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Review

Coronary Artery Disease Manifestations in HIV: What, How, and Why

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ABSTRACT

Understanding why persons with human immunodeficiency virus (HIV) have accelerated atherosclerosis and its sequelae, including coronary artery disease (CAD) and myocardial infarction, is necessary to provide appropriate care to a large and aging population with HIV. In this review, we delineate the diverse pathophysiologies underlying HIV-associated CAD and discuss how these are implicated in the clinical manifestations of CAD among persons with HIV. Several factors contribute to HIV-associated CAD, with chronic inflammation and immune activation likely representing the primary drivers. Increased monocyte activation, inflammation, and hyperlipidemia present in chronic HIV infection also mirror the pathophysiology of plaque rupture. Furthermore, mechanisms central to plaque erosion, such as activation of toll-like receptor 2 and formation of neutrophil extracellular traps, are also abundant in HIV. In addition to inflammation and immune activation in general, persons with HIV have a higher prevalence than uninfected persons of traditional cardiovascular risk factors, including dyslipidemia, hypertension, insulin resistance, and tobacco use. Antiretroviral therapies, although clearly necessary for HIV

RÉSUMÉ

Il est nécessaire de comprendre pourquoi les personnes infectées par le virus de l'immunodéficience humaine (VIH) souffrent d'athérosclérose accélérée et de ses séquelles, y compris la coronaropathie et l'infarctus du myocarde, afin d'être en mesure de dispenser des soins appropriés à une population nombreuse et vieillissante de personnes vivant avec le VIH. Dans cet article de synthèse, nous distinguons les diverses physiopathologies sous-jacentes des coronaropathies associées au VIH et nous analysons leur rôle dans les manifestations cliniques des coronaropathies chez les personnes vivant avec le VIH. Plusieurs facteurs contribuent à la coronaropathie associée au VIH dont, probablement au premier chef, l'inflammation chronique et l'activation du système immunitaire. L'activation accrue des monocytes, l'inflammation et l'hyperlipidémie observées dans l'infection à VIH chronique reflètent également la physiopathologie de la rupture des plaques. De plus, les mécanismes jouant un rôle central dans l'érosion des plaques, notamment l'activation du récepteur de type Toll-2 et la formation de pièges extracellulaires des neutrophiles, sont très présents dans l'infection à VIH. En plus de l'inflammation et de l'activation du système immunitaire

Effective and timely antiretroviral therapy (ART) has dramatically increased the life span of people with human immunodeficiency virus (HIV). Analysis of the **S**trategies for **M**anagement of **A**nti**r**etroviral **T**herapy (SMART) and **E**valuation of **S**ubcutaneous **P**roleukin **i**n a **R**andomized **I**nternational **T**rial (ESPIRIT) clinical trials demonstrated that persons with HIV who were started on continuous ART and achieved viral load suppression along with recovery of CD4+ T-cell count had mortality rates approaching those of the general population.[1] Not surprisingly, deaths from acquired immunodeficiency syndrome (AIDS)–defining illnesses have significantly decreased, but cardiovascular disease (CVD) mortality rates have more than doubled in persons with HIV, resulting in an approximately 3-fold increase in proportionate mortality due to CVD over the past 2 decades.[2,3] Despite effective HIV prevention efforts that have stabilized and in some areas decreased HIV incidence rates, HIV prevalence is on the rise largely because of longer life spans free from progression to AIDS among persons with HIV. Even in high-income countries, the median proportional increase in HIV prevalence was 13.6% between 2006 and 2011.[4] There are more than 1.2 million and 35 million adults with HIV in the United States and worldwide, respectively. Thus, there is a growing and aging HIV+ population with a high and increasing burden of CVD.

The increased risk of coronary artery disease (CAD) for persons with HIV has been demonstrated in several epidemiological analyses. Cohort studies that included uninfected control groups demonstrated a 2-fold greater risk of myocardial infarction (MI) for persons with HIV after adjusting for CVD risk factors.[5,6] However, these initial studies were

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treatment and survival, have had varied effects on CAD, but newer generation regimens have reduced cardiovascular toxicities. From a clinical standpoint, this mix of risk factors is implicated in earlier CAD among persons with HIV than uninfected persons; whether the distribution and underlying plaque content of CAD for persons with HIV differs considerably from uninfected persons has not been definitively studied. Furthermore, the role of cardiovascular risk estimators in HIV remains unclear, as does the role of traditional and emerging therapies; no trials of CAD therapies powered to detect clinical events have been completed among persons with HIV.

en général, les personnes vivant avec le VIH présentent une prévalence plus élevée de facteurs de risque cardiovasculaire que les personnes non infectées, y compris la dyslipidémie, l'hypertension, l'insulinorésistance et le tabagisme. Les thérapies antirétrovirales, malgré leur nécessité évidente pour le traitement et la survie des personnes infectées par le VIH, ont eu différents effets sur la coronaropathie, mais les schémas thérapeutiques plus récents présentent une toxicité cardiovasculaire moindre. D'un point de vue clinique, ce mélange de facteurs de risque joue un rôle dans la survenue plus précoce de la coronaropathie chez les personnes infectées par le VIH que dans la population non infectée; il n'a pas encore été déterminé si les caractéristiques de distribution et de contenu des plaques sous-jacentes de la coronaropathie chez les personnes vivant avec le VIH diffèrent considérablement de celles observées chez les personnes non infectées. De surcroît, le rôle des estimateurs du risque cardiovasculaire dans l'infection par le VIH demeure imprécis, tout comme celui des traitements classiques et des traitements émergents; aucun essai clinique sur le traitement des coronaropathies ayant la puissance nécessaire pour déceler des événements cliniques n'a été réalisé dans la population infectée par le VIH.

limited because of lack of key clinical risk factors, such as smoking history. More recently, the Veterans Aging Cohort Study showed a 1.5-fold greater risk of MI in HIV+ adults compared with uninfected controls even after adjusting for smoking and substance use.[7] Lower CD4+ T-cell count and elevated viral load were associated with greater MI risk.

Although the epidemiology of elevated CAD risks for persons with HIV is reasonably well defined, the underlying pathogenesis is complex and incompletely understood, as are the unique clinical manifestations of HIV-associated CAD. In this review, we will discuss clinical factors associated with CAD among persons with HIV as well as how these contribute to unique CAD manifestations among persons with HIV.

Traditional CAD Risk Factors in HIV

Adults with HIV have a higher prevalence of diabetes mellitus, hypertension, dyslipidemia, and tobacco use than uninfected persons.[8] After adjusting for confounding risk factors such as demographics, socioeconomic status, education, obesity, and hepatitis C virus infection, adults with HIV have a 3.8% higher prevalence of diabetes mellitus compared with the general population.[9] Adults with HIV have changes in adipose tissue, skeletal muscle, and liver that lead to insulin resistance. There is increased expression of proinflammatory cytokines (interleukin-6, tumor necrosis factor-α) by the adipocytes, which leads to inhibition of insulin signaling.[10] Adipose tissue T-cell profiles shift toward a proinflammatory state similar to that seen with obesity. This results in high adiponectin and soluble-tumor necrosis factor receptor 1 levels along with low leptin levels, leading to impaired glucose metabolism.[11]

Hypertension is present in 35% of all HIV-infected adults on ART across the world. HIV-infected adults with hypertension have a 2-fold higher risk of MI than uninfected controls with hypertension.[12] Many of the same pathways involving inflammation and immune activation are thought to play a role in hypertension for persons with HIV, although data regarding these pathways in HIV are limited. HIV infection also activates the renin-angiotensin-aldosterone system by promoting production of renin from CD4 T cells, which in turn interacts directly with the virus to stimulate replication.[13]

Dyslipidemia is present in more than half of adults with HIV. Different anti-retroviral drugs have varying effects on the different lipoprotein levels. Interestingly, untreated HIV has been associated with low levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein (LDL) cholesterol. However, after initiation of ART, there is an increase in total cholesterol and LDL cholesterol while HDL-C remains low.[14] Decreases in HDL-C levels can independently predict HIV-infected adults at increased risk of CAD.[15]

Although the increased prevalence of hypertension, diabetes, and dyslipidemia might in part be linked to HIV pathophysiology, it is important to recognize lifestyle differences in persons with HIV that make an impact on cardiovascular risk. Persons with HIV have been shown to be twice as likely to smoke cigarettes and significantly less likely to quit. This increased prevalence is associated with poor socioeconomic status and lower educational level.[16] Results from the **D**ata Collection on **A**dverse Events of **A**nti-HIV **D**rugs (D:A:D) study group showed that current smoking was associated with an approximately 3-fold increased risk in MI in persons with HIV.[17] Whether tobacco use increases the risk of CAD more in persons with HIV compared with uninfected adults because of an underlying proinflammatory state is not known.

Thus, the evidence suggests that HIV infection creates an environment that predisposes or accelerates the development of traditional CAD risk factors. The increased burden of these traditional risk factors undoubtedly contributes to the higher CAD risk in persons with HIV. Thus, addressing these known risk factors should be a public health priority in this population. Unfortunately, HIV-infected adults are significantly less likely to be prescribed aspirin, statin therapy, or antihypertensive medications compared with their uninfected counterparts.[18]

Antiretroviral Therapy and Risk of CAD

The use of ART and CAD in persons with HIV is historically and mechanistically intertwined. In the mid-1990s, HIV providers started to notice a correlation between ART, specifically protease inhibitors (PIs), and MI in persons with HIV.[19] Case reports showed that PIs increased triglyceride, LDL, and lipoprotein (a) levels.[20] Initial data from randomized controlled studies of early PIs demonstrated a trend toward increased risk of MI compared with nucleoside reverse transcriptase inhibitors (NRTIs) alone.[21] Three major trials have helped determine the effects of ART on overall and cardiovascular health of persons with HIV (Table 1). Because of increasing concerns about side effects from ART, a randomized clinical trial (SMART) was designed to assess the risks and benefits of reducing ART exposure by only intermittently using it based on the CD4+ T-cell count. The trial was stopped because of increased risk of HIV disease progression and death in the interrupted ART arm. Incidence of CVD was one of the secondary end points of the study and was also noted to be significantly higher in the interrupted ART arm. Although there was a marked reduction in LDL and triglycerides in the interrupted arm compared with the continuous arm, high-density lipoprotein (HDL) levels also decreased in the interrupted arm but remained stable in the continuous arm.[15] Thus, this study suggested a lower risk of CVD with continuous ART, even if there was some dyslipidemia associated with continuous ART.

The D:A:D study, a prospective observational study of more than 23,000 patients, showed a 26% relative increase in the rate of MI per year of exposure to ART, although the overall absolute risk of MI in this study was small.[22] Additional analysis of the D:A:D study cohort showed that there was a significantly increased risk in MI with PI exposure but not non-nucleoside reverse transcriptase inhibitor (NNRTI) exposure.[23] This risk was only partially mitigated after adjusting for dyslipidemia. The study also showed increased risk of MI in patients treated with abacavir, an NRTI. However, other studies have not demonstrated a significant association between abacavir and MI.[24] A case-control study in France did not demonstrate an increased risk of MI with abacavir, but did show a significantly increased risk of MI with cumulative exposure to all PIs except saquinavir.[25]

On the heels of the SMART trial, which demonstrated clear benefits of continuous vs interrupted ART, the **S**trategic **T**iming of **A**nti**r**etroviral **T**reatment (START) trial was designed to investigate immediate vs deferred ART initiation. The study randomized ART-naïve persons with HIV with CD4+ T-cell counts $>$ 500 cells/mm^3 to immediate ART initiation vs deferral of ART until CD4+ T-cell count declined to $<$ 350 cells/mm^3.[26] The results favored immediate treatment, with significant decreases in serious AIDS-related and non−AIDS-related events in the immediate therapy arm. The study was not powered to detect differences in CVD events, and no statistically significant differences in hard clinical CVD end points were observed. The study did show that immediate ART led to increased LDL and HDL levels.[27] This was most noticeable in patients on PIs. Integrase strand transfer inhibitors did not produce a significant change in LDL or HDL levels.

Although the evidence on ART-associated CAD risk is certainly incomplete, a few key points may be gleaned from the existing data. First, early and continuous ART is clearly better than no ART, both in terms of HIV/AIDS-related outcomes and in terms of most relevant non-AIDS end

Table 1. Cardiovascular benefits and effects of antiretroviral therapy

Study	Population	Design	Effect of ART
CD4+ Count-Guided Interruption of Antiretroviral Therapy. SMART Study Group. (2006)	5472 persons with HIV with CD4+ $>$ 350 cells/mm^3. Mean follow-up of 16 mo.	Randomized controlled trial. Viral suppression strategy (uninterrupted maximal suppression of HIV replication with ART) vs drug conservation strategy (deferral of ART until CD4+ $<$ 250 cells/mm^3 or development of opportunistic infections). Equal prevalence of PI use in both groups.	Increased all-cause mortality (HR, 1.8), serious opportunistic infections (HR, 6.6), and CVD (HR, 1.6) in the drug conservation strategy.
Class of Antiretroviral Drugs and the Risk of Myocardial Infarction. D:A:D Study Group. (2007)	23,437 persons with HIV with median CD4+ of 200 cells/mm^3. Median follow-up of 4.5 y per patient.	Prospective observational cohort study comprising 188 clinics in 21 countries in Europe, the United States, and Australia.	After adjustment for traditional cardiovascular risk factors including total cholesterol and HDL levels, and prior cardiovascular events, the relative rate of MI per year of PI exposure was significantly increased at 1.10.
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. INSIGHT START Study Group. (2015)	4685 persons with HIV with CD4+ $>$ 500 cells/mm^3. Mean follow-up of 3 y.	Randomized controlled trial. Immediate initiation (start ART immediately) vs deferred initiation (defer ART until CD4+ $<$ 350 cells/mm^3, or AIDS).	Decreased risk of serious AIDS-related event (HR, 0.28) and serious non−AIDS-related event (HR, 0.61) in the immediate initiation group. Two most common non−AIDS-related events were cancer and CVD.

AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CVD, cardiovascular disease; D:A:D, **D**ata Collection on **A**dverse Events of **A**nti-HIV **D**rugs; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HR, hazard ratio; PI, protease inhibitor; SMART, **S**trategies for **M**anagement of **A**nti**r**etroviral **T**herapy (SMART); START, **S**trategic **T**iming of **A**nti**R**etroviral **T**reatment.

points. This point is fundamental to interpreting any discussion of which specific therapies are most and least toxic, because therapy in general clearly wins against no therapy. The second point is that among ART strategies, chronic PI exposure does appear to be modestly associated with MI, perhaps because of dyslipidemia and insulin resistance. Among non-PI therapies, abacavir has been associated with elevated risk of MI in several, although not all, studies. It is important to note that disentangling the effect of a specific antiretroviral drug or class of drugs is difficult to do given that they are given in combination with other ART; additionally, understanding time and duration of drug administration may not be reliable in observational studies. The final and practical point is that monitoring lipid panels and glucose levels after starting ART is imperative to monitor for metabolic side effects common to some of these medications. Therefore, it is reasonable to discuss with HIV providers and patients changing to non−PI-based ART regimens if patients have known histories of CVD, high baseline CVD risks, or significant metabolic changes after starting PI-based ART. Regardless of the ART classes used, the protective effects of ART on overall health for persons with HIV clearly outweigh the small increased risk associated with certain antiretroviral drugs compared with others.

Pathophysiology and Related Manifestations of CAD in HIV

Acute coronary syndrome (ACS) can occur through different mechanisms, including but not limited to plaque rupture and plaque erosion. Microvascular disease, thrombosis, and endothelial function also play an important role in MI pathophysiology. Understanding these mechanisms is instructive to the study of how, when, and why CAD manifests in HIV. We discuss how these mechanisms may be exacerbated in chronic HIV infection, leading to various manifestations of CAD. An overview of the pathophysiology of CAD and related myocardial dysfunction in HIV is shown in Figure 1; clinical and immunological factors implicated in HIV-related CAD are shown in Figure 2.

Plaque rupture

Plaque rupture is traditionally considered the predominant mechanism of ACS in the general population. The pathophysiologic basis of plaque rupture is the concept of a vulnerable plaque, a thin-capped atheromatous lesion with a large lipid pool associated with overexpression of proinflammatory cytokines, procoagulant factors, and collagenases. Given the presence of dyslipidemia and inflammation in HIV, it would be reasonable to hypothesize that HIV-infected adults have an increased risk of plaque rupture. Analysis of the SMART trial did show that interleukin-6, high-sensitivity C-reactive protein, and D-dimer were associated with CVD events in HIV-infected adults independent of other CVD risk factors.[28] Early autopsy studies in young HIV-infected men showed striking atherosclerotic plaques similar to that seen in uninfected older people.[29] The lesions were diffuse and eccentric, and demonstrated fibrosis with foam cells. Vasculitis and calcifications were not present. Other studies have also shown increased coronary plaque burden in asymptomatic HIV-infected adults compared with similar controls,[30,31] although the distribution of CAD in persons with HIV vs uninfected persons with first episodes of ACS may be similar.[32]

More recently, coronary computed tomography angiography has been used to characterize the composition of coronary plaques and identify high-risk morphological features, such as positive remodeling and low attenuation. In treated HIV-infected adults, there is a higher prevalence of vulnerable plaque compared with uninfected controls with similar risk factors as determined by coronary computed tomography angiography.[33] These morphological criteria have been demonstrated in vulnerable plaques present in uninfected patients with plaque rupture. Interestingly, persons with HIV who presented with ACS had a lower plaque burden

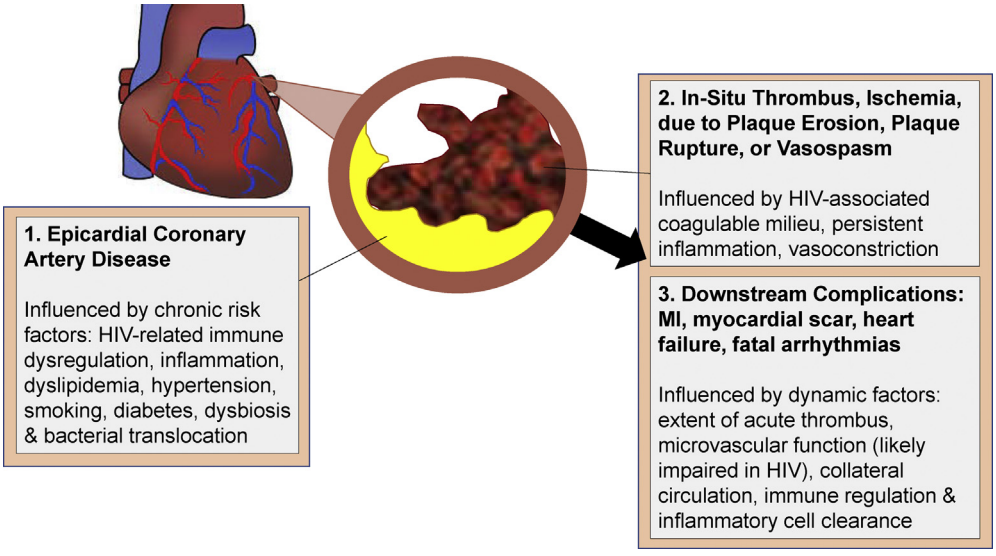

Figure 1. Pathophysiology of human immunodeficiency virus (HIV)-associated coronary artery disease (CAD) and acute coronary syndrome (ACS). MI, myocardial infarction.

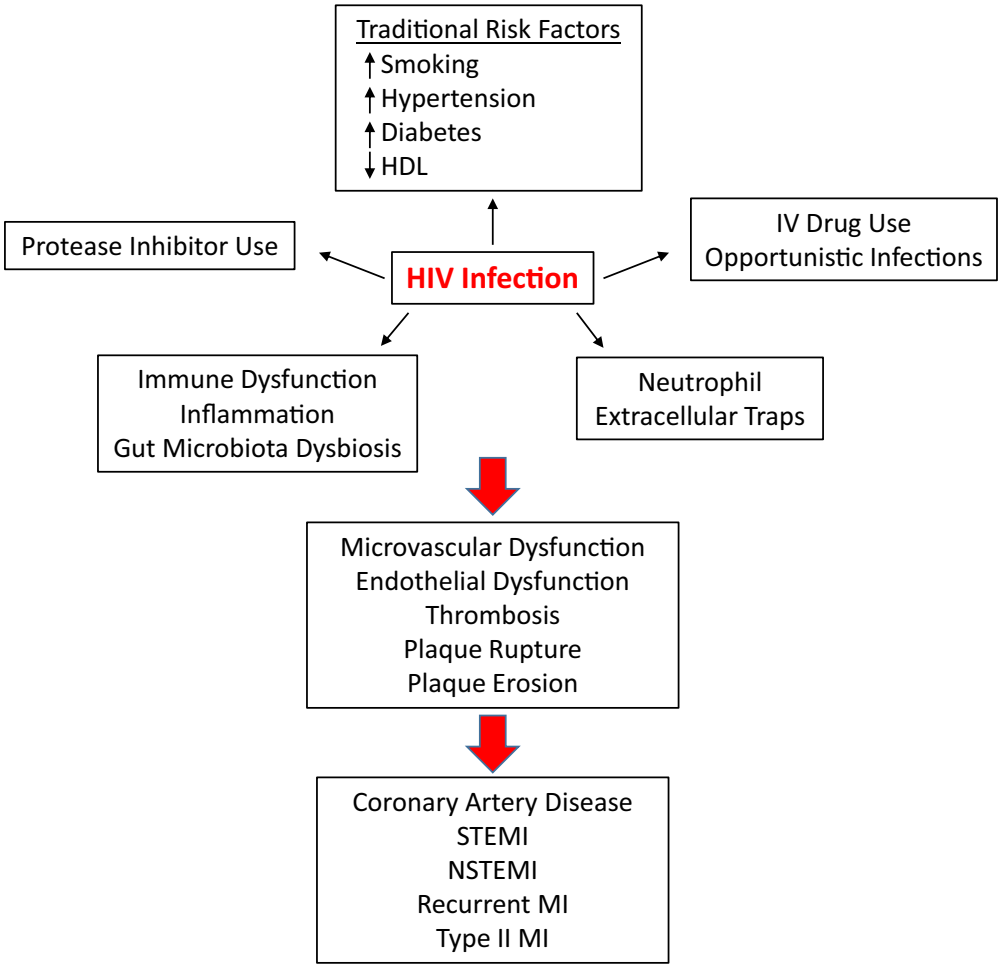

Figure 2. Clinical and immunologic factors implicated in HIV-associated CAD. HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IV, intravenous; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

compared with uninfected controls; this was likely driven by greater vulnerability and inflammation of the at-risk plaques among persons with HIV.[34] In this study, the persons with HIV (vs uninfected persons) had higher C-reactive protein levels despite being on more aggressive medical therapy with statins. These results suggest that there is higher plaque vulnerability in the HIV population, and novel treatments beyond current medical therapy may be needed to modify plaque stability to decrease the risk of MI.

Monocytes and macrophages play an important role in the development of a vulnerable plaque, especially in HIV. In chronic HIV, monocytes remain chronically infected despite ART; not surprisingly, numerous studies have supported the importance of monocyte-mediated inflammation in HIV-associated atherogenesis. A common marker of monocyte activation, soluble CD163, is significantly associated with vulnerable plaques in HIV-infected adults after adjustment for common cardiovascular risk factors.[33] Another marker of monocyte activation, soluble CD14, is likewise associated with plaque development.[35] Elevated levels of chemokines in HIV may also play a role in atherogenesis, leading to development of reactive oxygen species that promote the production of oxidized LDL. Scavenging of oxidized LDL by migrating monocytes leads to their transformation into foam cells, a key component of vulnerable plaques.[36]

Plaque erosion

Unlike plaque rupture, which is characterized by a foam cell–rich inflammatory atheroma, plaque erosion occurs in lesions that have fewer inflammatory cells, abundant extracellular matrix, and neutrophil extracellular traps (NETs).[37] Thus, the mechanism in HIV-associated ACS would seem to favor plaque rupture over erosion. However, deeper understanding of plaque erosion has led to potential pathways that might also be more prominently involved in chronic HIV infection. HIV is one of the few viruses that has been shown to induce NETosis.[38] Although NETs are an important part of innate immunity, they can also contribute to endothelial dysfunction and directly promote thrombosis. Recent evidence suggests overexpression of innate immune receptor toll-like receptor 2 (TLR2) leads to apoptosis of endothelial cells, which contributes to denudation, thus triggering thrombus formation in eroded lesions.[39,40] Interestingly, HIV structural proteins p17, p24, and gp41 have been shown to bind TLR2 and activate the nuclear factor kB signaling pathway.[41] TLR2

activation also promotes neutrophil recruitment and adhesion. Endothelial dysfunction is known to be present in HIV-infected adults, even those on effective ART.[42] However, the mechanisms remain unclear, although increased inflammation and immune cells activation are thought to play a role.[43] Thus, increased TLR2 activation and NETosis could be potential mechanisms through which HIV leads to endothelial dysfunction and plaque erosion.

Thrombosis and microvascular dysfunction

Although plaque rupture and plaque erosion are the primary mechanisms leading to ACS, thrombosis and microvascular dysfunction play an important role as well. Both plaque rupture and erosion create a thrombogenic environment that leads to thrombus formation and abrupt cessation of blood flow. Chronic HIV infection is a prothrombotic stat. Angiographic studies looking at HIV-infected adults presenting with ACS have shown an increased burden of thrombus in the infarct-related artery compared with uninfected controls.[44] One study used coronary intravascular ultrasound to demonstrate that a significant number of HIV-infected adults presenting with ACS had fresh thrombus with no or minimal underlying atherosclerotic disease.[45] The primary etiology for this prothrombotic state is not known but likely to be linked to the underlying inflammatory state. HIV-infected adults have also been shown to have lower protein C levels and higher factor VIII levels.[45]

Coronary microvascular structure and function have not been studied as extensively as epicardial CAD in general, and particularly among persons with HIV. The coronary microvasculature is responsible for controlling coronary vascular resistance and thus has a prominent role in coronary blood flow. The resistance of the microvasculature is based on endothelium-dependent vasoreactivity, changes in stretch receptors on vascular smooth muscle cells, and local metabolite concentrations.[46] Microvascular dysfunction not only leads to angina and myocardial dysfunction but also is involved in ACS pathogenesis. Microvascular dysfunction is well recognized through a phenomenon known as "no-reflow," which is defined as lack of myocardial reperfusion despite recanalization of the epicardial artery. However, there is also evidence that microvascular dysfunction even in the absence of obstructive epicardial CAD can lead to ACS.[47] There is growing evidence that markers of immune activation, inflammation, and thrombosis in HIV-infected adults contribute to microvascular dysfunction.[48]

Presentation and Outcomes of CAD and ACS in HIV

In light of the described pathophysiology underlying elevated risks for CAD and ACS in HIV, several observational studies have evaluated outcomes of ACS and coronary interventions in HIV (Table 2). One of the earlier studies evaluating the clinical features of ACS in persons with HIV showed that the HIV group was 10 years younger and had lower blood pressure, lower HDL level, and a lower Thrombolysis in Myocardial Infarction score compared with the uninfected control group.[49] A meta-analysis of 11 studies on ACS in persons with HIV found that the most common presentation was ST-segment elevation MI (STEMI), comprising 57.19% of the admissions. There was a high rate of in-hospital cardiovascular mortality (8%). Although single vessel disease was the most common angiographic finding, the presence of multivessel disease was higher in persons with HIV than in contemporary ACS registries of uninfected patients. At approximately 2-year follow up, the incidence of recurrent acute MI was high at 9.4% and need for repeat revascularization was 20%.[50]

As discussed in the previous section, the presence of vulnerable plaques and propensity for thrombus formation might explain the higher proportion of STEMI presentation. A more contemporary study used intravascular ultrasound in patients presenting with ACS to better characterize the underlying lesion. The majority of the clinical presentations in the HIV group of this study were STEMI. Furthermore, persons with HIV had lower plaque burden but had more noncalcified plaque as well as thrombus. Those with advanced disease, as characterized by CD4 $< 200/mm^3$, had a higher incidence of MI recurrence, repeat revascularization, and stent thrombosis.[51] In understanding the increased risk of repeat events, it is important to realize the difference in health care delivery in the HIV population. HIV-infected adults are prescribed dual antiplatelet and statin therapies for secondary prevention at significantly lower rates.[52] However, a study of 103 persons with HIV and 195 uninfected matched controls with ACS found that rates of in-stent restenosis for patients receiving percutaneous coronary intervention were similar, but recurrent ACS was significantly more frequent for persons with HIV, indicating that the high rate of recurrent MI may be due to the underlying pathophysiology of chronic HIV infection.[32] Although the increased risk of recurrent MI found in these studies may reflect the effect of increased inflammation and immune dysregulation on plaque vulnerability as well as suboptimal secondary prevention, the increased prevalence of type 2 MI in the HIV population may also play a role.[53] In a large multicenter cohort study looking at adjudicated MI, persons with HIV had almost double the rate of type 2 MI compared with the general population. Most likely causes of type 2 MI in this population were sepsis and illicit drug use. Although these conditions can certainly create a supply–demand mismatch leading to a type 2 MI, it is not known whether HIV infection increases the risk of type 2 MI possibly due to underlying microvascular ischemia.

As in the general population, persons with HIV receiving drug-eluting stents have fewer major adverse cardiovascular events than persons with HIV receiving bare metal stents.[54] Likewise, coronary artery bypass graft surgery appears to be

Table 2. Clinical differences in acute coronary syndrome in HIV vs uninfected patients

	HIV-infected vs uninfected adults
Demographics	10 y younger
Risk factors	Lower TIMI score, higher rates of tobacco use
Presentation	Increased prevalence of STEMI (> 50%)
Plaque morphology	Noncalcified plaque and increased thrombus
Mortality	Increased risk of 30-d in-hospital mortality
Recurrent MI	Increased risk possibly due to type 2 MI

HIV, human immunodeficiency virus; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

well tolerated for persons with HIV, who have similar 30-day postoperative cardiac event and procedural complication rates as uninfected persons, but higher rates of recurrent major adverse cardiovascular events due primarily to a need for revascularization with percutaneous coronary intervention.[55] Less is known regarding risk for myocardial dysfunction and heart failure due to ischemia and MI among persons with HIV. A small study of persons with HIV and uninfected controls with significant CAD and a history of known or likely silent MI who subsequently underwent cardiac magnetic resonance imaging found that persons with HIV had twice the MI-associated scar burden and significantly lower left ventricular ejection fraction.[56] Likewise, a study of persons with HIV and uninfected controls with abnormal cardiac stress testing who then underwent cardiac catheterization revealed that persons with HIV were significantly more likely to receive percutaneous coronary intervention, perhaps reflecting more functionally severe CAD among persons with HIV.[57] Certainly, more data are needed regarding the impact of coronary ischemia and infarction on myocardial function in HIV to better inform preventive and therapeutic efforts.

Although determining novel mechanisms in the HIV population will hopefully lead to new and effective treatments, understanding the pitfalls and nuances of current ACS and CAD treatment in persons with HIV is important as well. Treatment in this population can often be complicated by drug–drug interactions as well as decreased effectiveness of standard therapies (Table 3). The initial regimen for an ART-naïve patient with HIV consists of 2 NRTIs in combination with a third drug that can come from 1 of 3 drug classes: integrase strand transfer inhibitors, NNRTIs, or PIs. Of these classes of medications, NNRTIs and PIs have significant interactions with most statins.[58] Most PIs inhibit the metabolism of statins because of interaction with the CYP3A4 pathway, with ritonavir being the most potent and saquinavir being the least. Specifically, lovastatin and simvastatin are contraindicated with PIs.[59] Exceptions to this drug–drug interaction include pitavastatin and pravastatin, which are metabolized primarily by glucuronidation. Rosuvastatin, which is metabolized by CYP2C9, fluvastatin, and atorvastatin, can be used in patients on certain PIs but should be started at a low dose and slowly titrated with careful monitoring.[58] NNRTIs tend to stimulate statin metabolism, thus decreasing their effectiveness. Therefore, appropriate dosing and monitoring are essential.

Like statins, antiplatelet interactions are also primarily with PIs and NNRTIs. Prasugrel is a prodrug that is bioactivated by CYP3A4 to its active metabolite; thus, inhibition of CYP3A4 by PIs may decrease its clinical effect. On the other hand, ticagrelor is metabolized by CYP3A4, and thus concurrent administration with PIs can increase its effect and lead to bleeding. Although ritonavir is also an inducer of CYP2C19, the predominant pathway of clopidogrel bioactivation, pharmacogenomic studies have shown that rapid metabolizers of CYP2C19 did not experience a significant change in effectiveness of clopidogrel.[60] Thus, clopidogrel is usually the drug of choice in patients on PIs. Given that NNRTIs are typically inducers of CYP3A4, they usually do not have a significant clinical effect on any of the 3 commonly used antiplatelet drugs. However, the exceptions include efavirenz and etravirine, both of which inhibit CYP2C19 and thus can decrease the bioactivation of clopidogrel.[60] Thus, prasugrel and ticagrelor should be preferentially used in these patients.

Given the growing use of direct oral anticoagulants in the management of CAD, it is important to know their drug–drug interactions as well. Rivaroxaban and apixaban are substrates of CYP3A4, and thus concurrent administration with PIs can increase the bleeding risk while NNRTIs can decrease the clinical effect.[60] Dabigatran is primarily renally excreted and not metabolized by CYP450; thus, it is the drug of choice in patients on PIs and NNRTIs. It is important to note that the prodrug dabigatran etexilate is a substrate for P-glycoprotein, and coadministration with ritonavir, a P-glycoprotein inhibitor, can significantly increase the drug's bioavailability.[60] Therefore, administration times for the 2 drugs should be separated by 2 hours.

CAD in HIV-Infected Women

The relative risk difference in CAD for persons with HIV vs uninfected persons is particularly pronounced in women. Two studies found that the relative risk of MI was greater in women with HIV (relative risk for MI = 2.7-3 for women with HIV vs uninfected women) than men (1.4) when compared with uninfected controls.[5,61] In an analysis of women in the Veterans Aging Cohort Study, the adjusted hazard ratio for of MI and unstable angina was 2.8 in women with HIV compared with uninfected women.[62] The median age at the first event was also significantly lower in HIV-infected women at 49.3 years compared with 51.2 years for uninfected women.

In the general population, coronary vasospasm, coronary artery dissection, and microvascular disease—which are driven

Table 3. Drug Interactions between antiretroviral therapy and cardiovascular drugs

	Statins	Antiplatelets	Anticoagulants
Protease inhibitors - inhibit CYP3A4	Suggested use: 1. Pitavastatin and Pravastatin 2. Atorvastatin and Rosuvastatin (careful monitoring) Contraindicated: Lovastatin and Simvastatin	Clopidogrel: Drug of choice Prasugrel: Decreased activation Ticagrelor: Decreased metabolism	Dabigatran: Drug of choice (separate administration with Ritonavir by 2 h) Apixaban and Rivaroxaban: Decreased metabolism
Non-nucleoside reverse transcriptase inhibitors - induced CYP3A4	Increase metabolism. Careful monitoring is recommended because clinical efficacy might be decreased.	No clinical effect aside from Efavirenz and Etravirine, which inhibit CYP2C19, leading to decreased activation of clopidogrel.	Dabigatran: Drug of choice Apixaban and Rivaroxaban: Increased metabolism

in large part by local and systemic inflammation—are more prevalent in women with MI than men. Therefore, it is plausible that the underlying inflammatory milieu in chronic HIV infection might further potentiate these pathogenic processes in women with HIV. There is evidence that women with HIV have a higher burden of noncalcified plaque associated with increased markers inflammation and monocyte activation.[63] Furthermore, HIV infection may increase CAD risk in women through other pathways such as early and premature menopause secondary to coinfections and immune dysfunction.[64] Given that women represent 25% of persons with HIV, it is important to understand their increased risk of CAD to optimize prevention, screening, and treatment.

CAD Risk Prediction and Treatment

Accurate prediction of CVD, particularly atherosclerotic CVD (ASCVD), risk in HIV-infected adults is needed for clinicians to optimally weigh risks and benefits of preventive therapies. However, the accuracy and precision of CVD risk estimation tools require large derivation cohorts with many of the events in question. Given the relatively recent transition of HIV to a chronic disease marked by chronic complications, including CVDs, large-scale data with hard clinical CVD end points are relatively limited compared with the general population.[65] Several studies have evaluated CVD risk estimators derived in the general population, with the general finding that these tend to underestimate risk among persons with HIV. A study of the American College of Cardiology (ACC)/American Heart Association (AHA) ASCVD Risk Estimator in a large multicenter US cohort of persons with HIV demonstrated moderate calibration and consistent underprediction of ASCVD risk for persons with HIV, particularly for black men and in the moderate predicted risk range.[66] Including HIV-specific factors did not improve MI risk prediction in this study. Likewise, a single-center study that evaluated several risk estimation tools—the ACC/AHA ASCVD Risk Estimator and 2 Framingham Heart Study—based risk estimation tools—found systematic underestimation of CVD risk in a cohort of men with HIV.[67] Given concerns that risk estimation tools derived in the general population may not be appropriate for persons with HIV, the data collection on adverse effects of anti-HIV drugs study (D:A:D) group developed a CVD risk estimation model incorporating conventional CVD risk factors and HIV-specific risk factors such as CD4 count, cumulative PI and NRTI exposure, and current abacavir use.[68] In an internal validation, this model demonstrated somewhat better discrimination than Framingham-based models, although it was not directly compared with the ACC/AHA ASCVD Risk Estimator.[68] Other studies have incorporated biomarkers such as soluble CD14 but found only marginal improvement in discrimination.[35] Ultimately, more large-scale data with consistently adjudicated CVD outcomes are needed to derive HIV-specific CVD risk prediction equations that perform well enough to supplant than current general population-derived ones (eg, the ACC/AHA ASCVD Risk Estimator) in the routine care of persons with HIV. In the meantime, it is reasonable to treat the predicted risk from an estimator such as the ACC/AHA ASCVD Risk Estimator a low-end estimate, understanding that if certain high-risk HIV-related features (eg, low CD4 count or nadir, long duration of uncontrolled HIV virus, untreated hepatitis B or C co-infection) are present, the true ASCVD risk is likely $\geq 1.5\times$ the estimated risk.[65]

One of the reasons underlying the consistent underestimation the ASCVD risk in HIV may be the higher prevalence of type 2 MI in the HIV population. As discussed previously, in one multicenter cohort, half of the total MIs were type 2 in etiology.[53] Although most of these type 2 MIs are likely demand ischemia in the setting of increased atherosclerotic burden and metabolic needs, there may be unexplored pathways that increase the risk of MI in HIV-infected adults who have a concomitant infection.

Despite the increased risk and better understanding of plaque pathobiology, there is no HIV-specific treatment for prevention of atherosclerotic disease and MI. ART likely improves cardiovascular outcomes by decreasing inflammation and immune activation. Statin therapy has been shown to reduce both noncalcified plaque volume and number of vulnerable plaques in HIV-infected adults.[69] The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) is the first and largest ongoing trial that will help determine whether HIV-infected adults, who do not meet current indications for statin therapy, will benefit from a moderate-intensity statin. Perhaps the lack of a new therapy speaks to the fact that the fundamental mechanisms behind increased inflammation and immune activation despite ART have not been fully elucidated. Better understanding of how well-controlled chronic HIV infection affects the reticuloendothelial system, the gut mucosa, and the gut microbiota may also shed insight into how to improve prediction models and develop new therapies.

Conclusion

Chronic HIV infection creates a proinflammatory environment through gut mucosa breakdown, immune activation, and other pathways that are not yet fully explored. This stimulates atherosclerosis and development of vulnerable plaque both directly and indirectly by increasing the burden of cardiovascular risk factors. Along with increased thrombosis and endothelial and microvascular dysfunction, this leads to a significantly elevated risks of CAD and MI. Most antiretroviral therapies help improve overall cardiovascular outcomes by effectively treating the HIV infection. However, despite viremic control, there continues to be ongoing low-level HIV replication leading to increased inflammation. Further investigation is needed to understand these pathways to improve prognostic tools and trial new therapies specific to HIV-associated CVD.

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