Assessing Risk for Cardiovascular Disease in Patients With Human Immunodeficiency Virus

Why it Matters

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Physicians who regularly see patients with human immunodeficiency virus (HIV) are commonly asked the prognosis of someone with HIV infection today. Although the estimates vary depending on the CD4 cell count and age at diagnosis, studies suggest that survival for most people with HIV is currently measured in decades, not years. For example, in one study from Denmark the estimated median survival from age 25 in HIV-infected patients without hepatitis C was 39 years. Indeed, these per-person gains in survival accrued from antiretroviral therapy (ART) are of a magnitude unmatched in treatment of other diseases.

Effective ART has therefore led to a marked shift in the age distribution among people with HIV in the United States, and it is estimated that by 2015 more than half will be over 50 years of age. Given this improved survival, it is not surprising that people with HIV in whom therapy is successful are increasingly at risk for diseases of aging, in particular cardiovascular, renal, and “non-AIDS” neoplastic diseases. Furthermore, these complications seem to be occurring at higher rates than in age-matched control individuals, likely accounting for the fact that survival of HIV patients still does not match that in the uninfected population, even though viral replication can be controlled in the vast majority of patients in care. In addition, clinical observations from clinicians and patients, some of which have prominently appeared in the lay press, cite a process of accelerated aging and debility among those with HIV despite effective treatment.

With cardiovascular disease (CVD) in particular, several studies have documented that HIV itself is a potent risk factor. In one cross-sectional study of 433 HIV-positive patients and 5749 uninfected control individuals, carotid-artery intima-media thickness was significantly greater in HIV-positive patients than in the control individuals even after adjustment for demographic variables and traditional CVD risk factors. Indeed, the independent effect of HIV appeared to be of a similar magnitude to that of standard cardiac risk factors. An analysis of acute myocardial infarctions in a large healthcare system found that the rate of acute myocardial infarction among individuals with HIV was nearly 2-fold higher than in those without HIV, even after adjustment for age, gender, race, hypertension, diabetes mellitus, and dyslipidemia. What might be the explanation for the increased incidence of CVD among people with HIV? Several factors are likely contributing: (1) Patients with HIV infection have a high rate of other behavioral and demographic cardiac risk factors, especially smoking and lower socioeconomic status; (2) both HIV infection and several antiretroviral agents are associated with potentially atherogenic dyslipidemia, and some antiviral agents may worsen cardiovascular risk independently of their effect on lipids; and (3) HIV infection is associated with abnormal levels of both inflammation and immune activation, even among those who are asymptomatic and have relatively normal CD4 cell counts.

Strong support for the potentially deleterious effects of inflammation on outcomes in HIV comes from a comparative study of continuous versus intermittent ART. In the Strategies for Management of ART (SMART) study, patients with CD4 cell counts >350 cells/mm and no active symptoms of HIV disease were randomized to continuous ART or intermittent treatment, with therapy in the latter group to be resumed if the CD4 cell count fell to 250 cells or less. The study was stopped early because of an increased risk of both AIDS and non-AIDS events in those receiving intermittent treatment. Analysis of stored samples showed that the risk of all-cause mortality was strongly associated with levels of interleukin-6 and D-dimer, and that these levels were markedly higher in those receiving intermittent therapy. Unfortunately, although ART may reduce some markers of inflammation, levels of high-sensitivity C-reactive protein, interleukin-6, D-dimer, and cystatin-C were higher in treated HIV patients than in uninfected age-matched control individuals. Similarly, a prospective clinical trial comparing different treatment regimens showed that levels of high-sensitivity C-reactive protein were not reduced by durably suppressive ART over 96 weeks.

Inasmuch as heart disease is an increasing problem for HIV patients, an important clinical and research challenge is to identify potentially modifiable risk factors. In this issue of Circulation, Choi and colleagues evaluated data from the national registry of HIV-infected patients in the Veterans Health Administration, the largest provider of HIV care in the United States, to explore the association of kidney disease
with incident atherosclerotic CVD and heart failure.\textsuperscript{18} Kidney function was assessed using the Modification of Diet in Renal Disease formula to estimate glomerular filtration rate (GFR), and albuminuria was defined by urine dipstick measurements.

The study included over 17,000 patients, with 833 atherosclerotic and 370 heart failure endpoints. Kidney disease was strongly associated with both CVD and heart failure: those with eGFR $<30$ mL·min$^{-1}$·1.73 m$^{-2}$ and albuminuria $\geq 100$ mg/dL had an $\approx 6$-fold higher incidence of atherosclerotic CVD than did patients with no signs of kidney disease, and in this highest-risk group the incidence of heart failure was $>30$-fold higher. In multivariable models, with adjustment for well-recognized cardiovascular risk factors as well as HIV RNA and CD4 cell count, both eGFR and albuminuria remained independently associated with the composite outcome of either atherosclerotic CVD or heart failure.

Strengths of this study include its large size and inclusion of a population with universal access to care and treatment. In addition, the use of laboratory markers of kidney disease that are readily available to clinicians increases the likelihood that the findings will have practical applications. Indeed, measurement of serum creatinine (needed to calculate the eGFR by Modification of Diet in Renal Disease) and an annual urinalysis are already recommended as part of routine care.\textsuperscript{19}

Potential limitations of this study include the small proportion of women in the cohort, limiting generalizability, and the inability to exclude residual confounding. These issues notwithstanding, there is little reason to doubt the results. Kidney disease is well known in HIV-uninfected populations to be strongly associated with both CVD and heart failure, and the effect would plausibly be even stronger in patient populations already at greater risk for heart disease, such as those with HIV. In addition, the results offer a possible avenue for therapeutic intervention (for example, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) to improve both renal and cardiac outcomes.

The importance of this study is amplified by the high rate of kidney disease in patients with HIV. Kidney function is abnormal in up to 30% of patients with HIV, owing to a variety of factors, including HIV itself, the nephrotoxic effect of certain antiviral drugs, and the disproportionate burden of HIV infection among individuals of African descent, who are known to have increased susceptibility to HIV nephropathy in particular and renal disease in general.\textsuperscript{20} The results also provide a potential epidemiological explanation for the observed association between use of the antiretroviral agent abacavir and cardiovascular risk,\textsuperscript{21} inasmuch as abacavir is preferentially prescribed in place of tenofovir (which has potential nephrotoxicity) for individuals with abnormal renal function.

In summary, the study by Choi et al is a timely example of the burgeoning field in HIV medicine that is exploring long-term noninfectious complications. For those of us who cared for patients with HIV before 1996, when the average life expectancy for individuals with advanced AIDS was $<18$ months,\textsuperscript{22} the very existence of this field represents both a therapeutic miracle and a substantial clinical and research challenge.
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