

## EDITORIAL



## HIV Infection and Cardiovascular Disease — Is There Really a Link?

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Soon after the introduction of protease inhibitors and nonnucleoside reverse-transcriptase inhibitors for the management of human immunodeficiency virus (HIV) infection, clinicians observed unexpected cardiovascular events among patients receiving these new, combination, “highly active” antiretroviral regimens. Angina, myocardial infarction, and stroke were seen in patients who were relatively young. Providers became suspicious that these events were related either to chronic HIV infection, since patients were surviving for longer periods than they had in the past, or to the new anti-HIV regimens, which are associated with substantial metabolic abnormalities.

Between 1998 and 2003, several reports appeared to validate clinicians’ concerns. The French Hospital Database on HIV, which included data from nearly 20,000 men who had been exposed to a protease inhibitor (54 of whom had had a myocardial infarction), found that patients who had been treated with a protease inhibitor for more than 18 months had twice the risk of myocardial infarction that was seen among patients with less drug exposure.<sup>1</sup> The HIV Outpatient Study, which used a data base with more than 5700 outpatients, identified 21 myocardial infarctions and concluded that there was a trend toward an increased frequency of myocardial infarction since the widespread use of protease inhibitors beginning in 1996.<sup>2</sup> A review of claims for more than 28,000 HIV-infected Medicaid patients in California showed that younger patients (18 to 33 years of age) who were exposed to antiretroviral agents had twice the risk of coronary heart disease seen among age-matched, untreated persons.<sup>3</sup> The Kaiser Permanente Medical Care Program of Northern California compared rates of hospitalization

for coronary artery disease and reported that the rate of such hospitalizations among HIV-infected patients, regardless of whether they used antiretroviral agents, was 1.5 times that among their uninfected counterparts.<sup>4</sup> Thus, an emerging body of evidence suggested that as HIV-infected patients were living longer as a result of antiretroviral therapy, cardiovascular disease was developing at unexpected rates.

Earlier this year, an article in the *Journal* appeared to refute these observations. Bozzette and colleagues conducted a retrospective analysis of hospitalizations and deaths due to cardiovascular and cerebrovascular disease among approximately 36,000 patients with HIV infection in the Veterans Affairs (VA) Medical System.<sup>5</sup> The main outcomes were determined from hospital administrative data bases; data on mortality were obtained from the National Death Index. Between 1995 and 2001, the rate of admission for cardiovascular and cerebrovascular disease actually decreased, from 1.7 to 0.9 per 100 patient-years; the rate of death decreased from 21.3 to 5.0 deaths per 100 patient-years, a decrease of roughly 75 percent. Use of any class of antiretroviral therapy, alone or in combination, was associated with a decreased hazard of death from any cause. Thus, this large and carefully constructed study was reassuring in that cardiovascular disease, while present, was not becoming a substantial complication of HIV disease and its therapy.

In this issue of the *Journal*, Friis-Møller and collaborators present data from the prospective, multinational Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study.<sup>6</sup> This study collected data on more than 23,000 patients enrolled in 11 previously established cohorts in Europe, the United

States, and Australia. Atherosclerotic events were prospectively identified and independently validated. Over a median follow-up time of 1.6 years through February 2002, 126 patients had a myocardial infarction. Including in their analysis the cumulative duration of drug exposure, the authors determined that during the first four to six years of combination therapy, there was a 26 percent relative increase in the rate of myocardial infarction per year of exposure to antiretroviral drugs. The study did not have sufficient power to permit comparisons among patients receiving different types of antiretroviral regimens.

Why did these studies reach contradictory conclusions? They both assessed large patient cohorts, yet in neither investigation was the HIV-infected study group compared with an uninfected control group. In addition, the follow-up periods (3.3 years in the VA study and 1.6 years in the DAD Study) were limited in comparison with the 16-year follow-up driving many of the risk estimates derived from the Framingham Study.<sup>7</sup> In the DAD Study, outcomes were prospectively and independently verified, although not all events were classified as "definite." In the VA study, which relied on retrospective code abstraction, the accuracy of coded information could not be verified, and it was not certain that criteria for hospitalization were constant over this period of time. The absolute magnitude of the increase in risk observed in the DAD Study was small and could easily have been missed in the VA study. Subsequent, longer-term analyses of these cohorts will provide much-needed data.

If there is an increase in risk, is it due to HIV infection or to its treatment? It must be recognized that as HIV-infected patients live longer, their risk of cardiovascular disease, compounded by their preexisting burden of traditional risk factors, inevitably increases. More than half the patients in the DAD cohorts were current or former smokers; approximately 3 percent had diabetes, 7 percent hypertension, 21 percent an elevated total cholesterol level, 26 percent a low high-density lipoprotein (HDL) cholesterol level, and 32 percent an elevated level of triglycerides. Thus, some degree of the cardiovascular risk discussed above may have been the result of predisposing factors, independently of HIV infection. Alternatively, some cardiovascular events may have been a consequence of HIV infection, of antiretroviral therapy, or of a synergistic relation among all these risk factors.

Is it plausible that HIV infection itself could pro-

mote atherosclerosis through a proinflammatory effect on endothelial cells, much like the mechanism that has been hypothesized for other infectious agents such as cytomegalovirus, herpes simplex virus, or chlamydia? Or could HIV infection promote cardiovascular disease indirectly, by way of the lipid abnormalities it induces? The acquisition of HIV infection is associated with reductions in the HDL cholesterol level (by 12 mg per deciliter [0.3 mmol per liter]), as well as reductions in the total cholesterol and low-density lipoprotein cholesterol levels (by 30 mg per deciliter [0.8 mmol per liter] and 22 mg per deciliter [0.6 mmol per liter], respectively).<sup>8</sup> Hypertriglyceridemia is associated with disease progression and HIV viremia.<sup>9</sup>

Is it plausible that the antiretroviral drugs themselves promote atherosclerosis directly or indirectly? When administered to healthy volunteers for four weeks, indinavir caused significant endothelial dysfunction (as measured by invasive monitoring of arterial blood flow in response to vasoactive compounds), independently of drug-induced alterations in blood pressure or lipid profiles. Endothelial dysfunction detected by this investigative technique is highly correlated with coronary artery disease and the development of subsequent clinical events, suggesting a direct mechanism by which the drugs may promote cardiovascular disease, perhaps by affecting the ability of endothelial cells to produce nitric oxide.<sup>10</sup>

Much attention has been paid to the metabolic disturbances attributed to these drugs, which could indirectly promote atherosclerosis. Certain antiretroviral drugs, most notably the protease inhibitors, produce marked elevations in cholesterol and triglyceride levels. It is not uncommon for clinicians to see patients receiving protease-based antiretroviral regimens who have cholesterol levels above 250 mg per deciliter (6.5 mmol per liter) and triglyceride levels above 500 mg per deciliter (5.6 mmol per liter). In addition, certain antiretroviral agents are associated with insulin resistance. HIV-infected patients receiving antiretroviral therapy have also experienced changes in body habitus (lipodystrophy) that have themselves been associated with cardiovascular disease. Thus, treated patients may have lipodystrophy, diabetes, and atherogenic lipid profiles, which could be the routes by which these drugs cause premature atherosclerosis, perhaps in concert with direct toxic effects on the endothelium.

Are there studies of variables other than clinical end points that give further credibility to the

possibility that we are observing a true phenomenon? When assessed by electron-beam computed tomography, coronary-artery calcifications have been shown to be more common in patients with HIV infection than in uninfected patients. Similarly, ultrasonographic evidence of carotid intimal thickening has been documented. Both of these findings are predictive of the occurrence of clinical events among patients without HIV infection and are thus causes for concern.

Taken in aggregate, the weight of the evidence suggests that HIV-infected patients treated with combination antiretroviral regimens are at increased risk for the development of premature atherosclerotic complications. To balance efficacy with toxicity in determining the optimal strategy for the use of antiretroviral therapy, it is imperative to elucidate the magnitude and causes of the risk of premature atherosclerosis, the value of noninvasive tests for predicting cardiovascular and cerebrovascular risk, and the effectiveness of interventional strategies. It is logical to recommend changes in lifestyle, such as cessation of tobacco use, and to treat persons with atherogenic lipid profiles with dietary and pharmacologic interventions. While knowledge about mechanisms advances, it is prudent to consider therapy with hydroxymethylglutaryl-coenzyme A reductase inhibitors, the "statin" class of agents, which not only improve lipid profiles but also appear to improve endothelial function. However, given the complexity of the medical care of patients with HIV infection, we need to have unequivocal evidence that changes in our successful treatment paradigm are warranted. Antiretroviral therapies have been among the miracles of recent decades, yet we must work

toward mitigating the toxic effects that have the potential to diminish the quality and duration of patients' survival over the long term.

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