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Impact of Antiretroviral Therapy among HIV-1–Infected Patients with Pulmonary Hypertension

Str—We read with interest the recent article by Zuber et al. [1] on the effects of combined antiretroviral therapy (ART) among HIV-1–infected patients with pulmonary arterial hypertension (PAH), and we would like to both comment on and expand on some points raised by the article.

In their retrospective study, Zuber et al. [1] showed a decreased incidence of PAH from 1996 through 2001 that correlates with the introduction of HAART; in addition, the investigators showed that HAART significantly decreased mortality associated with PAH. In our previous retrospective study [2], we evaluated the effect of ART and HAART among HIV-1–infected patients with cardiac involvement during 1989–1998. In the study, we observed PAH in 3 (0.7%) of 454 patients who were treated with ART (consisting of 1 or 2 nucleoside reverse-transcriptase inhibitors), whereas we observed PAH in 10 (2.0%) of 498 patients who were treated with HAART (including a protease inhibitor) (P = .048). The results of our study seem to indicate that ART, and, in particular, HAART, did not influence the frequency of PAH among HIV-1–infected patients.

Furthermore, other studies failed to demonstrate any effect of ART on PAH. In particular, Nunes et al. [3] observed that the use of HAART with epoprostenol significantly decreased mortality among HIV-1–infected patients with PAH, whereas survival rates were worse among patients receiving HAART in the absence of epoprostenol therapy. Pellicelli et al. [4] also failed to show beneficial effects of HAART in HIV-1–infected patients with PAH; in fact, 2 patients with a low viral load who were treated with HAART showed an accelerated course of PAH, with worsening of pulmonary artery systolic pressure.

The pathophysiology of PAH in HIV-1 infection remains unclear. Mehta et al. [5], in an analytic review of 131 HIV-1–infected patients with PAH, observed that a direct action of HIV-1 has not been demonstrated and that there is no evidence of HIV-1 growth in cultured endothelial cells.

In our opinion, HIV-1–related PAH may be considered to be a multifactorial disease in which several conditions may be present or may be combined. In fact, several studies have demonstrated the following findings among patients with PAH: (1) increased production of inflammatory cytokines, including interleukin-1, interleukin-6 and TNF, endothelin-1, and vascular endothelial growth factors [5–7]; (2) presence of genetic mutations (receptor BMPR2 germline mutations) [8]; and (3) increased prevalence of the alleles HLA-DR6 and HLA-DR52 [9].

Taking all data together, we disagree with the final statement of Zuber et al. [1], which confirms the recommendation to treat all patients with PAH with HAART, irrespective of their CD4 cell counts. It is conceivable that retrospective studies might have been influenced by several biases and might not have had the statistical power to draw final conclusions with a strong recommendation to use HAART in cases of HIV-1–related PAH.

In conclusion, therapeutic responses to pulmonary vasodilator, antiretroviral, and anticoagulant agents are variable. It is crucial and necessary to design multicenter, prospective, and well-conducted studies to definitively assess the beneficial effect of HAART in HIV-1–infected patients with PAH. Such studies are particularly important to assess the effects of HAART in HIV-1–infected patients with higher CD4 cell counts (i.e., >350 cells/mm3), for whom antiretroviral therapy might be deferred or started only in particular circumstances.

Acknowledgment


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References


Reply to Torre and Pugliese

Sr—The letter by Torre and Pugliese [1] questions whether all patients with pulmonary hypertension related to HIV (PAHRH) should be treated with HAART, as we suggested on the basis of the results of our recent study [2]. Because PAHRH is a serious complication that, if untreated, has a high mortality rate, treatments that are targeted to reduce mortality are clearly indicated. In the era of HAART, pulmonary hypertension and its progression, more than the HIV infection itself, will determine the patient’s prognosis. However, in the pre-HAART era, approximately half of all patients with PAHRH died of HIV-related causes [3]. Treatment with intravenous epoprostenol, inhaled iloprost, and, more recently, oral bosentan have been shown to significantly decrease the right ventricular systolic pressure over right atrial pressure gradient in patients with PAHRH. Although not always proven, because of the lack of a control group, the magnitude of the decrease in pressure gradient achieved with these drugs is likely to have a positive impact on overall survival rates.

To our knowledge, our study [2] is the only one that has systematically evaluated the time course of the pressure gradient as a function of antiretroviral therapy in a larger patient population. In the study by Pugliese et al. [4], a difference in PAHRH frequency from 0.7% to 2.0% was reported between patients treated with 1 or 2 nucleoside analogues and patients treated with HAART during a later time period. Because the authors do not report the overall number of HIV-infected patients in their cohort, a calculation of incidence is not possible, and the data cannot be interpreted as showing an increase in PAHRH frequency due to HAART. The unusually high frequency of 2.0% suggests that a bias has affected the data; possibly there were more patients with PAHRH receiving HAART than patients not receiving antiretroviral therapy. More importantly, neither the definition of pulmonary hypertension nor the pressure gradient values nor their time course are mentioned in the article [4].

Current treatment recommendations for HAART only consider whether the CD4 cell count is >350 cells/mm³ if a patient is asymptomatic. However, we consider PAHRH to be a symptom of HIV infection, because it is epidemiologically linked to HIV infection, and, possibly, is associated with human herpesvirus 8 coinfection; pathological immune activation due to HIV; genetic factors; or other, yet unknown, factors. Although we agree that starting HAART at a CD4 cell count of >350 cells/mm³ is not warranted for the broad population of asymptomatic patients, HAART does lead to a decrease in immune activation, irrespective of the CD4 cell count. This effect may have indirectly contributed to the improved hemodynamics seen in our study. In the face of the rare occurrence—but high mortality—of PAHRH, we believe that every step should be taken to improve the prognosis of patients with PAHRH. On the basis of our data, we believe that HAART should always be initiated, because it stabilizes or decreases the pulmonary hypertension and prolongs survival [2]. Additional treatments that improve the hemodynamics should be started if a patient is moderately to severely symptomatic.

Among patients who are moderately symptomatic, the endothelin receptor antagonist bosentan seems to be the drug of choice, because of the availability of the drug in an oral formulation and because of its proven efficacy [5].

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