EDITORIAL COMMENT
Cardiovascular Risk in Patients With Human Immunodeficiency Virus Infection
Incomplete Data*
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Since the advent of highly active antiretroviral therapy (HAART) in 1996, the death rate from acquired immune deficiency syndrome (AIDS) in the U.S. has decreased dramatically. Because of HAART, it is not uncommon to meet patients who have lived with human immunodeficiency virus (HIV) infection for well over two decades. Shortly after its introduction, however, clinicians observed an increasing prevalence of a lipodystrophic syndrome among patients taking HAART that included hyperlipidemia, impaired glucose metabolism, and central adiposity (1,2). Although HAART-associated lipodystrophy shares similarities with the more common insulin resistance syndrome that predisposes patients to coronary artery disease (“Metabolic Syndrome,” MetS), they clearly are different disease processes. For example, an important component of HAART-associated lipodystrophy is peripheral fat wasting (lipatrophy), which is not seen in patients with coronary artery disease. It also is not clear if HAART-associated lipodystrophy carries the same cardiovascular risk as MetS.

To complicate cardiovascular risk assessment further, uncontrolled HIV infection also has been associated with dyslipidemia and premature atherosclerosis (1). Thus, the evaluation of cardiovascular risk in patients with HIV hinges upon a complex interplay of direct and indirect vascular effects of HIV infection, antiretroviral therapy, aging, and exposure to cardiovascular risk factors.

In the past five years, several cross-sectional and observational studies have tried to provide clinical and pathophysiological insights into these interrelationships. Unfortunately, the observational studies that have been published or reported at meetings have had significant limitations, including low rates of adverse cardiovascular events, a short duration of exposure to HAART, and the usual limitations associated with retrospective studies such as nonsystematic assessment of cardiovascular risk factors, a lack of medication compliance data, and problems with ascertaining case status (1,2). Despite these limitations, these studies (with one exception) have suggested that patients with HIV infection are at increased cardiovascular risk, and that use of protease inhibitors may be especially disadvantageous from a cardiac standpoint. Although two prospective observational studies also showed increased risk of myocardial infarction in patients receiving HAART, they also suffered from low cardiovascular event rates, and concerns have been raised about problems with case ascertainment and between-group differences in the duration of HIV infection (2).

Because of these limitations, many investigators have used surrogate imaging markers of atherosclerosis to evaluate cardiovascular risk. With one exception, these studies have demonstrated that use of HAART is associated with endothelial dysfunction, but each study was small and cross-sectional, with attendant biases and limitations. In these studies, atherogenic lipoproteins, markers of insulin resistance, and in some instances markers of virological control explained part of the differences in endothelial function (2). These observations have been corroborated by studies demonstrating that protease inhibitors damage endothelial cell mitochondrial deoxyribonucleic acid in culture, impair vasomotor function, and reduce endothelial nitric oxide synthase expression by coronary artery rings (3,4). Several studies also have shown an increased prevalence of carotid plaque or intima-media thickness (CIMT) among patients receiving protease inhibitors, but they also were small and cross-sectional.

The study by van Wijk et al. (5) adds to the growing literature suggesting that individuals receiving HAART have markers of vascular disease that are associated with increased cardiovascular risk. In this study, individuals on HAART had impaired flow-mediated vasodilation of the brachial artery, a marker of endothelial dysfunction. This agrees with previous literature, but is not conclusive because nitroglycerin-mediated vasodilation was impaired; making it unclear if the differences between the groups were due to endothelial dysfunction or a non-endothelium-mediated process.

A very interesting and important aspect of this study was classifying patients according to the presence of MetS, using the National Cholesterol Education Adult Treatment Panel III guidelines. Although this definition was not intended to be used for patients with lipodystrophy, HIV-infected patients with MetS had increased levels of apolipoprotein B-100, C-reactive protein, insulin, and 2-h insulin compared with HIV-infected patients without MetS and HIV-negative controls. These findings suggest that HIV-infected patients with MetS have markers of insulin resistance and increased cardiovascular risk (5). Indeed, the major strength of this report is the completeness of imaging and metabolic data. A study with this complete a dataset regarding

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HAART, metabolic risk factors, and cardiovascular imaging in patients with HIV and control subjects has not been reported previously, so it is unique in that regard.

The finding that CIMT was greater among HIV-infected patients with MetS is consistent with the metabolic data provided by the authors. This finding would have been more powerful if it had been corroborated by the aortic pulse wave velocity data; however, the sample size was relatively small. Also, certain markers of MetS in HIV-infected patients did predict increased pulse wave velocity, such as blood pressure, 2-h glucose, and fasting insulin, suggesting that insulin resistance may be involved in the pathophysiology of vascular dysfunction in patients on HAART. It is interesting that markers of inflammation and viral load were more associated with CIMT than flow-mediated vasodilation or pulse wave velocity, but these associations are somewhat difficult to interpret in the absence of information about the specific antiretroviral agents used by the subjects, because agents within classes have different effects on insulin-glucose metabolism and lipoproteins (1). Although the imaging data in this study do not conclusively demonstrate that MetS, as traditionally defined, is useful for identifying increased cardiovascular risk in HIV-infected patients, the metabolic abnormalities observed in MetS patients suggest that insulin resistance may be involved and that further studies are needed (5).

**Future directions.** To better understand cardiovascular risk in patients on HAART, larger, prospective studies are needed. The biases inherent in observational and cross-sectional studies are well known, and their results can be misleading. In designing prospective studies, longitudinal data regarding changes in structural and functional markers of vascular disease, risk factors, antiretroviral therapy, and virological control must be considered, as well as the effect of aging itself.

Two well-designed studies sponsored by the AIDS Clinical Trial Group (ACTG) recently have been completed. ACTG 5152s is a prospective study of 82 HIV-positive, treatment-naïve patients randomized to receive one of three HAART regimens that would be predicted to have very different effects on lipids and insulin-glucose metabolism. As expected, flow-mediated dilation was impaired before starting treatment, but improved significantly and to a similar degree in each arm after as few as four weeks of HAART (6). Nitroglycerin-mediated vasodilation did not change, indicating that use of HAART rapidly improved endothelial function and that cardiovascular risk may decrease as HIV infection comes under control. ACTG 5078 is a prospective cohort study of 134 subjects recruited into carefully matched triads based on HIV serostatus, antiretroviral therapy, and cardiovascular risk factors. At baseline, there were no differences in CIMT between the groups of HIV-infected patients (7). Three-year follow-up of changes in CIMT, risk factors, and virological markers are expected in early 2006. These studies will help clarify the major contributors to cardiovascular risk in patients with HIV infection.

**Conclusions.** In regard to cardiovascular risk in patients with HIV, we have incomplete data. Compared with the high death rate from AIDS in patients with inadequate viral suppression, cardiovascular event rates are low and control of viremia, regardless of the treatment strategy, is more important for long-term survival than any increase in cardiovascular risk that may be related to metabolic changes associated with HAART. Uncontrolled viremia may be more of a cardiovascular risk than controlled infection that results in hyperlipidemia and insulin resistance. The overall message is that obtaining and maintaining virological control is the overriding concern in patients with HIV infection. Metabolic and vascular effects secondary to HAART are secondary considerations, but are worthy of rigorous investigation, as suggested by the paper by van Wijk et al. (5).

**REFERENCES**


