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Kennedy Anna Houck   April 15, 2022
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Diabetes mellitus and tuberculosis treatment outcomes: Assessments of interactions between

hyperglycemia and human immunodeficiency virus in the state of Georgia, 2015-2020

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An abstract of

A thesis submitted to the Faculty of the

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Abstract

Diabetes mellitus and tuberculosis treatment outcomes: Assessments of interactions between hyperglycemia and human immunodeficiency virus in the state of Georgia, 2015-2020
By Kennedy Houck

Background: Separately diabetes mellitus (DM) and human immunodeficiency virus (HIV) are risk factors for poor outcomes among people with tuberculosis (TB). To date, information on the joint impact of diabetes and HIV on TB outcomes is limited. We aimed to (1) estimate the association between hyperglycemia with all-cause mortality and sputum culture conversion, and (2) estimate the effect of joint exposure to diabetes and HIV on TB outcomes.

Methods: We conducted a retrospective cohort study among patients with TB in Georgia between 2015-2020. Laboratory and state surveillance records were used to classify patients by diabetes and HIV status. Patients were followed during TB treatment to compare mortality and culture conversion by diabetes and HIV status. Robust Poisson regression was used to estimate risk ratios for all-cause mortality. Cox regression was used to estimate hazard ratios for time to culture conversion. Interaction between DM and HIV was assessed on the additive scale with risk differences and on the multiplicative scale with product terms in regression models.

Results: Of 1109 patients included in the analysis, 318 (28.7%) had diabetes, 92 (8.3%) were HIV-positive, and 15 (1.4%) had diabetes and HIV. Overall, 9.8% died during treatment. Diabetes was associated with an increased risk of death among patients with TB (aRR = 2.59, 95% CI: 1.62, 4.13). The hazard rate of conversion was similar among patients with and without diabetes (aHR = 1.07, 95% CI: 0.86, 1.33). We observed a non-significant trend toward biologic interaction between DM and HIV with all-cause mortality (AP = 23.30%, 95% CI: -48.40%, 95.00%), but did not observe interaction on the multiplicative scale (HIV-positive aRR = 3.03, HIV-negative aRR = 2.81, p = 0.54).

Conclusions: More than one-quarter of patients with TB in Georgia had diabetes at time of TB diagnosis. Diabetes alone and co-occurring diabetes and HIV were associated with an increased risk of mortality during TB treatment. These data suggest a potential synergistic effect between diabetes and HIV with increased risk of all-cause mortality during TB treatment.

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CHAPTER I
INTRODUCTION

1. Background

Tuberculosis (TB) is an infectious disease caused by the bacteria *Mycobacterium tuberculosis* (*M. tb*). The disease most commonly affects the lungs, but it can occur anywhere in the body. TB is spread via person-to-person transmission when a person with pulmonary TB coughs, sneezes, or talks (WHO, 2021b). Two TB-related conditions, latent TB infection and active TB disease, exist. Individuals with latent TB infection are infected with *M. tb* bacteria, but do not exhibit symptoms nor spread TB infection to others, whereas individuals with active pulmonary TB disease are infectious (CDC, 2014). An estimated two billion people are infected with *Mycobacterium tuberculosis* globally, representing 25% of the global population (CDC, 2021b). In 2020, approximately 10 million people developed active TB disease worldwide, with 1.5 million people dying of TB that same year (WHO, 2021b). Prior to COVID-19, tuberculosis was the leading cause of death by an infectious disease worldwide (WHO, 2021b). Upward of 13 million people in the United States are living with latent TB infection (CDC, 2022b). In 2021, a total of 7,860 cases of TB were reported in the U.S., an incidence rate of 2.4 per 100,000 persons (CDC, 2022b). Tuberculosis elimination, defined as less than one TB case per one million persons, represents a major policy objective in the United States. While the burden of TB in the United States has decreased, comorbidities such as human immunodeficiency virus (HIV) and diabetes mellitus (DM) present a challenge for U.S. TB elimination efforts.

Diabetes mellitus (DM) is a chronic disease that occurs when there is a deficiency in insulin production, or the body does not use insulin efficiently (WHO, 2021a). Insulin is a hormone that promotes the regulation of blood sugar levels. An estimated 37.3 million people in the United States have diabetes, representing 11.3% of the U.S. population (CDC, 2022a). Over

96 million people ages 18 years or older, 38% of the U.S. adult population, have pre-diabetes, a condition that is likely to result in progression to diabetes. Individuals with diabetes are more likely to develop infections than those without diabetes. Additionally, patients with DM are also more likely to experience worse outcomes from infection than those without DM (Geerlings & Hoepelman, 1999). Possible causes include deficiencies in innate immunity and an increased affinity of microorganisms to diabetic cells (Geerlings & Hoepelman, 1999). Mechanisms that impair host response to infection include suppression of cytokine production, defects in phagocytosis, dysfunction of immune cells, such as neutrophils, and failure to kill microorganisms (Berbudi et al., 2020).

Diabetes represents an important risk factor for lower respiratory infections, including TB. Patients with diabetes are at a three-fold increased risk of developing TB disease compared to those without diabetes (Jeon & Murray, 2008). Diabetes can impair the innate immune response of a host upon their first encounter with *M. tb* bacteria. Diabetes is associated with reduced phagocytosis within the first several weeks after infection with *M. tb* bacteria, findings that are consistent with observations in mouse models (Restrepo, 2016). Phagocytosis is a critical component of host innate immunity, as it signals the adaptive immune response of the host. Delays in the signaling of cell-mediated immunity contribute to a higher risk for TB infection and disease among patients with diabetes (Restrepo, 2016). Once individuals with diabetes are infected with *M. tb* bacteria, observed reductions in immune response, such as lower proportions of activated macrophages and pro-inflammatory cytokines, result in a higher frequency of adverse outcomes, including death (Restrepo, 2016).

Human immunodeficiency virus (HIV) is a virus that attacks the white blood cells of the host's immune system (WHO, 2022). HIV is transmitted by coming into direct contact with body

fluids containing the virus, such as blood, semen, and breast milk (HHS, 2019). In destroying

CD4 cells, a specific type of white blood cell, HIV weakens an individual's ability to fight

certain infections, such as tuberculosis. In 2019, an estimated 1.2 million people were living with

HIV, and 36,801 people were newly diagnosed with HIV in the United States (CDC, 2021a). The

hallmark of HIV infection is the gradual depletion of T-lymphocytes. As a result of

immunodeficiency, people living with HIV are at an increased risk of developing infections.

Both innate and adaptive immune responses of the host are affected. Two key mechanisms of

innate immunity, the activation of natural killer (NK) cells and the production of Type I-IFN, are

greatly impacted during HIV infection (Boasso et al., 2009). NK cells control microbial

infections by eliminating infected cells in the body. Type I-IFN help to prime the adaptive

immune response within a host (Boasso et al., 2009). HIV infection also leads to the

dysregulation of the adaptive immune response. HIV both depletes and alters CD4 T-cells within

a host (Boasso et al., 2009). CD4 cells are vital in immune response by stimulating other immune

cells, such as macrophages, B cells, and CD8 T-cells to fight infection. Human

immunodeficiency virus infection represents an important risk factor for opportunistic infections,

such as tuberculosis. HIV is the biggest risk factor for progression from latent TB infection to

active TB disease (CDC, 2016). A report published by the World Health Organization on Global

TB Control suggests that HIV is associated with a 37-fold increased risk of developing active TB

(Getahun et al., 2010). HIV infection increases the risk of progression to active TB disease by

targeting *M. tb*-specific T cells and polyfunctional T cells, and impairing TNF-mediated

apoptosis (Bruchfeld et al., 2015). Selective depletion of *M. tb*-specific CD4 T cells in HIV-

infected patients inhibits the host immune response to *M. tb* bacteria. Additionally, HIV

coinfected patients have been shown to have reduced numbers of polyfunctional T cells, which

are essential in host protection against *Mycobacterium tuberculosis* (Bruchfeld et al., 2015).

Finally, the effect of HIV and *M. tb* infection on macrophage apoptosis results in a delay of

antigen-specific immune responses (Bruchfeld et al., 2015). TB/HIV coinfection can also

increase the risk of progression to AIDS and the risk of death. HIV-positive TB patients have

been shown to have a four-fold increased risk of death compared to HIV-negative TB patients

from nine European countries (Karo et al., 2016). In patients who are coinfected, host responses

to *M. tb* increase HIV viral replication, leading to a depletion of cellular immunity (Gebremariam

et al., 2016). HIV infection can also cause unusual presentation of TB disease in patients, such as

smear negative pulmonary TB or extrapulmonary TB, leading to delayed diagnoses of TB, and

increasing the risk of death among these patients (Gebremariam et al., 2016).

Previous studies have reported that both HIV and diabetes are associated with poor TB

treatment outcomes (Adamu et al., 2017, Ali et al., 2016, Alisjahbana et al., 2007, Ambadekar et

al., 2015, Ambrosetti et al., 1996, Bashar et al., 2001, Centis et al., 1998, Chiang et al., 2009,

Dooley & Chaisson, 2009, Faurholt-Jepsen et al., 2013, Fielder et al., 2002, Gatechompol et al.,

2019, Gebremariam et al., 2016, Hasibi et al., 2008, Lawn et al., 2006, Lindoso et al., 2008,

Mboussa et al., 2003, Ogyiri et al., 2019, Oursler et al., 2002, Wang et al., 2009, Workneh et al.,

2016); however, none of these studies have assessed the joint impact of exposure to HIV and

diabetes. Well established factors associated with mortality and poor TB treatment outcomes

include male gender (Abebe & Angamo, 2015, Melese & Zeleke, 2018), older age (Abebe &

Angamo, 2015, Melese & Zeleke, 2018, Wen et al., 2018), and substance use (Chenciner et al.,

2021). Additional studies are needed to evaluate whether joint exposure to diabetes and HIV is

associated with poor TB treatment outcomes, such as mortality. A better understanding of the

interaction between diabetes and HIV with TB outcomes may help to inform treatment of TB disease in adults with HIV and/or diabetes.

We conducted a retrospective cohort study in the state of Georgia. In 2020, Georgia ranked sixth in the United States for the number of new TB cases among reporting states (GA DPH, 2021). In 2020, there were 221 cases reported in the state, for a case rate of 2.1 cases per 100,000 persons (GA DPH, 2021). Additionally, as of 2021, approximately 1 million adults, or 12.4% of the Georgia state adult population, had diabetes (American Diabetes Association, 2021). In 2019, there were 56,446 people living with HIV in Georgia, a case rate of 639 cases per 100,000 persons (AIDSVu, 2021).

2. Gaps and Purpose of Study

Previous studies have largely focused on the effects of HIV coinfection on TB treatment outcomes. Given that more people with TB are currently living with diabetes than HIV infection globally (Araia et al., 2020), it is important to evaluate the impact of diabetes co-occurrence on TB treatment outcomes. Using a retrospective cohort study, we hypothesized that diabetes is associated with poor TB treatment outcomes, and HIV coinfection would interact synergistically to negatively influence treatment outcomes. The main objectives of this study were:

1. To estimate the association between hyperglycemia, including diabetes and pre-diabetes, with all-cause mortality and *Mycobacterium tuberculosis* sputum culture conversion, and

2. To estimate the impact of joint exposure and statistical interaction of diabetes and HIV on TB treatment outcomes.

CHAPTER II

MANUSCRIPT

Introduction

Tuberculosis (TB) represents the second leading cause of death by an infectious disease worldwide. In 2020, there were 7,174 reported cases of TB in the United States, an incidence rate of 2.2 cases per 100,000 persons [1]. In 2019, there were 526 TB-related deaths, a rate of 0.2 deaths per 100,000 persons [2]. Since 1992, tuberculosis (TB)-related deaths in the United States have declined by 69.1% [3]. The risk of mortality, however, remains high for patients with comorbidities. Comorbidities such as human immunodeficiency virus (HIV) and diabetes mellitus (DM) place patients with TB at a higher risk of death.

In low burden settings, such as the United States, HIV has been estimated to increase the risk of death four-fold among patients with TB (95% CI 2.31, 7.99) [4]. Co-occurrence with diabetes also greatly complicates the management of TB disease. A meta-analysis conducted in both high and low burden settings suggests that diabetes is associated with a 1.89-fold increased risk of death among patients with TB (95% CI: 1.52, 2.36) [5]. The large prevalence of people living with HIV in the United States, and the increase in the prevalence of diabetes mellitus presents a new challenge for TB control in the country. In 2020, 4.8% of patients with TB had HIV in the United States [1]. The same year, an estimated 22.5% of patients with TB in the United States had diagnosed diabetes [1].

Twenty-seven previous epidemiologic studies conducted in a variety of settings have reported associations of diabetes and mortality among patients with TB, but the results have been inconsistent. Fourteen of the studies have reported statistically significant associations between diabetes comorbidity and mortality among patients with TB [6-19]. Thirteen studies did not

report a statistically significant association between diabetes comorbidity and mortality [20-32].
However, none of these studies assessed the joint impact of exposure to HIV and diabetes on
mortality and other TB treatment outcomes. Given current gaps in knowledge, we aimed to (1)
estimate the association between hyperglycemia (including diabetes and pre-diabetes) with all-
cause mortality and *Mycobacterium tuberculosis* sputum culture conversion and (2) to estimate
the impact of interaction between diabetes and HIV with TB treatment outcomes.

Methods

Study Design and Population

We conducted a retrospective cohort study among all tuberculosis cases reported in the
state of Georgia, United States between January 2015 and December 2020. In the state of
Georgia, all clinical and laboratory-confirmed cases of tuberculosis are reported to the
Department of Health. Patients were eligible for the cohort study if they had pulmonary or
extrapulmonary TB diagnosed by a positive culture of sputum or tissue, a positive nucleic acid
amplification (NAA) result, both compatible clinical symptoms and radiological findings, or a
combination of positive culture or tissue, clinical symptoms, and radiological findings. Eligible
study patients were aged 16 years or older, did not have a previous diagnosis of TB, and were
verified TB cases reported to the Georgia registry during the study period. Patients were
excluded from the study if they did not have a diabetes status indicated in their medical record,
or if they were missing both blood glucose or hemoglobin A1c laboratory results. Study patients
were followed during TB treatment until date of treatment completion, death, or loss to follow-
up, whichever event occurred first.

Study Measures and Data Collection

Study data were abstracted from the State Electronic Notifiable Disease Surveillance System (SendSS), a web-based database used to capture notifiable diseases in Georgia. SendSS records included patient-level demographic and clinical characteristics, medical history, and treatment outcomes, including death. The primary study outcome was all-cause mortality before or during TB treatment. Death before TB treatment was defined as death from any cause after TB diagnosis prior to treatment initiation. Death during TB treatment was defined as death from any cause before treatment completion or within 7 days of the treatment completion date. A secondary study outcome was time to sputum culture conversion. *Mycobacterium tuberculosis* (*M. tb*) sputum culture conversion was defined as the point at which *M. tb* bacteria was no longer detected in a patient's sputum sample. Date of consistent negative culture collection was obtained from SendSS. Date of consistent negative culture collection was the date at which two consecutive negative cultures, at least 30 days apart, were collected. Time until culture conversion during TB treatment was calculated as the number of days between treatment initiation and date of collection of first of two negative cultures.

The primary exposures of interest were diabetes status and HIV status. Diabetes status was ascertained through medical and laboratory records in SendSS. Study patients' diabetes status was defined as either: (1) no diabetes, (2) pre-diabetes, or (3) diabetes. Patients were classified as no diabetes if they did not have a diagnosis of diabetes mellitus (type 1 or 2) in their medical record and did not have a non-fasting blood glucose result greater than 140 mg/dL or a hemoglobin A1c result greater than 5.7%. If study patients did not have a diagnosis of diabetes mellitus (type 1 or 2) in their medical record, but had at least one non-fasting blood glucose result between 140 mg/dL and 199 mg/dL or a hemoglobin A1c result between 5.7% and 6.5%,

their diabetes status was pre-diabetes. Study patients' diabetes status was defined as diabetes if they had a diagnosis of diabetes mellitus (type 1 or 2) in their medical record or they had at least one non-fasting blood glucose result greater than 200 mg/dL or one hemoglobin A1c result greater than 6.5%. HIV status was ascertained through medical records in SendSS. If a study patient had a missing HIV result, they were classified as HIV unknown.

Other variables of interest in this study included demographic and social information, patient comorbidities, and clinical characteristics. Demographic information, such as age, sex, race, and ethnicity, was abstracted from the Report of Verified Case of Tuberculosis (RVCT) form in SendSS. The RVCT form is completed by interview by health care staff when a patient is diagnosed with TB. Social information, such as recent homelessness, incarceration, and alcohol and other substance use, was also obtained from the RVCT form in SendSS. Information on patient comorbidities, such as end stage renal disease (ESRD), was abstracted from patient medical records in SendSS. Finally, information on TB clinical features, such as baseline culture, site of TB disease, TST status, and drug susceptibility profile, was obtained from the RVCT form in SendSS.

Data Analyses

Bivariate analyses were conducted to compare unadjusted relationships between patient characteristics with diabetes status (primary exposure) and TB outcomes (primary outcome). To calculate p-values, we used the chi-square test for categorical variables, and the Kruskal-Wallis test for non-normally distributed continuous variables. Robust Poisson regression models were used to estimate the risk ratios (RRs) and 95% confidence intervals (CIs) for the relationship between diabetes and death before or during TB treatment [33]. We used Cox regression to

estimate hazard rate ratios (HRs) and 95% CIs for the outcome time to culture conversion. The proportional hazards assumption was assessed using log-log survival curves, Schoenfeld residuals, and time-dependent models. Covariates known to be associated with the outcomes and exposures based on review of literature and directed acyclic graph (DAG) theory were included in the Cox and robust Poisson regression models [34]. Biological interaction between HIV and diabetes and HIV and hyperglycemia was assessed to determine whether both risk factors worked synergistically to increase all-cause mortality among patients with TB. We evaluated biological interaction using three measures: (1) relative excess risk due to interaction (RERI), (2) attributable proportion due to interaction (AP), and (3) synergy index (S). If the 95% CI of the RERI and AP included 0.0 and the 95% CI of the synergy index included 1.0, we concluded there was no biological interaction [35]. Statistical interaction on the multiplicative scale was evaluated by including cross-product terms within multivariable models and calculating a likelihood ratio test statistic. Statistical analyses were performed using R software, version 1.3.1093 (R Core Team, Vienna, Austria).

Sensitivity and subgroup analyses

We performed sensitivity analyses to quantify systematic errors due to exclusion of participants with a missing loss to follow-up date for time to culture conversion analysis. To quantify error, we performed two additional regressions including those with a missing loss to follow-up date to determine changes in our estimates of the association between diabetes status and time to culture conversion. In the primary model, the 24 censored patients with a missing lost to follow-up date were excluded. In the first sensitivity model we included these patients and assigned them a censorship date six months after treatment start date. In the second model, the 24

censored patients with a missing lost to follow-up date were assigned a survival time equal to the median time to conversion for all members of the cohort. Cox regression models were used to evaluate the association between diabetes status and time to conversion in all models.

Subgroup analyses were performed to compare the demographic characteristics of patients without diabetes status information to those with a known diabetes status. Bivariate analyses were conducted to compare unadjusted relationships between characteristics with diabetes status and TB outcomes. To calculate p-values comparing values for patients without diabetes to those with an unknown diabetes status, the chi-square test for categorical variables and the Kruskal-Wallis test for non-normally distributed continuous variables were used.

Results

Study population and baseline characteristics

A total of 1703 verified TB cases were reported in SendSS between 2015 and 2020, of whom 1109 (65.1%) were 16 years or older, did not have a previous diagnosis of TB, and had a known diabetes status (Figure 1). Among the 1109 patients included in the analysis, 318 (28.7%) had diabetes, 149 (13.4%) were classified as having pre-diabetes, and 642 (57.9%) did not have diabetes (Table 1). A total of 391 patients had an unknown diabetes status and were excluded from the analysis (Supplement Table A). Of the 1109 patients, 92 (8.3%) were HIV-positive, 970 (87.5%) were HIV-negative, and 47 (4.2%) had an unknown HIV status. A total of 15 (1.4%) patients had both HIV and diabetes, and 11 (1.0%) had HIV and pre-diabetes (Table 1). Most TB patients were male (66.6%), non-Hispanic Black (45.3%), and non-U.S.-born (51.6%), with a median age of 48.0 years (IQR = 28.0) (Table 1).

Compared to TB patients without diabetes, TB patients with diabetes were more likely to be non-U.S.-born (57.1% vs. 49.4%, $p = 0.02$), and have end-stage renal disease (4.4% vs. 1.3%, $p < 0.01$); they were less likely to experience recent homelessness (4.8% vs. 8.5%, $p = 0.04$), and be HIV-positive (5.1% vs. 10.6%, $p < 0.01$). TB patients with diabetes were more likely to have a positive AFB smear (52.8% vs. 40.2%, $p < 0.01$), a positive baseline culture (87.3% vs. 77.4%, $p < 0.01$), and have PTB only (76.4% vs. 67.7%, $p = 0.02$) compared to those without diabetes. Compared to TB patients without diabetes, TB patients with pre-diabetes were less likely to have end-stage renal disease (0.7% vs. 1.3%, $p = 0.03$). TB patients with pre-diabetes were more likely to have a positive baseline culture (77.9% vs. 77.4%, $p = 0.01$) (Table 1).

All-cause mortality before or during TB treatment

Of the 1109 patients with TB, 109 (9.8%) died before or during TB treatment, including 56 (17.6%) of those with diabetes, 17 (11.4%) with pre-diabetes, and 36 (5.6%) with no diabetes ($p = 0.04$) (Table 2). In unadjusted analyses diabetes (cRR = 3.14, 95% CI: 2.11, 4.67) and pre-diabetes (cRR = 2.03, 95% CI: 1.18, 3.52) were associated with an increased risk of death among TB patients (Table 2). After adjusting for covariates, diabetes status was associated with an increased risk of death among TB patients (aRR = 2.59, 95% CI: 1.62, 4.13); pre-diabetes was not significantly associated with an increased risk of death (aRR = 1.89, 95% CI: 0.99, 3.61) (Table 4). Other factors associated with all-cause mortality included older age, occupation, heavy alcohol use, ESRD, positive AFB smear status, positive baseline culture, and miliary TB. Non-U.S.-born status and positive TST status at baseline were associated with a decreased risk of death (cRR = 0.52, 95% CI: 0.36, 0.76; cRR = 0.28, 95% CI: 0.13, 0.58) (Table 2).

Biologic and statistical interaction between diabetes and HIV with mortality

In analyses to assess biologic interaction between diabetes and HIV among patients with TB, we found the risk of all-cause mortality was highest among HIV-positive patients with diabetes (4/15, 26.7%) and HIV-negative patients with diabetes (45/281, 16.0%). Patients with HIV only (6/66, 9.1%) and patients with neither diabetes nor HIV (26/559, 4.7%) had the lowest risk of all-cause mortality (Table 5). We observed a trend toward synergism between HIV and diabetes (RERI = 1.34, 95% CI: -3.80, 6.47; AP = 23.30%, 95% CI: -48.40%, 95.00%; S = 1.39 (0.44, 4.41), yet results were not statistically significant (Table 5). In evaluating biologic interaction between hyperglycemia and HIV among patients with TB, the risk of all-cause mortality was highest among HIV-positive patients with hyperglycemia (5/26, 19.2%) and HIV-negative patients with hyperglycemia (57/411, 13.9%). Patients with HIV only (6/66, 9.1%) and neither hyperglycemia nor HIV (26/559, 4.7%) had the lowest risk of mortality (Table 5). We did not find evidence of biologic interaction between HIV and hyperglycemia in patients with TB (RERI = 0.20, 95% CI: -3.48, 3.87; AP = 4.80%, 95% CI: -80.90%, 90.50%; S = 1.07 (0.32, 3.52).

We also assessed interaction between diabetes and HIV with TB outcomes on the multiplicative scale. Among HIV-negative patients with TB, diabetes (cRR = 3.44, 95% CI: 2.17, 5.46) and pre-diabetes (cRR = 1.98, 95% CI: 1.03, 3.83) were associated with an increased risk of death before or during TB treatment (Table 3). After adjusting for age, sex, alcohol use, non-U.S.-born status, race/ethnicity, occupation, and baseline culture, the risk of death among HIV-negative TB patients with diabetes (aRR = 2.81, 95% CI: 1.60, 4.96) and pre-diabetes (aRR = 1.97, 95% CI: 0.91, 4.24) decreased slightly (Table 4). In unadjusted analyses among HIV-positive TB patients, diabetes and pre-diabetes were not significantly associated with an

increased risk of death (cRR = 2.93, 95% CI: 0.94, 9.12; cRR = 1.00, 95% CI: 0.13, 7.53) (Table 3). The multiplicative effect of diabetes status on all-cause mortality risk was nonsignificantly different across HIV status (p = 0.54). After adjusting for confounders, we found that the risk ratio of all-cause mortality comparing those with diabetes to those without diabetes was 3.03 (95% CI: 0.86, 10.63) among HIV-positive patients, and 2.81 (95% CI: 1.60, 4.96) among HIV-negative patients (Table 4).

Culture conversion

Among the 858 (77.4%) patients with a positive baseline culture, a total of 535 (62.4%) culture-converted during the study period, including 158 (59.2%) of those who had diabetes, 68 (62.4%) of those with pre-diabetes, and 309 (64.1%) without diabetes (Table 2). The median time to culture conversion was 39.0 (IQR = 45.0) days from the start of treatment. Compared to patients without diabetes, the adjusted hazard rate of culture conversion was similar in patients with diabetes (aHR = 1.07, 95% CI: 0.86, 1.33) (Table 4). In assessment of interaction, the adjusted hazard ratio for the effect of diabetes (compared to no diabetes) on culture conversion was also similar among patients with HIV (aHR = 1.25, 95% CI: 0.54, 2.88) and without HIV (aHR = 1.13, 95% CI: 0.90, 1.42).

Sensitivity and subgroup analyses

We conducted sensitivity analyses to evaluate bias in the association between diabetes status and the hazard rate of culture conversion due to exclusion of censored patients with a missing loss to follow-up date. When excluding the 24 censored patients with a missing TB treatment end date, among HIV-positive patients, the unadjusted hazard ratio of culture

conversion comparing patients with diabetes to those without was 1.61 (95% CI: 0.77, 3.36) (Supplement Table D). When the 24 censored patients with a missing TB treatment end date were included in the analysis (with assigned censorship date 6 months after treatment start or assigned median time to conversion), the hazard ratios for culture conversion comparing HIV-positive patients with diabetes to HIV-positive patients without were slightly attenuated in both models (cHR = 1.32, 95% CI: 0.63, 2.77; cHR = 1.49, 95% CI: 0.71, 3.13) (Supplement Table D). Among HIV-negative patients, when the 24 censored patients with a missing treatment end date were excluded, the unadjusted hazard ratio of culture conversion comparing patients with diabetes to those without was 1.17 (95% CI: 0.96, 1.44) (Supplement Table D). When the 24 censored patients with a missing TB treatment end date were included in the analysis, again, the hazard ratios for culture conversion comparing HIV-negative patients with diabetes to HIV-negative patients without were attenuated in both models (cHR = 1.12, 95% CI: 0.92, 1.38; cHR = 1.16, 95% CI: 0.94, 1.42) (Supplement Table D).

In subgroup analyses to compare the distribution of patients without diabetes status information to those with a known diabetes status we found that patient and clinical characteristics of patients without diabetes status information were similar to patients known to be without diabetes. There were no statistical differences in age (p = 0.17), sex (p = 0.23), occupation (p = 0.28), HIV status (p = 0.26), AFB smear status (p = 0.50), and baseline culture (p = 0.62) among patients without diabetes status information and those without diabetes (Supplement Table A).

Discussion

  Overall, we found that more than one-quarter of all patients with TB in the state of Georgia had co-occurring diabetes. The co-occurrence of diabetes among patients with TB (28.7%) was higher than that of coinfection with HIV (8.3%). Few TB patients in this cohort were both HIV-positive and had diabetes (1.4%). Importantly, we reported that nearly one in five patients with TB and diabetes died during TB treatment. For example, diabetes was associated with over a three-fold relative increased risk of death before or during TB treatment. Among HIV-negative patients, both diabetes and pre-diabetes (hyperglycemia) were associated with a three-fold and two-fold relative risk of increased death before or during TB treatment respectively. We also estimated that nearly one-quarter of the observed mortality in patients with both diabetes and HIV was due to synergism between the two risk factors. DM/TB co-occurrence is common among patients with TB in Georgia, and mortality among these patients is high. These results highlight the need for regular screening of TB patients for diabetes and HIV, and careful monitoring of patients with comorbidities. Regarding our secondary outcome of culture conversion, hyperglycemia was not significantly associated with decreased rates of conversion, regardless of HIV status.

  Several mechanisms have been proposed to explain why patients with DM/TB comorbidity are at a higher risk of death than patients without diabetes. Diabetes can impair host defense against pathogens by suppressing cytokine production, inhibiting phagocytosis, and causing the dysfunction of immune cells, such as neutrophils [36]. Once infected with *M. tb*, a lower proportion of activated macrophages and a lower proportion of pro-inflammatory cytokines result in a higher frequency of adverse outcomes among patients with diabetes and TB [37]. Our findings are consistent with those of other studies examining the association between

diabetes and mortality among patients with TB. For example, a systematic review of observational studies conducted in both high and low burden settings found that diabetes is associated with a nearly two-fold increased risk of death among patients with TB (RR = 1.89, 95% CI: 1.52, 2.36) [5]. Three other retrospective studies conducted in the United States found that diabetes was associated with an increased risk of death. A retrospective cohort study by Fielder et al. on 174 Baltimore TB patients between 1993-1998 found that after adjusting for age, the odds of death among patients with DM were 3.8 times those of patients without DM (OR = 3.8, 95% CI: 1.4, 10.3) [9]. A retrospective cohort study of 139 Baltimore adults with TB diagnosed between 1994-1996 by Oursler et al. 2002 found that after adjusting for confounders, the hazard of death among patients with TB and DM was 6.7 times that of TB patients without DM (95% CI: 1.6, 29.3) [10]. Finally, a retrospective cohort study conducted by Dooley et al. on 297 patients with TB in Maryland diagnosed between 2004-2005 found that the odds of death were 6.5 times greater in patients with DM than patients without, after adjusting for confounders such as HIV status, age, and weight (95% CI: 1.1, 38.0) [38].

Findings regarding our secondary outcome, culture conversion, are mixed. For example, Dooley et al. found that patients with diabetes had 61% lower odds of converting two months after treatment than those without diabetes; however, the finding was not statistically significant [38]. A systematic review of nine studies conducted in a variety of setting revealed that results regarding the risk of remaining sputum culture positive among patients with DM are heterogeneous, with estimates ranging from 0.79 to 3.25 [5]. A 2007 study conducted in Indonesia, however, found that the odds of remaining sputum culture positive at 6 months for DM patients were 7.65 times those of TB patients without DM (95% CI: 1.89, 30.95) [12]. It is important for future studies to evaluate the association between diabetes and positive TB

treatment markers, such as culture conversion, among patients. We did find evidence of a trend toward synergism between HIV and diabetes in TB patients in our cohort, a finding that is not consistent with the results of two other studies conducted in African countries. Faurholt-Jepsen et al. found that diabetes was associated with TB in the HIV uninfected (aOR = 4.2, 95% CI: 1.5, 11.6), and not the HIV infected (aOR = 0.1, 95% CI: 0.01, 1.8) participants, after adjusting for important confounders [39]. Additionally, a 2014 study from Botswana found that there was no difference in severe TB disease among HIV-positive patients with DM compared to HIV-negative patients with DM [40].

Our study is subject to several limitations that are important to note. First, we only considered a maximum of 15 laboratory values to classify patients by diabetes status, therefore, our primary exposure is subject to misclassification. However, laboratory data is typically a more reliable measure of diabetes status than self-report or medical record abstraction alone. Additionally, because data on our exposure was limited to reported laboratory values, we were unable to distinguish between type I, type II, and gestational diabetes. We also did not have access to data on the duration of DM disease or use of diabetes medications, and therefore, were unable to estimate the effect of chronic controlled versus uncontrolled hyperglycemia. While the information on our secondary exposure of interest, HIV infection, was more complete within the state surveillance system, we did not incorporate HIV treatment into our analyses. As a result, outcomes among HIV-positive patients in our cohort may differ vastly dependent on whether or not they are receiving treatment for HIV infection. Regarding our primary outcome, mortality, we were unable to determine if a patient's cause of death was due to TB disease or an unrelated cause. It is important to note that our study was conducted in a low TB burden setting, the United States. As a result, findings from this study may not be generalizable to high burden settings.

Nonetheless, our study population was diverse, and the data are widely generalizable to the entire state of Georgia and similar settings in the United States. Finally, in evaluating time to culture conversion among patients in the cohort, 24 (2.8%) patients had a missing follow-up information and were excluded from analysis. However, sensitivity analysis showed that including these 24 patients did not confer a considerable difference in the hazard ratio values.

Conclusion

We found that TB/DM co-occurrence is common among patients in Georgia, with prevalence estimates exceeding those of TB/HIV coinfection. This study found that diabetes was associated with an increased risk of all-cause mortality among TB patients, supporting the findings from previous research. We also found that there was a trend toward synergism between HIV and diabetes in patients with TB. Additional research is needed to understand the interactions between hyperglycemia and HIV and evaluate how these co-occurring conditions impact sputum culture conversion and TB outcomes in settings with a high burden of TB. Overall, our results highlight the need for regular screening of TB patients for DM, and careful management of co-prevalent patients.

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TABLES & FIGURES-RESULTS

Table 1. Baseline patient and clinical characteristics of adults with TB in the state of Georgia, 2015-2020 by diabetes mellitus status.

	Total (n = 1109) N (%)	Diabetes (n = 318) N (%)	Pre-Diabetes (n = 149) N (%)	No Diabetes (n = 642) N (%)	P¹	P²
Patient characteristics						
Age (years)						
Mean (SD)	48.7 (17.7)	57.1 (15.0)	50.9 (17.8)	44.0 (17.3)	<0.01	<0.01
Median (IQR)	48.0 (28.0)	58.0 (21.0)	50.0 (24.0)	41.0 (27.0)	<0.01	<0.01
Sex						
Male	739 (66.6)	216 (67.9)	99 (66.4)	424 (66.0)	0.56	0.75
Female	370 (33.4)	102 (32.1)	50 (33.6)	218 (34.0)	---	---
Race/Ethnicity						
NH Asian	244 (22.0)	108 (34.0)	28 (18.8)	108 (16.8)	<0.01	<0.01
NH Black	502 (45.3)	106 (33.3)	63 (42.3)	333 (51.9)	---	---
NH White	145 (13.1)	36 (11.3)	25 (16.8)	84 (13.1)	---	---
Hispanic	202 (18.2)	65 (20.4)	28 (18.8)	109 (17.0)	---	---
Other³	16 (1.4)	3 (1.0)	5 (3.3)	8 (1.2)	---	---
Occupation						
Employed	463 (44.0)	110 (36.2)	70 (49.3)	283 (46.8)	<0.01	0.03
Unemployed	441 (42.0)	125 (41.1)	48 (33.8)	268 (44.3)	---	---
Retired	147 (14.0)	69 (22.7)	24 (16.9)	54 (8.9)	---	---
Unknown/Missing	58	14	7	37	---	---
Foreign born						
Yes	571 (51.6)	181 (57.1)	74 (50.0)	316 (49.4)	0.02	0.13
No	535 (48.4)	136 (42.9)	75 (50.0)	324 (50.6)	---	---
Unknown/Missing	3	1	0	2	---	---
Recent homelessness						
Yes	76 (6.9)	15 (4.8)	7 (4.8)	54 (8.5)	0.04	0.98
No	1020 (93.1)	297 (95.2)	140 (95.2)	583 (91.5)	---	---
Unknown/Missing	13	6	2	5	---	---
In correctional facility						
Yes	30 (2.7)	6 (1.9)	0 (0.0)	24 (3.8)	0.13	0.09
No	1069 (97.3)	307 (98.1)	148 (100.0)	614 (96.2)	---	---
Unknown/Missing	10	5	1	4	---	---
Heavy alcohol use						
Yes	162 (15.3)	43 (14.2)	30 (20.8)	89 (14.6)	0.88	0.08
No	896 (84.7)	260 (85.8)	114 (79.2)	522 (85.4)	---	---
Unknown/Missing	51	15	5	31	---	---
Injection drug use						
Yes	15 (1.4)	5 (1.7)	3 (2.1)	7 (1.1)	0.52	0.74
No	1044 (98.6)	298 (98.3)	140 (97.9)	606 (98.9)	---	---
Unknown	50	15	6	29	---	---

ESRD						
Yes	23 (2.1)	14 (4.4)	1 (0.7)	8 (1.3)	<0.01	0.03
No	1083 (97.9)	304 (95.6)	147 (99.3)	632 (98.7)	---	---
Unknown/Missing	3	0	1	2	---	---
HIV status						
Positive	92 (8.7)	15 (5.1)	11 (7.8)	66 (10.6)	<0.01	0.26
Negative	970 (91.3)	281 (94.9)	130 (92.2)	559 (89.4)	---	---
Unknown	47	22	8	17	---	---
Clinical characteristics						
AFB smear status						
Positive	450 (44.6)	152 (52.8)	60 (46.2)	238 (40.2)	<0.01	0.21
Negative	560 (55.4)	136 (47.2)	70 (53.8)	354 (59.8)	---	---
Not Done/Missing	99	30	19	50	---	---
Baseline culture						
Positive	858 (80.3)	267 (87.3)	109 (77.9)	482 (77.4)	<0.01	0.01
Negative	211 (19.7)	39 (12.7)	31 (22.1)	141 (22.6)	---	---
Not Done/Missing	40	12	9	19	---	---
Site of TB Disease						
PTB only	790 (71.4)	243 (76.4)	113 (76.3)	434 (67.7)	0.02	0.88
PTB & EPTB	106 (9.5)	25 (7.9)	10 (6.8)	71 (11.1)	---	---
EPTB only	211 (19.1)	50 (15.7)	25 (16.9)	136 (21.2)	---	---
Unknown	2	0	1	1	---	---
TST status						
Positive	262 (71.2)	74 (69.2)	30 (63.8)	158 (73.8)	0.38	0.52
Negative	106 (28.8)	33 (30.8)	17 (36.2)	56 (26.2)	---	---
Not Done/Missing	741	211	102	428	---	---
Any lung cavity						
Yes	440 (55.1)	149 (58.9)	68 (61.3)	223 (51.3)	0.05	0.67
No	359 (44.9)	104 (41.1)	43 (38.7)	212 (48.7)	---	---
Unknown	310	65	38	207	---	---
Miliary TB						
Yes	52 (7.3)	19 (8.4)	5 (5.1)	28 (7.2)	0.59	0.30
No	661 (92.7)	207 (91.6)	93 (94.9)	361 (92.8)	---	---
Unknown	396	92	51	253	---	---
DST profile[4]						
None to RIF/INH	751 (89.5)	238 (90.8)	92 (85.2)	421 (89.8)	0.49	0.16
RIF or INH	79 (9.4)	23 (8.8)	14 (13.0)	42 (8.9)	---	---
MDR	9 (1.1)	1 (0.4)	2 (1.8)	6 (1.3)	---	---
Missing	19	5	1	13	---	---

[1]P-value comparing values for patients with diabetes versus patients with no diabetes.

[2]P-value comparing values for patients with pre-diabetes versus patients with no diabetes.

[3]Other race/ethnicity includes patients who identify as American Indian/Alaskan Native (non-Hispanic), Multiracial (non-Hispanic), or Unknown.

[4]Among culture-positive TB cases.

Table 2. Unadjusted risk ratios and hazard ratios for the association between characteristics at baseline, death before or during TB treatment, and any culture conversion among adults with TB in Georgia, 2015-2020.

| | Death before or during TB treatment[1] | | Any culture conversion[2] | | Time to culture conversion (days) |
	Cumulative incidence *N/T* (%)	Risk ratio (95% CI)	Cumulative incidence *N/T* (%)	Hazard ratio (95% CI)	Median (IQR)
Total cohort	109/1109 (9.8)	---	535/858 (62.4)	---	39.0 (45.0)
Diabetes status					
Diabetes	56/318 (17.6)	3.14 (2.11, 4.67)	158/267 (59.2)	1.12 (0.92, 1.35)	35.0 (40.8)
Pre-Diabetes	17/149 (11.4)	2.03 (1.18, 3.52)	68/109 (62.4)	1.05 (0.81, 1.37)	38.0 (49.5)
No Diabetes	36/642 (5.6)	REF	309/482 (64.1)	REF	41.0 (46.0)
Patient characteristics					
Age **(years)**					
≥55	79/433 (18.2)	6.82 (3.35, 13.90)	192/333 (58.0)	0.91 (0.74, 1.13)	40.0 (48.5)
45-54	16/189 (8.5)	3.16 (1.38, 7.25)	99/149 (66.4)	1.02 (0.79, 1.31)	39.0 (44.0)
35-44	6/188 (3.2)	1.19 (0.42, 3.38)	92/150 (61.3)	0.84 (0.65, 1.09)	40.5 (52.3)
16-34	8/299 (2.7)	REF	152/226 (67.3)	REF	35.0 (37.3)
Sex					
Male	79/739 (10.7)	1.32 (0.88, 1.97)	376/579 (64.9)	1.14 (0.94, 1.37)	43.0 (48.0)
Female	30/370 (8.1)	REF	159/279 (57.0)	REF	28.0 (42.5)
Race/Ethnicity					
NH Asian	17/244 (7.0)	0.92 (0.44, 1.91)	114/192 (59.4)	1.02 (0.75, 1.39)	34.0 (42.8)
NH Black	64/502 (12.7)	1.68 (0.91, 3.10)	246/390 (63.1)	1.15 (0.87, 1.51)	40.0 (45.8)
Hispanic	16/202 (7.9)	1.04 (0.50, 2.18)	105/155 (67.7)	1.28 (0.94, 1.74)	42.0 (43.0)
Other[3]	1/16 (6.3)	0.82 (0.11, 5.97)	5/13 (38.5)	0.59 (0.24, 1.46)	28.0 (69.0)
NH White	11/145 (7.6)	REF	65/108 (60.1)	REF	42.0 (52.0)
Occupation					
Unemployed	55/441 (12.5)	3.21 (1.91, 5.37)	218/343 (63.6)	1.10 (0.92, 1.33)	37.0 (40.0)

Retired	29/147 (19.7)	5.07 (2.90, 8.87)	65/118 (55.1)	0.90 (0.68, 1.18)	38.0 (48.0)
Employed	18/463 (3.9)	REF	237/359 (66.0)	REF	42.0 (46.0)
Foreign Born					
Yes	39/571 (6.8)	0.52 (0.36, 0.76)	259/424 (61.1)	0.95 (0.80, 1.13)	35.0 (41.5)
No	70/535 (13.1)	REF	275/431 (63.8)	REF	43.0 (47.5)
Recent homelessness					
Yes	9/76 (11.8)	1.28 (0.68, 2.44)	44/60 (73.3)	1.33 (0.98, 1.81)	43.5 (46.3)
No	94/1020 (9.2)	REF	490/787 (62.3)	REF	39.0 (45.0)
In correctional facility					
Yes	2/30 (6.7)	0.69 (0.18, 2.67)	18/27 (66.7)	1.07 (0.67, 1.70)	54.5 (116.8)
No	103/1069 (9.6)	REF	516/824 (62.6)	REF	39.0 (45.0)
Heavy alcohol use					
Yes	22/162 (13.6)	1.60 (1.03, 2.50)	98/138 (71.0)	1.26 (1.01, 1.57)	49.0 (57.5)
No	76/896 (8.5)	REF	420/680 (61.8)	REF	35.0 (45.0)
Injection drug use					
Yes	2/15 (13.3)	1.45 (0.39, 5.34)	11/13 (84.6)	1.32 (0.73, 2.40)	45.0 (44.5)
No	96/1044 (9.2)	REF	509/805 (63.2)	REF	39.0 (47.0)
ESRD					
Yes	8/23 (34.8)	3.77 (2.09, 6.80)	5/17 (29.4)	0.42 (0.17, 1.00)	59.0 (63.0)
No	100/1083 (9.2)	REF	529/839 (63.1)	REF	39.0 (45.0)
HIV Status					
Positive	11/92 (12.0)	1.40 (0.77, 2.52)	49/68 (72.1)	1.40 (1.04, 1.88)	25.0 (34.0)
Negative	83/970 (8.6)	REF	476/751 (63.4)	REF	40.5 (44.5)
Clinical characteristics					
AFB smear status					
Positive	40/450 (8.9)	1.72 (1.08, 2.72)	364/434 (83.9)	2.32 (1.92, 2.79)	47.0 (43.0)
Negative	29/560 (5.2)	REF	171/354 (48.3)	REF	22.0 (37.5)
Baseline culture					

Positive	95/858 (11.1)	2.60 (1.33, 5.06)	323/858 (37.6)	N/A	39.0 (45.0)
Negative	9/211 (4.3)	REF	0/0 (0.0)	REF	N/A
Site of TB Disease					
EPTB only	19/211 (9.0)	0.94 (0.58, 1.51)	7/128 (5.5)	0.04 (0.02, 0.08)	19.0 (21.5)
PTB & EPTB	14/106 (13.2)	1.37 (0.81, 2.34)	47/86 (54.7)	0.68 (0.51, 0.92)	36.0 (50.5)
PTB only	76/790 (15.5)	REF	481/644 (74.7)	REF	40.0 (45.0)
TST status					
Positive	11/262 (4.2)	0.28 (0.13, 0.58)	144/196 (73.5)	1.10 (0.80, 1.52)	34.0 (46.3)
Negative	16/106 (15.1)	REF	50/76 (65.8)	REF	35.5 (54.0)
Any lung cavity					
Yes	41/440 (9.3)	0.78 (0.53, 1.16)	300/391 (76.7)	1.83 (1.49, 2.25)	47.0 (42.0)
No	47/359 (13.1)	REF	135/271 (49.8)	REF	27.0 (48.0)
Miliary TB					
Yes	11/52 (21.1)	2.03 (1.15, 3.58)	24/40 (60.0)	1.07 (0.71, 1.61)	39.5 (38.5)
No	69/661 (10.4)	REF	353/550 (64.2)	REF	42.0 (44.0)
DST profile					
RIF or INH	4/79 (5.1)	0.44 (0.17, 1.17)	59/79 (74.7)	1.19 (0.90, 1.56)	47.0 (52.0)
MDR	0/9 (0.0)	0.00 (0.00, 0.00)	6/9 (66.7)	0.68 (0.30, 1.52)	99.0 (44.8)
None to RIF/INH	87/758 (11.5)	REF	463/751 (61.7)	REF	38.0 (45.5)

[1]A total of 4 patients died within 7 days of treatment termination.
[2]Among patients culture positive at baseline.
[3]Other race/ethnicity includes patients who identify as American Indian/Alaskan Native (non-Hispanic), Multiracial (non-Hispanic), or Unknown.

Table 3. Unadjusted risk ratios and hazard ratios for the association between diabetes and HIV status, death before or during TB treatment, and any culture conversion among adults with TB in Georgia, 2015-2020.

		Death before or during TB treatment[1]		Any culture conversion[2]		Time to culture conversion (days)
		Cumulative incidence *N/T* (%)	Risk ratio (95% CI)	Cumulative incidence *N/T* (%)	Hazard ratio (95% CI)	Median (IQR)
Total cohort		109/1109 (9.8)	---	535/858 (62.4)	---	39.0 (45.0)
HIV-positive (n = 92)	Diabetes	4/15 (26.7)	2.93 (0.94, 9.12)	9/13 (69.2)	1.61 (0.77, 3.36)	23.0 (18.0)
	Pre-Diabetes	1/11 (9.1)	1.00 (0.13, 7.53)	7/11 (63.6)	0.78 (0.35, 1.77)	23.0 (47.5)
	No Diabetes	6/66 (9.1)	REF	33/44 (75.0)	REF	27.0 (46.0)
HIV-negative (n = 970)	Diabetes	45/281 (16.0)	3.44 (2.17, 5.46)	144/325 (61.3)	1.17 (0.96, 1.44)	35.0 (40.3)
	Pre-Diabetes	12/130 (9.2)	1.98 (1.03, 3.83)	59/91 (64.8)	1.07 (0.81, 1.42)	41.0 (47.0)
	No Diabetes	26/559 (4.7)	REF	273/425 (64.2)	REF	42.0 (47.0)
HIV unknown (n = 47)	Diabetes	7/22 (31.8)	1.35 (0.47, 3.88)	5/19 (26.3)	0.92 (0.22, 3.87)	62.0 (37.0)
	Pre-Diabetes	4/8 (50.0)	2.13 (0.71, 6.40)	2/7 (28.6)	2.18 (0.36, 13.05)	10.0 (3.0)
	No Diabetes	4/17 (23.5)	REF	3/13 (23.1)	REF	28.0 (42.5)

[1]A total of 4 patients died within 7 days of treatment termination.
[2]Among patients culture positive at baseline.

Table 4. Adjusted risk ratios and hazard ratios for the association between diabetes and HIV status, death before or during TB treatment, and any culture conversion among adults with TB in Georgia, 2015-2020.

		Death before or during TB treatment[1]			Any culture conversion[2]		
		Model 1[3] aRR	Model 2[4] aRR	Model 3[5] aRR	Model 1[3] aHR	Model 2[6] aHR	Model 3[7] aHR
Total cohort (n = 1109)	Diabetes	2.09 (1.37, 3.17)	2.59 (1.62, 4.13)	2.60 (1.61, 4.18)	1.14 (0.93, 1.40)	1.18 (0.96, 1.45)	1.07 (0.86, 1.33)
	Pre-Diabetes	1.68 (0.97, 2.92)	1.77 (0.96, 3.29)	1.89 (0.99, 3.61)	1.06 (0.82, 1.39)	1.08 (0.83, 1.41)	1.05 (0.80, 1.37)
	No Diabetes	REF	REF	REF	REF	REF	REF
HIV-positive (n = 92)	Diabetes	2.18 (0.70, 6.82)	3.27 (0.95, 11.18)	3.03 (0.86, 10.63)	1.57 (0.75, 3.32)	1.38 (0.60, 3.17)	1.25 (0.54, 2.88)
	Pre-Diabetes	0.89 (0.11, 7.09)	0.79 (0.09, 7.23)	0.63 (0.07, 5.42)	0.78 (0.34, 1.77)	0.83 (0.36, 1.90)	1.11 (0.47, 2.60)
	No Diabetes	REF	REF	REF	REF	REF	REF
HIV-negative (n = 970)	Diabetes	2.31 (1.41, 3.77)	2.79 (1.61, 4.82)	2.81 (1.60, 4.96)	1.21 (0.97, 1.50)	1.24 (1.00, 1.54)	1.13 (0.90, 1.42)
	Pre-Diabetes	1.65 (0.85, 3.18)	1.80 (0.87, 3.75)	1.97 (0.91, 4.24)	1.09 (0.82, 1.45)	1.10 (0.82, 1.47)	1.00 (0.75, 1.34)
	No Diabetes	REF	REF	REF	REF	REF	REF
HIV unknown (n = 47)	Diabetes	0.99 (0.39, 2.47)	1.26 (0.46, 3.43)	1.25 (0.58, 2.71)	0.85 (0.20, 3.59)	0.96 (0.23, 4.06)	0.39 (0.09, 1.66)
	Pre-Diabetes	1.98 (0.72, 5.41)	1.73 (0.52, 5.82)	1.69 (0.62, 4.62)	1.84 (0.30, 11.12)	1.83 (0.30, 11.07)	9.04 (1.48, 55.26)
	No Diabetes	REF	REF	REF	REF	REF	REF

[1]A total of 4 patients died within 7 days of treatment termination.
[2]Among patients culture positive at baseline.
[3]Adjusted for age and sex.
[4]Adjusted for age, sex, alcohol use, foreign born, and occupation.
[5]Adjusted for age, sex, alcohol use, foreign born, race/ethnicity, occupation, and baseline culture.
[6]Adjusted for age, sex, and occupation.
[7]Adjusted for age, sex, AFB smear status, race/ethnicity, and occupation.

Table 5. Assessment of biologic interaction between diabetes, hyperglycemia, and HIV among adults with TB in the state of Georgia, 2015-2020.

	Cumulative incidence *N/T* (%)	Risk Ratio (95% CI)	RERI (95% CI)	AP (95% CI)	S (95% CI)
Diabetes			1.34 (-3.80, 6.47)	23.30% (-48.40%, 95.00%)	1.39 (0.44, 4.41)
Diabetes/HIV-positive	4/15 (26.7)	5.73 (2.29, 14.38)			
Diabetes/HIV-negative	45/281 (16.0)	3.44 (2.17, 5.46)			
No diabetes/HIV-positive	6/66 (9.1)	1.95 (0.84, 4.57)			
No diabetes/HIV-negative	26/559 (4.7)	REF			
Hyperglycemia			0.20 (-3.48, 3.87)	4.80% (-80.90%, 90.50%)	1.07 (0.32, 3.52)
Hyperglycemia[1]/HIV-positive	5/26 (19.2)	4.13 (1.73, 9.89)			
Hyperglycemia /HIV-negative	57/411 (13.9)	2.98 (1.91, 4.66)			
No hyperglycemia[2] /HIV-positive	6/66 (9.1)	1.95 (0.84, 4.57)			
No hyperglycemia /HIV-negative	26/559 (4.7)	REF			

[1]Includes patients who are classified as diabetic or pre-diabetic.
[2]Includes patients who are classified as non-diabetic.
RERI = relative excess risk due to interaction; AP = attributable proportion due to interaction; S = synergy index

Figure 1. Study flow diagram of adult patients with TB in the state of Georgia, 2015-2020.
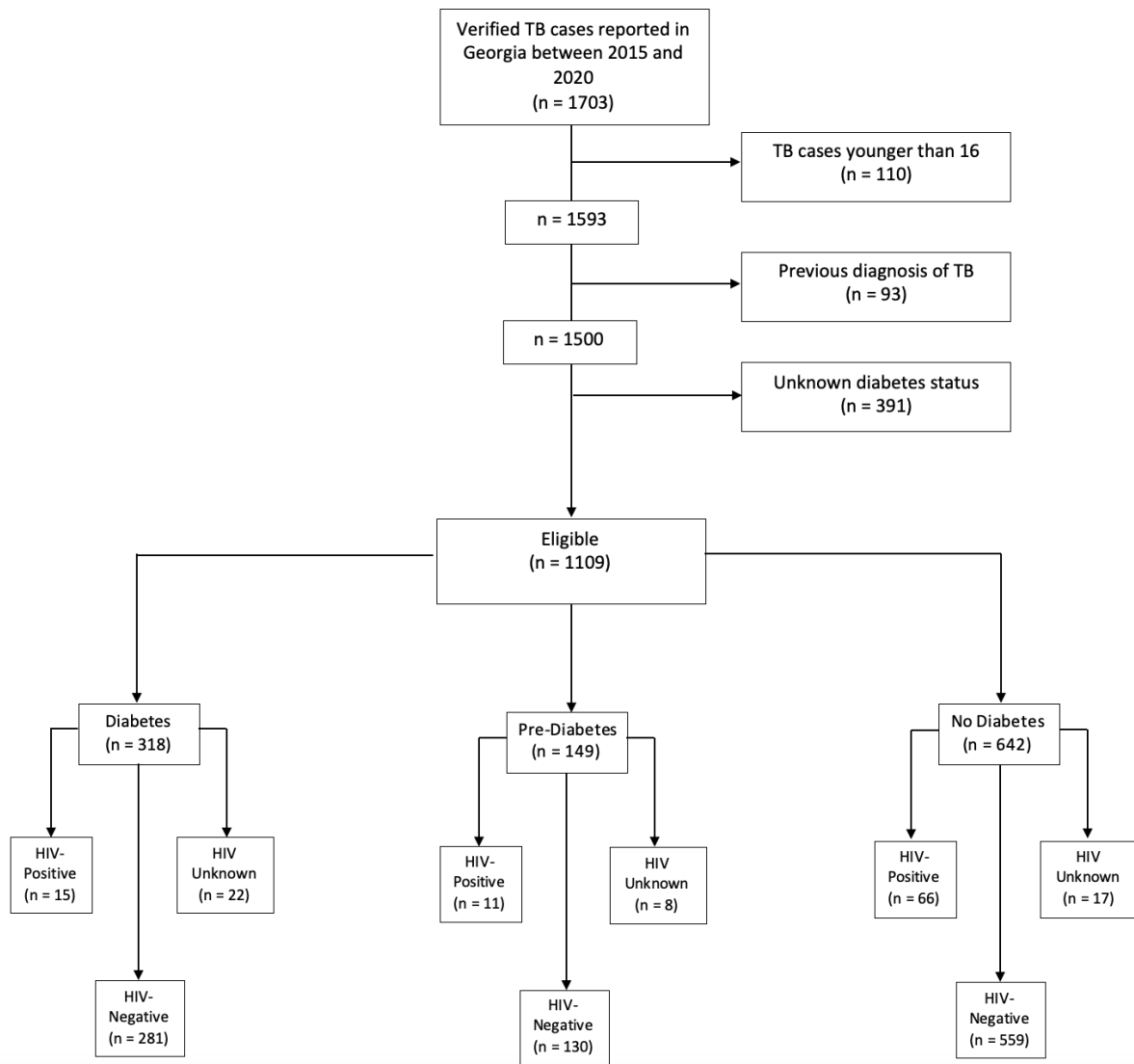
Figure 2. Time to any culture conversion among 1,109 adults with TB and diabetes, pre-diabetes, or no diabetes in the state of Georgia, 2015-2020.
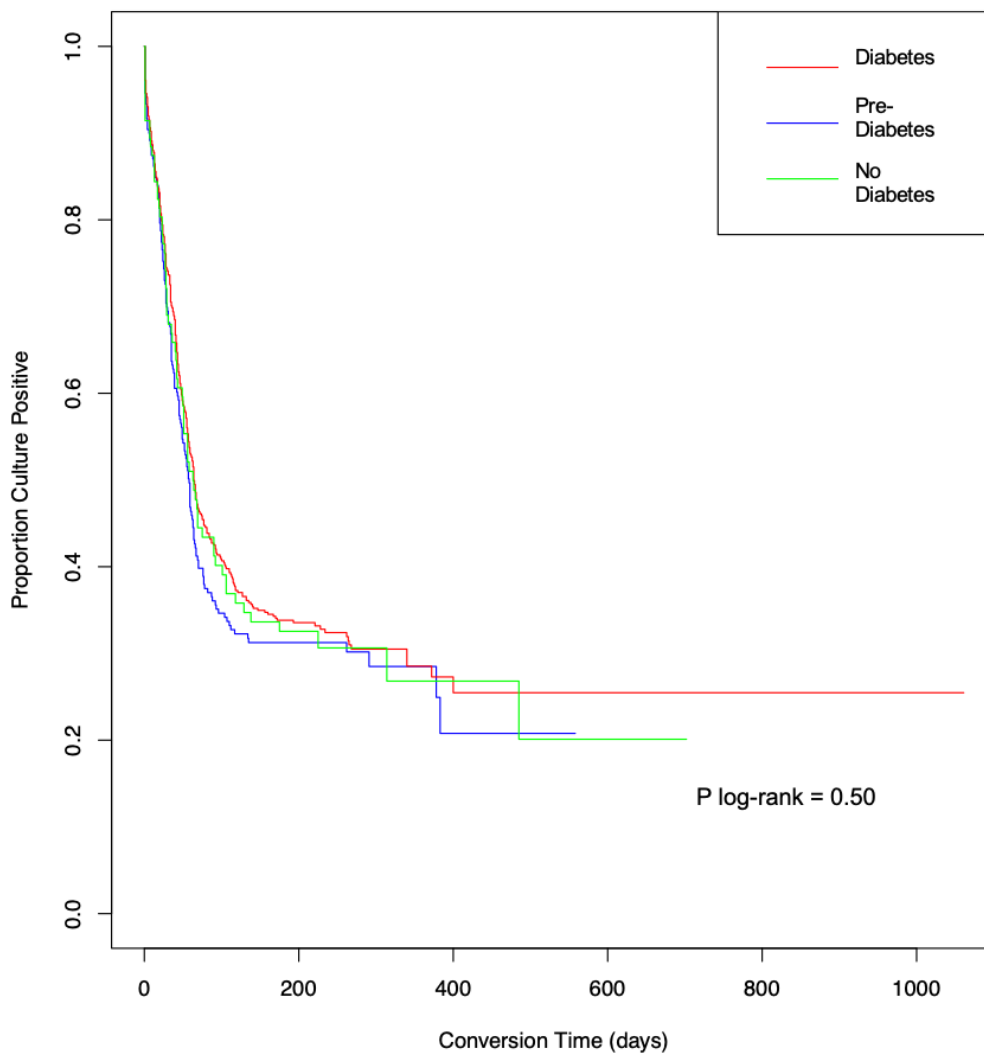
Diabetes	241	45	3	0	0	0
Pre-Diabetes	105	21	5	2	0	0
No Diabetes	461	110	15	4	1	1

Figure 3. Time to any culture conversion among 1,109 HIV-positive, HIV-negative, and HIV unknown adults with TB in the state of Georgia, 2015-2020.
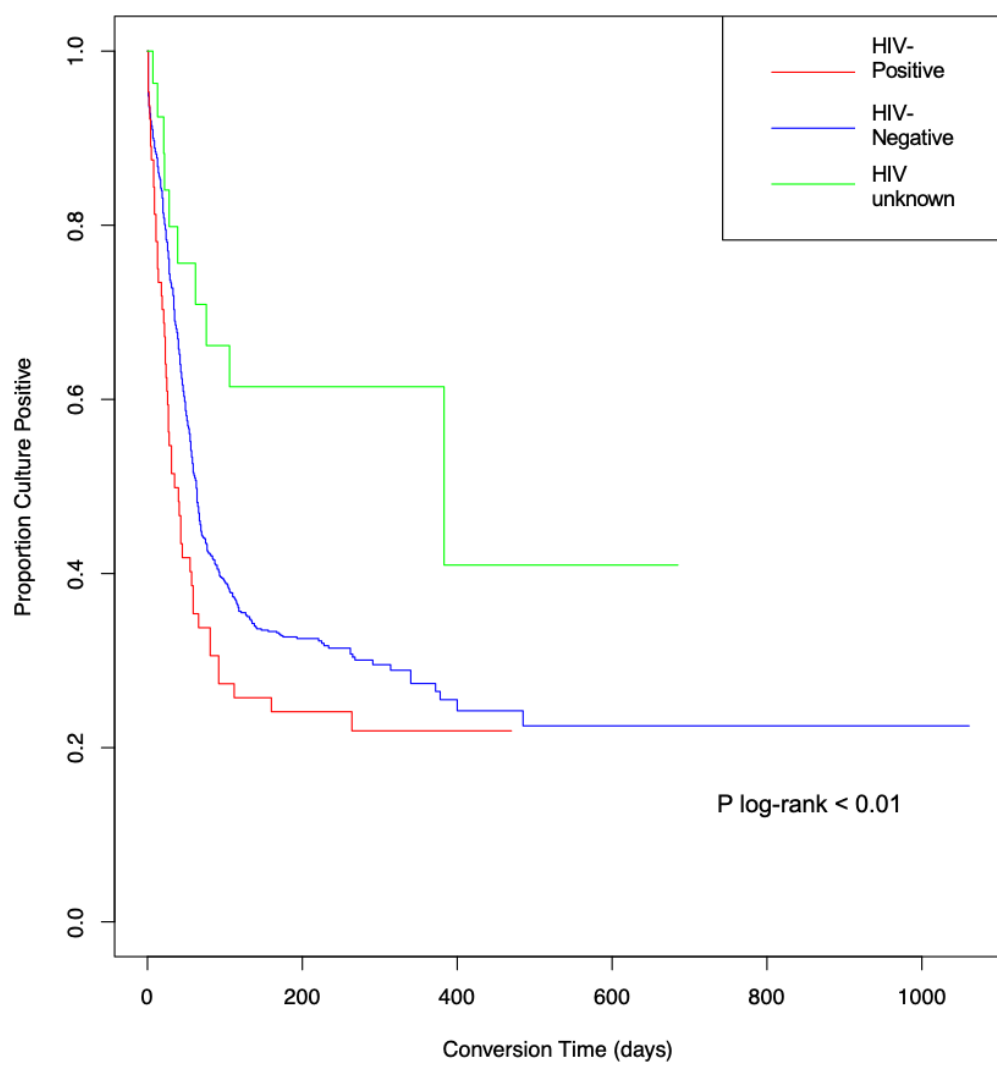
HIV-Positive	64	12	1	0	0	0
HIV-Negative	715	153	20	5	1	1
HIV unknown	28	11	2	1	0	0

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APPENDICES

Supplement Table A. Baseline patient and clinical characteristics of adult TB patients in the state of Georgia, 2015-2020 by diabetes mellitus status, including patients with unknown diabetes status.

	Total (n = 1500) N (%)	Diabetes (n = 318) N (%)	Pre-Diabetes (n = 149) N (%)	No Diabetes (n = 642) N (%)	Diabetes unknown (n = 391) N (%)	P[1]
Patient characteristics						
Age (years)						
Mean (SD)	47.9 (17.8)	57.1 (15.0)	50.9 (17.8)	44.0 (17.3)	45.7 (18.1)	0.17
Median (IQR)	47.0 (28.0)	58.0 (21.0)	50.0 (24.0)	41.0 (27.0)	42.0 (28.0)	0.17
Sex						
Male	983 (65.5)	216 (67.9)	99 (66.4)	424 (66.0)	244 (62.4)	0.23
Female	517 (34.5)	102 (32.1)	50 (33.6)	218 (34.0)	147 (37.6)	---
Race/Ethnicity						
NH Asian	351 (23.4)	108 (34.0)	28 (18.8)	108 (16.8)	107 (27.4)	<0.01
NH Black	683 (45.5)	106 (33.3)	63 (42.3)	333 (51.9)	181 (46.3)	---
NH White	189 (12.6)	36 (11.3)	25 (16.8)	84 (13.1)	44 (11.2)	---
Hispanic	256 (17.1)	65 (20.5)	28 (18.8)	109 (17.0)	54 (13.8)	---
Other[2]	21 (1.4)	3 (0.9)	5 (3.3)	8 (1.2)	5 (1.3)	---
Occupation						
Employed	616 (43.6)	110 (36.2)	70 (49.3)	283 (46.8)	153 (42.3)	0.28
Unemployed	609 (43.1)	125 (41.1)	48 (33.8)	268 (44.3)	168 (46.4)	---
Retired	188 (13.3)	69 (22.7)	24 (16.9)	54 (8.9)	41 (11.3)	---
Unknown/Missing	87	14	7	37	29	---
Foreign born						
Yes	797 (53.3)	181 (57.1)	74 (50.0)	316 (49.4)	226 (57.9)	0.01
No	699 (46.7)	136 (42.9)	75 (50.0)	324 (50.6)	164 (42.1)	---
Unknown/Missing	4	1	0	2	1	---
Recent homelessness						
Yes	104 (7.0)	15 (4.8)	7 (4.8)	54 (8.5)	28 (7.2)	0.48
No	1379 (93.0)	297 (95.2)	140 (95.2)	583 (91.5)	359 (92.8)	---
Unknown/Missing	17	6	2	5	4	---
In correctional facility						
Yes	47 (3.2)	6 (1.9)	0 (0.0)	24 (3.8)	17 (4.4)	0.62
No	1440 (96.8)	307 (98.1)	148 (100.0)	614 (96.2)	371 (95.6)	---
Unknown/Missing	13	5	1	4	3	---
Heavy alcohol use						
Yes	209 (14.7)	43 (14.2)	30 (20.8)	89 (14.6)	47 (12.8)	0.44
No	1216 (85.3)	260 (85.8)	114 (79.2)	522 (85.4)	320 (87.2)	---
Unknown/Missing	75	15	5	31	24	---
Injection drug use						
Yes	21 (1.5)	5 (1.7)	3 (2.1)	7 (1.1)	6 (1.6)	0.52

No	1406 (98.5)	298 (98.3)	140 (97.9)	606 (98.9)	362 (98.4)	---
Unknown	73	15	6	29	23	---
ESRD						
Yes	26 (1.7)	14 (4.4)	1 (0.7)	8 (1.3)	3 (0.8)	0.47
No	1468 (98.3)	304 (95.6)	147 (99.3)	632 (98.7)	385 (99.2)	---
Unknown/Missing	6	0	1	2	3	---
HIV status						
Positive	122 (8.6)	15 (5.1)	11 (7.8)	66 (10.6)	30 (8.4)	0.26
Negative	1299 (91.4)	281 (94.9)	130 (92.2)	559 (89.4)	329 (91.6)	---
Unknown	79	22	8	17	32	---
Clinical characteristics						
AFB smear status						
Positive	579 (42.9)	152 (52.8)	60 (46.2)	238 (40.2)	129 (37.9)	0.50
Negative	771 (57.1)	136 (47.2)	70 (53.8)	354 (59.8)	211 (62.1)	---
Not Done/Missing	150	30	19	50	51	---
Baseline culture						
Positive	1150 (79.9)	267 (87.3)	109 (77.9)	482 (77.4)	292 (78.7)	0.62
Negative	290 (20.1)	39 (12.7)	31 (22.1)	141 (22.6)	79 (21.3)	---
Not Done/Missing	60	12	9	19	20	---
Site of TB Disease						
PTB only	1059 (70.7)	243 (76.4)	113 (76.3)	434 (67.7)	269 (69.0)	0.64
PTB & EPTB	142 (9.5)	25 (7.9)	10 (6.8)	71 (11.1)	36 (9.2)	---
EPTB only	296 (19.8)	50 (15.7)	25 (16.9)	136 (21.2)	85 (21.8)	---
Unknown	3	0	1	1	1	---
TST status						
Positive	377 (72.5)	74 (69.2)	30 (63.8)	158 (73.8)	115 (75.7)	0.69
Negative	143 (27.5)	33 (30.8)	17 (36.2)	56 (26.2)	37 (24.3)	---
Not Done/Missing	980	211	102	428	239	---
Any lung cavity						
Yes	536 (52.8)	149 (58.9)	68 (61.3)	223 (51.3)	96 (44.4)	0.10
No	479 (47.2)	104 (41.1)	43 (38.7)	212 (48.7)	120 (55.6)	---
Unknown	485	65	38	207	175	---
Miliary TB						
Yes	72 (8.0)	19 (8.4)	5 (5.1)	28 (7.2)	20 (10.8)	0.14
No	826 (92.0)	207 (91.6)	93 (94.9)	361 (92.8)	165 (89.2)	---
Unknown	602	92	51	253	206	---
DST profile[3]						
None to RIF/INH	1011 (90.0)	238 (90.8)	92 (85.2)	421 (89.8)	260 (91.5)	0.15
RIF or INH	103 (9.2)	23 (8.8)	14 (13.0)	42 (8.9)	24 (8.5)	---
MDR	9 (0.8)	1 (0.4)	2 (1.8)	6 (1.3)	0 (0.0)	---
Missing	27	5	1	13	8	---

[1]P-value comparing values for patients with no diabetes versus patients with unknown diabetes status
[2]Other race/ethnicity includes patients who identify as American Indian/Alaskan Native (non-Hispanic), Multiracial (non-Hispanic), or Unknown.
[3]Among culture-positive TB cases.

Supplement Table B. Baseline patient and clinical characteristics of adult TB patients in the state of Georgia, 2015-2020 by HIV status.

	Total (n = 1109) N (%)	HIV-Positive (n = 92) N (%)	HIV-Negative (n = 970) N (%)	HIV Unknown (n = 47) N (%)	P^1	P^2
Patient characteristics						
***Age* (years)**						
Mean (SD)	48.7 (17.7)	45.9 (12.2)	48.5 (18.0)	57.9 (19.1)	0.26	<0.01
Median (IQR)	48.0 (28.0)	45.5 (17.3)	48.0 (29.0)	59.0 (29.5)	0.26	<0.01
Sex						
Male	739 (66.6)	65 (70.7)	643 (66.3)	31 (66.0)	0.40	0.96
Female	370 (33.4)	27 (29.3)	327 (33.7)	16 (34.0)	---	---
Race/Ethnicity						
NH Asian	244 (22.0)	8 (8.7)	224 (23.1)	12 (25.5)	<0.01	0.27
NH Black	502 (45.3)	66 (71.7)	420 (43.3)	16 (34.0)	---	---
NH White	145 (13.1)	6 (6.5)	132 (13.6)	7 (14.9)	---	---
Hispanic	202 (18.2)	8 (8.7)	184 (19.0)	10 (21.3)	---	---
Other[3]	16 (1.4)	4 (4.4)	10 (1.0)	2 (4.3)	---	---
Occupation						
Employed	463 (44.0)	32 (38.6)	416 (45.0)	15 (34.1)	<0.01	0.05
Unemployed	441 (42.0)	48 (57.8)	376 (40.7)	17 (38.6)	---	---
Retired	147 (14.0)	3 (3.6)	132 (14.3)	12 (27.3)	---	---
Unknown/Missing	58	9	46	3	---	---
Foreign born						
Yes	571 (51.6)	38 (41.3)	508 (52.5)	25 (54.3)	0.15	0.80
No	535 (48.4)	54 (58.7)	460 (47.5)	21 (45.7)	---	---
Unknown/Missing	3	0	2	1	---	---
Recent homelessness						
Yes	76 (6.9)	13 (14.8)	59 (6.1)	4 (8.9)	0.34	0.45
No	1020 (93.1)	75 (85.2)	904 (93.9)	41 (91.1)	---	---
Unknown/Missing	13	4	7	2	---	---
In correctional facility						
Yes	30 (2.7)	2 (2.3)	28 (2.9)	0 (0.0)	0.30	0.24
No	1069 (97.3)	86 (97.7)	937 (97.1)	46 (100.0)	---	---
Unknown/Missing	10	4	5	1	---	---
Heavy alcohol use						
Yes	162 (15.3)	15 (17.6)	141 (15.2)	6 (13.6)	0.56	0.78
No	896 (84.7)	70 (82.4)	788 (84.8)	38 (86.4)	---	---
Unknown/Missing	51	7	41	3	---	---
Injection drug use						
Yes	15 (1.4)	4 (4.8)	10 (1.1)	1 (2.3)	0.50	0.45
No	1044 (98.6)	79 (95.2)	923 (98.9)	42 (97.7)	---	---
Unknown/Missing	50	9	37	4	---	---
ESRD						

Yes	23 (2.1)	2 (2.2)	18 (1.9)	3 (6.4)	0.22	0.03
No	1083 (97.9)	88 (97.8)	951 (98.1)	44 (93.6)	---	---
Unknown/Missing	3	2	1	0	---	---
Diabetes status						
Diabetes	318 (28.7)	15 (16.3)	281 (29.0)	22 (46.8)	<0.01	0.01
Pre-Diabetes	149 (13.4)	11 (12.0)	130 (13.4)	8 (17.0)	---	---
No Diabetes	642 (57.9)	66 (71.7)	559 (57.6)	17 (36.2)	---	---
Clinical characteristics						
AFB smear status						
Positive	450 (44.6)	41 (47.7)	398 (44.6)	11 (34.4)	0.20	0.25
Negative	560 (55.4)	45 (52.3)	494 (55.4)	21 (65.6)	---	---
Not Done/Missing	99	6	78	15	---	---
Baseline culture						
Positive	858 (80.3)	68 (77.3)	751 (80.4)	39 (83.0)	0.44	0.66
Negative	211 (19.7)	20 (22.7)	183 (19.6)	8 (17.0)	---	---
Not Done/Missing	40	4	36	0	---	---
Site of TB disease						
PTB only	790 (71.4)	58 (63.1)	700 (72.3)	32 (68.1)	0.04	0.52
PTB & EPTB	106 (9.6)	20 (21.7)	83 (8.6)	3 (6.4)	---	---
EPTB only	211 (19.0)	14 (15.2)	185 (19.1)	12 (25.5)	---	---
Unknown	2	0	2	0	---	---
TST status						
Positive	262 (71.2)	13 (52.0)	243 (73.0)	6 (60.0)	0.67	0.36
Negative	106 (28.8)	12 (48.0)	90 (27.0)	4 (40.0)	---	---
Not Done/Missing	741	67	637	37	---	---
Any lung cavity						
Yes	440 (55.1)	16 (22.9)	404 (58.0)	20 (60.6)	<0.01	0.77
No	359 (44.9)	54 (77.1)	292 (42.0)	13 (39.4)	---	---
Unknown	310	22	274	14	---	---
Miliary TB						
Yes	52 (7.3)	9 (13.0)	42 (6.8)	1 (3.7)	0.18	0.53
No	661 (92.7)	60 (87.0)	575 (93.2)	26 (96.3)	---	---
Unknown	396	23	353	20	---	---
DST profile[4]						
None to RIF/INH	751 (89.5)	59 (88.0)	658 (89.5)	34 (91.9)	0.80	0.35
RIF or INH	79 (9.4)	6 (9.0)	71 (9.7)	2 (5.4)	---	---
MDR	9 (1.1)	2 (3.0)	6 (0.8)	1 (2.7)	---	---
Missing	19	1	16	2	---	---

[1]P-value comparing values for HIV-positive patients with HIV-negative patients.
[2]P-value comparing values for HIV-negative patients with HIV unknown patients.
[3]Other race/ethnicity includes patients who identify as American Indian/Alaskan Native (non-Hispanic), Multiracial (non-Hispanic), or Unknown.
[4]Among culture-positive TB cases.

Supplement Table C. Sensitivity analysis of unadjusted hazard ratios for the association between patient and clinical characteristics at baseline and time to culture conversion among TB patients in the state of Georgia, 2015-2020.

	Any culture conversion[1]		
	Hazard ratio[2] (95% CI)	Hazard ratio[3] (95% CI)	Hazard ratio[4] (95% CI)
Diabetes status			
Diabetes	1.12 (0.92, 1.35)	1.07 (0.88, 1.29)	1.10 (0.91, 1.33)
Pre-Diabetes	1.05 (0.81, 1.37)	1.10 (0.84, 1.42)	1.07 (0.82, 1.39)
No Diabetes	REF	REF	REF
Patient characteristics			
Age (years)			
≥55	0.91 (0.74, 1.13)	0.92 (0.74, 1.13)	0.91 (0.74, 1.13)
45-54	1.02 (0.79, 1.31)	1.02 (0.79, 1.32)	1.02 (0.79, 1.31)
35-44	0.84 (0.65, 1.09)	0.85 (0.66, 1.10)	0.84 (0.65, 1.09)
16-34	REF	REF	REF
Sex			
Male	1.14 (0.94, 1.37)	1.13 (0.94, 1.36)	1.13 (0.94, 1.36)
Female	REF	REF	REF
Race/Ethnicity			
NH Asian	1.02 (0.75, 1.39)	1.03 (0.76, 1.40)	1.03 (0.76, 1.39)
NH Black	1.15 (0.87, 1.51)	1.18 (0.90, 1.55)	1.16 (0.88, 1.52)
Hispanic	1.28 (0.94, 1.74)	1.26 (0.92, 1.72)	1.27 (0.93, 1.73)
Other[5]	0.59 (0.24, 1.46)	0.56 (0.22, 1.39)	0.57 (0.23, 1.42)
NH White	REF	REF	REF
Occupation			
Unemployed	1.10 (0.92, 1.33)	1.07 (0.89, 1.28)	1.09 (0.91, 1.31)
Retired	0.90 (0.68, 1.18)	0.91 (0.69, 1.20)	0.90 (0.69, 1.19)
Employed	REF	REF	REF
Foreign Born			
Yes	0.95 (0.80, 1.13)	0.93 (0.78, 1.10)	0.94 (0.80, 1.12)
No	REF	REF	REF
Recent homelessness			
Yes	1.33 (0.98, 1.81)	1.30 (0.95, 1.77)	1.32 (0.97, 1.80)
No	REF	REF	REF
In correctional facility			
Yes	1.07 (0.67, 1.70)	0.88 (0.55, 1.40)	0.98 (0.61, 1.57)
No	REF	REF	REF
Heavy alcohol use			
Yes	1.26 (1.01, 1.57)	1.21 (0.97, 1.51)	1.24 (1.00, 1.55)
No	REF	REF	REF
Injection drug use			
Yes	1.32 (0.73, 2.40)	1.38 (0.76, 2.50)	1.35 (0.74, 2.45)

No	REF	REF	REF
ESRD			
Yes	0.42 (0.17, 1.00)	0.44 (0.18, 1.06)	0.42 (0.18, 1.02)
No	REF	REF	REF
HIV Status			
Positive	1.40 (1.04, 1.88)	1.38 (1.03, 1.85)	1.39 (1.04, 1.87)
Negative	REF	REF	REF
Clinical characteristics			
AFB smear status			
Positive	2.32 (1.92, 2.79)	2.25 (1.87, 2.72)	2.31 (1.92, 2.79)
Negative	REF	REF	REF
Site of TB Disease			
EPTB only	0.04 (0.02, 0.08)	0.04 (0.02, 0.08)	0.04 (0.02, 0.08)
PTB & EPTB	0.68 (0.51, 0.92)	0.66 (0.49, 0.89)	0.67 (0.50, 0.91)
PTB only	REF	REF	REF
TST status			
Positive	1.10 (0.80, 1.52)	1.10 (0.79, 1.51)	1.10 (0.80, 1.52)
Negative	REF	REF	REF
Any lung cavity			
Yes	1.83 (1.49, 2.25)	1.82 (1.48, 2.23)	1.83 (1.49, 2.25)
No	REF	REF	REF
Miliary TB			
Yes	1.07 (0.71, 1.61)	1.01 (0.66, 1.52)	1.05 (0.69, 1.58)
No	REF	REF	REF
DST profile			
RIF or INH	1.19 (0.90, 1.56)	1.16 (0.88, 1.52)	1.18 (0.90, 1.54)
MDR	0.68 (0.30, 1.52)	0.71 (0.31, 1.58)	0.69 (0.31, 1.54)
None to RIF/INH	REF	REF	REF

[1]Among patients culture positive at baseline.

[2]24 censored patients with missing end date were excluded.

[3]24 censored patients with missing end date were assigned censorship date 6 months after start date.

[4]24 censored patients with missing end date were assigned median time to conversion for survival time.

[5]Other race/ethnicity includes patients who identify as American Indian/Alaskan Native (non-Hispanic), Multiracial (non-Hispanic), or Unknown.

Supplement Table D. Sensitivity analysis of unadjusted hazard ratios for the association between diabetes and HIV status and time to culture conversion among TB patients in the state of Georgia, 2015-2020.

		Any culture conversion[1]		
		Hazard ratio[2] (95% CI)	Hazard ratio[3] (95% CI)	Hazard ratio[4] (95% CI)
HIV-positive (n = 92)	Diabetes	1.61 (0.77, 3.36)	1.32 (0.63, 2.77)	1.49 (0.71, 3.13)
	Pre-Diabetes	0.78 (0.35, 1.77)	0.82 (0.36, 1.85)	0.79 (0.35, 1.79)
	No Diabetes	REF	REF	REF
HIV-negative (n = 970)	Diabetes	1.17 (0.96, 1.44)	1.12 (0.92, 1.38)	1.16 (0.94, 1.42)
	Pre-Diabetes	1.07 (0.81, 1.42)	1.17 (0.84, 1.48)	1.09 (0.82, 1.44)
	No Diabetes	REF	REF	REF
HIV unknown (n = 47)	Diabetes	0.92 (0.22, 3.87)	0.85 (0.20, 3.56)	0.90 (0.21, 3.75)
	Pre-Diabetes	2.18 (0.36, 13.05)	2.17 (0.36, 13.01)	2.19 (0.37, 13.10)
	No Diabetes	REF	REF	REF

[1]Among patients culture positive at baseline.
[2]24 censored patients with missing end date were excluded.
[3]24 censored patients with missing end date were assigned censorship date 6 months after start date.
[4]24 censored patients with missing end date were assigned median time to conversion for survival time.