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## “Coronary Artery Disease in Patients with HIV Infection: An Update”

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### Abstract

Premature cardiovascular disease among the HIV-infected population is of great concern among clinicians. The increased life expectancy of HIV-infected individuals is mainly due to early detection of infection and the advent of antiretroviral therapy. Once known as a deadly disease, HIV-infection has transitioned into a chronic condition. Cardiovascular disease in this population is thought to progress early due to traditional and non-traditional risk factors. Early detection of subclinical atherosclerosis has become a center of focus in research, as our complete understanding of this process is not yet well known. Advancements in cardiac CT angiography has enabled the exploration of coronary artery disease by further evaluation of coronary stenosis and plaque analysis. An increase in cardiovascular event rates in this population is currently thought to be linked to antiretroviral therapy, Framingham risk factors and HIV. We sought to present an updated comprehensive review of the available literature on HIV related to atherosclerosis and cardiovascular risk.

### 1. Introduction

The effect of antiretroviral therapy (ART) on individuals infected with human immunodeficiency virus (HIV) has dramatically shifted the paradigm of the disease. Initially regarded as a terminal condition, it is now considered a chronic manageable disease in regions with access to healthcare and ART. The evolution of this process has led to the increased prevalence of cardiovascular disease (CVD) due to a greater life expectancy and an increase in traditional CVD risk factors [1]. The association between HIV infection and CVD has been recognized for at least two decades, and possible mechanisms identified include vascular inflammation and endothelial dysfunction [2]. The complex interaction of HIV-related inflammation, immune activation and pro-coagulant mechanism is core to the development of CVD [3]. The effects of ART, smoking, diabetes mellitus, hypertension, and

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dyslipidemia in various combinations accelerates the process of atherosclerosis further, and eventually leads to an early development of acute coronary events [4,5]. These factors subsequently have led to the increased prevalence of subclinical atherosclerosis in HIV-infected individuals compared to HIV-negative individuals in North American and European studies [6,7,8]. Current evidence suggests even when traditional CVD risk factors are controlled, HIV-infected individuals remain at 2-fold risk of developing CVD [9]. CVD is the second leading cause of non-AIDS related mortality according to the Data collection on Adverse Events of Anti-HIV Drugs (D:A:D) study which followed HIV-infected individuals in Western countries for greater than 10 years [10].

Models have been developed and validated among the general population for risk stratification of CVD, such as the Framingham Heart Score (FHS) and the American Heart Association/American College of Cardiology (AHA/ACC) atherosclerotic cardiovascular disease risk score (ASCVD) [11,12]. Specific models have been further developed, such as D:A:D, to increase risk stratification accuracy in the HIV-infected population to include the influence of ART [13]. In a study comparing risk prediction models in the HIV-infected population, a higher overall CVD risk was attributed with the FHS than with ASCVD and D:A:D [14]. Risk stratification should also account for gender specific differences. The link between HIV-infection and CVD is derived from earlier studies which consisted mostly of men [10,6]. Few studies have specifically studied HIV-infected women, the ones that have all consistently found an increased risk of CVD with HIV-positive compared to HIV-negative women [15,16]. We attempt to present an updated comprehensive narrative review of the currently available literature related to HIV and atherosclerosis and cardiovascular risk.

## 2. HIV and Subclinical Atherosclerosis

Due to the accelerated process of atherosclerosis in the HIV-infected population considerable interest in the early diagnosis of subclinical atherosclerosis has gained momentum. Recent studies have focused on the detection of subclinical atherosclerosis as a surrogate marker for clinical cardiovascular events in the HIV-infected population [6]. Among the general population subclinical atherosclerosis is associated with an increased risk for coronary events [17]. Subclinical atherosclerosis can be assessed by non-invasive imaging: carotid intima media thickness (IMT) and carotid plaque can be measured by carotid ultrasonography, and coronary artery calcium (CAC) can be measured by non-contrast cardiac computed tomography (CT) [Table 1]. Carotid IMT has been shown to have a higher prevalence in HIV-infected individuals compared to HIV-negative individuals [18]. An increase in carotid IMT was found in a meta-analysis of 13 observational studies in HIV-infected adults [19]. It is suggested the process starts early, as HIV-infected children on ART have been shown to have an increase in carotid IMT as well [20]. In the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study, a large comparison of carotid IMT between HIV-infected and uninfected individuals, the degree of greater carotid IMT associated with HIV-infection was of similar magnitude than was being a smoker or having diabetes mellitus [21]. In a study comparing carotid IMT and CAC in the detection of atherosclerosis in HIV-infected subjects, a large subset of HIV patients was shown to have no detectable CAC but to have advanced subclinical atherosclerosis as assessed by carotid

IMT. Among those with undetectable CAC, 34% of HIV patients had markedly increased carotid IMT, 1mm, compared to controls ( $p<0.0001$ ) [18]. The Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN) study assessed carotid IMA at baseline and year two, and found that maintaining a clinically suppressed HIV viral load protected against atherosclerotic progression [22]. The study furthermore found that both HIV replication and exposure to certain antiretroviral medications contributed to an increase in CVD risk. After adjusting for the protective effects of viral suppression, the use of nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based ART was associated with a decrease in carotid IMT progression compared with protease inhibitor (PI)-based ART [22]. HIV suppression below clinical threshold was associated with less progression of atherosclerosis. Specifically, a persistently suppressed HIV RNA viral load ( $<400$  copies/ml throughout follow-up vs  $\geq 400$  copies/ml at 1 visit) [22].

Coronary artery calcification assessed by cardiac CT is a non-invasive modality used to identify subclinical atherosclerosis. Presence of CAC is well established to be independently associated with future CVD events and all-cause mortality in numerous studies [17,23–25]. By adding CAC assessment, the risk classification for CAD or stroke significantly improves when included with traditional risk factors [23,26,27]. Applying a CAC score alone to the HIV-infected population can be misleading. In a study among HIV-infected individuals receiving at least 8 years of ART, CAC was significantly lower compared to HIV-negative individuals [28]. The Multicenter AIDS Cohort Study (MACS) found that the prevalence of any CAC on non-contrast CT scans was 53.1% among HIV-infected men and 52.0% in uninfected men. After adjustment for a number of variables there was a greater prevalence of CAC in HIV-infected men (prevalence ratio [PR], 1.21 [95% CI, 1.08 to 1.35]). In fact, HIV-infected men were found to have a greater extent of non-calcified plaque after CAD risk factor adjustment [6]. A study comparing CAC in Multiethnic Study of Atherosclerosis (MESA) and Hawaii Aging with HIV Cardiovascular study (HAHCS) cohorts found that HIV patients were more likely to have CAC with increased likelihood of occurrence between 45 and 50 years of age [29]. The age of onset of CAC was not significantly different in MESA and HAHCS, but a more recent study looking at non-gated chest CT in hospitalized HIV patients showed that the age of onset of detectable CAC was in the third decade of this cohort [29,30]. In this study, approximately one-third of hospitalized HIV-infected individuals showed subclinical CAC. Age of patients and HIV duration were independent risk factors for development of CAC. Additionally, a lower viral load and higher CD4 cell count was strongly associated with CAC [30]. A recent study from Switzerland involving the Swiss HIV cohort utilizing CAC scoring among HIV-infected individuals reported a lower prevalence of calcified plaque than in HIV-negative individuals [36.9% vs. 48.6%,  $p<0.01$ ; adjusted odds ratio (aOR) 0.57; 95% confidence interval (CI) 0.40–0.82;  $P<0.01$ ] and advanced immunosuppression was associated with non-calcified/mixed plaque (aOR 1.97; 95% CI 1.09–3.56;  $p=0.02$ ) [31]. The MACS cohort evaluated racial differences and found a lower prevalence of CAC in black men compared to white men. This reflected less calcified plaque and stenosis rather than a lower overall prevalence of plaque [32].

Inflammatory and metabolic markers in HIV-infected individuals have also been shown to be associated with evidence of subclinical atherosclerosis or arterial dysfunction [33–36].

Inflammatory biomarkers in the blood of the general population, such as monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor (TNF)-alpha have been linked to the burden of CAC. Though the relationship of CAC and inflammatory biomarkers was often lost following correction for traditional cardiovascular risk factors [33]. The HAHCS cohort showed that in contrast to the general population, a higher MCP-1 and TNF-alpha predict the presence of CAC independent of traditional CVD risk factors in HIV-infected individuals adherent to ART [33]. The MACS group found the serologic biomarkers of monocyte activation, soluble CD163, soluble CD14 and MCP-1 to be elevated in treated HIV-infected individuals associated with atherosclerosis [34]. These studies suggest that HIV-mediated immune activation may play a role in CVD risk [33,34]. ART related atherosclerosis in the HIV-infected population remains a topic of interest and proposed mechanisms include metabolic derangements including insulin resistance, diabetes mellitus, and dyslipidemia which could partially be mediated by changes in adipokine homeostasis [5,37].

Despite advances in CT technology to reduce radiation exposure during CAC scans and its increased availability, CAC only partially reflects the pathophysiology in the HIV population [38–40]. Although the CAC scoring is a well-defined marker for atherosclerotic lesions and cardiac event risk in non-HIV population, it may not provide a reliable valuation of early atherosclerosis in young HIV patients in whom calcifications are absent [6,31,38]. On the other hand, coronary CT angiography (CTA) permits for accurate plaque characterization, quantification and degree of stenosis in patients with CAD [6,41,42]. Hence, non-contrast cardiac CT scans cannot identify non-calcified plaque (NCP) and is limited to measuring CAC [6].

### 3. HIV-Associated Coronary Artery Disease (Stenosis and Plaque)

Coronary atherosclerosis assessed by CTA allows for the ability to differentiate CAC plaque and NCP in addition to the amount of coronary artery stenosis [6,7]. Coronary CTA provides a non-invasive assessment of subclinical atherosclerosis which correlated with the amount of histologically confirmed NCP [38,43]. In studies using CTA, HIV-infected men have 59.0% prevalence of coronary atherosclerosis compared with 34.4% in non-HIV controls [8,14]. Additionally, HIV-infected women had significantly higher percentage of segments with NCP (74% vs 23%) compared with female HIV-negative controls [45]. The MACS study also utilizing coronary CTA in HIV-infected men found this population had a greater extent of NCP after CAD risk factor adjustment ( $p=0.026$ ) [6]. Another study reported an increase in NCP volume in HIV-infected men compared to non-HIV controls with a trend toward higher CAC score among patients with HIV ( $P = 0.08$ ) [8]. The HIV-infected group were found to have a higher coronary plaque volume [55.9 (0–207.7); (median interquartile range) vs. 0 (0–80.5)  $\mu\text{l}$ ;  $P = 0.02$ ] and plaque volume was associated with traditional markers of CVD risk and HIV-specific risk factors [8]. In relatively young HIV-infected patients an increased prevalence of plaque vulnerability has been found, including low attenuation plaque (22.8% versus 7.3%,  $p=0.02$ ), positively remodeled plaque (49.5% versus 31.7%,  $p=0.05$ ), and high-risk 3-feature positive plaque (7.9% versus 0%,  $p=0.02$ ) among HIV-infected patients versus controls with similar traditional cardiovascular risk factors [44]. A recent meta-analysis of 1229 asymptomatic HIV-positive patients on ART demonstrated a 3-

fold higher prevalence of vulnerable plaque (NCP) on coronary CTA, compared with HIV-negative control subjects [7]. The study additionally found that the level of CD4 cell count correlates with a significant increase in the number of vulnerable plaques [7]. A study reporting the angiographic pattern of CAD in HIV-positive patients undergoing percutaneous coronary intervention found that HIV-positive patients had a similar extent of CAD as compared to HIV-negative patients when matched for age, gender, diabetes and year of intervention [46]. Lesions detected in HIV-positive patients displayed none to mild calcification pattern, as expected based on previous studies [46]. Additionally, another angiographic study found that HIV-positive males presenting with an acute coronary syndrome, which included both ST-elevation myocardial infarction and non-ST-elevation myocardial infarction had an overall lower burden of coronary plaque, assessed with quantitative coronary angiography than matched HIV-negative male patients [47]. These angiographic studies appear to suggest that plaque vulnerability, and risk for rupture rather than total burden of atherosclerosis may be important in the pathophysiology of CAD in HIV-positive patients [46,47]. Calcified plaque reflects advanced and more stable atherosclerosis, but the HIV population appear to develop more vulnerable plaque or NCP and mixed plaque, similarly to NCP may be more prone to rupture [6]. Coronary CTA non-invasively can differentiate mixed plaque (plaque that has <50% calcification) from calcified plaque, which can lead to an advantage over invasive coronary angiography in plaque analysis [6]. Future studies are indicated to track the differences in the progression of the atherosclerosis process in the HIV population using coronary CTA.

#### 4. Cardiovascular Events in HIV

An increased risk for acute myocardial infarction (AMI) and other cardiovascular diseases has been found in the HIV-infected population compared to uninfected population in numerous studies [48,49]. Studies have suggested the increased risk of AMI among HIV-infected individuals is probably due to HIV, ART and Framingham risk factors [Table 2] [49–51]. The exact mechanism by which HIV infection increases the risk of AMI is currently unknown. A number of studies have speculated that the mechanism may involve inflammation, low CD4 cell counts, altered coagulation state, dyslipidemia, impaired arterial elasticity and endothelial dysfunction [49,52–57]. In HIV-infected patients, ART is associated with abnormal fat distribution and metabolic changes, which are linked to insulin resistance, diabetes and dyslipidemia [49,58,59]. Even though HIV and ART are associated with AMI, the Strategies for Management of Antiretroviral Therapy study (SMART) study found that continuous HIV viral suppression resulted in lower cardiovascular disease risk than drug conservation therapy which suggests that the HIV virus play the larger role [49,51].

The Veterans Aging Cohort Study-Virtual Cohort (VACS-VC) reported that HIV-infected veterans with three or more major CVD risk factors had absolute AMI rates that were 30 events per 10000 person years higher than those for uninfected veterans with the same CVD risk factor profile compared to 20 and 7 events per 10000 person years for those with 2 or 1 major CVD risk factors, respectively [48]. In this study, the traditional CVD risk factors were total cholesterol, cholesterol-lowering agents, hypertension, anti-hypertensive medications, smoking and diabetes [48]. Prehypertensive blood pressure and hypertensive

blood pressure among HIV-infected veterans had an increased AMI risk compared to uninfected, untreated individuals (hazard ratio [HR], 1.60 [95% confidence interval {CI}, 1.07–2.39]; HR, 1.81 [95% CI, 1.22–2.68]; HR, 2.57 [95% CI, 1.76–3.76]; and HR, 2.76 [95% CI, 1.90–4.02], respectively) [60].

A VACS-VC study also found that HIV-infected veterans had a higher risk of AMI while having the same baseline Framingham risk score as noninfected veterans and HIV infection was associated with an increase in AMI risk when added to a model of Framingham risk factors [49]. In combination with previous work by the D:A:D study, these studies suggest that the Framingham risk score may understate AMI risk among HIV-infected individuals and that the addition of HIV and ART to a model of traditional AMI risk factors can be clinically beneficial [49,50].

Recent studies have also found that HIV infection has also been associated with an increased risk of CVD in women [5,16]. Among women in the VACS-VC study, the incidence of CVD per 1000 person-years was significantly higher among HIV-positive (13.5; 95% confidence interval [CI]=10.1, 18.1) than HIV-negative women (5.3; 95% CI=3.9, 7.3;  $P<0.001$ ) [16]. HIV-positive women had an increased risk of CVD, compared to HIV-negative women (hazard ratio[HR]=2.8; 95% CI=1.7, 4.6;  $P<0.001$ ). HIV-infected women had a more than 2-fold increased risk of death, compared to uninfected women (HR=2.6; 95% CI, 1.7 to 3.9;  $P<0.001$ ) [16].

HIV infection is an independent risk factor for CVD, regardless of gender. In addition, ART, Framingham risk factors and important co-morbidities such as hypertension, dyslipidemia, diabetes and smoking may all contribute to CVD in men and women [16,49].

## 5. Conclusion

The paradigm of HIV and CVD remains to be a complex relationship. The pathophysiology underlying CVD in this population involves traditional risk factors, infection-related and ART-related factors. Risk stratification is the initial step to direct diagnostic exams, primary prevention and subsequent treatment. Detecting subclinical atherosclerosis as a surrogate marker for cardiovascular events can be achieved with non-invasive imaging, specifically evaluating carotid IMT, CAC and coronary plaque analysis. Advances in the analysis of coronary atherosclerosis using coronary CT angiography have led to the ability to identify high risk, vulnerable plaques among asymptomatic HIV-infected patients. This finding gives the potential to provide details on the differences in atherosclerotic process in the HIV-infected population. Opportunities to implement primary prevention in this population is key to reduce cardiovascular event rates. Further studies are needed to determine if routine use of coronary CT can be considered as a complimentary tool to evaluate high risk individuals with HIV.

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**Key Points**

- HIV increases risk of CVD, even when traditional risk factors are controlled.
- Traditional CVD risk models underestimate risk in the HIV population.
- Acute myocardial infarction event rate among HIV-infected individuals remains higher than the general population.
- Detection of subclinical atherosclerosis early in the HIV population could play a key role in reducing cardiovascular event rates.
- Plaque analysis by coronary CT angiogram is emerging as an important tool in understanding premature coronary artery disease.

Non-Invasive Imaging to Assess Subclinical Atherosclerosis in HIV-Infected Patients

**TABLE 1**

<b>Imaging Modality</b>	<b>Utility in HIV-Infected Patients</b>
Carotid Intima Media Thickness (IMT)	Increased carotid IMT is associated with coronary artery atherosclerosis and predict risk for vascular events (22)
Coronary Artery Calcium (CAC) on Non-Contrast Computed Tomography (CT)	CAC is independently associated with future cardiovascular events and all-cause mortality, but in HIV-infected patients CAC is found to be lower when compared to HIV-negative controls (17,23–25, 28)
Coronary CT Angiogram (CTA)	Coronary atherosclerosis assessed by CTA allows for the ability to differentiate CAC plaque and non-calcified plaque (NCP) in addition to the amount of coronary artery stenosis. HIV-infected patients have greater NCP than CAC. NCP or vulnerable plaque are at greater risk for rupture which leads to acute coronary syndrome (6–8,14)

**Table 2**

## Risk Factors for Cardiovascular Events in HIV

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Human Immunodeficiency Virus (HIV)
<i>Chronic Inflammation</i>
<i>Low CD4 Counts</i>
<i>Altered Coagulation State</i>
<i>Dyslipidemia</i>
<i>Impaired Arterial Elasticity</i>
<i>Endothelial Dysfunction</i>
Anti-retroviral Therapy (ART)
<i>Insulin Resistance</i>
<i>Diabetes Mellitus</i>
<i>Dyslipidemia</i>
Framingham Risk Factors
<i>Age</i>
<i>Smoking</i>
<i>Dyslipidemia</i>
<i>Hypertension</i>

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Risk factors for higher incidence of cardiovascular events in the HIV population has three broad categories and can be further subdivided into contributing risk factors (49–59)