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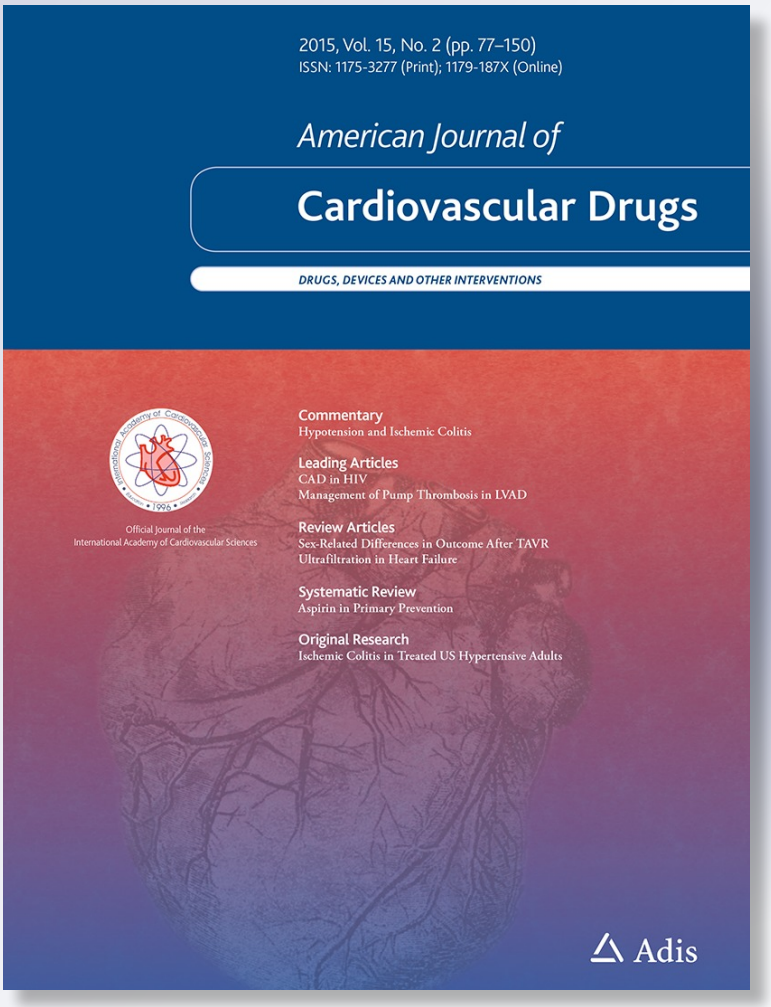

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LEADING ARTICLE

Coronary Artery Disease in Patients with HIV Infection

Amish A. Patel · Matthew J. Budoff

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Abstract HIV-infected patients are known to be at risk for premature coronary artery disease. This emerging paradigm is a rising concern for clinicians. Due to advances in the treatment of HIV, this once fatal infection has been transformed into a chronic illness. Traditional risk factors paired with the long-term use of antiretroviral therapy (ART) and chronic inflammation leads to premature atherosclerosis, particularly progression of atherosclerotic plaque. This population of patients requires early recognition of subclinical atherosclerosis, as well aggressive primary and secondary prevention strategies among the multi-disciplinary team of physicians caring for them. We sought to present a comprehensive review of the available literature related to HIV and atherosclerosis and cardiovascular risk.

Key Points

Recognize non-traditional and emerging risk factors for coronary artery disease (CAD) in the HIV population.

The benefit of continuous antiretroviral therapy remains the standard in CAD reduction.

Statins are suggested in the HIV population to reduce CAD but caution must be taken due to drug–drug interactions.

Due to possible underestimation of CAD in the HIV population, consider computed tomography and coronary angioplasty for preventative and therapeutic guidance, respectively.

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1 Introduction

Cardiovascular disease (CVD) has emerged as a significant threat to the HIV-infected population, in large part due to the effectiveness of antiretroviral therapy (ART) in treating HIV infection and extending life expectancy [1]. Currently, CVD is the second most frequent cause of death among HIV patients, with the first being cancer [2]. The subclinical makers of atherosclerosis, such as carotid, femoral, or iliac intima-media thickness are consistently greater and progress earlier among the HIV-positive population than among the general population [3, 4].

The D:A:D (Data Collection in Adverse Effects of Anti-HIV Drugs) study showed that risk for cardiovascular event was statistically increased by such traditional risk factors as age, male sex, greater body mass index (BMI), family history of CVD, and smoking [5]. This is exacerbated by HIV-specific risk factors such as low CD4 T-lymphocyte cell (CD4) count, co-infection with hepatitis C virus, and certain ARTs (Table 1). D:A:D showed that the dysmetabolic effects of HIV protease inhibitors (PI) increased the risk of diabetes mellitus, hypertension, and dyslipidemia [5]. In HIV-infected patients, the risk of myocardial infarction (MI) is approximately twofold [10], and the risk of sudden cardiac death is approximately fourfold [11] compared with the general population.

The MACS (Multicenter AIDS Cohort Study), initiated in 1983, is an on-going multicenter prospective, observational cohort study. It continues to conduct studies and publish key papers on the natural history of untreated and treated HIV infection [12]. A number of significant results a found that HIV-infected men had a greater extent of non-calcified coronary artery plaque (NCAP) [13]. In another study also using computed tomography coronary

Table 1 Cardiovascular risk factors in HIV [5–9]

Traditional	Nontraditional
Age	Low CD4 count
Sex	Lidodystrophy syndrome
Greater body mass index	Hepatitis C co-infection
Family history of premature heart disease	Metabolic syndrome
Smoking	End-stage renal disease
Diabetes	Antiretroviral therapy
Dyslipidemia	
Hypertension	

angiography (coronary CTA), an increased prevalence of vulnerable plaque features among relatively young HIV-infected men was found [14]. These findings are not only limited to the male HIV-infected population. A study that focused on the female HIV population found that young, asymptomatic HIV-infected women also demonstrate increased NCAP [15]. This has led to a surge in interest in the association between HIV infection and CVD, specifically NCAP due to the increase of major adverse cardiac events (MACE) associated with it [16]. It should be pointed out that the coronary plaque analysis from the MACS database was concluded using cross-sectional studies. This leaves the possibility that HIV-infected individuals have an overall greater risk profile than non-infected individuals. The MACS cohort is currently undergoing a second CTA at 5 years to evaluate for plaque progression in the HIV group using different retroviral therapies.

2 Pathophysiology of Coronary Artery Disease in Patients with HIV Infection

HIV acts by mainly targeting the CD4+ T cells and, to a lesser extent, macrophages and dendritic cells, which all play an essential role in immunity. The infection and massive depletion of CD4+ T cells represents the fundamental pathogenesis of HIV infection [17]. The pathophysiology of coronary artery disease (CAD) in HIV-infected patients is multifactorial and complex, combining traditional and non-traditional risk factors in addition to emerging risk factors. To date, factors associated with CAD in HIV have been determined indirectly or by association, which makes our understanding of the overall process limited. Prospective studies evaluating long-term CAD outcomes are needed.

CAD is the result of chronic inflammation of the arterial wall, which is lined by endothelial cells (ECs) and smooth-muscle cells [18]. HIV infection is associated with an increase in systemic inflammation and damage to the vascular endothelium [19]. This leads to HIV-positive individuals being prone to premature atherosclerosis. In atherosclerosis, the activation of ECs in response to an inflammatory state leads to the expression and release of cytokines and chemokines, specifically interleukin (IL)-6 and monocyte chemoattractant protein (MCP)-1. These have been suggested to play the key role in the initial phase of atherosclerosis [20–22]. An increase in IL-6 levels has been associated with an increase in cardiovascular mortality in HIV-infected individuals [20], and MCP-1 has been shown to play a part in the attraction, migration, and activation of monocytes [23]. When using mice deficient in MCP-1 or its receptor, C-C chemokine receptor (CCR)-2, to examine atherosclerosis, it was demonstrated that, in the absence of MCP-1 or its receptor, CCR-2, there was a substantial reduction in atherosclerosis [24].

Proinflammatory monocytes CD14+ CD16+ have also been implicated in the atherosclerosis disease process [25]. In a large study involving more than 200 patients with CAD, increased percentages of the CD14+ CD16+ monocytes were seen in the patient cohort [26]. A recent study analyzing coronary artery calcium (CAC) and inflammatory markers found that higher frequencies of CD16+ monocytes (lacking CD14 expression) predicted greater CAC progression [27].

CAC progression has been shown to be associated with increased cardiovascular morbidity and all-cause mortality [28, 29]. CAC has also been proven as an independent predictor of future risk of CVD events [30]. In HIV-infected patients, the disease process is thought to begin with an inflammatory state. Inflammation initiates the recruitment of monocytes; monocytes then migrate to the endothelium and differentiate to macrophages and foam cells. Foam cells transform and undergo apoptosis because of calcium-dependent endoplasmic reticulum stress, thus leading to atherosclerosis [31]. Excessive death of foam cells overloaded with cholesterol eventually forms the plaques in the arteries, induces further inflammation, and exacerbates metabolic dysregulation [32]. It is speculated that the HIV virus, which activates inflammation and lipid-markers, also triggers endoplasmic reticulum (ER) stress through its interaction with host genes that result in an imbalance of calcium [33]. Histopathologically, the vascular changes associated with HIV infection include eccentric atheromatous plaques composed of fibrous tissue, lipid, and calcium, with variable degrees of chronic inflammation and accelerated atherosclerosis [34]. A post-mortem study observed an unusual pattern of dystrophic vascular calcification in HIV+ patients who were treated with ART from all major class for a mean ± standard deviation (SD) duration in years of 4.6 ± 3.5, speculating that the metabolic derangements in HIV+ patients receiving ART may predispose them to this type of

atherosclerosis [35]. ART essentially acts to suppress the HIV viral load and is recommended for all HIV-infected individuals to reduce the risk of disease progression.

Current data on the effect of CD4 count and viral load on cardiovascular mortality have not been entirely consistent. The D:A:D study found there was no association between either the nadir CD4+ lymphocyte count or peak HIV-1 RNA level and the risk of MI [36]. In the prospectively recorded FHDH (French Hospital Database on HIV) study, lower nadir CD4 cell count and higher plasma viral load were associated with a statistically significant increased rate of MI, independent of exposure to ART and presence of traditional risk factors [37]. Therefore, it appears that age-related changes in combination with HIV infection and long-term ART therapy all likely contribute in a cumulative effect on the arterial walls to produce atherosclerosis.

3 Diagnosis

The first step in diagnosis of CVD in the HIV population begins with a thorough medical history, which would include a complete history of prior antiretroviral exposure. A further detailed assessment of CAD risk factors is then to be performed, including smoking history, family history of CAD, and fasting determinations of total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, Framingham Risk Score (FRS) or the atherosclerotic cardiovascular disease (ASCVD) risk assessment. As mentioned, recent analysis has suggested that chronic inflammation can partially attribute to the increased cardiovascular risk correlated with HIV infection [38, 39]. The underlying mechanism of this disease process is currently being studied and remains unclear. However, the atherosclerotic byproduct of this process can be detected with current cardiac imaging modalities, particularly cardiac CT.

Cardiac CT estimates CAC, which provides a noninvasive assessment of subclinical atherosclerosis that also correlates with the extent of histologically confirmed NACP [40, 41]. Additionally, CAC progression is independently associated with future risk of CVD events and all-cause mortality [28, 29]. The risk classification for CAD or stroke significantly improves by adding CAC assessment along with traditional risk factors [28, 42, 43]. However, in the HIV population, the generalized use of only CAC scoring could be deceptive. Recently demonstrated among an HIV population receiving ART therapy for at least 8 years, the extent of calcification was significantly reduced compared with HIV-seronegative controls [44]. In a study using coronary CTA, HIV-infected men were found to have a greater extent of non-calcified plaque after CAD risk factor adjustment [13]. Only a small number of studies have characterized the degree of both CAC plaque and NCAP in HIV-infected adults [45, 46]. One study found an increased NCAP volume in HIV-infected men compared with uninfected controls with a trend toward higher Agatston calcium scores among those patients with HIV. Within the HIV-infected group, plaque volume was associated with traditional markers of CVD risk and HIV-specific risk factors [45]. In another study, the data found an increased prevalence of vulnerable plaque features among a relatively young population of HIV-infected patients [14].

Though the routine use of coronary CTA to assess the degree of coronary atherosclerosis is still debated, it can provide preventive and therapeutic guidance in this high-risk population. Furthermore, specific risk factors identified in HIV-related atherosclerosis, such as chronic inflammation, immune activation, and effects of ART are not calculated with available risk scores. This can lead to underestimation of true cardiovascular risk in the HIV-infected population.

4 Prevention

The most important preventive measure for a high-risk population is lifestyle modification and statin use. A study analyzing data from MACS and the WIHS (Women's Interagency HIV Study) found HIV-infected individuals to have a higher prevalence of smoking (up to 40 %) and to meet criteria for being overweight or obese (BMI > 25), which increased predicted cardiovascular risk [47], thereby giving clinicians an opportunity to intervene on modifiable risk factors.

The first of these is smoking cessation, as smoking is a well-known cardiovascular risk factor. The American Heart Association has set forth guidelines for lifestyle management to reduce cardiovascular risk in the general population and these shouldalso be applied to this subgroup. These include improved diet and increased physical activity, both of which contribute to weight loss, lowering blood pressure, reduction in insulin resistance, and blood lipid modification [48].

Due to the increased risk of premature atherosclerosis associated with HIV infection, an aggressive implementation of cardiovascular therapies is required soon after diagnosis. As mentioned earlier, ART remains the first-line treatment for HIV infection. Combination ART is currently defined as any combination of three antiretroviral drugs, usually two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) plus a PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus an integrase inhibitor [49]. Effective ART reduces viral load, which is thought to decrease

the inflammatory effects of HIV and therefore reduce atherosclerosis [50].

The D:A:D study indicated that cumulative exposure to specific PIs (lopinavir–ritonavir and indinavir) and two NRTI drugs (abacavir and didanosine) was associated with an increased risk of MI [5, 51]. As the duration of exposure to PIs increases, the risk for MI also increases, as seen in the FHDH and D:A:D cohorts [37, 51]. The cumulative exposure to all studied PIs was associated with a higher risk of MI, with an odds ratio (OR) of 2.23 per 10 years of exposure [95 % confidence interval (CI) 1.17–4.24] [37]. However, the PI risk–benefit ratio continues to remain positive, as the increase in life expectancy in PI-based ART outweighs the risk of MI [52]. Neither of these cohorts found any significant association between the development of MI and cumulative exposure to an NNRTI [37, 51].

Of the NRTIs, the only significant association between MI risk and cumulative exposure was with abacavir [relative risk (RR) 1.07 (95 % CI 1.00–1.14)]; recent exposure (less than 6 months) to abacavir [RR 1.70 (95 % CI 1.17–2.47)] or didanosine [RR 1.41 (95 % CI 1.09–1.82)] were both associated with an increased risk of MI. There were no significant associations between MI risk and recent exposure to any of the other NRTIs, particularly tenofovir [51]. The SMART (Strategies for Management of Anti-Retroviral Therapy) study reported that the current use of abacavir was associated with an excess risk of CVD compared with other NRTIs. Adjusted hazard ratios for clinical MI or major CVD were 4.3 (95 % CI 1.4–13.0) and 1.8 (95 % CI 1.0–3.1), respectively [53]. A Canadian study also found an increased risk of MI with any exposure to abacavir [OR 1.79 (95 % CI 1.16–2.76)] [54].

In contrast, a retrospective study using the US Veterans Administration's Clinical Case Registry showed no significant association between abacavir use and MI risk [55]. The prospective FHDH study did not find any causal relationship, as the observed association with recent exposure to abacavir or didanosine was unstable in sensitivity analysis [37]. Three meta-analyses also showed no significant association between abacavir use and MI [56–58]. In a study analyzing the MACS and Women's Interagency HIV Study cohorts found abacavir use was not independently associated with elevated inflammatory markers (high sensitivity C-reactive protein, IL-6, or D-dimer) at 6 months after initiation [59].

The differences in these studies can be explained by the presence of confounding factors, such as smoking, kidney disease, cocaine and/or intravenous drug use, and potential for selection biases. Therefore, it is not currently possible to draw any conclusions regarding a causal relationship between treatment with abacavir and the risk for developing an MI [60]. This should be taken into account when considering specific ART therapy.

Table 2 Antiretroviral drug combinations to avoid [48, 63]

Protease inhibitor	HMG-CoA reductase inhibitors to avoid
Ritonavir (RTV)	Lovastatin, simvastatin
Atazanavir (ATV)/RTV	Lovastatin, simvastatin
Darunavir (DRV)/RTV	Lovastatin, simvastatin
Fosamprenavir (FPV)/RTV	Lovastatin, simvastatin
Lopinavir/ritonavir (LPV/RTV)	Lovastatin, simvastatin
Saquinavir (SQV)/RTV	Lovastatin, simvastatin
Tipranavir (TPV)/RTV	Atorvastatin, lovastatin, simvastatin

Alternative recommendations: use pravastatin or fluvastatin, which have the least potential for drug–drug interactions (except for pravastatin with DRV/RTV, which needs careful monitoring). May use atorvastatin or rosuvastatin with caution (start with the lower possible dose and titrate based on tolerance and lipid-lowering efficacy). Avoid atorvastatin with TPV

The recommendations to initiate medications for primary prevention do not differ from those for the general population. Statins are recommended for the increased risk of CVD in the HIV infection [61], although caution needs to be taken due to possible drug interactions. For instance, certain HMG-CoA reductase inhibitors are contraindicated in combination with PIs [62]. Lower-dose fluvastatin, rosuvastatin, pravastatin, and atorvastatin are recommended to avoid the increase of drug concentration induced by cytochrome P450 (CYP)-3A4 inhibition by PIs (Table 2). Evidence is clear that ART therapy significantly decreases the overall mortality associated with HIV infection. Despite concern that certain ART agents might be associated with cardiovascular risks, the discontinuation of HIV-suppressive therapy may result in an even greater risk of disease. A potential explanation for this finding is that HIV suppression in itself is cardioprotective by reducing proinflammatory cytokines (i.e., IL-6), which play a role in arterial inflammation [20]. The SMART study found that patients receiving episodic ART were at greater risk for cardiovascular events than were those receiving continuous therapy [64]. Therefore, the prevention of CVD should be focused on continuous ART, lifestyle modification, and consideration of lipid-lowering agents.

5 Conclusion

The life expectancy of the HIV-infected population continues to improve with ART therapy and nearly matches the general population when viral load is controlled [1]. Mortality from AIDS-related illnesses is steadily decreasing, while age-related disease such as CVD continues to increase in this population [65]. More profound is the evidence to suggest that subclinical atherosclerosis is being

found in relatively young HIV-infected patients [14, 15]. HIV suppression remains the standard in CVD reduction, as studies have suggested that higher CD4 cell counts and lower HIV RNA levels are associated with a decrease in MI risk [37, 64]. Opportunities for risk factor reduction such as lifestyle modification are required, and the implementation of pharmacologic therapy such as statins can be considered.

Once primary and secondary preventions have been exhausted and further risk stratification is needed, we suggest the novel use of coronary CTA to assess atherosclerotic plaque morphology among HIV-infected patients. The ability to compare plaque morphology between HIV-infected patients and non-HIV-infected patients with similar traditional cardiovascular risk factors can be a useful tool not only in epidemiological studies but also in clinical applications. Finally, we hope continued interest remains to verify current data and associations with prospective studies involving coronary plaque analysis.

Conflict of interest M. J. Budoff is a consultant for General Electric.

A. A. Patel has no conflict of interest to declare.

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