Tuberculosis risk factors and mortality for HIV-infected persons receiving antiretroviral therapy in South Africa

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Objective: To determine important risk factors for and impact of tuberculosis on survival in HIV-infected patients starting antiretroviral therapy (ART) in South Africa.

Design: Prospective trial of 1771 HIV-infected patients with either CD4 cell count less than 200 cells/μl or a prior AIDS-defining illness, enrolled in randomized trial of four antiretroviral regimens.

Methods: Data collected from patient records.

Results: A history of tuberculosis at study entry was reported by 27% of patients and correlated with poor baseline health status. A history of tuberculosis at baseline was associated with subsequent tuberculosis and death during ART, but was not itself an independent risk factor for poor outcome. Tuberculosis was diagnosed during ART in 14% of patients and was more frequent during the first 3 months. Tuberculosis during therapy was independently associated with increased hazard of other AIDS-defining events and death, regardless of when during ART tuberculosis occurred. ART that consistently suppressed circulating viremia reduced but did not eliminate tuberculosis risk.

Conclusion: In HIV-infected patients who started ART at low CD4 cell counts, tuberculosis at baseline was a predictor of death, but was not independent of other factors indicating poor baseline health status. Tuberculosis during follow-up was, in contrast, an independent predictor of death even after adjustments for baseline risk factors, including CD4 cell count and viral load. Virologic failure during ART was associated with a 55% increase in risk of tuberculosis. Thus, tuberculosis is a major marker for poor outcome both at baseline and during ART and is not completely eliminated by fully suppressive ART.

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Introduction

In the developing world, many patients either have a history of tuberculosis (TB) when they initiate antiretroviral therapy (ART) or they develop TB while receiving ART. ART diminishes the risk for TB as the CD4 cell count rises, yet the excess risk for TB is never eliminated even if CD4 cell count levels return to normal levels [1–12].

TB has been shown to be associated with excess mortality in HIV-infected patients who are not treated with ART.

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However, when patients start ART, it has neither been well delineated what influence a history of TB has on subsequent patient outcome, nor has it been clear what role incident TB has on their outcome, especially in patients who have consistent HIV suppression on ART. This report focuses on a large, well defined HIV-infected patient population in South Africa, who initiated ART under careful observation. The specific goal of this investigation was to examine risk factors for TB and mortality risk associated with TB [13]. This report emphasizes the importance of TB prevention programs if the outcome of ART is to be optimized.

Methods

Phidisa study

Phidisa is a joint observational cohort and randomized HIV treatment study for the South African National Defence Force (SANDF) and their dependants, which was designed and executed with close monitoring by South African and National Institutes of Health (NIH) regulatory authorities [13]. Phidisa II, the randomized component of Phidisa, had a 2×2 factorial trial comparing initial therapy of efavirenz (EFV) with lopinavir/ritonavir (LPV/r) and zidovudine (ZDV) + didanosine (ddI) with stavudine (d4T) + lamulamuvidine (3TC) in treatment-naive HIV-infected persons with less than 200 $CD4^+$ cell count/μl or a prior AIDS diagnosis [13].

All eligible participants were invited to enroll. The primary endpoint was the combined endpoint of HIV disease progression (new or recurrent AIDS-defining illness, including TB) and death. The Phidisa II study enrolled 1771 individuals from members of the military at six sites in South Africa between 2004 and 2007. Eligible persons were randomly allocated in a 1 : 1 : 1 : 1 allocation to one of four starting regimens: EFV + ZDV + ddI; EFV + d4T + 3TC; LPV/r + ZDV + ddI; or LPV/r + d4T + 3TC. Randomization was stratified by clinical site. All treatments were administered in an open-label manner. Patients with CD4 cell counts less than 200 cells/μl received pneumocystis pneumonia (PCP) prophylaxis with daily cotrimoxazole or dapsone.

No patients were known to have received isoniazid preventive therapy.

Patient assessment

At enrollment, details regarding previous episodes of TB or treatment for current TB were self-reported by patients based on a questionnaire and interview. WHO clinical staging was documented. A comprehensive assessment was made to exclude active TB and other opportunistic diseases. Nebulized sputum induction was available across all sites. For patients entering the study with suspected or documented active TB, randomization was deferred until successful completion of an induction course of anti-TB treatment as determined by the TB clinic. For patients who required anti-TB treatment following randomization, LPV/r was switched to EFV and/or rifabutin substituted for rifampin. Patients with active TB were referred to the South African Military Health Service (SAMHS) for administration and monitoring of anti-TB treatment according to the South African National Treatment Guidelines [14]. Participants were followed monthly for the first 3 months and every 3 months thereafter until 31 March 2008 for a median follow-up of 24.7 months.

Tuberculosis definitions

Baseline history of TB was defined as a history of pulmonary or extrapulmonary TB, or a history of taking multidrug regimens for TB in the past or at the time of baseline evaluation. A TB event (pulmonary or extrapulmonary) diagnosed during the study was reported as a study endpoint and was reviewed by an independent review committee. A confirmed pulmonary TB case had to include two of the following three criteria: fever, dyspnea, cough, weight loss, or fatigue; positive acid fast bacillus (AFB) smear on two or more sputa; and culture or PCR positive for *Mycobacterium tuberculosis* from sputum or bronchial lavage or lung tissue. A probable case of pulmonary TB had to meet the following four criteria: fever, dyspnea, cough, weight loss, or fatigue; abnormal chest radiograph; AFBs seen in sputum or lavage or lung tissue but not grown in culture; and response to antituberculous treatment. A confirmed case of extrapulmonary TB was defined by both of the following criteria: compatible symptoms; and culture or PCR from blood or affected tissue. A probable case of extrapulmonary TB was defined as meeting the following criteria: compatible symptoms plus one of: AFB identified in affected tissue or blood; concurrent diagnosis of pulmonary TB; or response to treatment. TB endpoints reported during the study that were not confirmed or probable as defined above are referred to as possible TB events.

Statistical analysis

The association of history of TB at baseline with other baseline patient characteristics was assessed using Fisher's exact test for categorical variables and two-sample *t*-test or a nonparametric Wilcoxon test for continuous variables. Baseline factors considered were as follows: Phidisa clinical site, sex, age, BMI, CD4 cell count, HIV viral load, hemoglobin, white blood cell count (WBC), serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT). The event rate (number of cases per 100 person-years) for TB during follow-up was assessed by endpoint review status (confirmed/probable versus possible) and timing of the event (0–3, 3–6, 6–12, 12–24, 24+ months).

The unadjusted association between TB history and risk of TB during follow-up was assessed by the log-rank test.

The association between risk of TB during follow-up and baseline risk factors was also assessed using a multivariate Cox regression model stratified on study site with the following factors: baseline history of TB, age, sex, BMI, baseline CD4 cell count, HIV viral load (on the log-scale), hemoglobin, WBC and SGOT. Separate analyses were done for confirmed/probable TB and all TB events. A similar analysis was performed to assess whether history of TB at baseline was associated with an increased mortality risk during follow-up.

Several exploratory Cox regression models were considered to understand better which individuals were at risk of getting TB during follow-up; these models included baseline WHO stage III/IV (yes/no) as a risk factor, reflecting a history of serious AIDS-defining illnesses (including TB), along with the other aforementioned baseline risk factors and CD4 cell count and viral load as time-varying covariates. Separate models examining associated risk factors for early TB events (<6 months) and late TB events (>6 months) were also considered.

The impact of newly diagnosed TB on the mortality hazard was estimated by including history of TB diagnosed during follow-up as a time-varying covariate in a multivariate Cox regression model stratified on study site and adjusting for baseline risk factors, and CD4 cell count and HIV viral load as time-varying covariates, as described above. This analysis was performed separately for all reported TB events and those designated as confirmed/probable TB by the endpoint review committee. The potentially time-varying nature of the mortality hazard associated with newly diagnosed TB was explored by estimating the hazard associated with TB separately for events in the first 6 months of follow-up compared to that after 6 months; and testing for whether there is a different short-term risk associated with TB (within first 6 months of getting diagnosed) versus a long-term risk of TB (>6 months after diagnosis).

Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA) and R version 2.8.1 (R Development Core Team, Vienna, Austria). All statistical tests were two-sided and performed at the 0.05 significance level.

Results

Tuberculosis risk

The Phidisa II cohort included 1771 HIV-positive individuals with median follow-up of 24.7 months [(interquartile range (IQR) 12.6–39.9]. This cohort included individuals that were of mean age 36 years and 32% were women. At baseline, the median CD4 cell count was 106 (IQR 44–154) cells/μl and viral load was 144 000 (IQR 53 500–307 000) copies/ml. There was little loss to follow-up in the Phidisa II study, with only about 5% of participants having more than 8 months since the last contact (roughly two visits) at the end of the study.

Table 1 presents clinical factors by baseline history of TB. In the unadjusted analyses, baseline history of TB was associated with Phidisa clinical site, being male, lower CD4 cell count, higher viral load, lower hemoglobin, and higher SGOT. In the multivariate logistic model, adjusting simultaneously for all individually significant factors, baseline history of TB was still significantly associated with clinical site ($P < 0.001$), being male ($P < 0.001$), lower BMI (0.006), lower baseline CD4 cell counts ($P < 0.001$), higher baseline HIV viral load ($P < 0.001$), and lower hemoglobin ($P < 0.001$). This suggests each of these risk factors has independent effects that were significantly associated with a history of TB.

Table 2 presents the number of participants and event rate (number per 100 person-years) for incident TB during follow-up. There were 254 individuals with at least one incident TB event during follow-up.

Baseline history of TB was associated with increased risk for TB (all events), with unadjusted hazard ratio of 1.36 [95% confidence interval (CI) 1.04–1.78] and log-rank

Table 1. Baseline clinical characteristics by baseline history of tuberculosis.

Characteristics	History of TB $N = 479$	No history of TB $N = 1290$	P value[a]
Age	36.2 (5.2)	35.8 (5.6)	0.142
Men (n,%)	365 (76.2%)	838 (65.0%)	<0.001
BMI – women	23.3 (5.3)	26.0 (5.7)	<0.001
BMI – men	21.8 (3.7)	23.1 (4.1)	<0.001
CD4 cell count	77.0 (61.1)	111.9 (64.9)	<0.001
Viral load	298 394 (275 026)	196 700 (215 383)	<0.001
Hemoglobin	11.9 (1.9)	12.9 (2.0)	<0.001
WBC	4.43 (2.1)	4.61 (1.9)	0.102
SGOT (IU/l)	50.8 (37.2)	43.9 (44.8)	0.001
SGPT (IU/l)	42.1 (43.6)	37.5 (46.1)	0.056

Unless otherwise noted, mean (SD) are presented ($N = 1769$). SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase. $N = 1769$: only 1769 of 1771 participants had tuberculosis (TB) history sufficiently collected on the baseline medically history form.
[a]P values are unadjusted from the Fisher's exact test for binary variables and the two-sample t-statistic with unequal variances for continuous covariates, except viral RNA for which a nonparametric Wilcoxon test was used.

Table 2. Tuberculosis incidence and mortality rates during follow-up as number per 100 person-years along with 95% confidence interval and number of events (*n*), broken down by timing of event.

	0–3 months	3–6 months	6–12 months	12–24 months	>24 months
Confirmed/probable TB	8.42 (6.07–11.67) $n=36$	3.24 (1.88–5.58) $n=13$	1.98 (1.17–3.34) $n=14$	2.21 (1.48–3.30) $n=24$	1.95 (1.26–3.02) $n=20$
TB – all events	19.88 (16.05–24.6) $n=84$	8.75 (6.25–12.25) $n=34$	6.06 (4.46–8.23) $n=41$	5.50 (5.23–7.14) $n=56$	4.11 (3.00–5.62) $n=39$
Death	16.89 (13.42–21.24) $n=73$	8.29 (5.92–11.60) $n=34$	5.78 (4.27–7.82) $n=42$	3.54 (2.60–4.83) $n=40$	1.75 (1.12–2.75) $n=19$

TB, tuberculosis.

P value (0.02; Fig. 1). When baseline factors of CD4 cell, log-viral load, age, BMI, sex, WBC, SGOT, and hemoglobin are included in the Cox model for risk, stratified on Phidisa site, baseline TB history was no longer significantly associated with risk of incident TB (all events or confirmed/probable); however, the association with hemoglobin, being male, and BMI remained significant. This suggests that baseline hemoglobin, BMI, and sex have important independent effects on the risk of TB during follow-up, whereas baseline history of TB is correlated with poor baseline health status and is not associated with an independent effect on risk of incident TB during follow-up over and above the risk associated with poor health. When baseline advanced WHO stage (stage III/IV – yes/no) was included in the multivariate model in place of baseline history of TB, results were similar and advanced WHO stage was also an independent predictor. In this model, keeping other factors the same, the hazard ratio (95% CI) for newly diagnosed TB associated with being male was 1.42 (1.02–1.99), advanced WHO stage 1.35 (1.01–1.80), a unit increase in BMI 1.06 (1.02–1.09), and a unit increase in hemoglobin 1.10 (1.02–1.18). For confirmed/probable TB events, there were no significant associations with baseline risk factors, with only low BMI and advanced WHO stage as marginally significant in the multivariate model. When viral load and CD4 cell count were included in the multivariate model for all TB events as time-varying covariates, instead of baseline levels, they were both more strongly associated and significant ($P<0.0001$ for both); both were also significant in the model for confirmed/probable TB ($P=0.02$ and $P<0.0001$, respectively).

For the early occurring TB events (<6 months), baseline BMI, viral load, WBC, and hemoglobin were significant factors. Late occurring TB risk (>6 months) was associated with the 6-month level of viral load, CD4

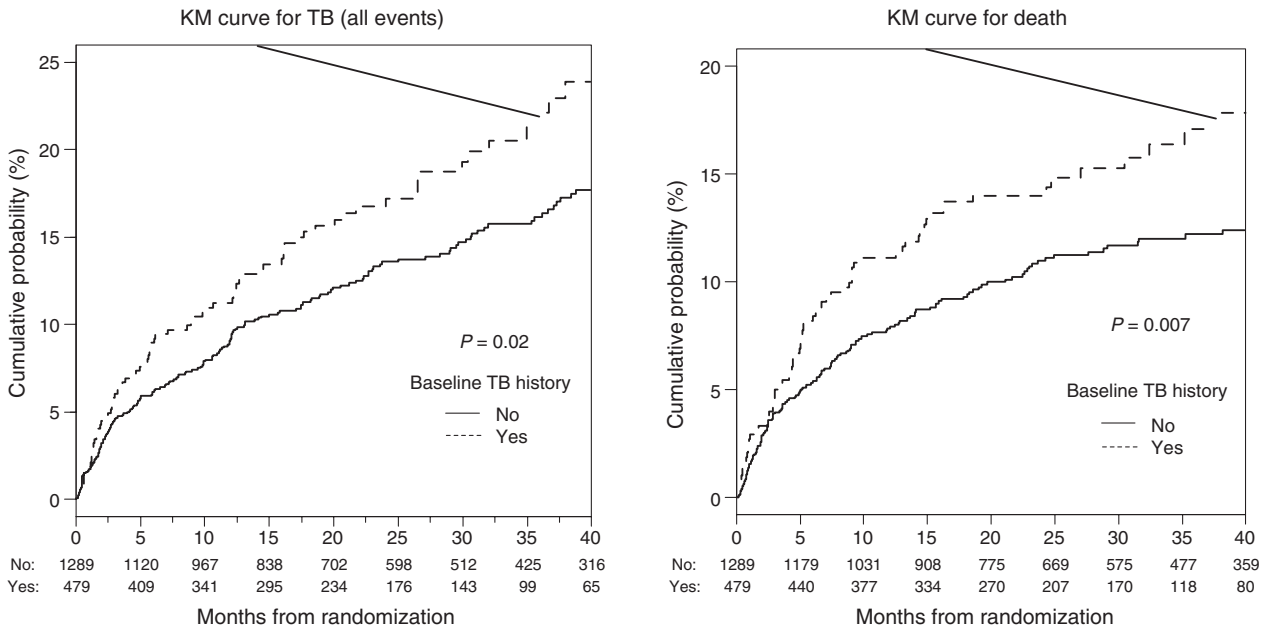

Fig. 1. Kaplan–Meier curves for the cumulative probability (%) of tuberculosis during follow-up (all events) and mortality by baseline history of tuberculosis. The log-rank *P* value for the difference in survival is also given. KM, Kaplan–Meier; TB, tuberculosis.

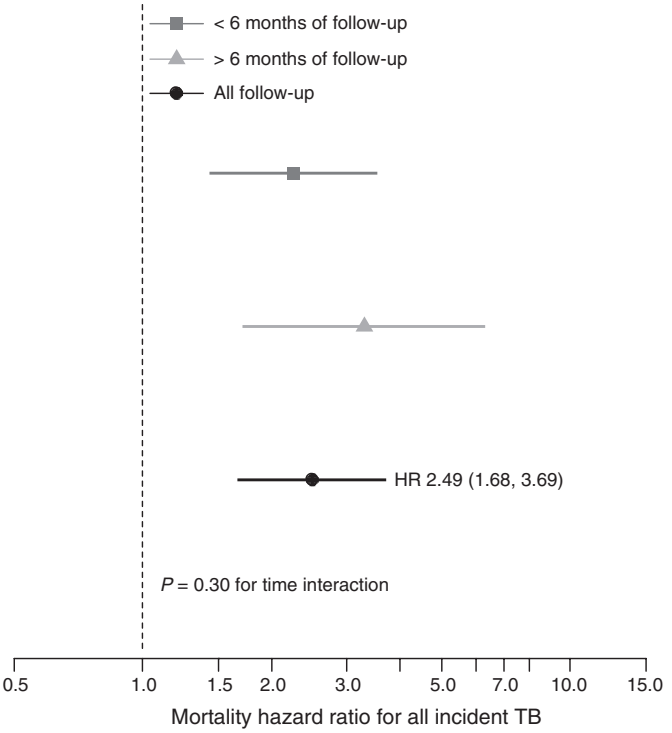

Fig. 2. Mortality hazard ratio and 95% confidence interval associated with a prior tuberculosis diagnosis during follow-up (all events) compared to no tuberculosis event, adjusted for CD4 cell count and log-HIV RNA level, and other baseline risk factors, broken down by timing of event. HR, hazard ratio; TB, tuberculosis.

cell count, hemoglobin, being male, and advanced baseline WHO stage marginally significant ($P = 0.06$ for both; data not shown).

Virologic failure is defined as having a viral load more than 400 copies/ml on any occasion 3 or more months after therapy initiation. At 3 months, 37% of participants were still not under virologic control. Considering the history of virologic failure as a time-varying covariate in the Cox regression model for TB risk, adjusting for baseline covariates and CD4 cell count as time-varying, a history of virologic failure is associated with a 1.54 times higher risk (95% CI 1.05–2.27) of being diagnosed with TB during follow-up compared to someone with a history of sustained viral control. Note, the analogous associated risk of virologic failure for other opportunistic infection was not significant [1.18 (0.63–2.19)].

A total of 112 of 1771 (6%) individuals were observed to have non-TB opportunistic infection(s) during follow-up and 38 of these 112 (34%) individuals also had a TB event during follow-up. Of the individuals with both types of events, seven of 38 had the event within 2 weeks of each other, 17 had TB first, and 14 had the other opportunistic illnesses first. The probability of having TB before other opportunistic infections, for individuals who had both infection types during follow-up, was not significantly different from 0.5 (McNemar's test, $P = 0.72$). Having another opportunistic illness in addition to TB was associated with a 2.85-fold risk (95% CI 1.75–4.64) for a later TB event compared to not having another opportunistic illness. Conversely, having a TB event during the follow-up was associated with a 2.71 (95% CI 1.56–4.70) times higher relative risk of a subsequent other AIDS-defining event compared to having no prior TB during follow-up.

Mortality risk

Figure 1 shows the Kaplan–Meier survival curves for overall mortality by baseline TB history. Baseline TB was individually associated with risk of death (log-rank $P = 0.007$). This association was no longer significant when adjusting for other baseline risk factors, suggesting that history of TB was not having an effect on mortality risk independent of poor baseline health status. Baseline factors that were significantly associated with increased mortality risk in the multivariate model included low BMI, low hemoglobin, high WBC, and low CD4 cell count. Similar results were obtained when examining the association between baseline TB and TB-free survival (data not shown). Similar results were also obtained when advanced WHO stage was included in the multivariate model in place of baseline TB history, with WHO stage also significantly associated with mortality risk. In this model, the mortality hazard ratio (95% CI) associated with baseline advanced WHO stage was 1.56 (1.12–2.17), with a 50-unit decrease in baseline CD4 cell count 1.42 (1.22–1.65), a unit decrease in BMI 1.07

(1.03–1.12), unit decrease in hemoglobin 1.13 (1.05–1.22), and a unit increase in WBC 1.07 (1.01–1.14).

There were 54 deaths (21.3%) among the 254 individuals with TB events during follow-up. When TB is included in the Cox regression model as a time-varying covariate, adjusted for baseline risk factors and CD4 and log viral load also as time-varying covariates, confirmed/probable TB during follow-up is associated with a mortality hazard ratio of 2.40 (95% CI 1.34–4.31) compared to having no prior TB event (of any type), and possible TB is associated with a hazard ratio of 2.54 (95% CI 1.62–3.99). There was little difference in the risk associated with confirmed/probable TB versus unconfirmed TB, with an overall mortality hazard ratio for any TB of 2.49 (95% CI 1.68–3.69). That is, at a given time, those individuals alive with prior TB during follow-up had about 2.5 times the risk of impending mortality compared to those with similar risk factors who did not have a TB event.

Table 2 shows the incidence of TB events and deaths by time intervals 0–3, 3–6, 6–12, 12–24, and more than 24 months. Observed rates for death and TB were higher earlier during follow-up. When the preceding analysis was repeated including a time interaction for the effect of TB on mortality risk and whether a TB event occurred in the first 6 months or after 6 months of follow-up, there was no significant difference in risk associated with the timing of the TB event (Fig. 2). Similar results were obtained when considering confirmed/probable TB events only (data not shown). Another way that the TB effect on risk could vary over time is that there could be a different mortality risk shortly after the TB diagnosis compared to a long-term risk. The Cox model that estimated these separate effects found a nonsignificantly higher risk of mortality within the first 6 months compared to later ($P = 0.16$). Compared to someone with no prior TB event, someone within the first 6 months after their incident TB had a 2.91-fold greater risk of death (95% CI 1.88–4.48), and someone who had a TB diagnosis more than 6 months prior had a 1.74-fold increase in risk (95% CI 0.90–3.35). These results are suggestive of an increased mortality risk associated with a TB diagnosis that wanes over time, perhaps due to successful treatment.

Discussion

In many parts of the world, TB and HIV infection are inextricably linked in the general population. This study focused on a South African population who is representative of many patient groups in whom TB and HIV infection both occur with high incidence. The study was large and included 3777 person-years of follow-up (mean 2.1 years per person) among individuals who volunteered for ART and had CD4 cell counts less than 200 cells/μl or a history of an AIDS-defining illness at study entry. These patients were typical of many patients in high endemic areas: they were young and mostly men, entering the study with relatively low CD4 cell counts (median 106; IQR 44– 154 cells/μl) and high viral loads (median 144 000; IQR 53 500–307 000 copies/ml). None were documented to have received ART or isoniazid prophylaxis prior to study enrollment.

A history of TB at study baseline clearly identified a group with a poorer health status than the group without a history of TB in terms of BMI, CD4 cell count, HIV viral load, and hemoglobin. By a multivariate Cox regression model, however, TB was not an independent risk factor for subsequent TB or death. Similar trends had been reported in a smaller case–control study from Uganda [15]. Thus, a history of TB is a marker for poor health status and identifies a patient population who will derive particular benefit from ART.

In this study, 254 patients (14%) had one or more TB events during follow-up while assigned to ART. The annualized rate of TB was 10.7 per 100 person-years (95% CI 9.2–12.5) in the first year and 4.8 (4.0– 5.9) after 1 year for all reported TB, which follows a similar trend reported from Cape Town and from Asia between 1996 and 2005 [7,10,16]. Thus, as in prior studies, ART reduced but did not eliminate the incidence of subsequent TB episodes. Patients with virologic failure had a substantially higher (55%) risk for developing TB than patients with virologic response past 12 weeks, which reinforces the plausible link between optimal virologic control and optimal TB prevention.

Patients who developed TB during follow-up had lower CD4 cell counts, higher viral loads, a higher likelihood of ART failure, and a higher occurrence of non-TB opportunistic infections than patients who did not develop TB. Adjusting for baseline factors, patients who developed another AIDS-defining event had a relative risk of developing TB of 2.85 (95% CI 1.75–4.64) compared to similar patients without such an event in the multivariate model. Conversely, those with a prior TB event had a 2.71 (95% CI 1.56–4.70) times higher risk for an AIDS-defining event than those without TB. This supports the concept that the development of TB correlates with a global immune defect that increases the likelihood of both TB and other AIDS-defining events [5,15,16].

Although baseline TB did not predict death as an independent risk factor, incident TB was associated with a hazard ratio for death of 2.49 (95% CI 1.68–3.69). Zhou *et al.* [16] found a similar hazard ratio in Asia for patients on ART, though patients entered that trial with a higher baseline CD4 cell count (majority over 300 cells/μl compared to a mean in this study of 106 cells/μl). This hazard ratio was similar to that of another South African cohort that was not receiving ART, (2.3) [17]. There were 54 deaths among the 254 individuals who developed TB

during follow-up, but unfortunately the cause of death could not be definitively determined for most patients, nor were there objective data in most cases to indicate whether their TB had responded to therapy.

This study did have limitations that are shared by most studies in sub-Saharan Africa: although a large number of TB cases were confirmed microbiologically, many TB diagnoses were based on empiric criteria; there was less intense documentation of likely AIDS-defining endpoints than in studies from North America or Europe, and there was a relatively short period of follow-up.

Thus, for patients in this geographic area who start ART with low CD4 cell counts, TB at baseline is a marker for poor health status, and this poor health status correlates with subsequent TB and death. Once ART is started, incident TB is independently associated with poor outcome. ART can substantially reduce the impact of incident TB, especially when patients have optimal virologic responses, but ART does not eliminate incident TB [18]. This study reinforces the concept that TB has a strong impact on the outcome of patients with HIV infection and re-emphasizes the importance of active TB screening prior to ART as well as during ART, the importance of nutrition, and the relevance of measures that both enhance availability of ART and multifaceted approaches to reduce the transmission of TB in healthcare facilities as well as the community.

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S.K. had a primary role in study design, patient care, data analysis, and manuscript preparation.

P.A.S. was the statistician for the study involved in study design, analysis, and manuscript preparation.

N.S., M.J.M., and L.M. had major roles in patient care and data collection.

P.S. and J.A.M. supervised laboratory study implementation and analysis.

H.M. participated in study design, data analysis, and manuscript development.

S.H. supervised and provided patient care, supervised collection of data, and participated in data analysis and manuscript preparation.

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