Impact of Highly Active Antiretroviral Therapy on the Incidence of Visceral Leishmaniasis in a French Cohort of Patients Infected with Human Immunodeficiency Virus

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The incidence of human immunodeficiency virus (HIV)–Leishmania coinfections in France was estimated on the basis of the French Hospital Database on HIV, and risk factors for the occurrence of visceral leishmaniasis (VL) were analyzed by a multivariate Cox model. VL was diagnosed in 165 of 55,626 HIV-infected patients followed since 1992. The incidence of VL decreased from 11.6 ± 1.2 per 10,000 persons-years before 1996 to 6.3 ± 0.7 per 10,000 persons-years after 1996, the year when highly active antiretroviral therapy (HAART) was initiated in France. The relative hazard (RH) for development of VL was higher in (1) intravenous drug users versus other transmission groups (RH = 1.56; 95% CI, 1.13–2.15), (2) patients living in southern France versus those living in northern France (RH = 3.36; 95% CI, 2.44–4.61), and (3) patients who had a CD4 cell count of ≤50/mm3 during their follow-up versus those who did not (RH = 6.45; 95% CI, 4.27–9.75) but was lower in (4) patients who received antiretroviral therapy including ≥3 drugs versus those who did not (RH = 0.41; 95% CI, 0.26–0.65). We found a significant decrease in the incidence of HIV-Leishmania coinfections after 1996, associated with the introduction of HAART in France.

Leishmaniasis due to Leishmania infantum is endemic in southern Europe. Since the beginning of the AIDS epidemic, >1900 human immunodeficiency virus (HIV)-Leishmania coinfections have been reported by the World Health Organization (WHO) (Philippe Desjeux, WHO-Geneva, personal communication). The majority of these cases were visceral leishmaniasis (VL) and were from Italy, France, Spain, and Portugal. During this period, ~40% of all VL cases were diagnosed in HIV-infected patients [1].

The introduction of highly active antiretroviral therapies (HAART) in the United States and Europe has resulted in a reduction of mortality, hospitalizations, and incidence of the primary opportunistic infections, such as pneumocystosis, cytomegalovirus, and atypical mycobacterial infections. Despite not being considered as an AIDS-defining illness, VL occurs in severely immunocompromised patients, with >90% of them having <200 CD4 cells/mm3 [1]. Therefore, we studied, in the largest cohort of VL cases, the impact that HAART has on the incidence and risk factors for occurrence of VL in HIV-infected patients in France, one of the European countries in which AIDS is most epidemic.

Patients, Materials, and Methods

Database. The French Hospital Database on HIV (FHDH) was started in 1992 in 68 French University Hospitals. The only criteria for inclusion in the FHDH are that an individual be infected with either HIV-1 or HIV-2 and provide written informed consent for enrollment. The standardized data-collection form, completed prospectively, includes demographic data, characterization of transmission group, value of biological markers, clinical manifestations, nature and starting date of treatments prescribed, and participation in clinical trials. At each hospital visit, each admission, or interval of ≥6 months, all variations in the patient’s clinical or biological status or treatment that have occurred since the last report date are entered in a follow-up form.

Patients. Patients included in the FHDH who had been followed since 1 January 1992 were studied. Only patients ≥15 years old who had been monitored in metropolitan France, with a follow-up occurring ≥6 months after entry into the study...
were included. Exclusion criteria were VL at entry (n = 32), previous history of VL (n = 47), and participation in a blind clinical trial evaluating antiretroviral (ARV) therapy (n = 717). For the present study, 796 patients were excluded, and data from 55,626 individuals were analyzed.

**Diagnosis of visceral leishmaniasis.** The diagnosis of clinical VL was based on the association between clinical signs of VL and the demonstration of *Leishmania* amastigotes by direct examination, histology, or positive culture of promastigotes in special media of bone marrow, blood, or visceral sample.

**Statistical analysis.** Time was measured from the first recorded CD4+ cell count (after 1 January 1992) to the first event (defined as diagnosis of VL, death, or last follow-up).

The annual incidence from 1 January 1992 through 31 December 1999 was estimated. Since HAART was introduced in France in March 1996, we compared the incidence of the first occurrence of VL both before and after 1 April 1996, both in the entire HIV-infected population and in the transmission groups (i.e., intravenous drug users [IVDUs] and non-IVDUs). Factors associated with VL were analyzed by both a univariate and a multivariate Cox proportional-hazards model. To account for delays in reporting, we used a censoring method recommended for cohort studies [2]. For patients still alive at a final follow-up during the 6 months before 31 December 1999 (the date on which the database was last updated), 31 December was used as the censoring date. The variables used to assess the impact that inclusion of these patients had on occurrence of VL during the 1992–1999 period were sex, age at the first event (as defined above), exposure status, and area of France (since VL is endemic in the Mediterranean region, France was divided into two areas, southern France and northern France). A CD4 cell count of <500 mm⁻³, the occurrence of an AIDS-defining illness, previous use of antifungal treatments (including fluconazole, amphotericin B, itraconazole, and/or ketoconazole), and ARV therapy during the follow-up period were considered as time-dependent covariates. The ARV therapy regimens were also considered in the intention-to-continue-treatment approach characteristic of therapy regimens for this infection [3]. Three types of ARV therapy were used: ARV monotherapy (1 ARV drug), ARV dual therapy (2 ARV drugs), and ARV multiple therapy (>3 ARV drugs, regardless of whether the therapeutic class was nucleoside reverse-transcriptase inhibitor [NRTI], non–nucleoside reverse-transcriptase inhibitor [NNRTI], or protease inhibitor [PI]).

To define AIDS diagnosis, we used clinical criteria of the 1993 CDC classification. All variables for which the *P* value for the univariate model’s relative hazard (RH) of occurrence of VL was <.2 were included in the multivariate model.

**Results**

**Patients’ characteristics.** VL was diagnosed in 165 of 55,626 HIV-infected patients followed from the beginning of 1992 through the end of 1999. The primary characteristics of the population studied are reported in table 1. VL was most often diagnosed in men (*P* = .062), IVDUs (*P* < .001), patients living in southern France (*P* < .001), patients with lower CD4 cell count (either at entry into the cohort or during follow-up) (*P* < .001), patients with AIDS-defining illnesses during follow-up (*P* < .001), and patients who had received previous antifungal therapy (*P* < .001); VL was less often diagnosed in patients treated with ARV multiple therapy (*P* = .009).

**Incidence of leishmaniasis-HIV coinfections.** The incidence of the first episode of VL, per 10,000 person-years (PYs), by calendar years, declined after 1996. Before 1 April 1996, 88 episodes of VL were diagnosed in 75,862 PYs, corresponding to an incidence of 11.6 ± 1.2 episodes per 10,000 PYs. After 1 April 1996, when HAART was first introduced in France, 77 episodes of VL were diagnosed in 122,057 PYs, corresponding to an incidence of 6.3 ± 0.7 episodes per 10,000 PYs. The univariate RH of development of VL after 1996, compared with that before 1996, was reduced by 46% (RH = 0.54; 95% confidence interval [CI] 0.40–0.71); a significant reduction was observed both in IVDUs (RH = 0.52; 95% CI, 0.32–0.82) and in non-IVDUs (RH = 0.64; 95% CI, 0.43–0.95).

**Risk factors for development of leishmaniasis.** Patients treated with ARV multiple therapy had a 59% reduction of risk, compared with patients who received no ARV therapy, ARV monotherapy, or ARV dual therapy (table 1). The presence of AIDS, a CD4+ count of <500 mm⁻³, and antifungal treatment during follow-up were also found to be independent predictors of occurrence of VL.

After adjustment in the Cox model, VL was more often diagnosed in IVDUs, in whom the risk was 1.56-fold higher (95% CI, 1.13–2.15) than that in non-IVDUs. Patients living in southern France had a 3.36-fold-higher (95% CI, 2.44–4.61) risk of presenting with VL than did those living in northern France. Since IVDUs are more numerous in southern France than in northern France (38.7% vs. 20.1%; *P* < .001), and because VL is endemic in southern France, we used another multivariate model, adjusted for a variable combining geographic residence and transmission group; compared with non-IVDUs living in northern France, the RH of presenting with VL increased sequentially in IVDUs living in northern France (RH = 1.76; 95% CI, 1.08–2.87) and in IVDUs living in southern France (RH = 3.67; 95% CI, 2.43–5.54) and was highest if patients were both IVDUs and living in southern France (RH = 5.24; 95% CI, 3.51–7.84).

**Discussion**

After toxoplasmosis and cryptosporidiosis, VL is the most common parasitic infection in HIV-infected patients in southern Europe [1]. Before the introduction of HAART, VL occurred in severely immunocompromised patients and was associated with frequent relapses and a poor prognosis [1]. Atypical clinical manifestations and unusual locations of parasites were frequent...
Table 1. Description of population and relative hazard (RH) (95% confidence interval [CI]) values for development of visceral leishmaniasis (VL), from first recorded CD4−/H11001 T cell count, in multivariate Cox proportional-hazards model of time of VL.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients without leishmaniasis (n = 55,461)</th>
<th>Patients with leishmaniasis (n = 165)</th>
<th>Result of multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of follow-up (IQR), months</td>
<td>38 (18–65)</td>
<td>18 (7–34)</td>
<td>1.56 (1.13–2.15) a</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>.006</td>
</tr>
<tr>
<td>Male</td>
<td>75.4%</td>
<td>80.6%</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>24.6%</td>
<td>19.4%</td>
<td>0.78 (0.53–1.15)</td>
</tr>
<tr>
<td>Age at episode of VL, mean ± SD, years</td>
<td>39.3 ± 9.2</td>
<td>39.1 ± 7.8</td>
<td></td>
</tr>
<tr>
<td>Transmission group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexuals/bisexuals, %</td>
<td>37.4</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>IVDUs, %</td>
<td>24.9</td>
<td>44.9</td>
<td></td>
</tr>
<tr>
<td>Heterosexuals, %</td>
<td>28.1</td>
<td>20.6</td>
<td></td>
</tr>
<tr>
<td>Individuals exposed to blood products, %</td>
<td>2.9</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Others and unknown</td>
<td>6.7</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Geographic residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern France</td>
<td>73.9%</td>
<td>44.2%</td>
<td>1</td>
</tr>
<tr>
<td>Southern France</td>
<td>26.1%</td>
<td>55.8%</td>
<td>3.36 (2.44–4.61)</td>
</tr>
<tr>
<td>Median first CD4 cell count (IQR), cells/mm³</td>
<td>262 (99–450)</td>
<td>133 (41–250)</td>
<td></td>
</tr>
<tr>
<td>Median duration of ARV therapy (IQR), months</td>
<td>33 (16–52)</td>
<td>18 (8–33)</td>
<td></td>
</tr>
<tr>
<td>Follow-up CD4 &lt;50/mm³ b</td>
<td>33.9%</td>
<td>78.8%</td>
<td>6.45 (4.27–9.75) c</td>
</tr>
<tr>
<td>Occurrence of AIDS-defining illness b</td>
<td>60.9%</td>
<td>47.3%</td>
<td>1.58 (1.12–2.24) d</td>
</tr>
<tr>
<td>Antifungal treatment b</td>
<td>37.9%</td>
<td>87.9%</td>
<td>2.45 (1.67–3.59) c</td>
</tr>
<tr>
<td>ARV therapy b</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>44.1%</td>
<td>61.8%</td>
<td>0.72 (0.50–1.03) c</td>
</tr>
<tr>
<td>Dual therapy (≥3 drugs)</td>
<td>52.6%</td>
<td>37.6%</td>
<td>0.93 (0.64–1.35) c</td>
</tr>
<tr>
<td>Multiple therapy (≥3 drugs)</td>
<td>55.4%</td>
<td>21.2%</td>
<td>0.41 (0.26–0.66) c</td>
</tr>
</tbody>
</table>

NOTE. IQR, interquartile range (25%–75%); PI, protease inhibitor.

a IVDUs vs. other transmission groups.
b Considered as a time-dependent covariate in the multivariate Cox model.
c Presence vs. absence.

[1] Although it was not considered to be an AIDS-defining condition, VL was found to have the characteristics of an opportunistic disease.

Our study, based on data from the FHDH, which comprises one of the largest cohorts of HIV-infected patients, including 165 HIV-infected patients with VL, showed a decline in the incidence of VL in France after the introduction of HAART. Preliminary studies by 1 local institution in Italy, 2 local institutions in Spain, and 1 local institution in France (our group), involving, respectively 31, 43, 72, and 39 patients, found a significant decline in the incidence HIV-Leishmania coinfections after the introduction of HAART [4–7]; however, these studies have been limited by the small number of patients enrolled.

The primary explanation for this decline, as for that in most opportunistic infections, is that the restoration of immune function after HAART may prevent the emergence of VL. The multivariate analysis showed that immunosuppression (CD4 cell count <50/mm³) is a major independent risk factor for the occurrence of VL. ARV therapy including ≥3 drugs was associated with the prevention of VL. Our results are in accordance with clinical observations. De La Rosa et al. [8] prospectively followed patients with subclinical VL (i.e., the presence of Leishmania species in bone-marrow aspirate, with no fever or splenomegaly and with a hemoglobin level <9 g/dL; 11 patients receiving HAART did not develop overt VL, whereas 2 of 6 who had received ARV therapy other than HAART (CD4− T cell counts of 20/mL and 82/mL) developed clinical VL. Those authors concluded that the decrease of plasma virus load and the increase of CD4− T-cell count induced by HAART most likely prevented the evolution of latent VL into symptomatic disease. Long-term remissions of VL after initiation of HAART have been reported, suggesting that HAART has an impact on the natural course of the parasitic disease in coinfected patients [9, 10]. By contrast, some patients with a history of VL who have responded to HAART have relapsed despite undetectable HIV load and partial restoration of CD4− T cell count; these patients might need ongoing secondary prophylaxis [11–14]. The origin of these relapses is not clear; however, the majority of relapses occurred in patients in whom the restoration of CD4− T cell count was less than that in patients who did not relapse [12–14].

Factors other than restoration of immune function also might account for the decline in the incidence of VL. PIs have shown antimicrobial properties, such as antifungal and antitoxoplasmic activities, in vitro [15]. Although it is unknown whether the PIs have antileishmanial activity, the possibility of a direct effect on latent leishmaniasis when they are used in HAART cannot be excluded. Nevertheless, when we adjusted
the model for the therapeutic class (rather than considering the treatment drugs as being undifferentiated; not shown), the RH of occurrence of VL was estimated to be (1) 0.65 (95% CI, 0.43–0.99; \( P = 0.044 \)) for people treated with NRTI, compared with those not treated with NRTI; (2) 0.40 (95% CI, 0.16–1.05; \( P = 0.062 \)) for those treated with NNRTI, compared with those not treated with NNRTI; and (3) 0.62 (95% CI, 0.40–0.95; \( P = 0.028 \)) for people treated with PI, compared with those not treated with PI. These results do not demonstrate that PIs have an anti-\( Leishmania \) activity, but they do suggest that the association between ARV multiple therapy and a protective effect against VL is probably an indirect effect due to restoration of immune function.

Another important finding of the present study is that \( Leishmania \) infection is significantly more frequent in IVDUs. After adjustment for the transmission group and geographic residence of the patients, our results showed for the first time that intravenous drug use and geographic residence are independent risk factors for the occurrence of VL. Spanish researchers have suggested that there is an anthroponotic cycle of \( Leishmania \) infection among IVDUs, in which needles replace sand flies [16]. Recent data have indicated that a significant number of syringes in a needle-exchange program in Madrid were contaminated by \( Leishmania \) [16]. Therefore, any change in IVDUs’ practices should have a potential impact on the incidence of VL in this population. The French health ministry has authorized both over-the-counter sale of syringes and needles in pharmacies and educational programs, to reduce the transmission of infectious agents between IVDUs; however, since this policy was first instituted in 1987, it must be noted (1) that, because our data begin with 1992, they cannot be used to explain an effect of this policy, which began in 1992 and (2) that the decline observed since 1996 may not be due to this policy. In addition, it should be noted that the decline in the incidence of VL was found both in IVDUs and in non-IVDUs.

The decline in the incidence observed in HIV-infected subjects could reflect a general change in the incidence of VL in France. There is no national registration of VL in France; however, in one of the main geographic foci of VL, the Alpes-Maritimes, the annual incidence of VL has been found to be stable in patients without HIV (P.M. and E.R., unpublished data), whereas it has been found to decline in HIV-infected individuals [6].

In conclusion, we have observed a significant decline in the post-1996 incidence of VL in HIV-infected subjects, associated with the introduction of HAART in France, which resulted in a 59% decreased risk in people treated with ARV multiple therapy. The impact of HAART treatment can be attributed to the restoration of immune function.

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