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iREVIEWS

STATE-OF-THE-ART PAPER

Arterial Disease in Patients With Human Immunodeficiency Virus Infection

What Has Imaging Taught Us?

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With advances in antiretroviral therapy (ART), individuals with human immunodeficiency virus (HIV) infection are living longer and increasingly die of non–HIV-related diseases, such as cardiovascular disease (CVD). Several observational studies suggest that HIV-infected patients on ART are at increased risk of CVD; however, the precise mechanisms underlying the association between HIV infection and CVD risk are uncertain. Atherosclerosis and arterial disease in HIV-infected individuals is a multifactorial process with several potential targets for research and therapeutic intervention. This paper critically reviews the contributions of imaging to our understanding of arterial disease, atherosclerosis, and CVD risk in HIV-infected individuals. In general, the findings of studies using carotid ultrasound, coronary computed tomographic angiography, and aortic positron emission tomography agree with those from observational studies of CVD events and suggest that HIV infection is associated with an increased risk of CVD. Observational studies of CVD outcomes and studies using carotid intima-media thickness suggest that there is a moderate increase in CVD risk related to HIV serostatus. Less can be said about the role of ART and specific ART therapies in CVD risk, mainly because imaging studies have had serious methodological limitations that diminish their generalizability. Brachial artery reactivity testing has been especially useful for elucidating the arterial pathophysiology of HIV infection and its treatments, as well as the arterial effects of interventions for treating HIV and dyslipidemia. Aortic positron emission tomography has been especially useful for evaluating arterial inflammation. Coronary artery calcium has not proven to be a useful marker of subclinical atherosclerosis in HIV-infected individuals. Imaging studies support the intriguing hypothesis that persistent inflammation and immune dysregulation contribute to increased CVD risk among treated and suppressed patients with HIV infection. (J Am Coll Cardiol Img 2014;7:515–25) © 2014 by the American College of Cardiology Foundation

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With the advent of potent combination antiretroviral therapy (ART), patients with human immunodeficiency virus (HIV) infection are living longer and increasingly are afflicted with chronic diseases that are common among individuals without HIV infection, such as cardiovascular disease (CVD), cancer, liver disease, and lung disease (1,2). Among HIV-infected individuals in the United States, CVD is the leading non–HIV-related cause of death, although in Europe, CVD death follows cancer and liver disease among the leading causes of mortality in this patient population (1,2). Several observational studies suggest that HIV-infected patients on ART are at increased CVD risk (3–8); however, the precise mechanisms underlying the association between HIV infection and CVD risk are uncertain (8,9). This paper critically reviews the contributions of imaging to our current understanding of arterial disease, atherosclerosis, and CVD risk in HIV-infected individuals.

ABBREVIATIONS AND ACRONYMS

AIDS = acquired immunodeficiency syndrome

ART = antiretroviral therapy

BART = brachial artery reactivity testing

CAC = coronary artery calcium

CTA = computed tomography angiography

CVD = cardiovascular disease

FMD = flow-mediated vasodilation

HIV = human immunodeficiency virus

IMT = intima-media thickness

MI = myocardial infarction

PET = positron emission tomography

HIV and CVD Risk

Some of the increased CVD risk associated with HIV infection is due to an increased burden of traditional risk factors such as cigarette smoking, which is 2 to 3 times more prevalent in individuals with HIV infection (10,11), and risk factors related to use of protease inhibitors, such as dyslipidemia and insulin resistance (11). In the Data Collection on Adverse Events of Anti-HIV Drugs study, exposure to protease inhibitors was an independent predictor of myocardial infarction (MI); however, the major predictors were established CVD, current or former smoking, and male sex, as well as increasing age and a family history of heart disease (12). In fully-adjusted models, diabetes mellitus, higher total cholesterol, and lower high-density lipoprotein cholesterol levels also were independent predictors of MI (12). In a recent observational study from the Veterans Aging Study Virtual Cohort, HIV-infected veterans (mostly men) had nearly a 50% increased relative risk of acute MI compared with those without HIV, after adjustment for traditional risk factors. In addition to HIV serostatus, other independent risk factors for incident MI were increasing age, hypertension, increasing low-density lipoprotein cholesterol, cigarette smoking, and renal disease (8). Thus, as in HIV-uninfected individuals, traditional risk factors powerfully predict CVD in those with HIV infection. However, hepatitis C coinfection, anemia, low CD4+ T-cell counts, and high HIV-1 ribonucleic acid (RNA) levels also predicted MI risk, suggesting that certain characteristics of individuals with HIV infection, in addition to traditional risk factors, may contribute to increased CVD risk (8). Certain protease inhibitors, such as lopinavir/ritonavir, indinavir, and amprenavir/fosamprenavir, have been associated with increased MI risk and certain nucleoside reverse transcriptase inhibitors, most notably abacavir and possibly didanosine, also may increase MI risk, although data are conflicting (13–15). The impacts of newer classes of antiretroviral agents such as CCR5 inhibitors and integrase inhibitors, which appear to have fewer lipid effects on CVD risk, are largely unknown at this time.

Although the use of ART has been associated with increased CVD risk, 1 large observational study demonstrated that HIV treatment did not increase short-term CVD risk (16). A growing body of evidence suggests that persistent inflammation and disordered immune regulation—which are present even among effectively-treated HIV-infected individuals—may increase CVD risk (17). In an observational study, the odds ratio for acute MI was >4-fold higher among patients with HIV and elevated C-reactive protein compared with those without HIV and with normal C-reactive protein (18). In the SMART (Strategies for Management of Anti-Retroviral Therapy) study, interruption of ART in individuals with chronic HIV infection was associated with high levels of interleukin-6 and D-dimers, biomarkers that were associated independently with all-cause mortality and CVD events; furthermore, ART initiation at higher CD4+ T-cell counts reduced serious non–acquired immunodeficiency syndrome (AIDS) events, which were mostly due to CVD, in a subset of participants who were ART-naive or had not been receiving ART for at least 6 months before participation (19,20). Indeed, although inflammation and immune dysregulation play key roles in accelerating atherosclerosis in individuals without HIV (21,22), the causes of ongoing inflammation and immune dysregulation in individuals with treated HIV infection appear to be more complicated than in individuals without HIV, whose inflammation is driven, in large part, by visceral adiposity and the metabolic syndrome (17). Atherosclerosis and arterial disease in HIV-infected individuals clearly is a multifactorial process (Fig. 1) with several potential targets for research and therapeutic intervention.

The extent by which HIV infection increases CVD risk beyond traditional risk factors and the

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