

# Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort

Stephen D. Lawn<sup>a,b</sup>, Motasim Badri<sup>a</sup> and Robin Wood<sup>a</sup>

**Objectives:** To determine the long-term incidence of tuberculosis (TB) and associated risk factors among individuals receiving HAART in South Africa.

**Design:** Prospective cohort study.

**Methods:** Microbiologically or histologically confirmed incident TB was identified in a hospital-based cohort of 346 patients receiving HAART between 1996 and 2005 in Cape Town.

**Results:** The TB incidence density rate was 3.5/100 person-years in the first year and significantly decreased during follow-up, reaching 1.01/100 person-years in the fifth year ( $P = 0.002$  for trend). TB incidence during the study was highest among patients with baseline CD4 cell counts  $< 100$  cells/ $\mu\text{l}$  and those with World Health Organization (WHO) clinical stage 3 or 4 disease (5.71 and 3.88/100 person-years, respectively). Risk of TB was independently associated with CD4 cell count  $< 100$  cells/ $\mu\text{l}$  (adjusted risk ratio [ARR], 2.38; 95% confidence interval (CI), 1.01–5.60;  $P = 0.04$ ), WHO stage 3 or 4 disease (ARR, 3.60; 95% CI, 1.32–9.80;  $P = 0.01$ ) and age  $< 33$  years (ARR, 2.86; 95% CI, 1.29–6.34;  $P = 0.01$ ). Risk of TB was not independently associated with plasma viral load, previous history of TB, low socioeconomic status or sex. Despite similar virological responses to HAART, blood CD4 cell count increases were much smaller among patients who developed TB than among those who remained free of TB.

**Conclusions:** Incidence of TB continues to decrease during the first 5 years of HAART and so HAART may contribute more to TB control in low-income countries than was previously estimated from short-term follow-up. Patients with advanced pretreatment immunodeficiency had persistently increased risk of TB during HAART; this may reflect limited capacity for immune restoration among such patients.

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## Introduction

Use of HAART has dramatically decreased HIV-associated morbidity and mortality in many high-income countries since the mid 1990s [1–4]. Suppression of viral replication permits both quantitative and functional reconstitution of the immune system [5,6]. As a result, primary and secondary prophylaxis for many

opportunistic infections that occur among patients with advanced immunodeficiency can subsequently be discontinued [7–10]. The risk of recurrence of these low virulence opportunistic pathogens, including cytomegalovirus, *Pneumocystis jirovecii*, *Mycobacterium avium* complex, *Toxoplasma gondii* and *Cryptococcus neoformans* is generally very low once blood CD4 cell counts have reached stable levels  $> 200$  cells/ $\mu\text{l}$  [7].

From the <sup>a</sup>The Desmond Tutu HIV Centre, Institute for Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa, and the <sup>b</sup>Clinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK.

Correspondence to Dr. S.D. Lawn, Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory 7925, Cape Town, South Africa.

E-mail: stevelawn@yahoo.co.uk

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Studies conducted in countries with either low or high TB prevalence have also shown that TB incidence is reduced by 70–90% in HIV-infected cohorts receiving HAART [11–16]. However, in contrast to low-virulence pathogens, increasing evidence suggests that significant rates of TB persist during HAART [16–18]. Therefore, although the risk of TB is greatly diminished during treatment, the risk nevertheless remains substantially higher than that among individuals who do not have HIV. This has important implications for the extent to which HAART may assist in TB control in low-income countries [19]. Modelling analysis suggests that good effective coverage with HAART in such communities may have relatively little impact on the overall burden of TB over a 20-year timespan [20]. The reason for this is that life expectancy is greatly extended during HAART and so treated patients may develop TB at a lower rate but over a much longer period of time [19,20]. However, these existing analyses were based upon data from a cohort with a short median duration of follow-up [16] and the longer-term effect of HAART on TB incidence rates remains undefined.

The existing TB control strategy of case-finding and directly observed treatment of sputum smear-positive patients using short-course antituberculosis treatment is proving inadequate in countries with a high burden of HIV [21,22]. The World Health Organization (WHO) has, therefore, formulated a strategic framework aimed at functional integration of control programmes for TB and HIV/AIDS [23]. HAART is one element within this framework but data are now needed to clarify the effect that HAART will have on TB control. This study determined TB incidence rates during HAART and identified risk factors for TB in a treatment cohort studied in Cape Town, South Africa, between 1996 and 2005.

## Methods

### Study population

The study was based on the Cape Town AIDS Cohort, which has been described in detail previously [16,24]. Patients were enrolled into this cohort from 1996 onwards when HAART was not available in the public sector in South Africa. These patients, therefore, accessed HAART through participation in multicentre phase III clinical trials at the New Somerset Hospital and the Desmond Tutu HIV Research Centre, University of Cape Town. Participants gave informed consent and clinical trials protocols were approved by the University of Cape Town Clinical Research Ethics Committee.

Enrolment criteria for HAART differed between the various trials but collectively encompassed patients with a wide spectrum of baseline blood CD4 cell counts and

clinical stages [16]. Patients were clinically staged using the WHO criteria. Demographic data were recorded, including socioeconomic status according to the Cape Metropolitan Council suburbs composite index, as described previously [16]. At baseline and at each follow-up time-point, patients were clinically assessed and symptomatic disease was investigated. All patients received at least three antiretroviral drugs: a non-nucleoside reverse transcriptase inhibitor and two nucleoside reverse transcriptase inhibitors; or three nucleoside reverse transcriptase inhibitors; or a protease inhibitor with two nucleoside reverse transcriptase inhibitors. Patients were reviewed routinely every 2–3 months or more frequently if clinically indicated. Blood CD4 cell counts and plasma viral load were measured every 2–3 months. Systematic clinical records were maintained and were used to update a prospective electronic database. Patients were excluded from the analysis if they were receiving TB treatment at enrolment.

### Case definition for tuberculosis

TB was defined as either *definite* – culture of *Mycobacterium tuberculosis* or a postmortem diagnosis of active TB – or *presumptive* – acid-fast bacilli present in sputum or tissue samples or caseating granulomata seen in histological samples obtained from a patient with a clinical presentation consistent with TB and who subsequently responded to antituberculosis treatment.

### Statistical analysis

Differences in proportions were compared by  $\chi^2$  test. Intraindividual paired comparisons of median CD4 cell counts and plasma HIV RNA concentrations were carried out using the Wilcoxon signed rank test. The Mann–Whitney *U* test was used to compare these values between different groups of subjects. Trend analyses were conducted using Cochran–Armitage test for linear trend. All tests were two sided and a *P* value of 0.05 was considered significant.

TB incidence density rate (IDR) was defined as the number of new episodes of TB occurring per 100 patient-years of observation. The analysis was further stratified by the baseline HIV RNA viral load ( $< 5$  or  $\geq 5 \log_{10}$  copies/ml), CD4 cell count ( $< 100$  or  $\geq 100$  cells/ $\mu\text{l}$ ), WHO clinical stage (stage 3 or 4 versus 1 or 2), socioeconomic status, previous history of TB, age (above or at/below median age), and gender. Different CD4 cell count categories were modelled, but a cut-off of 100 cells/ $\mu\text{l}$  was used in the final analysis because it was significantly associated with risk of TB in this cohort.

Kaplan–Meier plots were used for TB-free survival probabilities. TB-free survival was defined as the time from enrolment to the date of TB diagnosis, death from any cause or the last follow-up visit. TB-free survival was stratified further by baseline immunological and clinical

status and was compared using the generalized log rank test. Univariate and multivariate Cox proportional hazards regression models were fitted to determine the risk of TB, which was expressed as a rate ratio. Variables were considered for inclusion into the multivariate model if they were found associated with the risk of TB in the univariate analyses at  $P < 0.15$ . Past history of TB was included *a priori* in view of previously published findings [17]. The assumption of proportional hazards was examined by plotting the  $\log[-\log(\text{survival function})]$  estimates against log time plots. When determining the effect of response to HAART on risk of TB, blood CD4 cell count and plasma viral load measurements made within the 3 months prior to TB diagnoses were used. PEPI version 4.0 (Sagebrush Press, Salt Lake City, Utah, USA), STATISTICA release 6.6 (Tulsa, Texas, USA) and SAS version 8.2 (SAS, Cary, North Carolina, USA) software were used for data analysis.

## Results

### Patients and follow-up

Between 1996 and 2005, 363 patients received HAART. At enrolment, 17 patients were receiving TB treatment and were, therefore, excluded from the analysis. At baseline, the remaining 346 patients had a median age of 33 years [interquartile range (IQR), 28–40], 190 (55%) were male and 178 (51%) were of low socioeconomic status. Their median blood CD4 cell count was 242 cells/ $\mu\text{l}$  (IQR, 120–343); median plasma viral load was 4.9  $\log_{10}$  copies/ml (IQR, 4.4–5.5); 178 (51%) had

symptomatic disease (WHO clinical stages 3 or 4); and 47 (14%) had a previous episode of TB that had been diagnosed a median of 13 months (IQR, 9–23) prior to enrolment.

The median duration of follow-up was 40 months (IQR, 18–53; range, 0.78–104). During a total of 1108 person-years of observation, 27 cases of TB were diagnosed. Of these, 20 were presumptive and 7 definite; 22 were pulmonary and 5 were extrapulmonary. Of 30 deaths within the cohort, three (10%) were among those who were diagnosed with TB.

### TB incidence rates

All 27 episodes of TB occurred within the first 5 years of follow-up and the overall TB IDR was 2.44/100 person-years [95% confidence interval (CI), 1.61–3.54]. A significant reduction in IDR was observed over the 5-year period, decreasing from 3.35/100 person-years in the first year to 1.01/100 person-years in the fifth year (Fig. 1). It was possible that this decrease resulted from a changing cohort composition during follow-up. However, trend analysis revealed that the proportion of patients remaining in the cohort from year to year did not differ according the risk factors identified in subsequent analysis: WHO clinical stage ( $P = 0.41$  for trend), baseline CD4 cell count  $< 100$  cells/ $\mu\text{l}$  ( $P = 0.24$  for trend) and age ( $P = 0.07$  for trend).

### Baseline characteristics and risk of tuberculosis

TB incidence rates were calculated for patients stratified by baseline characteristics (Table 1). This analysis showed

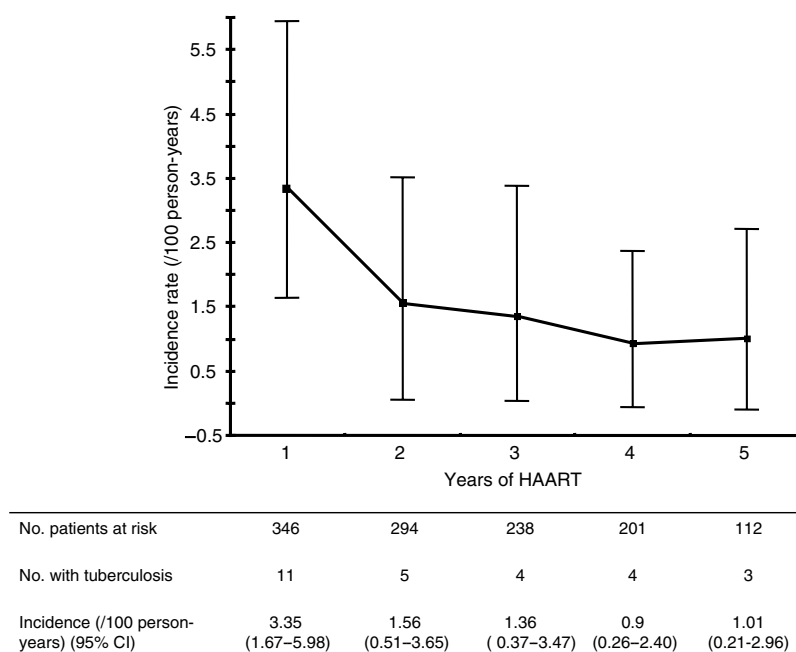


Fig. 1. Tuberculosis incidence density rates.  $P = 0.02$  for trend; slope  $y = -0.52x + 3.23$ ;  $R^2 = 0.72$ . CI, confidence interval.

**Table 1. Tuberculosis incidence density rate stratified by baseline sociodemographic and clinical characteristics.**

Characteristics	No. of patients	Person-years	No. with TB	TB IDR (95% CI) <sup>a</sup>	P value <sup>b</sup>
Total Patients	346	1108.8	27	2.44 (1.61–3.54)	
Age (years)					
< 33 <sup>c</sup>	162	475.5	18	3.79 (2.25–5.98)	
≥ 33	184	633.2	9	1.42 (0.65–2.70)	< 0.01
Sex					
Male	190	632.1	12	1.90 (0.98–3.31)	
Female	156	476.7	15	3.15 (1.76–5.19)	0.19
Socioeconomic status					
Low	178	650.6	17	3.03 (1.77–4.86)	
High	168	548.2	10	1.82 (0.88–3.36)	0.36
Past history of TB					
Yes	47	155.4	3	1.93 (0.39–5.64)	
No	299	953.5	24	2.52 (1.61–3.74)	0.64
CD4 cell count (cells/ $\mu$ l)					
≥ 100	273	898.8	15	1.67 (0.93–2.75)	
< 100	73	210.1	12	5.71 (2.95–9.96)	< 0.0001
Viral load (log <sub>10</sub> copies/ml)					
< 5	199	633.1	10	1.58 (0.76–2.90)	
≥ 5	147	475.9	17	3.57 (2.14–5.72)	0.04
WHO clinical stage					
Stage1 or 2	168	567.4	6	1.06 (0.39–2.30)	
Stage3 or 4	178	541.4	21	3.88 (2.40–5.98)	0.003

TB, tuberculosis; IDR, incidence density rate (per 100 person-years); CI, confidence interval.

<sup>b</sup>Obtained by  $\chi^2$  test for difference in TB IDR.

<sup>c</sup>Median age of the cohort.

significantly higher incidence rates among those with the following characteristics: age < 33 years (median age of the cohort), nadir blood CD4 cell counts < 100 cells/ $\mu$ l, baseline plasma viral load  $\geq$  5 log copies/ml and symptomatic (WHO stage 3 and 4) disease at enrolment. Incidence rates did not differ according to sex, socio-economic status or previous history of TB.

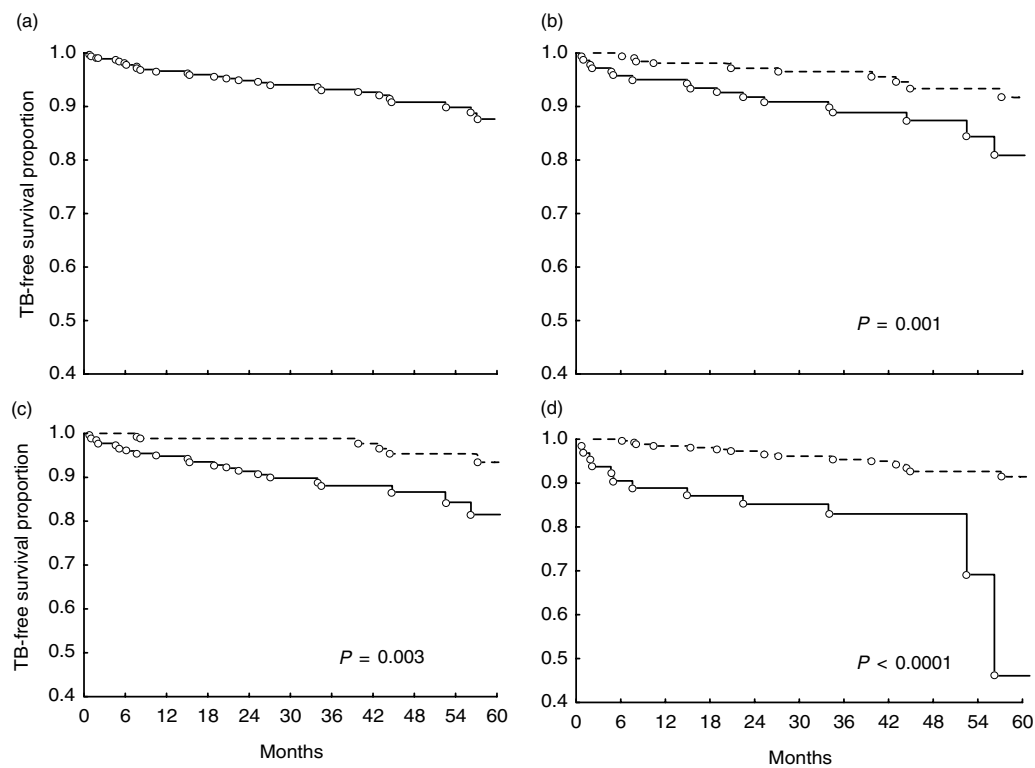
The TB-free survival proportion for the total cohort over the 5-year follow-up period was 0.88 (Fig. 2a). However, the 5-year TB-free survival proportion was significantly lower among patients with baseline CD4 cell count < 100 cells/ $\mu$ l than in those with  $\geq$  100 cells/ $\mu$ l (81% versus 92%; Fig. 2b). Similarly, the survival proportion was lower among patients with baseline WHO stage 3 or 4 compared with those with WHO stage 1 or 2 (81% versus 94%; Fig. 2c). The lowest 5-year TB-free survival proportion was among patients with WHO stage 3 or 4 disease and who also had a CD4 cell count < 100 cells/ $\mu$ l (Fig. 2d). Of the total TB episodes occurring among this latter subgroup, 50% developed during the first 6 months of HAART.

Cox regression analyses were used to analyse risk factors for TB and showed that the risk of TB was independently associated with a baseline CD4 cell count < 100 cells/ $\mu$ l, WHO clinical stage 3 or 4 and age < 33 years (Table 2). Past history of TB was included in the multivariate analysis *a priori* and, although it was not associated with risk of TB in the univariate analysis, there was a trend in multivariate analysis towards a past history having a protective effect against TB. A subanalysis assessing risk factors associated with development of TB during the first

year of ART alone showed that the single variable independently associated with risk of TB was a baseline blood CD4 cell count < 100 cells/ $\mu$ l (adjusted risk ratio, 6.14; 95% CI, 1.44–26.01;  $P = 0.01$ ).

### Tuberculosis and response to HAART

Having determined the effect of baseline patient characteristics on risk of TB, a further analysis examined whether the virological and immunological responses to HAART were also associated with risk of TB. Among the 27 patients who developed TB, the median plasma viral load at the time TB was diagnosed was 2.98 log<sub>10</sub> copies/ml (IQR, 2.60–4.16), which was significantly lower than that at enrolment (5.38 log<sub>10</sub> copies/ml; IQR, 4.69–5.87) ( $P < 0.0001$ ; Fig. 3a). Furthermore, the median blood CD4 cell count at the time of TB diagnosis (198 cells/ $\mu$ l; IQR, 79–397) was significantly higher than at baseline (112 cells/ $\mu$ l; IQR, 58–253) ( $P = 0.025$ ) (Fig. 3b). These data indicated that those who developed TB had responded virologically and immunologically to HAART at the time of TB diagnosis. However, although the rates of viral load suppression did not differ significantly between those patients who developed TB and those who remained free of TB (Fig. 3c), the immunological responses of the two groups differed markedly. The median increase in blood CD4 cell count among those who developed TB (74 cells/ $\mu$ l; IQR, 70–76) was significantly smaller than that of patients who remained free of TB (248 cells/ $\mu$ l; IQR, 185–312) ( $P = 0.007$ ; Fig. 3d). Therefore, TB developed among patients whose immunological responses to HAART were suboptimal.



**Fig. 2. Kaplan–Meier plots of tuberculosis (TB)-free survival proportion.** (a) In the total cohort; (b) among patients stratified by baseline CD4 cell count: ---, > 100 cells/ $\mu$ l; —, < 100 cells/ $\mu$ l; (c) among patients stratified by WHO clinical stage of disease: ---, ---, WHO stage 1 or 2; —, WHO stage 3 or 4; (d) among patients with baseline CD4 cell count < 100 cells/ $\mu$ l and WHO stage 3 or 4 (—) compared with the remainder of the cohort (---). *P* values from the log rank test are given.

## Discussion

This study documented the incidence rates and risk factors for TB in a South African cohort of patients receiving HAART over a median duration of follow-up

of 40 months. Previous studies in low-income countries have been of much shorter follow-up and have not documented time-dependent changes in TB incidence rates during HAART [15–17]. A further important strength of this cohort is that broad enrolment criteria for

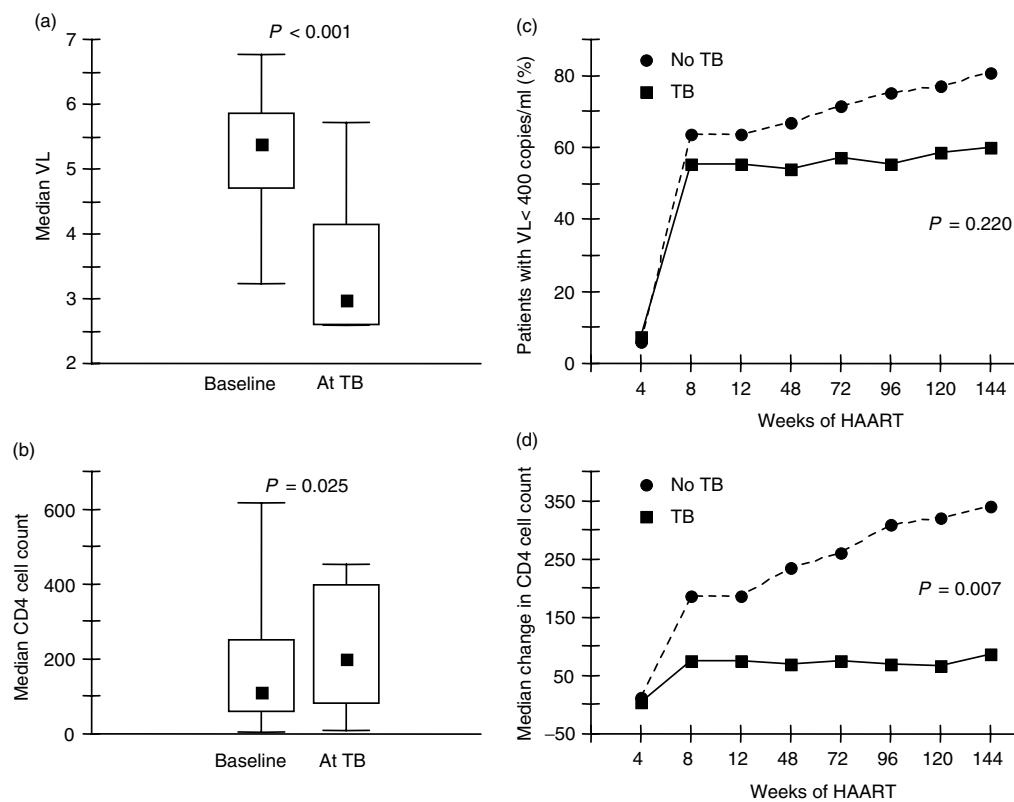
**Table 2. Cox regression analyses of predictors of tuberculosis in the whole cohort.**

Variable	Univariate analysis		Multivariate analysis	
	RR, (95% CI)	<i>P</i> value <sup>a</sup>	ARR, (95% CI)	<i>P</i> value <sup>a</sup>
Age (years)				
< 33 <sup>b</sup>	2.23 (1.02–4.88)	0.04	2.86 (1.29–6.34)	0.01
≥ 33	1		1	
Past history of tuberculosis				
Yes	0.76 (0.23–2.53)	0.66	0.31 (0.09–1.08)	0.07
No	1		1	
CD4 cell count (cells/ $\mu$ l)				
≥ 100	1		1	
< 100	3.50 (1.62–7.56)	0.001	2.38 (1.01–5.60)	0.04
Viral load (log <sub>10</sub> copies/ml)	1.74 (1.03–2.94)	0.04	1.28 (0.72–2.29)	0.40
WHO clinical stage				
Stage 1 or 2	1		1	
Stage 3 or 4	3.72(1.50–9.26)	0.005	3.60 (1.32–9.82)	0.01

RR, rate ratio; ARR, adjusted rate ratio; CI, confidence interval.

<sup>a</sup>Obtained by  $\chi^2$  test for difference in tuberculosis incidence density rate (per 100 person-years)

<sup>b</sup>Median age of the cohort.



**Fig. 3. Changes in plasma viral load (VL; log copies/ml) and blood CD4 cell counts (cells/ $\mu$ l) during HAART.** Among patients who developed tuberculosis (TB;  $n = 27$ ), median plasma VL at baseline was compared with that at the time TB was diagnosed (a), and the blood CD4 cell count at baseline was compared with that at the time of TB diagnosis (b). Box and whisker plots show the median (square), 25th and 75th centiles (box) and range (whiskers). (c) The percentage of patients with plasma VL suppressed to  $< 400$  copies/ml during follow-up comparing those who remained free of TB with those who developed TB. (d) The median change in blood CD4 cell count during follow-up from baseline, comparing patients who remained free from TB with those who developed TB.

HAART resulted in a cohort with diverse baseline patient characteristics, including a wide spectrum of baseline blood CD4 cell counts and WHO clinical stages of disease. This increased the power of the analysis to identify risk factors for TB. All diagnoses were supported by microbiological or histological evidence, further strengthening the data. However, the low event frequency beyond 5 years of follow-up prevented estimation of TB incidence rates beyond this time-point, and a larger cohort would be needed to examine this. Furthermore, data from this hospital-based cohort may not reflect TB incidence rates observed in community-based HAART programmes.

We have previously reported from this same cohort that HAART reduces the incidence of TB by approximately 80%; however, the mean duration of HAART in this previous analysis was 16.8 months [16]. Data in the present study showed an ongoing time-dependent reduction in TB incidence, which was more than three-fold lower in the third year of HAART compared with the first year. These data have implications for

mathematical modelling calculations that assume that HAART is likely to have limited impact on the TB incidence at the community level in low-income countries [20]. The previously reported TB incidence rate in this cohort was 2.4/100 person-years over a mean of 16.8 months receiving HAART [16]; however, the present data show that the rate further decreased to approximately 1.0/100 person-years after 5 years of treatment. These new data suggest that the likely long-term impact of HAART on the community burden of TB may be greater than previously estimated.

The decreases in TB incidence rates observed in this study are likely to reflect time-dependent changes in TB-specific immune function. The extent of immune reconstitution resulting from HAART is greatest during the first 2 years of treatment, with small further increments in CD4 cell numbers occurring in the longer term among some patients [19]. Such a pattern was mirrored by the reductions TB incidence rates observed in this study (Fig. 1). However, increasing evidence suggests that long-term restoration of immune cell

phenotype and function are limited, even among the minority of patients whose blood CD4 cell counts normalize [19,25,26]. From an immunological perspective, it is, therefore, unlikely that TB risk during long-term HAART will return to the levels seen among individuals who do not have HIV infection. An alternative explanation for the reduction in TB incidence rates during follow-up, the possibility that an element of survival bias may have resulted from deaths during follow-up ( $n = 30$ ), cannot be excluded. However, the majority of deaths occurred early after initiation of treatment and could not account for ongoing reduction in TB rates over several years. Moreover, analysis of cohort composition during follow-up did not reveal significant changes in the proportion of patients who had identified risk factors for TB.

We have shown in this study that age  $< 33$  years (median age of the cohort), baseline blood CD4 cell count ( $< 100$  cells/ $\mu$ l) and WHO clinical stages 3 and 4 were all independently associated with an increased risk of TB. It is unclear why younger age was a risk factor, but this may possibly reflect behavioural differences that affect exposure. In the analysis of baseline blood CD4 cell count as a risk factor, categorization of patients using a cut-off of 100 cells/ $\mu$ l represented the best-fit for regression analyses but does not necessarily represent a risk threshold. Risk factors for TB found in this study contrast markedly with the findings of a study from West Africa [17]. In this study, past history of TB was the only risk factor for development of TB during HAART. However, the study had design limitations related to the size of the study population, the number of TB cases, diagnostic criteria for TB and restricted cohort composition [27]. In settings with high TB incidence but low rates of multidrug resistance, a 6-month course of antituberculosis treatment containing rifampin might rather be expected to confer a time-limited reduction in TB risk among HIV-infected individuals, as was suggested by the trend seen in the multivariate analysis in the present study.

Among HIV-infected individuals who are not receiving HAART, risk of TB increases with increasing HIV-associated immunodeficiency [28]. The data presented here indicate that those with the most advanced pretreatment immunodeficiency (as shown by both blood CD4 cell count and WHO clinical stage) retain the highest risk of TB during HAART. This may reflect the fact that the greater the degree of pre-HAART immunodeficiency, the more prolonged the period of treatment required to restore immune function. Moreover, advanced pretreatment immunodeficiency also limits the extent to which immune function can be restored in the long term [19,25,26,29]. Treatment criteria in some national antiretroviral programmes in sub-Saharan Africa, including South Africa, include only those with stage 4 disease and CD4 cell counts  $< 200$  cells/ $\mu$ l (WHO 2002

recommendations [30]). Treatment according to these recommendations may limit the extent to which long-term TB-specific immune responses may be restored in many patients. This, in turn, may restrict the potential benefit of widespread use of HAART on TB control.

Our data show that TB developed among individuals who were responding to HAART. However, a more important finding was that median increases in blood CD4 cell count were much smaller among those who developed TB than in those who did not. Although virological response rates were also lower among those who developed TB, the difference was not statistically different and did not provide an explanation for the major difference in CD4 cell responses. Acute TB itself causes a transient CD4 lymphocytopenia, which may in part reverse during treatment [31]; however, this also would not explain the major persistent CD4 cell count difference between the two groups. The likeliest explanation is that a proportion of HIV-infected patients, especially those with low nadir CD4 cell counts, have poor CD4 cell responses to HAART [32,33] that may in some be related to lack of viral suppression. These patients are likely to retain a chronically heightened risk of TB.

Despite the major beneficial effects of HAART, TB incidence rates in this cohort after 5 years of HAART were still approximately 1000 cases per 100 000 population every year. Further longer-term studies of larger cohorts are needed to determine whether incidence rates continue to decrease beyond 5 years of HAART. Adjunctive strategies to reduce the risk of TB further should also be explored. Such interventions might include ones that boost immunological recovery during HAART, vaccination during HAART to increase TB-specific immunity or use of isoniazid prophylaxis coadministered with HAART. Such use of isoniazid within the South African national antiretroviral programme would raise two important issues. First, stavudine is used within the first-line regimen and concurrent use of isoniazid is likely to increase the high rates of drug-induced neuropathy [34]. Second, incidence rates of active TB during the initial months of HAART in local community-based programmes are extremely high [19], giving rise to the possibility that significant numbers of patients with undiagnosed active TB might inadvertently receive isoniazid monotherapy. Consequently, the practicalities and the risk-benefits of such a strategy would have to be carefully evaluated.

In summary, long-term HAART confers a greater reduction in TB risk than previously reported and HAART may, therefore, contribute more to TB control in low-income countries than previously estimated. TB risk is not only strongly associated with advanced baseline immunodeficiency but also with suboptimal CD4 cell count responses during HAART. Additional strategies to

reduce TB rates further during HAART need to be explored.

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