

# Association Between Human Immunodeficiency Virus Infection and Cardiovascular Diseases

## Finding a Solution to Double Jeopardy

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**Combination antiretroviral therapy (ART)** has affected the lives of human immunodeficiency virus (HIV)-infected individuals who have access to treatment and continues to narrow the gap in life expectancy between persons with HIV and the general population. Unfortunately, concomitant with this favorable outcome, noninfectious causes of morbidity and mortality, particularly cardiovascular disease (CVD), have had a disproportionately negative affect on ART-treated individuals with HIV, creating a “double jeopardy” phenomenon.

Shortly after recognizing the benefits of combination ART in suppressing HIV replication, restoring immune function, and prolonging life, physicians raised concerns about possible undesired toxicities of the therapy. The appearance of dyslipidemia and lipodystrophy highlighted the issue of increased CVD in HIV-infected individuals. Large cohort studies identified an increased risk of myocardial infarction (MI), seemingly in association with long-term ART and increased rates of MI in HIV-infected individuals compared with uninfected contemporaries.<sup>1,2</sup> However, the overall advantage of ART remains clear because large randomized clinical trials have shown that early and continuous administration of ART confers significant survival benefits, even when accounting for an increased rate of CVD.<sup>3,4</sup>

Traditional risk factors for CVD, exposure to ART, and the inherent immune activation associated with HIV infection all contribute to the increased incidence of CVD and may represent targets for intervention. Traditional CVD risk factors, such as hypertension, diabetes, smoking, and dyslipidemia, are increased among HIV-infected individuals and play a role in the development of CVD.<sup>2</sup> For example, rates of smoking are high among HIV-infected individuals, often 2 or 3 times that of the general population. In this context, current and past smoking doubled the risk of incident MI.<sup>1</sup> Encouraging trends showing a reduction in smoking in the general population are also reflected in persons with HIV, and observational cohorts have shown significant reductions among HIV-infected individuals in MI, CVD, and mortality following cessation of smoking.<sup>5</sup>

Hepatitis C virus (HCV) coinfection is also common in HIV-infected individuals and has been shown to increase the risk of CVD in these patients independent of other risk factors.<sup>6</sup> Anti-HCV therapy has reduced the incidence of cardiovascular complications in HCV monoinfected patients and may provide a similar benefit to HIV coinfecting patients. Future stud-

ies evaluating the long-term health benefits of newer HCV treatment regimens will illuminate the potential cardiovascular benefits of HCV clearance in the high-risk HIV-infected population.

Certain antiretroviral agents have been linked to CVD and there have been efforts to minimize adverse effects through selection of ART regimens as well as active development of equally potent antiretroviral agents with more favorable toxicity profiles. First-line ART recommendations now provide options that minimize the use of agents implicated in increased CVD risk. Prospective research initiatives, such as the Data Collection on Adverse Events of Anti-HIV Drugs, a multinational cohort study that focuses on recognizing adverse events such as MI, will provide valuable data on the future relationship between incident CVD, advances in ART, and targeting CVD risk reduction in HIV infection.

Independent of traditional risk factors and exposure to ART, HIV infection alone has been shown to increase the risk of CVD. Chronic inflammation and immune activation associated with HIV infection are widely felt to be key mediators of end-organ injury, including atherosclerosis, and appear to play a role in CVD even when HIV replication is seemingly well-controlled when receiving ART. Human immunodeficiency virus-infected individuals have significantly increased levels of inflammatory biomarkers, such as C-reactive protein, interleukin 6, D-dimer, and cystatin C, which have all been associated with CVD risk.<sup>7</sup> Additionally, arterial inflammation in HIV has been associated with increased plasma levels of soluble cluster of differentiation 163, a monocyte/macrophage marker linked to low-grade inflammation and atherosclerosis.<sup>8</sup> Novel imaging techniques, such as coronary computed tomographic angiography and flourodeoxyglucose positron emission tomography techniques, permit detailed quantification of coronary plaque and arterial inflammation associated with CVD. Using flourodeoxyglucose positron emission tomography, Subramanian et al<sup>8</sup> completed a cross-sectional study of HIV-infected individuals who were receiving ART without known CVD and found increased arterial inflammation in HIV-infected individuals compared with control individuals. In this regard, inflammatory biomarkers and advances in cardiac imaging can be used as research tools to delineate the role of immune activation in the development of atherosclerosis in HIV-infected individuals and may improve our ability to predict myocardial events related to atherosclerosis in this unique population.

Because of the underlying mechanisms of the disease, methods of predicting CVD in the general population may underestimate the degree of atherosclerosis among HIV-infected persons and inadequately identify those individuals who would benefit from primary prevention. In 2013, the American College of Cardiology and American Heart Association (ACC-AHA) released new guidelines on treating elevated cholesterol levels to reduce atherosclerotic cardiovascular risk in adults in the general population. These guidelines have not been thoroughly studied in the HIV-infected population and take into account only traditional risk factors for CVD. A study by Zanni and colleagues<sup>9</sup> using coronary computed tomographic angiography in HIV-infected patients without known CVD showed that based on the 2013 ACC-AHA guidelines, only 26% of individuals with high-risk morphology coronary plaque would fulfill the criteria for statin therapy. In this issue of *JAMA Cardiology*, Feinstein et al<sup>10</sup> prospectively evaluated the 2013 ACC-AHA guidelines and compared them with 2 HIV-specific data-derived models. The authors demonstrated that while the 2013 ACC-AHA guidelines were able to adequately discriminate MI risk in general, they were less effective in doing so among black men and women and white women. Additionally, the ACC-AHA guidelines underpredicted the number of MIs in low- to moderate-risk patients. Using models that included HIV-specific data factors did not improve predictive performance. Further studies are needed to evaluate the 2013 ACC-AHA guidelines and other novel prediction models in the HIV-infected population, specifically in groups in which the number of MIs was consistently underpredicted.

Lipid-lowering agents, such as statins, are used to mitigate CVD risk in the general population and have a wide range of immunomodulatory effects that may prove particularly beneficial for individuals with HIV. Administrative health care database research indicates decreased rates of MI in HIV-infected patients were associated with increased prescribing of lipid-lowering therapy between 1996 and 2011.<sup>11</sup> To further investigate the role of statins in decreasing CVD risk in HIV-infected individuals, a clinical trial funded by the National Institutes of Health called REPRIEVE began in 2015. This study will evaluate the effects of statin use on CVD in a diverse cohort of HIV<sup>+</sup> patients, including women and African American individuals whose risk of CVD is more difficult to predict using conventional guidelines. Researchers also hope to identify specific inflammatory biomarkers and imaging correlates that will provide a better understanding of the pathophysiologic mechanism whereby HIV and its associated immune activation contributes to excess CVD and how statins mitigate this risk.

As life expectancy in patients with HIV receiving ART continues to approach that of the general population, CVD will play an increasing role in morbidity and mortality. Further studies are needed to elucidate the mechanisms of CVD in the HIV-positive population and to develop comprehensive management strategies that appropriately identify and treat those at risk of poor cardiovascular outcomes, thus mitigating the potential for the double jeopardy of HIV infection and increased risk of CVD.

#### ARTICLE INFORMATION

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