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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

HIV-1–Associated Atherosclerosis

Unraveling the Missing Link

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ABSTRACT

Cardiovascular disease, including atherosclerosis and atherosclerosis-associated complications, is an increasing cause of morbidity and mortality in human immunodeficiency virus (HIV) patients in the post-antiretroviral therapy era. HIV alone accelerates atherosclerosis. Antiretroviral therapy; HIV-associated comorbidities, such as dyslipidemia, drug abuse, and opportunistic infections; and lifestyle are risk factors for HIV-associated atherosclerosis. However, our current understanding of HIV-associated atherogenesis is very limited and has largely been obtained from clinical observation. There is a pressing need to experimentally unravel the missing link between HIV and atherosclerosis. Understanding these mechanisms will help to better develop and design novel therapeutic interventions for the treatment of HIV-associated cardiovascular disease. HIV mainly infects T cells and macrophages resulting in the induction of oxidative and endoplasmic reticulum stress, the formation of the inflammasome, and the dysregulation of autophagy. These mechanisms may contribute to HIV-associated atherogenesis. In this review, we will summarize our current understanding and propose potential mechanisms of HIV-associated atherosclerosis.
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The current spectrum of human immunodeficiency virus (HIV) infections has dramatically shifted after the advent of effective antiretroviral therapy (ART). Although ART has successfully suppressed plasma viremia in HIV-infected (HIV^+) patients, it is not sufficient to eradicate HIV. Despite a monumental investment in vaccine development, there have been no effective vaccines to date. With the persistence of the virus and the dramatically increased life expectancy of HIV^+ patients who are stabilized on ART, the new challenge is the treatment of HIV-associated comorbidities, including HIV-associated neurocognitive disorders and cardiovascular disease (CVD) (1).

Atherosclerosis-associated CVD, including myocardial infarction (MI) and stroke, is currently one of the leading causes of mortality among HIV^+ patients (2–6). There is emerging evidence to indicate that HIV infection and subsequent inflammatory processes in humans accelerate atherogenesis. The study of simian immunodeficiency virus (SIV) infection in primates displays a similar pattern of accelerated atherogenesis, and thus serves as an important model system for HIV pathogenesis. However, the mechanisms for HIV- or SIV-induced atherogenesis remain unclear. HIV-associated atherogenesis may be further complicated by ART, drug abuse, other HIV-associated comorbidities (dyslipidemia, opportunistic infections [OIs], and renal disease), and traditional atherosclerosis risk factors (lifestyle, smoking, and so on) (2). In patients on ART, HIV infection not only mediates immune cell activation and endothelial dysfunction, but also activates an array of cellular pathways, such as inflammasome formation/caspase-1 activation, autophagy, oxidative stress (OS), and endoplasmic

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reticulum (ER) stress. These mechanisms have an established contribution in the development of traditional atherosclerosis. However, our understanding of the pathogenic roles of HIV infection, immune cell activation, and the cellular and molecular mechanisms underlying HIV-associated atherogenesis is very limited and has largely been obtained from clinical observation. In this review, we will summarize the current understanding of HIV-associated atherosclerosis, its complications, and its associated risk factors. Then, we will discuss the potential mechanisms underlying HIV-associated atherosclerosis and the use of animal models to further dissect its pathogenesis.

HIV INFECTION INCREASES ATHEROSCLEROSIS-ASSOCIATED CVD IN THE ART ERA

CVD among HIV$^+$ patients has drastically changed with the advent of ART. Early in the HIV epidemic, the predominant presentations of HIV-associated CVD were dilated cardiomyopathy, pericardial disease, pulmonary hypertension, HIV-associated malignancies, and OIs. Since the onset of ART, HIV$^+$ patients are increasingly at risk for more common cardiovascular complications associated with atherosclerosis, including MI, stroke, and heart failure (2–6).

The use of ART has increased the survival of HIV$^+$ patients to close to that of the general population. Although fewer HIV$^+$ patients are dying of AIDS-related complications, the prevalence of non-AIDS-related comorbidities, including atherosclerosis-associated CVD, remains increased compared with HIV$^-$ control subjects. CVD is the second leading cause of non-AIDS-related mortality in the United States and third in Europe among HIV$^+$ patients (6). Data suggest that HIV$^+$ patients have a higher prevalence of traditional risk factors, including hypertension, diabetes, and dyslipidemia (7). There is extensive evidence to suggest that even when controlled for these traditional cardiovascular risk factors, HIV$^+$ patients are still at a higher (1.5- to 3-fold) risk of developing CVD (8,9).

Two landmark clinical trials have provided valuable information with regard to ART and its timing in HIV infection as they relate to CVD: SMART (Strategies for Management of Antiretroviral Therapy) and START (Strategic Timing of Antiretroviral Treatment) (10). The SMART study showed that consistent use of ART in individuals with CD4$^+$ cell counts below 350/μl resulted in a decrease in AIDS-related adverse events and in CVD events (11). For those deferring or interrupting treatment, there was a 70% increased hazard of CVD events, suggesting the need for continuous ART in preventing HIV-associated chronic inflammation and mitigating CVD risk (11). In the START study, a 40% reduction in AIDS-related events was observed when ART was given immediately; however, this did not prevent CVD events (12). Although both the SMART and START studies support the notion that ART based on stricter CD4$^+$ thresholds will likely result in decreased CVD rates, ART is not sufficient to prevent CVD risk in HIV$^+$ patients. Data from the VACS (Veterans Aging Cohort Study) cohort showed that HIV$^+$ patients were at a higher risk of acute MI (hazard ratio: 1.48), even after adjustment for Framingham risk factors, comorbid conditions, and drug use (8). Thus, non-ART interventions are needed to decrease CVD risk among HIV$^+$ populations and to improve immune function.

HIV$^+$ individuals known as "elite controllers," that is, those who have undetectable plasma viral loads without ART, have increased coronary atherosclerosis and high immune activation, including elevated plasma soluble CD163 (sCD163) (13). In another cohort, HIV$^+$ elite controllers had a higher median carotid intima-media thickness (CIMT) than that observed in uninfected subjects, even after adjustment for traditional cardiovascular risk factors (14). These studies reinforce the role of inflammation, and not ART or virus, as the key mediator of HIV-associated CVD.

HIGH-RISK PLAQUE FEATURES IN HIV CVD

The presence of noncalcified plaques detected by coronary computed tomography angiography (CTA) in the general population is associated with higher rates of acute coronary syndrome when compared with mixed and calcified plaques (15–17). These noncalcified plaques in HIV$^+$ patients represent an early stage of atherosclerosis, and are more prone to rupture and thrombus formation compared with calcified plaques, likely leading to HIV-associated acute coronary syndrome (15). In well-controlled HIV$^+$ patients, studies show a higher prevalence of subclinical coronary atherosclerosis (16,17) and a greater burden of coronary atherosclerotic plaque, particularly noncalcified inflammatory plaques, in HIV$^+$ young men than in HIV$^-$ individuals with similar cardiovascular risk factors (16). Imaging studies using coronary CTA have shown that HIV$^+$ men have a 59.0% prevalence of coronary atherosclerosis compared with 34.4% in HIV$^-$ control subjects (16,18). In addition to HIV$^+$ men, HIV$^+$

ABBREVIATIONS AND ACRONYMS

ART = antiretroviral therapy
CVD = cardiovascular disease
ER = endoplasmic reticulum
HIV = human immunodeficiency virus
HIV$^+$ = human immunodeficiency virus-infected
MI = myocardial infarction
OS = oxidative stress
oxLDL = oxidized low-density lipoprotein
ROS = reactive oxygen species
SIV = simian immunodeficiency virus