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STATE-OF-THE-ART REVIEW

HIV, Combination Antiretroviral Therapy, and Vascular Diseases in Men and Women

Laszlo Kovacs, PhD,[a,*] Taylor C. Kress, BA,[a,*] Eric J. Belin de Chantemèle, DSc[a,b]

HIGHLIGHTS

- **CVD is the leading cause of death in PLWH on cART.**
- **Manifestations of HIV-related CVD differ by sex and females have an enhanced risk for CV events.**
- **Additional experimental studies are urgently required to understand the potential signaling mechanisms leading to the sex discrepancies in the prevalence of CV events.**

SUMMARY

Thanks to the advent of combination antiretroviral therapy (cART), people living with human immunodeficiency virus (HIV) (PLWH) experienced a marked increase in life expectancy but are now at higher risk for cardiovascular disease (CVD), the current leading cause of death in PLWH on cART. Although HIV preponderantly affects men over women, manifestations of HIV-related CVD differ by sex with women experiencing greater risks than men. Despite extensive investigation, the etiopathology of CVD, notably the respective contribution of viral infection and cART, remain ill-defined. However, both viral infection and cART have been reported to contribute to endothelial dysfunction, the precursor and major cause of atherosclerosis-associated CVD, through mechanisms involving endothelial cell activation, inflammation, and oxidative stress, all leading to reduced nitric oxide bioavailability. Therefore, preserving endothelial function in PLWH on cART should be a main target to reduce CVD morbidity and mortality, notably in females. (J Am Coll Cardiol Basic Trans Science 2022;7:410–421) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In 2019, approximately 38 million individuals were living with HIV/AIDS and 1.7 million people became newly infected worldwide. At the end of the same year, 25.4 million people received combination antiretroviral therapy (cART) which represents nearly 67% of HIV-infected individuals (1). Widespread access to and beneficial effects of cART, which are mainly attributable to the nearly complete inhibition of viral replication, have contributed to the dramatic reduction in mortality and resulted in a 39% decrease in AIDS-associated deaths since 2010 (1). Thanks to the advent of cART, HIV has shifted from an opportunistic, fatal disease to a noninfectious, chronic illness associated with accelerated development of cardiovascular disease (CVD) the etiology of which is still incompletely understood (2). A growing body of evidence supports the contribution of traditional risk factors (such as hypertension,

From the [a]Vascular Biology Center, Medical College of Georgia at Augusta University, Augusta, Georgia, USA; and the [b]Division of Cardiology, Department of Medicine, Medical College of Georgia at Augusta University, Augusta Georgia, USA. *Dr Kovacs and Mr Kress contributed equally to this work.

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dyslipidemia, diabetes, obesity, and smoking), but more importantly of the HIV infection itself, and of the side effects of cART to the development of CVD (3).

People living with HIV (PLWH) now have a greater life expectancy but are at elevated risk of CVD compared to age-matched uninfected individuals, and CVD has arisen as the main cause of death in HIV-infected patients (4,5). Recent systematic studies have shown that the risk for CVD is 2-fold higher in PLWH compared to the general population, and HIV-related CVD showed a 3-fold increase from 1990 to 2015 (6). Remarkably, the rate of HIV-associated CVD is unequal between the sexes with females experiencing much greater risk for developing CVD than males (7-11). Additionally, female PLWH exhibit elevated rates and risks for cardiovascular (CV) events and death compared to noninfected women (12). Therefore, biological sex appears to be an additional risk factor to consider when evaluating the risk of HIV acquisition and manifestations of the disease.

Although epidemiologic observations of CVD in PLWH are important for the management of HIV infection, identification of the underlying mechanisms is necessary for the prevention and treatment of CVD in PLWH on cART. Therefore, implementation and evaluation of clinical and experimental studies are important to understand the relationship between viral infection, cART, and CVD that can lead to the development of novel therapeutic strategies to treat CVD in PLWH. The aim of this review is to summarize the recent knowledge focusing on the epidemiological data on HIV-related vascular diseases including sex discrepancies, the clinical and experimental observations of the potential effect of HIV infection, and cART on vascular function and translational advances of the HIV animal models.

EPIDEMIOLOGY AND RISK FACTORS OF HIV-RELATED CVD

Many have shown that PLWH experience a wide range of vascular manifestations of CVD, including myocardial infarction (MI), heart failure (HF), cerebrovascular events, peripheral artery disease (PAD), and pulmonary hypertension (PH) (13). There is a consensus that rates of acute myocardial infarction (AMI) are elevated among PLWH. Studies from the United States and Europe confirmed the strong correlation between HIV and increased risk of AMI claiming that incident rates of AMI is greatly elevated in PLWH compared to the general population (8,14-16). In addition, the higher AMI risk was further increased with the existence of any CV risk factors in PLWH suggesting that reducing the traditional risk factors can attenuate the AMI risk (17). PLWH are also exposed to increased risk for HF, another major CV complication of the HIV-infected population (18). HIV infection significantly elevates the risk for HF with preserved ejection fraction, borderline HF with preserved ejection fraction, and HF with reduced ejection fraction (19). Besides these heart diseases, cerebrovascular events are also often reported as a complication of HIV and the prevalence of the disease is strikingly greater in PLWH versus people without HIV (20-22). Remarkably, the rate of cerebrovascular disease increases with age among PLWH; however, the effects of HIV status on the hazard for CVD decrease with aging, suggesting a reduction of the effect of HIV infection per se on the risk of cerebrovascular incidents in favor of a higher contribution of traditional risk factors and an increased prevalence of comorbidities in aging PLWH (9,10). A common clinical manifestation of atherosclerosis in PLWH is PAD that is associated with forthcoming CV incident such as MI and stroke (23,24). Compared to the general population, PAD occurs more often in PLWH, with a prevalence of PAD of 20.7% in PLWH versus 1% in noninfected individuals (25-27). Nonatherosclerotic CV complications of HIV include PH which has a higher incidence and poorer prognosis in PLWH compared to the general population (28,29). The most recent analysis showed that the global prevalence of PH was 8.3% in adults and 14.0% in adolescents with HIV versus a prevalence of PH of approximately 1% in noninfected individuals, indicating that PLWH are at elevated risk for this lung disorder (30,31).

Analysis of sex differences in HIV-related CVD show that female PLWH have increased risk of vascular diseases compared to males. Many have shown that AMI is more strongly associated with HIV in women than men and results from a US cohort have reported increased relative risk for the disease in women compared to men among PLWH (8). Others have also confirmed that female PLWH are exposed to higher risk of MI than males (15,32). Emerging data reveals that HIV infection is also a significant risk factor for HF in women (12). The relative risk of HF has been shown to be the highest in young people (20 to 29 years old) and in female PLWH and it displays a declining trend with age (33,34). HIV-positive women are also at a higher risk to experience stroke versus uninfected women and are at considerably greater risk for stroke and intracerebral hemorrhage than male PLWH, which collectively supports a stronger

ABBREVIATIONS AND ACRONYMS

cART = combination antiretroviral therapy

cIMT = carotid intima-media thickness

CVD = cardiovascular disease

HF = heart failure

HIV = human immunodeficiency virus

FMD = flow-mediated dilatation

MI = myocardial infarction

NO = nitric oxide

PAD = peripheral artery disease

PH = pulmonary hypertension

PLWH = people living with HIV

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association between HIV infection and cerebrovascular events in women than men (9,10,12). PAD and PH are 2 additional vascular diseases for which sex differences have been reported and for which healthy and HIV-infected women are at elevated risk (35,36). However, noninfected women and female PLWH with PAD are more frequently asymptomatic than men and have a better survival rate than men (35-39). Collectively, these data indicate that the health care burden of HIV-related CVD in women will likely go beyond that of men.

CLINICAL EVIDENCE OF THE EFFECT OF HIV INFECTION AND cART ON VASCULAR FUNCTION

The pathophysiology of HIV-associated vascular diseases is complex and multifactorial. Although it is currently recognized that traditional risk factors are increased in HIV-infected individuals, the prevalence of atherosclerosis-associated CVD remains 50% higher in PLWH after adjustment for traditional risk factors such as lipids, blood pressure, and smoking status (8,14,40-43). This indicates that viral infection per se and cART are independent risk factors for endothelial dysfunction and subsequent atherogenesis.

The endothelium forms the interior surface of blood vessels and plays a key role in vascular homeostasis by regulating vascular tone, nonthrombotic vascular surfaces, cell adhesion, and inflammation of the vessel wall (44). Endothelial dysfunction is characterized by diminished vasorelaxation, increased endothelial permeability, and elevated expression levels of inflammatory cytokines and adhesion molecules (45). Compelling evidence gives credence to the idea that endothelial function is impaired in PLWH and HIV-related endothelial dysfunction has been proposed as a crucial link between infection, chronic inflammation, activation of the immune system, and atherosclerosis (46,47). Clinical assessment of endothelial function includes noninvasive measurement of endothelium-dependent vasorelaxation such as flow-mediated dilatation (FMD) of the brachial artery and study of markers of endothelial cell activation such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and selectins (endothelial leucocyte adhesion molecule) (48,49). Several other biomarkers including inflammatory (eg, interleukin 6 [IL-6]; C reactive protein; and tumor necrosis factor-α [TNF-α]), coagulation (eg, D-dimer and von Willebrand factor [vWF]), and immune activation (eg, soluble CD163 [sCD163] and soluble CD14 [sCD14]) are also associated with endothelial dysfunction. Therefore, quantification of the levels of expression of these markers serves as an indicator of the pathophysiological changes in vascular function (50,51). Because endothelial dysfunction is an early event in the progression of atherogenesis, examination of carotid intima-media thickness (cIMT) and coronary atherosclerosis by computed tomography angiography are also important surrogate markers for impaired vascular function (52,53).

Because there is no tool to identify PLWH at high CV risk and there are lacking data from large-scale randomized controlled trials of HIV therapies, the American Heart Association has recently released a scientific statement for the prevention and the management of HIV-associated CVD (54). Strategies on management of CVD in PLWH are very limited despite the fact that clinical and experimental evidence has shown the impact of novel risk factors to HIV-related CV events. Screening for endothelial dysfunction and CVD in PLWH follows the current American Heart Association recommendations for the general population including measurements of FMD, cIMT, carotid plaque, and coronary artery calcium (55-57). These methods are effective to identify HIV-infected and noninfected patients at risk for developing CVD. Lifestyle optimization such as smoking cessation, limiting alcohol consumption, and use of statin and nonstatin lipid-lowering drugs or antithrombotic agents should be considered as intervention of atherosclerosis-associated CVD (58-62).

CONTRIBUTION OF VIRAL INFECTION TO ENDOTHELIAL DYSFUNCTION. In clinical settings, many studies have focused on better understanding the relationship between HIV infection/cART and the vascular biology of the endothelium. Oliviero *et al* (63) have shown that brachial FMD is impaired in naive untreated PLWH versus healthy patients and found a strong inverse correlation between FMD values and HIV mRNA levels, supporting a direct role for early stage of viral infection in vascular dysfunction. Plasma levels of VCAM-1, ICAM-1, E-selectin, and vWF are highly elevated in treatment-naive PLWH and show positive correlation with increased HIV viral load and the severity of the disease (64-66). Similarly, increased plasma levels of IL-6, C-reactive protein, D-dimer as well as sCD163 and sCD14 are associated with vascular dysfunction in cART-naive PLWH (67-69). Importantly, ongoing HIV replication and immune dysfunction have been shown to contribute to higher prevalence of increased biomarkers of inflammation and activation of the coagulation and immune system (70,71). Although controversial, increased cIMT, noncalcified coronary plaques, and carotid lesions

appear more prevalent in PLWH and directly related to low CD4+ cell count (63,72-76). Collectively these data support the contribution of unrepressed HIV viral infection in the development of endothelial injury and CV events.

With the advent of cART, successful viral repression, and restoration of CD4+ T cells, the latter findings are losing clinically relevance. However, compelling evidence does support the contribution of HIV viral infection to CVD despite low viremia. Some of the best evidence is notably provided by cART-free elite controllers who, despite undetectable viral load and physiological CD4+ T cells count, exhibit increased coronary atherosclerosis and high immune activation, thus supporting a direct critical role for viral infection and its associated effects on immune activation and inflammation in the development of vascular diseases (43,77). Further evidence supporting the contribution of viral infection to vascular disease has been provided by experimental models. The Tg26 mouse and HIV-1 rat are 2 transgenic rodents that ubiquitously express 7 of 9 viral proteins and are commonly used models to investigate the effects of viral infection independent of cART treatment (78,79). As with PLWH, these animals exhibit endothelial dysfunction, accelerated atherogenesis, and PH (78,80,81). Similarly, nonhuman primates infected with simian immunodeficiency virus develop atherosclerosis (82,83). Thanks to these experimental models, reduced nitric oxide (NO) bioavailability, increased inflammation, and increases in expression of cell adhesion molecules (CAMs) have been identified as contributing mechanisms to endothelial dysfunction. Excess oxidative stress rather than decreases in endothelial nitric oxide synthase expression and activity has been identified as the cause of reduced NO bioavailability (84,85). Ex vivo experiments in Tg26 mice reported increases in the expression of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase isoform, NOX1, in the aorta and restoration of endothelium-dependent relaxation with NOX1 inhibition (80). The HIV-1 rat, on the other hand, exhibits impaired reactive oxygen species (ROS) scavenging mechanisms involving decreases in superoxide dismutase and glutathione expression (84). The 2 viral proteins transactivator of transcription (tat) and negative factor (nef) are likely the origin of the increase in oxidative stress. Nef is reported to interact with p22-phox, a cofactor of NADPH oxidase NOX1 to upregulate its activity leading to increases in oxidative stress and reduction in NO bioavailability in isolated human neutrophils (86). Additionally, tat released from macrophages has the ability to increase oxidative stress in brain microvascular endothelial cells via activation of the nuclear factor κβ (NF-κβ) inflammatory pathway (87).

A common theme across the multiple in vivo models is the presence of an immune response and its contribution to the observed CVD. Tg26 mice and nonhuman primates both exhibit atherosclerosis partially mediated via the proinflammatory cytokine IL-18, a pathway which has not been examined in the HIV-1 rat (78). Despite this common theme, HIV-1 rats exhibiting PH present with increased inflammation via innate inflammatory response, histamine signaling, natural killer cell cytotoxicity, and neutrophil activation, again promoting the common theme of immune regulated CVD (81). In addition to IL-18 Tg26 mice exhibit increased inflammatory cytokines including IL-1β, TNFα, and IL-6 (78,88). Nonhuman primates exhibit gut microbiome translocation (which can result in chronic inflammation) and inflammatory-mediated diastolic dysfunction which chemokine receptor 5 (CCR5) inhibition restored (89,90). CCR5 is the entry way of HIV into uninfected cells CD4+ T cells, the primary target of HIV (91). Multiple HIV proteins interact with CCR5 including tat, which increases its expression, and envelope glycoprotein GP120 (gp120), which uses CCR5 as an entryway into the cell in vitro (78,92). Although not directly obtained in HIV conditions, CCR5 inhibition has been shown to decrease inflammation, improve endothelial function, and protect from atherogenesis, suggesting CCR5 involvement in endothelial dysfunction and vascular disease associated with viral infection (93-95). Cultured astrocytes incubated with gp120 released the proinflammatory cytokines TNFα, IL-1β, and IL-6 (96). Monocytes and macrophages incubated with tat have also been shown to release TNF-related products which can lead to apoptosis in uninfected CD4 T cells (97). Finally, the nef has been shown to increase the proinflammatory cytokines TNFα, IL-1β, and IL-6 when cultured with macrophages via NF-κβ mediated mechanisms (98). Collectively, these data establish a direct link between viral proteins and inflammation, which is highly clinically relevant as viral proteins remain in the circulation despite cART (99,100).

Finally, another well-established contribution to endothelial dysfunction and atherosclerosis is the increased expression of CAMs which are able to trap monocytes causing their translocation across the endothelium (101). Tg26 mice, HIV-1 rats, and nonhuman primates all exhibit increased expression of proatherogenic adhesion molecules such as VCAM-1 and ICAM-1 (102,103). In in vitro studies using

cultured endothelial cells, researchers have shown gp120 induced ICAM-1 expression in as little as 4 hours and tat and nef increased expression of both ICAM-1 and VCAM-1 (104-107). These in vitro studies performed in human umbilical vein endothelial cells also suggest that increases in these adhesion molecules are due to micro RNAs 221 and 222 and is NF-κβ pathway-dependent as well as the extracellular signal-related kinase 1/2 pathway-dependent (105,106).

In conclusion, viral infection contributes to CVD via mechanisms which include decreased NO bioavailability, increased inflammation, and increased expression of cell adhesion molecules. These results have been corroborated with multiple approaches including Tg26 mice, HIV-1 rats, and nonhuman primates infected with simian immunodeficiency virus along with multiple in vitro models. Altogether, these models provide strong evidence of mechanisms by which HIV viral infection independent of cART contributes to CVD.

CONTRIBUTION OF cART TO ENDOTHELIAL DYSFUNCTION. Analyses of the relationship between vascular dysfunction, progression rate of atherosclerosis, and cART have resulted in conflicting observations. Although evidence supports deleterious effects of cART on endothelial function, other studies report no or beneficial effects of cART **Table 1** summarizes the contribution of cART regimens to CVD. Several studies have notably shown exacerbated reduction in FMD in cART-treated versus cART-naive PLWH and established independent associations between cART and diminished endothelial function, especially among PLWH receiving a regimen containing protease inhibitors (PIs) (109,110,111,118). Additional reports support a higher prevalence of cIMT, noncalcified coronary plaques, and coronary artery stenosis in cART-treated PLWH versus cART-naive patients regardless of the composition of regimen and other reports suggest further increases with longer exposure to cART (40,124,126). In contrast, others have found no association between reduced vasorelaxation and cART (regardless of the use of PI-containing regimen) nor did they report contribution of PI-containing cART to cIMT progress (72,73,108,112). Lastly, few have reported improvement of branchial FMD in HIV-infected treatment-naive patients after administration of class-sparing antiretroviral regimens (121,122).

These conflicting observations regarding the contribution of cART also translate into inconsistencies regarding the effects of cART on markers of endothelial cell activation and inflammation including ICAM, VCAM, IL6, TNFα, and vWF. Although several studies report beneficial effect of cART on endothelial activation and systemic inflammation (regardless of the type of regimen), many others indicated a lack of influence, partial effects, or a failure to normalize to the levels of these markers in noninfected individuals (129-139).

Dyslipidemia initially appeared as the key mediator of cART-related vascular disease, notably PI-mediated endothelial dysfunction (110). However, reduction in plasma cholesterol and lipid levels did not restore endothelial function in PLWH on PI-containing regimens (140). Similarly, despite raising triglyceride levels, PI treatment did not induce endothelial dysfunction in healthy volunteers (141). Therefore, whereas dyslipidemia consistently develops with PI-containing regimens, it may likely not be the leading cause of cART-associated endothelial dysfunction. Using an experimental approach consisting of submitting mice to the PI ritonavir for 4 weeks, our group proposed alternate mechanisms, which notably demonstrated that ritonavir impairs endothelial function and NO bioavailability in vivo via indirect mechanisms involving reduced adipose mass and leptin levels leading to an endothelial leptin receptor dependent increase in NOX1 and oxidative stress as well as vascular inflammation (95). In opposition to in vitro studies reporting that ritonavir alone or in combination with various other cART alters NO production, induced marked increases in IL-6 and IL-8, and secretion of soluble ICAM and VCAM in endothelial cells in culture, we ruled out direct deleterious effects of ritonavir on endothelial cell function (142). Reduction in fat mass and adipokines (leptin) secretion are among the first and main side effects on PIs (143-145); therefore, the mechanisms proposed are likely translatable to humans.

Numerous confounding factors including the many combinations of cART possible and the heterogeneity of the population studied likely explain this lack of consistent results regarding the contribution of cART on endothelial function and vascular disease. Nevertheless collectively, these data support the individual contribution of cART to CVD through indirect metabolic alterations involving reduction in fat mass and alterations in adipokines levels as well as lipid metabolism which are major risk factor for atherosclerosis (146).

POTENTIAL CAUSES OF SEX-DIFFERENCES IN VASCULAR DISEASES ASSOCIATED WITH HIV. Sex-stratified analysis revealed that female PLWH are at elevated risk and rate of CV complications compared to male PLWH or noninfected women (12,33). Higher intrinsic immune activation in females has emerged

TABLE 1 Effect of cART on CVD

cART Regimen	Outcomes Studied	Finding	First Author (Ref. #)
PI (IDV, NFV, and RTV/SQV)	FMD	No change in FMD	Nolan (108)
PI[a]	cIMT	No change in cIMT	Hsue (74)
PI (IDV)	EDV, IMV	EDV and IMV impaired	Dubé (109)
(i) PI with NRTIs and/or NNRTIs or (ii) NRTIs alone or with NNRTIs PI (APV, IDV, NFV, RTV, SQV); NRTI (ABC, DDI, 3TC, d4T, AZT); NNRTI (DLV, EFV, NVP)	FMD	(i) FMD impaired (ii) No change in FMD	Stein (110)
PI regimen or non-PI regimen[a]	FMD, cIMT	FMD impaired, cIMT increased	Charakida (111)
PI regimen or non-PI regimen[a]	FMD	No change in FMD	Solages (112)
NRTIs with one or two PIs (IDV, RTV or SQV+RTV)	cIMT	cIMT increased	Seminari (113)
cART with a PI (IDV, NFV, SQV+RTV, or LPV+RTV)	PVW	Arterial stiffness increased	Schillaci (114)
(i) PI (IDV, NFV, RTV, SQV, NFV+ SQV or RTV+SQV) (ii) 2 NRTIs or 2NRTIs+ NNRTI	Carotid plaque	Carotid lesions increased in PI receiving group	Maggi (115)
HAART with PI[a]	cIMT	cIMT increased	Chironi (116)
PI-containing regimens and NNRTI-containing regimens[a]	FMD	FMD impaired	Andrade (117)
(i) NRTI+PI or PI+NNRTI +/- NRTI (ii) NRTI + NNRTI[a]	cIMT	No change in cIMT	Currier (72)
(i) PI regimen (NFV, IDV, LPV/RTV or dual PI) (ii) non-PI regimen (NNRTI+ NRTI)	cIMT	No change in cIMT	Currier (73)
ABC-sparing regimens and ABC-containing regimens	FMD	FMD impaired	Hsue (118)
Combination of three drugs simultaneously (NRTIs, NNRTIs and/or PIs) PI (SQV/RTV, LPV/RTV, NFV, ATV/RTV, IDV/RTV); NRTI (3TC, AZT, ABC, TDF, DDI, d4T); NNRTI (EFV, NVP)	FMD, cardiac perfusion PET	No change in FMD and cardiac perfusion	Lebech (119)
FTC/TDF/EFV	FMD	No change in FMD	Dysangco (120)
(i) PI-sparing regimen of NRTIs plus EFV, (ii) NNRTI-sparing regimen of NRTIs+LPV/RTV, (iii) NRTI-sparing regimen of EFV + LPV/RTV	FMD	FMD improved in each arm	Torriani (121)
PI-containing (IDV, LPV/RTV) regimen followed by HAART with 2 NRTIs (AZT and 3TC) and one NNRTI (EFV)	FMD	Normalized FMD	Arildsen (122)
HAART with PI, HAART with NNRTI[a]	cIMT cIMT	cIMT increased No change in cIMT	Mercie (123)
AZT/3TC/LPV/r or NVP/LPV/r	cIMT, arterial stiffness	cIMT increased, femoral artery stiffness increased	van Vonderen (124)
PI, NNRTI, NRTI (PI: IDV, RTV, SQV, NFV, LPV, APV, AZV); NNRTI (NVP, EFV, LOV); NRTI (AZT, d4T, 3TC, ABC, DDI, DDC, TDF)	cIMT	cIMT increased	Lorenz (40)
HAART including PIs, NNRTI, and NRTI[a]	PVW	Arterial stiffness increased	Lekakis (125)
HAART[a]	Coronary artery stenosis > 50%	Stenosis increased	Post (126)
2 NRTI (d4T and 3TC) and 1 NNRTI (EFV or NVP)	PWV, cIMT	No change in arterial stiffness and cIMT	Fourie (127)
2 NRTI (TDF/3TC, AZT/3TC, ABC/3TC or 3TC) plus either a NNRTI or a RTV-boosted PI	cIMT	No change in cIMT	Mosepele (128)

[a]The type of drug is not disclosed.

3TC = lamivudine; ABC = abacavir; APV = amprenavir; ATV = atazanavir; AZT = zidovudine; cART = combination antiretroviral therapy; cIMT = carotid intima-media thickness; d4T = stavudine; CVD = cardiovascular disease; DDC = zalcitabine; DDI = didanosine; DLV = delaviridine; EDV = endothelium-dependent vasodilation; EFV = efavirenz; FMD = flow-mediated dilation; FTC = emtricitabine; HAART = highly active antiretroviral therapy; IDV = indinavir; IMV = insulin-mediated vasodilation; LPV/r = boosted lopinavir; LOV = Loviride; NFV = nelfinavir; NNRTIs = non-nucleoside reverse transcriptase inhibitor; NRTIs = nucleoside reverse transcriptase inhibitors; NVP = nevirapine; PET = positron emission tomography; PI = protease inhibitors; PWV = pulse wave velocity; RTV = ritonavir; SQV = saquinavir; TDF = tenofovir.

as a potential explanation for this sex-discrepancy and higher prevalence of HIV-associated CVD. Notably, studies have reported that markers of innate immune activation such as CXCL10, sCD163, and sCD14 are increased and remain elevated in cART-naive and cART-treated women, respectively, compared to male PLWH (147,148). In comparison to male PLWH, women with a lower CD4+ count have higher levels of macrophage inflammatory markers including galectin-3 binding protein (Gal-3BP), sCD163, and sCD14 which is associated with greater prevalence of cIMT (149). Similarly, increased prevalence of noncalcified coronary plaques correlates with higher monocyte activation in female compared to male PLWH and noninfected individuals, and monocyte activation was further elevated with age among women versus men PLWH (150). Collectively, these data support a higher immune activation in females in response to HIV. The female sex hormones progesterone and estrogen may contribute to this sex

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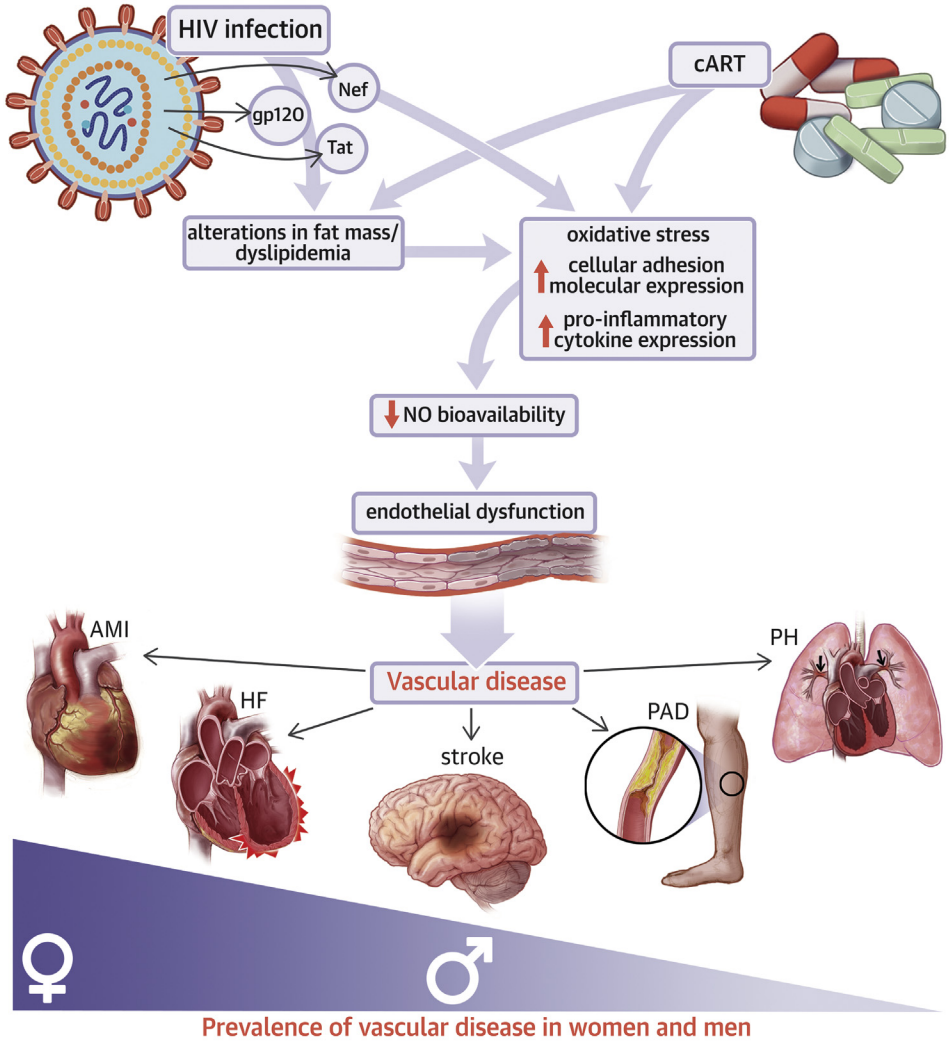
CENTRAL ILLUSTRATION **Contribution of HIV Infection and cART to HIV-Associated CVD**



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Schematic illustrating the potential mechanisms whereby viral infection and combination antiretroviral therapy contribute to vascular disease in patients living with HIV. AMI = acute myocardial infarction; cART = combination antiretroviral therapy; CVD = cardiovascular disease; HF = heart failure; HIV = human immunodeficiency virus; NO = nitric oxide; PAD = peripheral artery disease; PH = pulmonary hypertension

difference via regulating the interferon-α production by plasmacytoid dendritic cells upon Toll-like receptor 7 stimulation. Plasmacytoid dendritic cells from women produce significantly higher levels of interferon-α in response to HIV-1 that of men which is associated with greater CD8+ T cell activation at the same level of viral replication (151-153)

Some groups have shown that there is no sex difference in response to cART treatment whereas other groups demonstrated that women experience less of cART-related decrease in the main markers of inflammation and immune activation than men irrespective the type of regimen (154-157). These findings may explain the sex-based discrepancies in the prevalence of HIV-related CV events. Besides sex, many confounding factors should be considered when evaluating for CVD risk assessment including race, socioeconomic status, smoking, and drug use. Among PLWH, higher prevalence and suboptimal control of traditional vascular risk factors in minority and racial

groups, limited or no access to health care, excessive smoking, and substance abuse could contribute to the above-mentioned disparities (158-162). Female PLWH are often African American women who are exposed to higher risk of stroke and other CV events (159). In this particular female population, poor economic status, barriers to access health care, and greater added relative risk of smoking ultimately lead to a higher prevalence of CVD (160,161).

Together, these data suggest that the pathological mechanism responsible for the sex disparities in HIV-induced changes in vascular function is mainly attributable to the persistent higher immune activation and systemic inflammation potentially due to a reduced cART efficiency and other contributing factors such race/ethnicity, greater tobacco use, and poorer health-related quality of life as seen in women PLWH.

CONCLUSIONS

Although compelling evidence shows that CVD is the leading cause of death in PLWH on cART, the complexity of the disease, its multifactorial aspect, and the higher prevalence of traditional risk factors in PLWH have significantly impeded our advances in the understanding of its etiopathology. However, current compelling evidence derived from both clinical and experimental studies do strongly support independent contributions of both viral proteins and cART to endothelial dysfunction likely through indirect alterations in metabolic function and adipose mass distribution but also through sustained immune activation ultimately leading to impaired NO bioavailability and vascular dysfunction (**Central Illustration**). Experiments going forward would require deeper investigation of the underlying mechanisms and notably further analysis of the origin of the sex difference in the prevalence of CVD.

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ADDRESS FOR CORRESPONDENCE: Dr Eric J. Belin de Chantemèle, Vascular Biology Center, Medical College of Georgia at Augusta University, 1460 Laney Walker Boulevard, Augusta, Georgia 30912, USA. E-mail: ebelindechanteme@augusta.edu.

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