Published in final edited form as:

Ann Epidemiol. 2014 May ; 24(5): 369–375. doi:10.1016/j.annepidem.2014.01.012.

Diabetes mellitus and risk of all-cause mortality among patients with tuberculosis in the state of Georgia, 2009–2012

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Abstract

Purpose—To estimate the association between diabetes mellitus (DM) and all-cause mortality during tuberculosis (TB) treatment.

Methods—From 2009 to 2012 a retrospective cohort study among reported TB cases in Georgia was conducted. Patients aged ≥ 16 years were classified by DM and HIV status at time of TB diagnosis and followed during TB treatment to assess mortality. Hazard ratios (HR) were used to estimate the association between DM and death.

Results—Among 1,325 patients with TB disease, 151 (11.4%) had DM, 147 (11.1%) were HIV-infected, and 7 (0.5%) had both DM and HIV. Patients with TB-DM were more likely to have

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cavitary lung disease compared to those with TB alone (51.0% vs. 34.7%) and those with TB-HIV were more likely to have military/disseminated disease (12.9% vs. 3.4%) and resistance to rifampin or isoniazid (21.8% vs. 9.0%) compared with those without HIV infection ($p<0.05$). In multivariable analysis, DM was not associated with death during TB treatment (HR 1.22, 95% CI 0.70–2.12) or any death (aOR 1.05, 95% CI 0.60–1.84).

Conclusions—Among TB patients in Georgia, the prevalence of co-morbid DM and co-infection with HIV was nearly identical. In adjusted models, TB patients with DM did not have increased risk of all-cause mortality.

Keywords

Tuberculosis; Diabetes mellitus; Mortality; HIV; Georgia

INTRODUCTION

The incidence of active tuberculosis (TB) disease in the United States (US) has steadily declined during the past two decades from 26,673 reported TB cases (10.4 per 100,000) in 1992 to 9,951 reported cases (3.2 cases per 100,000) in 2012 [1]. Mortality among patients with TB in the US has also decreased. In 1992 the TB-related mortality rate was 0.7 per 100,000 and by 2011 had decreased to 0.2 per 100,000 [2]. Despite these decreases, subgroups of patients with TB remain at higher risk of death. Increased mortality has consistently been reported among those with multidrug-resistant (MDR) TB,[3–5] HIV co-infection,[6, 7] extrapulmonary TB,[8, 9] substance abuse,[10, 11] and concurrent chronic non-communicable diseases [12, 13]. Diabetes mellitus (DM), a non-communicable disease with a rapidly expanding prevalence in the US,[14] has been estimated to increase the risk of active TB disease approximately 3-fold [15] and may impact TB-related mortality [16]. A 2011 meta-analysis estimated that mortality was more likely among patients with TB and DM (TB-DM) compared to those without DM (unadjusted risk ratio [RR] 1.89, 95% CI 1.53–2.36) [17].

While the prevalence of DM among newly diagnosed patients with TB in the US is not well quantified a few regional studies have reported DM prevalence between 14 to 28% among US adults with TB [18–20]. The impact of DM on TB related mortality is incompletely understood and prior studies have generally not assessed the effect of DM on TB mortality in the US. The primary objectives of this study were: 1) to compare the demographic and clinical presentation characteristics of adult patients with TB and DM, TB and HIV, and TB without HIV or DM; 2) to estimate the association between DM and time until death during TB treatment. A secondary objective was to estimate the association between 1) DM and 2) HIV with any death (before or during TB treatment) among patients with TB.

METHODS

Setting and Participants

All TB cases reported between January 2009 and September 2012 in the state of Georgia, US, were included in this retrospective cohort study. In Georgia, all health care providers and laboratories are required by law to report clinical and laboratory confirmed TB cases to

the Georgia Department of Public Health department (GDPH) [21]. Eligible study patients included all patients with pulmonary or extrapulmonary TB (diagnosed by positive culture or a combination of compatible clinical symptoms, radiological findings, and/or response to empiric therapy) aged ≥ 16 years reported to the Georgia state registry during the study period. TB cases were followed during TB treatment until the date of therapy completion, death, loss to follow-up, or until March 2013, whichever occurred first.

Study Measures and Data Collection

The GDPH verified reported TB cases, monitored patients on directly observed therapy (DOT), and was responsible for systematic collection of all patient information. Standardized TB reporting forms documented TB diagnosis, patient demographic and clinical characteristics, and treatment outcomes. All data was entered into the State Electronic Notifiable Disease Surveillance System (SendSS), a secure web-based software tool.

The primary study outcome was time until death, measured among patients who died from any cause during TB treatment. Patients with a date of death (determined from SendSS) prior to TB treatment completion date were defined as a death during TB treatment. Time to death was calculated as the number of days between TB treatment start and death date. Patients who died before initiating TB treatment were defined as death before TB treatment. Any death included patients that died during TB treatment or before TB treatment initiation.

The primary exposures of interest in this study were DM and HIV status. Medical records were reviewed to determine DM status. All patients were asked if they had ever been diagnosed with DM, patients who self-reported having DM were categorized as DM patients. Patients were not systematically screened for DM but had blood chemistry tests (including glucose) performed at the time of TB diagnosis and treatment initiation. Standard state TB protocols included offering all TB patients HIV screening with an Enzyme-Linked Immunoabsorbent Assay (ELISA) test, positive ELISA were confirmed by Western Blot. Patients with missing HIV results were classified as HIV negative.

Additional patient covariates of interest measured by interview in the cohort included demographic information, socio-behavioral characteristics, comorbidities, and clinical features. MDR TB was defined as resistance to both rifampin and isoniazid. Occupation, country of birth, history of homelessness, incarceration history, alcohol use in the past year, and drug use (injection or non-injection) were self-reported during patient interviews conducted by health care providers. End stage renal disease (ESRD) was determined from medical records and patient charts. Sputum acid fast bacilli (AFB) smear status, AFB culture for *Mycobacterium tuberculosis* history of TB, tuberculin skin test (TST) result, chest radiograph findings (e.g., presence of lung cavity or miliary TB), and TB drug susceptibility information was abstracted SendSS.

Data Analyses

Data analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). The association between patient characteristics with TB-DM, TB-HIV, and TB only was

analyzed using bivariate analyses. We used χ^2 tests to calculate p-values for categorical variables, ANOVA procedures to compare differences in normally distributed continuous variables (means), and the Kruskal-Wallis test for comparison of non-normally distributed variables (medians). A two-sided p-value less than 0.05 was considered statistically significant throughout the analyses. Cox proportional hazards regression models were used to estimate the hazard rate ratios (HR) and 95% confidence intervals (CI) for time to mortality during TB treatment. Patients were censored at the time of treatment completion or last documented clinical visit date if death did not occur on or before either date of completion or last visit date. Proportional hazard assumptions were assessed graphically (log negative log curves), with goodness-of-fit tests (Schoenfeld residuals) and using time-dependent models [22]. Logistic regression models were used to estimate the odds ratio (OR) and 95% CI for the outcomes 1) death before TB treatment initiation and 2) any death (before or during TB treatment). Separate regression models and covariate selection strategies were created for estimates of the two primary exposures: 1) DM status and 2) HIV status. Selected covariates considered to be known confounders were included in Cox and logistic regression models based on bivariate associations or biologic plausibility with the primary exposures and outcomes, previous literature, or directed acyclic graph theory [23]. Statistical interaction was assessed between the primary exposures of interest and all covariates included in the final Cox model.

Ethical approval

The study was approved by the Institutional Review Boards (IRB) of Emory University and Georgia Department of Health.

RESULTS

A total of 1,428 patients with TB were reported to the state of Georgia during the study period. After excluding patients <16 years (N=103), 1,325 were included in baseline analyses. A total of 1,238 (93.4%) were included in longitudinal analyses, after excluding patients who died before TB treatment initiation (N=34) or who had no TB treatment follow-up information (N=53).

Among the 1,325 patients with TB included in the study, 151 (11.4%) had DM, 147 patients had HIV (11.1%), and seven (0.5%) patients had both DM and HIV. Most patients were male (66.5%) and US born (54.6%); the most common race/ethnicity was Non-Hispanic Black (48.2%) and the median age was 45 years (Table 1). Compared to patients with TB only (no DM or HIV), TB-DM patients had higher prevalence of ESRD (6.6% vs. 1.6%) but were less likely to be diagnosed in a correctional facility (2.0% vs. 9.4%) ($p<0.01$). Patients with TB and HIV were more likely to report heavy alcohol use (25.2% vs. 14.5%), drug use (28.0% vs. 7.7%), and recent homelessness (29.2% vs. 7.1%) than TB only patients ($p<0.01$) (Table 1).

Clinical TB characteristics at baseline differed among TB-DM patients, TB-HIV patients, and TB only patients (Table 1). TB-DM patients were more likely to have cavitary lung disease at time of TB diagnosis (51%) compared to patients with TB-HIV (19.9%) and TB only (34.7%) ($p<0.01$). Patients with TB-DM were more likely to be sputum AFB smear

positive (52.5%) compared to patients with TB-HIV co-infection (43.7%) and those with TB only (41.4%) ($p=0.06$). Overall extrapulmonary TB was common (28.8%) but more frequent among those patients with TB-HIV co-infection (38.1%) than among patients with TB-DM (25.9%) or TB only (26.6%) ($p<0.01$). Miliary or disseminated TB was more common among those with TB-HIV co-infection compared to patients with TB only (12.9% vs. 3.4%) ($p<0.01$). The overall prevalence of multidrug resistance was low (0.6%) among the cohort. Patients with TB-HIV were more likely to have single drug resistance (i.e., resistance to either isoniazid or rifampin) (21.8%) compared to patients with TB-DM (8.3%) or TB only (9.0%) ($p<0.01$).

Overall, 116 (8.8%) TB patients died, including 34 before TB treatment initiation (Table 1). During TB treatment, 83 (6.4%) patients died including 5.2% (52/1020) of TB only patients, 10.8% (16/151) of TB-DM, 10.1% (14/147) of TB-HIV, and 14.3% (1/7) of patients with DM, HIV, and TB ($p<0.01$). Among TB patients who completed treatment and did not die, the median treatment time was 212 days (interquartile range [IQR] 99 days). In unadjusted analyses, increased age, male sex, white race/ethnicity, being unemployed or retired, born in the US, ESRD, DM, HIV, and baseline positive culture status were associated with increased hazard of death during TB treatment (Table 2).

Compared to TB only patients, the unadjusted hazard of time to death during treatment was greater among TB-DM (crude hazard rate ratio [cHR] 1.88, 95% CI 1.10–3.20) (Table 3 and Figure 1). After adjusting for covariates associated with both mortality during TB treatment and DM status, the adjusted hazard of death among TB-DM patients was 1.22 (95% CI 0.70–2.12) times the hazard of death among TB patients without DM (Table 3). The estimated adjusted odds of any death among TB-DM patients was nearly the same as TB only patients (aOR 1.05, 95% CI 0.60–1.84).

The unadjusted hazard of death during TB treatment among patients with TB-HIV co-infection was 1.59 (95% CI 0.90, 2.79) times the hazard among TB patients who were HIV negative or unknown. After adjusting for covariates, the estimated adjusted hazard of death among TB-HIV patients increased to 2.18 (95% CI 1.15–4.15) times the hazard of death among TB patients without HIV (Table 3). Co-infection with HIV was also associated with increased odds of death before TB treatment initiation (adjusted OR [aOR] 4.42, 95% CI 1.80–10.86) and any death (aOR 3.32, 95% CI 1.74–6.32).

DISCUSSION

In this cohort of patients with TB from the US state of Georgia, DM was common among TB patients (11.5%) and similar in prevalence to co-infection with HIV (11.2%). In unadjusted analysis, DM was found to be associated with a nearly two-fold hazard of all-cause mortality during TB treatment. After adjusting for age and other confounders, TB-DM patients, compared to TB patients without DM, did not have significantly higher hazard of death during TB treatment (aHR 1.22, 95% CI 0.70–2.12). HIV co-infection, a well-described risk factor for poor outcomes among TB patients, was associated with an increased hazard of death during TB treatment (aHR 2.18, 95% CI 1.15–4.15) and any death (aOR 3.32, 95% CI 1.74–6.32).

Although HIV co-infection among TB patients is well-described, we found DM equally as common among this cohort of patients with TB. This finding is important to highlight as DM prevalence is increasing globally[24], which will likely also lead to an increase in TB-DM, a comorbidity that presents several new clinical challenges. The presence of TB may exacerbate hyperglycemia[16, 25], there are potential drug interactions between rifampicin and oral hypoglycemic agents[26], and there may be an increased risk of peripheral neuropathy in TB-DM patients with the use of isoniazid[27].

Several hypotheses have been postulated to explain mechanisms that could lead to increased risk of TB in patients with DM, and increased risk of mortality in TB-DM patients. Both mouse and human models have demonstrated that DM alters adaptive and cell-mediated immune responses [28–30]. Impaired alveolar macrophage activation due to glycation of binding sites may inhibit subsequent granuloma formation in TB-DM patients [31]. In addition, altered T-helper (Th) 1, Th 2, and Th 17 cytokine responses have been demonstrated among patients with TB-DM [29, 32]. Chronic hyperglycemia may disrupt the regulation of key cytokines, such as interferon-gamma,[30, 33] which in turn may increase the *M. tuberculosis* bacterial burden and subsequent risk of death in TB-DM patients.

The majority of previous studies that have examined mortality in TB patients with DM have reported an increased risk of death among TB-DM patients. For example, a 2011 systematic review showed that 95.5% (21 of 23) of studies found an increased unadjusted risk of death among TB-DM patients when compared to TB patients without DM [17]. However, the systematic-review had important limitations. First, follow-up time and mortality measurement was inconsistent across studies, some followed patients to the end of TB treatment while others followed patients beyond TB treatment completion. Second, of the 21 studies that reported increased unadjusted mortality risk, only 9 were powered to detect a statistically significant difference in the comparison, and only 4 studies adjusted for age and other confounders. Our unadjusted estimate (cHR 1.88, 95% CI 1.10–3.20) for death during treatment was remarkably similar to the unadjusted pooled risk ratio (RR) in the systematic review (RR 1.89, 95% CI 1.52–2.36). Our unadjusted estimate was confounded (mostly by age) and after controlling for covariates the adjusted estimate moved closer to the null (aHR 1.22, 95% CI 0.70–2.12). Given our findings and the association of DM with age and age with death, all future studies evaluating the association of DM with death among TB patients should at a minimum control for age.

In the US only three studies, all from Maryland and with low precision, have estimated the effect of DM on mortality during TB treatment [18, 19, 34]. A study by Dooley et al.[19] was the only work to estimate the association between DM and mortality during TB treatment with a model adjusting for age and HIV status (aOR 6.70, 95% CI 1.11–38.20). The two additional studies estimated the odds of death during TB treatment comparing patients with and without DM after adjusting only for age. Fielder et al.[34] estimated the odds of death among TB-DM was 3.80 (95% CI 1.42–10.16) times that of TB only patients, while Oursler et al.[18] estimated the same measure of effect at 6.70 (95% CI 1.57–28.52). In contrast to previous studies, we adjusted for potential socio-economic (race/ethnicity, occupation) and behavioral characteristics (heavy alcohol use) that could confound the association between DM and mortality. Additional geographically diverse studies that 1)

control for confounders and 2) assess DM control and management will provide better measures of association of DM and death among TB patients. Poor blood glucose control and inadequate access to DM care (among patients with TB) in resource limited settings may partially explain differences in the observed risk of mortality across studies. For example, a Tanzanian study of patients with TB conducted from 2006–2008 reported a much stronger association between DM and mortality compared to our findings. [35]

There are important limitations to note in our study. First, we relied on self-report and medical chart abstraction to determine whether TB patients had DM, and therefore the primary exposure of interest was subject to misclassification due to TB patients who did not know they had DM or who had never been screened. Similarly, we were unable to distinguish between type 1 and type 2 DM. However, patients who were classified with DM were unlikely to be non-DM patients, consequently the specificity of DM measurement in our cohort was likely high. Moreover, we do not have reason to believe that the misclassification of DM status was differential with respect to mortality during TB treatment and therefore our estimated effect of the dichotomous exposure (DM) on the outcome (death) is plausibly biased toward the null [36]. Second, our study did not have measures of glucose control or DM duration and therefore we could not estimate the effect of hyperglycemia or chronic DM (vs. acute hyperglycemia). If the effect of DM on mortality during TB treatment is modified by blood glucose level, our estimated null effect could be due to a mixing of the DM patients with higher blood glucose (and higher mortality risk) and those with controlled blood glucose (and lower mortality risk). Third, we did not have any measurements of body mass index (BMI) or anthropometry of TB patients. Similar to measures of glucose control, the effect of DM on mortality during TB treatment may be modified by BMI and our study was unable to assess this potential relationship. Finally, although all-cause mortality in this study was well documented during TB treatment, we were unable to determine if the cause of death was specific to TB disease. Similarly, we did not assess mortality after patients completed TB treatment and were therefore unable to estimate the association between DM and mortality in patients who may have died from TB disease after treatment ended.

Our study had excellent follow-up information from a large, well-characterized cohort of TB patients from US, a major strength of this study. Unlike previously published studies estimating the association between DM and mortality during TB treatment, we were able to estimate the association between DM and time to death adjusting for age, HIV status, and other potentially important confounders. The scope of our study was also innovative. We used survival analysis to estimate the association between DM and all-cause mortality, one of the few studies to do so to date and only the second among TB patients in the US. To our knowledge, no previous studies have compared the clinical presentation of TB-DM patients to clinical characteristics of TB-HIV patients.

Conclusion

With an increasing prevalence of DM across the world, it is critical to improve knowledge regarding the effects of the disease on public health, including co-morbidity with infectious diseases. We showed that DM is common among TB patients in Georgia, with DM co-

morbidity prevalence estimates similar to that of HIV co-infection. This study challenges previous unadjusted findings of increased mortality risk among TB patients with DM. Earlier studies concluded that DM increases the risk of death in TB patients, but we did not find a clinically meaningful association between DM and the hazard of all-cause mortality after adjusting for age, HIV, and other potential confounding factors. Nonetheless, more studies are needed to determine if poorly controlled blood glucose in patients with TB-DM increases the risk of mortality during TB treatment.

LIST OF ABBREVIATIONS AND ACRONYMS

AFB	Acid fast bacilli
aHR	Adjusted hazard ratio
cHR	Crude hazard ratio
CI	Confidence interval
DM	Diabetes mellitus
DOT	Directly observed therapy
ELISA	Enzyme-linked immunoabsorbent assay
EPTB	Extrapulmonary tuberculosis
ESRD	End stage renal disease
GDPH	Georgia Department of Public Health
HIV	Human immunodeficiency virus
HR	Hazard ratio
INH	Isoniazid
IQR	Interquartile range
MDR	Multiple drug-resistant
RIF	Rifampin
RR	Risk ratio
SD	Standard deviation
SendSS	State Electronic Notifiable Disease Surveillance System
TB	Tuberculosis
Th	T-helper
TST	Tuberculin skin test

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Figure 1.

Unadjusted cumulative all-cause mortality among tuberculosis patients with and without diabetes mellitus one year from initiation of TB treatment

Table 1
Diabetes mellitus, HIV, and baseline characteristics of adult TB patients in the state of Georgia 2009–2012

Patient characteristic (at TB treatment start)	No HIV/DM N=1020 N (%)	HIV N=147 N (%)	DM ^A N=151 N (%)	Total ^B N=1318 N (%)	P- value
Age (years)					
Mean (SD)	44.3 (17.8)	41.2 (10.0)	57.4 (14.4)	45.5 (17.3)	<0.01
Median (IQR) ^C	43.0 (27.0)	43.0 (16.0)	56.0 (19.0)	45.0 (26.0)	
16–24 ^B	151 (14.8)	9 (6.1)	0	160 (12.1)	<0.01
25–34	217 (21.3)	33 (22.5)	12 (8.0)	262 (19.9)	
35–44	164 (16.1)	46 (31.3)	11 (7.3)	221 (16.8)	
45–54	195 (19.1)	51 (34.7)	48 (31.8)	294 (22.3)	
55–64	144 (14.1)	7 (4.8)	35 (23.2)	186 (14.1)	
>65	149 (14.6)	1 (0.7)	45 (29.8)	195 (14.8)	
Sex					
Female	353 (34.6)	40 (27.2)	48 (31.8)	441 (33.5)	0.19
Male	667 (65.4)	107 (72.8)	103 (68.2)	877 (66.5)	
Race/Ethnicity					
NH Black ^C	447 (43.9)	114 (77.5)	73 (48.3)	634 (48.2)	<0.01
NH Asian	206 (20.2)	6 (4.1)	22 (14.6)	234 (17.8)	
NH White	171 (16.8)	7 (4.8)	26 (17.2)	204 (15.5)	
Hispanic	194 (19.1)	20 (13.6)	30 (19.9)	244 (18.5)	
Occupation ^C					
Employed	426 (41.8)	44 (29.9)	48 (31.8)	518 (39.3)	<0.01
Unemployed	347 (34.0)	94 (64.0)	53 (35.1)	494 (37.5)	
Retired	108 (10.6)	1 (0.7)	33 (21.9)	142 (10.8)	
Other/unknown ^D	139 (13.6)	8 (5.4)	17 (11.3)	164 (12.4)	
Foreign born ^C					

Patient characteristic (at TB treatment start)	No HIV/DM N=1020 N (%)	HIV N=147 N (%)	DM ^A N=151 N (%)	Total ^B N=1318 N (%)	P-value
No	516 (50.8)	109 (74.2)	92 (60.9)	717 (54.6)	<0.01
Yes	500 (49.2)	38 (25.9)	59 (39.1)	597 (45.4)	
Recent homelessness					<0.01
No	942 (92.9)	102 (70.8)	139 (92.7)	1183 (90.4)	
Yes	72 (7.1)	42 (29.2)	11 (7.3)	125 (9.6)	
In correctional facility when TB diagnosed ^B					0.01
No	920 (90.6)	133 (91.7)	147 (98.0)	1200 (91.6)	
Yes	95 (9.4)	12 (8.3)	3 (2.0)	110 (8.4)	
Heavy alcohol use					<0.01
No	858 (85.5)	107 (74.8)	129 (86.0)	1094 (84.4)	
Yes	146 (14.5)	36 (25.2)	21 (14.0)	203 (15.7)	
Drug use					<0.01
No	928 (92.3)	103 (72.0)	142 (94.0)	1173 (90.3)	
Yes	77 (7.7)	40 (28.0)	9 (6.0)	126 (9.7)	
End stage renal disease ^C					<0.01
No	1004 (98.4)	139 (94.6)	141 (93.4)	1284 (97.4)	
Yes	16 (1.6)	8 (5.4)	10 (6.6)	34 (2.6)	
TB Characteristics					
AFB smear status					0.06
Negative	542 (58.6)	76 (56.3)	64 (47.8)	682 (57.1)	
Positive	383 (41.4)	59 (43.7)	70 (52.2)	512 (42.9)	
Unavailable	95	12	17	124	
Baseline culture					0.53
Negative	177 (17.4)	26 (17.7)	18 (11.9)	221 (16.8)	
Pulm TB positive	576 (56.5)	89 (60.5)	89 (58.9)	754 (57.2)	

Patient characteristic (at TB treatment start)	No HIV/DM N=1020 N (%)	HIV N=147 (11.2) N (%)	DM ^A N=151 (11.5) N (%)	Total ^B N=1318 N (%)	P- value
EPTB positive	192 (18.8)	24 (16.3)	34 (22.5)	250 (19.0)	
Unavailable	75 (7.4)	8 (5.4)	10 (6.6)	93 (7.1)	
TB site of disease					
Pulm only	749 (73.4)	91 (61.9)	112 (74.2)	952 (72.2)	<0.01
Pulm and EPTB	66 (6.5)	30 (20.4)	14 (9.3)	110 (8.4)	
EPTB only	205 (20.1)	26 (17.7)	25 (16.6)	256 (19.4)	
Previous TB treatment					
No	959 (94.5)	135 (91.8)	142 (94.0)	1236 (94.1)	0.44
Yes	56 (5.5)	12 (8.2)	9 (6.0)	77 (5.9)	
TST status					
Negative	175 (23.5)	43 (55.8)	42 (42.4)	260 (28.3)	<0.01
Positive	569 (76.5)	34 (44.2)	57 (57.6)	660 (71.7)	
Not done/unknown	276	70	52	398	
Any lung cavity					
No	643 (65.3)	113 (80.1)	72 (49.0)	828 (65.0)	<0.01
Yes	342 (34.7)	28 (19.9)	75 (51.0)	445 (35.0)	
Miliary TB					
No	933 (96.6)	122 (87.1)	139 (96.5)	1194 (95.5)	<0.01
Yes	33 (3.4)	18 (12.9)	5 (3.5)	56 (4.5)	
DST profile					
None to RIF/INH	683 (90.6)	85 (77.3)	109 (90.1)	877 (89.0)	<0.01
RIF or INH	68 (9.0)	24 (21.8)	10 (8.3)	102 (10.4)	
MDR	3 (0.4)	1 (0.9)	2 (1.7)	6 (0.6)	
Unavailable	266	37	30	333	
TB Outcomes					

Patient characteristic (at TB treatment start)	No HIV/DM N=1020 (77.4) N (%)	HIV N=147 (11.2) N (%)	DM ^A N=151 (11.5) N (%)	Total ^B N=1318 N (%)	P- value
Treatment duration (days) ^E					
Mean (SD)	221 (101)	282 (127)	250 (137)	231 (111)	<0.01
Median (IQR)	207 (90)	292 (164)	223 (112)	212 (99)	
Death before treatment initiation					
No	997 (97.8)	139 (94.6)	148 (98.0)	1284 (97.4)	0.07
Yes	23 (2.3)	8 (5.4)	3 (2.0)	34 (2.6)	
Death during TB treatment					
No	945 (94.8)	125 (89.9)	132 (89.2)	1202 (93.6)	<0.01
Yes	52 (5.2)	14 (10.1)	16 (10.8)	82 (6.4)	
Time to death during treatment (days) ^F					
Mean (SD)	81 (82)	77 (82)	82 (90)	81 (83)	0.32
Median (IQR)	57 (82)	46 (139)	64 (112)	57(87)	
Death before or during TB treatment					
No	945 (92.7)	125 (85.0)	132 (87.4)	1202 (91.2)	<0.01
Yes	75 (7.4)	22 (15.0)	19 (12.6)	116 (8.8)	

Abbreviations: DM-diabetes mellitus; SD-standard deviation; IQR-interquartile range; NH-Non-Hispanic; Pulm-pulmonary; EPTB-Extrapulmonary TB; RIF-Rifampin; INH-Isoniazid; AFB-acid fast bacilli; MDR-multi-drug resistant

^A Diabetes mellitus status was self-reported or from abstracted from medical records.

^B Patients with both HIV and DM (n=7) are excluded from the table.

^C Statistically significant, two-sided p-value <0.05

^D Other indicates disabled, not eligible for employment, student, or homemaker E.

^E Among patients with treatment completion date, excluding deaths during treatment (N=1155)

^F Among patients who died during TB treatment (N=83)

Table 2

Unadjusted hazard rate ratios for baseline patient characteristics associated with death during TB treatment among patients in the state of Georgia, 2009–2012

Patient characteristic (at TB treatment start)	Died N=83/1238 (6.7) Died/N (%)	cHR (95% CI)
Diabetes mellitus		
No	66/1089 (6.1)	1.00
Yes	17/149 (11.4)	1.88 (1.10, 3.20)
Age (years)		
16–34	6/402 (1.5)	1.00
35–44	9/213 (4.2)	2.78 (0.99, 7.8)
45–54	19/276 (6.9)	4.58 (1.83,11.48)
55	49/347 (14.1)	10.24 (4.39, 23.92)
Sex		
Female	14/414 (3.4)	1.00
Male	69/824 (8.4)	2.55 (1.44, 4.53)
Race/ethnicity		
White	20/194 (10.3)	1.00
NH Black	54/592 (9.1)	0.85 (0.51, 1.42)
NH Asian	4/220 (1.8)	0.17 (0.06, 0.49)
Hispanic	5/226 (2.2)	0.21 (0.08, 0.56)
Occupation		
Employed	11/492 (2.2)	1.00
Unemployed	34/479 (7.1)	3.17 (1.61, 6.26)
Retired	24/124 (19.4)	9.87 (4.83, 20.16)
Other/unknown	14/143 (9.8)	4.84 (2.20,10.66)
Foreign born		
No	69/669 (10.3)	1.00
Yes	14/568 (2.5)	0.24 (0.13, 0.42)
Recent homeless		
No	75/1111 (6.8)	1.00
Yes	7/124 (5.7)	0.80 (0.37, 1.74)
Currently in correctional facility		
No	81/1132 (7.2)	1.00
Yes	1/103 (1.0)	0.14 (0.02, 1.03)
Heavy alcohol use		
No/unknown	65/1047 (6.2)	1.00
Yes	18/191 (9.4)	1.51 (0.90, 2.55)

Patient characteristic (at TB treatment start)	Died N=83/1238 (6.7) Died/N (%)	cHR (95% CI)
Drug use		
No	73/1113 (6.6)	1.00
Yes	6/117 (5.1)	0.73 (0.32, 1.68)
End stage renal disease		
No	75/1206 (6.2)	1.00
Yes	8/32 (25.0)	4.21 (2.03, 8.73)
HIV serologic status		
Negative/unknown	68/1098 (6.2)	1.00
Positive	15/140 (10.7)	1.59 (0.90, 2.79)
AFB sputum smear status		
Negative	33/655 (5.0)	1.00
Positive	35/498 (7.0)	1.40 (0.87, 2.25)
Unknown	15/85 (17.7)	3.74 (2.03, 6.89)
Baseline culture		
Negative/unknown	12/298 (4.0)	1.00
Positive	71/940 (7.6)	1.86 (1.01, 3.43)
TB site of disease		
Pulmonary only	56/913 (6.1)	1.00
Pulmonary and extra-pulmonary	11/105 (10.5)	1.67 (0.87, 3.18)
Extra-pulmonary only	16/220 (7.3)	1.09 (0.63, 1.91)
Previous TB treatment		
No	78/1167 (6.7)	1.00
Yes	4/70 (5.7)	0.86 (0.31, 2.34)
Cavitary lung disease on chest radiograph at time of TB diagnosis		
No	54/780 (6.9)	1.00
Yes	28/427 (6.6)	0.95 (0.60, 1.51)
Miliary/Disseminated TB		
No	78/1187 (6.6)	1.00
Yes	5/51 (9.8)	1.51 (0.61, 3.72)
Drug Susceptibility		
None to RIF or INH	59/827 (7.1)	1.00
Single Drug (RIF or INH)	7/96 (7.3)	0.97 (0.44, 2.13)
MDR-TB	1/6 (16.7)	1.86 (0.26, 13.57)
Unavailable	16/309 (5.2)	0.73 (0.42, 1.27)

Abbreviations: cHR-crude hazard ratio; CI-confidence interval; STD-standard deviation; IQR-interquartile range; NH-Non-Hispanic; RIF-Rifampin; INH-Isoniazid; AFB-acid fast bacilli; MDR-multi-drug resistant (resistance to at least both INH and RIF)

Table 3

Crude and adjusted estimates of the association between DM and HIV with death before TB treatment, during TB treatment, and any death among TB patients in the state of Georgia, 2009–2012

Models	Death before TB treatment		Death during TB treatment		Any death	
	cOR (95% CI)	aOR (95% CI)	cHR (95% CI)	aHR (95% CI)	cOR (95% CI)	aOR (95% CI)
1. Diabetes mellitus ^A						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	0.71 (0.21, 2.35)	0.42 (0.13, 1.42) ^C	1.88 (1.10, 3.20)	1.22 (0.70, 2.12) ^D	1.60 (0.96, 2.67)	1.05 (0.60, 1.84)
2. HIV status ^B						
Negative/unknown	1.00	1.00	1.00	1.00	1.00	1.00
Positive	2.41 (1.07, 5.43)	4.42 (1.80, 10.86)^C	1.59 (0.90, 2.79)	2.18 (1.15, 4.15)	2.01 (1.23, 3.29)	3.32 (1.74, 6.32)

^A **Models 1:** Three models were used to estimate the association between DM and death (defined separately in each of the three adjusted columns). In addition to DM, models were adjusted for age, sex, race/ethnicity, occupation, foreign born, heavy alcohol use, HIV status, and baseline TB culture.

^B **Models 2:** Three models were used to estimate the association between HIV and death (defined separately in each of the three adjusted columns). In addition to HIV, models were adjusted for age, sex, race/ethnicity, occupation, foreign born, DM, ESRD, heavy alcohol use, drug use, and baseline TB culture.

^C Adjusted for sex and age only.

^D In the adjusted model age, male sex, unemployed status, and HIV positive remained statistically ($p < 0.05$) associated with death during TB treatment.

Abbreviations: cOR-crude odds ratio; CI-confidence interval; aOR-adjusted odds ratio; cHR-crude hazard ratio; aHR-adjusted hazard ratio