Diabetes Mellitus, Cardiovascular Risk, and HIV Disease

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Metabolic abnormalities, including dyslipidemia, insulin resistance, diabetes, and increased inflammatory indexes, have been increasingly observed among HIV-infected patients in the current era of highly active antiretroviral therapy. The causes of these abnormalities are complex and multifactorial, likely related in part to the effects of HIV itself a chronic inflammatory condition; medication effects, eg, of specific protease inhibitors on lipid metabolism and nucleoside reverse transcriptase inhibitors on mitochondrial function; and changes in body composition, with relative losses in subcutaneous fat and gains in central adiposity with the institution of antiretroviral therapy. These changes may place HIV-infected patients at greater risk of cardiovascular disease. Indeed, although overall morbidity and mortality have decreased significantly with the institution of highly active antiretroviral therapy, concern has been raised that cardiovascular disease will become an increasing problem for such patients, especially as they age. In developed countries, management of HIV has increasingly become that of a chronic disease, in which the majority of patients who receive therapy can expect to live longer with the disease as a result of reductions in life-threatening opportunistic infections. In contrast, antiretroviral therapy is not currently available in some resource-poor settings, where morbidity and mortality rates from opportunistic infections remain high.

Recent data suggesting increased myocardial infarction rates are of particular concern for patients with chronic HIV infection. Increased myocardial infarction rates have been shown in both longitudinal cohort studies and retrospective data analyses from large US healthcare systems. Myocardial infarction rates have been shown to significantly increased both in relation to specific antiretroviral therapies and in HIV-infected patients relative to non–HIV-infected patients (relative risk [RR], 1.75; 95% CI, 1.51 to 2.02; \( P<0.0001, \) HIV versus non-HIV). It is important to emphasize that the absolute risk of myocardial infarction and cardiovascular disease remains low in young HIV patients, but the RR may increase beyond that expected with aging (Figure).

What are the specific mechanisms of increased cardiovascular disease (CVD) in HIV-infected patients? Recently, focus has shifted to the potential role of inflammation as a mediator of CVD risk in HIV-infected patients. In the Strategies for Management of Antiretroviral Therapy (SMART) study, patients were randomized to continuous (viral suppression group) or episodic (drug conservation group) antiretroviral therapy on the basis of prespecified immunologic parameters. One of the hypotheses of SMART was that “treatment-sparing strategies might provide the benefits of antiretroviral therapy while minimizing the risk of adverse events associated with long-term use” (page 2284). In contrast to the anticipated result, there were relatively more cases of cardiovascular disease in the intermittent therapy group. Although a single unifying hypothesis to explain this result has not yet been accepted, increased inflammation related to less consistent control of viremia in the episodic treatment group has been postulated, as well as differential effects on lipids. Preliminary data from SMART and other studies suggest a potential link between HIV infection, myocardial infarction, and inflammation as measured by specific inflammatory indexes and measures of altered fibrinolysis. Further work is need to determine the specific mechanisms by which inflammation might contribute to increased CVD in HIV, the degree to which this risk is related to or independent of more traditional risk factors, appropriate markers to discern this risk, and strategies to reduce inflammation.

Despite the flurry of recent interest in inflammation, we should not forget that traditional risk factors shown to be of importance in non–HIV-infected patients may well contribute to increased CVD in HIV. This is particularly true if the risk is more prevalent in HIV than non-HIV patients, as with smoking. In this regard, recent studies demonstrate an increased prevalence of type 2 diabetes mellitus (DM) and insulin resistance among HIV-infected patients. Physiological studies have shown that specific antiretroviral drugs are associated with insulin resistance. For example, specific protease inhibitors impair insulin signaling via effects on Glut-4, whereas specific nucleoside reverse transcriptase inhibitors induce mitochondrial dysfunction as a mechanism of insulin resistance. Moreover, changes in body composition, including loss of beneficial subcutaneous fat and gain of harmful visceral fat, contribute to insulin resistance. Treatment studies have shown beneficial effects of metformin and glitazones on insulin resistance among patients with impaired glucose tolerance. However, large studies demonstrating the prevention of DM with pharmacological and/or lifestyle strategies, analogous to the Diabetes Prevention Program, have not been completed and are much needed in the HIV population.

A critical unanswered question regarding the assessment, prevention, and management of metabolic abnormalities in HIV-infected patients is the degree to which traditional risk factors such as DM and dyslipidemia increase cardiovascular risk in the HIV population. This is an important question because HIV-infected patients may be younger, more racially diverse, and leaner and may have other risk factors and
comorbid conditions that impact the effects of a known risk factor. Moreover, although DM in non–HIV-infected patients is likely to result from a genetic predisposition and environmental modifiers such as obesity, DM may result from the effects of specific antiretroviral drugs on glucose transport and mitochondrial function, with a consequent reduction in subcutaneous fat and ectopic fat collection in the liver and muscle in HIV patients. Therefore, it is not clear whether results from studies in non–HIV-infected patients are directly applicable to the HIV population.

The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study has shown that the increased RR of myocardial infarction with protease inhibitor use (1.16; 95% CI, 1.10 to 1.23; \( P \leq 0.001 \)) is partially attenuated by controlling for dyslipidemia, diabetes, and hypertension (to 1.10; 95% CI, 1.04 to 1.18; \( P = 0.002 \)), suggesting that the effects of antiretroviral therapies on traditional cardiac risk factors might contribute in part to the increased myocardial infarction rate.\(^7\) Triant et al\(^8\) also demonstrated that traditional risk factors, including DM, dyslipidemia, and hypertension, contribute to the increased RR of a myocardial infarction in HIV compared with non-HIV patients, with adjustment for differences in age and demographics between HIV and non–HIV patients. Controlling for dyslipidemia attenuated the increased RR for acute myocardial infarction in HIV compared with non–HIV patients by 10%. Similarly, controlling for DM also attenuated the RR by 10%. Inclusion of hypertension, diabetes, and dyslipidemia together attenuated the RR of a myocardial infarction by 25%.\(^5\) Moreover, higher smoking rates in HIV-infected patients are likely to contribute to the increased risk of myocardial infarction in this population.

Although data from prior studies suggest that traditional risk factors such as DM and dyslipidemia contribute to cardiac risk in the HIV population, clear prospective data on the cardiovascular risk associated with diabetes were, until now, lacking. The study by Worm et al\(^{10}\) in this issue of Circulation is important and answers some basic questions about the cardiovascular risk associated with diabetes mellitus in the HIV population. In this study, Worm et al again use the DAD study, a longitudinal prospective cohort study of 33,347 HIV patients followed up for 159,971 person-years at 212 clinics primarily in Europe. The definition of diabetes consisted of a confirmed fasting glucose \( \geq 126 \text{ mg/dL} \), a physician-reported diagnosis, or institution of antidiabetic medicines. A composite end point of myocardial infarction, invasive coronary procedure, and fatal CVD event was used in the primary analysis, but secondary sensitivity analyses were performed using more stringent definitions, excluding revascularization procedures from the outcome, and limiting the outcome to fatal CVD. All analyses were adjusted for gender, age, HIV transmission mode, ethnicity, smoking, family history of coronary heart disease (CHD), and calendar year. Using the definitions chosen, 2.9% of the study population had preexisting DM, and 1.1% had preexisting CHD at study entry.

In the primary results for the composite end point, Worm et al demonstrate that compared with patients without DM or preexisting CHD at baseline, the RR of a new CHD event in those with DM but no preexisting CHD was 3.03 (95% CI, 2.34 to 3.93; \( P = 0.001 \)), whereas the RR of a recurrent CHD event was 9.04 (95% CI, 7.10 to 11.49; \( P = 0.0001 \)) in patients with preexisting CHD and no DM. In terms of actual event rates, these data translate into events per 1000 person-years of follow-up of 3.4 for those with no preexisting DM or CHD, 16.4 for those with preexisting DM alone, 76.4 for patients with preexisting CHD alone, and 101.9 for patients with both risk factors. Similar results were confirmed in sensitivity analyses using more stringent definitions of CHD outcome.

A primary objective of the DAD team was to determine whether DM was a “CHD risk equivalent,” eg, whether DM conferred a risk similar to having preexisting CHD itself. The basis for this concept comes from a number of studies, notably the study of Haffner et al\(^{20}\) in which the 7-year incident rates of myocardial infarction were not different among patients with preexisting DM but no preexisting myocardial infarction (20.2%) compared with those with preexisting myocardial infarction but no DM (18.8%). In contrast, the analogous numbers in the current DAD study by Worm et al would be 7.6% for preexisting DM without preexisting CHD and 31.1% for preexisting CHD without preexisting DM. In both studies, the event rates for patients with neither risk factor are lower: 3.5% in the Haffner et al study and 1.6% in the DAD study.

How should these data be interpreted? Should one conclude from the DAD study that DM is not a CHD risk equivalent in the HIV population? Although it is true that DM was not as strong a risk factor as preexisting CHD itself, there may be reasons to explain why these data differ from those obtained in non–HIV patients. Moreover, an interpretation of the results that focuses exclusively on the nonequivalency of DM and preexisting CHD misses the larger, more important point that DM is a strong risk factor for CVD in HIV. In the study by Haffner et al,\(^{20}\) patients with DM were significantly older (58 versus 48 years) than in the DAD study. In addition, the reported duration of diabetes was longer, 8 years compared with 5 years in the DAD study. Therefore, it is not surprising that preexisting diabetes was shown to be a more significant risk factor, equal to preexistent CHD, in the prior studies of non–HIV-infected patients. However, on the basis of differences in the study design and demographics, comparison of the DAD study with other studies in non–HIV patients may not be relevant. Instead, we should examine the
DAD study for what it is and for the important data it provides us in the unique population of HIV-infected patients. Viewed this way, the study of Worm et al shows conclusively that DM is a major risk factor for CVD in HIV-infected patients. After full adjustment for other covariates, the RR of a new CHD event was 2.41 (95% CI, 1.91 to 3.05; \( P=0.0001 \)) for preexisting DM and 7.52 (95% CI, 6.02 to 9.39; \( P=0.0001 \)) for preexisting CHD. The study also shows that the strength of the association between DM and CHD increased with age and longer duration of DM. It may well be that in older HIV patients with longer duration of DM, DM would be a CHD risk equivalent.

The clinical implications and message from the study of Worm et al should be the need to aggressively screen for, prevent, and treat DM among HIV-infected patients because the presence of DM increases the risk of a future CHD event by almost 2.5 fold. As HIV patients age as a population and develop DM for longer periods of time, DM may become an even greater risk for myocardial infarction. The data are all the more relevant if we consider that the background rate of DM was \( \approx 5\% \) in the DAD study using fasting criteria or clinical diagnosis. However, other studies suggest that the prevalence and incidence of DM might be even higher. For example, Brown et al\(^\text{13}\) demonstrated a DM prevalence of 14\% versus 5\% comparing men in the Multicenter AIDS Cohort Study (MACS) study with HIV-negative controls. Similarly, Triant et al\(^\text{8}\) demonstrated a prevalence of DM using Medical Expenditure Panel Survey data for myocardial infarctions among HIV-infected patients. AIDS. 2008;22:F17–F24.

Taken together, these studies suggest an increased prevalence of DM and a significant CV risk associated with DM in the HIV population. The data highlight the need for more aggressive screening for DM in the HIV population, the development of targeted prevention and treatment strategies with glucose and hard cardiovascular end points, and prioritization of further studies to determine the unique mechanisms of DM in the HIV population. In so doing, we will likely save lives.

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**References**

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