Coinfection by HTLV-I/II is associated with an increased risk of strongyloidiasis and delay in starting antiretroviral therapy for AIDS patients

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ABSTRACT

Objective: To compare the clinical characteristics and outcomes of HIV-1-HTLV-1 coinfected patients, in Bahia, Brazil. **Methods:** Retrospective, comparative study. **Results:** Among a total of 123 consecutive HIV infected patients, 20 men (20.6%) and 6 women (23.1%) had detectable antibodies against HTLV-I/II. The major risk factor associated with coinfection by HTLV was intravenous drug use (57.7% of coinfected patient *versus* 9.2% of HTLV seronegative patients, $p < 0.0001$). Coinfected patients had higher absolute lymphocyte counts (1,921 + 762 *versus* 1,587 + 951, $p = 0.03$). Both groups of patients had similar means of CD4+ and CD8+ cell counts. However, among patients with AIDS CD4+ cell counts were significantly higher among those coinfected with HTLV-I/II (292 ± 92 cells/mm^3, *versus* 140 ± 177cells/mm^3, $p = 0.36$). The frequency and type of opportunistic infections were similar for both groups, but strongyloidiasis and encephalopathy were more frequently diagnosed in coinfected patients ($p < 0.05$). On the other hand, patients coinfected with HTLV-I/II received significantly less antiretroviral therapy than singly infected by HIV-1. **Conclusion:** Coinfection by HTLV-I/II is associated with an increased risk of strongyloidiasis for HIV patients. Higher CD4 count may lead to underestimation of immunodeficiency, and delay to initiate antiretroviral therapy.

Keywords: HIV; HTLV-I/II; coinfection *Strongyloidiasis*; CD4/CD8.

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INTRODUCTION

The human immunodeficiency virus type-I (HIV-1) is the causative agent of the acquired immunodeficiency syndrome (AIDS). Human T-cell leukemia/lymphoma virus type I (HTLV-I) is conclusively associated with adult T-cell leukemia/lymphoma (ATLL), and tropical spastic paraparesis/HTVL-associated myelopathy (TSP/HAM). The role of HTLV-II infection as a cause of disease is still controversial.[1-5] These infectious agents all share a similar pattern of transmission. The established routes of infection are sexual, parenteral (blood transfusion, needle sharing or percutaneous exposure), and vertical (congenital or via breastfeeding).[6-11] Coinfection with these two distinct retroviruses has been frequently reported in the last few years.[12-16]

There is some evidence suggesting that double infection by HIV-HTLV may alter the clinical and laboratory course of AIDS, but the real impact of coinfection on clinical presentation and outcome of AIDS patients remains to be determined.[17-19]

Bahia, a northeastern state of Brazil, is an endemic area for HTLV infection. A recent report showed a prevalence rate of 1.8% of HTLV-I/II antibodies among the general population.[20] The reported incidence of AIDS cases in Salvador, the capital city of Bahia state, is 16.3/100,000 inhabitants.[21] In a previous, cross-sectional study of 895 HIV-infected patients we detected a rate of coinfection by HTLV-I/II of 16.7%.[16]

This study was conducted in order to identify potential differences in the clinical evolution of HIV infected patients with or without HTLV-I/II coinfection, as well as to ascertain the impact of coinfection on the surrogate markers of HIV infection. Since highly active antiretroviral therapy (HAART) has dramatically modified the natural course of HIV infection, we retrospectively evaluated patients diagnosed before the HAART era.

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We declare no conflict of interest

MATERIAL AND METHODS

Patient population

A total of 123 consecutive patients seen at the AIDS clinics of the *Hospital Universitário Prof. Edgard Santos*, in Salvador, Brazil, during the years of 1994 and 1995, were selected. To be eligible for the study, patients had to have a Western blot (WB)-confirmed infection by HIV-1, a previous test for HTLV-I/II antibodies (or stored serum sample), and a follow-up period of more than 6 months. The period of time was chosen in order to evaluate the impact of coinfection among patients before triple antiretroviral therapy was introduced as the standard of care for Brazilian patients with AIDS. Information on age, gender, route of transmission of retroviral infection, date of diagnosis, and clinical stage, both at the time of diagnosis and at the final evaluation were obtained from medical records or directly from the physicians responsible for the patients care. Clinical course, including the frequency and type of opportunistic infections (OI) or malignancies, use of antiretroviral drugs, the duration of therapy, and duration of follow-up was also recorded. The 1993's CDC revised classification was used for disease staging. All data were retrospectively collected from patients' medical charts.

Laboratory data used for comparison between the two groups were CD4 and CD8 cell counts, hemoglobin levels, and absolute number of lymphocytes. Two independent reviewers, who were blinded to the results of HTLV-I/II serology, performed data collection.

Serology tests

Screening for HIV-1 antibodies was performed by EIA (Genetic Systems, Seattle, WA) and confirmed by WB (Cambridge-Biotech, Rockville-MD). Antibodies against HTLV-I/II were detected using an EIA kit (Coulter Corporation, Hialeah, FL), and confirmed with WB (Fujirebio, Tokyo, Japan). The reactive samples (presence of any band on WB) were then retested with a synthetic peptide-based ELISA (Coulter Select - Coulter Corporation) and by a WB (Diagnostics Biotechnology, Singapore) containing envelope recombinant proteins (rgp46-I and rgp46-II), which allows for the discrimination between HTLV-I and II infection.[22-24]

Statistical analysis

Descriptive statistics were calculated and proportions were compared by calculating odds ratio (OR) and estimating 95% confidence intervals (CI) by the Cornfield method. Yates-corrected chi-square analysis was used to measure associations and calculate 2-tailed *P* values. Means were compared using Student's *t* test, and the Kruskal-Wallis test, when applicable. All calculations were performed by using EPIINFO 6.01b.

RESULTS

Medical records were reviewed for 123 patients (97 male), who fulfilled the inclusion criteria for the study. Twenty men (20.6%) and 6 women (23.1%) had detectable antibodies against HTLV-I/II (Table 1). Median follow-up time was 16

Table 1. Frequency of episodes of diagnosed infections according to the serological status for HTLV-I/II infection

	Infection HTLV serology			
	Negative	**HTLV-I**	**HTLV-II**	***P* value***
P. jiroveci pneumonia	20	1	1	0.3
CNS toxoplasmosis	14	5	-	0.8
Oral candidiasis	146	15	1	0.2
Esophageal candidiasis	17	1	1	0.4
Tuberculosis	37	10	1	0.8
Strongyloidiasis	2	3	1	0.04
CNS cryptococosis	2	0	1	0.8
Recurrent herpes	31	2	1	0.4
CMV	10	2	0	0.9
Kaposi's sarcoma	9	1	0	0.8
Bacterial infections	119	26	1	0.3
Cryptosporidiasis	6	0	0	0.6
Isosporiasis	4	1	0	0.9
Diarrhea	178	25	5	0.3
Peripheral neuropathy	5	2	0	0.8
Herpes zoster	12	4	1	0.8
Encephalopathy	1	2	0	0.04

**P* value comparing negative and positive patients for HTLV-I/II antibodies.

Table 2. Mean age and gender distribution for HIV-1 infected patients according to their serology results for HTLV-I and HTLV-II

	HTLV serology results				
	Negative	**HTLV-I**	**HTLV-II**	**HTLV-I/II**	***P* value**
Age (mean ± sd)	33.2 ± 8.8	33.5 ± 7.4	35.5 ± 11.1	33	0.9
Gender					
Male	77 (79%)	17 (81%)	0.3 (75%)	0	0.3
Female	20 (21%)	4 (19%)	0.1 (25%)	1(100%)	
Total	97	21	04	01	

months (range 6-56 months). The mean age was significantly higher for men as compared to women (34.5 ± 8.1 and 29 ± 8.8 respectively, $P = 0.002$) but there was no difference between the mean age for HTLV-positive and negative patients (Table 2).

Risk factors for coinfection: the major risk factor associated with coinfection by HTLV was intravenous drug use (IVDU). Among HTLV seropositive patients, 57.7% had a history of IVDU as the risk behavior for acquiring retroviral infections, compared to 9.2% among patients without HTLV coinfection ($P < 0.0001$). Infection by HTLV-I/II was not associated with blood transfusion, sexually transmitted diseases (STD), or sexual behavior (Table 3).

Clinical characteristics: at the time of the first visit to the clinic, 73 (59.3%) patients were asymptomatic, while the remaining 50 patients had an established diagnosis of AIDS (category C by CDC criteria). The frequency of episodes of OI diagnosed during follow-up were compared according to the serological results for HTLV-I/II infection: there was no difference in the overall frequency of OI for both groups, but strongyloidiasis was diagnosed in 4/26 coinfected, compared to 2/97 in singly infected patients (OR = 8.55; 95% CI: 1.21-73.62, $P = 0.02$, Fisher exact test). In addition, two episodes of encephalopathy were diagnosed during the study period in HTLV-positive, but no case was detected among singly infected patients ($P = 0.04$, Fisher exact test).

Table 3. Risk factors for acquisition of retroviral infection among singly and dually infected patients

Risk factors	**Negative**	**HTLV-I**	**HTLV-II**	**HTLV-I/II**	***P* value***
Blood transfusion	0.5	0.1	0.1	0.1	0.4
IVDU	0.9	12	0.3	-	< 0.0001
Homosexual activity	45	10	-	-	0.2
Previous STD	29	08	0.2	-	0.7
Sex with prostitutes	0.2	0.1	-	-	0.9
None of the above		10	-	-	NS

IVDU, intravenous drugs user; STD, sexually transmitted diseases; NS, nonsignificant.
*P value comparing negative and positive patients for HTLV-I/II antibodies. The total may exceed the sample size, due to positive history for more than one risks in the list.

Laboratories results

Hemoglobin levels were similar for both singly (11.9 ± 2.2 g/dL) and doubly infected (12 ± 2.3 g/dL) patients ($P > 0.05$).

Patients coinfected by HTLV-I/II had absolute lymphocytes counts significantly higher than those infected by HIV-1 alone (1,921 ± 762 *versus* 1,587 ± 951, $P = 0.03$). However, when they were stratified by clinical status, asymptomatic patients presented a similar number of lymphocytes, regardless of their HTLV-I/II serology status, while coinfected, symptomatic patients, had significantly higher lymphocyte counts (887 ± 515 cells/mm^3 *versus* 1,687 ± 731 cells/mm^3, $P = 0.02$, Kruskal-Wallis test).

A total of 75 patients had at least one available CD4 and CD8 counts. Mean CD4 and CD8 cells counts were similar in both groups of patients($P = 0.07$, and $P = 0.4$ for each mean count, respectively, Kruskal-Wallis test). However, coinfected patients diagnosed with AIDS at the time of their first visit had a mean CD4 count (292 ± 92 cells/mm^3 *versus* 149 ± 178 cells/mm^3, $P = 0.03$, Kruskal-Wallis test), absolute lymphocyte counts significantly higher. Coinfected patients who developed AIDS during follow-up also had higher baseline CD4 count (679 ± 247 cells/mm^3), than singly infected patients (303 ± 249 cells/mm^3; $P = 0.07$, Kruskal-Wallis test). This difference was not observed for patients who remained asymptomatic throughout the study period (525 ± 270 cells/mm^3 *versus* 532 ± 261 cells/mm^3 for HTLV negative and positive patients respectively $P = 0.9$, Kruskal-Wallis test). Since the study included patients followed before viral load tests were available, this information was not analyzed. Table 4 summarizes the laboratory results.

Table 4. CD4+, CD8+ and lymphocyte counts (mean ± SD) of patients according to their HTLV serology

Laboratory		HTLV serology				
Values/clinical		**Negative**	**HTLV-I**	**HTLV-II**	**HTLV-I/II**	***P* value***
Status	n	102	25	0.4	0.1	
Symptomatic	50					
CD4 cell counts	25	140 ± 177	292 ± 92	-	-	0.036
CD8 cell counts	25	695 ± 403	839 ± 537	-	-	0.6
Lymphocytes	50	887 ± 515	1,687 ± 731	-	-	0.02
Asymptomatic*	73					
CD4 cell counts	50	434 ± 281	537 ± 269	504	832	0.5
CD8 cell counts	50	1,300 ± 883	797 ± 308	465	1,965	0.1
Absolute lymphocyte count	72	2,013 ± 912	2,257 ± 835	1,845 ± 630	2,255	0.8
All patients	123					
CD4 cell counts	75	334 ± 284	432 ± 237	504	832	0.2
CD8 cell counts	75	1,112 ± 813	810 ± 339	465	1,965	0.2
Absolute lymphocyte count	123	1,563 ± 952	958 ± 816	1,638 ± 490	2,255	0.1

P values were calculated by Kruskal-Wallis test, and compare HTLV I/II negative and positive patients.
*Only 50 patients had available CD4 cell counts.

Progression to clinical disease during the follow-up period was similar for singly and coinfected patients (24/60 and 3/13, respectively, RR = 0.58; CI 0.20 - 1.63 $P = 0.3$). Use of antiretroviral drugs was more frequent among patients infected by HIV-1 alone (64.3%) compared to those coinfected by HTLV-I/II (42.3%) ($P = 0.04$, Yates corrected). This difference was more evident when we analyzed patients without a clinical picture of AIDS (non-category C disease): only 16.4% of coinfected patients were on antiretroviral therapy, in contrast to 51% of singly infected patients (RR = 0.23; 95% CI: 0.06-0.97 $P = 0.04$, Yates corrected).

DISCUSSION

Chronic infection by HIV is associated with immunodeficiency, caused by progressive CD4 lymphocyte depletion. Infection by HTLV-I may also be related to some degree of perturbation of the immune response among patients that harbor the virus, but usually do not exhibit clinical symptoms.[25]

While there is evidence suggesting that coinfection by HIV-HTLV viruses may modify the clinical and laboratory findings during the course of HIV infection, the lack of conclusive studies leaves the clinical impact of HTLV infection on HIV infected patients open to controversy. The present report provides additional support for the contention that patients harboring HIV and HTLV may present a modified clinical course of the HIV infection, characterized by a higher frequency of some clinical events.

The demographic characteristics for singly and doubly infected patients were comparable in this report. In contrast, a previous, larger study, detected a higher prevalence of HTLV-I coinfection among women, in Bahia.[26] This discrepancy may be due to the smaller sample size of this work, which probably lacked sufficient power to detect differences in coinfection rates by gender (only 6 women were coinfected).

Surrogate markers for HIV infection showed a distinct pattern for singly and doubly-infected patients. The absolute lymphocyte counts were quite different in the two groups, with higher counts among HTLV coinfected patients. Similar number of lymphocytes in asymptomatic patients in both groups suggests that lymphocyte depletion occurs more slowly in coinfected patients during the course of HIV infection.

The analysis of CD4 cell count provided a similar picture. Asymptomatic patients had comparable counts of CD4 cells, but in contrats it was higher among coinfected patients presenting with clinical disease. CD8 cell counts were not related to the status HTLV infection, regardless of the patient's clinical status. Similarly, hemoglobin levels were comparable in both groups.

The frequency of *S. stercoralis* OI was significantly higher among coinfected patients, as it was for encephalitis without other identifiable etiology. Infection by HTLV-I has been associated with higher risk for *S. stercoralis* parasitism in HIV-negative patients.[27-30] In a previous report, we also detected higher prevalence of *S. stercoralis* infection in

HIV-positive patients, compared to seronegatives.[31] The present report provides evidence that this association in HIV-HTLV coinfected patients is even higher than in HIV-1 singly-infected individuals.

The association between coinfection and encephalopathy is less clear: HTLV-I infection is associated with TSP/HAM, a clinical entity characterized by signs and symptoms of myelopathy, but displaying some evidence of brain involvement, such as perivascular infiltrates, demyelinization, and white matter destruction. In addition, other severe involvement of central nervous system has been reported.[32-35] Unfortunately, the retrospective design of the present study did not allow to clarify the exact cause of death of these two patients.

The rate of clinical evolution from asymptomatic infection to AIDS during the follow-up period was similar for both groups. However, the use of antiretroviral drugs was more frequent among singly-infected patients suggesting that the abnormalities in the number of lymphocytes and the CD4+ count induced by HTLV coinfection may delay the initiation of antiretroviral therapy in coinfected patients, as predicted by Schechter *et al.* in a previous report.[15] Since CD4 cell count is still the main marker to define the best moment to start antiretroviral therapy and/or prophylaxis for OI, this fact may add a clinically relevant problem to physicians, when attending patients in endemic areas for these two agents.

The finding that cell subsets count is similar among asymptomatic patients, but significantly different among those with clinical symptoms suggests that the decrease in CD4 cell counts occurs later in the evolution of coinfected patients. Nonetheless, the higher CD4 cell counts do not provide any immunological benefit. It is likely that immunological changes secondary to the progression of HIV infection may also be affected, or may modify the lymphoproliferative response that usually follows HTLV infection. However, the mechanisms and intensity of such immune modifications are still unclear.

Finally, the extent to which HIV/HTLV coinfection modifies clinical outcomes of HIV infected patients remains unclear. There are some evidence supporting the hypothesis that coinfection by these agents may modulate the clinical presentation of these individuals, with an increase in the frequency of some parasitic diseases, and of severe forms of scabies.[31,36] In addition, there are evidence supporting a potential impact of coinfection on survival, which was shorter for coinfected patients than for those infected by HIV-1 alone.[37,38]

Our study also presents some limitations, that could have influenced the results: first, the retrospective design may prevent definitive conclusions, although, since HAART is currently the standard of care for all patients in need of treatment we could not evaluate the impact of increased CD4 cell counts on physicians' decision on when to start therapy. On the other hand, the higher proportion of IVDU among coinfected patients could also be confounding factor of lower rate of antiretroviral treatment among coinfected patients. It could be true for asymptomatic patients, but our data showed that even patients with a clinical picture of AIDS had decreased chance of receiving therapy, which could not be explained on the basis of patients' risk behavior. It makes more sense to conclude that the discrepancy between CD4 cell count and clinical status was probably the factor that misled physicians in deciding the optimal time to start treatment. In addition, we did not have information on how many patients had stools examination performed for *S. stercoralis* parasitism, but in AIDS patients such parasite usually causes severe diarrhea and the stools examination routinely performed in these situations, making unlikely that a symptomatic patient not having had a proper diagnostic investigation.

Our results confirm previous studies reporting higher CD4 cell counts in coinfected patients, and suggest that such phenomenon may mislead physicians in the choice of the optimal time to start antiretroviral therapy.[15,39] It can not be ruled out the delay in starting antiretroviral therapy as one of the potential explanation for the higher mortality detected among coinfected individuals caused by increased CD4 cell counts, rather than a direct effect of HTLV-I on AIDS progression. The increased frequency of *S. stercoralis* infection and encephalopathy also indicates that coinfection may modify the course of HIV disease. However, the available data provide only limited evidence and definitive answers will require larger, prospective studies.

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