Metabolic and Cardiovascular Complications in HIV-Infected Patients: New Challenges for a New Age

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In the more than 30 years since AIDS was first recognized, there has been a sea change in the challenges facing human immunodeficiency virus (HIV)-infected patients and their caregivers. Now that antiretroviral therapy (ART) suppresses viral replication and prevents AIDS-related complications in the majority of HIV-infected patients [1], different clinical problems from those faced in the first decades of the epidemic have emerged. In particular, chronic conditions typical of aging, including cardiovascular disease, diabetes, bone fractures, and malignancies, are occurring in HIV-infected patients at a higher rate and at an earlier age than in uninfected individuals [2]. To provide an overview of the current state of our knowledge and a guide to future approaches for meeting these challenges, the Harvard University Center for AIDS Research organized a multidisciplinary symposium on metabolic and cardiovascular complications in HIV-infected patients; this supplement is an outgrowth of presentations made at that symposium.

Among the most important clinical problems facing HIV-infected patients is a rising rate of cardiovascular disease. The World Health Organization projects that ischemic heart disease will be the leading cause of death in the general population in both low- and high-income countries by 2030 [3]. A number of studies, summarized by Triant, have shown that HIV-infected patients have higher rates of cardiovascular disease than do uninfected individuals, even after accounting for traditional risk factors. This excess risk may be due in part to toxicity from particular antiretroviral medications, such as some protease inhibitors and abacavir. However, recent studies have suggested that uncontrolled HIV replication itself is associated with cardiovascular disease and that, on balance, ART may be cardioprotective—a realization that led to a push for earlier ART in patients at high risk for coronary artery disease [4].

Understanding which HIV-infected patients are at the highest risk for cardiovascular events, therefore, is important for targeting interventions to reduce the burden of disease. The strengths and shortcomings of current cardiovascular risk estimation models, such as the venerable Framingham risk score, are expertly discussed by D’Agostino, one of the fathers of this important tool. His conclusion: Although the Framingham risk function provides some help in predicting the risk of cardiovascular disease in HIV-infected patients—and indeed for the time being it should be used in deciding which patients to target for risk-reduction interventions—there is a need for new assessment tools specifically tailored to HIV-infected patients.

The reason that cardiovascular prediction tools developed for the general population are not adequate for HIV-positive patients may be because of unique factors in the infected population that contribute to cardiovascular disease. As reviewed by Stanley and Grinspoon, there is a high rate of metabolic abnormalities in HIV-infected patients, including body composition changes, dyslipidemia, insulin resistance, and diabetes—all of which may contribute to cardiovascular disease. A deeper
understanding of these cardiometabolic abnormalities has led to new treatment strategies, including use of agents that improve insulin resistance, aggressive management of dyslipidemia, and therapies that target increased abdominal fat accumulation, such as the recently approved growth hormone–releasing factor tesamorelin.

Although metabolic abnormalities underlie much of the increased risk of cardiovascular disease in HIV-infected patients, it is difficult to disentangle the relative roles of several potential contributors, such as antiretroviral medications, viremia, immunodeficiency, and abnormal immune activation. One approach is to study HIV elite controllers (infected patients who maintain undetectable plasma viral loads without taking ART). The finding that elite controllers have more atherosclerosis than HIV-negative patients [5] suggests that factors other than ART, detectable viremia, or overt immunodeficiency may contribute to excess cardiovascular risk in infected patients—and implies that other HIV-related factors, such as elevated immune activation and inflammation, may be playing an important role [6]. This insight fits nicely with the growing recognition that chronic inflammation and abnormal metabolism are integral to the development of atherosclerosis in HIV-negative individuals. As summarized by Lo and Plutzky, atherosclerosis is the result of a complex interplay among the endothelium, inflammatory cells (monocytes, macrophages, T cells, and B cells), and metabolic factors, such as lipids.

In addition to these mechanisms, there are unique immunologic factors—reviewed by Hsue et al, Deeks, and Hunt et al—that may contribute to the pathogenesis of cardiovascular disease in HIV-infected patients. Patients who are not receiving ART have high levels of immune activation, which are due at least in part to ongoing viral replication. Although suppression of viral replication by ART reduces immune activation, T-cell activation levels remain elevated in treated HIV-infected patients compared with uninfected individuals [7,8]. Moreover, elevated levels of inflammatory biomarkers are associated with cardiovascular disease and mortality in infected patients. The relative roles of microbial translocation, copathogens (such as cytomegalovirus), and residual HIV replication in maintaining this inflammatory state need to be determined. Interventions aimed at each of these potential pathways are currently in clinical trials.

Finally, lest one think that metabolic complications of HIV infection are limited to the cardiovascular system, Harris and Brown highlight the fact that bone loss is accelerated in HIV-infected patients, which contributes to higher fracture rates in this population. As with cardiovascular disease, bone disease in HIV-infected patients has multiple mechanisms, including high rates of traditional risk factors (smoking in particular) and effects on bone of the virus itself, immunodeficiency, and antiretroviral medications, most notably tenofovir. Studies of bone disease in HIV elite controllers might help tease out the relative contributions of these factors. For now, screening for and treatment of osteoporosis using standard medications are the mainstays of clinical care.

In sum, this supplement highlights current challenges in the management of HIV-infected patients. Metabolic and cardiovascular complications of HIV infection will grow in importance as HIV-infected patients live longer and grow older. By 2015, it is estimated that more than half of those living with HIV infection in the United States will be aged >50 years, and millions of infected people around the world are rapidly gaining access to lifesaving ART. Immediate attention to the fundamentals of preventive care for cardiovascular and metabolic complications is essential to improving the lives of HIV-infected patients. Future research on metabolic and cardiovascular complications in HIV-infected patients may provide a new understanding of these diseases in both infected and uninfected populations.

Notes

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