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Burden of disease and risk factors for death among children treated for tuberculosis in Malawi

Robert J. Flick^{1,2,3}, Maria H. Kim^{1,4}, Katie Simon^{1,4}, Adamson Munthali¹, Mina Hosseinipour^{2,5}, Nora E. Rosenberg^{2,5}, Peter N. Kazembe^{1,4}, James Mpunga⁶, and Saeed Ahmed^{1,4}

¹Baylor College of Medicine Children's Foundation Malawi, Lilongwe, Malawi

²University of North Carolina Project-Malawi, Lilongwe, Malawi

³University of Colorado School of Medicine, Denver, United States

⁴Baylor International Pediatric AIDS Initiative at Texas Children's Hospital, Baylor College of Medicine, Houston, United States

⁵University of North Carolina at Chapel Hill, Chapel Hill, United States

⁶Malawi Ministry of Health National Tuberculosis Programme, Lilongwe, Malawi

SUMMARY

SETTING—Tuberculosis is a leading cause of childhood death. There is limited patient-level data on pediatric TB in Malawi that can be used to guide programmatic interventions.

OBJECTIVE—To describe pediatric tuberculosis case burden, disease pattern, treatment outcomes, and risk factors for death and poor outcome.

DESIGN—We conducted a retrospective cohort study utilizing routinely collected data in treatment registers. Odds ratios for factors associated with poor outcome and death were calculated separately using generalized estimating equations.

RESULTS—Children represented 8% (371/4,642) of tuberculosis diagnoses. Median age was 7 (IQR 2.8–11) and 32.8% (113/345) were HIV-infected. Of these, 54.0% were on antiretroviral therapy (ART) at time of anti-tuberculosis treatment (ATT) initiation, 21.2% started ART during ATT, and 24.8% had no documented ART. The treatment success rate was 77.3% (11.2% cured, 66.1% completed treatment) with 22.7% experiencing a poor outcome (9.5% died, 13.2% were lost to follow-up). Being on ART at time of ATT initiation was associated with an increased odds of death compared to initiating ART during ATT (aOR=2.75, 95% CI 1.27–5.96).

Corresponding author: Saeed Ahmed, MD, MSc, Baylor College of Medicine Children's Foundation Malawi, Private Bag B-397, Malawi (saeeda@bcm.edu).

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Authors' contributions

Conceived the study: SA, MHK

Analyzed the data: RJF, NER

Wrote the paper: RJF, MHK, KS, AM, MH, NER, PNK, JM, SA

CONCLUSION—Children represent a small proportion of diagnosed tuberculosis cases and experience poor outcomes. Higher odds of death among children already on ART raises concerns over the management of these children in routine settings. Further discussion and research is warranted on pediatric-specific strategies to improve outcomes among these children.

Keywords

epidemiology; pediatric tuberculosis; treatment outcomes; case finding; HIV

INTRODUCTION

Tuberculosis (TB) is a leading cause of childhood death worldwide.¹ In high burden settings, TB is a common cause of pediatric pneumonia and has been microbiologically confirmed post-mortem in a quarter of African children who died while hospitalized.^{2,3} Treatment outcomes remain poor in resource-constrained settings where up to half of children less than one year of age who present with advanced disease die.⁴ However, treatment success rates in excess of 90% are possible in developed settings with access to rapid detection and treatment initiation.⁵

Only one-third of the estimated one million cases of TB in children that occurred in 2010 were reported.^{6,7} This is in part due to challenges with TB diagnosis in children. These include protean clinical presentation, the limited ability of children to produce sputum, and paucity of tuberculosis bacilli in samples that are produced.⁸ Because of the rapid progression from infection to clinical disease—typically in less than 12 months—there is a limited time window for clinicians to identify children at risk of exposure and those in the early stages of disease.^{8,9} HIV-infected children face unique risks because of the higher rate of household exposure to TB, faster progression from infection to disease, and the high incidence of other infections that may complicate diagnosis.^{10,11} Further, countries with the highest burden of tuberculosis have limited diagnostic capacity, usually relying on sputum microscopy, a test with low sensitivity in the few children who can produce specimens.¹²

Planning effective child-focused TB interventions requires detailed evidence to guide implementation, however patient-level data is often scarce. In Malawi, a resource-limited landlocked country of 16 million people in sub-Saharan Africa, the most recent published data describes pediatric TB from 1998, before the rollout of HIV diagnosis and treatment services and decentralization of TB treatment.¹³ In preparation for a community health worker-based intervention, we conducted a pre-intervention assessment to describe the pediatric TB case burden, disease pattern, treatment outcomes, and risk factors for poor outcome and death.

STUDY POPULATION AND METHODS

Study design and setting

We conducted a retrospective cohort study utilizing routinely collected programmatic data in Malawi Ministry of Health (MOH) treatment registers at ten health facilities (six hospitals, four health centers) in Malawi's central region with a total estimated catchment area

population in 2012 of 742,000 (4.6% of the national population).¹⁴ Children under 15 years of age comprise 49% of this population.¹⁵ Pertinent health indicators in the central region are similar to the rest of the country, however the southern region is an important outlier apropos HIV prevalence, where estimated HIV prevalence is roughly twice as high as the central (14.5% vs 7.6%) and northern (6.6%) regions.¹⁵

The facilities surveyed serve diverse settings, from peri-urban to rural, and all are the site of a community health worker-based outreach program called Tingathe that has been described elsewhere.^{16,17} Hospitals and health centers vary primarily by the concentration of infrastructure and experienced personnel—hospitals often have at least one medical doctor on staff, and may have access to chest radiography, whereas health centers typically do not.

Half of all people living with HIV in Malawi are on antiretroviral therapy (ART), but only one-quarter of HIV-infected children are on treatment.¹⁸ The annual incidence rate of TB is estimated at 227 cases per 100,000, and approximately half of all TB patients in Malawi are HIV-infected.¹⁹

Diagnosis and management of TB and HIV in children

A case of pediatric TB was defined as any person less than 15 years of age recorded in a TB treatment register. Malawi National Tuberculosis Program (NTP) guidelines recommend a flexible approach to the diagnosis of TB in children that incorporates findings from physical examination, patient history, chest radiography, and/or sputum smear microscopy.²⁰ Smear microscopy was the only microbiological test widely available during the study period. A diagnosis of TB is most commonly made by clinical officers and nurses. After diagnosis, health surveillance assistants dispense medication, assess adherence, screen for adverse effects and treatment failure, and trace household contacts. Individuals diagnosed with TB are managed on an outpatient basis when possible, with monthly facility visits of medication refills.

Standard anti-tuberculosis treatment (ATT) for patients newly diagnosed with pulmonary TB is per Malawi MOH and WHO guidelines: a two month intensive phase of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by a four month continuation phase of isoniazid and rifampicin.^{20,21} All patients started on ATT are referred for HIV counseling and testing, with ART initiated within two weeks for HIV-infected patients. All TB and HIV care is provided free of charge and is decentralized to the health center level. Every individual who receives ATT is recorded in a TB treatment register, along with their demographic information, and details of their diagnosis and course of treatment. Standardized treatment outcomes are recorded for every patient (Box 1). Children under five years who live in the same household as an individual diagnosed with pulmonary TB are eligible for a six-month course of isoniazid preventive therapy.

Box 1**Standardized definitions of treatment outcomes***

Term	Definition
Cured	A patient with positive smear or culture results at ATT initiation whose results are negative in the last month of ATT and on at least one prior occasion
Treatment completed	A patient with negative or unavailable smear or culture results at the beginning of treatment who finished a full course of ATT
<i>Treatment Success[†]</i>	<i>Sum of patients with outcomes “Cured” and “Treatment completed”</i>
Died	A patient who dies for any reason while receiving ATT
Lost to follow-up [‡]	A patient whose ATT was interrupted for two months or more
<i>Poor outcome[‡]</i>	<i>Sum of patients with outcomes “Died” or “Lost to follow-up”</i>
Transferred Out [¶]	A patient who was transferred to another treatment facility for ATT

* ATT denotes anti-TB treatment

[†] Summary outcomes generated for analysis

[‡] Includes patients with no recorded outcome two months after anticipated date of treatment completion

[¶] Excluded from outcomes analysis

Data collection and analysis

Facilities were visited during June-August 2013. TB treatment registers maintained by MOH TB officers containing records for patients initiating ATT were scanned, de-identified, and entered into a Microsoft Excel database. Data from 1 January 2011 through the date of facility visit was used for all analyses except annual incidence estimates. These calculations used a subset of data (January – December 2012) as this time period contained the most complete records. The number of pediatric cases documented in TB treatment registers and projections for health facility catchment area population was used for this analysis.²²

Outcomes analysis

Patients with no documented outcome more than two months after the anticipated treatment completion date were presumed to have been lost to follow-up (LTFU). Patients who transferred out and those who were still on treatment at time of data abstraction were excluded from outcomes analysis. A summary outcome measure, “treatment success”, was created that combined patients who were cured or completed treatment (Figure 1). Two separate analyses were then conducted. One combined patients who experienced death or LTFU into a summary category, “poor outcome”, and compared against patients with treatment success. Because of potential bias introduced by the presumption of LTFU status for patients with no documented outcome, we conducted a second analysis comparing only patients who died to those with treatment success.

Analysis was conducted using a preset significance level of 0.05. Pearson’s χ^2 and Fisher’s exact tests were used to compare differences in categorical variables, and two-tailed student’s t-tests were used to compare continuous variables. Odds ratios (OR) with 95% confidence intervals (95% CI) and robust standard errors were calculated using generalized estimating equations with logit link and exchangeable correlation matrix to account for

correlation between observations at the same site. Multivariate analysis was conducted using a backward elimination approach. For each exposure-outcome variable pairing, a directed acyclic graphs (DAG) was drawn. All factors identified as potential confounders from each paring's DAG were included in a preliminary model. Potential confounders were then eliminated step-wise, with variables retained at a p-value of 0.05. This approach allowed distinct models to be generated for each independent variable to produce adjusted odds ratios (aOR). Kaplan-Meier curves were generated for survival analysis with death as the primary outcome. All analysis was done using Stata Special Edition, version 14.1 (Stata-Corp LP, College Station, TX, USA).

Ethics

The study was approved by the Malawi National Health Science Research Committee and the Baylor College of Medicine Institutional Review Board.

RESULTS

Burden of pediatric TB

From January 2011 through date of facility visit, 4,642 patients were treated for TB, of whom 371 (8.0%) were children. The proportion of children among all TB cases varied across facilities and over time (median=7.9%, interquartile range [IQR] 2.7–8.3; Figure 2). One facility did not record any pediatric patients. District hospitals demonstrated a higher proportion of pediatric cases compared to other facilities (9.3% vs 3.3%, $p=0.007$). Bacteriologic confirmation was rare (10.2%). Between January and December 2012, 2,111 individuals (199 children, 1,912 adults) were diagnosed with TB, representing 10.4% of Malawi's total number of case notifications. The age-specific annual incidence rate for this period was 56 per 100,000 for children and 496 per 100,000 for adults (Table 1).

Characteristics of children treated for TB

The majority (63.1%, 234/371) of pediatric patients were in the 5–14 age group (median age=7, IQR 2.8–11) and were male (54.7%, 203/371; Table 2). All patients were newly treated except for eight who had relapsed and two who had missing data. The type of TB varied significantly according to age category. Smear-negative pulmonary TB was the most common type (47.4%) followed by extrapulmonary TB (EPTB; 42.3%). Smear-positive pulmonary TB was rare (10.2%) and was only documented in the 5–14 year age group. Of the 144 patients treated for EPTB with site of involvement recorded, lymph node involvement was most common (36.8%), followed by pleural (20.8%), vertebral (16.7%), and pericardial (16.0%) involvement (Table 3). No miliary TB was recorded.

HIV prevalence

Most children treated for TB had known HIV status (347/371, 93.5%). Of these, 32.6% (113/347) were HIV-infected. Of 347 children with known status, most (57.1%) had been tested before ATT initiation, 36.9% were tested after their TB diagnosis, and 6.1% had unknown HIV test timing. 6.5% (24/347) of children had unknown HIV status, and of these, 7/24 were documented as having unknown serostatus whereas the remainder were missing any documentation. More than half (54.0%, 61/113) were already on ART at the time of

ATT initiation, 21.2% started ART during ATT, and 24.8% had no documented ART. Children who were already on ART at the time of TB diagnosis were older than those not on ART (mean age 7.4 vs 6.0, $p=0.034$)

Outcomes

Of the 371 children treated for TB, 72 were still on ATT at time of data collection and four transferred out. The 295 remaining children were included in the outcomes analysis. Of the 295, 77.3% were treated successfully (11.2% cured, 66.1% completed treatment) and 22.7% experienced a poor outcome (9.5% died, 13.2% LTFU). Children less than one year had a significantly lower proportion of poor outcome (19.0%, $p<0.001$). Children older than five years had a significantly higher proportion of death (10.8%, $p<0.001$)

Risk factors for poor outcome vs treatment success

Smear-positive TB was associated with decreased odds of poor outcome ($aOR=0.12$, 95% CI 0.02–0.76, Table 4) compared to smear-negative and EPTB when adjusting for age and HIV status. Among EPTB patients with documented anatomic site of involvement, pericardial ($aOR=4.07$, 95% CI 1.65–10.05) and pleural ($aOR=3.60$, 95% CI 1.35–9.62) involvement were associated an increased adjusted odds of poor outcome compared to patients with lymph node involvement when adjusting for age, sex, and HIV status.

Risk factors for death vs treatment success

Children already on ART at time of ATT initiation experienced an increased odds of death compared to those who initiated ART during ATT after controlling for age, type of TB, and sex ($aOR=2.75$, 95% CI 1.27–5.96). The majority of deaths in this group occurred within the first two months of ATT (Figure 3). Age between 1–4 years was associated with decreased odds of death after adjusting for HIV status and type of TB ($aOR=0.53$, 95% CI 0.29–0.96). Among EPTB patients, pericardial ($aOR=15.21$, 95% CI 1.36–169.50) and pleural involvement ($aOR=13.55$, 95% CI 1.63–112.7) were associated with an increased adjusted odds of death when controlling for HIV status, however with wide confidence intervals.

DISCUSSION

This study is the first in over a decade, and notably the first in the era of widely available HIV diagnosis and treatment, to describe patient-level data on pediatric tuberculosis diagnosis and management under operational conditions in Malawi. Importantly, these findings suggest children make up a low proportion of all patients treated for TB (8%) and that children already on ART at time of ATT initiation have a higher odds of death.

The burden of pediatric TB is primarily a function of the burden of TB among adults, who are usually the source of disease. In countries with complete modeling data that are similar in demography and incidence rate—notably Tanzania and Uganda—the true proportion of all TB cases that occur in children exceeds 15%.²³ An even lower proportion of all patients treated for TB were children in this study compared to some previous work (8% vs 11.9%), despite an increase in the proportion of the total population who are children.^{13,24,25} Even at hospitals, which are arguably best equipped to diagnose TB in children, the proportion of

pediatric cases was just 9.3%. It is therefore likely that given the demographics and high prevalence of TB among adults the 8% proportion reflects gaps in the effectiveness of case-finding in children. The greatest number of cases occurred in the 5–14 year age group. This age category is typically defined by lower rates of TB,⁸ suggesting under diagnosis in children less than five years.

Major changes in TB service delivery may further explain the decrease in children as a proportion of all TB cases. Diagnosis and treatment services have been decentralized from 43 district and central hospitals in 1998 to almost 700 hospitals and health centers in 2013. The greater lab, radiologic, and clinical capacity found in district and central hospitals may allow these facilities to more frequently establish a diagnosis of TB in children compared to health centers. The nearly three-fold higher proportion of pediatric cases observed in district hospitals supports this hypothesis (9.3% vs 3.3%, $p=0.007$), as do other studies.¹³ Therefore the 8% proportion observed in this study may reflect a preferential increase in adult case-finding at the peripheral facilities that began offering these services in the last decade.

The relatively high proportion of children with unknown HIV status (6.5%) is troubling and suggests that provider-initiated testing and counseling (PITC) is still not universal at one of the most critical points for HIV screening. Further, this finding is unlikely to be simply a relic of missing documentation as almost one-third of patients had their status actively recorded as unknown. This finding corroborates other work in Malawi's central region demonstrating suboptimal HIV testing coverage rates at high-yield service delivery points.²⁶

The overall treatment success rate was 77.3%, higher than the previously reported rate of 45% but short of the WHO target of 85%.¹³ In stark contrast to past studies, we did not find an association between HIV status and poor outcome or death, suggesting this improvement is likely due to greatly expanded access to HIV diagnosis and treatment services.²⁷ While this drastic improvement is commendable, factors associated with death warrant further investigation.

The increased odds of death in HIV-infected children already on ART is particularly troubling. ART status remained strongly associated with death even after controlling for multiple potential confounders. Importantly, the finding remained robust in the death analysis that excluded children with missing data, reducing the likelihood of bias introduced by incomplete records. Among patients with outcome timing available, deaths tended to occur during the first two months of ATT (Figure 3). The most likely etiology of this finding depends on whether these patients were recently initiated on ART, or had been on long-term treatment before death. Early mortality due to advanced disease at presentation is well described for patients early in their ART course.²⁸ Additionally, new TB cases may represent TB unmasking IRIS that may be associated with higher mortality.²⁹

Among children on long term ART, virological failure (VF) is a major concern. VF is significantly more prevalent and harder to detect in children compared to adults. Up to one in five children experience VF within three years of ART initiation, with exposure to nevirapine-based regimens (such as the first-line pediatric regimen in Malawi), poor adherence, and adolescence associated with increased risk.^{30–32}

Caution is warranted in interpreting the increased odds of death in HIV-infected children already on ART, especially given the dataset's lack of detailed ART versus ATT initiation time, the retrospective nature of the study, and the low rates of bacteriological confirmation that may have led to misdiagnosis of TB. What is clear however is children on ART who are diagnosed with TB in routine settings die at higher rates compared to patients who newly initiate ART. Incident TB in these children, regardless of etiology, should prompt more intensive clinical investigation. Additional work is needed to understand the true etiology of this association, and to design services that meet the unique needs of HIV-infected children on ART. Given the additive impact of IPT among patients with early ART in reducing rates of severe illness from TB and other pathogens, its potential as a treatment strategy among HIV-infected children on ART warrants discussion.³³

EPTB was far more common than previously reported in Malawi.^{13,34} This should be interpreted with caution as no EPTB cases were microbiologically confirmed. Distribution of EPTB by anatomic site largely corresponded with what has previously been reported, with lymph, pleural, and vertebral predominating. Of note is the lack of miliary TB, however this may be a reflection of limited use of chest radiography or incomplete reporting. The relatively low number of patients with TB meningitis may reflect high BCG coverage in Malawi or challenges in the diagnosis of TB meningitis.³⁵

Several limitations additional to those mentioned above are important to recognize. First, our estimates for annual incidence rates rely heavily on projections of facility catchment area population that are open to scrutiny. Second, our use of routine program data introduces greater possibility for documentation errors compared to a controlled setting. However, we feel this approach was necessary to best ascertain the current state of pediatric TB management at public facilities. Further, our major risk factors were associated with death, and this analysis excluded missing records thereby minimizing any adverse impact of missing data on our results.

CONCLUSIONS

The proportion of pediatric TB among notified cases is 8% and lower than expected given established TB incidence rate and population demographics. Treatment outcomes, while improved in the era of HIV diagnosis and treatment services, remain poor with more than one in five children experiencing a poor outcome. Children already on ART at time of ATT initiation are more likely to die compared to those who initiate ART during ATT. There is an urgent need for pediatric-specific strategies for intensified case finding and improved management of HIV-infected children on ART. Given the success of community health worker-driven interventions in addressing pediatric HIV in this setting,^{16,17,36} we are using this data to integrate pediatric TB case-finding and management into an existing community health worker focused intervention.

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Figure 1.
Overview of outcome analyses*
ATT denotes anti-TB treatment

Figure 2.
Pediatric case load and rate of bacteriological confirmation of tuberculosis over time

Figure 3.
Kaplan-Meier survival curve describing HIV-infected children according to ARV status

Table 1

Age-specific annual incidence rates of tuberculosis in 2012

Age group	Reported TB cases during 2012	Population at risk 1 January 2012 ²²	Age group-specific incidence rate per 100,000 population
<1	12	28,475	42
1–4	49	113,902	43
5–15	138	213,566	65
<15	199	355,943	56
>15	1,912	385,605	496

Table 2

Patient characteristics and outcomes according to age group^{*}

Characteristic	Age group				Total (N=371) n (%)	P-value
	Less than 1 yr (N=24) n (%)	1–4 years (N=113) n (%)	5–14 years (N=234) n (%)			
Gender						
Male	13 (54.2)	64 (56.6)	126 (53.8)	203 (54.7)	0.886 [‡]	
Female	11 (45.8)	49 (43.4)	108 (46.2)	168 (45.3)		
TB Type						
Smear-positive PTB	0 (0)	0 (0)	38 (16.2)	38 (10.2)	<0.001	
Smear-negative PTB	20 (83.3)	63 (55.8)	93 (39.7)	176 (47.4)		
EPTB	4 (16.7)	50 (44.2)	103 (44.0)	157 (42.3)		
HIV Status						
Negative	12 (50.0)	69 (61.1)	151 (64.5)	232 (62.5)	0.027	
Positive	6 (25.0)	36 (31.9)	71 (30.3)	113 (30.5)		
Exposed	1 (4.2)	1 (0.9)	0 (0)	2 (0.5)		
Unknown	5 (20.8)	7 (6.2)	12 (5.1)	24 (6.5)		
ART Status ¹						
On ART at diagnosis	1 (16.7)	17 (47.2)	43 (60.6)	61 (54.0)	0.109	
Started during TB Tx	3 (50.0)	7 (19.4)	14 (19.7)	24 (21.2)		
Did not start/unknown	2 (33.3)	12 (33.3)	14 (19.7)	28 (24.8)		
Outcomes ²						
Cured	0 (0)	0 (0)	33 (17.0)	33 (11.2)	<0.001	
Treatment completed	17 (81.0)	57 (71.3)	121 (62.4)	195 (66.1)		
Died	2 (9.5)	5 (6.3)	21 (10.8)	28 (9.5)		
Lost to follow-up	2 (9.5)	18 (22.5)	19 (9.8)	39 (13.2)		
Summary measures						
Treatment success	17 (81.0)	57 (71.3)	154 (79.4)	228 (77.3)		
Poor outcome	4 (19.0)	23 (28.8)	40 (20.6)	67 (22.7)		

^{*} ART denotes antiretroviral therapy, ATT anti-TB treatment, PTB pulmonary tuberculosis, and EPTB extrapulmonary tuberculosis

[‡] χ^2 used for this calculation; Fisher's exact tests used for all others

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Of 113 HIV-infected patients
Excludes 72 patients still on treatment and 4 patients who transferred out

Table 3

Anatomic site of involvement for 144 patients with extrapulmonary TB *

Site	n (%)
Lymph nodes	53 (36.8)
Pleura	30 (20.8)
Vertebrae	24 (16.7)
Pericardium	23 (16.0)
Ascites	9 (6.3)
Meningitis	2 (1.4)
Osseous †	2 (1.4)
Empyema	1(0.7)

* 13 patients missing documentation of site

† Excluding vertebral

Table 4

Odds ratios for poor outcome and death^{*}

Characteristic	Odds Ratio for poor outcome [†] (95% CI)		Odds Ratio for death [‡] (95% CI)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Age group				
<1 year	0.93 (0.27–3.15)	0.62 (0.16–2.46) ^{¶¶}	0.81 (0.21–3.11)	0.39 (0.12–1.25) ^{¶¶a}
1–4 years	1.52 (0.70–3.27)	1.49 (0.70–3.19) ^{¶¶}	0.62 (0.33–1.62)	0.53 (0.29–0.96) ^{¶¶a}
5–14 years	Referent		Referent	
Sex				
Female	Referent		Referent	
Male	1.13 (0.75–1.70)	1.11 (0.69–1.77) ^{¶¶}	1.26 (0.37–4.23)	1.02 (0.26–4.08) ^{¶¶a}
HIV				
Negative	Referent		Referent	
Positive	1.50 (0.96–2.34)	1.50 (0.96–2.34)	1.49 (0.50–4.42)	1.47 (0.49–4.41) ^a
Unknown	1.48 (0.52–4.20)	1.48 (0.52–4.20)	1.00	1.00
ART History ³				
Started ART during ATT	Referent		Referent	
Started ART before ATT	2.35 (0.81–6.83)	2.54 (0.69–9.38) [‡]	3.26 (1.03–10.34)	2.75 (1.27–5.96) ^{‡¶a}
Unknown ART status	1.97 (0.46–8.42)	2.01 (0.43–9.48) [‡]	0.75 (0.29–2.46)	0.53 (0.08–3.45) ^{‡¶a}
TB Type				
Smear negative PTB	Referent		Referent	
Smear positive PTB	0.10 (0.01–0.85)	0.12 (0.02–0.76) ^{‡¶¶}	1.00	1.00
EPTB	0.74 (0.52–1.05)	0.70 (0.49–1.00) ^{‡¶¶}	1.31 (0.55–3.10)	1.53 (0.77–3.05) ^{‡¶¶}
Site of involvement ⁴				
Lymph node	Referent		Referent	
Vertebrae	0.36 (0.05–2.43)	0.40 (0.07–2.16) ^{‡¶¶}	2.58 (0.14–48.0)	3.17 (0.36–28.3) ^{¶¶}
Pericardium	3.90 (1.64–8.70)	4.07 (1.65–10.05) ^{‡¶¶}	15.61 (1.10–220.9)	15.21 (1.36–169.5) ^{¶¶}
Pleura	3.28 (1.27–8.48)	3.60 (1.35–9.62) ^{‡¶¶}	13.72 (1.92–97.9)	13.55 (1.63–112.7) ^{¶¶}
Other site ⁵	1.33 (0.18–9.62)	1.55 (0.24–10.03) ^{‡¶¶}	4.82 (0.16–144.6)	6.56 (0.49–88.3) ^{¶¶}

Symbols indicate which variables were controlled for in final adjusted model:

[†] : age,

[‡] : sex,

[¶] : HIV status,

^a TB type

* ART denotes antiretroviral therapy, ATT anti-TB treatment, PTB pulmonary tuberculosis, and EPTB extrapulmonary tuberculosis

¹ Defined as death or lost to follow-up. 295 observations included in analysis

² Restricted to patients with known dead vs treatment success outcome. 256 observations included in analysis

³ 92 observations included in poor outcome analysis, 78 observations included in death analysis

⁴ 117 observations included in poor outcome analysis, 102 observations included in death analysis

⁵ Includes meningitis, ascites, osseous, empyema