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REVIEW ARTICLE

Good Fences Make Good Neighbors: Human Immunodeficiency Virus and Vascular Disease

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Cardiovascular disease, venous thrombosis, and microvascular disease in people with HIV (PWH) is predicted to increase in an aging HIV-infected population. Endothelial damage and dysfunction is a risk factor for cardiovascular events in PWH and is characterized by impaired vascular relaxation and decreased nitric oxide availability. Vascular disease has been attributed to direct viral effects, opportunistic infections, chronic inflammation, effects of antiretroviral therapy, and underlying comorbid conditions, like hypertension and use of tobacco. Although biomarkers have been examined to predict and prognosticate thrombotic and cardiovascular disease in this population, more comprehensive validation of risk factors is necessary to ensure patients are managed appropriately. This review examines the pathogenesis of vascular disease in PWH and summarizes the biomarkers used to predict vascular disease in this population.

Key words: biomarkers; cardiovascular disease; endothelium; HIV; thrombosis.

INTRODUCTION

Patients with human immunodeficiency viral (HIV) infection have an improved prognosis on antiretroviral therapy (ART) [1]. This is associated with a concomitant drop in the prevalence of opportunistic infections and a corresponding increase in life expectancy [1–3]. Noncommunicable diseases have become a major cause of morbidity and mortality in these patients, including large vessel disease (occlusive vasculitides and aneurysms), cardiovascular disease (CVD), and venous thromboembolism [4–13]. Thrombotic disease is pathological clotting in the vascular system. In arteries, abnormal clotting can result in peripheral vascular disease, myocardial infarction, and cerebrovascular accidents [8]. Venous clots can dislodge and travel to the pulmonary vasculature, a phenomenon known as pulmonary thromboembolism [11]. In the microvasculature system, small disseminated clots can be seen with microangiopathic thrombotic processes, including thrombotic thrombocytopaenic purpura (TTP), TTP-like syndrome, and disseminated intravascular coagulopathy (DIC) [14]. Abnormal clotting in the entire vascular tree occurs in people with HIV (PWH). Thrombotic risk in PWH has been attributed to a number of factors, including the presence of opportunistic infections, prolonged immobility, antiretroviral drugs and other treatments, comorbid conditions (including hypertension and diabetes), and the impact of HIV, itself, on the endothelium [15–17]. This review will look at the interaction between HIV, the vascular wall, and pathogenic thrombosis.

THE ENDOTHELIUM

The endothelium is a monolayer of cells that lines the blood vessels [18, 19]. It is a highly specialized organ that is responsible for control of both inflammation and coagulation. The endothelium-lining arteries, veins, and capillaries show differential response to stressors that are physiological adaptations to the anatomical location [19]. These stressors include differential shear stress (high in the arterial system and lower in the venous system) that can result in location-specific gene transcription [19].

Under normal conditions, the endothelium is a selectively permeable, anticoagulant surface. It produces a number of molecules that act to limit clotting by inhibiting both platelet activation and coagulation factors (Table 1).

In response to pro-inflammatory stimuli or trauma, the endothelium upregulates cellular adhesion molecules and procoagulant factors and becomes more permeable (Table 2) [19]. This allows leukocytes to translocate across the endothelial surface and into the tissue. There is a local shift from

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Table 1. Anticoagulant Factors and Vasodilators Produced by the Endothelium

Anticoagulant Factor	Function
Heparan sulphate	Combines with antithrombin and inactivates coagulation factors IIa and Xa [19]
Prostacyclin	Platelet inhibition [19]
Cluster of differentiation (CD) [39]	Scavenges adenosine diphosphate released by activated platelets to inhibit platelet aggregation [20]
Endothelial protein C receptor	Binds activated protein C to potentiate its activity; complex also acts to protect endothelial cells through the activity on protease-activated receptor-1 and -2 [21]
Thrombomodulin	Forms a complex with thrombin to activate protein C, which binds and inactivates factors V and VIII (with protein S as a cofactor) [22]
Tissue factor pathway inhibitor	Inhibits the tissue factor-VIIa complex and factor Xa [23]
Primary vasodilator	
Nitric oxide (endothelium-derived)	Mediates vasodilation; inhibits platelet activation [24, 25]
Endothelium derived hyperpolarizing factor	Mediates smooth muscle relaxation and causes vasodilation [26]

an anticoagulant to a procoagulant surface [27]. Tissue factor may be exposed by trauma, secreted into the peri-endothelial space in endothelial vesicles, or upregulated on leukocytes (especially monocytes) [28, 29] and platelets, resulting in activation of the coagulation cascade and clot initiation. Platelets are activated by exposure to subendothelial tissue (primarily collagen) and provide a secondary surface for coagulation, resulting in clot propagation [30].

Following endothelial injury, a number of processes are initiated to repair the damaged endothelium and allow for clot resorption [40]. Bone-marrow–derived endothelial progenitor cells home to sites of vascular injury and stimulate angiogenesis [40–42]. Platelets and endothelial cells secrete a number of growth factors (including vascular endothelial growth factor), cytokines (including TGF-beta), and chemokines (including CXCL-12 or stromal derived factor-1) that restore barrier function and stimulate endothelial cell proliferation [43–45]. Clot resolution occurs with activation of proteases, like plasmin (through the function of tissue plasminogen activator or tPA present on endothelial cells) [46], which break down fibrin clots with resulting production of fibrin degradation products (measured as D-dimers). This process reduces local hypoxia with stabilization of hypoxia-inducible factor-1, which also can contribute to repair [19].

ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is a state of aberrant endothelial cell activation that is associated with thrombosis [47]. Endothelial dysfunction classically is associated with arterial atherosclerosis, but it can be more broadly defined to include a prothrombotic state throughout the vasculature [48]. Multiple pathophysiological mechanisms contribute to a phenotype that is characterized by reduced dilatation, decreased arterial compliance, and local inflammation with reduced vascular repair and angiogenesis [19]. Bioavailability of nitric oxide, a key vasodilator and platelet inhibitor, is significantly reduced [25]. The pro-inflammatory mediators that are produced by the damaged endothelial tissue also act directly to upregulate tissue factor expression by leukocytes and to activate platelets [28, 49, 50]. Cyclo-oxygenase enzymatic activity is upregulated in response to various inflammatory stimuli and results in increased production of prostaglandin E2 and thromboxane A2, which stimulate platelet activation and aggregation [38, 51].

PATHOPHYSIOLOGICAL MECHANISMS ASSOCIATED WITH DEVELOPMENT OF ENDOTHELIAL DYSFUNCTION IN PWH

Chronic Inflammation Caused by HIV Infection

HIV infection is a cause of chronic inflammation [49]. A detailed description of the causes of inflammation in PWH is outside the scope of this article. Briefly, rapid depletion of $CD4^+$ T cells from the gut-associated lymphoid tissue and, especially, Th17 subsets disrupts the gastrointestinal barrier function with translocation of microbial products across the interface [49, 52]. This directly stimulates innate pattern recognition molecules, like toll-like receptors (TLRs), with activation of pro-inflammatory signaling pathways like NFκB. TLRs 7 and 9 also are activated directly by HIV, because low-grade viral replication persists even on therapy [49]. Innate immune effector cells activated through pattern recognition receptors produce pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β [53]. The presence of HIV DNA in the cytoplasm of target cells also activates caspase-1, resulting in increased apoptosis [54]. Chronic inflammation has been associated with functional and quantitative abnormalities in multiple leukocytes subsets. This includes monocyte and neutrophil activation, CD4+ T cell dysfunction and apoptosis, CD8+ T cell activation, and B cell activation [49].

Chronic inflammation results in a state of abnormal endothelial cell activation that has been compared to changes seen in aging [55]. This is characterized by reduced number and function of endothelial progenitor cells with reduced capacity to repair endothelial damage [40, 47, 56]. Damage to endothelium can result from the release of oxygen-free radicals by activated immune cells, including activated monocytes and lymphocytes. Pro-inflammatory cytokines like TNF-α bind

specific endothelial receptors triggering endothelial apoptosis and activation [50]. Neutrophil activation may result in the production of cytotoxic neutrophils extravasation traps (NETs) that interact directly with coagulation activators and may promote leukocyte adherence [57]. In animal models, neutrophil activation and NETosis is associated with increased risk of thromboembolism [58].

Direct Effects of HIV on Endothelial Cells

The ability of HIV to infect endothelial cells directly is controversial. Small preliminary studies (in vitro) suggested that some endothelial cells could harbor infectious viruses, although larger scale studies have disputed this [59, 60]. It is clear, however, that HIV viral proteins can have a detrimental effect on the endothelium with subsequent dysfunction. Tat activates endothelial signaling pathways with downstream reduction in transcription of nitric oxide synthetase and upregulation of monocyte chemoattractant protein-1 (MCP-1) and cell adhesion molecules [61, 62]. This promotes both leukocyte activation and leukocyte adhesion to the endothelium. Nef activates pro-inflammatory pathways, including NF-κB and NFAT-1, in both endothelial cells and macrophages, promoting alterations in the monocyte phenotype towards pro-inflammatory cells and release of free radicals that can directly damage the endothelium [63]. In addition, Nef can affect cholesterol transport that predisposes to the formation of foam cells [63]. The HIV envelope proteins, gp-120/41, activate the p38 map kinase pathway that has been linked to increased endothelial permeability, endothelial cell apoptosis, and vasoconstriction [64].

Large Vessel Arteritis and Thrombosis in HIV

Aneurysmal disease and occlusive large vessel disease has been well-described in PWH. Histologically, this disease is pleomorphic with some studies reporting an appearance similar to panarteritis nodosa and others reporting transmural inflammation [65]. The pathogenesis of large cell arteritis is delineated incompletely. Upregulation of chemokine secretion can result in transmural cellular infiltrates with compromise of the *vasa vasorum*. A suggestion that HIV proteins may mimic arterial proteins with a subsequent cross-reactivity. Aside from direct effects on endothelial cells, studies suggest that arterial smooth muscle cells and fibroblasts may be susceptible to direct HIV infection [65-69]. This may result in weakening of the vascular wall and subsequent dilation [67, 70]. This area does, however, require further elucidation.

HIV-Associated Communicable Diseases

HIV-associated immunodeficiency increases the predisposition to and persistence of a number of infections. Chronic infections are associated with a number of changes, including upregulation of procoagulant factors and platelet activation, and mediate a direct effect on endothelial cells. *Mycobacterium tuberculosis* has been identified in endothelial cells in extrapulmonary infection [71]. Mycobacterial infection is an independent risk factor for thromboembolism and microvascular abnormalities [71, 72]. Parasitic infections like *Toxoplasma gondii* upregulate endothelial adhesion molecules to assist with invasion [73]. In addition, dysbiosis and microbiome perturbations in the gastrointestinal, respiratory, and urogenital tracts occurring in PWH are an independent risk factor for cardiovascular disease [74].

Endothelial cells are targets for *Herpesviridae*, including cytomegalovirus, Epstein-Barr virus, Kaposi-sarcoma herpes virus (KSHV), and varicella-zoster virus. Persistent infection with these viruses have been associated, especially in aging or otherwise immunodeficient patients, with an increased risk of vasculitis [75] and endothelial dysfunction [76], mediated through inflammatory signaling pathways [73] and through endothelial cell apoptosis [78]. KSHV, specifically, secretes cytokine homologs like viral IL-6 that have been implicated in both mediating a pro-inflammatory milieu and in atypical angiogenesis [79]. Herpes simplex viruses may infect the endothelium with subsequent apoptosis [76]. Finally, other concomitant viral infections (including persistent hepatitis C viral infection) have been linked to increased risk of cardiovascular disease [81, 82].

Traditional Risk Factors for Cardiovascular Disease in the ART HIV Era

Traditional risk factors for endothelial dysfunction include the presence of diabetes mellitus, hypertension, and hyperlipidaemia. These conditions contribute significantly to CVD risk in PWH [83, 84]. Chronic inflammation (with circulating pro-inflammatory cytokines) can predispose to insulin resistance through the phosphorylation of insulin receptor substrate-1 [85, 86]. Antiretroviral therapy is associated with lipid- abnormalities and dysregulation of glucose-processing pathways, which are independently associated with an increased risk of type 2 diabetes mellitus [85]. Hypertension in PWH is common and a number of potential pathogenic mechanisms have been identified, including lipodystrophy, a pro-inflammatory state associated with the secretion of cytokines and adipokines, and renal disease [87]. HIV protease is molecularly homologous to renin, and renin levels are often inappropriately high [88, 89]. Hypertension is exacerbated by worsening endothelial dysfunction [87]. Dyslipidaemia is a common complication of both treated and untreated HIV infection [90, 91]. In ART-naïve patients, this may be mediated by direct effects of the virus and the inflammatory milieu. Lipid processing and transportation is altered in PWH. Modified lipids may directly activate pattern recognition receptors [90]. Finally, substance use, especially tobacco use, is increased in PWH [88]. Risk of arterial disease is significantly higher in PWH who smoke and there is a concomitant increased mortality [6, 93].

Antiretroviral Drugs

Antiretroviral therapy has reduced the morbidity and mortality of HIV infection, affording improved life expectancy,

but long-term therapy can result in endothelial toxicity and vascular dysfunction. This has been linked with a number of metabolic abnormalities, including lipid abnormalities and predominantly an increase in circulating low-density lipoprotein and cholesterol levels [94]. The classes of drugs most commonly implicated are protease inhibitors. The majority of inflammatory and cardiovascular disease biomarkers show a decline with effective therapy, however, confirming a benefit of ART even for cardiovascular disease outcomes [90, 95–97].

CLINICAL BIOMARKERS OF ENDOTHELIAL DYSFUNCTION IN PWH

Attempts have been made to identify appropriate biological markers to predict and monitor cardiovascular disease risk in PWH with varying results. Early findings from the SMART (strategic timing of antiretroviral treatment) trial suggested that elevated highly sensitive C-reactive protein (CRP) and D-dimer results correlated with cardiovascular mortality in HIV-infected patients [98]. Summary data on the findings of selected trials investigating biomarkers related to thrombosis and accelerated atherogenesis are presented in Table 3. The most commonly measured biomarkers included IL-6 [29, 53, 56, 97–108], highly sensitive CRP [7, 28, 98, 99, 101–104, 106, 108, 109] and D-dimer levels [7, 28, 98, 99, 101–104, 106, 108, 109]. In addition, a number of studies measured markers of endothelial adhesion or activation, or both, including soluble intercellular adhesion molecule-1 and soluble vascular cell adhesion molecule-1 [7, 15, 17, 50, 97, 106–108, 110–112], monocyte activation (sCD163, sCD14, or changes in monocyte phenotype) [15, 28, 29, 50, 56, 96, 97, 100, 107–114], and platelet activation (expression of s- and p-selectin) [30, 33, 115]. Limitations exist in many studies examining biomarkers for CVD outcomes. Confounding variables include the age of the patients at analysis, the treatment status of the patients, the ART drug regimen used, and the presence of concomitant diseases. Not all studies include an HIV-uninfected control group. There is significant variation in the selection of biomarkers, measurement modality, and timing of measurement. Prediction of CVD outcomes often is correlative looking at surrogate markers of arterial disease, like flow-mediated dilation and carotid intimal medial thickness. Importantly, in studies looking at PWH after ART initiation, however, biomarkers did not always fully normalize, which suggests ongoing inflammation [17, 49, 100]. Ongoing study protocols include combinations of these markers [116, 117].

Few biomarkers have been studied in the ART era in the context of venous thrombosis or microvascular disease, and none have been conclusively linked to diagnosis or prognostication of occlusive vasculitis or aneurysmal disease [65]. This may represent a future study focus.

CLINICAL SCORING SYSTEMS

A number of clinical scoring systems exist to assess arterial, venous, and microvascular thrombosis risk (Table 4). Although thrombosis throughout the vascular tree is described in PWH, relatively few of these scoring systems have undergone validation in this patient cohort. No published performance evaluations of venous thromboembolic scoring systems or microvasculature scoring systems exist in PWH, although small case series have

Table 2. Procoagulant Substances Produced by the Endothelium [36]

Factor	Site of Storage or Expression	Function
Activation of the coagulation cascade		
Tissue factor	Subendothelial tissue including fibroblasts. Induced on endothelial cells in vivo. Expressed by leukocytes during inflammation (specifically monocytes) [31]	Activates the extrinsic coagulation pathway resulting in thrombin generation [31]
Factor VIII	Endothelial cells [32]	Stabilizes factor IX [32]
Platelet activation		
Collagen and subendothelial matrix	Subendothelial tissue [33]	Promotes platelet adhesion, activation, and aggregation [33]
Cellular adhesion molecules, including p-selectin and e-selectin, ICAM-1, and CXC12 [34]	Endothelial cells [33]	Promotes platelet adhesion, activation, and aggregation [33]
Von Willebrand Factor [35]	Weibel-Palade bodies [35]	Enables platelet adherence to exposed collagen through its interaction with platelet receptor Ib-V-IX (protects factor VIII from degradation [36, 37])
Eicosanoids, including prostaglandins and thromboxane A2 [38]	Endothelial cells [38]	Promotes platelet aggregation [38]
Vasoconstrictive agents		
Endothelins (predominantly endothelin-1) [39]	Endothelial cells, vascular smooth muscles cells, and reproductive system [39]	Activates endothelin receptors, increases production of reactive oxygen species, and reduces bioavailability of nitric oxide [39]

Table 3. Selected Studies of Biomarkers for Cardiovascular Disease in PWH

Author and Year	Number of HIV-infected Participants and Treatment Status	Number of Uninfected Controls	Biomarkers and Measurement Modality	Major Findings
2008 Von Hentig [33]	18 HIV-infected patients pre- and post-ART initiation	—	*Platelet activation*: platelet expression of CD62P, CD40L, and CD41 (flow cytometry)	Platelet function unaltered on PI-containing ART regimen; CD40L and CD41 both increased on PI regimen
2008 Kuller [98]	250 HIV-infected patients on continuous ART and 249 patients on drug interruption protocol	—	*Cytokines*: IL-6 *Inflammatory markers*: hsCRP, amyloid-A, amyloid-P *Coagulation markers:* D-dimers, PT fragment 1,2	IL-6, CRP, and D-dimers independently predicted all-cause mortality in HIV-infected patients
2009 Francisci [15]	56 HIV-infected patients pre- and post-ART treatment on PI or NNRTI and 10 patients not on ART	28	*Cytokines:* sCD40L, MCP-1 *Endothelial markers:* P-selectin, sVCAM-1 *Coagulation markers:* vWF, tPA	CD40L and tPA within normal limits in HIV-infected patients; p-selectin was elevated at baseline and remained elevated on treatment; vCAM-1, vWF, and MCP-1 decreased significantly on treatment irrespective of regimen
2010 Jong [118]	86 HIV-infected patients pre- and post-ART initiation	71	*Coagulation markers*: vWF PT fragment 1 and 2, TAT complex, endogenous thrombin potential, APC, protein-S and -C	Significantly increased vWF and D-dimers, APC ratio, and decreased free and bound protein-C and -S in HIV-infected patients; all markers except APC ratio improved with ART initiation
2010 Funderburg [28]	60 HIV-infected patients, majority on ART	19	*Microbial products*: LPS *Monocyte activation*: sCD14, TF expression by monocytes *Coagulation markers*: D-dimers	Monocyte expression of TF correlated with sCD14 and markers of immune activation in HIV-infected patients
2012 Funderburg [29]	57 HIV-infected patients on ART	23	*Microbial products:* LPS *Monocyte activation*: sCD14, monocyte CD62P and TF expression *Cytokines*: IL-6 *Inflammatory markers*: hsCRP	HIV-infected patients showed increased frequency of non-classical and intermediate monocytes that resembled profiles in associated with acute coronary syndrome; these monocytes express CD62P and TF and are related to T-cell activation, IL-6 and viral load
2012 Mayne [115]	46 HIV-infected patients, 73% on ART	18	*Platelet activation*: patient P-selectin and TF expression	HIV-infected patients showed higher levels of platelet activation
2012 Olmo [97]	54 HIV-infected patients—34 on continuous treatment and 20 with treatment interruption	—	*Cytokines*: IL-6, IL8, sCD40L, MCP-1 *Endothelial adhesion markers*: sP-selectin, 1 sVCAM-1 sICAM-1 *Coagulation*: tPA	MCP-1 and sVCAM-1 increased relative to baseline in with treatment-interruption; sCD40L, tPA, and sP-selectin increased in both treatment arms relative to baseline
2013 Ronsholt [17]l	70 HIV-infected patients on ART with viral suppression	16	*Cytokines*: IL-8, β2-MI TNF-α *Endothelial markers*: sVCAM-1 sICAM-1, sE-selectin, sP-selectin	HIV-infected patients on long-term therapy showed increased levels of β2-MI, IL-8, and sICAM-1
2013 Baker [113]	163 HIV-infected patients—54 ART-naïve and 109 ART-treated	—	*Monocyte activation*: Monocyte microparticles with TF expression *Cytokines*: IL-6 *Coagulation markers*: D-dimers, vWF	Monocyte-microparticle TF expression correlated with inflammatory and coagulation biomarkers in HIV-infected patients
2013 Baker [119]	717 HIV-infected patients—500 on continuing ART and 271 with treatment interruption	—	*Coagulation markers:* FVIII, AT, protein C	Patients in the interrupted treatment wing had transient increases in procoagulant factors and decreases in anticoagulant factors, increasing thrombin generation potential
2015 Van den Dries [114]	Retrospective review of Dutch HIV-infected cohort	—	*Markers of monocyte activation*: sCD14, LPB *Coagulation markers*: vWF	vWF increased in all HIV-infected patients but significantly higher in patients with first and recurrent venous thrombosis; higher risk of venous thrombosis in HIV-infected patients
2015 O' Halloran [110]	25 HIV-infected patients pre and post-ART initiation	15	*Monocyte activation markers:* sCD14, sCD163 *Cytokines*: sCD40L *Endothelial adhesion markers*: sP-selectin, 1 sVCAM-1 sICAM-1 *Coagulation factors*: vWF	All biomarkers were significantly higher pre-ART initiation compared with controls and reduced after therapy in HIV-infected patients; only GPVI reduced to levels comparable to controls
2015 Nkambule [30]	58 HIV-infected patients pre-ART initiation	38	*Platelet activation*: platelet aggregation and CD62P and CD36 expression on platelets	Platelet expression of CD62P increased in HIV-infected patients; CD62P and CD36 expression correlated with viral load; response in keeping with hypersensitivity on platelet aggregation

Table 3. Continued

Author and Year	Number of HIV-infected Participants and Treatment Status	Number of Uninfected Controls	Biomarkers and Measurement Modality	Major Findings
2016 Siedner [120]	105 HIV-infected patients on ART	100	*Cytokine*: IL-6 *Monocyte activation:* Kyrenunine: tryptophan ratio, sCD14 *Sonographic*: Ankle-brachial index	Increased arterial stiffness in HIV-infected patients; declines in inflammatory markers (IL-6, KTR and sCD14s) predicted a lower CIMT and hence atherosclerotic burden
2016 Haissman [109]	50 untreated and 155 ART treated HIV-infectedpatients	105	*Monocyte activation:* sCD14 *Coagulation markers*: D-dimers *Radiological*: Myocardial perfusion defect, CIMT *Other* Asymmetric dimethylargininine	Concentrations of ADMA in infected patients and higher levels in untreated individuals; ADMA associated with viral load, sCD14, D-dimers and low CD4+ T cell count but not with CIMT or subclinical atherosclerosis
2016 Grund [101]	3766 HIV-infected on ART	—	*Cytokines*: IL-6 *Coagulation*: D-dimers *Inflammatory*: hsCRP	260 patients had significant non-AIDS events or death and this was independently associated with increased IL-6, D-dimers, and hsCRP levels
2016 Freiburg [102]	249 patients measured prior to seroconversion, prior to ART initiation and post ART initiation	—	*Cytokines*: IL-6 *Coagulation markers*: D-dimers	Increased IL-6 and D-dimer levels post-seroconversion; D-dimer levels remained elevated and were associated with non-AIDS related adverse events
2016 Borges [103]	4304 HIV-infected patients	—	*Cytokines*: IL-6 *Coagulation markers*: D-dimers	IL-6 better predictor with all-cause mortality and cardiovascular disease than D-dimers or hsCRP
2016 Kulkarni [50]	19 HIV infected patients on ART	49	*Monocyte activation/adhesion markers*: VLA-4, LFA-1, fractalkine, CD11c, sCD14, sCD163 *Endothelial adhesion markers* sICAM-1 sVCAM-1 *Other*: Lp-PLA2	Endothelial activation markers increased in HIV infected individuals; decreased levels of fractalkine expression and increased levels of LFA-1 expression on circulating monocytes
2017 Dysangco [111]	28 HIV-infected patients on ART and 44 HIV-infected patients ART-naive	39	*Arterial dilatation endothelial markers*: sVCAM-1 *Monocyte activation*: CD163 *Inflammatory markers*: β2-MI, IP10, TNFR2	HIV-infected ART naïve patients had higher levels of inflammatory and endothelial adhesion markers (including sCD163, TNFR2, TIM and VCAM-1), but there was no difference in FMD amongst the groups
2017 Baker [104]	4299 HIV-infected patients on immediate or deferred ART	—	*Cytokines*: IL-6 *Coagulation markers*: D-dimers	Increased IL-6 and D-dimer levels consistently associated with AIDS– and non–AIDS related deaths
2017 Grome [112]	70 HIV-infected patients on ART	—	*T-cell activation, senescence, and exhaustion. Macrophage activation:* sCD163, sCD14 *Chemokines*: MIP-1α *Endothelial markers*: sICAM-1 sVCAM-1 *Radiological*: Flow-mediate dilation	Decreased flow mediated dilation was associated with CD8+ T cell activation sICAM-1 and sVCAM-1 were associated with soluble markers of monocyte activation
2017 Maggi [7]	119 ART-naïve HIV-infected patients stratified to receive efavirenz, atazanavir or darunavir based-regimens	—	*Endothelial adhesion*: sVCAM-1 sICAM-1 Radiological: CIMT *Coagulation markers:* D-dimers	Patients on Darunavir at higher risk of pathological intimal thickening; endothelial markers remained static, but D-dimer levels fell consistently
2018 Viskovic [105]	181 virally suppressed HIV-infected patients on ART	—	*Cytokines:* CD40L,MCP-1,IL-8,IL-6 *Inflammatory marker:* hsCRP *Endothelial markers:* P-selectin, tPA	Markers used to construct an inflammatory burden score (IBS), which correlated positively with the presence of dyslipidaemia (total cholesterol:HDL ratio)
2018 Seang [56]	57 HIV-infected patients on ART	—	Endothelial progenitor cells *Cytokine:* IL-6 *Monocyte activation*: sCD163	Undetectable EPC levels associated with higher CVD risk, decreased IL-6 levels, and increased sCD163 (monocyte activation) in HIV-infected patients
2018 Rezer [53]	10 HIV-infected patients on long-term ART	10	*Cytokines*: IL-6, IFN-γ, IL-17, TNF-α, IL-2, IL-4, IL-10 *Inflammatory markers*: hsCRP *Cardiac markers*: Troponin, CK-MB, LDH	Increased levels of IL-6 and IFN-γ in HIV-infected patients; no increases in levels of enzymatic cardiac markers in HIV-infected patients
2018 Peterson [106]	326 ART-naïve HIV-infected patients with CD4+ T cell count >500	—	*Cytokines*: IL-6, IL-27 *Endothelial adhesion markers*: sVCAM-1, sICAM-1 *Inflammatory markers*: hsCRP, serum amyloid A *Coagulation*: D-dimers Sonographic: Radial artery waveform	Increased levels of IL-6 and hsCRP inversely related to small arterial elasticity in HIV-infected patients
2018 Mosepele [107]	112 HIV-infected patients with viral suppression on long-term ART	84	*Cytokines*: IL-6 *Monocyte activation:* sCD163 *Endothelial adhesion*: sVCAM-1 sICAM-1, sE-selectin *Radiological*: CIMT	HIV infection increased levels of sICAM-1 and sVCAM-1 but not E-selectin; IL-6 showed no relationship with biomarkers of endothelial dysfunction

Table 3. Continued

Author and Year	Number of HIV-infected Participants and Treatment Status	Number of Uninfected Controls	Biomarkers and Measurement Modality	Major Findings
2019 Subramanya [108]	452 HIV-infected patients on ART	276	*Cytokines*: IL-6, TNF-α *Endothelial markers*: sICAM-1 *Monocyte activation*: sCD163 *Inflammatory markers*: CCL2, hsCRP, TNFR1, TNFR2 *Coagulation*: Fibrinogen, D-dimers	Elevated CCL2, IL-6, sCD163, CRP increased risk of carotid plaque independent of cardiovascular risk factors sTNFR2, ICAM-1, and fibrinogen predicted CIMT in HIV uninfected men; 8 biomarkers increased significantly in HIV-infected patients

Abbreviations: ADMA, asymmetric dimethylargininine; APC, activated protein C; ART, antiretroviral therapy; AT, antithrombin; â2MI, â2-microglobulin; CD, cluster of differentiation; CIMT, coronary artery intimal medial thickness; CK-MB, creatine kinase; hsCRP, highly sensitive C-reactive protein; LDH, lactate dehydrogenase; LFA-1, leukocyte functional adhesion molecule-1; IL, interleukin; IP10, interferon-ā induced protein 10; LPB, lipopolysaccharide binding protein; Lp-PLA2, lipoprotein-associated phospholipase A2; MCP, monocyte-chemoattractant protein-1; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PT, prothrombin; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; TAT, thrombin-antithrombin complexes; TF, tissue factor; TNFR, tumour-necrosis Factor á receptor; tPA, tissue plasminogen activator; VLA-4, very late antigen-4; vWF, von Willebrand factor.

Table 4.

Scoring System	Developer	Parameters	Studies in PLWH	Utility
Cardiovascular disease				
Framingham [123]	National Heart Institute/ Boston University	Age, tobacco use, systolic blood pressure, total cholesterol, HDL cholesterol	Modified Framingham scores generally outperformed other scoring systems in large cohorts [128] although systems often either overpredicted [129] or underpredicted [125] cardiovascular risk [123].SCORE generally performed least well [124]. SCORE and D:A:D consistently underestimated cardiovascular risk [117, 128]	10-year risk of coronary artery disease only
D:A:D* [123]	D:A:D Study Group	Modified Framingham incorporating previous tobacco use, family history, and previous or current idinavir and lopinavir treatment		5-year risk of coronary artery disease only
SCORE** [117]	European Society of Cardiology	Gender, age, systolic blood pressure, smoking status, and total cholesterol/HDL cholesterol ratio		10-year risk of coronary artery disease only
ASCVD*** [117]	American Heart Association	Age, gender, race, total cholesterol, HDL, blood pressure, and smoking		10-year risk of coronary artery disease or stroke
PROCAM**** [130]	Institute of Atherosclerosis Research at the University of Munster, Germany	Gender, age, serum HDL and LDL cholesterol and triglyceride levels, smoking status, diabetes, family history of coronary heart disease, and systolic blood pressure		10-year risk of coronary artery disease or stroke
Venous thromboembolic disease				
Caprini Score [131]	American College of Chest Physicians	Age, planned surgery and type, immobility, inherited thrombophilic state, recent stroke, presence of a cast, serious comorbidity (including malignancy), chronic obstructive pulmonary disease, inflammatory bowel disease, central venous access, use of oral contraceptives, pregnancy or recent miscarriage, swollen legs, varicose veins, or morbid obesity	Not assessed in PWH	Thromboembolic disease, especially deep-vein thrombosis
Rogers Score (Patient Safety in Surgery Score) [132]		Biochemical—albumin, bilirubin, sodium Haematological—recent tranfusion and haematocrit Patient factors—American Society Anesthesia risk, ventilation, respiratory distress Surgical factors—type, infection, complexity and emergency		Thromboembolic disease, especially deep-vein thrombosis
Microvascular circulatory disease				
DIC ISTH [14, 133]	International Society of Thrombosis and Hemostasis	Platelet count, D-dimers, and prothrombin time in correct clinical context	Utilized as a diagnostic score in PWH [14, 121, 122], but there were no validation studies	Disseminated intravascular coagulation
DIC—JSTH [134]	Japanese Society of Thrombosis and Hemostasis	Clinical features, platelet count, D-dimers, prothrombin time, and antithrombin		Disseminated intravascular coagulation
DIC JAAM [134]	Japanese Association for Acute Medicine	Septic score, platelet count, D-dimers, amd prothrombin time		Disseminated intravascular coagulation
PLASMIC [135]	Harvard TMA Research Collaborative	Clinical—no active cancer, no history of transplant Laboratory— platelet count, haemolysis, Mean Cell Volume, International normalized ratio, Creatinine		Thrombotic thrombocytopaenic purpura

*Data Collection on Adverse Events of Anti-HIV Drugs, **Sytematic COronary Risk Evaluation ***Atherosclerotic cardiovascular disease risk equation ****Prospective Cardiovascular Munster

referenced these scores [14, 121–122]. Arterial scoring systems have been more extensively studied. The Framingham risk score, based on the ongoing Framingham heart study, was initially designed to look at heart disease in nondiabetic, Caucasian participants between the ages of 30 and 69 [123]. A number of modifications have been introduced, including an ART regimen specifically for PWH—the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D score) [123]. Other scoring systems that have been evaluated include the systematic coronary risk evaluation (SCORE), atherosclerotic cardiovascular disease risk score (ASCVD), and prospective cardiovascular munster (PROCAM) scores. In PWH, these scoring systems have shown variable performance across validation studies. The Framingham risk score has generally shown the best predictive value for CVD in PWH with D:A:D, with the ASCVD and SCORE systems showing more consistent under-prediction in large European and American cohorts [117, 124–125]. Only smaller cross-sectional evaluations have been undertaken in low and middle-income countries [123, 126–127]. Despite the relatively poor predictive power and data fit shown in many analyses, these scoring systems continue to form the basis of clinical trials in this cohort of patients.

Modeling studies suggest a significant health economic burden of cardiovascular disease in PWH that is predicted to increase as the HIV-infected population ages [136–137]. Understanding the underlying pathogenesis, assessing risk, and identification and validation of appropriate biomarkers will be important. This includes the development of risk scores for microvascular and venous thrombosis. Cardiovascular disease risk is increased in patients who are untreated or who fail to achieve or maintain viral suppression, and early initiation of ART is the mainstay of therapy. In addition, traditional cardiovascular risk factors, including tobacco use, dyslipidaemia, hypertension, and diabetes should be aggressively managed in this population along with chronic infections that can cause chronic inflammation and predispose to vascular disease [138].

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