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The incidence of cerebral and extracerebral toxoplasmosis among 1,699 HIV-infected patients followed in the SEROCO and HEMOCO cohorts (1988–1995) was studied. It increased from 0.7 per 100 person-years in 1988 to 2.1 per 100 person-years in 1992, as a result of the increasing prevalence of patients with CD4 cell counts below 200/µL. It decreased thereafter to 0.2 per 100 person-years in 1995, while the proportion of patients receiving specific prophylaxis was increasing. A Toxoplasma antibody titer of >150 IU/mL was an important predictor of toxoplasmosis (adjusted relative risk [aRR], 3.6 [95% confidence interval, 2.1–6.0]), independent of a CD4+ cell count of <200/µL (aRR, 20.8) and specific prophylaxis (aRR, 0.2 [0.1–0.3]). The median CD4+ cell count was 389/µL at the time the antibody titer was first noted to be >150 IU/mL, while the median CD4 cell count at onset of toxoplasmosis was 58/µL. Thus, disease was diagnosed 10 days to 74 months after the rise in Toxoplasma antibody titers. While the risk factors for development of toxoplasmosis remain incompletely defined, the importance of specific prophylaxis for patients with low CD4 cell counts and high Toxoplasma antibody titers is supported by these findings.

Assessment of risk factors for opportunistic infections in HIV-infected patients helps to establish the indications for and type of specific prophylaxis. The CD4 cell count is an index of immunodeficiency, and the risk of opportunistic infection increases markedly when values fall below 200/µL [1]. The specific risk of toxoplasmosis is also estimated on the basis of the patient’s specific serological status: the presence of Toxoplasma antibodies indicates latent infection that may reactivate as the immunodeficiency progresses [2]. Patients who are seronegative for Toxoplasma are considered to be at a lower risk for developing toxoplasmic encephalitis, but there are few data on the incidence of primary infections and the risk of severe toxoplasmosis (cerebral or extracerebral) for these patients [3–5].

It is recommended that serological testing for Toxoplasma be done soon after the diagnosis of HIV infection [6]; the presence of antibodies reflects latent infection with Toxoplasma gondii. High titers of IgG to Toxoplasma or an increase in the specific IgG titer is more frequent in HIV-infected patients who develop toxoplasmic encephalitis than in other patients [7–11]. In patients with CD4 cell counts below 200/µL, an antibody titer of >150 IU/mL was found to be predictive of toxoplasmic encephalitis [7]. The delay between the antibody increase and the onset of toxoplasmosis remains to be determined and might be an important factor concerning the start of prophylaxis.

In this study we examined the serological and clinical features of cases of toxoplasmosis occurring among 1,699 HIV-infected patients followed between 1988 and 1995 in the French HEMOCO and SEROCO cohorts, before the era of protease inhibitors. We also studied the incidence of seroconversion and serological reactivation in the course of HIV infection and estimated their predictive value for toxoplasmosis.

Patients and Methods

Study Population and Follow-Up

The study population consisted of 1,699 patients followed between 1988 and 1995 in two multicenter French cohorts used to study the natural history of HIV infection in hemophiliacs (HEMOCO cohort) [12] and nonhemophiliac adults (SEROCO cohort) [13, 14]. In both cohorts the patients were volunteers, and HIV infection was defined by a positive ELISA and confirmatory western blot. In the SEROCO cohort the patients were enrolled no more than 1 year after the diagnosis of HIV seropositivity, unless their date of infection was known. Patients were seen every 6 months, or every 3 months in cases of clinical or biological deterioration. At inclusion and each follow-up visit, patients underwent a physical examination and laboratory tests, including a CD4 cell count, immunoglobulin assay, and Toxoplasma antibody titer determination. The date on which specific primary prophylaxis for toxoplasmosis was...
started (with cotrimoxazole, pyrimethamine plus dapsone, or pyrimethamine alone) was noted.

For patients with suspected toxoplasmosis, the results of radiological examinations (including brain CT and/or MRI), the treatment administered, and the response to therapy were recorded. Antiretroviral therapy was prescribed before the onset of AIDS for 41% of patients. Treatment always started with zidovudine alone. Only 8% later switched to combination therapy (usually with zidovudine plus didanosine). None of these patients had received a protease inhibitor before the cutoff date for analysis (1 January 1996).

**Toxoplasma Serology**

IgG and IgM antibodies to *Toxoplasma* were measured at each visit, and an aliquot of serum was kept frozen. Depending on the center visited and date of visit, an indirect immunofluorescence antibody technique or a commercial ELISA kit (mainly IMX [Abbott Laboratories, Abbot Park, IL], Platelia [Sanofi Diagnostics Pasteur, Marnes la Coquette, France] or VIDAS [bioMérieux, Marcy l’Etoile, France]) was used. IgG titers were always expressed in IU/mL and were considered positive at values ≥10 IU/mL. IgM values were expressed qualitatively (presence or absence). Seroconversion was diagnosed when a patient with a negative IgG serology subsequently had an IgG titer of ≥10 IU/mL in association with the presence of IgM. The proportion of specific antibodies in the total pool of IgG, termed the *Toxoplasma* immune load [15, 16], was calculated as the ratio of *Toxoplasma* IgG antibody titer (IU/mL) to total serum level of IgG (µg/mL); results were expressed in IU/µg.

**Diagnosis of Cerebral and Extracerebral Toxoplasmosis**

Cases of toxoplasmosis were reported by each center at the time of diagnosis. The location (cerebral, pulmonary, ocular, or disseminated) was specified, together with the main diagnostic criteria (clinical signs, including ophthalmologic findings; radiological signs on brain CT or MRI; demonstration of *T. gondii* on stained smears or by mouse inoculation or tissue culture; and response to specific therapy). For this study each case was reexamined by a validation committee using medical and laboratory files and was classified according to the degree of diagnostic reliability. Toxoplasmosis was considered (1) definite if *T. gondii* was visualized or isolated from blood or any tissue, in addition to the finding of clinical and radiological signs; (2) probable if clinical and radiological signs improved on specific treatment; and (3) possible when clinical and radiological manifestations improved but did not resolve with specific therapy or when the diagnosis could not be confirmed retrospectively (medical file not available).

**Statistical Analysis**

The cutoff date for this analysis was 1 January 1996. Incidence rates were computed as the number of events per 100 person-years (py) at risk. The Poisson distribution was used to estimate the 95% confidence interval (CI) of the incidence rates [17]. The relative risks (RRs) associated with the factors of progression to toxoplasmosis were estimated by the fitting of a Cox model with fixed or time-dependent variables [18]. Different thresholds of positivity of IgG antibody titers (from 50 to 350 IU/mL, by 50-step progression) and immune load (from 25 to 175 IU/µg, by 25-step progression) were tested for their predictive value on the occurrence of toxoplasmosis. The analyses were performed with use of SAS software (SAS Institute, Cary, NC).

**Results**

Between January 1988 and January 1996, 1,502 patients in the SEROCO cohort (438 women and 1,064 men) and 197 patients in the HEMOCO cohort were recruited. Their baseline characteristics are shown in table 1. During follow-up (median duration, 60.5 months after inclusion, corresponding to 7,649 py), 488 patients’ conditions progressed to CDC (Centers for Disease Control and Prevention) group C status, and 390 deaths were recorded.

**Cases of Toxoplasmosis**

One hundred sixteen patients developed definite, probable, or possible toxoplasmosis (table 2). The cerebral location was largely predominant, occurring in 103 (88.8%) of the 116 cases; other forms were pulmonary, ocular, and disseminated. The median CD4 cell count was 58/µL at the onset of toxoplasmosis. Eighteen (15.5%) of the patients had received specific prophylaxis before onset (cotrimoxazole, 11; clindamycin, 2; dapsone, 1; and pyrimethamine alone, 4). This proportion was

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**Table 1. Characteristics of HIV-infected patients included in the SEROCO and HEMOCO cohorts (1988–1995).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with toxoplasmosis</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>116</td>
<td>1,699</td>
</tr>
<tr>
<td>Median age (y) at inclusion</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Median CD4 cell count at inclusion (no./µL)</td>
<td>286</td>
<td>462</td>
</tr>
<tr>
<td>No. (%) with negative <em>Toxoplasma</em> serology* at inclusion</td>
<td>10 (8.6)</td>
<td>468 (27.5)</td>
</tr>
<tr>
<td>Median <em>Toxoplasma</em> IgG antibody titer at inclusion (IU/mL)</td>
<td>142</td>
<td>66</td>
</tr>
<tr>
<td>Median follow-up (mo)</td>
<td>46.8</td>
<td>60.5</td>
</tr>
<tr>
<td>No. (%) of deaths during follow-up</td>
<td>94 (81.0)</td>
<td>390 (22.9)</td>
</tr>
<tr>
<td>No. (%) who received primary prophylaxis for toxoplasmosis</td>
<td>18 (15.5)</td>
<td>501 (29.5)</td>
</tr>
</tbody>
</table>

* *Toxoplasma* IgG antibody titer of <10 IU/mL.
  † In patients seropositive for *Toxoplasma*. 

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Table 2. Cases of toxoplasmosis, according to their localization, occurring in the SEROCO and HEMOCO cohorts (1988–1995).

<table>
<thead>
<tr>
<th>Localization</th>
<th>Possible</th>
<th>Probable</th>
<th>Definite</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral</td>
<td>48</td>
<td>54</td>
<td>1</td>
<td>103 (88.8)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>7 (6.0)</td>
</tr>
<tr>
<td>Ocular</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Disseminated</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>49 (42.2)</td>
<td>62 (53.5)</td>
<td>5 (4.3)</td>
<td>116 (100.0)</td>
</tr>
</tbody>
</table>

incidence of toxoplasmosis increased from 0.68/100 py (0.08–2.47) in 1988 to 2.10/100 py (1.36–3.10) in 1992, and it fell thereafter to 0.19/100 py (0.01–1.04) in 1995. As shown in figure 1, the trends in the incidence of toxoplasmosis, in the proportion of patients with CD4 cell counts of <200/µL, and in the proportion of patients receiving prophylaxis for toxoplasmosis appeared to be linked. The increasing number of patients with CD4 cell counts of <200/µL at a time when prophylaxis for toxoplasmosis was not routinely prescribed (1988–1992) no doubt accounts for the increasing number of cases. Indeed, the estimated incidence of toxoplasmosis among patients with CD4 cell counts of <200/µL remained stable between 1988 (6.9/100 py) and 1992 (6.7/100 py). After 1992, the decreasing incidence of toxoplasmosis was probably linked to the widespread use of prophylaxis.

Figure 1. Trends in toxoplasmosis incidence (— — —; per 100 person-years), prevalence of toxoplasmosis prophylaxis (□; percentage of patients), and prevalence of CD4 cell counts <200/µL (●; percentage of patients) among the SEROCO and HEMOCO cohorts, 1988–1995.

The *Toxoplasma* serology was positive in 113 patients (97.4%), with a median *Toxoplasma* IgG titer of 150 IU/mL at the time of diagnosis (first quartile = 60; third quartile = 240); none had detectable IgM antibodies at the time of diagnosis. Among these 113 patients, 78 (69.0%) had had an increase in the *Toxoplasma* IgG titer (to ≥150 IU/mL) before clinical onset, within a median of 25 months previously (range, 10 days to 74 months). Three patients remained seronegative at the onset of toxoplasmosis; the absence of specific antibodies was confirmed by a negative dye test and negative direct agglutination test on frozen sera. In two antibody-negative patients with possible toxoplasmic encephalitis, the last serological tests were performed 2 and 5 months before the diagnosis, and no further frozen sera were available. The third patient had probable ocular toxoplasmosis, and his serology remained negative after diagnosis (in 11 months of follow-up). The CD4 cell counts of these three patients were 66/µL, 1/µL, and 150/µL at diagnosis.

During the study period the overall incidence of toxoplasmosis was estimated at 1.53/100 py (95% CI, 1.25–1.81). The incidence of toxoplasmosis was significantly lower than that of patients who did not develop toxoplasmosis (30.5%; *P* < .001).

A total of 12,288 serological results were analyzed. At the time of their inclusion in the study, the *Toxoplasma* serological status was determined for 1,683 patients (data were missing for 16). Serology was negative for 468 patients (27.8%). The remaining 1,215 had serological evidence of exposure to *Toxoplasma*, with a median specific IgG titer of 66 IU/mL and a median immune load of 34.8 IU/µg. The antibody titers and immune load values had a log-normal distribution.

ELISA methods were increasingly used over the years, accounting for 39.6% of antibody titer determinations in 1988 and 91.4% in 1995. As the conversion factor between immunofluorescence and ELISA antibody titers is unclear [19], subsequent statistical analyses were based only on the subset of 903 patients tested exclusively with ELISA methods. Among these patients, 253 (28.0%) were seronegative at inclusion, and 14 seroconverted during follow-up, giving an incidence of 1.63...
seroconversions/100 py at risk (95% CI, 0.89–2.73). Among these 14 seroconverters the median CD4 cell count was 496/µL (range, 243–891/µL) at the time of seroconversion. None of them developed cerebral or extracerebral toxoplasmosis during follow-up.

Among the 903 patients always tested by ELISA, 322 (35.7%) had a titer of IgG antibody to *Toxoplasma* of ≥150 IU/mL either at inclusion (n = 187) or during follow-up; the incidence of increases in antibody to ≥150 IU/mL during follow-up can thus be estimated at 4.92/100 py (95% CI, 4.09–5.75). The median CD4 cell count at the time of this increase was 389/µL. The antibody increase occurred when the CD4 cell count was >200/µL in 81.4% of cases.

### Risk Factors for Cerebral or Extracerebral Toxoplasmosis

Candidate risk factors for toxoplasmosis were the patients’ baseline characteristics and time-dependent factors such as an increase in the antibody titer to ≥150 IU/mL, a fall in the CD4+ cell count to <200/µL, and the lack of specific prophylaxis (table 3). Age, sex, and the cohort in which patients were enrolled (hemophiliacs vs. nonhemophiliacs) were not related to the risk of toxoplasmosis. A low CD4 cell count at inclusion (fitted as a continuous variable) and a reduction in the CD4 cell count to <200/µL (fitted as a time-dependent variable) were associated with toxoplasmosis in univariate and multivariate analyses (adjusted RR = 1.22 for a difference of 100 CD4 cells/µL at inclusion and 20.83 for a CD4 cell count of <200/µL during follow-up). Prophylaxis was only slightly protective, according to univariate analysis. Its effect became marked in the multivariate analysis after adjustment for the CD4 cell count (adjusted RR = 0.18).

When the *Toxoplasma* antibody titer increased to >150 IU/mL (fitted as a time-dependent variable), patients were at a higher risk of toxoplasmosis in both univariate and multivariate analysis (adjusted RR = 3.53). Similar results were obtained when the immune load threshold of 50 IU/µg was used (adjusted RR = 3.94) instead of an antibody titer of ≥150 IU/mL. The choice of these thresholds (an antibody titer of ≥150 IU/mL or an immune load of ≥50 IU/µg) was made by studying the risk of toxoplasmosis according to different thresholds in maximal values reached during follow-up. The risk of toxoplasmosis increased when the maximum antibody titer was ≥150 IU/mL or when the maximum immune load was ≥50 IU/µg.

The incidence of toxoplasmosis (table 4) was low among seronegative patients (0.33/100 py). It remained low in *Toxoplasma*-seropositive patients with a CD4 cell count of ≥200/µL, although it increased to 0.53/100 py when the IgG antibody titer was ≥150 IU/mL. After the CD4 cell count had fallen below 200/µL, the incidence of toxoplasmosis increased significantly (to 3.45/100 py) among patients with antibody


<table>
<thead>
<tr>
<th>Variable</th>
<th>crRR</th>
<th>95% CI</th>
<th>P value</th>
<th>aRR</th>
<th>95% CI</th>
<th>P value</th>
<th>aRR*</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at inclusion (for a 10-y increase)</td>
<td>1.14</td>
<td>0.90–1.42</td>
<td>NS</td>
<td>1.22</td>
<td>1.00–1.35</td>
<td>.05</td>
<td>1.22</td>
<td>1.00–1.35</td>
<td>.05</td>
</tr>
<tr>
<td>Female (vs. male)</td>
<td>0.75</td>
<td>0.42–1.35</td>
<td>NS</td>
<td>0.18</td>
<td>0.09–0.38</td>
<td>&lt;.0001</td>
<td>0.19</td>
<td>0.09–0.43</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hemophiliacs (vs. others)</td>
<td>1.20</td>
<td>0.66–2.28</td>
<td>NS</td>
<td>25.02</td>
<td>10.72–58.38</td>
<td>&lt;.0001</td>
<td>21.06</td>
<td>8.25–53.76</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CD4+ cell count at inclusion (per 100-cell/µL decrease)</td>
<td>1.65</td>
<td>1.35–1.83</td>
<td>&lt;.0001</td>
<td>20.83</td>
<td>8.15–53.27</td>
<td>&lt;.0001</td>
<td>20.38</td>
<td>8.15–53.27</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Fall in CD4+ cell count to &lt;200/µL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific prophylaxis</td>
<td>0.86</td>
<td>0.43–1.76</td>
<td>NS</td>
<td>0.18</td>
<td>0.09–0.38</td>
<td>&lt;.0001</td>
<td>0.19</td>
<td>0.09–0.43</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><em>Toxoplasma</em> IgG antibody titer of ≥150 IU/mL</td>
<td>4.29</td>
<td>2.55–7.21</td>
<td>&lt;.0001</td>
<td>3.53</td>
<td>2.12–6.01</td>
<td>&lt;.0001</td>
<td>NC</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Toxoplasma</em> immune load of ≥50 IU/µg</td>
<td></td>
<td></td>
<td></td>
<td>3.94</td>
<td>2.28–6.99</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: aRR = adjusted relative risk; crRR = crude relative risk; NC = not computed.

* Adjusted relative risk from multivariate analysis using immune load instead of IgG titer.

† Time-dependent variable.

Table 4. Incidence of toxoplasmosis and 95% confidence intervals, as related to *Toxoplasma* IgG antibody titers and CD4 cell counts.

<table>
<thead>
<tr>
<th>Toxoplasmosis</th>
<th>No. of events/no. exposed</th>
<th>Incidence per 100 person-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seronegative for <em>Toxoplasma gondii</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count of ≥200/µL and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG titer of &lt;150 IU/mL</td>
<td>2/443</td>
<td>0.14 (0.03–0.52)</td>
</tr>
<tr>
<td>IgG titer of ≥150 IU/mL</td>
<td>4/236</td>
<td>0.53 (0.14–1.35)</td>
</tr>
<tr>
<td>CD4 cell count of &lt;200/µL and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG titer of &lt;150 IU/mL</td>
<td>17/206</td>
<td>3.45 (1.95–5.46)</td>
</tr>
<tr>
<td>IgG titer of ≥150 IU/mL</td>
<td>37/166</td>
<td>9.64 (6.88–13.28)</td>
</tr>
</tbody>
</table>
titers remaining below 150 IU/mL. It was even higher (9.64/100 py) after the antibody titer increased to >150 IU/mL.

Discussion

This longitudinal analysis of clinical and serological data on 1,699 HIV-infected patients offered a unique opportunity to study the course of toxoplasma infection during HIV disease progression.

Among these patients, 116 cases of cerebral or extracerebral toxoplasmosis were observed, given a mean incidence of 1.52/100 py. This high incidence of toxoplasmosis is not surprising, given the high prevalence (72.2%) of latent toxoplasma infection at enrollment, as in the general French population [5]. The incidence of toxoplasmosis varied with time, rising from 0.68/100 py in 1988 to 2.10/100 py in 1992, owing to the progression of HIV disease in the cohort and the limited use of prophylaxis during this period. Incidence dramatically fell between 1992 and 1995, after the widespread introduction of specific prophylaxis.

As previously described [2], toxoplasmosis was observed at an advanced stage of HIV disease, when the median CD4 cell count was only 58/μL. The cerebral location was the most frequent (95% of cases). Eighteen patients had been prescribed prophylaxis for toxoplasma infection. Although compliance was not specifically assessed, such prophylactic failures could be attributed to irregular intake (explicitly recorded for five patients who took cotrimoxazole). Poor efficacy of single-drug regimens (clindamycin [n = 2], dapsone [n = 1], or pyrimethamine [n = 4]) might also explain some of these apparent failures.

The follow-up of Toxoplasma antibody titers allowed us to compare the incidence of toxoplasmosis among seronegative and seropositive patients and, in the latter group, to estimate the toxoplasmosis-predictive value of an increased antibody titer. For patients who were seronegative at entry, the incidence of seroconversion was 1.63/100 py (CI, 0.89–2.73), in keeping with previously published values in France for HIV-infected patients (1%–2%) [4, 5] and pregnant women (2%) [20] and for North American HIV-infected patients (2%) [3]. None of the 14 seroconversions were accompanied by severe clinical manifestations, suggesting that the risk of severe toxoplasmosis immediately following primary toxoplasma infection is low in HIV-infected patients. However, three cases of ocular or cerebral toxoplasmosis were documented, involving patients who remained persistently seronegative for both IgG and IgM antibodies. The possibility that a primary acquired infection failed to elicit an antibody response because of the patients’ profound immunodeficiency cannot be ruled out.

For these reasons, behavioral recommendations to prevent T. gondii contamination are warranted for Toxoplasma-seronegative patients with low CD4 cell counts [6]. In countries where the incidence of toxoplasmosis is high, seronegative patients with low CD4 cell counts should be examined once a year for Toxoplasma antibodies. In the search for Toxoplasma antibodies, attention should be paid to the sensitivity of the test used, in order to discriminate seropositivity from seronegativity, and to its reproducibility for determination of IgG antibody titers. Several commercial ELISA kits fulfill these criteria, but the dye test or the sensitive agglutination test may also be recommended for assessment of seropositivity in patients with low levels of antibodies.

Seropositivity for Toxoplasma was associated with a much higher risk of toxoplasmosis. At the time of diagnosis, the median antibody titer was 150 IU/mL (with no detectable IgM antibodies). It has already been observed that the antibody titer frequently increases before clinical onset [7–11]. Using a threshold titer of 150 IU/mL, which was previously found to be indicative of a higher risk of toxoplasmic encephalitis in patients with low CD4 cell counts [7], we found that 78 of the 116 patients who developed toxoplasmosis had had such an increase in the IgG antibody titer, from 10 days to 74 months (median, 25 months) earlier. This interval was no doubt underestimated, as 59% of these patients already had such a level of IgG antibodies at inclusion. A rise in the antibody titer to >150 IU/mL was associated with a higher risk of toxoplasmosis (adjusted RR = 3.53). The IgG value of >150 IU/mL was found to be the most predictive and discriminatory among those tested.

The increase in the Toxoplasma IgG titer is very likely to be specific for Toxoplasma and not due to a polyclonal increase in immunoglobulins. Indeed, by studying the anti-Toxoplasma immune load, we found that a threshold of 50 IU/μg was predictive of toxoplasmosis. Israelski et al. [21] also observed frequent increases in the Toxoplasma antibody titers in HIV-infected patients, with no concomitant rise in total IgG or rubella-specific IgG levels.

Assuming that this response is specific, it could result either from reactivation of a chronic infection or from reinfection. This latter possibility cannot be ruled out, in view of occasional reports of congenital toxoplasmosis following reinfection in seropositive pregnant women [22–24]. In a recent study in mice [25], animals chronically infected with one strain could be reinfected by a different strain, with invasion of the brain by the reinfecting strain. If reinfection can occur in humans, however, it is unlikely to explain all the antibody increases, which occurred at a much higher rate than seroconversions.

Several lines of evidence favor reactivation of chronic infection. Experimental models have clearly shown the role of cell-mediated immunity and cytokines in the containment of chronic toxoplasmosis [26]. These functions are profoundly altered in advanced HIV infection. In our patients, most of the antibody titer increases occurred a long time before clinical onset (median, 25 months), and the median CD4 cell count at the time of the antibody increase was 389/μL. This suggests that rupture of dormant cysts, which probably underlies these serological reactivations, is not closely related to the CD4 cell count but rather to a functional immune defect such as an impaired blasto-
genetic response to Toxoplasma antigen [27, 28]. Following reac-
tivation, parasite spread would be contained in those patients 
with relatively intact immune functions and lead only to a 
humoral response. By contrast, reactivating toxoplasmosis 
would have clinical repercussions in patients with more pro-
found immunodeficiency, e.g., at a late stage of HIV disease, 
when cellular responses to Toxoplasma antigen are impaired. 

A potential limitation of our study is the fact that 48 of the 
103 cases of cerebral toxoplasmosis reported by the clinicians 
were only “possible” (mainly because the medical file was 
not available, making impossible the retrospective ascertain-
ement by the validation committee). The analysis of risk factors 
for toxoplasmosis was therefore repeated after excluding these 
48 cases; similar relative risks were found, although confidence 
intervals could contain “1” due to the smaller sample size 
(data not shown).

A fall in the CD4 cell count to <200/µL remains the most 
powerful predictor of toxoplasmosis in HIV-infected patients 
and is the point at which to start specific prophylaxis. However, 
an IgG titer of ≥150 IU/mL should be considered as a specific 
marker of a parasitologic event and a risk factor for later onset 
of cerebral or extracerebral toxoplasmosis, especially when the 
CD4 cell count is <200/µL. Testing for Toxoplasma antibodies 
should therefore be performed every 6 months for patients with 
advanced immunodepression. Our findings reinforce the need 
for prescription of and compliance with specific prophylaxis, 
whose efficacy, established from randomized trials, could also 
be observed between 1988 and 1995 in these cohorts of HIV-
infected patients.

Acknowledgments

The authors thank Prof. J.L. Vilde and Prof. C. Leport for their 
contribution in initiating this work, Prof. Ph. Thulliez for control-
ling sera by dye test and sensitized agglutination test, N. Bia-
lowons, D. Laskri, D. Ramirez, A. Sarr, and A. Wade for data 
collection, and A. Persoz and F. Boufassa for data management.

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