

Association between tuberculosis and HIV disease progression in a high tuberculosis prevalence area

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SUMMARY

SETTING: Adult human immunodeficiency virus (HIV) clinics affiliated to the University of Cape Town, South Africa.

OBJECTIVE: To assess the impact of tuberculosis on HIV-1 disease progression in an area with high tuberculosis prevalence and minimal antiretroviral therapy use.

DESIGN: Prospective patient cohort study.

METHODS: Age, race, risk status, CD4+ T-lymphocyte count, history of AIDS, prophylactic co-trimoxazole and antiretroviral therapy were controlled for in a time-dependent Cox proportional hazards regression model.

RESULTS: Tuberculosis fulfilling the case definition developed in 158/609 patients in the 5-year observation period. Tuberculosis was associated with an increased risk of AIDS (adjusted risk ratio [RR] = 1.60, 95% con-

fidence interval [CI] 1.08–2.41; $P = 0.02$) and death (adjusted RR = 2.16, 95% CI 1.29–3.59; $P = 0.003$). In a stratified analysis, the increased mortality associated with tuberculosis was observed only in patients with CD4+ T-lymphocyte count >200 cells/ μ l and in those without AIDS at baseline.

CONCLUSION: The onset of tuberculosis in HIV-infected patients is associated with an increased risk of AIDS and death. Although a causal link cannot be established in an observational study, our findings support the view that prolonged immune activation induced by tuberculosis leads to prolonged increased HIV replication and consequent accelerated disease progression.

KEY WORDS: HIV infection prognosis; survival; tuberculosis; AIDS; CD4+ T-lymphocyte

TUBERCULOSIS is the most frequently diagnosed disease in human immunodeficiency virus (HIV) infected patients world-wide. In vitro studies have shown that tuberculosis increases the ability of HIV to replicate by activating CD4+ T-lymphocytes and macrophages harbouring latent HIV. The onset of tuberculosis in HIV-infected patients causes marked release of pro-inflammatory cytokines that activate lymphocytes and macrophages. This results in an increased HIV viral load.¹ Transient increases in viral load occur with opportunistic infections,² but two large African studies of patients with tuberculosis and no access to antiretroviral therapy found that viral load did not decrease despite effective anti-tuberculosis therapy,^{3,4} and cellular immune activation markers persisted.³

Epidemiological studies assessing the effect of tuberculosis on HIV progression have shown inconsistent results. Some studies concluded that there was no discernible decrease in survival or evidence of major acceleration of HIV disease attributable to tuberculosis in patients with HIV infection,^{5,6} while other studies have documented either a significantly reduced survival,^{7,8} or an increased frequency of

AIDS-defining illness following the diagnosis of tuberculosis in HIV-infected patients.⁹ Furthermore, while prevention of active tuberculosis in HIV-infected patients was observed to reduce mortality in tuberculin skin test positive patients in one meta-analysis,¹⁰ no significant reduction was observed in another.¹¹

Studies assessing the impact of HIV-associated tuberculosis on disease progression have generally been conducted in industrialised countries where injecting drug use is strongly associated with tuberculosis.^{12,13} The outcome in injecting drug users with HIV infection may be confounded by factors such as drug overdose, violence or poor treatment adherence.¹⁴ Tuberculosis, however, occurs much more frequently in developing countries than in industrialised countries, and accounts for more than one third of mortality among HIV-infected patients in sub-Saharan Africa.^{15,16} As access to antiretroviral therapy is limited in Africa owing to lack of resources,¹⁷ the effect of tuberculosis on the natural history of HIV infection can be more accurately assessed in such a setting.

Cape Town has a very high prevalence of tuberculosis,¹⁸ which is also the commonest AIDS-defining

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condition.¹⁹ Local health care facilities are generally better than elsewhere on the continent,²⁰ allowing the diagnosis and treatment of most opportunistic infections. However, antiretroviral therapy is not available for treating patients in the public sector, and few are able to purchase these drugs privately. The objective of this study was to assess the impact of tuberculosis on HIV-1 disease progression in a cohort of adult patients.

MATERIALS AND METHODS

This was a prospective cohort study of adult (≥ 18 years of age) HIV-infected patients attending the two HIV clinics affiliated to the University of Cape Town (New Somerset and Groote Schuur Hospitals). At the time patients were accrued into this cohort, there were virtually no other facilities for HIV care available in the public sector in our area. There was thus unlikely to be referral bias among patients using public sector facilities. The study was approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town.

Follow-up was repeated at 3–6 monthly intervals, or more frequently if clinically indicated. CD4+ T-lymphocyte counts were measured approximately 6 months by flow cytometry. HIV infection was confirmed by ELISA and/or Western blot on two separate blood specimens (HIV-2 is very rare in Cape Town and Western blots have been discontinued²¹). Demographic, clinical and laboratory data were prospectively entered into a database established in 1992. The study cohort was limited to patients whose initial clinic visit was between 1992 and 1996.

The records of all patients diagnosed with tuberculosis during the study period were reviewed. Patients diagnosed with tuberculosis were treated with a 6-month rifampicin-based short-course regimen. The tuberculosis case definition in this study was either 1) definite tuberculosis: culture of *Mycobacterium tuberculosis* or an autopsy diagnosis, or 2) probable tuberculosis: a positive smear or a histological diagnosis together with a compatible clinical picture. In line with the national policy, positive sputum smears were not confirmed by culture. Patients were excluded from the study if the diagnosis of tuberculosis did not fulfil the case definition. Pulmonary tuberculosis was defined as sputum smear or culture positive disease, or a pulmonary infiltrate or pleural effusion on chest radiograph. Extra-pulmonary tuberculosis was defined as disease outside these sites.

AIDS was defined using the 1987 Centers for Disease Control case definition.²² Tuberculosis was not considered as an AIDS-defining illness for this analysis as we were examining the effect of tuberculosis on disease progression. The incidence density rate of newly diagnosed AIDS-defining illness (defined as a new or recurrent episode) in the follow-up period for tuberculosis cases and the comparison group was

defined as the number of AIDS-defining events occurring in patients without an AIDS-defining illness at baseline per 100 patient-months of follow-up.²³ The incidence density ratio (IDR) was derived by dividing the incidence density rate in the tuberculosis group by that in the comparison group.²³ The IDR was then adjusted by stratifying according to use of antiretroviral therapy, age and CD4+ T-lymphocyte count. Adjusted IDRs were calculated using the Mantel-Haenszel method.²³

Survival was defined as the time from inclusion (or date of tuberculosis diagnosis for incident cases of tuberculosis) to the date of last follow-up visit or death. The overall survival proportions for tuberculosis cases and the comparison group were estimated using the Kaplan-Meier method. The generalised log rank test was used to compare survival curves. To compare survival of the two groups at different levels of immunosuppression, the Kaplan-Meier analysis was further stratified according to baseline CD4+ T-lymphocyte count: >400 , 201–400 and <200 cells/ μl , and according to history of previous AIDS-defining illnesses.

Cox proportional hazards regression models were fitted to determine the unadjusted risk of death associated with tuberculosis and to adjust for potential confounding variables. Observed survival distributions met the assumptions of proportionality of the hazards model.²⁴ The Cox models included a priori variables known or thought likely to be associated with outcomes of interest. Age, race, risk status, CD4+ T-lymphocyte count, history of an AIDS-defining illness at baseline, and use of antiretroviral and prophylactic co-trimoxazole therapies were included as possible confounding variables. Tuberculosis was modelled as a time-dependent variable and the CD4+ T-lymphocyte count in patients with tuberculosis was assessed at the time of diagnosis of tuberculosis (or within 3 months of the diagnosis). Ninety-five per cent confidence intervals (95%CI) around the risk ratio were calculated using Rothman's approximation method.²³

To assess whether tuberculosis might have induced CD4+ T-lymphopenia at the time tuberculosis was diagnosed, the 45 cases diagnosed during follow-up (incident cases) were further analysed. The CD4+ T-lymphocyte counts 3–6 months before and after the date of diagnosis were compared with the count at the time of diagnosis, using Friedman non-parametric analysis of variance (ANOVA, multivariate analysis) and Wilcoxon non-parametric signed rank (bivariate analysis) tests.²⁵ The choice of these tests was based on the finding that the CD4+ T-lymphocyte counts, when tested for normality using the Shapiro-Wilks test,²⁵ were significantly non-normally distributed. Another Cox proportional hazards regression model including the CD4+ counts 3–6 months before or after, rather than at the tuberculosis diagnosis date,

Table 1 Baseline demographic and clinical characteristics in a cohort of HIV-infected patients with tuberculosis and a comparison group without tuberculosis, 1992–1996

Characteristic	TB group (n = 158) n (%)	Comparison group (n = 451) n (%)	P value*
Male	79 (50)	251 (58)	0.09
Mean age (standard deviation)	32 (9.1)	32 (8.8)	—
Race [†]			<0.001
Asian	11 (7)	19 (4.4)	
Black	107 (67.6)	221 (48.8)	
Coloured	30 (19)	117 (25.5)	
White	10 (6.3)	96 (21)	
Sexual preference and risk behaviour			<0.01
Homosexual	10 (6.3)	89 (19.6)	
Heterosexual	125 (79)	306 (67.6)	
Intravenous drug user	1 (0.6)	—	
Blood transfusion	2 (1.3)	7 (1.6)	
Unknown	20 (12.7)	51 (0.11)	
Use of antiretroviral therapy	3 (1.93)	44 (9.7)	<0.001
Use of prophylactic co-trimoxazole	71 (44.9)	116 (25.6)	<0.001
Baseline CD4+ T-lymphocyte [‡]			<0.001
≤200 cells/μl	71 (45)	149 (33)	
201–400 cells/μl	45 (29)	155 (34)	
>400 cells/μl	42 (26)	147 (33)	
Baseline AIDS-defining illness	17 (10.8)	24 (5.3)	<0.001

* χ^2 test.[†] Four category political classification used under apartheid, and strongly correlated with socio-economic status.[‡] CD4+ T-lymphocyte count within 3 months of the diagnosis of tuberculosis for incident cases.

was then fitted. Using this method, it was thus possible to determine estimates for the effect of tuberculosis and of CD4+ T-lymphocyte count (and of the other variables included in the model) which 'removed' the transient reduction in CD4+ T-lymphocyte count which may have been caused by tuberculosis.

RESULTS

Between 1992 and 1996, a total of 647 patients attended the clinics for their initial visit. Tuberculosis was diagnosed in 196 patients. Thirty-eight of these were excluded, as they did not fulfill the case definition for the diagnosis of tuberculosis. The study cohort thus consisted of 609 patients with 158 (25.9%) cases of tuberculosis. Baseline data are given in Table 1.

There were 113 prevalent (diagnosed at the initial visit) and 45 incident (diagnosed after entry) cases of tuberculosis. Tuberculosis was pulmonary in 90 (57%), pulmonary and extra-pulmonary in 37 (23.4%), and extra-pulmonary alone in 31 (19.6%). The tuberculosis diagnosis was definite in 69 cases (43.7%) and probable in the remainder, of which 80 (50.6%) were smear positive and nine (5.6%) diagnosed on histology. Tuberculosis caused a significant transient CD4+ T-lymphopenia (Figure 1) in the 45 incident cases in whom this could be investigated.

Follow-up was comparable in the two groups (mean 11.5 and 14.6 months respectively; $P = 0.7$). The proportion of patients lost to follow-up in the

two groups (defined as not being seen at the clinics for >12 months before the end-point of the study) was not significantly different (33 [20.9%] in tuberculosis cases vs. 104 [23.1%] in the comparison group, $P = 0.57$).

The median time of progression to AIDS, in patients free of AIDS at baseline, was 6 months for tuberculosis cases compared with 14.5 months for the comparison group ($P = 0.05$). The more rapid progression to AIDS in tuberculosis cases remained significant after controlling for potentially confounding variables (risk ratio [RR] = 1.60, 95% CI 1.08–2.41; $P = 0.02$). Other factors associated with progression to AIDS were CD4+ T-lymphocyte count ≤ 200 cells/μl (RR = 2.36, 95% CI 1.59–3.50; $P < 0.001$) and co-trimoxazole prophylaxis, which was protective against the onset of AIDS (RR = 0.21, 95% CI 0.14–0.33; $P < 0.01$). In addition, 47 AIDS-defining illnesses occurred in 33 tuberculosis patients over 1803.4 patient-months (incidence density = 2.6/100 patient-months), compared with 43 AIDS-defining illnesses over 6618.7 patient-months in 34 patients in the comparison group ([incidence density = 0.7 per 100 patient-months], [crude incidence ratio = 3.7, 95% CI 2.85–6.28]). Table 2 shows the adjusted IDRs of AIDS-defining illness across the different strata of age, use of antiretroviral therapy and baseline CD4+ T-lymphocyte count.

Of the 609 patients, 103 (17%) died over the 5-year period: 50 (31.7%) tuberculosis cases and 53 (11.7%) in the comparison group. Mortality rate was

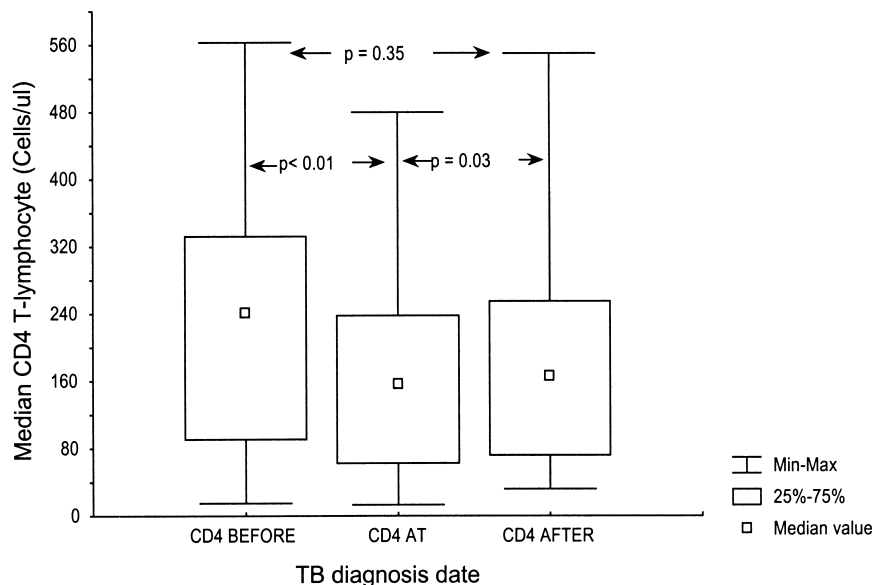


Figure 1 Median CD4+ T-lymphocyte count before, at and after tuberculosis diagnosis in incident tuberculosis cases ($n = 45$), HIV adult clinics, Cape Town, South Africa, 1992–1996.

significantly higher in tuberculosis cases compared to the comparison group (2.8/100 vs. 0.8/100 patient-months respectively; RR = 2.29, 95%CI 1.61–3.25; $P < 0.001$). Among the 50 deaths occurring in the tuberculosis group, two patients died during the first month after the start of anti-tuberculosis therapy and may have died of tuberculosis;³ a further 24 deaths occurred in the following 5 months. Twenty-nine of the 50 patients who died were diagnosed with other AIDS-defining illnesses after the development of tuberculosis.

A separate analysis was conducted to ascertain the survival of the 38 cases who were excluded as they did not fulfil the case definition. Seven cases in this group attended the clinics only once and were then lost to follow-up. Among the remaining 31 cases, seven (22.6%) died during a median follow-up of 12.7 months. Their median survival time was 37.2 months (interquartile range 21.6–44.7). Mortality in this group was not significantly different from that reported among tuberculosis cases retained

Table 2 Incidence of AIDS-defining illness in a cohort of HIV-infected patients with tuberculosis ($n = 158$) and a comparison group without tuberculosis ($n = 451$) stratified by age, use of antiretroviral therapy and CD4+ T-lymphocyte count

Variable	Group	n^*	Person-months	Incidence density [†]	IDR (95%CI)	Adjusted IDR [‡] (95%CI)
Overall	TB group	47	451.7	10.4	1.5 (1.02–2.32)	
	Comparison group	43	635	6.8		
Age ≤ 32 years	TB group	21	260.8	8.1	1.6 (0.74–3.19)	1.71 (1.12–2.0)
	Comparison group	11	210	5.2		
Age > 32 years	TB group	26	190.9	13.6	1.8 (1.08–3.03)	
	Comparison group	32	425	7.5		
Antiretroviral used	TB group	2	47.7	4.2	0.4 (0.1–1.9)	1.58 (1.03–2.0)
	Comparison group	14	144	9.7		
No antiretroviral used	TB group	45	404	11.0	1.9 (1.18–3.0)	
	Comparison group	29	491	5.9		
CD4+ count (≤ 200 cells/ μ l)	TB group	31	249.8	12.4	1.7 (1.03–2.78)	1.59 (1.06–2.0)
	Comparison group	31	421.5	7.4		
CD4+ count > 200	TB group	16	201.9	7.9	1.4 (0.67–2.98)	
	Comparison group	12	213.5	5.6		

* n = number of newly diagnosed AIDS-defining illnesses.

[†] Incidence density = $n/100$ person-months.

[‡] Adjusted IDR = Mantel-Haenszel statistic.

IDR = incidence density ratio; CI = confidence interval.

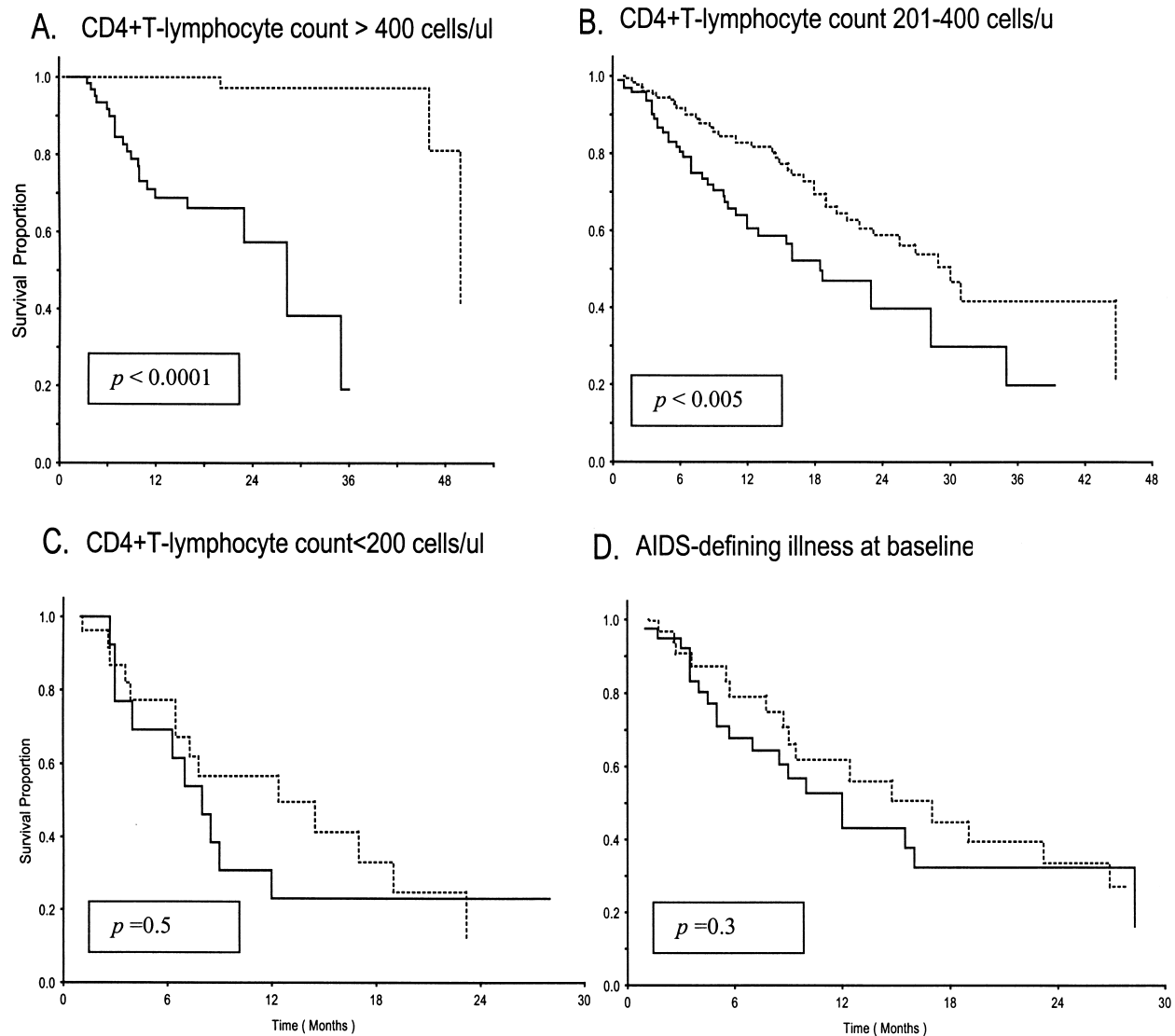


Figure 2 Survival probabilities according to CD4+ T-lymphocyte count (A, B, C) and history of AIDS-defining illness (D) in a cohort of patients with tuberculosis (—) and a comparison group without tuberculosis (.....), HIV adult clinics, Cape Town, South Africa, 1992–1996. CD4+ T-lymphocyte counts in the incident cases of tuberculosis were taken within 3 months of diagnosis.

in the cohort studied (RR = 0.58, 95%CI 0.24–1.45; $P = 0.24$).

The median survival of tuberculosis cases was significantly shorter than that of the comparison group (23.9 and 47.7 months respectively; $P < 0.001$). The Kaplan-Meier survival probability of tuberculosis cases was consistently less than that of the comparison group (69% vs. 92% at 1 year, $P < 0.0001$; 49% vs. 82% at 2 years, $P < 0.0001$; and 28% vs. 64% at 3 years, $P < 0.0001$). In a stratified analysis the difference in survival between tuberculosis cases and the comparison group was not observed in patients presenting with advanced disease (CD4+ T-lymphocyte count ≤ 200 cells/ μ l or history of an AIDS-defining illness at baseline) (Figure 2).

Multivariate Cox proportional hazards regression revealed that even after controlling for differences in baseline characteristics and known predictors of mor-

tality in HIV infection, tuberculosis conferred an increased independent risk of death in HIV-infected patients (RR = 2.16, 95%CI 1.29–3.59, $P = 0.003$) (Table 3). The association of tuberculosis with increased mortality persisted after ‘removing’ the transient reduction in the CD4+ T-lymphocyte count that may have been induced by tuberculosis (RR = 1.90, 95%CI 1.16–3.1; $P = 0.01$) (Table 3).

DISCUSSION

This prospective cohort study was undertaken to assess the effect of tuberculosis on the natural history of HIV infection in patients from a high tuberculosis prevalence setting. The major findings were a significantly reduced survival and an increased frequency of AIDS-defining illness in HIV-infected patients with tuberculosis. To our knowledge, this is the first study

Table 3 Predictors of mortality in a cohort of HIV-infected patients before and after accounting for CD4+ T-lymphopenia induced by tuberculosis at diagnosis: univariate and multivariate models

Variable	CD4+ count at TB diagnosis				CD4+ count 3–6 months before or after TB diagnosis			
	Univariate model RR (95%CI)	P	Multivariate model RR (95%CI)	P	Univariate model RR (95%CI)	P	Multivariate model RR (95%CI)	P
CD4 ≤200 cells/μl	2.59 (1.61–4.15)	0.01	2.48 (1.11–5.53)	0.02	2.10 (1.22–3.66)	0.01	1.84 (1.06–3.19)	0.03
Antiretroviral therapy	0.79 (0.48–1.31)	0.36	1.55 (0.18–2.96)	0.18	0.79 (0.48–1.31)	0.36	1.01 (0.49–2.05)	0.9
Co-trimoxazole prophylaxis	0.70 (0.51–0.95)	0.05	0.49 (0.02–0.78)	0.002	0.70 (0.51–0.95)	0.05	0.49 (0.30–0.8)	0.004
Tuberculosis*	2.05 (1.38–3.07)	0.01	2.16 (1.29–3.59)	0.03	2.05 (1.38–3.07)	0.01	1.90 (1.16–3.1)	0.01
Age >32 years	1.04 (0.70–1.54)	0.85	1.30 (0.85–1.97)	0.22	1.04 (0.70–1.54)	0.85	1.23 (0.81–1.87)	0.32
Baseline AIDS-defining illness	1.75 (1.10–2.78)	0.01	2.28 (1.36–3.78)	0.01	1.75 (1.10–2.78)	0.01	2.29 (1.38–3.78)	0.01
White race group†	0.64 (0.42–0.99)	0.04	0.86 (0.61–1.2)	0.35	0.64 (0.42–0.99)	0.04	0.80 (0.42–1.57)	0.53
Homosexual group†	0.64 (0.43–0.96)	0.03	0.86 (0.69–1.08)	0.87	0.64 (0.43–0.96)	0.03	0.95 (0.52–1.77)	0.65

Cox proportional hazards regression analyses.

* A time-dependent variable.

† Compared to other groups as reference (see Table 1).

RR = risk ratio; CI = confidence interval.

to show both a significantly reduced survival and a higher rate of AIDS-defining illness in HIV-infected patients with tuberculosis relative to those without tuberculosis, and to quantify and allow for the transient CD4+ lymphopenia induced by tuberculosis at diagnosis. The confounding effects of antiretroviral therapy and injecting drug use^{13,14} on the natural history of HIV disease were largely absent in this cohort.

The 24-month median survival of the HIV-infected patients with tuberculosis in this study is comparable to that reported from USA^{6,26} and Europe.⁸ It is noteworthy that the similar survival of these patients was achieved with minimal use of antiretroviral therapy. Survival of patients with HIV-associated tuberculosis is much shorter elsewhere in sub-Saharan Africa.^{27,28} Factors contributing to the improved survival of patients in this study compared with that of other African series include access to rifampicin,²⁸ widespread use of co-trimoxazole prophylaxis,^{29,30} and facilities to diagnose and treat other opportunistic infections.

The risk ratio of death in HIV-infected patients with tuberculosis observed in the present study (2.16 and 1.90 before and after adjusting for the transient CD4+ lymphopenia at tuberculosis diagnosis) is similar to findings of retrospective studies from the USA,⁶ France⁷ and ex-Zaire.³¹ However, in patients previously diagnosed with AIDS, no acceleration of HIV disease attributable to tuberculosis was found.³² These apparently contradictory results are consistent with the finding in the present study that the effect of tuberculosis on HIV disease progression was not observed in patients with advanced disease. This suggests that the effect of tuberculosis as a co-factor for accelerating the clinical course of HIV infection is no longer discernible in patients with advanced disease.

The CD4+ T-lymphocyte in peripheral blood is one of the most important determining factors for the occurrence of various opportunistic infections, and is a reliable prognostic indicator for the progression of HIV infection to AIDS.³³ Lymphocytes have a central role in

human defences against mycobacteria,³⁴ and CD4+ T-lymphocytes are the key cells in protective immunity in tuberculosis.³⁵ However, it is not certain whether a low CD4+ T-lymphocyte count at the time of diagnosis of tuberculosis implies that the low count is a predisposing factor for or a consequence of the disease. Comparing the CD4+ T-lymphocyte count prior to, at and immediately after the onset of tuberculosis in the incident patients, we observed significant transient CD4+ lymphopenia in our incident tuberculosis patients and a normalised CD4+ T-lymphocyte count with tuberculosis treatment. This finding suggests that the CD4+ lymphopenia was a reaction to mycobacterial infection and not a manifestation of accelerated immune deficiency, as has been suggested previously,³⁶ and that tuberculosis is a reversible cause of CD4+ lymphopenia.

There are several limitations to this study. Due to the design of our study, it is not possible to distinguish whether tuberculosis is acting as a marker of a severe immune suppression (for which the CD4+ T-lymphocyte count provides an incomplete guide), or whether it is an independent factor for the accelerated course of HIV disease observed in this cohort. Viral load, which is the best predictor of HIV disease progression,³⁷ was not measured in the present study. There were no accurate data available on cause of death; in the cohort with tuberculosis it is unlikely that tuberculosis was a major cause of death because of the time to death after starting anti-tuberculosis therapy. Excess mortality occurring after the first month of anti-tuberculosis therapy is generally attributable to other causes.^{6,38} Our study design was such that prevalent cases of tuberculosis with newly diagnosed HIV would only be included if they survived to attend their first clinic visit, which is typically one month after discharge. Only two of the 45 incident cases of tuberculosis died in the first month after the start of anti-tuberculosis therapy. Multidrug-resistant tuberculosis, which is associated with high mortality in HIV-infected patients,³⁹ is uncommon, and is not

associated with HIV infection in our area.⁴⁰ The exclusion of the 38 patients treated for tuberculosis who did not fulfil the case definition is not likely to have introduced bias, as their survival was not significantly different from that in the tuberculosis cohort.

The greater frequency of AIDS-defining illness observed in tuberculosis cases was argued in a similar study to be due to possible detection bias whereby cases might have been followed more closely than the comparison group.⁷ Detection bias is not a likely explanation for the higher rate of AIDS-defining illness occurring in patients with tuberculosis relative to the comparison group in this study, as the intensity of follow-up and the proportion of patients lost to follow-up in the two groups were not significantly different. The relatively high rate of loss to follow-up in this cohort is a further limitation, but it is difficult to maintain long-term follow-up in our setting. No information was available about compliance with tuberculosis treatment in this study. It is thus not possible to exclude non-compliance with treatment as an effect modifier of the impact of tuberculosis on survival.

The association between HIV disease progression and the onset of tuberculosis noted in this study is biologically plausible.¹ This finding is of clinical and public health importance. Tuberculosis is one of the few preventable and curable diseases in the wide spectrum of HIV/AIDS associated conditions. Early detection and effective treatment of tuberculosis as well as the provision of prophylaxis against tuberculosis is likely to impact favourably on the prognosis of HIV infected patients. This strategy is of particular relevance in high tuberculosis prevalence areas where access to antiretroviral therapy is currently limited.

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R É S U M É

CADRE : Dispensaires pour adultes infectés par le virus de l'immunodéficience humaine (VIH) affiliés à l'Université du Cap, Afrique du Sud.

OBJECTIF : Evaluer l'impact de la tuberculose sur la progression de la maladie due au VIH-1 dans une zone à prévalence élevée de tuberculose et à utilisation minimale du traitement antirétroviral.

SCHEMA : Etude prospective d'une cohorte de patients.

METHODES : L'âge, la race, la situation de risque, les décomptes de lymphocytes-T CD4, les antécédents de SIDA, la prophylaxie au cotrimoxazole et le traitement antirétroviral ont été soumis à contrôle dans un modèle de Cox de régression des risques proportionnels liés au temps.

RÉSULTATS : Une tuberculose répondant à la définition des cas s'est développée chez 158 de 609 patients au cours de la période d'observation de 5 ans. La tuberculose était associée à un accroissement de risque de SIDA

(ratio de risque ajusté [RR] = 1,60 ; intervalle de confiance 95% [IC] 1,08-2,41 ; $P = 0,02$) et de décès (RR ajusté = 2,16 ; IC95% 1,29-3,59 ; $P = 0,003$). Lors de l'analyse stratifiée, l'augmentation de mortalité associée à la tuberculose n'a été observée que chez les patients dont les décomptes de lymphocytes-T CD4 étaient supérieurs à 200 cellules/ μ L et chez ceux n'ayant pas de SIDA au point de départ.

CONCLUSION : Le développement de la tuberculose chez les patients infectés par le VIH est associé à un risque accru de SIDA et de décès. Bien qu'un lien de causalité ne puisse être établi dans une étude d'observation, nos données soutiennent l'idée qu'une activation immunitaire prolongée induite par la tuberculose entraîne une répliation accrue et prolongée du VIH et par voie de conséquence une progression consécutive accélérée de la maladie.

R E S U M E N

MARCO DE REFERENCIA : Dispensarios de adultos para el virus de la inmunodeficiencia humana (VIH), afiliados a la Universidad de Cape Town, en Sud África.

OBJETIVO : Evaluar el impacto de la tuberculosis en la progresión de la enfermedad por VIH-1 en un área con alta prevalencia de tuberculosis y uso mínimo del tratamiento anti-retroviral.

DISEÑO : Estudio prospectivo de cohorte de pacientes.

MÉTODOS : Se controlaron la edad, raza, estado de riesgo, recuento de linfocitos TCD4+, historia de SIDA, profilaxis con co-trimoxazol y tratamiento anti-retroviral para un modelo de Cox de regresión de los riesgos proporcionales dependientes del tiempo.

RESULTADOS : La tuberculosis, que cumplía con las definiciones establecidas, se desarrolló en 158/609 pacientes en el período de observación de 5 años. La tuberculosis estuvo asociada con un aumento en el riesgo

de SIDA (relación ajustada de riesgo [RR] = 1,60 ; 95% intervalo de confianza [IC] 1,08-2,41 ; $P = 0,02$) y de muerte (RR ajustado = 2,16 ; 95%IC 1,29-3,59 ; $P = 0,003$). En un análisis estratificado, el aumento de la mortalidad asociada con la tuberculosis se observó sólo en los pacientes con un recuento de linfocitos TCD4+ >200 células/ μ L y en aquellos sin SIDA inicial.

CONCLUSIÓN : La aparición de la tuberculosis en los pacientes infectados por VIH está asociada con un riesgo aumentado de SIDA y de muerte. Aunque una relación casual no puede establecerse en un estudio de observación de casos, nuestros hallazgos apoyan la impresión que la activación inmunológica prolongada inducida por la tuberculosis conlleva a una replicación aumentada y prolongada del VIH y por consecuencia a una progresión acelerada de la enfermedad.