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Increased mortality associated with treated active tuberculosis in HIV-infected adults in Tanzania

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SUMMARY

Active tuberculosis (TB) among HIV-infected patients, even when successfully treated, may be associated with excess mortality. We conducted a prospective cohort study nested in a randomized TB vaccine trial to compare mortality between HIV-infected patients diagnosed and treated for TB (TB, n=77) and HIV-infected patients within the same CD4 range, who were not diagnosed with or treated for active TB (non-TB, n=308) in the period 2001–2008. Only twenty four subjects (6%) were on antiretroviral therapy at the beginning of this study. After accounting for covariate effects including use of antiretroviral therapy, isoniazid preventive therapy, and receipt of vaccine, we found a four-fold increase in mortality in TB patients compared with non-TB patients (adjusted Hazard Ratio 4.61; 95% Confidence Interval (CI): 1.63, 13.05). These findings suggest that treatment for TB alone is not sufficient to avert the excess mortality associated with HIV-related TB and that prevention of TB may provide a mortality benefit.

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Competing interests
None declared.

Keywords

TB prevention; survival; CD4 counts

INTRODUCTION

Tuberculosis (TB) is the leading cause of death among human immunodeficiency virus (HIV)-infected patients in Africa.[1] The impact of TB is more evident in areas with a heavy burden of HIV-TB co-disease. In Tanzania for instance, an estimated 2.7% (28,116/1.05 million) of all HIV-infected persons in 2007 also had active TB, of whom, 71% died.[2] The advent of combination antiretroviral therapy (cART) in the mid-1990s[3] transformed the treatment for HIV worldwide. As a result, AIDS-associated morbidity dropped dramatically in many high-burden countries, followed by mortality decline a decade later.[4] In spite of this success, the prevalence of HIV-associated TB remains high in most sub-Saharan African countries.[2]

Several studies have examined the effect of HIV-associated TB on mortality.[5–10] Most of these studies have found increased mortality, but it is not clear if this mortality is the result of death due to TB disease, increased progression to AIDS, or both. We therefore performed a prospective cohort analysis to examine whether HIV-infected patients who completed TB treatment had a higher mortality than similar HIV-infected patients who did not develop active TB, using a cohort of adults enrolled in a randomized trial of a TB vaccine in Tanzania. This study was conducted before recent trials demonstrated the mortality benefit of early cART intake in HIV-associated TB.[11,12,13]

METHODS

Study population

The DarDar randomized vaccine trial was a collaborative work between Dartmouth Medical School (New Hampshire, USA), Muhimbili University of Health and Allied Sciences (MUHAS) (Dar es Salaam, Tanzania), and Boston University School of Public Health (BUSPH) (Massachusetts, USA). The aim of the trial was to examine the efficacy of an inactivated whole cell mycobacterial vaccine for HIV-infected adults. The trial was conducted at the Infectious Diseases Centre (IDC) in Dar es Salaam, Tanzania between September 2001 and January 2008.[14]

Subjects in the DarDar trial were recruited from voluntary counseling and testing (VCT) sites, and non-governmental organizations (NGOs). A study nurse was designated to visit VCT sites each weekday to assist in recruitment process. Study visits for the trial vaccine were done at baseline, then after 2 months, 4 months, 6 months, 12 months, and then every 3 months. Eligibility criteria were age 18 or above, a *Bacillus Calmette-Gurin* (BCG) scar, CD4 counts ≥200/mm^3, two positive tests for HIV enzyme-linked *immunosorbant* assay (ELISA), no active TB, and a signed informed consent for HIV testing and participation in the study. In addition, for the present analysis, we excluded two observations with unusual recorded CD4 counts measurements (>3,000 cells/mm^3) and 166 patients with history of treatment for active TB prior to inclusion in the vaccine trial, as the interest of this study was on the effect of treated TB that occurred during follow-up, when administration of TB drugs during follow-up could be closely monitored by our study team.

Pregnant women were not immediately eligible for the vaccine trial but could defer participation until after giving birth. The study was approved by Dartmouth College, Boston University, and MUHAS Institutional Review Boards.

Assessment for TB

All study subjects were HIV-infected. Baseline HIV tests were performed in the Department of Medicine Research Laboratory at MUHAS using ELISA (Beringer, Wellcozyme and Veronstika).

Patients were questioned about symptoms of TB at all vaccine and clinic visits. Those suspected to have active TB were evaluated on a case-by-case basis by project clinicians using routine clinical, radiographic, and microbiologic diagnostic tools.[14] In certain situations, evaluation also included a 10-day course of antibiotics for common bacterial pneumonia. Based on these assessments, suspected TB patients were referred by project clinicians to the National Program for TB and Leprosy (NTLP) for the final decision on whether or not to treat for TB.

Evaluation for active TB was conducted to all subjects by study staff and included a physical examination, chest radiograph, three expectorated sputum samples for AFB stain and culture (one spot sample and two first morning samples; standard techniques including culture on Lowenstein Jensen agar), and an automated mycobacterial blood culture (a single 5-ml sample until March 2004, then two 5-ml samples; MBBacT; bioMérieux, Durham, North Carolina, USA). All potential TB cases were reviewed by a blinded panel of three consultants who independently classified cases as definite, probable, possible, or unlikely based on rigorous study definitions.[14] The current analysis was based on definite and probable cases.

Treatment for active TB was based on the NTLP guidelines, independent of vaccine status. Standard treatment at the inception of the study was two months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by six months of isoniazid and ethambutol (eight months total). Standard treatment after the change in NTLP guidelines on February 1, 2006 (which excluded ethambutol) was two months of isoniazid, rifampicin and pyrazinamide followed by four months of isoniazid and rifampicin (six months total). Both regimens were given by DOT. Drug sensitivity tests were performed at the MUHAS laboratory to ensure that patients were offered appropriate treatment. All patients on treatment were instructed to bring their TB treatment record into each study visit.

At each examination, patients were evaluated for referral to an appropriate HIV Care and Treatment Center (CTC), and were informed if they met criteria for initiation of ART as outlined in the Tanzania National AIDS Control Programme (NACP) guidelines.[15] All subjects with a positive tuberculin skin test and no prior history of active TB were offered a six-month course of IPT. Co-trimozaxole was offered to subjects with CD4 counts < 200.

We defined a ‘TB’ subject as someone diagnosed for active definite or probable TB for the first time during follow-up and completed TB treatment. Conversely, we defined a ‘non-TB’ subject as someone who did not develop active TB during the study.

Matching and controlling for confounding

To exclude deaths directly attributable to TB disease, we excluded subjects who were still receiving TB therapy. We matched non-TB subjects to TB subjects beginning at the completion of TB treatment for the TB subjects and that time of a similar CD4 counts for the non-TB subjects (CD4 counts were matched to within 50 cells/mm^3). Thus, follow-up in both groups was initiated at the matching time (t_0, Figure 1). We matched on CD4 counts at the matching time but not with other potential confounders to avoid overmatching. These other potential confounders were controlled for in the regression model: ART status at the time of matching, co-trimoxazole status at the time of matching, trial vaccine status, age, DarDar baseline tuberculin skin test (TST) status, and gender. We matched every TB subject

with four non-TB subjects. When CD4 counts were not available at the exact time of interest, we linearly interpolated counts assuming a constant decline between recorded observations.

Outcome assessment

The outcome was death (i.e. all-cause mortality). Information regarding the date of death was obtained from medical records, relatives, or confidantes. Putative causes of deaths were obtained by interviewing relatives of the deceased regarding symptoms, medical evaluations, and medications prescribed in the period immediate before death. Neither autopsies nor reliable information on the causes of deaths were available for most patients. We censored two patients who died from a motor accident. Subjects were followed from the start of follow-up to death, withdrawal/loss to follow-up or study termination (i.e. 31st January 2008), whichever occurred first.

Statistical analysis

We performed descriptive analyses to explore distribution characteristics of subjects in the matched sample. Kaplan Meier curves were plotted to compare the death rates between the TB group and the non-TB group. Although CD4 counts were measured on multiple occasions, there were very few measurements taken after matching to allow us to perform accurate assessment of CD4 change over time in the two groups. However, we explored the overall trajectory of CD4 counts across groups (by including both pre-match and post-match CD4 counts) using non-parametric locally weighted scatter plot smoothing curves (figure 2). A Cox proportional hazards model was used to analyze the effect of TB on mortality, accounting for potential confounders. Although information on ART and co-trimoxazole was collected at matching and during follow-up, there were not sufficient follow-up data points on these variables to accurately fit models for time-dependent confounding (i.e. structural nested models or marginal structural models). Thus, to overcome the problem, confounding by these variables was accounted for by regression adjustment at matching, and their effects as competing risks during follow-up was accounted for in the primary analysis by censoring subjects immediately after initiation of ART or co-trimoxazole treatment. Statistical analyses were performed to ensure that the proportional hazards assumptions for the validity of the Cox model were not violated. Analysis was performed using SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina) and S-Plus version 8.0.4 (TIBCO Software Inc., Palo Alto, California).

RESULTS

Study population

The DarDar trial enrolled 2013 subjects. One hundred and sixty nine subjects had a history of treatment for TB before being enrolled in the trial and were excluded from the present analysis. Also excluded were seven patients who had no follow-up and 27 patients with unconfirmed TB (“possible” or “unlikely”) who completed TB treatment. We therefore had 1810 subjects before matching. There were 135 subjects with definite or probable active TB. Of these, we excluded seven subjects with TB but no evidence of ever receiving TB treatment following diagnosis, 51 subjects who did not complete TB treatment, and one subject with missing TST results. We thus had 77 subjects in the TB group. Of these, thirty (39%) met the definition for ‘definite TB’ and 47 (61%) met the definition for ‘probable TB’. We selected 308 CD4-matched subjects who never developed active TB during follow-up as a comparison group. We therefore had a total of 385 subjects for analysis, contributing 9531 person-months of follow-up.

The subjects were predominantly female (75%), single (63%), with median age 33 years, and had never been on ART medication (92%). The median follow-up was two years. There were 32 deaths, 11 in the TB group and 21 in the non-TB group (Tables 1 and 2). A previous study done on DarDar participants[16] identified two eligible patients with multidrug-resistance TB. None of these patients were part of this substudy. Twenty nine of 56 TB patients (52%) who did not complete treatment died during the duration of the DarDar trial.

Outcomes

Kaplan-Meier curves showed a higher mortality for patients in the TB group than patients in the non-TB group (Figure 3). Crude death rate was eight per 1000 person-months in the TB group compared with three per 1000 person-months in the non-TB group (log rank P value= 0.01). The adjusted Cox proportional hazards model indicated a four-fold increased mortality in the TB group than the non-TB group (Hazard Ratio= 4.61; 95% Confidence Interval (CI): 1.63, 13.05) (Table 3). The median time to TB for cases was 22 months (interquantile range (IQR): 13–36 months), the median time to completion of TB treatment for cases was 30 months (IQR: 21–43 months), and the median time to t_0 for non-TB cases was 23 months (IQR: 14–36 months). Throughout follow-up there was no TB patient who had TB recurrence after successfully completion of therapy.

CD4 count declines over time

When analyzed from the beginning of the vaccine study follow-up, it can be seen that TB patients had a lower initial CD4 counts than non-TB patients (Figure 2). In the early part of follow-up, CD4 counts decreased in both groups. However, as can be seen in figure 2, the average counts for TB patients rebounded after about 40 months of being in the study, while there was no rebound seen in the non-TB group. These results were essentially unchanged when persons receiving ART were excluded, or when persons who died were excluded (data not shown).

DISCUSSION

Our findings suggest a strong association between successfully treated TB disease and increased mortality in HIV-infected adults in Tanzania. Compared with patients with a similar severity of HIV disease who did not develop active TB, patients who developed and completed treatment for active TB had a greater than four-fold increase in mortality.

In most other studies that have observed such an increase, patients with TB also had a more rapid progression to new onset AIDS-associated opportunistic infections, suggesting that the mechanism for this increased mortality was an enhanced immune deficit. However, only two of the studies looked directly at decreases in CD4 counts or increases in HIV viral load. Whalen et al. found that patients with TB had a greater rise in viral load after TB than did control patients, but this difference was not statistically significant (p=0.17),[8] while Leroy et al found that a higher proportion of patients with TB progressed to CD4<50 than did control patients, but this also was not statistically significant (p=0.09).[10] We were also unable to document a significantly more rapid decline of CD4 cell counts after TB. This suggests that other factors may be contributing to the increased mortality in this population. One possibility might be *M. tuberculosis*–induced impairment of the lung function; a recent report showed that TB, even when successfully treated, leaves patients with substantial pulmonary impairment.[17]

While we cannot draw firm conclusions from our study, the increase in CD4 counts over time among the TB patients suggests that a more rapid decrease in immune competence may not be the cause of increased mortality in our patients who were treated for TB. This is

consistent with a recent report from Uganda, where TB patients had decreased cellular markers of immune activation as TB treatment progressed (in the absence of ART), despite the absence of an effect on the CD4 counts or HIV loads of the patients.[18]

In our study we observed increases in CD4 counts in TB patients after TB treatment. One possible explanation would be systematic ART initiation following TB treatment. However, only 6 of our TB patients were known to have initiated ART during follow-up, and when these 6 were excluded from the CD4 count analysis, the effect persisted. Similarly, exclusion of subjects with TB who died during the study did not markedly change the curve, indication that death of those with low CD4 counts did not explain the rise in the group mean CD4 count. Thus, we conclude that this rise in CD4 counts can be attributed to the effect of TB treatment on CD4 counts, as reported previously.[19]

Our study had three important limitations. First, about a quarter of patients had their CD4 counts interpolated at the time of matching (all in the non-TB group), thus residual confounding on mortality results can not be ruled out. Second, due to the small number of subjects on ART, we could not evaluate the combined effect of TB treatment and ART on mortality prevention. However, of the 26 patients on ART in our study cohort (Table 1), only two died by the end of follow-up, suggesting that ART could have prevented deaths in some of these patients. All patients meeting WHO guidelines for ART initiation were referred repeatedly to CTC designated clinics, but the uptake was low at the time of the trial. Finally, there could have been residual confounding due to unmeasured factors such as lifestyle variables, HIV subtypes, and comorbidities that could have affected mortality in ways that we could no assess.

The main strengths of this study included a close monitoring on administration of TB treatment which reduced misclassification of treatment effect and the availability of CD4 counts at multiple visits over time, which allowed us to asses the overall trends in CD4 counts over time.

In summary, we show that active TB, even when adequately treated, is strongly associated with increased mortality among HIV-infected patients treated for TB in the absence of antiretroviral therapy. This study confirms findings from previous studies that active TB is associated with increased mortality among HIV-infected patients. Therefore, prevention of TB disease should be a high priority among HIV-infected populations in areas where co-infection is common. Results from this study underscore the need for more widespread and effective implementation of Isoniazid preventive therapy, as recommended by WHO in the “3 I’s” Initiative.[20,21] This should go parallel with integration of TB and HIV treatment for prevention of TB and mortality.[11,12,13]

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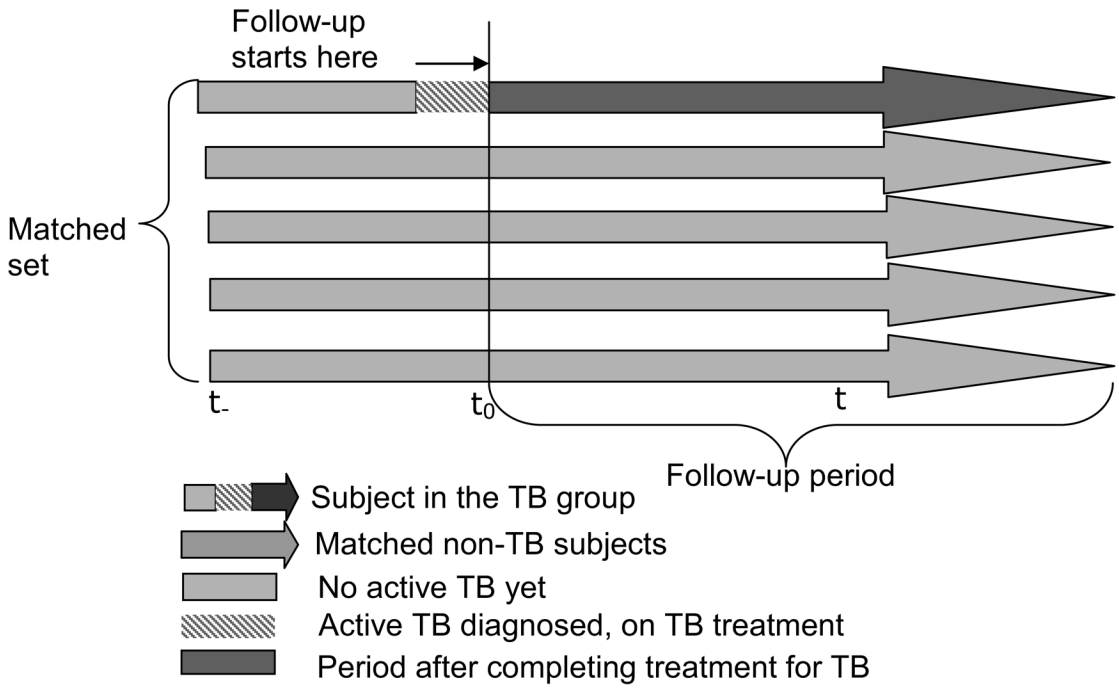

Figure 1.
Diagrammatic representation of the matching process. Each arrow represents one subject.

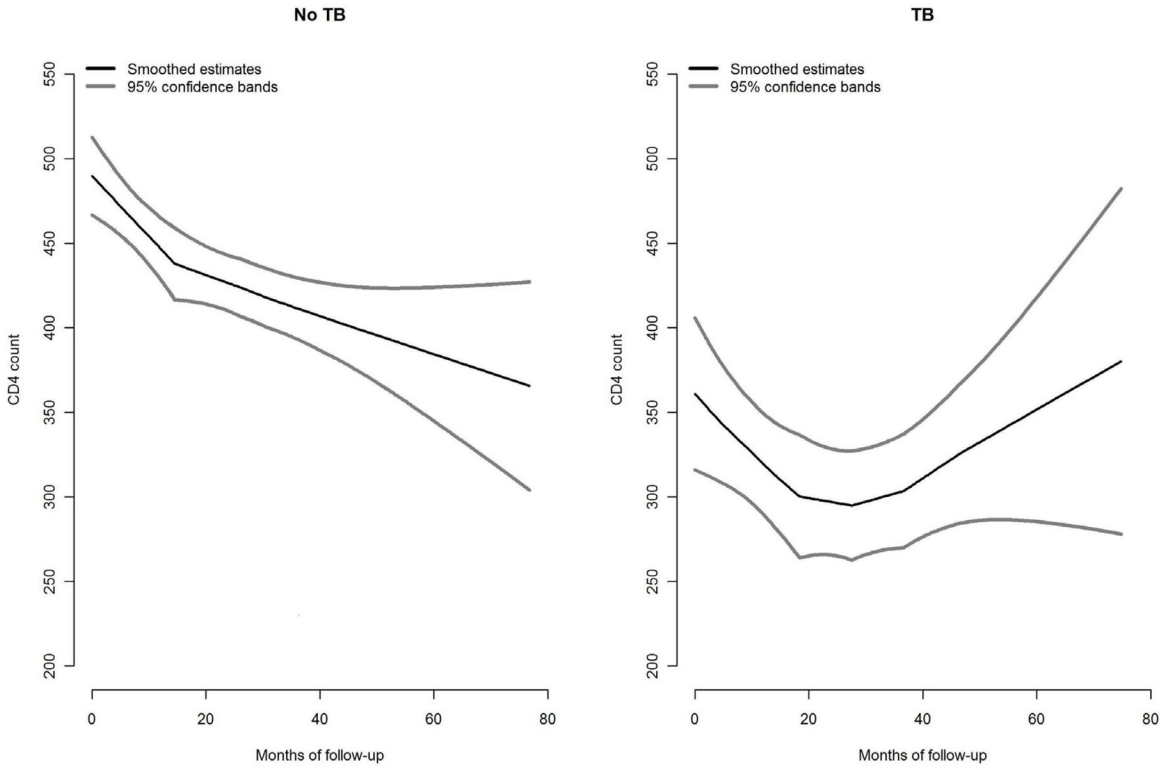

Figure 2.

Left panel shows mean CD4 count among non-TB patients. Right panel shows mean CD4 count among TB patients. The curves cover the entire duration of the DarDar trial, pre- and post- matching periods. This study covers only the post- matching period.

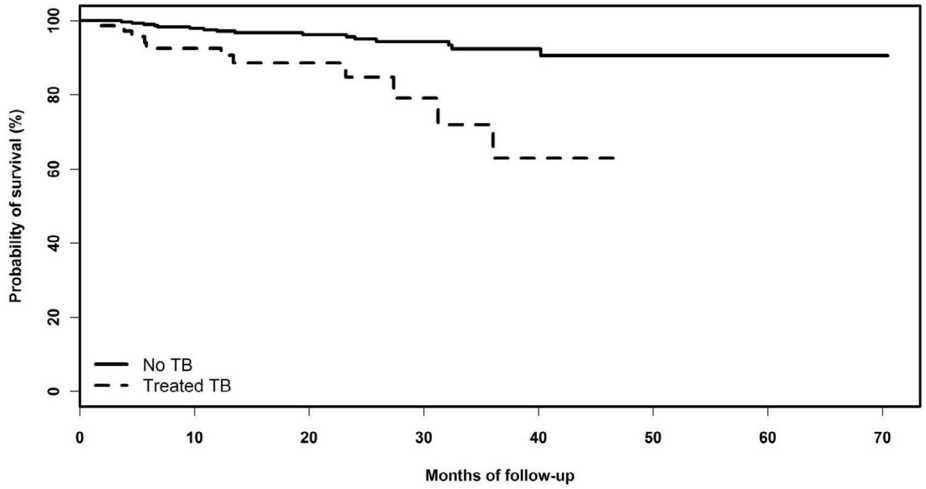

Figure 3.
Kaplan-Meier curves comparing the probability of survival between the TB group (dashed line) and the non-TB group (solid line).

Table 1

Distribution characteristics of patients

		TB group (N=77)		Non-TB group (N=308)	P value for the absolute difference in IP
Variable	**Total**	**No. Deaths (IP in %)[1]**	**Total**	**No. Deaths (IP in %)**	
Overall	77	11 (14.3)	308	21 (6.95)	0.071
Age					
18–<30	27	5 (18.52)	113	4 (3.54)	0.026
30–<40	34	3 (8.82)	116	9 (7.76)	0.826
40–<50	13	3 (23.08)	63	7 (11.11)	0.359
50–70	3	0 (0.00)	10	1 (10.00)	0.786
Gender					
Females	59	8 (13.56)	228	12 (5.26)	0.060
Males	18	3 (16.67)	74	9 (12.16)	0.652
Marital status					
Married or cohabiting	28	4 (14.29)	110	9 (8.18)	0.396
Single	49	7 (14.29)	192	12 (6.25)	0.116
Source of referral					
Any Muhimbili clinic	7	0 (0.00)	26	2 (7.69)	0.635
Infectious Diseases Centre	5	1 (20.00)	18	0 (0.00)	0.250
NGO VCT	39	7 (17.95)	157	10 (6.37)	0.061
Self referred	12	1 (8.33)	38	4 (10.53)	0.907
Other	14	2 (16.67)	63	5 (7.94)	0.523
CD4 count at or around the matching time					
<200	49	7 (14.29)	191	11 (5.76)	0.090
200–<250	6	2 (33.33)	23	4 (17.39)	0.537
250–<300	7	0 (0.00)	28	4 (14.29)	0.437
300–<350	6	0 (0.00)	24	1 (4.17)	0.806
≥350–2000	9	2 (22.22)	36	1 (2.78)	0.137
On ART at matching					
On medication	4	0 (0.00)	20	2 (10.00)	0.711
Not on medication	73	11 (15.07)	282	19 (6.74)	0.054

		TB group (N=77)		Non-TB group (N=308)	P value for the absolute difference in IP
Variable	**Total**	**No. Deaths (IP in %)[1]**	**Total**	**No. Deaths (IP in %)**	
On ART at some point during follow-up					
On medication	6	0 (0.00)	20	2 (10.00)	0.611
Not on medication	71	11 (15.49)	282	19 (6.74)	0.047
Vaccine arm					
M. vaccae	28	7 (25.00)	146	9 (6.16)	0.016
Placebo	49	4 (8.16)	156	12 (7.69)	0.893
Isoniazid preventive therapy (at DarDar baseline)					
Not eligible for therapy	50	6 (12.00)	214	15 (7.01)	0.303
Eligible, not adhered	7	4 (57.14)	10	2 (20.00)	0.335
Eligible, adhered	20	1 (5.00)	78	4 (5.13)	0.957
On co-trimoxazole at matching					
On medication	38	6 (15.79)	78	5 (6.41)	0.173
Not on medication	39	5 (12.82)	224	16 (7.14)	0.296
On co-trimoxazole at some point during follow-up					
On medication	68	10 (14.71)	135	8 (5.93)	0.073
Not on medication	9	1 (11.11)	167	13 (7.78)	0.705

[1] IP stands for incidence proportion

Table 2

Distribution characteristics of patients by death and person-time

	TB group (N=77)		Non-TB group (N=308)		P value for the absolute difference in death rate
Variable	**Total person-months**	**No. Deaths**	**Total person-months**	**No. Deaths**	
Overall	1333.27	11	7801.57	21	0.002
Age					
18–<30	508.70	5	2884.00	4	0.001
30–<40	564.53	3	3116.77	9	0.353
40–<50	178.07	3	1561.43	7	0.039
50–70	81.97	0	239.37	1	0.558
Gender					
Females	962.23	8	5960.53	12	0.001
Males	371.03	3	1841.03	9	0.446
Marital status					
Married or cohabiting	493.00	4	4983.83	9	0.006
Single	840.27	7	2817.73	12	0.151
Source of referral					
Any Muhimbili clinic	136.20	0	646.80	2	0.516
Infectious Diseases Centre	97.57	1	544.40	0	-
NGO VCT	693.33	7	4232.37	10	0.001
Self referred	178.20	1	726.73	4	0.986
Other	229.97	2	1651.26	5	0.187
CD4 count at or around the matching time					
<200	790.13	7	4896.53	11	0.002
200–<250	108.43	2	680.77	4	0.163
250–<300	178.13	0	777.83	4	0.339
300–<350	92.77	0	497.70	1	0.666
≥350–2000	163.80	2	948.73	1	0.010
On ART at matching					
On medication	104.10	0	428.47	2	0.486
Not on medication	1229.17	11	7373.10	19	<0.001

	TB group (N=77)		Non-TB group (N=308)		P value for the absolute difference in death rate
Variable	**Total person-months**	**No. Deaths**	**Total person-months**	**No. Deaths**	
On ART at some point during follow-up					
On medication	157.03	0	428.47	2	0.392
Not on medication	1176.23	11	7373.10	19	<0.001
Vaccine arm					
M. vaccae	450.97	7	3824.87	9	<0.001
Placebo	882.30	4	3966.7	12	0.481
Isoniazid preventive therapy (at DarDar baseline)					
Not eligible for therapy	845.67	6	5431.27	15	0.043
Eligible, not adhered	116.37	4	254.63	2	0.062
Eligible, adhered	371.23	1	2115.67	4	0.003
On co-trimoxazole during matching					
On medication	506.80	6	1550.70	5	0.021
Not on medication	826.47	5	6250.87	16	0.083
On co-trimoxazole at some point during follow-up					
On medication	1227.37	10	3562.83	8	0.004
Not on medication	105.90	1	4238.73	13	0.254

Table 3

Comparison of mortality between the TB and the non-TB group

	Hazard ratio [95% CI]	
	Crude	**Adjusted[1]**
TB group (n=77)	4.42 [1.72,11.33]	4.61 [1.63,13.05]
Non-TB group (n=308)	1.00	1.00

[1]Adjusted for age, sex, vaccine status, and co-trimoxazole