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Inflammation, Immune Activation, and Cardiovascular Disease in HIV

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Keywords

Inflammation; Immune Activation; Atherosclerosis; HIV; Cardiovascular Disease

Introduction

The development of atherosclerosis is a complex process involving endothelial dysfunction and arterial inflammation. Additionally, systemic inflammation likely exacerbates atherogenesis as several studies have shown a relationship between cardiovascular disease (CVD) and chronic inflammatory disorders such as systemic lupus erythematosus and rheumatoid arthritis [1, 2]. Chronic HIV is also considered a state of persistent inflammation that likely plays a role in accelerated biologic aging and development of conditions such as CVD. With increased use of combination antiretroviral therapy (cART), especially in resource-rich countries, CVD has in fact become one of the leading causes of morbidity and mortality in patients with HIV [3], and the proportionate CVD-related mortality rate may be rising over time despite declines seen in the general population and those with inflammatory polyarthropathies [4]. Moreover, several epidemiologic studies in HIV-infected patients have shown an increased risk of myocardial infarction and stroke that persists even when controlling for traditional CVD risk factors [5–11], suggesting contributory effects of non-traditional risk factors such as immune activation. As a result, investigators are now evaluating interventions that can reduce inflammation and lower CVD in people living with HIV. Additionally, more aggressive treatment with existing therapies such as lipid lowering medications and modern cART regimens may substantially reduce the risk of MI in HIV [12]

Vascular Immunobiology of Atherosclerosis

Although all three layers of the artery and several different cell types are involved in atherosclerotic plaque development, the actions of macrophages, T-cells, and smooth muscle cells at the tunica intima have best been studied to date. A simplified model is presented here and in Figure 1. Activation of the overlying endothelium is a critical first step in

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atherogenesis. Normally, the endothelium helps prevent thrombus formation and is a regulator of vascular permeability, inflammation, and tone. In response to proatherogenic stimuli, the endothelium alters production of nitric oxide (NO), which affects vascular tone, increases permeability, allowing entry of lipids, and expresses chemokines like monocyte chemoattractant protein-1 (MCP-1) and adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1), which results in leukocyte transendothelial migration [13, 14]. These effects are observable as a thickening of the tunica intima associated with the presence of subendothelial pools and leukocytes in the vessel wall [15].

Once in the arterial wall, scavenger receptors on macrophages recognize modified forms of low-density lipoprotein (LDL) such as oxidized LDL (oxLDL), resulting in differentiation to foam cells that are characterized by intracellular accumulation of lipids and production of pro-inflammatory cytokines and matrix metalloproteinases (MMP). Fragments of LDL are also likely presented to naive T-cells that can later enter the vessel wall and secrete pro-inflammatory molecules, leading to changes in macrophages, endothelial cells, and smooth muscle cells that promote further progression of the atherosclerotic plaque [16].

Eventually, the area of intimal thickening may progress into a fibroatheroma, characterized by the presence of a necrotic (or lipid) core. The necrotic core is largely defined by two features. The first involves the presence of dead or dying cells, largely macrophages, releasing intracellular lipids into the lipid core. The second features a dearth of extracellular matrix proteins, likely as a result of MMPs and other peptidases that contribute to structural instability of the arterial wall. Other notable components of fibroatheromas are intra-plaque calcifications and the overlying fibrous cap. The fibrous cap lends structural support to the growing plaque, but unfortunately, some fibrous caps are vulnerable to erosion or rupture, resulting in thrombus formation and potentially myocardial infarction, stroke, or sudden cardiac death [15].

Insights from Cardiac Imaging into the Unique Pathophysiology of Cardiovascular Disease in HIV

Although the relative risk of CVD is increased in patients with HIV, one limitation in studying CVD in this generally young patient population has been the relatively low absolute event rate in terms of CVD deaths [17]. As a result, several investigators have utilized cardiac imaging to document the burden of subclinical CVD, better understand the underlying pathophysiological mechanisms, and follow response to treatment interventions.

Carotid Ultrasound

One of the most widely utilized cardiac imaging modalities has been ultrasound of the carotid arteries, measuring various endpoints including carotid intima-media thickness (CIMT), presence of plaque, and progression or regression of CIMT. In the general population, CIMT has been associated with increased risk of MI and stroke [18, 19]. In patients with HIV, studies involving carotid ultrasound have often differed in terms of patient population, study design, and ultrasound technique, likely accounting for some of the conflicting results. The weight of evidence, however, suggests that CIMT and presence of

plaque are greater in patients with HIV than uninfected controls, independent of traditional CVD risk factors [20, 21].

Cardiac Computed Tomography

Computed tomography has also become a useful tool in assessing subclinical CVD. Coronary artery calcium (CAC) scoring is an independent predictor of CVD risk in the general population [22, 23]. In a meta-analysis, however, CAC score was not significantly higher in patients with HIV compared with uninfected controls [20]. The CAC score though may underestimate atherosclerotic burden in patients with HIV, especially compared to other imaging modalities. Among patients with undetectable CAC, more patients with HIV have increased CIMT [24] and non-calcified plaque on cardiac computed tomography angiography (CCTA) [25] compared to patients without HIV. In addition to non-calcified plaque, CCTA can also detect high-risk morphologic features of coronary atherosclerosis such as plaque volume, low attenuation, positive remodeling, spotty calcification, and the napkin ring sign, which in the general population have been associated with culprit lesions in acute coronary syndrome [26]. In patients with HIV, several studies have reported an increased prevalence of non-calcified, low attenuation, and positively remodeled plaque compared with uninfected controls matched for traditional CVD risk factors [27–29]. Together, these data suggest that HIV infection is associated with accelerated development of atherosclerosis and possibly an altered plaque morphology that is more prone to rupture, findings that are congruent with the increased risk of MI and stroke reported in observational studies [30].

Functional Imaging with 18FDG PET-CT

Ultrasound and computed tomography, however, do not directly characterize the underlying biological process occurring within the atheroma. 18-Fluorodeoxyglucose (18FDG) coupled with positron emission tomography-computed tomography (PET-CT) is a molecular imaging modality that identifies sites of increased glucose metabolism such as malignancies and inflammatory processes. Given what is known about the dynamic inflammation involved in atherosclerosis, 18FDG PET-CT has also been utilized in research settings to study CVD and arterial inflammation at sites such as the carotid artery or aorta. In the general population, arterial inflammation on 18FDG PET-CT has been shown to independently predict cardiovascular events [31, 32]. In patients with HIV without known CVD, Subramanian and colleagues showed that aortic inflammation on 18FDG PET-CT was significantly increased compared to Framingham Risk Score-matched uninfected controls; that the degree of 18FDG uptake equaled those observed in uninfected subjects with known CVD; and that 18FDG PET-CT activity was associated with soluble CD163 (sCD163), a marker of monocyte/macrophage activation [33]. Additionally, higher levels of aortic 18FDG uptake have been associated with an increased prevalence of high-risk coronary plaque features on CCTA in patients with HIV [34]. Thus, these studies describe a significant relationship between systemic immune activation, arterial inflammation, and rupture-prone coronary lesions.

Chronic Inflammation and Endothelial Dysfunction in Patients with HIV

Chronic Inflammation in Untreated Patients with HIV

Untreated HIV infection leads to generalized activation of the immune system. Non-HIV specific T-cell activation has been observed and the frequency of activated CD8+ T-cells is greater than the frequency of HIV-specific T-cells [35, 36]. Moreover, this widespread stimulation of T-cells probably occurs through several different mechanisms, one of which likely includes activation of innate immunity. Studies have shown that sCD163 and inflammatory (CD14+CD16+) monocytes correlate with higher levels of CD8+ T-cell activation [37]. Therefore, immune activation in untreated HIV is pervasive, involving both HIV-specific and non-specific responses as well as both the adaptive and innate immune systems.

Chronic Inflammation in cART-Treated Patients with HIV

Viral suppression with cART alleviates but does not normalize immune activation in most patients with HIV. For example, cART reduces T-cell activation [38] (see Table 1), but levels remain elevated compared to uninfected controls [39, 40]. Additionally, other markers of inflammation and monocyte activation, including interleukin-6 (IL-6), high sensitivity C-reactive protein (hs-CRP), D-dimer, sCD163, and soluble CD14 (sCD14) decrease with cART [38, 41], but remain higher compared to HIV-uninfected individuals [37, 42–45]. It is important to note that studies differ regarding which markers decline and to what degree, with some even normalizing to levels seen in the general population. Although the reasons for this variable response are still under investigation, one potential factor is the timing of cART initiation. In some studies, earlier commencement is associated with greater improvements in markers of immune activation such as sCD163 levels [37], activated T-cells [46], IL-6, and hs-CRP [47]. Thus, treatment with cART at higher CD4+ T-cell counts may further reduce immune activation but whether this translates into reductions in CVD remains under investigation.

Endothelial Dysfunction and Activation in Patients with HIV

Markers of endothelial cell activation and dysfunction are also altered in patients with HIV. Brachial artery reactivity testing to measure flow mediated dilation (FMD) is a measure of endothelial function and is a predictor of CVD in the general population [48]. In HIV, case-control studies have shown varying results regarding the effect of HIV on FMD, likely due to small sample sizes and differences in imaging techniques [49–51]. However, in a prospective, randomized trial, cART improved FMD [52], suggesting a relationship between viremia and endothelial dysfunction. Moreover, soluble VCAM-1 (sVCAM-1), a marker of endothelial activation, is higher in HIV-infected patients, declines with cART treatment, but remains elevated compared with HIV-uninfected patients [53, 54]. These studies also showed a relationship between sVCAM-1, inflammatory cytokines, and CIMT, supporting potential relationships between inflammation, endothelial activation, and CVD in HIV.

Immune Activation and CVD in Patients with HIV

Inflammation and Coagulation

Several biomarkers of immune activation have been related to both subclinical and clinical CVD in patients with HIV (see Table 1). Circulating markers of general inflammation such IL-6 and hs-CRP are well known independent predictors of CVD in the general population [55, 56]. In patients with HIV, hs-CRP has been associated with CIMT progression [57], and both hs-CRP and IL-6 increase the risk of CVD and mortality [58–62]. Given the known relationship between inflammation and coagulation, it is not surprising that D-dimer, a product of the coagulation cascade, is also increased in HIV [42] and has been strongly associated with mortality and CVD in patients with HIV [59–63]. It remains unclear, however, whether the relationship between coagulation and CVD is causal or simply a marker of heightened inflammation. Theoretically, a procoagulable state could contribute to the risk of CVD as myocardial infarction and stroke are acute thrombotic events. Furthermore, platelets appear to function abnormally in patients with HIV as studies have shown increased tendencies for platelet aggregation, activation, and expression of tissue factor (TF), a pro-coagulant molecule [64–66].

Monocytes/Macrophages

Given the central role of monocyte-derived macrophages in atherogenesis, it is not surprising that several lines of evidence suggest a relationship between macrophage activation and CVD in HIV. Monocytes are generally divided into three different subsets based on their expression of CD14 and CD16 as classical (CD14++CD16−), inflammatory (CD14++CD16+), and patrolling (CD14+CD16++). In the general population, the percentage of inflammatory monocytes independently predicts clinical CVD events [67], and patients with acute coronary syndrome have increased percentages of both inflammatory and patrolling monocytes along with TF expression [68]. Thus, some monocytes, especially those with reduced cellular CD14 expression and increased CD16 expression may be proatherogenic. Untreated HIV-infected patients also have increased percentages of inflammatory and patrolling monocytes with tissue factor expression, similar to uninfected patients suffering acute coronary syndrome [68]. This suggests that HIV infection may create an environment that promotes the development of proatherogenic monocytes, possibly as a direct result of HIV itself or potentially through indirect mechanisms such as increased presence of other microbial agents. Additionally, reduced cellular expression of CD14 has been associated with CIMT [69], and CD16 expression on monocytes appears to independently predict progression of coronary artery calcium [70]. Beyond cellular markers, a relationship between soluble markers of monocyte activation and CVD has also been established. Soluble CD14, a receptor for lipopolysaccharide (LPS) and a marker of macrophage activation, independently predicts all-cause mortality and has been associated with both subclinical and clinical CVD [43, 71–74]. Furthermore, sCD163 has been shown to be related to arterial inflammation on 18FDG PET-CT and coronary plaque on CCTA [29, 33, 43, 75].

In addition to activation, HIV infection may also lead to macrophage dysfunction in cholesterol handling, which could contribute to the development of atherosclerosis.

Cholesterol can be moved from macrophages to high-density lipoprotein in a process known as reverse cholesterol transport, which is thought to protect against atherosclerosis. One of the initial steps involves macrophages and their cholesterol efflux capacity (CEC). In animal studies, HIV impairs ATP-binding cassette transporter A1 (ABCA1) dependent CEC in murine macrophages [76]. In human studies, patients with HIV have reduced ABCA1-dependent CEC compared to uninfected controls [77], and initiation of cART during acute HIV infection restores CEC [78].

T-cells

In contrast to monocytes/macrophages, a relationship between T-cell activation and CVD in patients with HIV is less certain. In cross sectional studies, the percentage of activated T-cells (based on CD38 and HLA-DR expression) was associated with prevalence of CIMT [79, 80] and carotid artery stiffness [81]. On the other hand, two case-control studies found no relationship between activated T-cells and clinical cardiovascular events [60, 63], and one cross-sectional study showed no correlation between T-cell activation and CIMT [82]. Thus, further research is needed to determine whether a relationship exists and if so, whether the relationship is causal or represents a marker for some other closely related process such as immunodeficiency, as low CD4+ T-cell counts have been linked to CVD along with nadir CD4+ T-cell counts in several [7, 28, 83–87] but not all studies [88].

Net Benefits of cART on Immune Activation and CVD

Early Initiation of cART

Current and nadir CD4+ T-cell counts are related to delayed initiation of cART, which in conjunction with observations that some CVD-related markers of immune activation such as sCD163 may normalize when cART is started during acute infection, suggests that earlier initiation of cART may improve CVD by reducing immune stimulation. This hypothesis was explored in the Strategic Timing of Antiretroviral Treatment (START) trial, which randomized patients with HIV to early initiation of cART at CD4+ T-cell counts > 500 cells/uL versus delayed initiation at CD4+ T-cell counts > 350 cells/uL [89]. The trial was stopped early after an average follow-up time of 3 years as an interim analysis showed a significant decrease in serious AIDS and non-AIDS related events and death in the early treatment group (HR 0·43 [95% CI 0·3–0·62]). CVD event rates, however, were not different between the two groups, possibly as a result of lower event rates than predicted due to the younger age of the population (median age was 36 years-old) and the early termination of the study.

Cardiometabolic Risk with cART

Large observational studies have shown that some anti-retroviral therapies are associated with an increased risk of MI [90–93] that may be related to metabolic side effects of cART such as dyslipidemia [91], glucose intolerance [94, 95], and lipodystrophy [96, 97]. Furthermore, based on in vitro studies, some antiretroviral medications may have direct proatherogenic effects on vascular endothelium, macrophages, and platelets [98]. The protease inhibitor, ritonavir, reduces cholesterol efflux from macrophages, decreases endothelial nitric oxide production, and is cytotoxic to endothelial cells. A number of

protease inhibitors have also been shown to promote CD36-dependent cholesterol accumulation in macrophages. Additionally, efavirenz may promote leukocyte adhesion to endothelial cells, and abacavir could increase platelet reactivity. Further *in vivo* studies of these agents are important, as the proatherogenic properties of these specific medications have largely been established from *in vitro* studies and beneficial effects on viremia and inflammation may contribute to clinical benefits on CVD.

Newer antiretroviral therapies, on the other hand, may have fewer cardiometabolic complications [99]. Thus, some modern antiretroviral therapies may not be associated with an increased risk of MI [100]. This absence of CVD risk with newer antiretrovirals, however, may simply be a result of insufficient observational time for complications to have developed or aggressive treatment of traditional CVD risk factors in the modern era.

Lessons from Treatment Interruption and Elite Controllers

Clues regarding the relative influence of inflammation versus cART-related cardiometabolic toxicity on CVD in HIV come from treatment interruption trials and studies of elite controllers. The Strategic Management of Antiretroviral Therapy (SMART) trial randomized patients to a drug conservation group with intermittent cART to maintain CD4+ T-cell counts > 350 cells/uL or a viral suppression group with continuous cART. They showed an increase in mortality and CVD [101] in the drug conservation group, which was partially related to increased markers of inflammation [59, 61]. Thus, cART appears to have a net benefit in reducing CVD as any potential cardiometabolic toxicity appears to be outweighed by decreased immune activation and viral suppression.

Studies with elite controllers, a rare subset of patients with HIV who maintain undetectable viral loads without cART, provide additional support to the greater role of immune activation over cART toxicity in the development of atherosclerosis in virally suppressed HIV-infected patients. In cross-sectional studies, elite controllers have been found to have an increased prevalence of CIMT on carotid ultrasound and coronary plaque on CCTA compared with uninfected controls in conjunction with elevated levels of C-reactive protein, sCD14, and sCD163 [102, 103]. Thus, these patients with HIV without exposure to cART also have accelerated atherosclerosis, which may be a result of heightened immune activation.

Causes of Chronic Inflammation in Patients with HIV

Several reasons likely contribute to ongoing immune activation in cART-treated HIV-infected patients (see Figure 2). Although our understanding is still incomplete, possible explanations include microbial translocation, co-infections, and continued presence of HIV RNA at low levels below the detection of clinical assays.

Microbial Translocation

GI tract structural integrity is influenced by the underlying mucosal immune system and likely also the microbiota in the gut itself. One of the key events of early HIV infection is mucosal inflammation and a massive depletion of CD4+ T-cells in the intestinal lymphoid tissue, which is not fully reversed with cART [104–107], resulting in alterations to expression of genes related to GI barrier function [108]. Furthermore, the gut microbiome is

altered in patients with HIV, and these alterations have been linked to mucosal and systemic inflammation [109].

Studies have demonstrated an increase in epithelial apoptosis in the small intestine and decreased expression of tight junction proteins in the large intestine of HIV-infected individuals [110, 111], likely resulting in increased GI permeability [110]. Furthermore, animal studies with pathologic SIV infection and in vitro studies with HIV have shown that the structural breakdown of the GI tight epithelial barrier leads to in situ translocation of microbes from the GI lumen into the body [112, 113]. Additionally, microbial byproducts can be detected in the circulation. One study showed that patients with HIV have elevated levels of LPS, a component of gram-negative bacteria. Initiation of cART resulted in a decline in LPS concentrations that remained elevated compared to uninfected controls [114]. Once microbial products have entered the host, they can be recognized by the immune system, resulting in immune activation, which in turn could result in CVD. Plasma levels of LPS and bacterial 16S rDNA, for example, have been related to markers of inflammation, monocyte activation, and T-cell activation [114–116]. Furthermore, LPS levels in cART-treated patients with HIV have also been directly linked to progression of CIMT [71].

Co-Infections

Patients with HIV are often co-infected with various microbes, especially other chronic viral infections. This additional infectious burden may lead to increased immune activation and thus CVD. In HIV, Hepatitis C (HCV) co-infection, for example, results in higher levels of sCD163 [53, 117], activated T-cells [118] and increased risk of CVD [7, 119, 120], although it is unknown whether HCV directly contributes to CVD risk or is a surrogate marker for another potential risk factor such as intravenous drug use. Some evidence suggests that it may be more than a surrogate marker as suppression of HCV with PEGylated alpha interferon and ribavirin reduces T-cell activation and markers of vascular inflammation in co-infected individuals [121, 122]. However, no studies to date have shown that treatment of HCV results in improvements in subclinical or clinical CVD. Furthermore, newer, more effective agents to treat HCV have been developed and investigating their impact on reducing inflammation and CVD will be an important area for future research.

Cytomegalovirus (CMV) is highly prevalent (75–90%) in patients with HIV [123] and for unknown reasons, the percentage of CMV-specific CD8+ T-cells in cART-treated patients may be twice that of HIV-uninfected controls [124], suggesting an increased immune response associated with CMV co-infection. In the general population, CMV has been associated with both subclinical and clinical CVD [125, 126]. In HIV, CMV antibody levels are associated with increased IL-6 and sCD14 levels [127], sCD163 [75], coronary plaque burden on CCTA [27], and prevalence of carotid artery lesions [128]. Additionally, higher CMV-specific T-cell responses in co-infected patients have been associated with increased CIMT in some [129] but not all studies [82]. In a large, prospective observational study of patients with HIV, CMV seropositivity was associated with non-AIDS morbidity and mortality including CVD [123]. Moreover, short-term treatment of CMV with valgancyclovir [130] in patients with HIV reduced CD8+ T-cell activation, but whether

treatment could be sustained long enough to result in improvements in atherosclerotic disease is uncertain.

HIV Viremia

Several in vitro studies have shown potential mechanistic links between HIV viral proteins and processes of immune activation and atherogenesis (see Figure 1) [98]. The viral protein, Nef, for example, has been shown to reduce endothelial NO production, promote secretion of endothelial-cell derived MCP-1, induce endothelial cell apoptosis, increase inflammatory cytokine release from macrophages, and inhibit macrophage cholesterol efflux capacity. It remains uncertain, however, whether these in vitro observations occur in vivo.

In addition, clinical data has supported an association between viremia and CVD. In an observational study, HIV replication has been associated with myocardial infarction [87], and reduction of viremia with initiation of cART improves vascular function [52]. Furthermore, in the SMART study, continuous cART resulted in less cardiovascular events compared with intermittent or delayed therapy [101, 131]. Together, these data link viremia with atherosclerosis and highlight the importance of viral suppression with modern cART regimens to reduce CVD.

Antiretroviral therapy, however, cannot eradicate HIV from the body. Even when patients have undetectable viral loads based on current clinical assays, ultrasensitive methods can still detect HIV RNA in the plasma [132, 133]. Although it is theoretically possible that residual viremia stimulates the immune system and contributes to CVD, these relationships have yet to be proven. Furthermore, determining the source of residual viremia remains under investigation but could lead to additional therapeutic strategies for CVD and chronic inflammation. Residual viremia may be the result of low levels of ongoing replication in active HIV reservoirs or may represent release of non-productive virus from latent reservoirs. If active replication is occurring and contributing to persistent inflammation, intensification therapy with additional antiretroviral medications in theory should further decrease viral loads and immune activation. Studies to date, however, have shown no significant reductions in viremia and most, but not all, studies have been unable to detect a decline in markers of inflammation [134–139]. One potential explanation is that some antiretroviral therapies may not achieve therapeutic levels at all sites with active replication [140]. Thus, intensification therapy may be ineffective in suppressing the active viral reservoir, or active replication may not be a major contributor to residual viremia and inflammation.

Novel Use of Interventions to Reduce Immune Activation and CVD in HIV

The mounting evidence connecting increased risk of CVD and immune activation suggests that anti-inflammatory drugs may provide benefit in patients with HIV (see Table 1). Although some medications such as pentoxifylline [141] and salsalate [142, 143] have had disappointing results in reducing immune activation markers and/or subclinical CVD endpoints, other therapies are currently being investigated. A pilot study using methotrexate in cART-treated patients with HIV is underway and will assess safety and efficacy on inflammation and endothelial function (NCT0194911). Furthermore, biologic agents such as

the IL-6 receptor antagonist tocilizumab (NCT02049437) and the IL-1 antagonist canakinumab (NCT02272946) are also being investigated for effects on endothelial dysfunction and arterial inflammation.

Targeting Microbial Translocation and Intestinal Inflammation

In addition to anti-inflammatory medications, investigators are also targeting the underlying processes that promote chronic immune activation. Trials involving intensification therapy for residual viremia and therapies for HCV and CMV have been discussed above. Interventions aimed at reducing microbial translocation have taken several different approaches that have been met with varying results. Mesalamine, an agent used for intestinal inflammation in ulcerative colitis, failed to reduce circulating markers of inflammation as well as T-cell activation in intestinal tissue and the periphery [144]. Sevelamer, a phosphate binding agent that also has a high affinity for LPS, did not decrease markers of immune activation and microbial translocation [145]. On the other hand, investigational IL-7 administration in humans [146] and IL-21 administration in SIV-infected rhesus macaques [147], given in addition to cART, showed improvements in intestinal immunity and peripheral markers of immune activation. Probiotics, which may alter the GI microbiota, have been shown to decrease markers of microbial translocation, inflammation, coagulation, and T-cell activation [148–150] with some markers being reduced to levels seen in HIV-uninfected patients. These studies were small and effects of probiotics on individual markers differed between studies. Together, however, these data suggest that altering the microbiome may reduce chronic inflammation but whether this translates into cardiovascular benefit remains undetermined. Quinolines such as chloroquine and hydroxychloroquine have also been tested in patients with HIV with inconclusive results regarding effects on microbial translocation and inflammation [151–155], possibly due to differences in the dose of medication used or whether patients were treated with cART. Recent studies with these two medications are either ongoing or have yet to publish final results (NCT01232660 and NCT00819390). Finally, teduglutide—a glucagon-like-peptide-2 analog thought to promote intestinal epithelial function—is currently being studied in a randomized, controlled trial for effects on microbial translocation, immune activation, arterial inflammation, and coronary plaque on CCTA (NCT02431325).

Traditional Cardiometabolic Therapies to Reduce Immune Activation in HIV

One interesting study has shown that currently available therapies may reduce the risk of CVD substantially. In a large, retrospective study of patients with HIV, Klein and colleagues reported a declining risk of MI over time in conjunction with increased prescriptions for lipid lowering and anti-hypertensive treatment and better control of HIV with cART. Importantly, the risk of MI was equivalent between HIV-infected and uninfected individuals in the most recent year of the study (2010–2011), during which time HIV-infected patients had a lower Framingham Risk score [12]. Thus, although these findings require further validation, they suggest that current cardiometabolic therapies could potentially have a profound impact in ameliorating CVD, especially those that have additional effects on inflammation.

Effects of Statins on Inflammation and CVD in HIV

Statins are known for the ability to improve lipids and prevent CVD [156]. They are also believed to possess anti-inflammatory effects. In patients with HIV, statins reduce several markers of immune activation and improve subclinical CVD. In the SATURN-HIV study, rosuvastatin was associated with decreases in sCD14, percent of non-classical monocytes with tissue factor expression, and percent of activated T-cells [157]. The rosuvastatin group also had a slower progression of CIMT and the greatest benefit was seen in those with higher levels of inflammatory markers at baseline [158]. In another randomized, placebo-controlled trial, atorvastatin resulted in reductions in coronary plaque volume and number of lesions with high risk morphology on CCTA [159]. The improvements in atherosclerosis observed in these studies may be partially related to reductions in plasma oxLDL [160, 161], and one in vitro study showed that infusion of oxLDL increases macrophage activation and promotes development of proatherogenic monocytes [162]. Thus, oxLDL may represent one mechanism through which statins exert their anti-inflammatory effects.

In general, randomized clinical trials of statins in patients with HIV have been limited to small sample sizes or subclinical cardiovascular endpoints. As a result, a large, multi-center, randomized, placebo-controlled trialed named REPRIEVE has been initiated to determine potential benefits of statin therapy in preventing CVD in HIV-infected individuals. This large 6,500 person trial will assess effects on major adverse cardiovascular events (MACE) and will include a mechanistic study to also assess effects on plaque and immune function (NCT02344290).

Effects of Other Cardiometabolic Therapies on Inflammation and CVD in HIV

There are several other medications regularly used in treatment of cardiometabolic diseases whose effects on immune activation have been investigated in patients with HIV. Other than statins, other medications for dyslipidemia such as fish oil have failed to reduce markers of inflammation in most [163_165] but not all studies[166], although the type and dose of fish oil used varied. Recently, extended release niacin and fenofibrate showed no effect on reducing hs-CRP, IL-6, or D-dimer [167]. In addition to treatment for dyslipidemia, treatments for platelet inhibition and hyperglycemia have been or are currently being studied. Although a short, one-week study showed that low-dose aspirin attenuates sCD14 and activated T-cells in cART-treated patients with HIV [66], a longer 12-week randomized controlled trial showed no effects of high or low-dose aspirin on monocyte activation (sCD14, sCD163), proatherogenic monocyte subsets, T-cell activation, and endothelial dysfunction [168]. Furthermore, metformin is being used in a 24-week pilot study to determine potential effects on immune activation and coronary lesions on CCTA (NCT02383563).

Relationship between the Renin-Angiotensin-Aldosterone System, Inflammation and Cardiometabolic Disease in HIV

Additionally, the renin-angiotensin-aldosterone system (RAAS) may also be related to inflammation and cardiometabolic disease in patients with HIV. Aldosterone concentrations were found to be higher in HIV-infected patients compared to uninfected individuals in a RAAS activated state that was achieved by a low-sodium diet. Aldosterone concentrations

were also associated with visceral adiposity and insulin resistance [169]. The relationship between RAAS activation in HIV may in part be related to RAAS activation in adipocytes as a result of antiretroviral therapy, particularly ritonavir-boosted PIs [170]. Furthermore, in those with HIV, RAAS activation in those on a low sodium diet resulted in elevated hs-CRP and IL-6 levels [169], implicating a relationship between the RAAS system and inflammation in HIV-infected patients. Moreover, the angiotensin converting enzyme (ACE) inhibitor, lisinopril, reduces levels of hs-CRP and TNF-alpha [171]. Currently, several studies are evaluating the effects of blocking the RAAS system with eplerenone, telmisartan, and losartan on inflammation, visceral adipose tissue, insulin resistance, flow mediated dilation, and progression of CIMT (NCT01928927, NCT01529749, NCT02049307, NCT0185294, NCT01405456).

Conclusion

Chronic HIV infection results in a state of persistent inflammation and immune activation, which in turn promotes CVD, a significant contributor to morbidity and mortality. Combined antiretroviral therapy reduces but does not normalize immune activation, which may provide cardioprotection. The use of cART, however, is evolving and whether changes such as earlier initiation lead to cardiovascular benefit remains to be seen. The reason for chronic inflammation, even with cART treatment, is likely multifactorial, including microbial translocation, co-infections, and possibly ongoing low-levels of viremia. Currently available cardiometabolic medications such as statins can have a profound impact on CVD, partly as a result of beneficial reductions in immune activation, but their safety and efficacy in this patient population requires validation. Furthermore, investigators are also studying novel therapies that reduce inflammation directly by dampening the immune system or indirectly by targeting underlying causes that may drive chronic inflammation. CVD is likely to worsen as this patient population ages, and thus, understanding the various risk factors for CVD in this unique cohort and developing effective therapeutic strategies are paramount in reducing morbidity and mortality for patients living with HIV.

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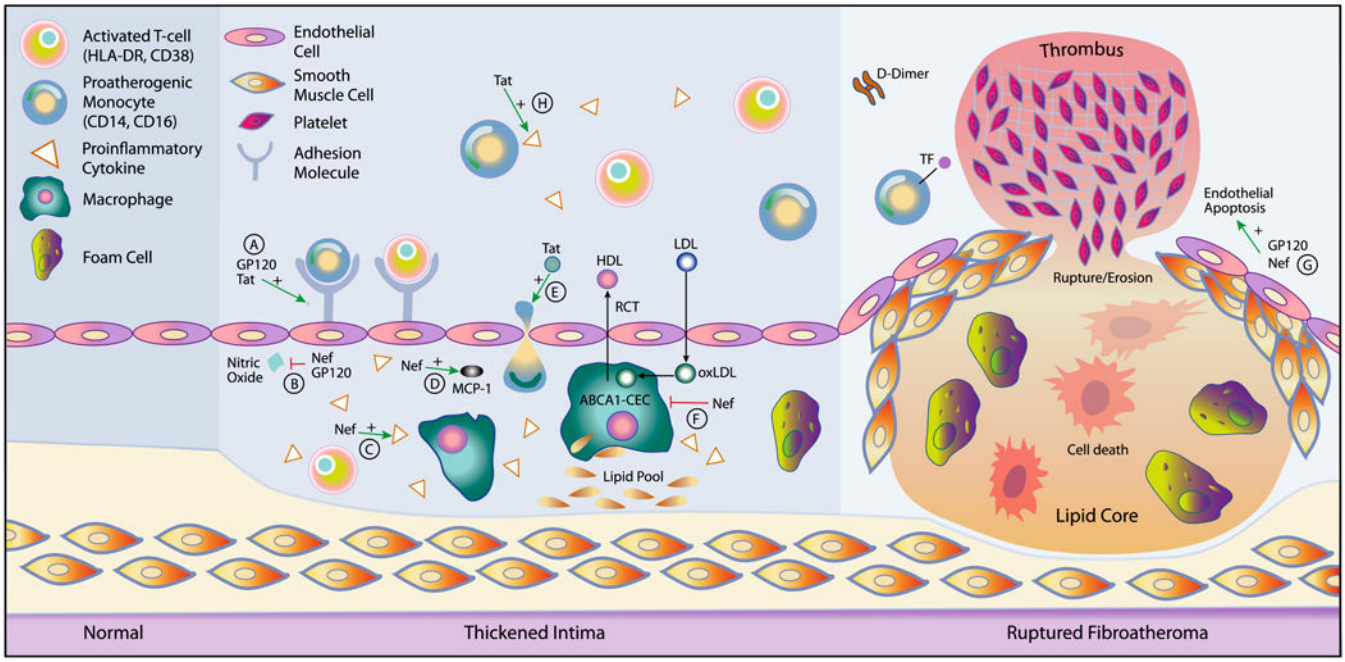

Figure 1.

Effects of HIV Viral Proteins on the Development of Atherosclerosis. In vitro studies have shown the following proatherogenic effects of HIV viral proteins: A) Tat and gp120 induces expression of adhesion molecules [179, 180]; B) Nef and gp120 reduce endothelial NO production [181, 182]; C) Nef increases inflammatory cytokine release including IL-6 and TNF-alpha from macrophages [183]; D) Nef promotes MCP-1 secretion from endothelial cells [184]; E) Tat stimulates MCP-1 mediated monocyte transmigration [185]; F) Nef inhibits ABCA1-dependent CEC of macrophages [76]; G) Nef and gp120 may induce endothelial apoptosis, which could promote fibroatheroma rupture/erosion, resulting in formation of an acute thrombus [186, 187]; H) Tat stimulates IL-6 production from peripheral blood monocytes [188]. In vitro studies have also shown potential proatherogenic effects of specific ARTs including increased leukocyte adhesion to endothelial cells with efavirenz [189]; increased platelet reactivity with abacavir [190]; reduced cholesterol efflux from macrophages, decreased endothelial nitric oxide production, and endothelial cytotoxicity with ritonavir [191–193]; and CD36-dependent cholesterol accumulation in macrophages with certain protease inhibitors [194]. ABCA1 = ATP-binding cassette transporter-A1, CEC = cholesterol efflux capacity, RCT = reverse cholesterol transport, TF = tissue factor, HDL = high-density lipoprotein, LDL = low-density lipoprotein, oxLDL = oxidized LDL, MCP-1 = monocyte chemoattractant protein-1.

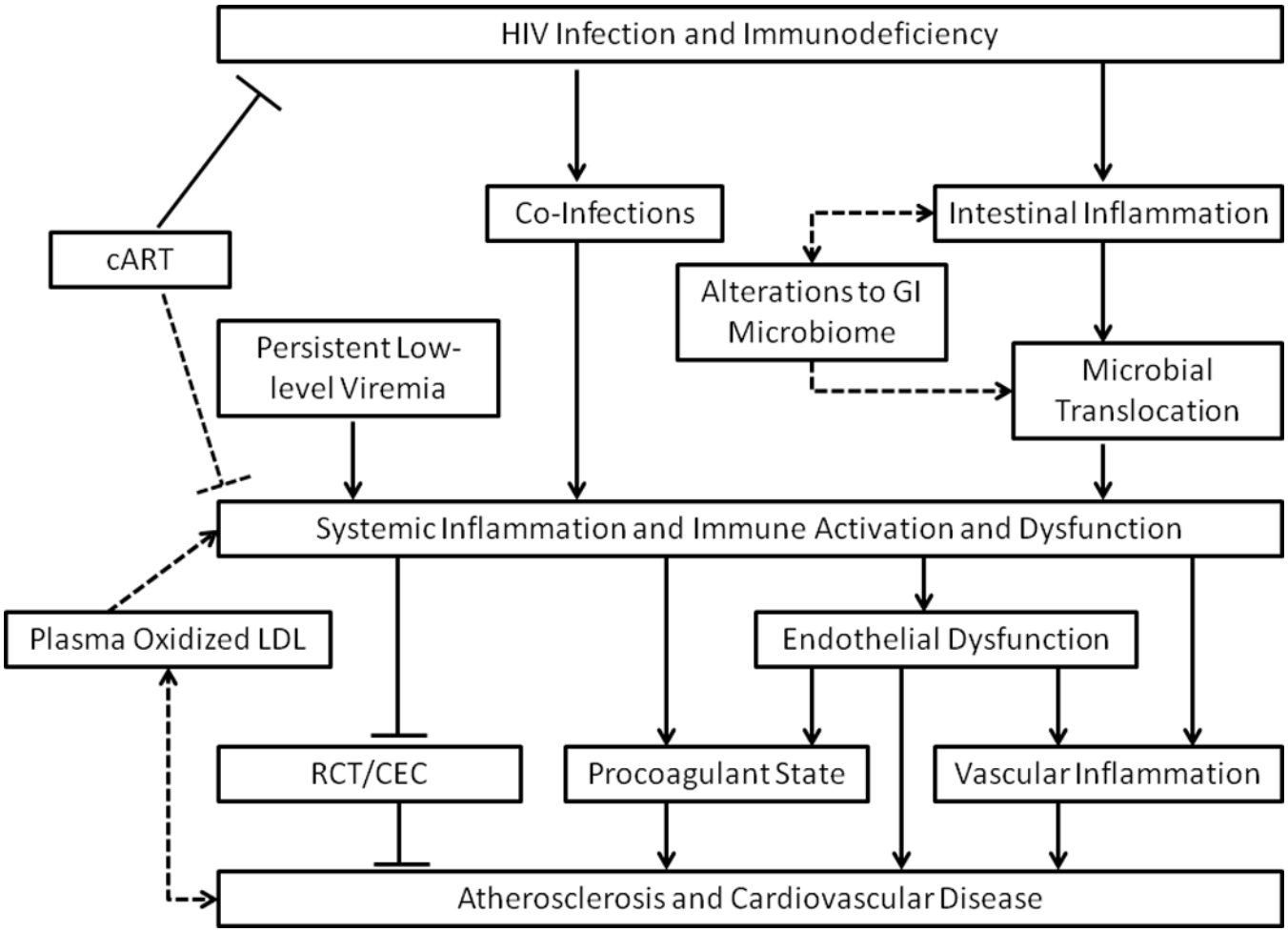

Figure 2.

Pathways Involved in the Development of Immune Activation and Atherosclerosis in HIV. Arrows indicate a contributory effect. Terminal lines indicate an inhibitory effect. Dotted Lines indicate a potential yet uncertain relationship. cART = combined antiretroviral therapy, RCT = reverse cholesterol transport, CEC = cholesterol efflux capacity, GI = gastrointestinal, LDL = low-density lipoprotein.

Table 1

Atherosclerosis-related immune markers and associated treatment in HIV-infected individuals

Immune Marker	Subclinical Atherosclerosis	Cardiovascular Disease	Immune Marker Reducing Therapy
hs-CRP	CIMT progression[57]	MI and major CVD event[58, 59]	Probiotics[149], Lisinopril[171], Panobinostat[172], ART [38]
IL-6		MI, stroke, and major CVD event[59, 60]	Probiotics[149], Panobinostat[172], Fish Oil[166], Hydroxychloroquine [153], ART [38]
D-dimer		MI, stroke, and major CVD event[58_60]	Probiotics [150], rhIL-7 [146], ART [38]
LPS	CIMT progression[71]		Hydroxychloroquine [153], ART [41]
MCP-1	CIMT, stenosis ≥ 50%, CAC, coronary segments with plaque[27, 43, 173]		
oxLDL	CIMT[173]		Rosuvastatin[160], Atorvastatin[161], Sevelamer[145]
sCD163	CAC; vulnerable, total, non-calcified, mixed, and calcified plaque; coronary stenosis ≥ 50%[29, 43, 75]		Aprepitant[174], ART [38]
sCD14	Non-calcified plaque, CIMT and coronary stenosis ≥ 50%[43, 71, 73, 75]	Highest quartile sCD14 w/CVD death,[72] MI, and stroke[60]	Rosuvastatin[157], rhIL-7 [146] Prebiotics [175], Aspirin [66], ART [41]
CD14+CD16+ monocytes	CAC progression[70]		Panobinostat[172], ART [38]
CD4+CD38+HLADR+ T-cells	CIMT[80]		Probiotics[149], Rosuvastatin[157], Atorvastatin [176] Aspirin [66], ART [38]
CD8+CD38+HLADR+ T-cells	CIMT[79, 80]		Probiotics[149], Rosuvastatin[157], Atorvastatin [177], Chloroquine [152] Leflunomide [178], ART [38]

hs-CRP = High sensitivity C-reactive protein, LPS = lipopolysaccharide, IL-6 = interleukin-6, MCP-1 = monocyte chemoattractant protein-1, oxLDL = oxidized low density lipoprotein, sCD163 = soluble CD163, sCD14 = soluble CD14, CIMT = carotid intima media thickness, CAC = coronary artery calcium, MI = myocardial infarction, CVD = cardiovascular disease, ART = antiretroviral therapy, rhIL-7 = recombinant human interleukin 7