Perspective

Metabolic Complications of HIV Infection and Its Therapies

Non-AIDS morbidity and mortality are increasingly common in the HIV-infected population. Chronic inflammation and immunosenescence result in early onset of conditions associated with aging, including atherosclerosis and frailty. Risk for non–AIDS-related morbidity is also related to the metabolic effects of antiretroviral therapy and the increased prevalence of traditional cardiovascular and other risk factors in the HIV-infected population. Risk reduction is centered on maintaining full viral suppression and aggressively implementing measures to reduce standard modifiable risk factors. This article summarizes a presentation by Edgar Turner Overton, MD, at the IAS–USA continuing education program held in New York, New York, in October 2013.

Keywords: cardiovascular disease, chronic inflammation, diabetes, frailty, HIV, immunosenescence, non-AIDS morbidity, obesity

As of 2013, approximately 90% of HIV-infected patients engaged in care in Ryan White HIV/AIDS Program clinics throughout the United States are on fully suppressive antiretroviral therapy, with viral replication being fully suppressed in most individuals. As AIDS-related mortality has decreased, a substantial challenge facing practitioners is the increasing prevalence of non-AIDS morbidity and mortality in HIV-infected patients. Diseases that are increasingly common in the HIV-infected population include diabetes, cardiovascular disease, kidney problems, cognitive impairment, osteoporosis, hypogonadism, and frailty. These conditions, many of which are associated with aging in the general population, appear to occur prematurely or at an accelerated rate in the HIV-infected population. An example of the shift from AIDS-related to non–AIDS-related mortality is provided by a 2006 ART-CC (Antiretroviral Therapy Cohort Collaboration) study showing that the frequency of opportunistic infection as cause of death in HIV-infected patients decreased from 32% in the pre–potent antiretroviral therapy era to 19% thereafter, with the proportion of deaths increasing from 3.2% to 9.9% for hepatitis and liver disease, from 2.5% to 4.9% for non-AIDS malignancies, and from 1.3% to 4.3% for cardiovascular disease and diabetes.[1,2]

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Atherosclerotic Heart Disease

Although there has been much debate about cardiovascular risk in HIV infection, the preponderance of data points to a 1.5- to 2-fold higher risk of myocardial infarction (MI) or other cardiovascular death in HIV-infected persons than in HIV-uninfected persons. A study by Triant and colleagues, for example, showed a relative risk for MI of 1.75 in HIV-infected patients, and as shown in Figure 1, the MI event curves for the HIV-infected and HIV-uninfected groups separate at an early age, with the difference increasing with advancing age.[3] These findings suggest that there is accumulating risk of MI in HIV-infected patients, likely representing a combination of factors that includes prolonged exposure to antiretroviral therapy and presence of other HIV-related comorbidities. The increasing frequency of cardiovascular disease with aging is of particular concern given the estimate that 50% of HIV-infected patients will be older than 50 years by 2015.[4]

Modifiable risk factors for cardiovascular heart disease include inactivity and poor diet, abdominal obesity, smoking, hypertension, hyperglycemia, insulin resistance, and lipid abnormalities. In addition to these risk factors, HIV-infected patients are subject to risk posed by the infection itself and by potential adverse metabolic effects of antiretroviral therapy, both of which can contribute to cardiovascular disease and other non–AIDS-defining comorbidities. HIV infection leads to chronic immune activation and inflammation, alters lipoproteins to produce an atherogenic lipid profile, induces a hypercoagulable state, and results in CD4+ T cell depletion and immunosenescence. Antiretroviral therapy has some toxicity, including insulin resistance, an atherogenic lipid

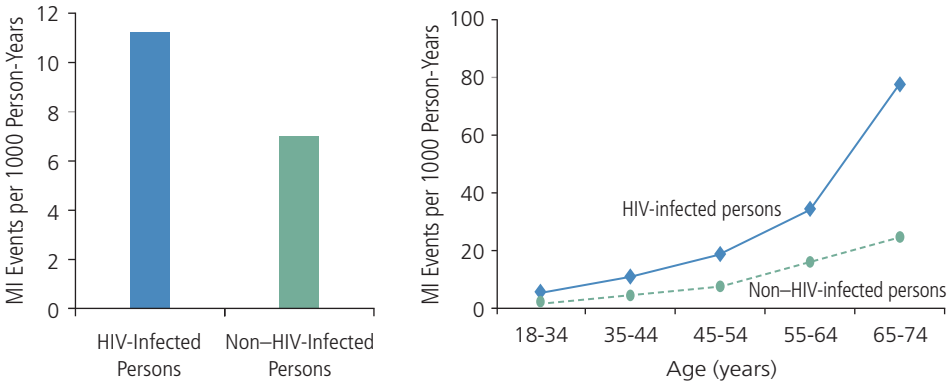

Figure 1. Rates of myocardial infarction (MI; left) and rates of MI by age (right) in HIV-infected and HIV-uninfected persons. Adapted from Triant et al.[3]

profile, mitochondrial toxicity, and body fat changes. Uncontrolled HIV viremia leads to endothelial dysfunction mediated by immune activation that can be partially offset by antiretroviral therapy.

Thus, the first step in addressing cardiovascular risk in HIV-infected patients is to suppress viral replication with antiretroviral therapy. However, even with suppression of viremia, residual vascular inflammation poses a risk, including an increase in the number of metabolically active macrophages and the frequency of noncalcified, metabolically active, rupture-prone plaques.[5,6] These plaques have been observed in HIV-infected patients at a median age of 40 years to 45 years and differ from the more stable calcified plaques typically seen in aging.

To address modifiable risk factors, practitioners should focus on the ABCD'S of cardiovascular risk management: aspirin, blood pressure, cholesterol, diabetes, and smoking. An example of how efforts to reduce modifiable risk factors may be resulting in disease reduction is provided by recent data from the Kaiser Permanente health care system in California.[7] During the years 2002 through 2003, the crude rate of hospitalization for MI in HIV-infected members reached a high of 3.7 per 1000 person-years, statistically significantly higher than the rate of 1.7 per 1000 person-years in HIV-uninfected members ($P < .001$). Data from 2006 through 2008 indicate that the rate decreased to 2.5 per 1000 person-years in HIV-infected members, which is not statistically significantly different from the rate of 2.0 per 1000 person-years in the HIV-uninfected population ($P = .088$) and marks the first period since before 1996 in which there was no statistically significant difference in the hospitalization rates for MI among the 2 groups. Over the same period of 1996 through 2008, the use of lipid-lowering therapy in HIV-infected members on antiretroviral therapy increased from virtually 0% (in 1996 and 1997) to greater than 30% in patients on combination antiretroviral regimens.

Frailty

Frailty is characterized by unintentional weight loss, weakness (typically manifested as reduced grip strength or proximal muscle weakness), symptoms of exhaustion, slowness (measured as slowing on a timed walk), and decreased physical activity. A diagnosis of frailty is commonly based on the presence of at least 3 of these 5 associated characteristics.[8] Frailty typically occurs as part of the aging process late in the lifetime of a person or animal. It is considered an end-stage process and consists of loss of functional homeostasis (eg, immune and endocrine dysregulation), leaving individuals unable to recover fully after stressors and predisposing them to poor health outcomes, including increased morbidity and mortality.

In conditions of heightened inflammation, such as rheumatoid arthritis and HIV infection, what appears to be accelerated aging occurs, with those affected becoming frail at earlier ages than those without such conditions. For example, a 2011 MACS (Multicenter AIDS Cohort Study) report demonstrated that frailty (defined as the presence of at least 3 of the 5 above conditions) was present in 14.8% of HIV-infected men versus 8.1% of matched HIV-uninfected controls aged 50 years to 59 years, 19.9% versus 10.0% of those aged 60 years to 69 years, and 33% versus 23% of those older than 69 years.[9]

With regard to similarities and differences in frailty characteristics among the elderly and HIV-infected patients, prevalence in the elderly increases from approximately 3% to 5% at age 65 years to 32% at age 90 years, whereas prevalence in HIV-infected groups has been reported at 5% to 20% at median ages of between 40 years and 50 years. In the elderly, prevalence is greater among women than men and greater among Hispanics and US blacks than among US whites, with the lowest prevalence found among European whites. In contrast, there do not appear to be differences in prevalence by race or sex among HIV-infected persons.[10-13] In the frail elderly, there is increased comorbidity, including cognitive impairment and depression, postoperative risk, falls, cross-infection, polypharmacy, social isolation, hospitalization, institutionalization, and high mortality risk. There is similar increased morbidity, including cognitive impairment and depression, in HIV-associated frailty, as well as increased nonelective hospitalization, duration of inpatient stay, and unemployment.[10,14]

Inflammation and immunosenescence have been associated with frailty in the geriatric and HIV-infected populations. In the elderly, residual, or sterile, inflammation occurs when inflammatory response results in terminally differentiated T cells with a senescent profile. Accumulation of these T cells results in a proinflammatory milieu that is nonresponsive to new antigen challenges. In the elderly, this process has been associated with chronic viral infection, most notably cytomegalovirus infection. What may be occurring in the HIV-infected population is chronic inflammation and an acceleration of immunosenescence that result in a frailty phenotype.

Obesity and Inflammation

Obesity also contributes to systemic inflammation. As people become obese, fat cells in abdominal and visceral fat increase in size and begin to secrete cytokines that recruit macrophages and activated T cells into the adipose tissue. Inflammation results from the accumulation of these cells and the induction of apoptosis of the fat cells by activated T cells. The fat cells then release proinflammatory cytokines and oxidized lipoproteins that contribute to chronic inflammation.

Reducing Inflammation

Interventions to reduce inflammation that are of particular importance in HIV-infected patients are to maintain maximum viral suppression with antiretroviral therapy, stop smoking, maintain normal weight or lose at least 5% to 10% of body weight if overweight, exercise, consume a healthy diet, reduce alcohol intake, and avoid illicit drug use.

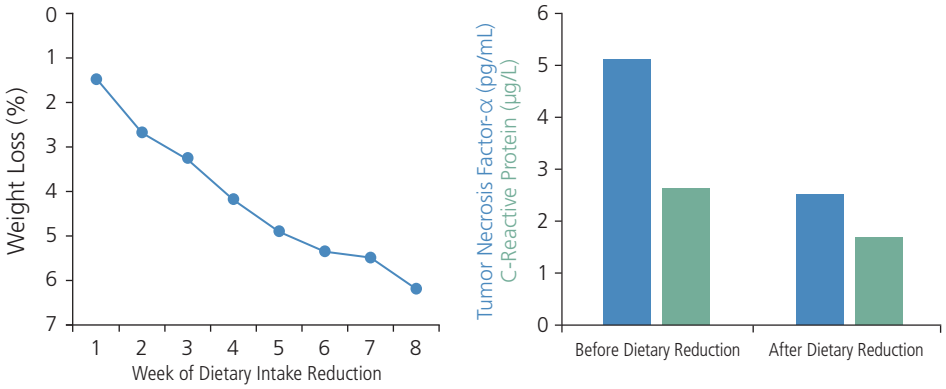

Figure 2. Effect on weight (left) and inflammatory markers (right) of reducing dietary intake by 500 calories per day for 8 weeks in obese persons. Adapted from Hermsdorff et al.[15]

Figure 2 shows the marked effect that a reduction in dietary intake of 500 calories per day can have on body weight and markers of inflammation in obese persons. After 8 weeks, participants lost 6% of body weight and showed a marked decline in levels of the markers of systemic inflammation tumor necrosis factor-α and C-reactive protein.[15]

Calorie-dense foods and portion distortion are now major problems in America. Rather than eating a 600-calorie, quarter-pound hamburger, many Americans eat a 1300-calorie, half-pound hamburger with supersized fries. Twenty years ago, a plain bagel was 3 inches in diameter and contained 140 calories, but today's bagel is 6 inches across and contains 350 calories. Figure 3 shows the increasing prevalence of obesity and diabetes in the United States over the past 10 years to 20 years.[16-18]

Obesity is increasingly common in HIV-infected patients. Recently reported data from the SUN (Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy) study, which included a representative sample of 494 patients (78% male, 61% white, 27% black, and 10% Hispanic) with a median body mass index of 26 kg/m^2, showed that approximately 23% of patients were obese, 38% were overweight, 38% were normal weight, and 2% were underweight. Obesity was associated with insulin resistance, elevated levels of cholesterol and inflammatory markers, and increased atherosclerosis.[19]

Conclusions

The increasing prevalence of non-AIDS comorbidities in HIV-infected

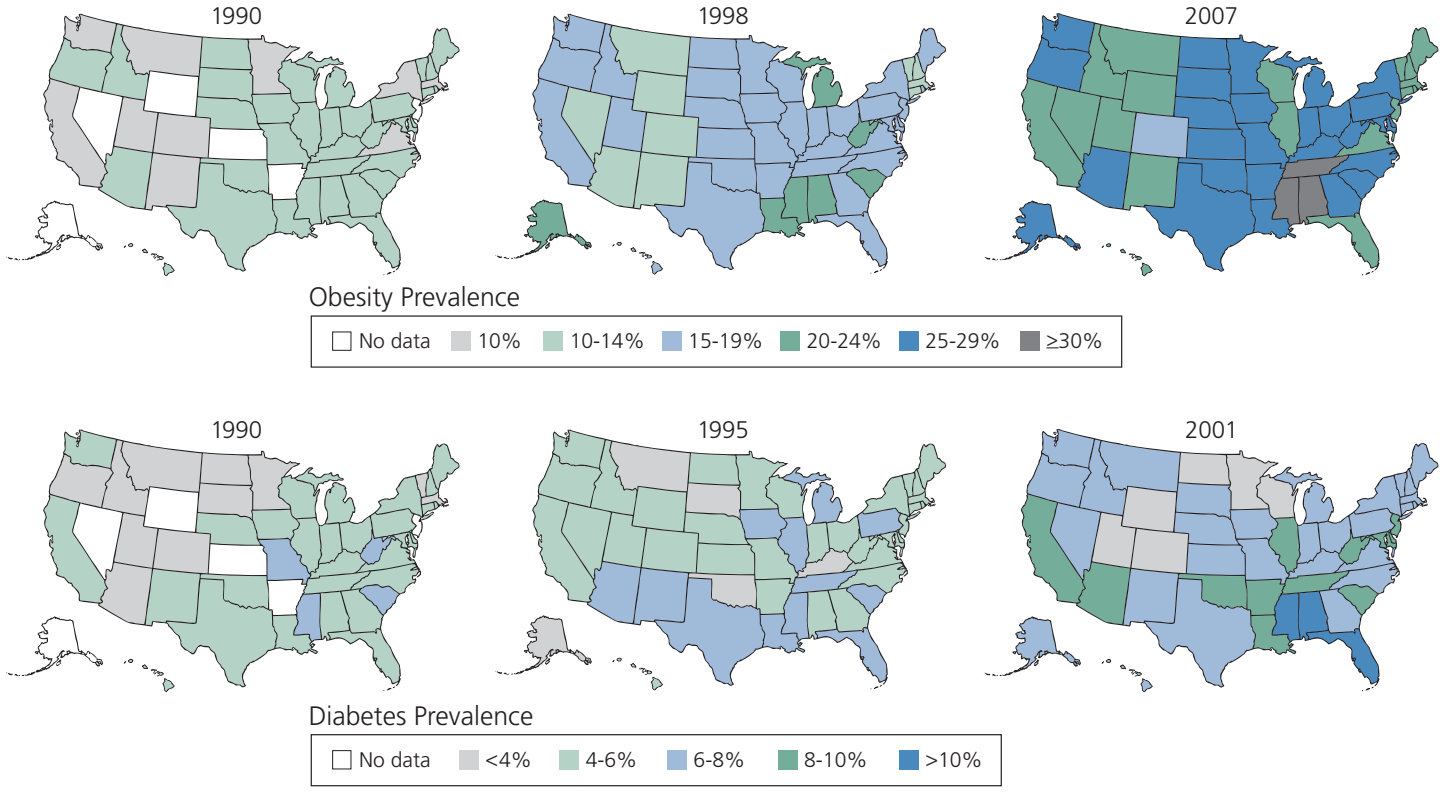

Figure 3. Increasing prevalence of obesity (BMI ≥ 30) from 1990 to 2007 (top) and of diabetes (including gestational diabetes) from 1990 to 2001 (bottom) in the United States. Adapted from Centers for Disease Control and Prevention[16] and Mokdad et al.[17,18]

patients reflects a number of factors. Traditional risk factors play a contributing role and include genetics, diet, environmental factors, and lifestyle determinants such as tobacco, alcohol, or illicit drug use. HIV infection itself increases the risk of developing comorbidities through persistent inflammation and immune activation, and long-term antiretroviral therapy adds to this risk through direct toxic effects, insulin resistance, promotion of an atherogenic lipid profile, mitochondrial toxicity, and associated body fat changes.

Goals for the future include more clearly identifying the respective roles of HIV infection and antiretroviral therapy in the risk for developing comorbidities and determining whether these effects are reversible, including whether early institution of antiretroviral therapy is important in this regard. Although some aspects of the management of metabolic and inflammatory dysregulation in HIV-infected patients may differ from the management of risk factors in HIV-uninfected persons, a major component of risk reduction remains a heavy emphasis on reducing standard, modifiable risk factors.

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