory and stimulatory effects of IL-32 on HIV-1 infection. *J Immunol.* **2022**;209(5):970–978. doi:10.4049/jimmunol.2200087
51. Semango G, Heinhuis B, Plantinga TS, et al. Exploring the role of IL-32 in HIV-related Kaposi sarcoma. *Am J Pathol.* **2018**;188(1):196–203. doi:10.1016/j.ajpath.2017.08.033
52. Law CC, Puranik R, Fan J, Fei J, Hambly BD, Bao S. Clinical Implications of IL-32, IL-34 and IL-37 in Atherosclerosis: speculative Role in Cardiovascular Manifestations of COVID-19. *Front Cardiovasc Med.* **2021**;8:630767. doi:10.3389/fcvm.2021.630767
53. Yang Z, Shi L, Xue Y, et al. Interleukin-32 increases in coronary arteries and plasma from patients with coronary artery disease. *Clin Chim Acta.* **2019**;497:104–109. doi:10.1016/j.cca.2019.07.019
54. Jin S, Liu X, Wang Y, Yu J, Jiang M. Effects of IL-32 polymorphisms and IL-32 levels on the susceptibility and severity of coronary artery disease. *J Clin Lab Analysis.* **2022**;36(1):e24114. doi:10.1002/jcla.24114
55. Damen MSMA, Popa CD, Netea MG, Dinarello CA, Joosten LAB. Interleukin-32 in chronic inflammatory conditions is associated with a higher risk of cardiovascular diseases. *Atherosclerosis.* **2017**;264:83–91. doi:10.1016/j.atherosclerosis.2017.07.005
56. Bunet R, Roy-Cardinal MH, Ramani H, et al. Differential impact of IL-32 isoforms on the functions of coronary artery endothelial cells: a potential link with arterial stiffness and atherosclerosis. *Viruses.* **2023**;15(3):700. doi:10.3390/v15030700
57. Li Y, Wang Z. Interleukin 32 participates in cardiomyocyte-induced oxidative stress, inflammation and apoptosis during hypoxia/reoxygenation via the NOD2/NOX2/MAPK signaling pathway. *Exp Ther Med.* **2022**;24(3):567. doi:10.3892/etm.2022.11504
58. Nold-Petry CA, Rudloff I, Baumer Y, et al. IL-32 promotes angiogenesis. *J Immunol.* **2014**;192(2):589–602. doi:10.4049/jimmunol.1202802
59. Liu J, Li W, Wang J, et al. IL-32 regulates trophoblast invasion through miR-205-NF κ B-MMP2/9 axis contributing to the pregnancy-induced hypertension†. *Biol Reprod.* **2024**;111(4):780–799. doi:10.1093/biolre/iaoe118
60. El-Far M, Hanna DB, Durand M, et al. Brief report: subclinical carotid artery atherosclerosis is associated with increased expression of peripheral blood IL-32 isoforms among women living with HIV. *J Acquir Immune Defic Syndr.* **2021**;88(2):186–191. doi:10.1097/QAI.0000000000002746
61. El-Far M, Durand M, Turcotte I, et al. Upregulated IL-32 expression and reduced gut short chain fatty acid caproic acid in people living with HIV with subclinical atherosclerosis. *Front Immunol.* **2021**;12:664371. doi:10.3389/fimmu.2021.664371
62. Ramani H, Gosselin A, Bunet R, et al. IL-32 drives the differentiation of cardiotropic CD4⁺ T cells carrying HIV DNA in people with HIV. *J Infect Dis.* **2024**;229(5):1277–1289. doi:10.1093/infdis/jiad576
63. Ramani H, Cleret-Buhot A, Sylla M, et al. Opposite roles of IL-32 α versus IL-32 β/γ isoforms in promoting monocyte-derived osteoblast/osteoclast differentiation and vascular calcification in people with HIV. *Cells.* **2025**;14(7):481. doi:10.3390/cells14070481
64. Triant VA, Lyass A, Hurley LB, et al. Cardiovascular risk estimation is suboptimal in people with HIV. *J Am Heart Assoc.* **2024**;13(10):e029228. doi:10.1161/JAHA.123.029228
65. Barlianto W, Wulandari D, Sari TL, Rachmaningrum RR, Asasain RI. Effects of Nigella sativa on disease activity, T lymphocytes and inflammatory cytokine profiles in pediatric systemic lupus erythematosus: a randomized controlled trial. *Narra J.* **2024**;4(3):e1063. doi:10.52225/narra.v4i3.1063