Influence of Highly Active Antiretroviral Therapy on the Outcome of Subclinical Visceral Leishmaniasis in Human Immunodeficiency Virus–Infected Patients

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Seventeen human immunodeficiency virus–infected patients who were harboring untreated subclinical visceral leishmaniasis (VL) were prospectively followed up. None of the 11 patients who received highly active antiretroviral therapy (HAART) presented with symptomatic VL during follow-up, whereas 2 out of 6 patients who received therapy other than HAART had an episode of overt kala-azar. These findings suggest that HAART does not induce the evolution of latent VL into symptomatic disease.

The introduction of highly active antiretroviral therapy (HAART) has modified the course of HIV infection. Because of this therapy, HIV-infected patients who receive HAART have fewer opportunistic infections and survive longer than do HIV-infected patients who do not receive HAART [1]. However, opportunistic diseases, such as cryptococcal meningitis [2], cytomegalovirus retinitis [3], lymphadenitis associated with Mycobacterium avium complex infection [4], and others, may appear a few weeks after HAART is started, despite a significant increase in the patient’s CD4+ cell count. This fact has led some researchers to speculate that recovery of the inflammatory response that is induced by HAART could uncover latent disorders [5].

Visceral leishmaniasis (VL) occurs frequently in HIV-infected patients who live in the Mediterranean basin [6]. A significant proportion of leishmanial infections remain dormant in HIV-infected individuals [7], but some leishmanial infections evolve into overt kala-azar [7, 8]. To our knowledge, there have been no studies on the effect of HAART on VL. However, on the basis of a report of cases of symptomatic VL that appeared in patients shortly after initiation of HAART [9], we hypothesized that some patients with latent infections could develop symptoms after initiation of such therapy. In this report, we describe the evolution of infections in a group of patients with latent VL who received antiretroviral therapy after VL was diagnosed.

Materials and methods. Three hundred fifty-five HIV-infected patients who attended our institution from January 1993 through August 1998 were invited, regardless of their symptoms, to participate in a study that aimed to assess the prevalence of VL in our area [6]. A total of 314 patients (88.5%) agreed to be studied and underwent sternal bone marrow aspiration. All individuals gave written informed consent to participate in the study. VL was diagnosed when amastigotes were found on Giemsa-stained slides and/or when promastigotes were cultured on Evans modified Tobie’s medium. VL was considered subclinical if the patient met the following criteria: no fever, no splenomegaly, and a hemoglobin level of <9 g/dL. If there was fever, splenomegaly, or a hemoglobin level of ≥9 g/dL, these conditions had to be attributable to another concomitant disease, and they had to have abated with the specific treatment of the disease, without antileishmanial therapy.

Nineteen (6%) of these patients had subclinical VL. These patients received antileishmanial therapy according to the discretion of the investigator and the patient’s wishes. Therefore, 2 patients were treated with antileishmanial drugs when the diagnosis of subclinical VL was made. The remaining 17 subjects were included in the study.

The 17 patients with untreated subclinical VL were prospectively followed up every 12 weeks. At each visit, clinical, hematological, virological, and immunological evaluations were performed. At the least, analysis of a bone marrow aspirate for Leishmania species was performed when patients had unexplained fever, liver or spleen enlargement, or a significant decline in the leukocyte, platelet, or RBC count. When these symptoms coincided with a finding of Leishmania species in bone marrow aspirates by use of Giemsa staining and/or culture with Evans modified Tobie’s medium, a diagnosis of symptomatic VL was made.

Patients received antiretroviral therapy according to the drugs available at the time of the study and according to in-
Results. The characteristics of the study population at the time of diagnosis of subclinical VL are shown in table 1. The median duration of follow-up was 29 months (range, 6–66 months). Eleven patients received HAART (i.e., a combination that includes, at least, a transcriptase inhibitor for which the patient was naïve plus 1 protease inhibitor) after a diagnosis of subclinical VL was made. Four of these individuals (patients 3, 4, 5, and 6; figure 1) were given HAART within 4 months after diagnosis.

For the 11 patients who received HAART, the median CD4⁺ cell count at the start of therapy was 65 cells/mm³ (range, 1–651 cells/mm³). Nine of the 11 patients who received HAART had increases in CD4⁺ cell counts that were >25% of the CD4⁺ T cell counts at baseline (the median increase in the CD4⁺ cell count at week 12 after the start of HAART was 92 cells/mm³ [range, −6–363 cells/mm³]). In addition, 8 of these 11 patients had decreases in plasma virus load levels (at least 1 logarithmic unit below baseline values) 12 weeks after HAART was started. At this time, 6 patients had plasma HIV levels of <200 copies/mm³.

None of the patients who received HAART presented with symptomatic VL. However, 2 of the 6 patients who did not receive HAART had an episode of overt kala-azar occur at 24 and 26 months after diagnosis of subclinical VL (for patients 1 and 2, respectively; figure 1). These patients had CD4⁺ T cell counts of 20 cells/mm³ and 82 cells/mm³, respectively, at the time that HAART was begun. One of the 4 patients who started receiving HAART within the first few months after being given a diagnosis of subclinical VL had an episode of herpes zoster 2 months later (patient 4; figure 1). Two patients were lost to follow-up.

Discussion. In this study, none of the 11 HIV-infected patients with subclinical VL who were receiving HAART developed symptomatic VL, whereas 2 patients who were receiving an antiretroviral regimen other than HAART developed overt kala-azar during follow-up. Thus, HAART does not appear to induce evolution of latent VL into symptomatic disease.

The present study is limited because of the relatively small sample size. However, studies about the influence of HAART on subclinical VL are lacking; to our knowledge, this is the first report of a prospective study of HIV-infected patients with latent VL who were receiving HAART.

Table 1. Characteristics of HIV-infected patients who were receiving highly active antiretroviral therapy (HAART) at the time of diagnosis of subclinical visceral leishmaniasis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients given HAART (n = 11)</th>
<th>Patients not given HAART (n = 6)</th>
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<tbody>
<tr>
<td>Men, no. (%)</td>
<td>11 (100)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Age, median y (range)</td>
<td>31 (24–41)</td>
<td>33 (29–41)</td>
</tr>
<tr>
<td>CD4⁺ cell count, median cells/mm³ (range)</td>
<td>119 (1–1358)</td>
<td>48.5 (20–120)</td>
</tr>
<tr>
<td>Duration of follow-up, median mo (range)</td>
<td>32 (12–66)</td>
<td>28 (6–33)</td>
</tr>
<tr>
<td>Patients with risk factor, no. (%)</td>
<td>8 (72.7)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>IDU</td>
<td>3 (27.3)</td>
<td>2 (33.3)</td>
</tr>
</tbody>
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NOTE. IDU, injection drug use.
Antiretroviral therapy other than HAART was not randomly assigned to the patients that we studied, since antiretroviral drugs were used according to their availability. This fact might have introduced some bias. However, CD4+ cell counts were similar for all patients at the start of both regimens, a fact that serves as an argument against the existence of a selection bias.

Some patients included in this study received HAART more than 6 months after diagnosis of VL, but since leishmanial infection has been reported to be a persistent disorder [7, 10, 11], it was probably present in the patients when they began receiving HAART. In fact, 9 patients included in this study underwent sequential bone marrow examinations as part of another investigation; in 5 of these patients, *Leishmania* amastigotes were found at different times (authors’ unpublished data). In any case, the effect of HAART on the outcome of latent VL is undoubtedly shown by the 4 patients who started receiving HAART within 4 months after diagnosis of VL.

After patients started receiving HAART, the appearance of symptoms of an established subclinical infection seems to be a consequence of the recovery of an appropriate inflammatory response against the pathogen [12]. The lack of evolution of latent VL into symptomatic VL in our patients should not be attributed to either a failure to control virus replication or a lack of increased T cell counts. In fact, significant increases in CD4+ cell counts and decreases in plasma HIV levels were observed in most patients who were receiving HAART. Moreover, 1 patient had reactivation of an opportunistic disease (herpes zoster).

In addition to increasing T cell counts and reducing immune system activation, HAART leads to increased levels of T-helper type 1 cytokines [13]. This fact could explain why patients who were receiving HAART did not develop overt kala-azar, since an adequate T-helper type 1 cytokine response is associated with control of leishmanial infection [14].

If the effect of HAART on HIV-infected patients with latent VL, as reported here, is confirmed, a drop in the incidence of symptomatic VL should be observed in conjunction with the use of HAART, as has been shown for other opportunistic disorders [15]. More studies that address this issue are needed.

References