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Impact of pulmonary tuberculosis on survival of HIV-infected adults: a prospective epidemiologic study in Uganda

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Abstract

Background—Retrospective cohort studies of tuberculosis suggest that active tuberculosis accelerates the progression of HIV infection. The validity of these findings has been questioned because of their retrospective design, diverse study populations, variable compliance with anti-tuberculous therapy and use of anti-retroviral medication. To assess the impact of tuberculosis on survival in HIV infection we performed a prospective study among HIV-infected Ugandan adults with and without tuberculosis.

Methods—In a prospective cohort study, 230 patients with HIV-associated tuberculosis and 442 HIV-infected subjects without tuberculosis were followed for a mean duration of 19 months for survival. To assess changes in viral load over 1 year, 20 pairs of tuberculosis cases and controls were selected and matched according to baseline CD4 lymphocyte count, age, sex and tuberculin skin test status.

Results—During the follow-up period, 63 out of 230 tuberculosis cases (28%) died compared with 85 out of 442 controls (19%), with a crude risk ratio of 1.4 [95% confidence interval (CI), 1.07–1.87]. Most deaths occurred in patients with CD4 lymphocyte counts $< 200 \times 10^6$ cells/l at baseline ($n = 99$) and occurred with similar frequency in the tuberculosis cases (46%) and the controls (44%). When the CD4 lymphocyte count was $> 200 \times 10^6$ /l, however, the relative risk of death in HIV-associated tuberculosis was 2.1 (95% CI, 1.27–3.62) compared with subjects without tuberculosis. For subjects with a CD4 lymphocyte count $> 200 \times 10^6$ /l, the 1-year survival proportion was slightly lower in the cases than in the controls (0.91 versus 0.96), but by 2 years the survival proportion was significantly lower in the cases than in the controls (0.84 versus 0.91; $P < 0.02$; log-rank test). For subjects with a CD4 lymphocyte count of 200×10^6 cells/l or fewer, the survival proportion at 1 year for the controls was lower than cases (0.59 versus 0.64), but this difference was not statistically significant ($P = 0.53$; logrank test). After adjusting for age, sex, tuberculin skin test status, CD4 lymphocyte count, and history of HIV-related infections, the overall relative hazard for death associated with tuberculosis was 1.81 (95% CI, 1.24–2.65). In a nested Cox regression model, the relative hazard for death was 3.0 (95% CI, 1.62–5.63) for subjects with CD4 lymphocyte counts $>$

$200 \times 10^6/l$ and 1.5 (95% CI, 0.99–2.40) for subjects with a CD4 lymphocyte count of $200 \times 10^6/l$ or fewer.

Conclusion—The findings from this prospective study indicate that active tuberculosis exerts its greatest effect on survival in the early stages of HIV infection, when there is a reserve capacity of the host immune response. These observations provide a theoretical basis for the treatment of latent tuberculous infection in HIV-infected persons.

Keywords

HIV-1; tuberculosis; survival; Africa; prospective cohort study

Introduction

The World Health Organization (WHO) estimated that by 1997, 15.3 million people worldwide were infected with both HIV-1 and *Mycobacterium tuberculosis*, most of them in sub-Saharan Africa. As HIV-1 spread across Africa, and throughout the world, there has been a resurgence of tuberculosis attributed to HIV-1. Indeed, the hallmark of HIV-1 infection is the progressive decline and dysfunction of CD4 lymphocytes [1], cells that are critical in containing infection with *M. tuberculosis*. HIV-1 infection confers the greatest known risk for the development of active tuberculosis, both for reactivation of latent infection [2] or progressive primary disease [3]. Moreover, in HIV-1 infection, tuberculosis is associated with a high mortality, even when it is properly treated [4–7]. Worldwide, tuberculosis is the major cause of death in HIV-1 infection.

However, the interaction between HIV-1 and tuberculosis is bi-directional. The effects of tuberculosis on HIV-1 infection have been observed both at the cellular and clinical levels. Although there is evidence that tuberculosis enhances viral replication through mechanisms that involve activation of the cell-mediated immune system through cytokine networks [8–11], the epidemiological findings have been inconsistent. A number of studies have shown that tuberculosis alters the progression of HIV disease, as measured by survival [12–15], whereas other studies have not [16,17]. The inconsistency in the findings may result from underlying differences in the immune function of study populations, the choice of the comparison group, or the analytic methods. As a group, however, all of these studies are limited by the retrospective design, small sample size, the variability in compliance with anti-tuberculous therapy or antiretroviral drug use, or a bias towards advanced HIV-1 disease. In some of the studies, a cohort effect may exist as patients were recruited over a period of one decade.

The current study addresses some of these limitations as it is a prospective cohort study that examines the impact of tuberculosis on survival in a cohort of Ugandan adults with a spectrum of HIV-1 infection during a 3-year period. In this cohort, compliance with anti-tuberculous therapy was monitored and antiretroviral therapy was unavailable. We found that pulmonary tuberculosis was associated with reduced survival and that the effect on disease progression and survival may exert its greatest impact early in the course of HIV-1 infection, before advanced immunosuppression develops.

Methods

Study design and populations

In a prospective comparative cohort design, the survival experience was compared between HIV-infected individuals with and without pulmonary tuberculosis. Between February 1993 and May 1994, 230 cases of smear-positive pulmonary tuberculosis presenting to the National Tuberculosis and Leprosy Programme in Kampala, Uganda were eligible for the study and

enrolled after history and physical examination, sputum smear for acid-fast bacilli, and chest radiography. Pulmonary tuberculosis was defined as sputum smear-positive disease confirmed by culture in a patient with the clinical signs and symptoms consistent with active tuberculosis. All cases of tuberculosis received daily self-administered anti-tuberculous therapy including isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months followed by 6 months of daily isoniazid and rifampin. The comparison, or control group, for this study comprised subjects without tuberculosis who were enrolled in the placebo arm of a concurrent clinical trial of preventive therapy for tuberculosis [18] and were followed at Mulago Tuberculosis Clinic. Before enrollment in the preventive therapy trial, active tuberculosis was rigorously excluded with a thorough history and physical examination, sputum smear and culture, and chest radiography. Exclusion criteria for both groups included: Karnofsky performance status < 60, positive urine pregnancy test, residence greater than 20 km from the clinic, and WHO clinical stage IV, not including tuberculosis.

Subjects in both groups were seen monthly for 6 months then quarterly thereafter. Both groups were monitored at Mulago Tuberculosis Clinic by the same team of physicians, nurses and ancillary personnel. The same follow-up protocol and data collection forms were used for each group. When a subject missed a scheduled visit or failed to show urinary metabolites of isoniazid, home health visitors visited the homes of these subjects and motivated them to attend the clinic for evaluation and to take the medication as prescribed. Compliance with anti-tuberculous therapy was promoted through regular health education and monitored with urine testing for isoniazid metabolites. Subjects in the comparison group were actively screened for tuberculosis twice a year with chest radiography and sputum microscopy and culture. If tuberculosis was suspected, these subjects underwent further diagnostic evaluation and were started on anti-tuberculous therapy. Both groups received standard management for HIV-1 infection available in Uganda during the study which included treatment of oral thrush, herpes zoster, herpes simplex and recurrent bacterial infections. Antiretroviral therapy was not the standard of practice in Uganda during this study and was not given to subjects.

This study was approved by the Ugandan National AIDS Scientific Subcommittee of the Uganda National Council for Science and Technology and the institutional review board at Case Western Reserve University. Oral informed consent was obtained by trained counselors in the native language of the study subject.

Study outcomes

The main study outcome was observed survival defined as the period between enrollment in the study and death or censoring. Subjects were censored at the last clinic visit when they were known to be alive or at the end of the study observation. Subjects in the comparison group who developed tuberculosis during follow-up were censored at the time tuberculosis was diagnosed. Mortality was assessed through a standard interview of family members or review of hospital records. Failure to keep a scheduled appointment prompted a home visit to determine the vital status of the study subject. The date of death and prominent symptoms at the time of death were also obtained from family members.

To assess the change in viral load during observation, a sample of 20 cases was matched to 20 controls according to baseline age, gender, CD4 lymphocyte count, and presence of cutaneous anergy. The levels of HIV RNA were then compared within and between groups at baseline and 12 months.

Measurements

Demographic and clinical information was obtained through standardized interviews and physical examination performed by trained Ugandan medical officers. Socioeconomic status

was assessed by a trained Ugandan social scientist after an in depth interview to characterize personal possessions, occupation, income, housing and mode of transportation. At the time of screening, venous blood was collected for HIV-1 enzyme immunoassay (EIA) testing, complete blood and differential counts (Coulter T540 system), serum creatinine and aspartate aminotransferase. HIV infection was documented by enzyme-linked immunosorbent assay (ELISA; Recombigen HIV-1 env and gag ELISA, Cambridge BioScience, Worcester, Massachusetts, USA); one of 10 HIV-1 EIA positive and one of 25 HIV-1 negative sera underwent confirmatory testing by HIV-1 Western immunoblotting (BioRad Novapath, Hercules, California, USA). HIV viral load was measured in plasma using the AMPLICOR HIV-1 MONITOR test with additional primers for non-B clade virus [19,20]. At the time of screening, all subjects underwent Mantoux skin testing using five tuberculin units of purified protein derivative (PPD; Tubersol, Connaught Laboratories, Swiftwater, Pasadena, USA) and 0.1 ml *Candida* antigen (*Candida albicans* allergic extract, Berkeley Biologics, Berkeley, California, USA; 1 : 50 final concentration). Between 48 and 72 h, experienced observers recorded the results of each skin test in millimeters. Cutaneous anergy was defined as absence of reactivity (0 mm of induration) to both PPD and *Candida* antigens. Subjects had posterioranterior chest X-rays taken at baseline and then at 6-month intervals during follow-up. Expecterated sputum specimens were collected, digested with 3% NaOH, concentrated, and stained for acid fast bacilli with Ziehl–Neelsen stain at the Uganda Tuberculosis Investigations Bacteriological Unit, Wandegaya. AFB smears were reviewed by trained technicians who graded the smears by the number of acid-fast organisms seen on light microscopy according to criteria established by the WHO [21]. Specimens were cultured for *M. tuberculosis* on Lowenstein–Jensen medium slants, incubated at 37°C in air and examined weekly until positive or for 8 weeks.

Analytic strategy

Baseline characteristics for both the tuberculosis cases and the comparison group were compared using the χ^2 test for categorical data and Student's t test for continuous variables. Mortality rates were estimated and stratified according to CD4 lymphocyte count, history of opportunistic infection, anemia, wasting, and tuberculin skin test. Stratum specific relative risks were estimated with 95% confidence intervals (CI). Overall survival distributions for both groups were estimated using the Kaplan–Meier method and compared using the log-rank test [22]. A series of Cox proportional hazards models [23] were fit after testing for the proportional hazards assumption for each variable. In each model, the dependent variable was the observed survival; independent variables tested included clinical and demographic characteristics, CD4 lymphocyte count, tuberculin skin test, and history of or presence of one or more HIV-related conditions. Variables that were associated with survival in a univariate analysis ($P < 0.15$) were evaluated in a series of multivariable models. Models were compared using likelihood ratio tests. Once significant variables of survival were identified, the variable for tuberculosis status was added to the model and statistical significance assessed. The hazard ratio for death among subjects with tuberculosis compared to subjects without tuberculosis was estimated with 95% CI. A similar analysis was performed to compare survival between tuberculosis patients and HIV-infected controls without tuberculosis but with one or more HIV-related conditions. All two-way interactions between tuberculosis status and other main effects were examined. The only significant interaction was with the body mass index. Thus, separate models were developed for subjects according to the body mass index above or below the median value (21 kg/m²). Once the overall model was developed, a nested Cox regression model was used to estimate the hazard ratio within two strata defined by CD4 lymphocyte counts at baseline: 0–200 × 10⁶cells/l and > 200 × 10⁶cells/l.

Results

A total of 672 subjects met entry criteria for the study: 230 subjects were tuberculosis cases and 442 were HIV-infected subjects without evidence for tuberculosis. The mean age for the tuberculosis cases and the comparison group was similar (29.2 versus 30.6 years). A smaller proportion of the tuberculosis cases was female compared to the control group (51 versus 73%). The mean Karnofsky performance status was similar between the tuberculosis cases and the controls (83 versus 90). The distribution of subjects in high, middle, and low socioeconomic groups was the same for the tuberculosis cases and the controls (1, 26 and 73% respectively). As expected, most patients presenting with tuberculosis had one or more classic symptoms of tuberculosis such as persistent cough, anorexia, night sweats, and fatigue (Table 1). The frequency of HIV-related conditions at the time of presentation was greater in the control population compared with the tuberculosis cases. Chronic diarrhea and oral thrush occurred with comparable frequency between the two groups, but the history of herpes zoster and pruritic papules was more common in the control subjects. Tuberculosis cases had reduced body mass index, lower hemoglobin levels and larger tuberculin skin test reactions compared with the control group (Table 1). The mean absolute CD4 lymphocyte count tended to be lower in the tuberculosis cases than the controls (376 versus 431×10 cells/l; $P = 0.09$), though the overall frequency distributions were similar between the two groups. The proportion of subjects lost to follow-up was similar in the cases and the controls (88 versus 89%); the mean duration of follow-up was also similar (1.7 versus 1.6 years).

During the mean follow-up period of 19 months, 63 of 230 tuberculosis cases (28%) died compared with 85 of 442 controls (19%), for a crude risk ratio of 1.4 (95% CI, 1.07–1.87). The majority of deaths ($n = 99$) occurred in subjects with CD4 counts $< 200 \times 10$ cells/l at baseline and occurred with similar frequency in the tuberculosis cases and the controls (46 versus 44%; relative risk, 1.05; Table 2). When the CD4 count was above 200 cells/ μ L, however, the relative risk of death in HIV-associated tuberculosis was 2.1 compared with subjects without tuberculosis (Table 2). The relative risk of death associated with tuberculosis was also increased after stratifying by history of HIV-related conditions and tuberculin skin test < 5 mm. When stratifying by hemoglobin or body mass index, the mortality rate was slightly higher in the control subjects versus cases when anemia (hemoglobin ≤ 10 mg/dl) or wasting (body mass index ≤ 21 kg/m²) were present. When subjects were not anemic or had a body mass index > 21 kg/m², the risk of death among cases was increased.

In a Kaplan–Meier analysis, the overall, unadjusted survival for cases of tuberculosis was similar to that of the control group ($P < 0.09$, log-rank test), though the cases had a lower survival proportion after 1 year. When this analysis was stratified according to the baseline CD4 lymphocyte count, survival in tuberculosis cases was reduced compared with the controls when the CD4 lymphocyte count was $> 200 \times 10$ cells/l but not when it was $< 200 \times 10$ cells/l (Fig 1a and 1b). For subjects with CD4 lymphocyte counts $> 200 \times 10$ cells/l the 1-year survival proportion was slightly lower in the cases than in the controls (0.91 versus 0.96), but by 2 years the survival proportion was significantly lower in the cases than in the controls (0.84 versus 0.91; $P < 0.02$, log-rank test). For subjects with CD4 counts of 200×10 cells/l or fewer, the survival proportion at 1 year for the controls was lower than cases (0.59 versus 0.64), but this difference was not statistically significant ($P = 0.53$, log-rank test). Of note, during the first 3 months of observation, four deaths occurred in the cases and seven in controls, indicating that early mortality from tuberculosis did not account for differences in survival.

In a univariate Cox proportional hazards model, the unadjusted relative hazard for death in tuberculosis cases compared with the controls was 1.7 (95% CI, 1.19–2.39; Table 3). In addition, gender, hemoglobin, body mass index, history of HIV-related conditions, CD4 lymphocyte count, and tuberculin skin test were associated with survival (Table 3). After

adjusting for age, sex, tuberculin skin test status, CD4 lymphocyte count, and history of HIV-related conditions, the relative hazard for death was 1.8 (95% CI, 1.24–2.65). In a nested Cox regression model adjusting for these same covariates (Table 4), the relative hazard for death was 3.0 (95% CI, 1.62–5.63) for subjects with CD4 lymphocyte count $< 200 \times 10$ cells/l and 1.5 (95% CI, 0.99–2.40) for subjects with a CD4 lymphocyte count of 200×10 cells/l or fewer. When hemoglobin and body mass index were included in this model, there was a statistically significant interaction between tuberculosis and body mass index ($P = 0.003$) but not between tuberculosis and hemoglobin ($P = 0.19$). Separate nested Cox regression models were therefore fit according to body mass index (Table 4). For subjects with body mass greater than the median value of 21 kg/m^2 , the relative hazard for death was 6 fold greater in the tuberculosis cases than in the control subjects, regardless of the baseline CD4 lymphocyte count (Table 4). When the body mass index was $< 21 \text{ kg/m}^2$, then the risk of death was increased only among subjects with CD4 lymphocyte counts $> 200 \times 10$ cells/l, though this was not statistically significant (relative hazard, 2.2; $P = 0.23$).

When survival was compared between tuberculosis cases and HIV-infected controls with one or more HIV-related conditions, a similar pattern of risk was found. In a Cox regression model adjusting for age, sex, tuberculin skin test reaction, the risk of death in the tuberculosis cases compared with controls with another HIV-related condition was 1.81 (95% CI, 0.88–3.70) for subjects with CD4 count $> 200 \times 10$ cells/l and 0.83 (95% CI, 0.53–1.30) for subjects with CD4 count $< 200 \times 10$ cells/l.

In a random sample of 20 tuberculosis cases drawn from the study population and 20 controls matched for age, sex, and CD4 count, plasma HIV RNA was measured at the time of enrollment and again at 1 year. The mean level of the log-transformed viral load from baseline did not differ in the cases and controls (4.4 versus 4.5 $\log_{10}$ copies/ml; $P = 0.34$, non-parametric test). During the first year of follow-up, the viral load increased in the tuberculosis cases by an average of 0.49 $\log_{10}$ ($P = 0.04$, paired t test) and 0.06 $\log_{10}$ in the controls ($P = 0.82$, paired t test), but the change in viral load between groups did not reach statistical significance ($P = 0.17$).

Discussion

In this prospective cohort study of HIV-infected Ugandan adults, pulmonary tuberculosis was associated with reduced survival, but the effect varied according to the stage of HIV disease. In subjects with less advanced immunosuppression, as indicated by a CD4 lymphocyte count $> 200 \times 10$ cells/l, the effect of tuberculosis on survival was substantial, whereas in subjects with advanced immunosuppression, the effect on observed survival was minimal. These findings were consistent whether comparing the survival among tuberculosis cases with all control subjects or only those with one or more HIV-related conditions. The effect of tuberculosis on survival also differed by body mass. In this case, wasting lessened the effect of tuberculosis on survival. The current results indicate that tuberculosis accelerates HIV disease progression as measured by overall survival and that this effect is greatest early in the course of HIV-1 infection when cellular immune function is preserved.

There is a growing body of immunologic and virologic data that provides a potential mechanism for the epidemiologic observations on the impact of tuberculosis on HIV-1. In the HIV-infected individual, the development of tuberculosis activates a T cell mediated immune response, mediated through cytokine networks, that may initiate a sequence of cellular events that both enhances viral production and promotes spread of infection to uninvolved cells. In HIV-infected patients with tuberculosis, there is evidence for cellular immune activation [24] and over-expression of tumor necrosis factor (TNF)- α by PPD-stimulated peripheral blood mononuclear cells [25]. Further, the level of cellular activation of monocytes in tuberculosis

is sufficient to enhance susceptibility to productive infection with HIV *in vitro* [8]. The immune activation of tuberculosis appears to augment viral replication as measured in the plasma [26] and the lung [27,28]. HIV expression may be enhanced by proinflammatory cytokines, such as TNF- α [29], and by mycobacterial products [11,30]; HIV-1 expression may be up- or down-regulated by anti-inflammatory cytokines such as interleukin-10 [31] or transforming growth factor- β [32,33]. The balance of these cytokines, acting in autocrine and paracrine loops, is probably a key determinant of HIV-1 replication in tuberculosis [9].

In this study there was a modest, but significant, increase in viral load among tuberculosis cases during the first year after diagnosis and treatment of tuberculosis. A similar increase in viral load was not observed in the control subjects who were matched by CD4 count. Although the absolute change in viral load was not significantly different between the groups, the sample size was small for this analysis. The rising levels of HIV RNA in tuberculosis patients seen in this study are consistent with other studies [34–36]. This increment in viral load after the initiation of therapy may result from the release of TNF- α [37] or from a reversal of the immunosuppression related to tuberculosis [38]. These observations, and the proposed mechanism for co-pathogenesis, provide rationale for the use of cytokine inhibitors in the treatment of HIV-associated tuberculosis. To date, two TNF- α inhibitors, pentoxifylline and thalidomide, have been shown to decrease plasma HIV RNA and reduce levels of immune activation markers, though no consistent reduction of TNF- α is seen [34,39]. The effect of these and other immune modulators on survival in HIV-associated tuberculosis remains to be established.

In this cohort, among subjects with preserved immune function, the difference in the observed survival distributions between tuberculosis cases and the controls is entirely consistent with a co-pathogenesis hypothesis. In subjects with advanced immunosuppression, the similarity in survival distributions among the tuberculosis cases and controls may seem at first contradictory but, in fact, refines the hypothesis. In advanced stages of HIV infection, we propose that viral replication has escaped the influence of the host response to HIV-1 and that infected cells are already stimulated to elaborate maximal amounts of intact virus. The additional effect of tuberculosis may have minimal effect in this milieu of immune activation and unchecked viral replication. It is also possible that in more advanced HIV-1 disease, the competing risks of death from other causes obscures any effect due to tuberculosis.

The findings of this study are consistent with the hypothesis that tuberculosis acts as a co-factor in disease progression of HIV, but this is not the only possible interpretation of the findings. The major competing hypothesis is that tuberculosis is a marker for advanced disease in HIV infection and that unmeasured differences in risk of death account for the observations. Although the two groups differed in a number of baseline characteristics, they were closely matched in terms of CD4 lymphocyte count, the marker of immune function available during the study. Based on the matched-pairs analysis, the viral load did not differ between cases and controls for a given level of CD4 count. This observation offers further support that patients had similar risk for HIV disease progression within a given stratum of CD4 lymphocyte count. The CD4 lymphocyte count was also the most important prognostic measure in the analysis. Even when adjusting for CD4 lymphocyte count, tuberculosis remained associated with shortened survival.

One question that arises is whether the impact on survival is specific to tuberculosis. In our analysis, we compared the survival of tuberculosis patients to survival in HIV-infected subjects without tuberculosis but with one or more HIV-related conditions. Our conclusions regarding tuberculosis and survival are consistent regardless of the comparison group chosen. Previous epidemiologic studies report that other opportunistic infections besides tuberculosis are associated with a reduced survival and have a greater relative risk of death than tuberculosis

itself [16,17,40]; however, these cohorts comprised patients with advanced disease, as indicated by the presence of opportunistic infections and median CD4 cell counts $< 200 \times 10$ cells/l [41]. If immune function is an effect modifier of the interaction between tuberculosis, HIV infection and survival, as suggested by the findings of the current study, then one would not expect to observe the impact of tuberculosis on survival in these cohorts. But unlike opportunistic infections, which occur only with advanced immunosuppression, *M. tuberculosis* is a virulent organism which can develop at any point in the course of HIV-1 disease. Early in HIV-1 disease when cell-mediated immunity is preserved, tuberculosis may affect the natural history of HIV-1 at a time when opportunistic infections generally do not occur. In advanced HIV-1 disease, the impact of tuberculosis on survival may be modest when compared to opportunistic infections which carry substantial disease-specific mortality.

The observed differences in survival may arise from deaths due to tuberculosis or from HIV-related deaths. In this study, all tuberculosis cases were given standard anti-tuberculous therapy and the majority responded with sterile sputum cultures by 2 months. We do not have detailed information about the cause of death from autopsy studies, but because there were no differences in early mortality between the case and control groups, we assume that deaths in the cases were not caused by tuberculosis. Previous studies have indicated that when HIV-infected persons die from tuberculosis, these deaths occur during the early phase of therapy [4,6]. In this young HIV-infected Ugandan population, complications of HIV-1 besides tuberculosis are the most likely cause of death.

The analysis of this cohort points to body mass index as another effect modifier of the tuberculosis-HIV interaction. Although weight loss is a sign of tuberculosis, and hence highly correlated with disease, it may also be a marker for the stage of HIV-1 infection. For this reason, we examined the effect of tuberculosis after stratifying the analysis by the median value for the body mass index. In this stratified analysis, tuberculosis was associated with reduced survival among subjects without wasting, whereas it had minimal effect among wasted individuals. Thus, low body mass index acts like a marker for advanced HIV disease, similar to the low CD4 counts, so that differences in survival, if any, are minimal. An alternative explanation for this finding posits that control patients with wasting may have had occult disseminated tuberculosis and hence were misclassified. In this case, the differences in observed survival between the controls and the cases of tuberculosis would be mitigated. During the recruitment of the control group, disseminated disease was not evaluated unless suspected on clinical grounds alone.

Tuberculosis holds a primary place in the importance of the global HIV epidemic. Tuberculosis represents the leading cause of death worldwide in HIV infection. *M. tuberculosis* is a virulent organism that can produce disease in HIV-infected persons at any stage of disease, even when the immunosuppression is minimal. In settings of high transmission of tuberculosis, HIV-infected persons are at great risk both for reactivation, progressive primary disease, and reinfection, and provide a fuel for the continuing epidemic of tuberculosis, particularly in Africa. The findings from this study indicate that active tuberculosis will exert its greatest effect on survival when it develops during the early stages of HIV infection, when there is a reserve capacity of the host immune response. These findings provide theoretical rationale for the treatment of latent tuberculous infection in HIV-infected persons, especially those with preserved immune function.

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Fig. 1. Survival distributions of tuberculosis cases and controls with baseline CD4 lymphocyte $> 200 \times 10^6$ cells/l (Fig. 1a) and $\leq 200 \times 10^6$ cells/l (Fig. 1b). Survival distributions were estimated using the Kaplan–Meier method and differences tested using the log-rank test.

Table 1

Baseline characteristics of HIV-infected tuberculosis cases and controls.

Characteristic	Cases (n = 230)	HIV-infected controls (n = 442)	P
Males [n (%)]	111 (48)	120 (27)	0.000
Bacillus Calmette–Guérin vaccine scar [n (%)]	124 (54)	273 (62)	0.000
HIV-related conditions ^a [n (%)]	72 (31)	219 (50)	0.000
Chronic diarrhea [n (%)]	32 (14)	74 (17)	0.34
Oral thrush [n (%)]	24 (10)	56 (13)	0.39
History of herpes zoster [n (%)]	22 (9)	80 (18)	0.003
History of pruritic papules [n (%)]	17 (7)	130 (29)	0.000
Appetite [n (%)]	130 (57)	74 (17)	0.000
Weight loss [n (%)]	197 (86)	164 (37)	0.000
Fever [n (%)]	144 (63)	114 (26)	0.000
Nightsweats[n(%)]	152 (66)	58 (13)	0.000
Cough [n (%)]	226 (98)	194 (44)	0.000
CD4 lymphocyte count ($\times 10^6/l$) [n (%)]			
0–200	82 (36)	138 (31)	0.12
201–500	87 (38)	152 (34)	
> 500	61 (26)	152 (34)	
0–200	82 (36)	138 (31)	0.24
> 200	148 (64)	304 (69)	
Body mass index (kg/m ²) [mean (SD)]	19.2 (2.7)	22.5 (3.5)	0.000
PPD induration (mm) [mean (SD)]	14.5 (6.8)	8.0 (8.0)	0.000
Hemoglobin (mg/dl) [mean (SD)]	10.3 (2.3)	12.5 (1.9)	0.000
Absolute lymphocyte count ($\times 10^6$ cells/l) [mean (SD)]	2087 (933)	2123 (861)	0.62
CD4 lymphocyte count ($\times 10^6$ cells/l) [mean (SD)]	376 (311)	431 (367)	0.09

^a HIV-related conditions includes oral thrush, herpes zoster, chronic diarrhea and pruritic papules.

Table 2

Stratified analysis of mortality according to key variables [deaths/number at risk (%)].

Category	Cases	HIV-infected controls	Relative risk of death	95% CI
CD4 lymphocyte count ($\times 10^6$ cells/l)				
0–200	38/82 (46)	61/138 (44)	1.1	0.78–1.42
> 200	25/148 (17)	24/304 (8)	2.1	1.27–3.62
Previous HIV-related condition				
Yes	32/72 (44)	69/219 (32)	1.4	1.02–1.95
No	31/158 (20)	16/223 (7)	2.7	1.55–4.82
Hemoglobin (mg/dl)				
≤ 10	38/100 (38)	22/49 (45)	0.8	0.57–1.27
> 10	25/128 (20)	63/393 (16)	1.2	0.80–1.85
Body mass index (kg/m ²)				
≤ 21	51/180 (28)	48/154 (31)	0.9	0.65–1.27
> 21	12/50 (24)	37/288 (15)	1.9	1.05–3.33
Tuberculin skin test induration (mm)				
< 5	13/27 (48)	44/168 (26)	1.8	1.15–2.93
≥ 5	50/203 (25)	41/274 (15)	1.7	1.39–2.39

CI, Confidence interval.

Table 3

Univariate analysis of factors associated with survival.

Characteristic	Relative hazard	95% Confidence interval	P
Tuberculosis case	1.7	1.19–2.39	0.004
HIV-infected control	1.0		
Age (years)			
≤ 30	0.9	0.64–1.22	0.42
> 30	1.00		
Sex			
Male	1.4	1.04–1.97	0.035
Female	1.00		
Tuberculin skin test induration			
< 5 mm	1.9	1.42–2.77	0.0002
≥ 5 mm	1.00		
Hemoglobin (mg/dl)			
≤ 10	2.9	2.07–3.98	0.00000
> 10	1.00		
Body mass index (kg/m ²) ^a			
≤ 21	2.5	1.79–3.62	0.00000
> 21	1.00		
CD4 count (×10 ⁶ cells/l)			
≤ 200	1.0	-	0.0000
201–500	0.2	0.16–0.34	
> 500	0.1	0.04–0.13	
History of HIV-related condition ^b			
Yes	3.5	2.48–5.01	0.00000
No	1.00		

^aMedian value for body mass index was 20.8 kg/m².^bHIV-related conditions include oral thrush, chronic diarrhea, herpes zoster, and pruritic papules.

Relative hazards [95% confidence intervals (CI)] for death among tuberculosis (TB) cases compared with controls, stratified according to the median value of the body mass index.

Table 4

	Stratified models					
	Overall model			Body mass index > 21 (kg/m ²)		
	Relative hazard	95% CI		Relative hazard	95% CI	Body mass index ≤21 (kg/m ²) Relative hazard 95% CI
CD4 cell count (× 10 ⁶ cells/l)						
> 200						
TB case	3.0	1.64–5.66	6.2	1.74–22.07	2.2	0.96–5.01
Control	1.0		1.0		1.0	
≤ 200						
TB case	1.5	0.99–2.39	6.4	2.19–18.68	0.9	0.54–1.52
Control	1.0		1.0		1.0	
Age (years)						
>30	0.9	0.72–1.39	1.3	0.74–2.38	0.9	0.63–1.47
≤ 30	1.0		1.00		1.00	
Sex						
Male	1.3	0.94–1.85	1.2	0.60–2.25	1.2	0.78–1.80
Female	1.0		1.00		1.00	
History of HIV-related condition						
Yes	3.0	2.11–4.40	4.0	2.03–8.11	2.6	1.64–4.11
No	1.0		1.00		1.00	