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 the mortality rate associated with 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.

We successively evaluated an additional cohort of 600 HIV-1–infected patients who had cardiac involvement and who were treated with HAART during 1999–2001. Table 1 shows, for this cohort of patients, the incidence of ICD and the mortality rate associated with cardiac involvement (primarily with complications of dilated cardiomyopathy and cardiac ischemia).

Correspondence

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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<td>Ischemic cardiovascular disease</td>
<td>67 (12.3)</td>
<td>14 (3.7)</td>
<td>10 (1.7)</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)</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

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Doxycline for Treatment of Community-Acquired Pneumonia

Sir—The recent Clinical Infectious Diseases supplement entitled The Clinical Significance of Drug-Resistant Streptococcus pneumoniae for the Treatment of Com- munity-Acquired Pneumonia (CAP) was disappointingly silent about doxycycline. As noted by File, the Infectious Diseases Society of America (IDSA) practice guidelines of 2000 for the management of CAP state that doxycycline is 1 of 3 equivalent alternative regimen for outpatients who lack modifying factors [1, 2]. Thus, it is puzzling that Lynch and Martinez [3] state unequivocally that macrolides are the drugs of choice in this context and that they do not discuss doxycycline. In the article by File, the results reported in table 3 [1, p. S22], which provides only semi- quantitative susceptibility data, suggest that doxycycline is equivalent to macrolides with respect to in vitro activity against S. pneumoniae, within each stratum of penicillin susceptibility [1]. Unfortunately, the more extensive tables on primary susceptibility provided by Thornsberry et al. [4] do not include data for either a tetracycline derivative or doxy- cycline, even though these drugs presumably are more relevant in the treatment of CAP than are clindamycin and amoxicil- lin-clavulanate, for which data are shown.

Doxycycline may be an inexpensive fluoroquinolone-sparing alternative for treatment of CAP [5]. Thus, it deserves more attention in a state-of-the-art review of drug-resistant S. pneumoniae and the contemporary management of CAP than it received in this supplement. The absence of an interested corporate sponsor probably has contributed substantially to the unfortunate paucity of available data from clinical trials and in vitro susceptibility studies and the lack of authoritative at- tention to doxycycline in the treatment of CAP. If so, support from the IDSA, the Centers for Disease Control and Preven- tion, the Department of Veterans Affairs, the National Institutes of Health, and/or other noncommercial parties with an in- terest in controlling medical costs and preventing antibiotic resistance may be needed to address this deficit.

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References

Reply

Sir—In his letter, Dr. Johnson [1] describes one of the dilemmas confronted by guideline committee members when recom- mendations are developed—namely, the issue of formulating statements on the basis of well-controlled clinical trials (i.e., evidenced-based recommendations). Al- though all 3 of the guidelines recently published in North America for the manage- ment 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 hospi- talized on the general ward), it is acknowl- edged 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 Thorns- berry et al. [5] does not include doxycy-