Effect of Highly Active Antiretroviral Therapy on Ischemic Cardiovascular Disease in Patients with HIV-1 Infection

Str—In their recently published article, David et al. [1] raised important concerns about the risk factors for ischemic cardiovascular disease (ICD). In particular, these investigators showed that ICD events are more common among patients with a lower CD4 lymphocyte count and among patients with more-prolonged exposure to nucleoside reverse-transcriptase inhibitors (NRTIs); they also showed that exposure to protease inhibitors (PIs) was not directly associated with a greater risk of development of ICD. However, the investigators did not rule out the possibility that longer duration of exposure to PIs might be related to increased risk for ICD.

The role of PIs and, more generally, highly active antiretroviral therapy (HAART) in cardiac involvement is still controversial, even though several studies have indirectly shown that PIs can be implicated in the development of ICD because of several associated metabolic complications, including atherogenic dyslipidemia [2, 3]. In a previous study of a cohort of 1042 patients with HIV-1 infection, we observed a marked and significant reduction in cardiac involvement (primarily with complications of dilated cardiomyopathy and cardiac ischemia).

As shown in table 1, there was a progressive and significant decrease in the incidence of ICD among HIV-1–infected patients who were treated with HAART, especially during the last 3 years of our evaluation (1999–2001). In addition, we noted a significant reduction in the mortality rate associated with cardiac involvement in the groups of patients who were treated with HAART (in 1996–1998 and in 1999–2001). However, it should be noted that blood levels of cholesterol were significantly increased in the 2 cohorts of patients treated with HAART (mean cholesterol level [±SD], 234 ± 10 mg/dL [in 1996–1998] or 227 ± 35 mg/dL [in 1999–2001]), compared with those noted in patients treated with NRTIs only (mean cholesterol level [±SD], 176 ± 29 mg/dL [in 1989–1995]; \( P < .001 \), by the Mann-Whitney \( U \) test).

In contrast, we noted significant decreases in the blood levels of triglycerides in the cohorts of patients who were treated with HAART (mean triglyceride level [±SD], 166 ± 62 mg/dL [in 1996–1998] or 205 ± 75 mg/dL [in 1999–2001]), compared with those noted in the cohort of patients treated with NRTIs (mean triglyceride level [±SD], 224 ± 90 mg/dL; \( P = .001 \), by the Mann-Whitney \( U \) test).

In their study, David et al. [1] postulated that the duration or the severity of immunosuppression in HIV-1–infected patients could be a risk factor for ICD. It has been reported that ischemia and arrhythmia are probably the result of a direct effect of HIV-1 and its products on the vascular endothelium, myocardial cells, and, by interference, the ionic pumps [5, 6]. Thus, in our opinion, HAART, by acting directly on HIV-1 replication, is able to decrease the incidence of several infectious and noninfectious complications associated with AIDS, including cardiac involvement.

Although particular increases in hyperlipidemia and accelerated atherosclerosis were noted in patients who were treated with HAART, the beneficial effects of HAART on HIV-1 replication and the role of such therapy in decreasing the incidence of several AIDS-associated complications outweigh the adverse events associated with these drugs. However, we agree with Dr. David and colleagues that there is a need to focus preventive measures on known cardiovascular risk factors.

### Table 1. Incidence of cardiac ischemia and death related to cardiac involvement among 1526 HIV-1–infected patients during 3 observational periods.

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<tr>
<td>Ischemic cardiovascular disease</td>
<td>67 (12.3)</td>
<td>14 (3.7)(^a)</td>
<td>10 (1.7)(^a)</td>
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<tr>
<td>Death due to cardiac involvement</td>
<td>17 (3.1)</td>
<td>6 (1.6)</td>
<td>4 (0.7)(^b)</td>
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</table>

**NOTE.** Data are no. (%) of patients.

\(^a\) \( P < .0001 \) when compared with the first period of observation (1989–1995) of the cohort group (by Fisher’s exact test).

\(^b\) \( P = .0031 \) when compared with the first period of observation (1989–1995) of the cohort group (by Fisher’s exact test).
and that prospective cohort studies are needed to evaluate the effect of HAART in decreasing cardiac involvement in patients with HIV-1 infection.

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References


Clinic Infectious Diseases 2002, 35:632–3


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Clinical Infectious Diseases 2002, 35:632
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Reply

Sr.—In his letter, Dr. Johnson [1] describes one of the dilemmas confronted by guideline committee members when recommendations are developed—namely, the issue of formulating statements on the basis of well-controlled clinical trials (i.e., evidence-based recommendations). Although all 3 of the guidelines recently published in North America for the management of community-acquired pneumonia (CAP) include various recommendations for the use of doxycycline as an option for empiric therapy for ambulatory patients (and, in 1 statement, as part of potential combination therapy for patients hospitalized on the general ward), it is acknowledged that this recommendation is based primarily on in vitro data rather than on substantial clinical data [2–4]. Dr. Johnson indicates that the review article by Thornsberry et al. [5] does not include doxycy-