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HIV-Associated Cardiovascular Disease Pathogenesis: An Emerging Understanding Through Imaging and Immunology

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ABSTRACT: Cardiac abnormalities were identified early in the epidemic of AIDS, predating the isolation and characterization of the etiologic agent, HIV. Several decades later, the causation and pathogenesis of cardiovascular disease (CVD) linked to HIV infection continue to be the focus of intense speculation. Before the widespread use of antiretroviral therapy, HIV-associated CVD was primarily characterized by HIV-associated cardiomyopathy linked to profound immunodeficiency. With increasing antiretroviral therapy use, viral load suppression, and establishment of immune competency, the effects of HIV on the cardiovascular system are more subtle. Yet, people living with HIV still face an increased incidence of cardiovascular pathology. Advances in cardiac imaging modalities and immunology have deepened our understanding of the pathogenesis of HIV-associated CVD. This review provides an overview of the pathogenesis of HIV-associated CVD integrating data from imaging and immunologic studies with particular relevance to the HIV population originating from high-endemic regions, such as sub-Saharan Africa. The review highlights key evidence gaps in the field and suggests future directions for research to better understand the complex HIV-CVD interactions.

Key Words: cardiomyopathies ■ coronary artery disease ■ heart failure ■ inflammation ■ ventricular dysfunction, left

The scale-up of antiretroviral therapy (ART) has transformed HIV infection from an invariably fatal condition to a chronic manageable carriage. Life expectancy among people living with HIV (PLWH) has increased, with non-AIDS–related death rates now 4-fold higher compared with AIDS-related rates and cardiovascular disease (CVD) accounting for a large proportion of this mortality. The burden of HIV-associated CVD globally is not distributed equally with sub-Saharan Africa (SSA) suffering the greatest impact (Figure 1).[1–5]

The current paradigm is that atherosclerotic coronary artery disease (CAD) driven by vascular inflammation is the primary pathology of HIV-associated CVD resulting in ischemic injury and infarction of the myocardium. This paradigm, based on studies performed predominantly in North American and European populations, has strongly influenced the contemporary clinical approach and informed guidelines that focus on addressing traditional atherosclerotic risk factors in HIV.[6–10] These studies have also guided recent large-scale clinical trials, showing improved outcomes across PLWH receiving lipid-lowering therapy.[11]

However, questions arise about the applicability of the current paradigm to populations with HIV in SSA, which harbors two-thirds of the 38 million PLWH. We propose that a nonischemic inflammatory cardiomyopathic process may be a more important mechanism, particularly in populations with a low prevalence of CVD risk factors.

This review will explore the evidence for the role of nonischemic inflammatory cardiomyopathy as an important mechanism of HIV-associated CVD and, in particular, its relevance to the SSA population. It will also critically

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Nonstandard Abbreviations and Acronyms

18F-FDG-PET	18F-fluorodeoxyglucose positron emission tomography
ART	antiretroviral therapy
CCL	C-C motif chemokine ligand
CCR	C-C motif chemokine receptor
CD14	cluster of differentiation 14
CMR	cardiac magnetic resonance imaging
CTCA	computed tomography coronary angiography
CX3CL1	C-X3-C motif chemokine ligand 1
CX3CR1	C-X3-C motif chemokine receptor 1
DAD	Data Collection on Adverse Events of Anti-HIV Drugs
Gal-3	galectin-3
HIVAC	HIV-associated cardiomyopathy
hsCRP	high-sensitivity C-reactive protein
IL	interleukin
iNOS	inducible nitric oxide synthase
INSTI	integrase strand transfer inhibitor
MI	myocardial infarction
Nef	negative regulatory factor
PLWH	people living with HIV
PWOH	people without HIV
sCD163	soluble CD163
SMART	Strategies for Management of Antiretroviral Therapy
SSA	sub-Saharan Africa
sST-2	soluble ST-2
Tat	transactivator of transcription
TGF-β1	transforming growth factor-β1
TNF-α	tumor necrosis factor α

review the current understanding that HIV-associated CVD is predominantly caused by atherosclerotic coronary artery disease.

EPIDEMIOLOGY OF CLINICAL HIV–ASSOCIATED CVD

In the pre-ART era, cardiac presentations of HIV infection were dominated by cardiomyopathy, which carried a poor prognosis.[12] Individuals with HIV-associated cardiomyopathy (HIVAC) confirmed on endomyocardial biopsy were at almost 6 times the risk of death compared with death rates among individuals with other forms of cardiomyopathy.[13] In the era of highly effective ART, the focus of HIV-associated CVD has shifted from a disease of the myocardium toward atherosclerotic coronary artery disease,[6] predominantly driven by data from PLWH in high-income countries (Table 1).[9,14]

Heart Failure

Although HIV infection is an independent risk factor for the development of heart failure, the phenotype has changed over time.[16] HIVAC, characterized by increased left ventricular dilatation and reduced function, was the prevalent phenotype before the implementation of ART.[17] Reductions in the prevalence of HIVAC in high-income countries were documented following widespread ART use.[18] A meta-analysis encompassing 26 studies indicated a decrease in left ventricular systolic dysfunction prevalence among PLWH from 20% in the pre-ART era (before 1996) to 10% in studies conducted post-2004.[19] The heart failure phenotype appears to have shifted to subclinical left ventricular systolic dysfunction and diastolic dysfunction.[19] Four of the 26 studies analyzed were from SSA countries.[20–23] Despite these changes, compared with individuals without HIV infection, PLWH have a 1.8-fold increased risk of developing heart failure.[16] This risk is further exacerbated by poor HIV control even after adjusting for traditional cardiovascular risk factors.[24]

In SSA, as in high-income countries, HIVAC was documented in up to one-third of PLWH before the availability of ART.[25] Echocardiographic studies in ART-naive populations in Ghana and Rwanda reported HIVAC prevalence of 34%[20] and 17%,[26] respectively. The South African Heart of Soweto study showed that 10% of all hospitalized patients with an incident cardiac pathology were HIV positive (n=518/5328). The mean age of this cohort was 40 years, and 54% of them were receiving ART. HIVAC was the most common etiology in these patients, equating to 38% (n=196/518) of cases followed by pericardial pathology at 13% (n=65/518). Noticeably, ischemic pathology only accounted for 3% (n=14/518) of cases.[27] Despite these findings, the true burden of HIV-associated heart failure in the region is still uncertain as ART coverage has improved significantly in recent years.[28]

Ischemic Heart Disease

Several cohort studies, alongside pooled analysis, have shown that PLWH face a significantly elevated risk of acute myocardial infarction (MI) compared with people without HIV (PWOH), even after adjusting for traditional cardiovascular risk factors.[4,14,29,30] All of this evidence, based on longitudinal studies, originates from studies in North America and Europe.[14] This elevated risk appears to persist among individuals who consistently achieve HIV viral load levels of <500 copies/mL over time.[29] The body of evidence pointing toward an excess risk of MI in PLWH has culminated in the recent randomized trial to

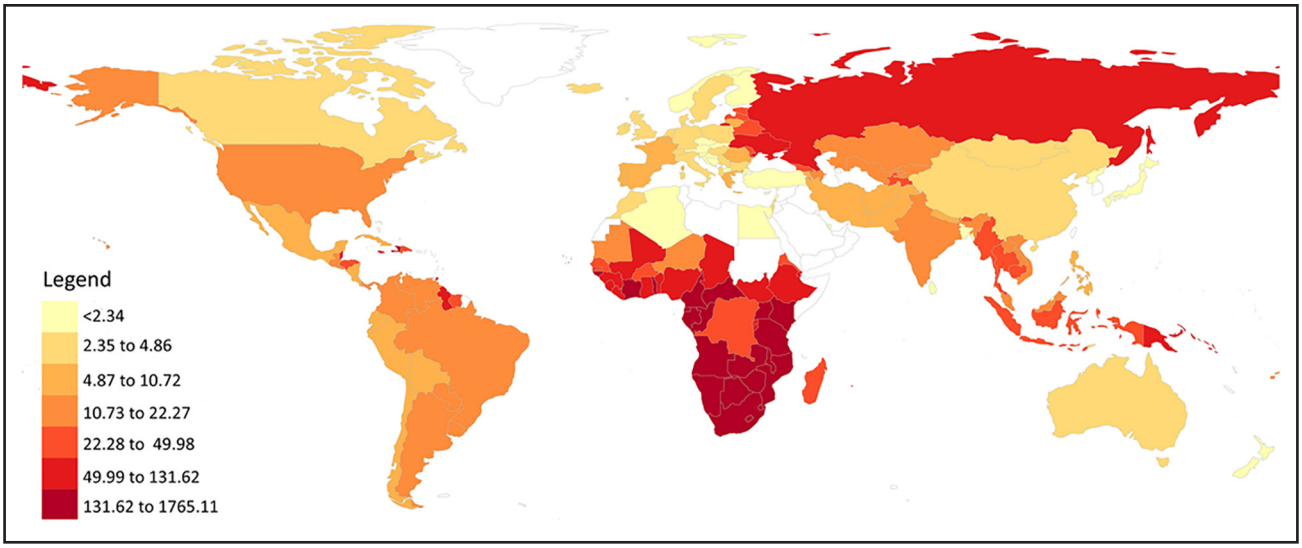

Figure 1. The global burden of HIV-associated cardiovascular disease.
Cartograms showing HIV attributable disability-adjusted life-years per 100 000 people for HIV-associated cardiovascular disease.[14] Each color represents a septile.

reduce vascular events in HIV trial (REPRIEVE) investigating the use of statins to improve cardiovascular outcomes in PLWH.[11] Pitavastatin was shown to reduce the risk of major adverse cardiac events by 35% in PLWH at low-to-moderate risk of CVD over a median follow-up of 5 years. The REPRIEVE population consisted of 70% men with 50% of the overall population being smokers: a demographic different from the HIV population in SSA (Table 2).[35] Only 15% of the REPRIEVE population was recruited from SSA, which calls into question its generalizability to the global HIV population.[11]

The relationship between HIV and coronary artery disease in SSA remains unknown. To our knowledge, there are no cohort studies from SSA that have investigated the association between HIV and ischemic heart disease.[36] The lack of HIV-specific research in this area is compounded by the limited data in the region on the burden of coronary artery disease in the general population.[37,38] Among the limited studies that have explored the relationship between HIV and coronary artery disease in SSA, the Heart of Soweto Study was a South African registry study that captured all new cases of heart disease between 2006 and 2008 presenting to a tertiary cardiology center in Johannesburg. A diagnosis of coronary artery disease was made in 10.9% (581/5328) of the cohort, and only 2.4% of these cases (14/581) were PLWH. These results suggest a comparably low burden of HIV-associated atherosclerotic disease in this population.[27,39] A recent analysis of electrocardiograms (ECGs) from a rural Tanzanian cohort indicated that PLWH were five times more likely to exhibit ischemic changes on their ECGs than to age- and sex-matched PWOH.[40] Although not specific, these contrasting findings highlight the importance of future studies in SSA HIV populations to determine the risks of coronary artery disease associated with HIV infection.

MECHANISMS OF NONISCHEMIC HEART FAILURE IN HIV

The epidemiological evidence for the association between heart failure and HIV suggests a potential role for a nonischemic inflammatory cardiomyopathy that causes myocardial injury. Here, we will review the evidence derived from immunologic and advanced imaging studies that shape our understanding of the pathophysiological

Table 1. Epidemiological Evidence for Cardiovascular Complications in PLWH

Outcome	Study design	No. of studies	HR	No. of studies from SSA	Source	Comment
MI	Systematic review and meta-analysis	5	1.79 (1.54–2.08)	0	Shah et al[14]	HR for incident MI in PLWH compared with PWOH
Heart failure	Systematic review and meta-analysis	5	1.48 (1.31–1.67)	0	Li et al[15]	HR for incident heart failure in PLWH compared with PWOH
Cardiovascular events	Systematic review and meta-analysis	5	2.36 (1.50–3.70)	0	Shah et al[14]	HR for incident cardiovascular event (including cardiovascular mortality) in PLWH compared with PWOH

HR indicates hazard ratio; MI, myocardial infarction; PLWH, people living with HIV; PWOH, people without HIV; and SSA, sub-Saharan Africa.

Table 2. Comparative Overview of HIV Demographics and Cardiovascular Risk Factors in Eastern/Southern Africa and North America/Europe

Variable	Eastern and Southern Africa	North America/Europe
HIV population	20.8 (17.4–24.5) million	2.3 (1.9–2.6) million[28]
Sex, % women	64%	20%[28]
Population affected	HIV is firmly established in the general population (prevalence of 5.9%) with gay men and accounting for 0.84% of PLWH	Low HIV prevalence in the general population (0.2%) with gay men and intravenous drug abusers accounting for 2.82% and 0.81% of PLWH,[28] respectively
Transmission, general population	72% of transmission in the general population	4% of transmission in the general population[28]
Transmission, key population	8% transmission in the gay population and across intravenous drug abusers	79% transmission in the gay population and across intravenous drug abusers[28]
Cardiovascular risk factors	Prevalence ratio HIV: general population	Prevalence ratio HIV: general population
Smoking	1.21 (0.68–2.15)	2.16 (1.1–4.25)[31]
Hypertension	0.75 (0.68–0.83)	1.12 (1.02–1.23)[32]
Diabetes	0.64 (0.18–2.23)	4.6 (3.0–7.1)[33,34]

PLWH indicates people living with HIV.

mechanisms that underpin this inflammatory cardiomyopathy. It is likely that these mechanisms proceed at cellular and tissue levels similar to the pathophysiological mechanisms observed in other forms of viral myocarditis.[41] This involves 3 distinct stages: the acute stage triggered by viral entry and replication, a subacute stage where inflammatory cells infiltrate the myocardium, and a chronic stage leading to cardiac remodeling.[41] The pathological mechanisms and the evidence base underpinning them are outlined in this section and summarized in Figure 2. Few of the studies that inform these mechanisms have been performed in SSA. Table 3 summarizes some of these key studies that have specifically investigated HIV populations in SSA.

Acute Phase of Myocardial Damage in HIV

The acute phase of myocarditis is characterized by viral entry into the cardiomyocyte and activation of the innate immune response. Historically, there has been some debate about whether HIV could directly infect cardiomyocytes. Early in the HIV epidemic, in situ hybridization of myocardial tissue from autopsies of AIDS patients with HIVAC in the United States demonstrated the presence of HIV.[58–60] This raised the possibility that HIV directly infected cardiomyocytes, a theory supported by in vitro experiments demonstrating that HIV can enter rat ventricular myocytes. However, these experiments also noted an absence of viral replication 3 to 4 days following infection raising questions about their mechanistic significance.[61] Other studies, involving human fetal cardiomyocytes, failed to demonstrate that HIV could directly infect cardiomyocytes.[62] In contrast, HIV is capable of infecting noncardiomyocyte inflammatory cells, specifically macrophages and T lymphocytes, within the myocardial tissue. It is from these cells that the virus is likely to exert its greatest effect on the myocardium.[63,64] In a study of myocardial tissue from patients with HIVAC, only inflammatory cells and not cardiomyocytes displayed HIV genetic material.[63] In addition, there was perivascular macrophage infiltration of the myocardium with adjacent cardiomyocyte apoptosis.

HIV-Specific Proteins and Their Contribution to Myocardial Injury

HIV envelope glycoprotein 120 (gp120), a surface protein of HIV, facilitates the virus's entry into cells.[65] In myocardial tissue from patients with HIVAC, gp120 was found to be expressed abundantly in macrophages and T cells but less so in cardiomyocytes.[63] From these infected macrophages, gp120 can induce apoptosis of adjacent cardiomyocytes via both mitochondria-controlled and cardiomyocyte surface death receptor-controlled pathways.[61]

Nef (negative regulatory factor) is an auxiliary protein of HIV that is expressed by proviral DNA.[66] Nef has been shown to cause direct cardiotoxicity through the inhibition of autophagy, a homeostatic cellular process that clears and degrades damaged organelles and proteins.[67] Nef is detectable in the plasma of PLWH even in the presence of ART, suggesting that it may exert its effect on the myocardium in immunocompetent patients both locally or from remote tissues.[68] Tat (transactivator of transcription) may also contribute to myocardial injury in HIV. Targeted myocardial HIV Tat transgenic mice develop depression in both systolic and diastolic function. This appears to be mediated by cardiac mitochondrial damage indicating a possible mechanism by which Tat exerts a cardiotoxic effect.[69]

Role of Opportunistic Infections and Cardiotropic Viruses

Both opportunistic infections and cardiotropic viruses may further exacerbate the initial myocardial insult caused by HIV. Before the widespread implementation of ART, opportunistic infections of the myocardium had been found in patients with AIDS. A study from the Congo

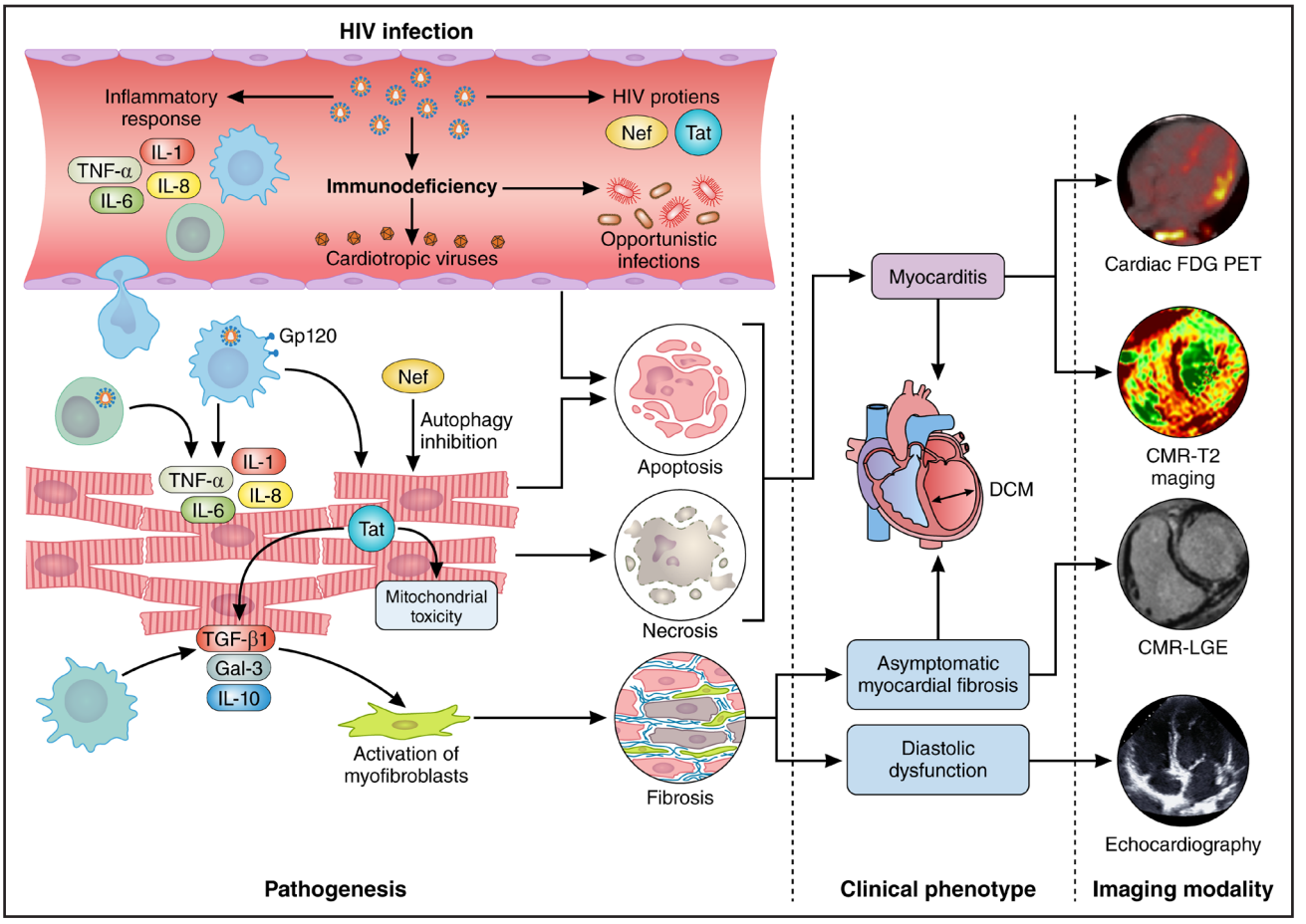

Figure 2. HIV-associated nonischemic cardiomyopathy pathogenesis, the downstream clinical phenotype, and cardiovascular imaging modality.

Inflammation stimulated by HIV infection leads to monocyte recruitment and infiltration of the myocardium with macrophages and lymphocytes. HIV-specific proteins, including HIV envelope glycoprotein 120 (gp120), Nef (negative regulatory factor), and Tat (transactivator of transcription), exert local cardiotoxic effects. Cardiotropic viruses and opportunistic infections caused by profound immunodeficiency may drive further myocardial damage. The inflammatory response, together with HIV-specific proteins, promotes fibrosis by leading to the activation of myofibroblasts and the subsequent development of myocardial fibrosis. CMR indicates cardiac magnetic resonance imaging; DCM, dilated cardiomyopathy; FDG-PET, fluorodeoxyglucose positron emission tomography; IL, interleukin; LGE, late gadolinium enhancement; and TNF-α, tumor necrosis factor α. Image credit: Sceyence Studios.

recruited 157 PLWH without cardiac disease at baseline. Over a 7-year follow-up (between 1987 and 1994), 35% developed a dilated cardiomyopathy. Autopsies were performed on 16 patients with AIDS and HIVAC, all of which demonstrated acute myocarditis with lymphocytic infiltration. Furthermore, 50% demonstrated cardiac involvement of an opportunistic infection (3 *Toxoplasma gondii*, 3 *Cryptococcus neoformans*, and 2 *Mycobacterium avium*).[25]

Cardiotropic viruses may also play a role in the development of nonischemic cardiomyopathy. The largest autopsy study across 440 patients with AIDS from Italy demonstrated that 30 patients had lymphocytic interstitial myocarditis. Among them, 7 had myocardial tissue culture positive for coxsackievirus, 2 with Epstein-Barr virus, and 1 with cytomegalovirus.[70] A South African study performed endomyocardial biopsies in patients with HIVAC and found that almost half had myocarditis and a significant burden of cardiotropic viruses.[42] Tissue biopsies revealed Epstein-Barr virus (65%), herpes simplex virus (50%), parvovirus B19 (14%), and cytomegalovirus (7%). The mean viral burden in HIVAC biopsies was 2.5 viruses per case compared with 1.1 viruses per case compared with biopsies from patients with HIV-negative dilated cardiomyopathy.[42]

The cardiac involvement of both opportunistic infections and cardiotropic viruses has been predominantly observed in the pre-ART era. There has been a major reduction in the risk of opportunistic infections with ART use in high-income and lower-middle–income settings.[71] The contribution of opportunistic infections and cardiotropic viruses in the ART-era remains less certain.

Subacute Immune Phase of Myocardial Inflammation in HIV

The HIV-infected innate immune cells and cardiac cells release cytokines and chemokines, leading to the activation and subsequent infiltration of innate immune cells

Table 3. Summary of Studies Performed Investigating the Pathogenesis of HIV-Associated Cardiovascular Disease in Sub-Saharan Africa

Author	Year	Country	Population	Methodology	Finding
Longo-Mbenza et al[25]	1998	Congo	157 consecutive PLWH not on ART and without cardiac lesions and no other AIDS-defining illnesses at baseline	Serial echocardiography over a 7-y follow-up period. Autopsies were performed on those who died.	Cardiac lesions occurred in 55% of patients during a 7-y follow-up. Of 16 autopsies, 100% had evidence of lymphocytic myocarditis and 50% had evidence of opportunistic infection.
Shaboodien et al[42]	2013	South Africa	14 PLWH with HIV-associated cardiomyopathy compared with 8 with idiopathic dilated cardiomyopathy and 11 heart transplant recipients	Endomyocardial biopsies performed	Myocarditis was present in 44% of HIV-associated cardiomyopathy cases, 36% of heart transplant recipients, and 25% of idiopathic dilated cardiomyopathy cases.
Fourie et al[43]	2015	South Africa	144 PLWH (66 on ART) and 165 PWOH matched on age, gender, and BMI.	cIMT measured	cIMT did not differ between PLWH and PWOH. No difference between ART-treated and ART-naive PLWH.
Feinstein et al[6]	2017	Uganda	109 PLWH age- and sex-matched 100 PWOH	cIMT measured	HIV status was associated with a lower cIMT.
Mospele et al 2017[44]	2017	Botswana	208 PLWH on ART with suppressed HIV VL and 224 PWOH	cIMT and plasma sCD163 measured	PLWH had higher levels of monocyte activation (evidenced by elevated sCD163), but this was not associated with higher sCD163.
Alencherry et al[45]	2019	Uganda	100 PLWH on ART in Uganda compared with the age of 100 y and sex-matched PWOH. 167 PLWH on ART in the United States compared with the age of 63 y and sex-matched PWOH.	Comparison of CAC score and inflammation in PLWH in Uganda and the United States	Ugandans were less likely to have CAC >0 (vs US subjects) after adjustment for age, sex, and HIV status (OR, 0.07 [95% CI, 0.04–0.14]) HIV status was not associated with increased CAC in Ugandans (OR, 2.2 [95% CI, 0.74–6.4])
Nonterah et al[46]	2019	Kenya, Burkina Faso, Ghana, and South Africa	8872 adults, mean age of 50±6 y, and 978 (11%) PLWH	cIMT measured	HIV status was associated with a lower cIMT.
Shuldiner et al[47]	2020	South Africa	134 PLWH on continuous ART for >12 mo and with a suppressed viral load; 95 PWOH matched on age, sex, and hypertension	Cross-sectional study of CMR	PLWH had high levels of myocardial fibrosis by ECV fraction compared with PWOH 30.4% vs 29.3% (OR, 1.2 [95% CI, 0.1–2.3]). No difference in the prevalence of LGE 72% vs 72% (OR, 0.98 [95% CI, 0.54–1.80])
Robbertse et al[48]	2022	South Africa	73 ART-naive newly diagnosed PLWH compared with 22 PWOH	CMR performed before and 9 mo after initiation of ART	Greater degree of myocardial edema and fibrosis present at baseline in PLWH. Significant improvements in markers of myocardial edema and a decrease in extracellular volume after 9 mo of ART, which correlated with reductions in HIV VL and inflammation markers
Peterson et al[49]	2023	South Africa	69 PLWH on continuous ART for >12 mo and with a suppressed HIV VL and without CVD	Cross-sectional study using CMR and simultaneous protein biomarkers and cell phenotyping	Positive association between ECV fraction and percentages of circulating nonclassical and intermediate monocyte phenotypes reflecting inflammation and tissue injury
Longenecker et al[50]	2022	Uganda	100 PLWH on ART in Uganda compared with the age of 100 y and sex-matched PWOH	Cross-sectional study of CTCA	HIV status not associated with CAD (OR, 0.55 [95% CI, 0.23–1.30]). HIV status associated with more severe CAD among those with the disease (OR, 10.9 [95% CI, 1.67–70.45])
Lawal et al[51]	2019	South Africa	121 PLWH and 121 PWOH, aged 18–40 y referred for oncological or inflammatory indication for PET. Recruited individuals with low CVD risk only	Retrospective review of FDG-PET	Marginally higher vascular inflammation seen in PLWH as measured by the aortic tissue background ratio
Ssinabulya et al[52]	2014	Uganda	245 PLWH. 145 were ART-naive and 100 PLWH had received ART for the median of 7 y.	Cross-sectional study measuring traditional CVD risk factors and biomarkers of inflammation. Correlated with cIMT measurement	18% prevalence of subclinical atherosclerosis with independent predictors including age, BMI, and high LDL. hsCRP was positively correlated with traditional cardiometabolic risk factors.

(*Continued*)

Table 3. Continued

Author	Year	Country	Population	Methodology	Finding
Siedner et al[53]	2016	Uganda	105 PLWH over the age of 40 y initiating ART	Metabolic profiling including hemoglobin A1c and lipid levels, and cIMT, assessed before and 6 mo after ART initiation	Pre-ART HIV VL level correlated with high cIMT. Lower levels of soluble CD14 and IL-6 at 6 mo post-ART initiation predicted lower cIMT.
Dirajlal-fargo et al.[54]	2021	Uganda	20 PLWH between the ages of 10–18 y on ART age- and sex-matched to PWOH	Cross-sectional study. Measurement of serum lipid composition, cIMT, and plasma markers of inflammation, monocyte activation, and T-cell activation	PLWH had an altered lipidome relative to PWOH, which correlated with levels of hsCRP, soluble CD164, and T-cell activation
Fourie et al.[55]	2011	South Africa	300 PLWH newly diagnosed, ART naive. Age, gender, and BMI matched to PWOH	Cross-sectional study. Measurement of inflammatory biomarkers and lipid levels	PLWH had higher IL-6, CRP, ICAM-1, and VCAM-1 compared with PWOH
Huaman et al[56]	2021	Uganda	100 PLWH on ART in Uganda compared with 100 age- and sex-matched PWOH	Cross-sectional study assessing monocyte phenotypes	PLWH had a higher proportion of inflammatory CD14+CD16+monocytes. PLWH had an increased expression of the chemokine receptor CX3CR1 in total monocytes
Shakil et al[57]	2023	Uganda	200 PLWH with at least 1 cardiometabolic risk factor	Prospective cohort study and measurement of plasma biomarker and subsequent CT coronary angiography performed after 2 y	TNF-α and sCD163 were predictive of CAD in women Fibrinogen levels only were predictive of CAD in men.

ART indicates antiretroviral therapy; BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; cIMT, carotid intima-media thickness; CMR, cardiac magnetic resonance imaging; CRP, C-reactive protein; CT, computed tomography; CTCA, computed tomography coronary angiography; CVD, cardiovascular disease; CX3CR1, C-X3-C motif chemokine receptor 1; ECV, extracellular volume; FDG-PET, fluorodeoxyglucose positron emission tomography; hsCRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; LDL, low-density lipoprotein; LGE, late gadolinium enhancement; OR, odds ratio; PLWH, people living with HIV; PWOH, people without HIV; sCD163, soluble CD163; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule 1; and VL, viral load.

in the myocardium.[72] Activated resident macrophages in particular produce proinflammatory cytokines and chemokines.[73,74] TNF-α (tumor necrosis factor α) is highly relevant and has been shown to be overexpressed in cardiac tissue of patients with HIVAC.[61,75] In addition, the staining intensity of TNF-α in endomyocardial biopsy samples of patients with HIVAC was associated with mortality and inversely associated with CD4 T-cell counts.[75] TNF-α levels are increased further by gp120, which can stimulate its release from activated macrophages in addition to inducing inducible nitric oxide synthase (iNOS) expression via IL (interleukin)-1β production in cardiac myocytes.[76] TNF-α impairs cardiac function by inducing cardiomyocyte apoptosis, triggering the expression of iNOS, and interfering with intracellular calcium release during systolic contraction.[74] To support the importance played by immune cell infiltration in HIV-induced cardiac damage, the inhibition of CCR (C-C motif chemokine receptor) 5, known to mediate both immune cell recruitment and HIV entry into cells, was found to significantly reduce viral load and prevent diastolic dysfunction in simian immunodeficiency virus–infected macaques.[77]

Myocardial inflammation in HIV infection can be visualized using cardiac magnetic resonance imaging (CMR). CMR utilizes T2 weighted images, native T1 mapping, and extracellular volume fraction calculation to noninvasively assess the degree of myocardial edema and diffuse myocardial fibrosis in the myocardium. A German cohort of PLWH with well-controlled disease who underwent CMR was found to have higher levels of myocardial inflammation calculated by higher native T1 relaxation times and higher T2 signal intensity ratio.[78] Our analysis that pooled 7 studies from China,[79] Peru,[80] the United States,[81,82] Germany,[78] the United Kingdom,[83] and South Africa[47] demonstrated that PLWH had a significantly higher pooled mean difference in native T1 time compared with PWOH (33.7 ms [95% CI, 11.8–55.7]; $P<0.05$).[9] In 73 PLWH who were naive of ART in South Africa, Robbertse et al[48] demonstrated a higher degree of myocardial edema represented by T1 relaxation times. This is thought to represent inflammatory cell infiltration of the myocardium. In the same study, this edema appeared to resolve with significant reductions in T1 relaxation times 9 months after the initiation of ART. Finally, imaging studies evaluating the cellular infiltration phase of inflammation are absent and will likely provide supplementary information as shown with other infective states such as COVID-19.[84,85]

Single-cell sequencing has been extensively used to investigate CVD,[86] revealing changes in immune cell clusters in heart failure[87] and MI,[88] as well as the heterogeneity of immune cells in endarterectomy plaque samples.[89] Spatial transcriptomics has been used to map site-specific pathways leading to atherosclerotic plaque rupture[90] and also the pathogenesis of viral myocarditis.[91] Similarly, a proteomics atlas of atherosclerosis has

been proposed,[92] and a protocol for spatial proteomics in 3-dimensional intact specimens has been developed.[93] However, to date, none of these techniques have been used to uncover specific immune pathways, leading to specifically HIV-driven myocardial damage. However, single-cell analysis of immune cell transcriptome during HIV infection and therapy has already been used to investigate transcriptional profiles of atypical B cells,[94] common and unique gene expression profiles in infected CD4+T cells,[95] and novel subset of cytotoxic-like plasmacytoid dendritic cells in people with HIV-1.[96] Therefore, in the near future, different omics platforms will be fundamental to better define mechanisms at the immune/vascular and immune/cardiac interplay in PLWH.

Cardiac Remodeling and Fibrosis Phase

Myocardial fibrosis has been increasingly identified as an important hallmark of nonischemic cardiomyopathy in HIV.[9] The inflammatory processes described above, caused by HIV and triggering a cytokine storm, eventually lead to cardiomyocyte death and the replacement of myocardium with a collagen-based scar. This fibrosis can lead to impairment in contractility and function in addition to providing a proarrhythmogenic substrate increasing the risk of sudden cardiac death.[97] Data from the United States in 2012 demonstrated that PLWH were at a 4.5-fold higher risk of sudden cardiac death compared with those uninfected.[98] A recent elegant histological study from the same group showed a 43% increase in avascular myocardial fibrosis in HIV-infected hearts compared with uninfected people on autopsy in individuals with sudden cardiac death.[98]

Imaging studies using CMR have demonstrated that PLWH are at a higher risk of myocardial fibrosis, represented by the presence of late gadolinium enhancement, than PWOH.[78,80,83] Holloway et al[7] were the first to identify a high prevalence of late gadolinium enhancement in PLWH compared with PWOH in a cohort of patients from the United Kingdom (76% versus 13%). Since then, several studies have investigated the prevalence of myocardial fibrosis in PLWH using CMR, and a pooled analysis of 16 studies demonstrated a wide prevalence range of myocardial fibrosis in PLWH from 5% to 84%. Overall pooled analysis demonstrated that PLWH had over twice the risk of myocardial fibrosis, by late gadolinium enhancement, compared with uninfected comparators. The age of the population studied did not modulate this relationship, and not enough data were available to assess whether the duration of HIV infection impacted the degree of myocardial fibrosis on CMR. These findings should be interpreted with some caution due to the substantial heterogeneity and the fact that only 1 CMR study was from the SSA region (Figure 3).[47]

The mechanistic pathways leading to myocardial remodeling and fibrosis in HIV remain uncertain, but chronic inflammation is likely to play a crucial role.[99,100] Despite HIV viral suppression, residual immune activation and subsequent chronic inflammation persist in PLWH.[101] Chronic HIV infection may represent a perpetuation of the classical remodeling phase of viral myocarditis. In this state of chronic immune activation, macrophages and lymphocytes that have infiltrated the myocardium are likely to be perpetually activated.[102] Macrophages, in particular, are central to the development of myocardial fibrosis as demonstrated in a macaque (simian immunodeficiency virus) model, where monocyte and macrophage migration to the heart was blocked using a monoclonal antibody, natalizumab. This is an IgG4κ monoclonal antibody that binds to α4-integrin and prevents inflammatory cells from

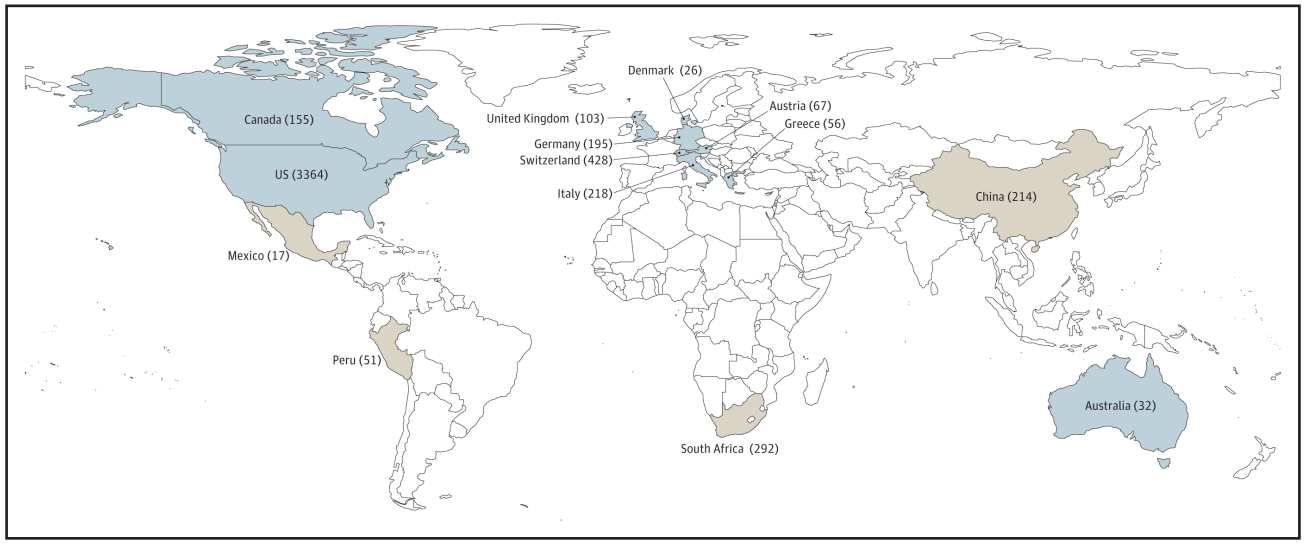

Figure 3. The geographic distribution of advanced cardiovascular imaging studies in HIV.
Numbers in parentheses represent the total number of participants with HIV included in the studies evaluated in this review. Blue indicates high-income countries, and beige indicates upper-middle–income countries classified by the World Bank Income Group.[9]

crossing blood vessels.[103] In animals that received natalizumab, there were significant reductions in CD163+ and CD68+ macrophages in the myocardium compared with controls. This was accompanied by a lower level of fibrosis.[104] Macrophages exhibit functional plasticity depending on their environment and can modulate their cytokine and growth factor expression profile.[105] It has been postulated that in a state of chronic immune activation, macrophages release profibrotic cytokines, such as IL-10 and TGF-β1 (transforming growth factor-β1), leading to increased collagen I and III deposition and subsequent myocardial fibrosis.[100,102]

Linking Inflammation to Myocardial Fibrosis

Attempts have been made to establish whether the myocardial fibrosis observed on CMR in PLWH is correlated with markers of inflammation. In a cohort of women living with HIV in the United States without CVD and well-controlled HIV, diffuse myocardial fibrosis was not only more prevalent compared with HIV-negative controls but also associated with the macrophage activation marker sCD163 (soluble CD163).[81] This association suggests a potential role for chronic immune activation in driving the myocardial disease. However, a South African study failed to identify a link between circulating inflammatory proteins (TNFR-I [tumor necrosis factor receptor 1], IL-6, sCD14, and sCD163) and myocardial fibrosis as measured by extracellular volume fraction.[49] Myocardial fibrosis has been positively associated with percentages of circulating nonclassical and intermediate monocyte phenotypes that reflect inflammation and tissue injury.[49]

Inflammatory Biomarkers and Cytokines Associated With Myocardial Fibrosis

The cytokine TGF-β1 has been referred to as the master regulator of fibrosis[106] and has been implicated in HIV-associated myocardial fibrosis. TGF-β1 is elevated in PLWH and is a marker of disease progression. Levels of TGF-β1 are also increased in ART-nonadherent individuals compared with ART-adherent individuals.[107,108] The HIV protein Tat has also been shown to increase levels of TGF-β1. In the mouse myocardium, administration of recombinant Tat protein was found to cause myocardial fibrosis and simultaneously increase the expression of TGF-β1.[109] Platelet-derived TGF-β1 has also been shown to mediate HIV protease inhibitor–induced cardiac dysfunction,[110] highlighting the need to better understand the contribution of this protein to myocardial fibrosis in PLWH.

Two further proteins may mediate myocardial fibrosis in HIV: Gal-3 (galectin-3) and sST-2 (soluble ST-2). Gal-3 is a regulatory protein that is part of the β-galactoside and has become an important CVD biomarker. It has been implicated in a range of CVDs including heart failure,[111] atherosclerosis,[112] atrial fibrillation,[113] and valvular heart diseases.[114] Under normal physiological conditions, it is expressed at low levels; however, in disease states such as heart failure, its expression increases substantially.[115,116] It activates fibroblasts and macrophages within the myocardium, leading to the induction of myocardial fibrosis. Interestingly, the HIV protein Tat has been shown to significantly increase the expression of Gal-3. This interaction highlights a unique mechanism by which HIV infection may lead to myocardial fibrosis.[117] It activates both fibroblasts and macrophages in the myocardium and has been shown to induce myocardial fibrosis.[118]

sST-2 is a decoy receptor for IL-33. The relationship between IL-33 and sST-2 is normally protective against myocardial fibrosis.[119,120] In the context of heart failure, sST-2 serves as a biomarker of myocardial fibrosis and cardiac remodeling. sST-2 levels correlate with the severity and prognosis of heart failure, making it a valuable tool for risk stratification and monitoring of disease progression.[121] Secemsky et al[122] demonstrated in PLWH a relationship between diastolic dysfunction, sST-2, and all-cause mortality. They suggest that sST-2 in PLWH may be a mediator of the myocardial fibrosis extensively described in CMR studies. A direct link between myocardial fibrosis and inflammation was offered by 2 recent studies performed in women with HIV, demonstrating, respectively, a correlation between plasma osteopontin, a predictor of heart failure, myocardial fibrosis and the expression of 2 important chemokine receptors central to myocardial inflammation, CCR2 and CX3CR1 (C-X3-C motif chemokine receptor 1) in monocytes,[123] and a correlation between myocardial fibrosis, reduced diastolic function, and elevated systemic monocyte activation.[81]

While our understanding of myocardial inflammation in HIV remains incomplete, the increased circulating levels of Gal-3 and sST-2 in PLWH highlight potential pathways through which HIV may contribute to myocardial fibrosis, suggesting new avenues for targeted therapeutic interventions and research.

MECHANISMS OF CORONARY ARTERY DISEASE IN HIV INFECTION

Vascular Inflammation and Atherosclerosis

It is well established that atherosclerosis, the process of plaque formation in the vascular intima, is a chronic vascular inflammatory process.[124,125] One of the key mechanisms postulated in HIV-associated CVD is that the virus causes vascular inflammation, leading to atherosclerosis and subsequent ischemic heart disease.[6,126] Molecular and anatomic imaging alongside immunologic studies provide insights into the pathogenesis of atherosclerosis in HIV. The hypothesized pathological mechanisms of HIV-associated coronary artery disease are outlined in Figure 4.

Molecular Imaging

Vascular 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) imaging identifies areas

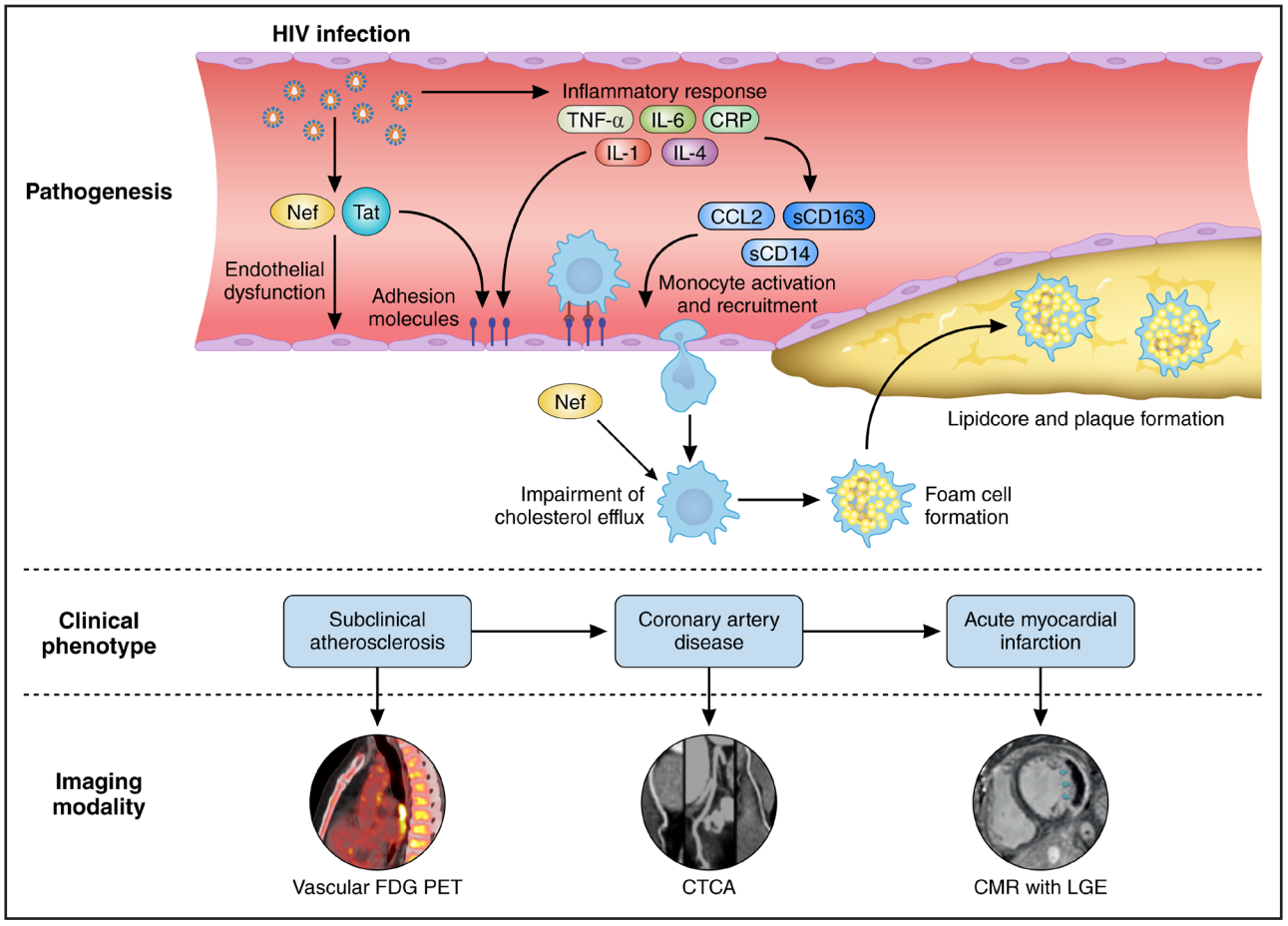

Figure 4. Mechanisms of HIV-associated atherosclerotic coronary artery disease pathogenesis, clinical phenotype, and the appropriate cardiovascular imaging modality.

HIV infection causes a strong inflammatory response, which leads to the release of cytokines that cause monocyte activation and recruitment to the endothelium. Adhesion molecules are also stimulated, which facilitates macrophages entering the endothelial layer. Specific HIV proteins drive endothelial dysfunction, stimulate adhesion molecules, and can impact the efflux of cholesterol in macrophages contributing to foam cell formation. CCL2 indicates C-C motif chemokine ligand 2; CD14, cluster of differentiation 14; CMR, cardiac magnetic resonance imaging; CRP, C-reactive protein; CTCA, computed tomography coronary angiography; FDG-PET, fluorodeoxyglucose positron emission tomography; IL, interleukin; LGE, late gadolinium enhancement; Nef, negative regulatory factor; sCD163, soluble CD163; Tat, transactivator of transcription; and TNF-α, tumor necrosis factor α. Image credit: Sceyence Studios.

of high glucose uptake by activated macrophages within atherosclerotic plaques. It has been used in HIV-negative populations to identify and characterize vascular inflammation in atherosclerosis.[127] Higher 18F-FDG uptake indicates increased inflammatory activity and faster progression of atherosclerosis, which is associated with an increased risk of future cardiovascular events.[128,129]

Subramanian et al[8] first demonstrated that PLWH recruited from North America, who were on stable ART and without CVD, had higher aortic 18F-FDG uptake compared with PWOH matched for baseline cardiovascular risk. This was supported by 2 further studies across PLWH without CVD and on ART.[51,130] Lawal et al[51] compared the aortic tissue background ratio (TBR) of PLWH in South Africa to age- and sex-matched controls and found marginally higher levels of vascular inflammation that appeared independent of CD4 T-cell count and HIV viral load. However, the retrospective study design and the fact that participants were undergoing 18F-FDG-PET in view of suspected inflammatory disease or malignancy limit the validity of these findings.

Other studies using 18F-FDG-PET in American and Danish cohorts of PLWH to assess vascular inflammation have found no difference in aortic FDG uptake between PLWH and PWOH.[131,132] One clinical trial conducted in the United States investigated the role of statins in modulating vascular inflammation in ART-established PLWH but without CVD.[133] At 12 months, there was no difference in aortic 18F-FDG uptake in those receiving statins compared with placebo.

Importantly, 18F-FDG-PET studies to date have been restricted to predominantly male participants in their fifth decade in nonendemic regions usually with known cardiovascular risk factors.[9] In contrast, the majority of PLWH in SSA are women, typically younger, and with a lower cardiovascular risk profile.[28,53,134,135] There exists

only 1 molecular imaging study evaluating vascular inflammation in HIV populations from SSA.[51]

Evidence From Anatomic Imaging

Computed tomography coronary angiography (CTCA) has been used to further describe the extent and severity of coronary artery disease in HIV. Again, the majority of studies originate from North America/Europe and have shown diverging results. A cohort of North American homosexual men with HIV and high prevalence of vascular risk factors showed that 8 out of 10 individuals had evidence of coronary plaque and were at a 1.5-fold higher risk of coronary disease compared with uninfected individuals.[136] Later studies from Canada,[137] Switzerland,[138] and the United States,[139] however, failed to detect an association between HIV infection and the presence of coronary plaque in PLWH. Studies have also indicated a heightened risk of obstructive and clinically significant coronary stenosis, defined as a >50% obstruction of the coronary lumen, in PLWH.[136,140]

Evidence synthesis of CTCA studies showed significant heterogeneity, with the prevalence of coronary artery disease in HIV ranging from 17.1% to 77.8%.[9] Similarly, compared with uninfected comparators, pooled analysis showed significant heterogeneity with prevalence ratios ranging from 0.33 (95% CI, 0.01–15.90) to 5.19 (95% CI, 1.26–21.42).[9] Metaregressions to explore whether particular HIV-specific or non-HIV risk factors modulated this relationship indicated that only the proportion of smokers in the population and mean body mass index were significantly associated with coronary artery stenosis on CTCA. There was no relationship between mean CD4 T-cell count, nadir CD4 T-cell count, time on ART, and the proportion of patients on ART.

There is little evidence from SSA to support a relationship between HIV and coronary artery disease in PLWH. Alencherry et al[45] compared the coronary artery calcium score of PLWH on ART to age- and sex-matched and risk factor–matched PWOH across populations in Uganda and the United States. Ugandans had markedly lower coronary artery calcium scores than individuals from the United States. Furthermore, HIV was not associated with a higher coronary artery calcium score.[45] Recent data from Uganda showed a near 2-fold lower prevalence of coronary pathology across PLWH compared with uninfected controls alongside lower rates of coronary calcification in HIV.[50] Carotid intimal-media thickness (cIMT) measurement using ultrasound is a cheaper alternative assessment of atherosclerosis to CTCA. Studies in Uganda and South Africa have failed to show a difference in cIMT between PLWH compared with HIV-negative comparators.[43,141] The largest study of its kind including 8872 participants from Kenya, Burkina Faso, Ghana, and South Africa did not find HIV to be a risk factor for higher cIMT.[46]

Immunologic Evidence

The immunologic evidence for HIV-associated atherosclerosis is in part derived from several inflammatory biomarker studies. Circulating inflammatory biomarkers strongly associated with atherosclerosis such as IL-6 and C-reactive protein, and levels of the coagulation marker D-dimer, are consistently elevated in PLWH even in the presence of controlled viremia.[142,143] This was demonstrated in the SMART study (Strategies for Management of Antiretroviral Therapy) that revealed increased mortality in participants with higher IL-6 and D-dimer levels, a finding reproduced by others.[144,145] More recently, several soluble markers of inflammation (sCD14, sCD163, TNFR-I, TNFR-II, CCL [C-C motif chemokine ligand] 5, CX3CL1 [C-X3-C motif chemokine ligand 1], and IL-10) have shown associations with pericoronary inflammation in HIV.[146] Similarly, within HIV-endemic areas in SSA, particularly in Uganda, there was a clear association between inflammation and subclinical CAD in adult women, both with and without HIV.[57] hsCRP (high-sensitivity C-reactive protein) showed a positive correlation with traditional cardiometabolic risk factors in PLWH.[52] Moreover, persistent immune activation despite viral suppression mediated by ART was predictive of future atherosclerotic burden among PLWH.[53] Altered lipid profiles and inflammation were also linked to vascular disease in HIV-positive children.[54] Additionally, in newly diagnosed, untreated HIV-1-infected South Africans, systemic inflammation was associated with endothelial dysfunction, a significant contributor to atherosclerosis development.[43] Overall, these findings suggest that inflammatory biomarkers that are known to predict cardiovascular events in the general population and are associated with major adverse cardiovascular events are both elevated and predict cardiovascular events in PLWH.[147]

It is noteworthy that among PLWH in Uganda, there is an expansion of the inflammatory monocyte subset, accompanied by enhanced expression of the monocyte CX3CR1 chemokine receptor.[56] This finding holds significance in the context of CVD, considering that monocytes from PLWH on ART display a high frequency of cells producing IL-1β.[148] These cells have been shown to be a major source of IL-6 production and systemic inflammation in PLWH at risk for CVD. Pharmacological targeting of IL-1β has been recently shown to significantly reduce the rate of recurrent cardiovascular events.[149] Similarly, the targeting of IL-6 is currently under intense investigation in people with CVDs (https://www.clinicaltrials.gov; unique identifier: NCT05021835).[150] Other proinflammatory cytokines, such as IL-17A, macrophage inflammatory protein-1 alpha (MIP-1α/CCL3), IL-4, and type I interferon, have also been found to be associated with subclinical atherosclerosis in PLWH with suppressed viremia.[151,152]

The above studies suggest an inflammatory process mediates the risk of coronary atherosclerosis in HIV both

in the Global North and the Global South. HIV infection leads to an increase in IL-6 and TNF-α secretion that stimulate the release of chemokine (C-C motif) ligand 2 (CCL2 also known as monocyte chemoattractant protein-1), which is a key activator and recruiter of monocytes to the vascular endothelium.[153,154] Several studies have established a connection between CCL2 and HIV-induced atherosclerosis. CCL2 is found in high levels in PLWH and is associated with immunodeficiency (high viral load and low CD4 T-cell counts) and atherosclerotic burden in the thoracic aorta.[155] In a cohort of men with HIV, CCL2 levels were higher compared with HIV-negative controls and showed a significant association with subclinical atherosclerosis and coronary stenosis detected by CTCA. Besides CCL2, several other markers of macrophage activation including galectin-3-binding protein, sCD163, and soluble CD14 (cluster of differentiation 14) have been detected at increased levels in PLWH and associated with coronary atherosclerosis.[156,157]

This immune response to HIV infection stimulates endothelial cells to recruit leukocytes to the subendothelial layer and in the perivascular space. During HIV infection, elevated levels of cytokines (TNF-α, IL-1, and IL-4) and chemokines (CCL2 and CCL3) upregulate adhesion molecules that recruit monocytes to the endothelium.[158] These monocytes, driven by the inflammatory milieu, subsequently differentiate into macrophages and foam cells resulting in the initiation and acceleration of atherosclerosis. Evidence for this hypothesis is shown by the efficacy of maraviroc, a CCR5 antagonist, which led to significant improvements in several markers for cardiovascular risk, endothelial dysfunction, arterial stiffness, and early carotid atherosclerosis in HIV-treated patients[159] and decreased ritonavir-induced atherogenesis and advanced atherosclerosis by reducing vascular inflammation in mice.[160]

Two HIV proteins, Tat and Nef, have also been implicated in the pathogenesis of HIV-associated atherosclerosis. Tat, whose primary role in HIV infection is to improve the efficiency of viral replication, can be excreted by infected T cells and monocytes into the extracellular environment. Its implication in atherosclerosis is via several postulated mechanisms. First, it promotes cytokine production from monocytes and stimulates the release of CCL2.[161] Second, it increases the adhesion of monocytes and T cells to the vascular endothelium.[162] Third, it can induce endothelial dysfunction[163] and, in mouse models, can directly increase the size of atherosclerotic lesions.[164] Nef protein also drives lymphocyte chemotaxis and macrophage activation via CD36.[165] In addition, through the inhibition of ATP-binding cassette transporter A1, it impairs cholesterol efflux from infected macrophages and facilitates the transformation of these into foam cells.[166]

More recently, clonal hematopoiesis was found to be higher in PLWH, associated with subclinical atherosclerosis but not with elevated levels of inflammatory biomarkers.[167] Immune cell senescence has also been shown to predict subclinical atherosclerosis in PLWH.[168,169] There is also evidence that HIV alters the metabolism in immune cells leading to a proinflammatory phenotype.[170] Finally, the potential contribution of trained immunity to HIV-associated atherosclerosis should also be taken into consideration. Following an initial infection, long-term epigenetic reprogramming allows innate immune cells to provide enhanced response to subsequent infections. Although only a few studies have focused on trained immunity in the context of HIV infection,[171] trained immunity has received growing attention in atherosclerosis[172] and may represent an important missing link to explain HIV-associated cardiovascular comorbidities.

In summary, the mechanisms through which HIV drives atherosclerosis are related predominantly to a surge of cytokines and chemokines during HIV infection accompanied by the atherogenic effects of HIV-specific proteins. This leads to systemic immune cell activation, accelerated immune cell senescence, and ultimately increased endothelial dysfunction and vascular inflammation. Of note, the use of statins such as rosuvastatin reduced significantly several inflammatory biomarkers and immune activation in ART-treated individuals.[173] Further aspects such as the contribution of immunometabolism or trained immunity to HIV-associated CVD still need to be fully elucidated.

Role of ART in Cardiovascular Pathology

Class of ART and Cardiovascular Pathology

ART has transformed the HIV epidemic and changed the nature of cardiovascular risk in PLWH. With earlier ART regimens, concerns were raised about the cardiotoxic effects. The DAD study (Data Collection on Adverse Events of Anti-HIV Drugs) provided evidence across a cohort of over 23 000 patients recruited from Europe and Australia between 1999 and 2001, showing that the use of ART was associated with a 26% relative increase in the rate of MI during the first 6 years of treatment.[174] The DAD study was then followed by 2 clinical trials evaluating intermittent ART and delayed ART initiation and risk of adverse events. The SMART study randomized patients recruited from the United Kingdom, Australia, and Denmark with a CD4 T-cell count over 350 cells/μL to receive either continuous ART compared with episodic ART when the CD4 count dropped below 250 cells/μL. Continuous ART provided a 70% reduction in the risk of major cardiovascular events.[175] Notably, major adverse cardiovascular events occurred 5× more often than opportunistic infections in the treatment interruption group.[175] The International Network for Strategic Initiatives in Global HIV Trials - Strategic Timing of Antiretroviral Therapy study (INSIGHT-START) was a large multinational trial that recruited 4685 PLWH across 35

countries including Uganda, Mali, Nigeria, and South Africa. Delaying ART in asymptomatic immunocompetent PLWH in the trial was associated with a high risk of both AIDS and non-AIDS events.[176]

Protease inhibitors (PI) have traditionally been thought to increase the risk of CVD. Further analyses from the DAD cohort demonstrated an increased risk of MI with the use of protease inhibitors. This risk appeared to be at least partly explained by dyslipidemia.[177] A meta-analysis of observational studies indicated that recent use of PI was associated with a doubling in the odds of MI.[178] The authors highlight the low quality of the studies that inform this evidence. A meta-analysis of randomized trials, underpowered to assess cardiovascular outcomes and of short duration, found no association between PI use and MI.[179] The cardiovascular risk is not equal across different PIs. The DAD study demonstrated that the cumulative use of ritonavir-boosted darunavir, but not ritonavir-boosted atazanavir, was associated with an increased risk of CVD.[180] Although the increased risk of CVD with PIs is likely a class effect, atazanavir appears not to confer an excess risk of CVD.[6,181]

Abacavir, a nucleoside reverse transcriptase inhibitor, has been the focus of significant attention due to concerns about its CVD risk profile. The DAD cohort identified that recent abacavir use was associated with an increased risk of MI and a meta-analysis of observational studies confirmed this association.[178,182] How abacavir exerts detrimental cardiovascular effects is not known but may involve platelet activation[183,184] and endothelial dysfunction.[185] The cardiotoxicity of abacavir remains an area of uncertainty and debate in light of a US Food and Drug Administration sponsored trial meta-analysis of randomized control trials, which did not show an excess of MI.[186]

The relatively newer integrase strand transfer inhibitors (INSTIs) are now the mainstay of ART and recommended first-line treatment in HIV guidelines, given their improved virological efficacy and lower potential for drug-drug interactions. INSTIs, although initially thought to be less cardiotoxic, have been found to increase the incidence of arterial hypertension and diabetes.[187] The International Cohort Consortium of Infectious Disease (RESPOND) collaboration (comprising 17 European and Australian HIV cohorts) also found an increased risk of cardiovascular events with the use of INSTIs that was observed only within the first 2 years of use.[188] In contrast, the HIV Swiss cohort did not find the same risk.[189] INSTIs are still considered less cardiotoxic; however, the excess risk detected in the RESPOND collaboration may represent a bias toward prescribing INSTI-based regimens to patients at higher risk of CVD.

How ART Modulates HIV-Associated CVD Pathogenesis: Imaging Data

Advanced cardiovascular imaging has provided a greater understanding of how ART treatment affects the progression of HIV-associated CVD. The degree to which myocardial inflammation occurs before ART initiation has been assessed by CMR in several studies. Menacho et al[80] recruited 51 PLWH in Peru, 25 of whom were treatment-naive. Untreated PLWH had high T1 values and extracellular volume compared with those on ART, suggesting a greater degree of myocardial edema and fibrosis before initiating ART.[80]

Two studies evaluated the changes in myocardial pathology with ART initiation showing diverging results. One case series (n=17) from Mexico, involving ART-naive patients, showed that 1 in 3 individuals had evidence of myocarditis on CMR. Following ART establishment, myocarditis resolved in 4 of the patients but persisted in 2, and developed in a further 3 patients. While these findings may hint toward the possibility of an immune reconstitution syndrome propagating myocardial inflammation, others have demonstrated the protective effect of ART.[190] Robbertse et al[48] demonstrated a reduction of magnetic resonance imaging–based parameters of myocardial fibrosis (global native T1 times and extracellular volume fraction) following ART initiation with a concurrent improvement in CD4 counts and viral load suppression. Although this study did not assess clinical outcomes, measure myocardial inflammatory cell infiltration, or assess correlations with circulating markers of cardiac injury, it demonstrates 2 important points. First, untreated HIV causes myocardial injury based on imaging. This is likely driven by the cytokines released during HIV replication. Separate biomarker studies have supported these radiological findings, showing elevated troponin levels in PLWH who are ART naive and abating with viral suppression.[191] Second, these findings highlight ART's potential cardioprotective role in reversing inflammatory changes caused by HIV.

The impact of ART on vascular inflammation was explored by Zanni et al[192] in 12 ART-naive men who underwent an 18F-FDG-PET scan and CTCA before and 6 months after the initiation of ART. Inflammation in the aorta increased marginally 6 months after the initiation of ART despite a reduction in viral load and improved immune function. The total coronary plaque volumes also increased in those who had any coronary plaque on CTCA at baseline (although the study was not powered for this end point). Ongoing vascular inflammation after the initiation of ART may represent ongoing immune activation, ART-mediated effects through changes in cholesterol levels, or a degree of immune reconstitution syndrome. To observe a reduction in vascular inflammation, a longer delay between initiating ART and performing the PET scan may be necessary.

Both the SMART and INSIGHT-START trials provide robust evidence of the importance of continual and prompt ART treatment.[175,176] Across patients on already established ART, it may be important that maintaining viral suppression and preventing transient HIV viremia

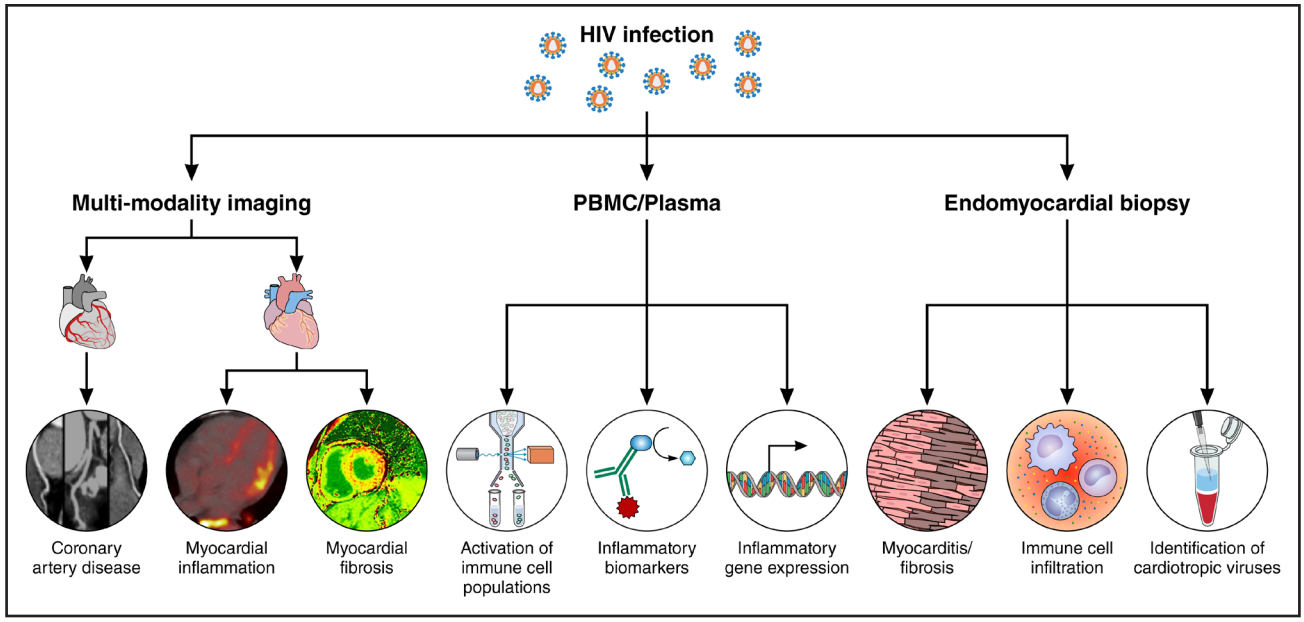

Figure 5. Approach to studying HIV-associated cardiovascular disease.
The imaging modalities highlighted are for research purposes and are not clinical recommendations. CTCA indicates computed tomography coronary angiography; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; and PBMC, peripheral blood mononuclear cells. Image credit: Sceyence Studios.

may be an important strategy to avert future CVD. Several mechanistic imaging studies support the hypothesis that consistent viral load suppression reduces cardiovascular risk. McLaughlin et al[193] recruited 152 PLWH with suppressed viral loads and demonstrated that higher levels of HIV RNA and HIV DNA were associated with incident plaque development after adjusting for cardiovascular and HIV-associated risk factors. This is supported by The Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN Study) that demonstrated among participants on ART, suppressed viral load at baseline, and maintaining that suppression during the median 2-year follow-up was associated with less cIMT progression.[194] Additionally, progression of coronary artery stenosis is greater in patients who have suboptimal ART adherence and have blips in their viral load (measured as 50–500 copies/mL) over a median of 4.5 years of follow-up.[195] Viral blips can occur as a consequence of a brief increase in replication from the HIV reservoir. This reservoir consists of long-lived cells harboring HIV in a latent state with the potential to replicate.[196] Further research is needed to better understand the significance of viral blips, especially as there are marked disparities between populations who are adherent to ART and those who are not. Despite this evidence, however, the degree to which low levels of detectable viral load in PLWH on ART increase the risk of CVD is not fully understood.

FUTURE DIRECTIONS

Inflammation and immune activation persist even in patients on ART with viral suppression. The mechanisms by which this leads to HIV-associated CVD remain unknown. The current understanding of the mechanisms and timing of myocardial inflammation and fibrosis development in PLWH is limited. The contribution of chronic inflammation to myocardial fibrosis prevalence and the subsequent impact on CVD outcomes remains unknown. As such, despite the use of ART, PLWH continue to experience an excess risk of CVD. Increasing evidence hints at the importance of a nonischemic cardiomyopathic process driving HIV-associated CVD, particularly in HIV-endemic regions.

The REPRIEVE trial underscores the necessity for primary prevention strategies in HIV-associated CVD but also demonstrates that future research must rigorously address the notable underrepresentation of SSA populations.[11,35] Carefully designed studies across appropriate populations are now urgently needed to define the primary pathogenic mechanisms explaining the rising epidemic of HIV-associated CVD (Figure 5). How these pathogenic mechanisms manifest in anatomic, functional, and molecular cardiovascular imaging and relate to the underlying immune basis propagating HIV-associated CVD is likely to be a key area of research in the near future.

ARTICLE INFORMATION

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Disclosures

None.

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