Human immunodeficiency virus infection and human African trypanosomiasis: a case–control study in Côte d'Ivoire*

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Abstract

To assess the association between human immunodeficiency virus (HIV) infection and human African trypanosomiasis (HAT) in Côte d'Ivoire in West Africa, a cross-sectional case–control study was conducted on 301 HAT patients recruited in the main foci of the country. For each HAT patient, 3 controls, matched for sex, age and residence, were selected. Data relating to socio-demographic factors and potential risk factors for Trypanosoma brucei gambiense and HIV infections were obtained, and serum samples were collected for HIV-1 and HIV-2 tests. A positive test consisted of enzyme immunoassay reactive to HIV-1, HIV-2 or both and confirmed by a synthetic peptide test or Western blot. Data were analysed using conditional logistic regression with EGRET software. No statistically significant difference was found between the prevalence of HIV infection in HAT patients and controls (4.3% and 3.5% respectively; crude odds ratio (OR) 1.28, 95% confidence interval (CI) 0.65–2.50). In multivariate analysis, allowance for 5 covariates did not change the association between the 2 infections (adjusted OR 1.27, 95% CI 0.64–2.52). Although this study had limited statistical power, no significant association was found between HIV infection and T. b. gambiense infection in rural Côte d'Ivoire. Studies are needed to determine whether HIV infection influences the clinical course of HAT, a question not addressed in the present study.

Keywords: trypanosomiasis, Trypanosoma brucei gambiense, human immunodeficiency virus, lack of association, Côte d'Ivoire

Introduction and Background

Infection with human immunodeficiency virus (HIV), the causative agent of the acquired immunodeficiency syndrome (AIDS), is characterized by a profound defect in the host immune response, affecting especially cell-mediated immunity and resulting in the occurrence of various opportunistic infections (PANTALEO et al., 1993; WEISS, 1993). There is concern that the epidemiology of certain endemic diseases in the tropics could be altered by HIV infection (SMITH et al., 1988; MORROW et al., 1989; FLEMING, 1990), although systematic study of this subject has been limited. The greatest attention has been given to the association between HIV infection and tuberculosis, which is having a major public health impact (DE COCK et al., 1992). No direct or clinically important interaction with HIV infection has been demonstrated for leprosy (LUCAS, 1993) or malaria (NGUYEN-DINH et al., 1987; GREENBERG et al., 1991), and the rarity of a number of other endemic diseases in AIDS patients in the tropics has been commented upon (LUCAS, 1990). Many of the opportunistic infections in AIDS patients are caused by intracellular protozoa (CANNING, 1990; PLEEMING, 1990). Studies from Mediterranean countries and Latin America have shown that visceral leishmaniasis occurs as an opportunistic infection in persons with AIDS (FERNANDEZ-GUERRERO et al., 1987; MONTALBAN et al., 1989). Although the epidemiological association between HIV infection and Typanosoma cruzi infection has not been explored, the clinical features of Chagas disease may be altered in HIV-infected persons (SOLARI et al., 1993). The situation, with respect to human African trypanosomiasis (HAT) is a potential cause for concern (ESTAMBALE & KNIGHT, 1992). Interaction between HAT and HIV infection is biologically plausible, since cell-mediated immunity is important in the host response to HAT. If an association did exist, it could have important implications for the epidemiology and control of HAT.

Although studies from Central African (NOIREAU et al., 1987; LAZAR ET AL., 1992) failed to show evidence of a significant association between HIV infection and HAT, there have been few populations in which adequate spread of the 2 infections has occurred for epidemiological interactions to become apparent. An epidemic of T. brucei rhodesiense HAT has been occurring during the last decade in Busoga District, Uganda (MBULAMBERI, 1989; OKIA et al., 1994), where a high prevalence of HIV infection has been observed over the same period. No definitive data exist to show a change in the epidemiology of HAT under the influence of HIV infection in that region.

Hardly any investigations of HAT and HIV infection have been conducted in West Africa. We therefore performed this study to examine whether an association exists between HIV and T. b. gambiense infection in rural Côte d'Ivoire, one of the few countries in that region where rates of both infections are sufficiently high to address this question.

Subjects and Methods

The study was conducted in the main foci of HAT in Côte d'Ivoire between 1991 and 1993. Cases were recruited in the areas of Zoukoubeu, Bouaké and Issia in the middle west of the country. The populations of 88 villages, all located in the forest belt, were surveyed for HAT. These areas are inhabited by multi-ethnic populations, of whom about 40% are indigenous (Niaboua, Bete and Gouro), the remaining being immigrants from other areas of Côte d'Ivoire (Baoué, Dioula, Senoufo, and others) or neighbouring countries (Mossi, Gourounsi, Dioula, Senoufo, amongst others). People live either in villages or in satellite hamlets and permanent encampments near to or inside plantations. The population is involved in cultivation of coffee and cocoa.

Patient recruitment

HAT patients were recruited through mass surveys, conducted jointly by the teams of l'Institut Pierre Richet (IPR), Bouaké and the Projet de Recherches Cliniques sur la Trypanosomiasis (PRCT), Daloa. The survey protocol was similar to that described by MEDA et al.
The card agglutination test for trypanosomiasis (CATT) (Magnus et al., 1978) was used on blood obtained by finger prick to screen all subjects for HAT antibodies. Parasitological diagnostic confirmation was through direct examination of the aspirate from palpable lymph nodes, when appropriate, or through the use of the miniature anion-exchange centrifugation technique (MAECT) (Lumsden et al., 1979).

Definition of HAT cases
A person was considered to have HAT if he/she was reactive in the CATT and had parasitological evidence of T. b. gambiense in the blood or lymph node fluid.

Selection of controls
Three CATT-negative controls, matched for sex, age (±5 years) and area of residence, were selected for each case during the mass surveys. Controls were identified among consecutive persons examined directly after the corresponding infected individual (the case). Controls with a past history of HAT were excluded from the study.

Sample size
The results of the national serosurvey carried out in 1990 showed an overall prevalence rate of HIV infection of 5-7% in areas outside the major city, Abidjan (Soro et al., 1990). In view of these results and on the following assumptions (α=0.05; power=0.80; prevalence rate of HIV in patients=10%; risk ratio for HIV infection=2; ratio of controls to cases=3:1), the minimum sample size required to show an association between HIV infection and HAT was 296 cases.

Field data collection
Epidemiological data were collected in the field, both for cases and controls, using a standard questionnaire that had been previously pre-tested and validated (Meda et al., 1993). This questionnaire was administered in French or a local language by 2 trained interviewers. Patients and matched controls were interviewed by the same person. The questions dealt with socio-demographic factors and potential confounders for HIV and T. b. gambiense infections, such as ethnicity, religion, marital status, education, occupation, geographical origin, type of residence (village or encampment), history of travel abroad, history of parenteral injections, and previous history of treated or untreated sexually transmitted disease (STD). The time frame for the events of interest was 2 years before the interview. The life-time history of blood transfusion was also assessed. Although relevant to HIV infection, contacts with prostitutes and numbers of sex partners were not investigated; questions regarding these issues would have been socially unacceptable and would have created resistance to the study and the HAT control activities. All activities in the field were undertaken under the supervision of one of the authors (H. A. M.).

Intravenous blood specimens (5 mL) were collected from all cases and controls. Serum specimens were separated for T. b. gambiense antibody detection in the field. For HIV tests, serum samples were stored in a portable refrigerator while field work was conducted. At the end of each day, specimens were transported to the laboratory of RCT. They were divided into aliquots and stored frozen until processed for HIV testing.

Laboratory tests for HIV infection
Serological tests for antibodies to HIV-1 and HIV-2 were performed in the laboratory of Project RCT, Abidjan, using commercial assays. Serum specimens were tested by whole virus specific enzyme immunosorbent assay (EIA) (Genetic Systems, Seattle, Washington, USA) for HIV-1 and HIV-2. Positive specimens were supplementally tested by synthetic peptide EIA (Pepti-Lav 1-2, Diagnostics Pasteur, Paris) (De Cock et al., 1990). Specimens that were positive by whole virus EIA but negative by synthetic peptide EIA were tested by virus specific Western blot (HIV Blot 2-2, Diagnostic Biotechnologie, Geneva, Switzerland for HIV-1; New-Lav Blot 2, Diagnostics Pasteur, Paris, France for HIV-2). A positive test required a positive EIA reaction for HIV-1, HIV-2 or both, confirmed by synthetic peptide EIA or Western blot. Since a confidential identification number for each specimen was used, the laboratory technician was blinded to the trypanosomiasis status of the subjects.

Statistical analysis
Data were entered into a personal computer using Dbase III Plus and analysed using Epi-Info and Egret softwares. Using Egret, conditional logistic regression was performed to calculate the crude odds ratio (OR) for the association between HAT and HIV infection or potential confounders. A multivariate procedure was used to compute the adjusted estimates of the ORs, allowing for potential confounders and testing for effect modification. The regression model included all variables with a value of P equal to 0.10 or less in the univariate step. The 95% confidence intervals (CI) of the OR for each variable in the model were also computed, together with the value of P between the strata. The α error was set at the 0.05 level.

Ethical approval
The study was conducted in accordance with national practice and with the ethical approval of the Research Subcommittee of the Côte d'Ivoire National AIDS Control Programme. Blood samples were not linked to identifying information about the HIV status. Pre- and post-test counselling was offered to patients with HAT at the RCT clinic.

Results
The total population screened numbered 55,344; 302 HAT cases were detected (prevalence rate 5.5 per 1000). Controls were not available for a small number of patients. Thus, a total of 301 matched sets was used in the analysis: 295 quadruplets, 5 triplets and 1 pair. Cases and controls were comparable with respect to the matching variables and occupation (Table 1). The mean ages were 29.3 years (SD 16.8; range 2-74) for controls and patients, respectively.

Table 1. Distribution of sex, age, type of residence and occupation of human African trypanosomiasis cases and matched controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td>Number</td>
<td>301 (100%)</td>
<td>896 (100%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>166 (55.1%)</td>
<td>483 (53.9%)</td>
</tr>
<tr>
<td>Female</td>
<td>135 (44.9%)</td>
<td>413 (46.1%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-14</td>
<td>72 (23.9%)</td>
<td>215 (24.0%)</td>
</tr>
<tr>
<td>15-44</td>
<td>172 (57.1%)</td>
<td>508 (56.7%)</td>
</tr>
<tr>
<td>45-79</td>
<td>57 (18.9%)</td>
<td>173 (19.3%)</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Village</td>
<td>42 (14.0%)</td>
<td>121 (13.5%)</td>
</tr>
<tr>
<td>Encampment</td>
<td>259 (86.0%)</td>
<td>775 (86.5%)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmer</td>
<td>292 (97.0%)</td>
<td>871 (97.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (3.0%)</td>
<td>25 (2.8%)</td>
</tr>
</tbody>
</table>

29-1 years (standard deviation [SD] 16.5; range 2-79) and 29-3 years (SD 16.8; range 2-74) for controls and patients, respectively.

On univariate, matched analysis, only 5 variables (covariates) were associated with HAT at the P<0.1 level (Table 2). The percentage distribution of ethnicity in cases and controls was closely similar (22.9% and 24.4% of indigenous persons, respectively; uncorrected χ²=0.28, P=0.59). However, in the matched analysis, a significant difference was observed (P=0.04). For the
variable "religion", only one stratum (animist) was significant, but we decided to include the whole variable in the model. Allowing for the 5 covariates of interest, a multivariate model was fitted to the data. The association between HIV infection and HAT remained weak and non-significant (Table 2). In that model, the significant effect of ethnicity disappeared, while that of the other covariates was not affected (Table 2).

The respective prevalence rates of HIV infection in HAT patients and controls did not differ significantly (Table 2). When the analysis was restricted to the subjects aged more than 14 years, the crude estimates of the ORs for the association between HIV and T. b. gambiense infections did not change significantly, and neither did the adjusted ORs obtained from multivariate analysis (data not shown).

Discussion
An early investigation of HIV infection in patients admitted to hospital with HAT in Côte d'Ivoire between 1983 and 1987, conducted using stored sera, showed a prevalence rate of 1.7% (POVEDA et al., 1989). The prevalence rate of HIV infection has increased substantially in all parts of the country since that time (Soro et al., 1990; Djomand et al., in press). The nation-wide survey published in 1990 (Soro et al., 1990) showed overall prevalence rates of 5-7% in rural and semi-urban areas.

The prevalence rate of HIV infection among HAT patients (4.3%) reported here was 6 times higher than that reported by POVEDA et al. (1989) for the period 1983-1987. However, the prevalence rate among our controls was 3.5%, a difference which did not differ significantly from that observed in cases.

Because the prevalence rates of HIV infection among cases and controls were below the expected rates upon which our sample size calculation was based, our study may have suffered from insufficient power to detect a significant difference if one existed. The lack of association between HIV infection and HAT in this West African region is, however, consistent with available information from elsewhere in Africa (Nogoue et al., 1987; Louis et al., 1991; Peppin et al., 1992); nevertheless, it should be interpreted with slight caution.

The design of each of the previously reported studies was different, and all have been subject to criticism (Veas & Rey, 1991), including concerning choice of controls. Another potential weakness in all the studies quoted, as well as in ours, was selection bias. If HAT patients concurrently infected with HIV have a reduced survival time, then they may have been less likely to be included in the surveys than seronegative patients, in which case the strength of association between the 2 infections would have been underestimated. Such a bias might be greater when cases are recruited through cross-sectional case-control surveys than in a prospective design (nested case-control study).

The age profile of the study population could have influenced the results, since 72 cases aged 2-14 years and 215 controls of the same age group were included in the analysis. We can presume that the prevalence of HIV infection is very low among children compared to adults. However, when the analysis was restricted to the subjects aged more than 14 years, the association between HAT and HIV infection remained non-significant.

We found that a history of transfusion was a risk factor for HAT, while travel abroad and being an animist were associated with a reduced risk. We cannot explain the protective effect of animism but wonder whether it is related to residence, and thus risk of exposure to tsetse flies (Laveissiere et al., 1986). Travel abroad may be associated with a lower risk for HAT because travellers are frequently foreigners who have spent less time in the HAT endemic area. The association between HAT and blood transfusion, which persisted after non-matched comparison of cases and controls stratified by HIV status (data not shown), is intriguing and merits further investigation. Transfusion is well recognized, of course, as a risk factor for transmission of T. cruzi (Appleman et al., 1993).

The clinical effects of HIV infection on HAT remain to be explored. Pronounced immunological changes occur in the late stage of HAT and relative immunosuppression develops, affecting both cellular and humoral immunity (Greenwood et al., 1973; Manfield, 1981; Cox, 1992). T cell subsets and cytokines have complex effects and interactions in parasitic infections (Cox & Liew, 1992) and, in HAT, tumour necrosis factor affects the processes of parasite control, immunosuppression and pathology (Lucas et al., 1993). Retroviral infection depleting CD4+ cells is thought to be a potential risk factor for reactivation of Chagas disease in persons chronically infected with T. cruzi (see Rocha et al., 1994), and immune activation in HIV-infected tuberculosis patients is possibly associated with increased HIV replication and an increase in the progression rate of HIV

Table 2. Univariate and multivariate analysis of human immunodeficiency virus (HIV) infection in human African trypanosomiasis cases and matched controls

<table>
<thead>
<tr>
<th>Variablesa</th>
<th>Cases</th>
<th>Controls</th>
<th>Univariate analysis ORb P</th>
<th>Multivariate analysis ORc P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
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<tr>
<td>Indigenous</td>
<td>69 (22.9%) 219 (24.4%)</td>
<td>3.26 (10.04-10.20) 0.04 2.84 (0.83-9.74) 0.10</td>
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<tr>
<td>Other</td>
<td>232 (77.1%) 677 (75.6%)</td>
<td></td>
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<td></td>
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<tr>
<td>Education</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>255 (85.0%) 728 (81.2%)</td>
<td>0.64 (0.41-1.01) 0.06 0.70 (0.44-1.12) 0.14</td>
<td></td>
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<tr>
<td>Yes</td>
<td>45 (15.0%) 168 (18.8%)</td>
<td></td>
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<tr>
<td>Religion</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Christian</td>
<td>72 (23.9%) 171 (19.0%)</td>
<td>0.75 (0.48-1.20) 0.23 0.68 (0.42-1.09) 0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muslim</td>
<td>155 (51.5%) 470 (52.5%)</td>
<td>0.56 (0.34-0.93) 0.03 0.57 (0.34-0.98) 0.04</td>
<td></td>
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<tr>
<td>Ancest</td>
<td>74 (24.6%) 255 (28.5%)</td>
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<tr>
<td>Travel abroad</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>264 (87.7%) 717 (80.0%)</td>
<td>0.52 (0.35-0.78) 0.002 0.50 (0.33-0.76) 0.001</td>
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</tr>
<tr>
<td>Yes</td>
<td>37 (12.3%) 179 (20.0%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>297 (98.7%) 895 (99.9%)</td>
<td>12.00 (1.34-107.40) 0.03 13.49 (1.44-126.10) 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (1.3%) 1 (0.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>288 (95.7%) 865 (96.5%)</td>
<td>1.28 (0.65-2.50) 0.47 1.27 (0.64-2.53) 0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>13 (4.3%) 31 (3.5%)</td>
<td></td>
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<td></td>
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</tbody>
</table>

aVariables were entered in the model according to the order shown in this Table.
bCrude odds ratio; 95% confidence interval in parentheses.
cAdjusted odds ratio; 95% confidence interval in parentheses.
disease (WALLIS et al., 1993). An unfavourable outcome for HAT and HIV disease in persons with both infections would not be surprising, but no data on this are available.

In conclusion, we were unable to show that HIV infection is associated with HAT in rural Côte d’Ivoire, although our study suffered from lower statistical power than expected. Future studies should consider using a nested case–control design and aim at a larger sample size. Finally, there is a need for studies to examine the clinical effects of HIV infection on HAT which, if they exist, may be potentially important as HIV infection spreads in rural areas of HAT endemic countries.

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References


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Further details can be obtained from: Dr L. M. Gibbons, International Institute of Parasitology, 395A Hatfield Road, St Albans, Hertfordshire, AL4 0XU, UK.

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