Higher mortality in HIV-2/HTLV-1 co-infected patients with pulmonary tuberculosis in Guinea-Bissau, West Africa, compared to HIV-2-positive HTLV-1-negative patients

Hans Norrgren [a,*], Sana Bamba [b], Zacarias J. Da Silva [c], Tuija Koivula [d], Sören Andersson [d]

[a] Department of Clinical Sciences, Division of Infection Medicine, Lund University, 221 85 Lund, Sweden
[b] Raoul Follereau Hospital, Bissau, Guinea-Bissau
[c] National Public Health Laboratory, Bissau, Guinea-Bissau
[d] Swedish Institute for Infectious Disease Control, Stockholm, Sweden

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ABSTRACT

Objectives: To investigate the effect of human T-lymphotropic virus type 1 (HTLV-1) on CD4 counts and mortality in tuberculosis (TB) patients with or without human immunodeficiency virus (HIV).
Methods: A prospective study on 280 hospitalized patients with pulmonary TB was performed in Guinea-Bissau, 1994–1997, including HIV, CD4 counts and clinical outcome. We compared the CD4 count levels at the time of inclusion between HIV-negative and HIV-positive patients, with or without HTLV-1. Mortality was determined while patients were on treatment for TB.
Results: Median CD4% was significantly higher in HIV-positive subjects co-infected with HTLV-1 compared to HTLV-1-negative patients. Two hundred thirty-three individuals were included in the analysis of mortality, and among HIV-negative subjects the mortality was 18.6/100 person-years. In HIV-2-positive HTLV-1-negative subjects the mortality was 39.5/100 person-years and in HIV-2/HTLV-1 co-infected patients it was 113.6/100 person-years (adjusted mortality rate ratio 4.7, 95% CI 1.5–14.4; $p < 0.01$). When all HIV-positive patients were analyzed together, corresponding mortality rates were 53.5/100 person-years and 104.8/100 person-years, respectively (not significant).
Conclusions: HIV/HTLV-1 co-infected patients hospitalized for pulmonary TB had a high mortality and had significantly higher CD4% compared to only HIV-positive subjects. This may imply that HTLV-1 has an adverse effect on the immune system in HIV-infected subjects, independently of the CD4 count, that makes co-infected subjects more vulnerable to TB.

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1. Introduction

The deleterious effects of the human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* infections (MTB) worldwide, and especially in developing countries, are well-known. Furthermore, HIV-infected subjects are more susceptible to MTB, and tuberculosis (TB) is the most common cause of death in HIV-positive adults living in developing countries.[1] The first isolated human retrovirus was human T-lymphotropic virus type 1 (HTLV-1), and it is spread endemically in sub-Saharan Africa, Japan, South America and the Caribbean.[2] HTLV-1 infection has been associated with a wide range of diseases, including adult T-cell leukemia/lymphoma (ATL), HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), uveitis, and autoimmune manifestations,

as well as infection with *Strongyloides stercoralis*.[3] It has also been shown that HTLV-1-positive asymptomatic subjects have a suppressed Mantoux test (PPD, purified protein derivative test) compared to HTLV-1-negative controls.[4–6]

Several studies of co-infection of HIV-1 and HTLV-1 have shown increased CD4 count levels compared to HIV-1 mono-infection.[7–11] However, in one study no association was found between co-infection of HIV/HTLV-1 and higher CD4 counts.[12] In some reports, the progression to AIDS or death has been found to be faster in HIV-1/HTLV-1 co-infection compared to HIV-1-positive HTLV-1-negative subjects,[11,13] while in one study no difference was demonstrated.[10]

The association between HTLV-1 and TB has been examined in a few studies with contradicting results.[14] We have recently published a paper from a prospective TB study conducted in Guinea-Bissau on hospitalized patients with pulmonary TB, and we could not find any association between HTLV-1 infection and TB in HIV-negative patients, but in HIV-positive patients there was a

significant association between HTLV-1 infection and TB.[15] To our knowledge only one study has previously investigated the outcome of TB in HTLV-1-infected patients, and the results indicated a higher mortality in HTLV-1-infected patients compared to HTLV-1-negative subjects, although no statistical analysis was performed.[16]

Guinea-Bissau has the highest prevalence of HIV-2 in the world, and in recent years HIV-1 has increased rapidly and the prevalence is now approximately 5% among pregnant women in the capital Bissau.[17] HTLV-1 is endemic in the country and the prevalence was reported to be 3.6% in a population-based study from Bissau in 2000.[18] In the same study population the incidence of TB was 471 per 100 000 person-years, among the highest noted in the world.[19]

Following our above-mentioned prospective study of TB patients in Guinea-Bissau, we have now investigated the mortality while patients were on treatment for TB and have related it to immunological parameters and HIV/HTLV-1 status. The results of this study were presented in part at the 14th International Conference on Human Retrovirology, July 2009.[20]

2. Materials and methods

Patients hospitalized for pulmonary TB at the Raoul Follereau Hospital in Bissau between 1994 and 1997 were consecutively screened, and adults (aged ≥15 years) living in Bissau with no previous history of TB were enrolled. The diagnosis of pulmonary TB was culture-confirmed in 145 cases, and in 135 subjects the diagnosis was based on a smear-positive sputum sample or on clinical and radiological criteria (infiltrative, nodular, or cavitary lesions). After informed consent was obtained from the patient, a blood sample was drawn for the analyses of HIV and T-lymphocyte subsets. Subsequently the frozen blood sample was also analyzed for antibodies to HTLV-1/2. A PPD test was done intradermally (2 TU) and was considered positive when the induration diameter was >5 mm. Standard national treatment regimens were used, which for HIV-negative patients at that time included 2 months of streptomycin, rifampin, isoniazid and pyrazinamide, followed by 6 months of isoniazid and thioacetazone. HIV-positive patients initially received 4 months of rifampin, isoniazid, pyrazinamide and ethambutol, and then 4 months of isoniazid and thioacetazone. However, during the study period treatment guidelines were changed for HIV-positive patients from isoniazid and thioacetazone during the continuation phase to isoniazid and ethambutol. Some of the HIV-positive patients also received rifampin during the continuation phase. This treatment regimen was used at that time in several African countries due to lower costs, but since then newer treatment regimens have been adopted. The study period included the whole treatment period of 8 months. Patients were hospitalized for approximately 2 months, and during this phase daily visits were undertaken to the wards in order to follow the clinical outcome in the participants. During the ambulatory phase of the treatment, participants were visited every month in the home by a specially appointed nurse, and at the end of the treatment period a final evaluation was done by a doctor.

Treatment failure was defined as persisting symptoms of TB and sputum smear positivity at the end of the study period. Due to the outbreak of a civil war in Guinea-Bissau in June 1998, a small subset of individuals (nine HIV-negative individuals) was followed for only 6 months; however these subjects were considered clinically cured by the study personnel at this point in therapy. Due to the unexpected and unreported loss of a study nurse during the investigation, the follow-up was interrupted in 47 patients, hence these patients were excluded from the follow-up analysis. Thus, a total of 280 patients were included in the study for the analysis of immunological parameters, but only 233 subjects were available for the mortality analysis. No antiretroviral treatment was given since it was not available in the country at the time when the study was conducted.

All sera were screened by the Enzygnost HIV-1+2 ELISA (Behring, Marburg, Germany). Confirmation was carried out according to an alternative confirmatory strategy including two separate HIV-1 and HIV-2 ELISAs, Enzygnost anti-HIV-1 and Enzygnost anti-HIV-2 (Behring), and a rapid simple assay, Recombigen HIV-1/HIV-2 RTD (Cambridge Biotech Ltd, Galway, Ireland).[21] Sera dually reactive for HIV-1 and HIV-2 were further tested by Peptilav 1–2 (Sanofi Diagnostics Pasteur, Marnes-la-Coquette, France).

Detection of antibodies to HTLV-1/2 was achieved using the Organon Vironostika HTLV-1 (Organon Teknika BV, Boxtel, the Netherlands) and the Murex HTLV-1/2 GE80/81 (Murex Diagnostics Ltd, Dartford, UK) tests. Positive reactions were confirmed by Western blot (WB) – the Diagnostic Biotechnology HTLV-blot 2.3 (Genelabs Diagnostics, Singapore). The criteria for HTLV seropositivity were reactivity with at least one core band and at least two envelope bands. The recombinant gp46-I and gp46-II bands were used to differentiate between HTLV-1 and HTLV-2. T-lymphocyte subsets were determined at the National Public Health Laboratory (LNSP) in Bissau by flow cytometry (FACStrak, Becton Dickinson, San Jose, CA, USA) using three two-color immunofluorescence reagents: CD45/CD14, CD3/CD4 and CD3/CD8 (Simultest, Becton Dickinson). Leukocytes were counted with a Coulter Counter CBC 5 (Coulter Electronics Ltd, Luton, UK). Sputum microscopy and TB culture were performed according to standard methods at the National Public Health Laboratory, as previously described.[22]

2.1. Statistical analysis

Odds ratios (OR) with 95% confidence intervals (CI), p-values of Chi-square tests, Fisher's exact test and the Mann–Whitney test were calculated with Epi Info (Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA and World Health Organization, Geneva, Switzerland). Many data were not normally distributed, so the central tendency and dispersion are given by median and P25 and P75 interquartile ranges (IQR). For the analysis of mortality, subjects who discontinued treatment or who were lost to follow-up contributed with person-years until their last control (taking therapy). Multivariate logistic regression analyses were performed

Table 1
Prevalence of HTLV-1 (%) among 280 hospitalized patients with pulmonary tuberculosis, stratified by HIV status and gender

	HIV-negative	HIV-1	HIV-2	HIV-1 + HIV-2	HIV-positive
N	162	26	60	32	118
Male	3/104 (2.9)	1/17 (5.9)	5/31 (16.1)[a]	3/16 (18.8)[a]	9/64 (14.1)[a]
Female	3/58 (5.2)	2/9 (22.2)	7/29 (24.1)[a]	8/16 (50)[b]	17/54 (31.5)[b,c]
Total	6/162 (3.7)	3/26 (11.5)	12/60 (20)[b]	11/32 (34.4)[b]	26/118 (22.0)[b]

HTLV, human T-lymphotropic virus; HIV, human immunodeficiency virus.
[a] $p < 0.05$, Chi-square test for paired comparison between the indicated HIV-positive groups and the HIV-negative subjects.
[b] $p < 0.001$, Chi-square test for paired comparison between the indicated HIV-positive groups and the HIV-negative subjects.
[c] $p < 0.05$, Chi-square test for paired comparison between HIV-positive men and women.

Table 2
Median values (interquartile ranges in parentheses) of lymphocyte subsets and number of subjects (percentages in parentheses) of subjects with negative PPD and negative sputum culture of *Mycobacterium tuberculosis* among 280 hospitalized patients with pulmonary tuberculosis, stratified by HIV and HTLV-1 status

	HTLV-1	HIV-negative	HIV-1	HIV-2	HIV-1 + HIV-2	HIV-positive
N	Negative	156	23	48	21	92
	Positive	6	3	12	11	26
CD4%	Negative	40 (33–46)	11 (9–17)	13 (7–28)	15 (5–25)	13 (7–26)
	Positive	40 (33–42)	21 (6–40)	22 (13–35)	23 (13–37)	22 (13–37)[b]
Total CD4[a]	Negative	666 (487–919)	162 (80–215)	243 (60–391)	182 (107–389)	177 (75–389)
	Positive	695 (496–1085)	838 (341–1296)[c]	247 (123–594)	204 (116–541)	284 (129–594)
CD8%	Negative	27 (22–35)	56 (49–68)	44 (36–60)	53 (47–62)	51 (39–64)
	Positive	31 (28–32)	48 (48–58)	47 (29–57)	49 (40–60)	48 (39–60)
Total CD8[a]	Negative	506 (347–655)	704 (435–1481)	550 (279–1079)	661 (333–1076)	652 (337–1184)
	Positive	516 (448–657)	1915 (1555–3293)[c]	470 (454–638)	699 (358–984)	638 (462–983)
Negative PPD	Negative	44/124 (35.5)	12/20 (60)	19/33 (57.6)[d]	6/13 (46.2)	37/66 (56.1)[e]
	Positive	2/6 (33.3)	1/2 (50)	4/11 (36.4)	7/11 (63.6)	12/24 (50)
Negative TB culture	Negative	54/137 (39.4)	11/21 (52.4)	16/45 (35.6)	11/19 (57.9)	38/85 (44.7)
	Positive	0/5	0/2	6/10 (60)	6/10 (60)	12/22 (54.5)

PPD, purified protein derivative (Mantoux) test; HTLV, human T-lymphotropic virus; HIV, human immunodeficiency virus.

[a] The number of analyzed HTLV-1-negative and HTLV-1-positive subjects was 151, 22, 45, and 19, and 6, 3, 11, and 11, respectively, in HIV-negative, HIV-1-positive, HIV-2-positive, and HIV-1 + HIV-2-positive subjects, respectively .

[b] $p < 0.05$, Mann–Whitney test for paired comparison of HIV-positive HTLV-1-negative and HTLV-1-positive subjects.

[c] $p < 0.05$, Mann–Whitney test for paired comparison of HIV-1-positive HTLV-1-negative and HTLV-1-positive subjects.

[d] $p < 0.05$, Mann–Whitney test for paired comparison of HIV-2-positive and HIV-negative HTLV-1-negative subjects.

[e] $p < 0.05$, Mann–Whitney test for paired comparison of HIV-positive and HIV-negative HTLV-1-negative subjects.

using STATA (Stata Corp., TX, USA). Age was treated as a continuous variable in the regression analyses.

3. Results

Among the 280 study subjects, the total prevalence of HIV-1 was 9.3%, of HIV-2 was 21.4%, and of HIV-1 + HIV-2 was 11.4%. The prevalence of HTLV-1 according to HIV status and gender is shown in Table 1. No patient was found to be HTLV-2-positive. The prevalence of HTLV-1 was significantly higher in HIV-2, HIV-1 + HIV-2, and in all HIV-positive patients combined as compared to HIV-negative subjects. There was a trend towards a higher HTLV-1 prevalence among women compared to men in all groups, which became significant when all HIV-positive patients were analyzed together. The median age of HIV-negative subjects was 30 years, of HIV-1 subjects was 30.5 years, of HIV-2 subjects was 42.5 years, and of HIV-1 + HIV-2-positive subjects was 40 years. No significant differences in median age were noted between HTLV-1-positive and HTLV-1-negative patients in the HIV-2 and HIV-1 + HIV-2-positive groups, but in the HIV-negative and HIV-1-positive groups median age was significantly higher in HTLV-1-positive subjects compared to HTLV-1-negative individuals (data not shown).

In Table 2 we present the immunological differences between HTLV-1-negative and HTLV-1-positive patients according to HIV status. The proportions of subjects with a negative PPD and negative culture of TB are also shown for each group. No difference could be found in any of the immunological parameters between HTLV-1-negative and HTLV-1-positive patients in the HIV-negative group, but in the three different HIV-positive groups there was a trend towards higher CD4% among the HTLV-1-positive subjects (although not significant). However, when all HIV-positive subjects were taken together, the difference was significant, which was also verified in a logistic regression analysis adjusting for age and gender ($p = 0.01$; 95% CI 1.9–13.6). Regarding total CD4 counts the pattern was similar, but here the difference was significant only in the HIV-1- positive group ($p < 0.05$). When looking at CD8% and total CD8 counts, similar values were found in HTLV-1-negative and HTLV-1-positive patients regardless of HIV status, with the exception of total CD8 counts in HIV-1-positive subjects. However, this was due to high lymphocyte counts in the three individuals in this group (data not shown), which also explains the surprisingly high total CD4 counts in this group. As could have been expected, significantly more HIV-positive patients had a negative PPD compared to HIV-negative subjects (HTLV-1-negative individuals only), but no significant differences were

Table 3
Outcome of treatment in 233 patients with pulmonary tuberculosis (percentages in parentheses), stratified by HIV and HTLV-1

	HTLV-1	Treatment discontinued	Loss to follow-up	Case-fatality during treatment	Treatment failure after 8 months of treatment	Clinical cure after 8 months of treatment[a]
HIV-negative	Negative	7 (5.6)	20 (15.9)	15 (11.9)	7 (5.6)	77 (61.0)
	Positive	0	1 (25)	0	0	3 (75)
HIV-1	Negative	0	4 (20)	8 (40)[c]	2 (10)	6 (30)[b]
	Positive	1 (33.3)	0	1 (33.3)	0	1 (33.3)
HIV-2	Negative	3 (6.8)	2 (4.5)	12 (27.3)[b]	6 (13.6)	21 (47.8)
	Positive	0	0	5 (71.4)	0	2 (28.6)
HIV1 + HIV-2	Negative	1 (5.3)	4 (21.1)	7 (36.7)[b]	3 (15.8)	4 (21.1)[c]
	Positive	0	3 (30)	5 (50)	1 (10)	1 (10)
HIV-positive	Negative	4 (4.8)	10 (12.0)	27 (32.5)[d]	11 (13.3)	31 (37.4)[d]
	Positive	1 (5)	3 (15)	11 (55)	1 (5)	4 (20)

HTLV, human T-lymphotropic virus; HIV, human immunodeficiency virus.

[a] Nine HIV-negative individuals were followed for only 6 months, but were considered clinically cured by the study personnel at this point in therapy.

[b] $p < 0.05$, Chi-square test for paired comparison between the indicated HIV-positive groups and the corresponding HIV-negative group.

[c] $p < 0.01$, Chi-square test for paired comparison between the indicated HIV-positive groups and the corresponding HIV-negative group.

[d] $p < 0.001$, Chi-square test for paired comparison between the indicated HIV-positive groups and the corresponding HIV-negative group.

Table 4

Mortality rate during treatment of pulmonary tuberculosis among 233 patients, stratified by HIV and HTLV-1 status

	HTLV-1	No. of subjects	Person-years	No. deceased	Mortality rate, n/100 person-years	Mortality rate ratio (95% CI), p-value	Adjusted[a] mortality rate ratio (95% CI), p-value
HIV-negative	Negative	126	80.7	15	18.6		
	Positive	4	2.5	0	0		
HIV-1	Negative	20	11.1	8	72.1		
	Positive	3	1.4	1	71.4	1.1 (0.1–8.9), p = 0.98	
HIV-2	Negative	44	30.4	12	39.5		
	Positive	7	4.4	5	113.6	3.2 (1.1–9.1), p = 0.03	4.7 (1.5–14.4), p = 0.008
HIV-1 + HIV-2	Negative	19	9.0	7	77.8		
	Positive	10	4.7	5	106.4	1.3 (0.4–4.1), p = 0.65	
HIV-positive	Negative	83	50.5	27	53.5		
	Positive	20	10.5	11	104.8	2.0 (1.0–4.0), p = 0.06	1.7 (0.9–3.6), p = 0.13

HTLV, human T-lymphotropic virus; HIV, human immunodeficiency virus; CI, confidence interval.

[a] Adjusted for age and gender.

found between HTLV-1-negative and HTLV-1-positive individuals in any group. Nor could we see any differences between men and women with regard to PPD reactivity in relation to HTLV status (data not shown). A trend towards higher proportions of negative TB cultures could be observed in HIV-positive subjects, but no significant differences were found.

For the analysis of clinical outcome, 233 individuals were available for an evaluation (Table 3). No significant differences were found regarding treatment discontinuation, loss to follow-up, or treatment failure at the end of the treatment period. However, the case-fatality was higher in all HIV-positive groups compared to HIV-negative subjects (only HTLV-1 negative patients); the mortality rates are shown in Table 4. Overall, HIV-positive patients had several times higher mortality compared to HIV-negative subjects. In HIV-negative subjects no HTLV-1-positive patient died (although there were few patients in this group), and in HIV-1-positive patients the same mortality was found in HTLV-1-negative and HTLV-1-positive subjects. However, the highest mortality was found in HIV-2-positive and HTLV-1-positive individuals (113.6/100 person-years), which was significantly higher compared to HIV-2-positive and HTLV-1-negative patients (mortality rate ratio 3.2; $p < 0.05$). The mortality rate ratio further increased to 4.7 (95% CI 1.5–14.4; $p < 0.01$) when adjusting for age and gender in a logistic regression analysis. In HIV-1 + HIV-2-positive subjects there was a trend towards higher mortality in HTLV-1-positive patients, although not significant. When all HIV-positive patients were analyzed together the adjusted mortality rate ratio between HTLV-1-positive and negative subjects was 1.7 (95% CI 0.9–3.6; $p = 0.13$).

We further investigated if HTLV-1 had a different impact on the mortality at the different stages of immunosuppression in HIV-positive subjects. In Table 5 we show the mortality in all HIV-positive subjects taken together (since they were too few to be divided into

each HIV-positive group) according to CD4 counts and HTLV-1 status. Interestingly, HTLV-positive patients had a trend towards higher mortality at all CD4 count levels, reaching significance in subjects with CD4% $\geq$25 or a total CD4 count between 200 and 349.

4. Discussion

In the present study of hospitalized patients with pulmonary TB we found that HIV-positive patients with concomitant HTLV-1 infection had significantly higher CD4% than HIV-positive patients without HTLV-1. When performing separate analyses of HTLV-1-positive patients co-infected with either HIV-1, HIV-2, or HIV-1 + HIV-2, a trend towards higher CD4% was found in all groups of HIV, but the number of patients in the different groups was not sufficient for conclusive analyses. In spite of this we noted a trend towards higher mortality in HIV/HTLV-1 co-infected patients as compared to HIV mono-infected subjects, and in HIV-2/HTLV-1 co-infected patients the difference became significant compared to HIV-2 singly infected individuals.

The finding of higher CD4 counts in HIV-1/HTLV-1 co-infected patients has been observed in other studies.[7–11] Regarding HIV-negative patients, we could not detect any difference in CD4 counts between HTLV-1-positive and HTLV-1-negative subjects. The reasons for this discrepancy of CD4 development associated with HTLV-1, depending on concomitant HIV or not, are not clear. It has been speculated that the higher CD4 counts in co-infected subjects could represent HTLV-1-associated non-specific lymphocyte pro-liferation.[8] Detailed analyses of increased turnover and peripheral expansion mechanisms during concomitant HTLV and HIV infection are needed in order to further elucidate this.

Previous studies have demonstrated a weaker reaction to PPD in HTLV-1-positive subjects compared to HTLV-1-negative controls.[4–6] We could not find any difference between HTLV-1-positive and

Table 5

Mortality rate during treatment of pulmonary tuberculosis among 103 HIV-positive patients, stratified by CD4 counts and HTLV-1 status

	HTLV-1	No. of subjects	Person-years	No. deceased	Mortality rate n/100 person-years	Mortality rate ratio (95% CI), p-value
CD4% $\leq$14	Negative	45	21.6	23	106.5	
	Positive	7	2.1	5	238.1	2.2 (0.8–5.7), p = 0.12
CD4% 15–24	Negative	13	9.6	2	20.8	
	Positive	6	3.6	2	55.6	2.8 (0.4–20.1), p = 0.31
CD4% $\geq$25	Negative	25	19.3	2	10.4	
	Positive	7	4.8	4	83.3	7.5 (1.4–41.1), p = 0.02
Total CD4 <200	Negative	42	20.3	20	98.5	
	Positive	8	3.8	5	131.6	1.3 (0.5–3.4), p = 0.63
Total CD4 200–349	Negative	12	9.3	1	10.8	
	Positive	4	2.0	3	150.0	12.3 (1.3–119.9), p = 0.03
Total CD4 $\geq$350	Negative	24	18.4	3	16.3	
	Positive	7	4.6	2	43.5	2.6 (0.4–15.7), p = 0.31

HTLV, human T-lymphotropic virus; HIV, human immunodeficiency virus; CI, confidence interval.

HTLV-1-negative patients in either HIV-negative or HIV-positive patients, although significantly more HIV-positive subjects had a negative PPD compared to HIV-negative patients (HTLV-1-negative individuals only). There were no gender differences in our material, as has been shown in a previous study.[6] However, the previous observations of negative PPD were found among asymptomatic healthy subjects, whereas our study cohort consisted of patients with pulmonary TB, which could affect the results.

We found a significantly higher mortality in HIV-2/HTLV-1 co-infected patients compared to only HIV-2-positive subjects. A similar trend was found among HIV-1 + HIV-2-positive patients, but in the HIV-1-positive group no difference was observed. However, the number of patients in the HIV-1-positive group was rather limited. At the time when the study was performed, HIV-2 was the dominant type of HIV in Guinea-Bissau, and the prevalence of HIV-1 was still quite low, which explains the limited number in this group.[23] Moreover, with the relatively short period of HIV-1 prevailing in Guinea-Bissau, the impact on general health would still be limited at the time of this study. It is likely that many of the HIV-2-infected patients in our study cohort had had their infection for a substantially longer time period than the HIV-1-infected individuals. Thus, any impact of carrying HIV and HTLV-1 concomitantly would probably be more apparent in persons with a longer period of virus carriage.

In a number of studies, the mortality of HIV-2 has been shown to be significantly lower than that of HIV-1, but higher than among HIV-negative controls.[24–26] Our results indicate that HTLV-1 could be an important cofactor for HIV-2-related mortality in TB patients. In a study of a rural population in Guinea-Bissau no enhancing effect of HTLV-1 co-infection on HIV-2 mortality was found, but the risk of death increased with higher HTLV-1 provirus load.[27] Further studies are needed to explore the influence of HTLV-1 on HIV-2-associated morbidity and mortality.

Interestingly, when we compared the mortality according to different CD4 count levels at the time of diagnosis in HIV-positive patients, we noted a trend towards higher mortality at all CD4 count intervals among the HTLV-1-positive patients compared to HTLV-1-negative subjects. Furthermore, the differences were significant in the group with CD4% $\geq$25 and in total CD4 counts between 200 and 349. However, the number of patients, in particular in the HTLV-1-positive groups, was limited, so the results must be interpreted with caution. As could have been expected, the mortality was highest in the strata with the lowest CD4 counts, both in HTLV-1-positive and HTLV-1-negative patients (except in HTLV-1-positive patients with CD4 counts of 200–349), which suggests that CD4 count is the dominant predictor of clinical outcome; however in all strata it also appeared as if HTLV-1 had an additive inverse effect on the mortality. This indicates that the effects of HIV on the immune system cannot solely be linked to CD4 cell counts when a person is co-infected with HTLV-1. As compared to HIV single infection, the prognostic value provided by CD4 cell levels concerning disease progression appears to be poor. In our study the influence of HTLV-1 on mortality appeared to occur in the higher CD4 cell count strata. We do not have any clear explanation for these somewhat contradictory findings, but it may be that the effects on the immune system caused by HTLV-1 are more visible in the higher CD4 strata where the effect of HIV on the clinical outcome is less noticeable.

HTLV-1 has been shown to have proinflammatory and carcinogenic effects, and is also associated with several infectious disorders in HIV-negative individuals.[3] In a recently published population-based study from Guinea-Bissau, an increased mortality was detected in HIV-negative HTLV-1-positive subjects compared to HTLV-1-negative individuals.[26] In HTLV-1/HIV-1 co-infected subjects a higher mortality compared to HIV-1 mono-infected individuals has been reported from Brazil,[13] but in a study from Louisiana, USA, no significant difference was observed in mortality between HTLV-1/HIV-1 co-infected and HIV-1 mono-infected subjects.[10] To our knowledge only one study has previously investigated the mortality in patients with TB co-infected with HIV-1 and HTLV-1, and the results revealed a higher mortality in the co-infected group compared to only HIV-1-infected patients, although no statistical comparison was performed.[16]

The biological explanation for a higher mortality in HTLV-1 and HIV-1 or HIV-2 co-infected TB patients is not obvious, since HTLV-1 elicits a strong Th1-type response, which would be expected to have a suppressive effect on the TB infection as well as the HIV infections, and rather give an improved outcome.[28] It has been suggested that the negative effect on clinical outcome of HTLV-1 in HIV-1/HTLV-1 co-infected subjects could be mediated by upregulation of HIV expression due to strong activation of cytokines promoting HIV replication,[29] and this could well be the case in co-infected patients with TB. Regarding studies of HIV viral load in HIV/HTLV-1 co-infected subjects, a study from Brazil reported no significant difference in HIV-1 viral load between HIV-1/HTLV-1 co-infected and HIV-1 mono-infected subjects,[30] and in a study from Guinea-Bissau HIV-2/HTLV-1 co-infected subjects had a significantly lower HIV-2 viral load as compared to HIV-2-infected subjects alone.[27] Unfortunately HIV viral load and HTLV-1 proviral load determinations were not available in the present study. The scarcity of data on the effects of the co-infections studied here warrants further studies, but also reflects the complexity of studies of the impact of more than one infection at a time, on each other and on the host. In an environment with a high endemic pressure of many infectious diseases it is important to take into account the effects each microorganism will have on the final clinical picture.

In conclusion we have observed a high mortality in HIV/HTLV-1 co-infected patients with pulmonary TB, and in HIV-2/HTLV-1-positive patients the difference was significant compared to only HIV-2-positive subjects. These effects were noted despite significantly higher CD4%, which implies that HTLV-1 might have an adverse effect on the immune system irrespective of CD4 count. It is of importance that clinicians are aware that HIV/HTLV-1 co-infected patients can contract TB and perhaps other opportunistic infections despite high CD4 counts. HTLV-1 may be an important inducer of HIV-2-associated mortality in TB patients. Co-infections with several microorganisms may give unexpected clinical pictures, difficult to predict based on information from each of the single infections involved.

Acknowledgements

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